NDA/BLA Multidisciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	220149
Priority or Standard	Priority
Submit Date(s)	July 18, 2025
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PDUFA Goal Date	March 18, 2026
Division/Office	DDD/OII
Review Completion Date	TBD
Established/Proper Name	Icotrokinra
(Proposed) Trade Name	ICOTYDE
Pharmacologic Class	Interleukin-23 (IL-23) receptor antagonist
Code name	JNJ-77242113
Applicant	Janssen Biotech, Inc.
Dosage form	Tablets
Applicant proposed Dosing Regimen	200 mg orally once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of moderate-to-severe plaque psoriasis (PsO) in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	200965009|Plaque Psoriasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adults and pediatric patients 12 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	200965009|Plaque Psoriasis (disorder)
Recommended Dosing Regimen	200 mg orally once daily

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DEPI=Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DRM=Division of Risk Management
DPV=Division of Pharmacovigilance
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Icotrokinra is an orally administered peptide that selectively binds to the IL-23 receptor (IL-23R) and antagonizes the binding of IL-23. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Icotrokinra inhibits the IL23/IL-23R-dependent release of proinflammatory cytokines. Icotrokinra is a new molecular entity for oral administration (200 mg tablets) and, as an oral presentation, differs from other currently approved IL-23 antagonists which are injectable monoclonal antibodies.

The pathogenesis of psoriasis may be related to excessive activation of immune-mediated pathways that include IL-23. IL-23 is implicated in the induction and proliferation of Th17 and Th22 cells and is important in chronic immune-mediated inflammatory disease. Activation of the signaling cascade involving these pathways leads to further proliferation of inflammatory mediators. IL-23 pathway activation is upregulated in psoriasis and lesional psoriatic skin demonstrates increased IL23R transcript expression. Targeting this pathway has demonstrated clinical improvement in patients with moderate to severe psoriasis.

NDA 220149 is an original NDA for icotrokinra and was submitted on July 18, 2025. The proposed indication is for the treatment of moderate-to-severe plaque psoriasis (PsO) in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 200 mg administered orally once daily on an empty stomach.

The Agency concluded that the proposed proprietary name, ICOTYDE, was conditionally acceptable from both a promotional and safety perspective. (Refer to Proprietary Name Review by Mishale Mistry, PharmD, MPH, Division of Medication Error Prevention and Analysis [DMEPA] dated September 19, 2025).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from four adequate and well-controlled Phase 3 clinical trials (PSO3001(ICONIC-LEAD), PSO3002 (ICONIC-ADVANCE 1), PSO3003 (ICONIC-TOTAL), PSO3004 (ICONIC-ADVANCE 2), which provide evidence of the effectiveness of icotrokinra for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older weighing at least 40 kg who are candidates for systemic therapy or phototherapy.

In the clinical trials, the efficacy of icotrokinra for the treatment of patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy was evaluated and compared to placebo for the co-primary endpoints at Week 16 for each study.

The co-primary efficacy endpoints for each study (PSO3001, PSO3002, and PSO3004) were:

- IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16.
- PASI 90 at Week 16.

Study PSO3003 did not have a co-primary endpoint designated because the objective of this study was to evaluate subjects with plaque psoriasis in the scalp, genitals, and hands and feet; therefore, PASI 90 was not appropriate for capturing this outcome. The primary efficacy endpoint for Study PSO3003 was:

- IGA (overall) score of 0/1 and a ≥2-grade improvement from baseline at Week 16.

Secondary endpoints in Study PSO3003 evaluated efficacy in the scalp, genitals, and hands and feet.

In each of the Phase 3 studies, the co-primary or primary endpoints were met. In all studies, icotrokinra was superior to placebo for the co-primary or primary (PSO3003) endpoints with a p-value of <0.001 for each endpoint in each study.

In addition, the efficacy of icotrokinra was compared to deucravacitinib in studies PSO3002 and PSO3004. In PSO3002 and PSO3004, icotrokinra was superior to deucravacitinib for all multiplicity-controlled key secondary endpoints. In Study PSO3002 at the 16-week comparison between icotrokinra and deucravacitinib, IGA response was 68.5% for icotrokinra and 50.2% for deucravacitinib, with a p-value <0.001, and PASI90 was 55.0% for icotrokinra to 29.6% for deucravacitinib, also with a p-value <0.001. In study 3004, IGA response for icotrokinra was 70.5% to 54.1% for deucravacitinib with a p-value <0.001, and PASI90 was 57.1% for icotrokinra to 33.9% for deucravacitinib with a p-value <0.001.

The Applicant has demonstrated that icotrokinra is effective for its intended use in the proposed target population and has met the evidentiary standard required by 21 CFR 314.126 (a)(b) to support approval of this NDA. The Office Signatory agrees with this assessment and conclusion.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic immune-mediated skin disease that affects approximately 125 million people worldwide. The most common clinical presentation, plaque psoriasis, appears as sharply demarcated, erythematous scaly patches or plaques that occur on extensor surfaces and is associated with significant impairment in quality of life. Icotrokinra is an orally administered peptide that selectively binds to the IL-23 receptor (IL-23R) and antagonizes the binding of IL-23. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. The pathogenesis of psoriasis may be related to excessive activation of immune mediated pathways that include IL-23. Icotrokinra is proposed as a once daily orally administered 200 mg tablet for the treatment of moderate to severe plaque psoriasis in adults and adolescents (pediatrics) ≥12 years to <18 years (who also weigh at least 40 kg) who are candidates for systemic or phototherapy.

Current therapeutic options for the treatment of adults with moderate to severe plaque psoriasis include biologics (TNF inhibitors, IL-12/23 inhibitor, IL-17 inhibitors, and IL-23 inhibitors), oral systemic medications (tyrosine kinase 2 [TYK2] inhibitor, methotrexate, apremilast, acitretin, and cyclosporine) and UV-B/PUVA phototherapy. No currently approved therapy results in complete responses or sustained remission, and there are limitations in many that restrict their use in all patient populations, including pediatrics.

Substantial evidence of effectiveness for icotrokinra for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older who also weigh at least 40 kg who are candidates for systemic therapy or phototherapy was provided from four multicenter, randomized, double-blind and placebo-controlled trials (PSO3001, PSO3002, PSO3003, PSO3004), which enrolled 2367 adult and 72 adolescent subjects with moderate-to-severe plaque psoriasis. An active comparator, deucravacitinib, administered as an oral 6-mg dose, was also included in Trials PSO3002 and PSO3004 through Week 24. The target population for Trials PSO3001, PSO3002, and PSO3004 was subjects with moderate to severe plaque psoriasis, defined by a PASI≥12, IGA ≥3, and BSA≥10%, who were candidates for phototherapy or systemic treatment; Studies PSO3002 and PSO3004 enrolled adult subjects and Study PSO3001 enrolled adults and adolescents 12 years to <18 years. Study PSO3003 had inclusion criteria, which allowed inclusion of subjects with psoriasis in “special areas” (scalp, genital, hand/foot) including a total BSA ≥1% at screening and baseline, and IGA (overall)≥2 and at least one of the following: ss-IGA≥3 (scalp) and/or sPGA-G≥3 (genital) and/or hf-PGA ≥3 (hand/foot). Trial PSO3003 enrolled adults and adolescents 12 years to <18 years.

The co-primary efficacy endpoints of an IGA Score of 0 or 1 plus a ≥2-grade improvement from baseline and a PASI-90 response were assessed at Week 16. In Trials PSO3001, PSO3002, and PSO3004, icotrokinra was superior to placebo for the coprimary

endpoints with p-values of <0.001. In Trial PSO3003, icotrokinra was superior to placebo for the primary endpoint of IGA Score of 0 or 1 plus a ≥2-grade improvement from baseline (p<0.001) with support from secondary endpoints related to the special areas of the scalp and genitals.

Table 1. Results for the Primary Endpoint(s) – Trial PSO3001, Trial PSO3002, Trial PSO3003, Trial PSO3004

	PSO3001 ICONIC-LEAD		PSO3002 ICONIC-ADVANCE 1		PSO3003 ICONIC-TOTAL		PSO3004 ICONIC-ADVANCE 2	
	Icotrokinra (N=456)	Placebo (N=228)	Icotrokinra (N=311)	Placebo (N=156)	Icotrokinra (N=208)	Placebo (N=103)	Icotrokinra (N=322)	Placebo (N=82)
IGA 0/1 (Week 16)	65%	8%	68%	11%	57%	6%	71%	9%
Risk difference (95% CI)	56% (50%, 62%)		58% (50%, 64%)		51% (42%, 59%)		63% (53%, 70%)	
p-value	<0.0001		<0.0001		<0.0001		<0.0001	
PASI-90 (Week 16)	50%	4%	55%	4%			58%	1%
Risk difference (95% CI)	45% (40%, 50%)		51% (44%, 57%)		Not included.		57% (49%, 62%)	
p-value	<0.0001		<0.0001				<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adclrori.xpt, adpasiri.xpt
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA 0/1, achievement of Investigator Global Assessment score of clear (0) or almost clear (1) with a ≥2-grade improvement from baseline; PASI-90, achievement of ≥90% improvement in Psoriasis Area Severity Index score from baseline
Note: The results for Trial PSO3004 were based on 320 subjects on the icotrokinra arm and 81 subjects on the placebo arm, excluding the subjects from Site CB4-US10098 for which GCP noncompliance issues were identified.

Efficacy was similar in subjects across subgroups by baseline demographic characteristics, age (adult versus adolescent), disease characteristics, and prior psoriasis treatment. In Trial PSO3001, adult subjects in PSO3001 who achieved clinical response (PASI-75 or IGA 0/1 response) at Week 24 were rerandomized to placebo or icotrokinra. The icotrokinra group showed higher maintenance rates than the randomized withdrawal group at Week 52.

The safety of icotrokinra, assessed using integrated data from four Phase 3 trials (PSO3001, PSO3002, PSO3003, PSO3004), was adequate to characterize the safety profile of icotrokinra. There was an overall imbalance in the number of deaths between the treatment arms (five deaths on the icotrokinra arm, and none on placebo or deucravacitinib) including both during the initial 16-week placebo-controlled period through the extension period. Two deaths occurred during the 16 weeks placebo-controlled period (gastrointestinal bleeding and cardiovascular event). Two of the deaths (one in placebo-controlled period, one in extension period) were related to gastrointestinal bleeding. Upon detailed review of the cases related to gastrointestinal bleeding, there were multiple confounding factors in each case, however, a causal effect of icotrokinra could not be ruled out. Two other deaths were cardiovascular-related in subjects who had cardiovascular risk factors (one placebo controlled period, one extension period). Patients with psoriasis have an increased risk of cardiovascular events related to underlying systemic inflammation related to

psoriasis. The fifth death (extension period) had characteristics that suggested a missed diagnosis of malignancy prior to randomization. While there were confounding factors for the two events resulting in death, both events were notable for having occurred while on icotrokinra, and two SAE GI -related events also occurred in subjects receiving icotrokinra (gastric ulcer perforation in the extension period and rectal bleeding reported under the 120-day safety update). Due to the seriousness of these events, occurrence of the events in participants exposed to icotrokinra treatment only in the clinical trials, and given that drug causality cannot be ruled out, these events are recommended to be included in Section 6 of the Prescribing Information. SAEs occurred at similar rates between icotrokinra and placebo for the 16-week controlled period. In the 16-week placebo-controlled period, there were a small number of malignancies in subjects receiving icotrokinra. There was no predominant type or organ system that was identified in these cases. In several cases, there was clinical evidence that the malignancy was present but undiagnosed at the time of study enrollment. EAIRs did not suggest a trend for malignancy with icotrokinra treatment over time.

No increase in serious infections, MACE events, depression or suicidal behavior were reported with icotrokinra compared to placebo in the icotrokinra clinical program. No cases of new tuberculosis or reactivation of tuberculosis in subjects with LTBI were seen in the program. The most common adverse reaction occurring in the pooled safety analysis set, (AR) occurring >1% in icotrokinra and >0.5% difference from placebo were headache (4.1%), nausea (1.2%), cough (1.2%), fungal infection (1.1%), and fatigue (1.0%). These identified adverse reactions are recommended to be included in Section 6 of the product labeling.

Based on the available safety and efficacy data, the overall risk-benefit profile is favorable and supports the approval of icotrokinra 200 mg for oral administration for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older who also weight at least 40 kg who are candidates for systemic therapy or phototherapy.

Prescription and patient labeling, including a Medication Guide, as well as enhanced pharmacovigilance are adequate to manage the risks of icotrokinra in the postmarketing setting and a Risk Evaluation and Mitigation Strategy (REMS) is not needed. To evaluate for drug-associated risks of major maternal or fetal outcomes, assess impact on lactation, and determine benefit-risk in the pediatric population 4 years to less than 12 years of age, postmarketing studies will be required for the specific pregnancy and pediatric populations. Recommended postmarketing requirements under 505 (o) include pregnancy and lactation studies, and a safety and pharmacokinetic trial in pediatric subjects 4 years to <12 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy to address the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

The available safety and efficacy data support the approval of icotrokinra for the treatment of adults and pediatric patients 12 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Although there are a number of FDA-approved treatments with an acceptable risk-benefit profile for this indication, none of these treatments provide a response in all patients, and may be associated with one or more serious risks; as such, there is a need for additional therapeutic options.		
Dimension	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	Psoriasis is a common, chronic, inflammatory skin disorder associated with substantial impairment of quality of life. The prevalence of psoriasis in the United States is approximately 2-3% (Armstrong et al. 2021), of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Comorbidities that reported to be associated with psoriasis include depression, suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.	Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and potential for associated comorbidities.
Current Treatment Options	FDA-approved drugs for the treatment of moderate to severe psoriasis include tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab, infliximab, certolizumab), IL-12/23 antagonists (ustekinumab), IL-17A antagonist (secukinumab and ixekizumab), IL-17A receptor antagonist (brodalumab), IL-23 antagonists, (guselkumab, tildrakizumab, and risankizumab), and the TYK2 inhibitor, deucravacitinib; other small-molecule immune modulators include methotrexate, apremilast, acitretin, and cyclosporine. Other treatment modalities include phototherapy with either PUVA (UVA light with methoxsalen) or UVB light (narrow or broadband). All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. There are limitations on all approved treatments from contraindicated populations and conditions, safety concerns, and accessibility.	FDA-approved drugs for the treatment of psoriasis while effective, have limitations including non-responders and lack of durable response or remission. There are restrictions that limit use of some therapeutic options in specific patient populations. Immunomodulating therapies including IL-17 and IL-23 inhibitors have warnings for serious infections and reactivation of LTBI. There are limited therapies that are approved for use in pediatrics.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Substantial evidence of effectiveness of icotrokinra for the treatment of adults and pediatric patients 12 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy was provided from four multicenter, randomized, double-blind and placebo-controlled trials (PSO3001, PSO3002, PSO3003, PSO3004). In these trials, 2367 adult subjects and 72 pediatric subjects with moderate to severe plaque psoriasis were treated with icotrokinra 200 mg daily. The Coprimary Efficacy Endpoint for Studies PSO3001, PSO3002, and PSO3004 was: • IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16. • PASI 90 at Week 16. The objective of Study PSO3003 was to evaluate subjects with plaque psoriasis in the scalp, genitals and hands and feet and therefore had a primary efficacy endpoint for Study PSO3003 of: • IGA (overall) score of 0/1 and a ≥2-grade improvement from baseline at Week 16. In each of the Phase 3 studies, the coprimary or primary endpoints were met. In all studies, icotrokinra was superior to placebo for the coprimary or primary (PSO3003) endpoints with p-value<0.001 for each endpoint in each study. In addition, the efficacy of icotrokinra was evaluated and compared to deucravacitinib in studies PSO3002 and PSO3004, in which all	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trial designs were randomized, double-blind, and placebo controlled. Replicate studies for the primary efficacy endpoint were conducted and 2 studies included an active comparator. The co-primary endpoints of IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 are established as clinically meaningful. Icotrokinra offers a clinically meaningful clinical benefit with a route of administration that differs from other currently approved IL-23 antagonist therapies and may increase access for some patients as an orally administered drug. Additionally, efficacy in adolescents was similar to efficacy in adults and icotrokinra may offer an alternate treatment option for adolescents.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	multiplicity-controlled key secondary endpoints against deucravacitinib were met. Adult participants with moderate to severe plaque psoriasis in PSO3001 who achieved clinical response (PASI 75 or IGA 0/1 response) at Week 24 were rerandomized to placebo or icotrokinra. The icotrokinra group showed higher maintenance rates than the randomized withdrawal group at Week 52. Statistically significant improvements in scalp and genital psoriasis were observed from PSO3003. Efficacy was similar in subjects across subgroups for baseline demographic characteristics, age (adult vs. adolescent), disease characteristics, and prior psoriasis treatment.	
Risk and Risk Management	The safety of icotrokinra for the treatment of adults and adolescents with moderate to severe plaque psoriasis was assessed primarily from pooled data from four Phase 3 studies (PSO3001, PSO3002, PSO3003, and PSO3004). All studies are ongoing and continuing to collect safety data for up to 3 years of icotrokinra exposure past the data cut off for this submission. The size of the safety database, consistent with ICH E1A, included 2367 subjects who were ≥12 years of age and received at least one dose of icotrokinra 200 mg once daily (1296 subjects were randomized to and received icotrokinra during the placebo-controlled period. After 16 weeks, 520 subjects initially randomized to placebo switched to and received open-label icotrokinra, and after 24 weeks, 551 subjects initially randomized to active control switched to and received open-label icotrokinra). Of this total, 1849 were exposed for at least 6 months, and 648 were exposed for at least 1 year. A total of 72 adolescents ≥12 to <18 years of age were exposed to icotrokinra. Seventy-one adolescents were exposed for at least 6 months, and	The size of the database and duration of treatment are adequate and consistent with ICH E1A. The demographic characteristics of the population reflect the general population of patients with plaque psoriasis who would be candidates for icotrokinra. Recommend labeling to include warnings and precautions for serious infection, active or untreated LTBI and concomitant treatment with icotrokinra, and completion of vaccine schedules prior to initiation of treatment with icotrokinra. The safety database is considered limited to assess the risk of icotrokinra use in specific populations, including pregnant

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	forty-five were exposed for at least 1 year. The demographics of the safety population are sufficiently representative of the target population. Consideration of risks associated with approved IL-23 inhibitors influenced analysis of the safety data for icotrokinra. Analysis of adverse reactions was focused on the immunomodulatory mechanism of action (IL-23 inhibition), including focus on serious infections, viral reactivation, malignancy and LTBI reactivation. Additionally, there were two unexpected cases of fatality related to GI bleed in subjects who were receiving icotrokinra, one occurring in the placebo control period and one in the extension period. There were also two GI serious adverse reactions (gastric ulcer perforation during the extension period and rectal bleeding reported under the 120-day safety update report). While it is acknowledged that there are multiple confounding factors in the gastrointestinal bleeding related deaths and GI serious adverse events, a causal relationship cannot be excluded as these events only occurred in subjects who received icotrokinra, and the subject population of patients with psoriasis is not generally considered to be at risk for mortality from GI bleeding events. Therefore, these serious gastrointestinal events are recommended for inclusion in the USPI in the ADVERSE REACTIONS, Clinical Trials Experience subsection as low-frequency serious adverse reactions. The most common serious adverse events observed on icotrokinra treatment included infective exacerbation of COPD, pneumonia, diverticulitis, and bacterial gastroenteritis. These events had subject risk factors including diabetes, metabolic syndrome, and obesity that are confounding factors for these events. EAIR rates suggested no	and lactating females, as well as pediatric subjects <12 years of age. Therefore, a PREA PMR is recommended for a pediatric study to assess the PK and safety of icotrokinra in pediatric subjects 4 years to less than 12 years of age with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Additionally, a descriptive pregnancy safety study and a lactation study are recommended as PMRs. These PMR requirements in conjunction with routine and enhanced pharmacovigilance and communication of adverse reactions via prescribing information and patient labeling are adequate to manage the risks of the product. A REMS is not recommended for this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	increased risk over time. There were no cases of LTBI reactivation, including in patients who had not received LTBI treatment. The most common adverse reactions observed from the placebo-controlled period in subjects receiving icotrokinra were headache, nausea, cough, fungal infection, and fatigue. Limitations of the safety database submitted by the Applicant limited ability to identify risks that might occur with long-term use of icotrokinra. The database also is limited to identify adverse pregnancy, fetal or infant outcomes including any risk associated with pregnancy and lactation. The safety database did not include pediatric subjects <12 years of age. Therefore, to evaluate for drug-associated risks of major maternal or fetal outcomes, assess impact on lactation, and determine benefit-risk in the pediatric population 4 years to <12 years of age, postmarketing studies and a trial are recommended to be required for the specific pregnancy and pediatric populations, respectively.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Sections 8.1.1-8.1.4 and Section 8.2.6
		X	Observer reported outcome (ObsRO)	Sections 8.1.1-8.1.4
		X	Clinician reported outcome (ClinRO)	Sections 8.1.1-8.1.4
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2. Therapeutic Context

2.1. Analysis of Condition

Epidemiology

Psoriasis affects approximately 125 million people worldwide with a broad geographic distribution. It is a chronic immune-mediated skin disease with the most common variant being plaque psoriasis. Adults are the primary population affected, estimated at 3.2%, however it also may affect approximately 0.13% of children. There tends to be a bimodal age distribution with presentation at ages 18 to 39 years and ages 50 to 69 years. Males and females are equally affected. Genetic and environmental factors may be important at onset.

Clinical Presentation

The most common presentation is plaque psoriasis, which consists of sharply demarcated, erythematous scaly patches or plaques that occur on extensor surfaces are pathognomonic for psoriasis. The characteristic lesions include erythema, thickening and scale. Other forms include guttate, erythrodermic, and pustular psoriasis. Psoriasis may also present in the intertriginous and genital areas, palms, soles, and nails. Psoriasis occurring in these areas can cause markedly decreased quality of life. Pruritus can be significant and affects quality of life.

Psoriasis is associated with higher risk for cardiometabolic comorbidities than the general population. Vascular inflammation and high risk coronary atherosclerotic plaques, similar to prevalence in hyperlipidemic patients. The proportion of psoriasis patients with moderate to severe coronary artery calcification is similar to those with type 2 diabetes. Psoriasis is associated with an increased risk of myocardial infarction, stroke, and cardiovascular mortality and appears to be an independent risk factor for adverse cardiovascular outcomes. Other comorbid conditions include depression, anxiety, and suicidal ideation. Psoriasis is also associated with a four-fold greater risk of inflammatory bowel disease compared to the general population.

The pathogenesis of psoriasis may be related to excessive activation of components of the adaptive immune system. This activation is believed to start with activated myeloid dendritic cells, which once activated, secrete IL-12 and IL-23 which in turn induce differentiation of naïve T cells to Th1 cells. In contrast, IL-23 induces the survival and proliferation of TH17 and TH22 cells. TH1 cells secrete interferon gamma and TNF-alfa, TH22 cells secrete IL-22 and TH17 cells secrete IL-17, IL-22, and TNF alpha. IL-23 signaling is mediated by Tyk2-Jak2 and STAT3, which leads to further transcription of key inflammatory mediators. The downstream effect is keratinocyte proliferation, increased expression of angiogenic mediators and endothelial adhesion molecules, and infiltration of immune cells into lesional skin. IL-23-mediated activation of the TH17 pathway is thought to have a predominant role in these pathways.

IL-23 is important in the pathogenesis of chronic immune mediated inflammatory disease. IL-23 is involved in normal immune response, however, in excess, such as may occur in inflammatory conditions, plays a role in chronic inflammation associated with immune diseases. Targeting the IL-23 pathway is a validated approach for treating moderate-to-severe plaque psoriasis.

IL-23 receptor protein is expressed on immune cells in healthy individuals (including MAIT cells, CD3+CD56+ cells, CD4+ and CD8+, and NK cells). IL-23 pathway activation is upregulated in psoriasis with increased IL23R transcript expression in lesional psoriatic skin. IL23R transcript expression generally is restricted to the T cell population, while the ligand expression occurs across a broader population of cells. IL-23 modulation may be more targeted to T-cell populations involved in upregulation of IL-23 in psoriasis and may be differentiated from monoclonal antibodies which target IL-17.

2.2. Analysis of Current Treatment Options

Treatment Options

Mild psoriasis is generally regarded as ≤3 to 5% affected BSA and is typically treated with topical corticosteroids, vitamin D analogs (calcitriol without or with calcipotriol or calcipotriene), calcineurin inhibitors (tacrolimus and pimecrolimus), keratolytics (tazarotene and salicylic acid), and targeted phototherapy.

Moderate to severe psoriasis generally involves more extensive BSA and is treated with systemic treatments which include biologics and/or oral medications and/or UV-B/PUVA phototherapy. These modalities may be used individually or in combination.

There are four mechanistically distinct classes of biologics approved for treatment of moderate to severe psoriasis.

TNF (alpha) Inhibitors decrease the downstream inflammatory cascade central to psoriasis pathogenesis. Most common adverse events are nasopharyngitis, upper respiratory tract infection, and injection site reactions. Safety concerns include increased rates of serious infections, internal malignancies, increased skin cancer (nonmelanoma skin cancers); Contraindications include active TB, advanced CHF, hepatitis B, demyelinating diseases, including multiple sclerosis. Patients with LTBI can receive TNF inhibitors if concurrently treated for LTBI. Drugs in this class include infliximab, certolizumab, adalimumab, etanercept; all are for subcutaneous administration, except for infliximab.

Ustekinumab is an IL-12/23 inhibitor, which inhibits both cytokines via the shared p40 subunit; the therapeutic effect primarily through inhibition of IL-23. Safety concerns with Ustekinumab which are reflected in labeling include risk of serious infections, malignancies, hypersensitivity reactions, posterior reversible encephalopathy syndrome, and noninfectious pneumonia. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting

treatment with Ustekinumab. Live vaccinations are to be avoided. The most common adverse events reported are nasopharyngitis, upper respiratory tract infections, headache, and fatigue.

IL-17 inhibitors target either IL-17 ligand or its receptor. Secukinumab and ixekizumab inhibit IL-17A ligand; bimekizumab inhibits both IL-17A and IL-17F ligands. Brodalumab inhibits IL-17 receptor alpha. IL-17 inhibitors seem to have an acceptable safety profile; however, labeling reflects safety concerns. Warnings and Precautions with secukinumab include serious infections, inflammatory bowel disease, and hypersensitivity reactions. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with Ustekinumab. Live vaccinations are to be avoided. The most common adverse reactions are nasopharyngitis, diarrhea and upper respiratory tract infection.

Ixekizumab safety concerns include serious infections, hypersensitivity, and inflammatory bowel disease. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with ixekizumab. Live vaccinations are to be avoided. The most common adverse reactions are injection-site reactions, upper respiratory tract infections, nausea, and tinea infections. Brodalumab carries a box warning for suicidal ideation and behavior and labeled warnings for hypersensitivity reactions, serious infections, eczematous eruptions, and Crohn's disease. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with brodalumab. Live vaccinations are to be avoided. The most common adverse reactions include arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections.

IL-23 inhibitors inhibit the p19 subunit of IL-23, reducing the activity of the Th17 pathway. The most common adverse events are URI and injection-site reactions. Approved drugs in this class include guselkumab, tildrakizumab, and risankizumab, all of which are administered by subcutaneous injection. Guselkumab carries warnings and precautions for hypersensitivity reactions and infections. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with guselkumab. Live vaccinations are to be avoided. The most common adverse reactions are upper respiratory infections, headache, injection site reactions, arthralgia, bronchitis, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. Tildrakizumab carries warnings and precautions for hypersensitivity and risk of infection. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with tildrakizumab. Live vaccinations are to be avoided. The most common adverse reactions include upper respiratory infections, injection site reactions, and diarrhea. Risankizumab warnings and precautions include increased risk of infection. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with risankizumab. Live vaccinations are to be avoided. The most common adverse reactions are upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections.

Oral Systemic Treatments

There are a number of available oral therapies which include deucravacitinib, methotrexate, apremilast, acitretin, and cyclosporine. Safety concerns with deucravacitinib reflected in labeling include hypersensitivity, risk of infection, malignancy, including lymphoma, rhabdomyolysis, elevation of serum triglycerides and liver enzymes. Additionally, TYK2 inhibition may share some potential risks associated with JAK inhibition. Patients should be evaluated and treatment initiated for latent tuberculosis prior to starting treatment with deucravacitinib. Live vaccinations are to be avoided. The most common adverse reactions are upper respiratory infections, blood creatine phosphokinase increased, herpes simplex, mouth ulcers, folliculitis and acne. Warnings and precautions for methotrexate include risk of serious infections, neurotoxicity, secondary malignancies, and infertility. Live vaccinations should be avoided. Common adverse reactions include stomatitis, leukopenia, nausea, and abdominal dysfunction.

Apremilast includes warnings and precautions for hypersensitivity, including cases of angioedema and anaphylaxis, diarrhea, nausea, vomiting, depression, weight loss, and interactions with cytochrome P450 enzyme-inducing drugs. The most common adverse reactions include diarrhea, nausea, and headache. Acitretin is a systemic retinoid with significant restrictions including use in pregnancy due to risk of teratogenicity. Acitretin is also contraindicated in patients with severely impaired liver or kidney function and in patients with chronic abnormally elevated blood lipid values. An increased risk of hepatitis has been reported with use. Cyclosporine use has been associated with an increased risk of skin malignancies in psoriasis patients treated with PUVA or UVB, and methotrexate or immunosuppressive agents. Cyclosporine can cause systemic hypertension and nephrotoxicity.

No currently approved therapy results in complete responses or sustained remission, and there are limitations in many that restrict their use in all patient populations, including pediatrics.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Icotrokinra is a new molecular entity and is not currently marketed in the United States; therefore, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

On May 27, 2021, the Applicant submitted a request for a Pre-IND meeting to discuss opening an IND for the use of JNJ-77242113, and oral interleukin-23 receptor (IL23R) antagonist, in the treatment of psoriasis (PsO). On July 30, 2021, the Agency responded with comments regarding CMC control strategy and the adequacy of the nonclinical safety program intended to support the Phase 2b clinical study in a subsequent IND submission.

On November 12, 2021 the Applicant submitted an IND application and a Notice of Intent to Request Special Protocol Assessment for Carcinogenicity Protocols. This was done in anticipation of submitting a 2-year rat carcinogenicity protocol for review by the Division and the Carcinogenicity Assessment Committee (CAC).

On December 1, 2021 the Applicant submitted a new IND for JNJ-77242113. The first clinical trial to be conducted under the IND was Protocol 77242113PSO2001, entitled "A Phase 2b Multicenter, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy and Safety of JNJ-77242113 for the Treatment of Moderate-to-Severe Plaque Psoriasis." Study 77242113PSO2001 was planned to begin under the IND end of January 2022. On February 2, 2022, A Study May Proceed letter was sent to the Applicant.

On June 21, 2023, an End-of Phase 2 (EOP2) was held during which comments were provided regarding the nonclinical safety pharmacology, toxicology, and clinical pharmacology program needed to support further development and registration, characterization of ADA samples for the Phase 3 studies, the size and design of the Phase 3 studies, including a proposal in to include adolescents in Phase 3, and Phase 3 study endpoints, dosing regimen, safety monitoring, study design including active comparator (deucravacitinib), study design including psoriasis in special areas, statistical approach, size of the safety database for registration, and management of LTBI and label implications.

Specifically, meeting minutes issued on July 19, 2023 communicated the following regarding the proposed Phase 3 studies:

Based on the meeting minutes and the response document for JNJ-77242113 (plaque psoriasis treatment), here are the key takeaways:

- Primary Endpoint: The Applicant changed the coprimary endpoint from PASI 75 to the more stringent PASI 90 at Week 16, alongside IGA score of 0 or 1 with ≥2-grade improvement from baseline, which the Agency found acceptable.
- Dosing Regimen: The Agency noted that the proposed 200 mg once daily dose has not been previously evaluated in clinical trials. While exposure-response modeling suggests it may be comparable to 100 mg BID, the adequacy will be determined during NDA review.
- Clinical Development Program: The Phase 3 program includes three randomized, double-blind, placebo-controlled trials (PSO3001, PSO3002, and PSO3003) enrolling approximately 1,650 subjects, with specific concerns raised about the PSO3003 study design for special area psoriasis populations.
- Safety Monitoring: The Agency recommended active assessment for neuropsychiatric adverse events, including depression screening (PHQ-9 or QIDS-SR-16) and suicidal ideation monitoring (C-SSRS), as well as comprehensive cardiovascular event monitoring including MACE and thrombotic events.

- Tuberculosis Testing Strategy: Although the Applicant's LTBI monitoring approach was deemed reasonable, the Agency stated that the data would likely be insufficient (b) (4) even with additional biomarker measurements and animal model studies.
- Active Comparator Study: The Applicant agreed to conduct a second deucravacitinib-controlled study (PSO3004) to support comparative labeling claims, as the Agency generally requires replication from two adequate and well-controlled trials for such claims.
- Clinical Pharmacology: The Agency requested additional justification for waivers of Mass Balance, Renal Impairment, and Hepatic Impairment studies, as well as a separate waiver request for QT/QTc prolongation assessment with scientific justification.
- Diversity Plan Requirements: The Agency requested more specific enrollment targets for underrepresented racial/ethnic groups (rather than the broad "20 to 35% skin of color" goal), expansion to include sex and age demographics, and detailed plans for data characterization in these populations.
- Safety Database: For moderate to severe psoriasis, the proposed safety database (approximately 1,295 patients at 6 months, 527 at 1 year) appeared reasonable, but the Agency expressed concerns about adequacy for mild psoriasis or special area psoriasis subpopulations.

On July 28, 2023, August 8, 2023, and October 2, 2023, the Applicant submitted protocols for the Phase 3 trials. The protocols were reviewed and found to be safe to proceed and adequately designed to meet stated objectives. Subsequent protocol amendments were made to align with EU CTR process.

The SAPs for PSO3001, 3002, 3003 and 3004 were submitted on March 20, 2024, August 1, 2024, and August 28, 2024. They were reviewed and found to support the objectives of the study. Recommendations included reduction of number of secondary endpoints, specifying how missing data would be prevented or minimized, conducting sensitivity analyses for missing data as assumptions, and basing the definition of eligibility for the randomized withdrawal on one of the primary endpoints.

The Applicant submitted an Initial Pediatric Study Plan (iPSP), which was agreed with the Agency on March 10, 2023 and finalized on August 14, 2024. The following elements were agreed: 1) a waiver for the study of JNJ-77242113 in infants and children <4 years of age with moderate to severe plaque psoriasis; 2) a plan to conduct a clinical study in adolescents 12 to <18 years of age concurrently or within the adult Phase 3 psoriasis study; 3) a deferral for children 4 to < 12 years of age with pediatric psoriasis to allow for the safety data from adult and adolescent subjects with psoriasis to be evaluated and risk/benefit in adults and adolescents with psoriasis is established prior to proceeding with this study.

On December 9, 2024, a preliminary Pre-NDA meeting was held with the Applicant. On December 23, 2024, Pre-NDA meeting minutes were communicated to the Applicant regarding the content, structure, and technical components of the NDA.

The main discussion points of the meeting are summarized below:

- Clinical Trial Program: The efficacy package includes four Phase 3 clinical trials (PSO3001, PSO3002, PSO3003, and PSO3004) with approximately 2,400 subjects exposed, including about 70 adolescents. Efficacy comparisons with placebo are limited to the first 16 weeks, with two trials comparing to deucravacitinib through 24 weeks. Phase 3 efficacy data for estimating efficacy rates in the Phase 3 population will not be pooled.
- Safety Database Agreement: The Agency agreed the Applicant's proposed safety database is adequate for registration, with approximately 533 subjects exposed to the 200 mg QD dose for 1 year at the time of NDA submission.
- Pooled Safety Analysis Requirements: The Agency requested specific pooled safety analyses across multiple analysis sets, including placebo-controlled periods (Weeks 0 to 16), active comparator-controlled periods (Weeks 0 to 24), and long-term exposure data (Weeks 0 to 52). Appropriate statistical approaches should be used due to unequal randomization ratios and sample sizes, the Agency emphasized using study size-adjusted rates rather than crude pooling to avoid Simpson's paradox.
- Liver Safety Monitoring: The Agency identified liver safety as an important topic requiring hepatocellular and cholestatic drug-induced liver injury (DILI) screening plots with corresponding summary tables for potential Hy's Law cases, defined as total bilirubin ≥2× ULN within 30 days after ALT or AST ≥3× ULN without cholestasis.
- Clinical Pharmacology: The Agency noted the proposed content seemed reasonable but emphasized full agreement was premature since some studies are ongoing. The final to-be-marketed formulation must be used in pivotal Phase 3 trials, and exposure-response analyses for both efficacy and safety are required.
- Nonclinical Package: The Agency agreed that the nonclinical data package (including pharmacokinetics) appeared reasonable to support registration for the intended indication.
- Statistical Analysis Plan: The Agency recommended submitting the SAP for the Integrated Summary of Safety (ISS) and Summary of Clinical Safety (SCS) for Agency review, given the ongoing nature of Phase 3 trials and limited information on planned safety analyses.
- Tuberculosis Management: The Applicant intends (b) (4) using a decision analytic/quantitative benefit-risk model, though FDA reserved final evaluation for NDA review.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Division requested and collaborated with the Office of Scientific Investigations (OSI) to select sites for clinical inspections. Sites were selected based on high enrollment of subjects and

for data verification for the primary endpoints of IGA and PASI at baseline and Week 16 for all treatment arms. Four sites were chosen for inspection.

The inspection for Agnieska Dragan's site, POLAND, Site CB4-PL10015 was permanently closed after GCP issues led to termination by the Applicant. Subjects at this site either transferred to another site or withdrew. Three subjects transferred to Pawel Brzewski's site (Pawel Brzewski, POLAND<-CB4-PL1009). The inspection team therefore planned to review the data for these three subjects during the inspection for Dr. Brzewski's site.

LEAD (N=36):

- Pawel Brzewski, POLAND, CB5-PL10009 for efficacy (n=12).
- Darryl Toth, CANADA, Site BR5-CA10022 (n=24).

ADVANCE 1 (N=32):

- Ansgar Weyergraf, GERMANY, Site BR4-DE10032 (n=14).
- Darryl Toth, CANADA, Site BR4-CA10022 (n=18).

ADVANCE 2 (N=19):

- Pawel Brzewski, POLAND, CB4-PL10009 for efficacy (n=16) + transferred subjects from Agnieska Dragan, POLAND, Site CB4-PL10015 (n=3).

At Dr. Weyergraf's site, Subject (b) (6) (icotrokinra arm) experienced a mild adverse event (AE, common cold) that was entered into the eCRF 7 months late and was not included in the 120-day safety update report (SUR). This was previously communicated to the Division on January 5, 2026. Additionally, Subject (b) (6) (placebo to icotrokinra arm) was discontinued after an elevated PHQ-9 score (15, moderately severe depression) while on icotrokinra. This was reported as a study discontinuation but not recorded as a separate AE.

The clinical reviewer concludes that these two findings in the OSI report did not affect the interpretation of safety.

Otherwise, inspections did not find significant concerns regarding the conduct of the clinical trials or GCP or regulatory compliance. Overall, the data generated by the clinical sites and submitted by the Applicant appear acceptable in support of the proposed indication.

After the review had started, there was a notification of GCP Noncompliance for the clinical trial: 77242113PSO3004 for related IND 156446 (NDA 220149). The Applicant has become aware of potential GCP noncompliance issues at the site of Dr. Paul W Wallace, Principal Investigator. The Applicant is currently conducting further investigations of potential noncompliance at Dr. Wallace's site referring or related to the following allegations without limitation:

- Study coordinator removed confidential patient source documentation that has since been returned to the site of Dr. Wallace. Participants have been sent certified letters from Dr. Wallace's site to notify participants of this privacy issue.
- Accuracy of the information related to the discontinuation of seven of the eight study subjects who occurred from September to October 2025.
- Reliability of patient reported outcome data at this site.

The outcome of this investigation, including any potential impact to data and analyses submitted to NDA 220149, will be communicated to the central IRB and FDA.

The Applicant was requested to conduct a 100% source documentation audit of the site to verify accurate reporting of key safety and efficacy data. The Applicant responded to the IR on January 28, 2026. The Applicant's assessment is that the GCP noncompliance allegations at Site US10098 do not have an impact on the overall efficacy and safety review of NDA 220149. The Applicant plans to close the site and, out of an abundance of caution, are proposing to remove the efficacy data from this site from the label—which will be reflected in the next labeling response.

The Agency acknowledges and agrees with this proposal to remove identified non-GCP compliant data from the identified subjects from the efficacy analysis. The primary clinical reviewer concurs with the Applicant's assessment that the GCP noncompliance allegations at Site US10098 do not have an impact on the overall efficacy and safety review of NDA 220149.

4.2. Product Quality

Per CMC Review Team assessment memo dated January 28, 2026, the assessment recommendation is still adequate for the drug substance review. The updates can be found in the assessment of the impurity information, specifically the nitrosamine risk assessment.

Icotrokinra HCl is a small peptide, IL-23 receptor agonist. Icotrokinra HCl was developed as an immediate-release tablet for oral administration in 200 mg strength for treatment of moderate to severe plaque psoriasis. The drug substance is a nonstoichiometric crystalline HCl salt that is hygroscopic. It is soluble in 0.1 N NaOH, phosphate buffer pH 12, 0.1 N HCl, and citrate acid buffer pH 2. The critical quality attributes of the drug substance are the appearance, identity, assay, chloride content, organic purity, residual solvents, water content, and inorganic purity. Icotrokinra HCl is manufactured (b) (4). The (b) (4) proposed regulatory starting materials are considered adequate. The description of the manufacturing process is adequate. The drug substance is (b) (4) Sufficient characterization data are provided to support the proposed drug substance structure. The specifications provide sufficient controls for the identity, purity, strength, and quality of the drug substance. The Applicant provides sufficient data to demonstrate adequate control of process-related impurities. The origins of the specified impurities are discussed. All specified impurities are qualified through toxicology studies. The analytical test methods are adequately described. Noncompendial test methods have been

adequately validated. Clinical, nonclinical, and registration drug substance batch data are provided. The batch data show the manufacturing process can consistently produce drug substance of high purity and within specifications.

The primary container closure system for the drug substance is (b) (4) . The proposed retest period for icotrokinra HCl of (b) (4) months when stored at (b) (4) is supported by the provide long-term stability data and may be granted.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant submitted a 505(b)(1) application for their proposed product, icotrokinra (JNJ-77242113), oral tablet to treat moderate-to-severe plaque psoriasis (PsO) in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. Based on a Weight of Evidence (WOE) assessment as per the ICH S11 guidance, a juvenile animal toxicity study is not needed to support the clinical study in pediatric subjects 4 to 17 years of age. A waiver for the conduct of a 2-year rat study was granted previously based on the WOE assessment as per the ICH S1B(R1) guidance, but the Applicant conducted the study due to other regulatory considerations and the final study report was submitted to the NDA.

The nonclinical studies submitted to the NDA include pharmacology, pharmacokinetics, and toxicology studies.

No test article-related findings were observed in the standard battery of safety pharmacology studies (cardiovascular, neurological and respiratory parameters). Pivotal repeat-dose oral toxicity studies were conducted in rats (6 months) and monkeys (9 months). No test article-related findings were noted and the No-Observed-Adverse-Effect Levels (NOAELs) were identified as the high doses tested in these pivotal repeat-dose toxicity studies (20 mg/kg/day in the 6-month rat study, and 200 mg/kg/day in the 9-month monkey study).

Icotrokinra was negative in the Ames test, an in vitro human lymphocyte chromosome aberration assay, and an in vivo erythrocyte micronucleus assay and comet assay in rats.

Icotrokinra was not carcinogenic in a 6-month oral transgenic mouse carcinogenicity study or a 2-year oral rat carcinogenicity study.

Icotrokinra had no adverse effects on fertility or embryonic development at oral doses up to the high dose tested, 20 and 70 mg/kg/day for male and female rats, respectively.

In an embryo-fetal toxicity study in rats, no maternal or embryofetal toxicity was noted at oral doses up to 1000 mg/kg/day, the highest dose tested. In an embryofetal toxicity study in rabbits, abortions and higher fetal incidence of fused ribs were observed at 500 mg/kg/day, the highest dose tested.

In a pre- and postnatal developmental study in rats, no maternal or developmental toxicity were noted at oral doses up to 200 mg/kg/day, the high dose tested.

Icotrokinra did not show phototoxic potential in an in vitro neutral red uptake phototoxicity assay.

(b) (4) impurities (b) (4) were qualified in a 1-month oral rat study.

This NDA is approvable from a pharmacology/toxicology perspective. There is no recommended nonclinical PMC/PMR for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

(b) (4)

5.3. Pharmacology

Primary Pharmacodynamics

Icotrokinra is 13-amino-acid peptide composed of natural and unnatural amino acids. It is a small-molecule IL-23R) antagonist that binds directly to IL-23R and prevents IL-23p19 from engaging its receptor, thereby inhibiting proximal IL-23R signaling and downstream effector functions (e.g., cytokine secretion) involved in the pathogenesis of plaque psoriasis.

Monkey, rat, rabbit, and mouse IL-23R extracellular domain proteins share 95.5%, 76.8%, 72.4%, and 70.5% sequence homology, respectively, with the human IL-23R. Surface plasmon resonance (SPR) analysis shows that icotrokinra has high binding affinities to human, monkey and rat IL-23R. The equilibrium dissociation constant values (Kd) for human, monkey, rat,

rabbit, and mouse IL-23R were 1.9pM, 2.5pM, 23pM, 420pM, and 86000pM, respectively. Of note, in a different study involving SPR analysis, the average Kd for human IL-23R was 7pM.

The species cross-reactivity of icotrokinra was determined functionally for rat IL-23R and cynomolgus monkey IL-23R. Icotrokinra inhibited IL-23-induced IL-17A release by rat splenocytes in a concentration-dependent manner, confirming the cross-reactivity for rat IL-23R. Icotrokinra also inhibited the binding of IL-23 to recombinant cynomolgus monkey IL-23R. In summary, JNJ-77242113 exhibits selectivity and picomolar inhibitory potency against human IL-23R and is functionally active towards the rat and cynomolgus monkey IL-23R target. The data support the use of rats and monkeys in toxicology studies to support the safety of the drug product.

Icotrokinra inhibited IL-23-stimulated IFN-γ production, blocked IL-23-induced STAT3 phosphorylation in a concentration-dependent manner but had no effect on IL-12-induced STAT4 phosphorylation. In vitro and ex vivo potency of icotrokinra was investigated using rat whole blood. Icotrokinra appeared to inhibit IL-23-induced IL-17A release in whole blood in a dose-dependent manner.

In an IL-23 induced skin inflammation model in SD rats, oral dosing with icotrokinra (1, 3, 10, 30, 100, and 300 mg/kg BID) was initiated prophylactically starting 1 day prior to and continued through Day 3. An anti-IL-23 mAb (administered intraperitoneally on Day -1 and Day 3) was included in all studies as a positive control and comparator. Icotrokinra attenuated IL-23-induced expression of IL-17A, IL-17F, and IL-22 mRNA in a dose-dependent manner, achieving a comparable degree of inhibition as an anti-IL-23 antibody at icotrokinra doses of 10 mg/kg (BID) or higher. Icotrokinra inhibited IL-23-induced ear thickening to a similar extent as that of the anti-IL-23 antibody treatment.

Five (b) (4) impurities (b) (4) demonstrated a concentration-dependent binding to IL-23R with Kd values of (b) (4) These five (b) (4) impurities inhibited IL-23-induced STAT3 phosphorylation in human PBMCs in a concentration dependent manner. Small amounts of (b) (4) have been detected in some human plasma samples following the administration of icotrokinra. The presence of these impurities in the drug substance appears to be at a low concentration (b) (4) and has been qualified in a 1-month oral rat toxicology study.

Secondary Pharmacodynamics

In vitro selectivity of JNJ-77242113 was evaluated against a panel of 44 targets including receptors, ion channels, enzymes, and transporters. At a concentration of 10µM, inhibition or activation less than 25% was observed for 42/44 of the targets, and an increase in activity was observed for COX1 (28.2%) and PDE3A (37.6%) enzymes. The activity against these two

intracellular enzymes at 10 µM is not considered clinically relevant considering that the target clinical C_{max} (~ 1nM) is substantially lower.

Safety Pharmacology

- Cardiovascular Effects
  - In a hERG tail current assay, the IC_{50} for the inhibitory effect of icotrokinra was not determined, but it can be assumed to be greater than 14µM. In a second hERG tail current assay, the IC_{50} for the inhibitory effect of icotrokinra on hERG potassium current was not calculated but it can be assumed to be greater than 300µM. The estimated IC_{50} of both studies provide a very large safety margin over the highest observed human C_{max} under the maximal clinical use conditions.
  - There were no treatment-related findings, and the NOEL was identified as 300 mg/kg, the highest dose given via oral gavage in a monkey study.
- Neurological Effects
  - There were no treatment-related findings noted up to 24 hours postdose. The NOEL was identified as 600 mg/kg, the highest dose given via oral gavage to male SD rats.
- Respiratory Effects
  - There were no treatment-related findings. The NOEL was identified as 600 mg/kg, the highest dose given via oral gavage to male SD rats.

5.4. ADME/PK

Table 2.

Type of Study	Major Findings
Absorption	Summary Icotrokinra showed low permeability in vitro, and the low permeability was unlikely due to P-gp transport. The PK of icotrokinra was evaluated following single-dose intravenous (IV), oral, or subcutaneous (SC) administration to fasted and fed mice, rats, and monkeys in non-GLP studies described below. The IV and SC doses ranged from 1 to 2 mg/kg. The oral doses ranged from 2.5 to 1000 mg/kg. Following single IV doses, the $t_{1/2}$ was shorter (<1 hour) in rodents compared with that of dogs and monkeys ($t_{1/2}$=approximately 3 hours). Following single oral doses, the absorption was rapid, and the t_{max} ranged from 0.5 to 2 hours. Icotrokinra has very low oral bioavailability in all tested nonclinical species (approximately 0.1-0.7%). In dogs, systemic exposure was much higher under the fasted condition compared to the fed condition following a single oral dose of 100 mg. For nonclinical evaluations in the mouse, rat, rabbit, dog, and monkey, icotrokinra was administered as JNJ-77242113-AAC (hydrochloride) or JNJ-77242113-AAJ (acetate) formulated in a solution. Several PK studies in dogs were also conducted with clinical tablet formulations of JNJ-77242113-AAC (hydrochloride). Due to the comparable oral exposures observed in rats for doses relevant to clinical doses, both forms (hydrochloride and acetate forms) were referred as icotrokinra herein.

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>In vitro</td><td></td></tr>
<tr><td>Study #: FK14168
Study #: FK13809</td><td>Icotrokinra showed low apical-to-basolateral permeability in Caco-2 cell monolayers with 100µM icotrokinra.
Icotrokinra showed low bidirectional permeability in vitro in a concentration range of 1 to 300µM. In a P-glycoprotein (P-gp)-transfected cell line, icotrokinra was not a substrate of P-gp and it did not inhibit P-gp in the tested concentration range, suggesting that the low permeability was likely not related to P-gp transport.</td></tr>
<tr><td>Mice</td><td></td></tr>
<tr><td>Study #: FK13751
IV/oral study in mouse</td><td>Single IV (2 mg/kg) or oral (20 mg/kg) dose (solution, AAJ) in male mice
<table>
<tr><th>Route/ Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>t_{max} (h)</th><th>AUC_{last}(h·ng/mL)</th><th>AUC_{inf} (h·ng/mL)</th><th>CL (mL/min/kg)</th><th>Vss (L/kg)</th><th>$t_{1/2}$ (h)</th><th>F (%)</th></tr>
<tr><td>IV/ 2</td><td>6847</td><td>-</td><td>3637</td><td>3650</td><td>9.24</td><td>0.576</td><td>0.925</td><td>-</td></tr>
<tr><td>Oral/ 20</td><td>68</td><td>2</td><td>197</td><td>202</td><td>-</td><td>-</td><td>1.06</td><td>0.55</td></tr>
</table></td></tr>
<tr><td>Rats</td><td></td></tr>
<tr><td>Study #: FK13750
IV/oral/SC PK in rat</td><td>Single IV (2 mg/kg), oral (2, 20, 30, 100 and 300 mg/kg) or SC (2 mg/kg) dose (solution, AAJ) in male rats
<table>
<tr><th>Route/ Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>t_{max} (h)</th><th>AUC_{last} (h·ng/mL)</th><th>AUC_{inf} (h·ng/mL)</th><th>CL (mL/min/kg)</th><th>Vss (L/kg)</th><th>$t_{1/2}$ (h)</th><th>F (%)</th></tr>
<tr><td>IV/2</td><td>6952</td><td>-</td><td>3805</td><td>3807</td><td>8.77</td><td>0.459</td><td>0.762</td><td>-</td></tr>
<tr><td>Oral/20</td><td>8.68</td><td>2</td><td>32.8</td><td>44.2</td><td>-</td><td>-</td><td>2.36</td><td>0.12</td></tr>
<tr><td>Oral/30</td><td>134</td><td>0.5</td><td>175</td><td>181</td><td>-</td><td>-</td><td>1.76</td><td>0.32</td></tr>
<tr><td>Oral/100</td><td>76.3</td><td>1</td><td>277</td><td>317</td><td>-</td><td>-</td><td>-</td><td>0.17</td></tr>
<tr><td>Oral/300</td><td>134</td><td>1</td><td>613</td><td>1117</td><td>-</td><td>-</td><td>-</td><td>0.11</td></tr>
<tr><td>SC/2</td><td>1497</td><td>1</td><td>4389</td><td>4422</td><td>-</td><td>-</td><td>-</td><td>116</td></tr>
</table></td></tr>
<tr><td>Dogs</td><td></td></tr>
<tr><td>Study #: FK13847
IV/oral PK in dog</td><td>Single IV (0.5 mg/kg) or oral (10 mg/kg) dose (solution, AAJ) in male beagle dogs
<table>
<tr><th>Route/ Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>t_{max} (h)</th><th>AUC_{last} (h·ng/mL)</th><th>AUC_{inf} (h·ng/mL)</th><th>CL (mL/min/kg)</th><th>Vz (L/kg)</th><th>$t_{1/2}$ (h)</th><th>F (%)</th></tr>
<tr><td>IV/0.5</td><td>8160</td><td>-</td><td>5900</td><td>6070</td><td>1.37</td><td>0.4</td><td>3.4</td><td>-</td></tr>
<tr><td>Oral/10</td><td>169</td><td>0.7</td><td>581</td><td>807</td><td>-</td><td>-</td><td>6</td><td>0.67</td></tr>
</table></td></tr>
<tr><td>Study #: FK14413
Tablet formulation comparison in dog</td><td>Single oral (200 mg) (tablet, AAC) in male beagle dogs under fasted condition
<table>
<tr><th>Route/ Dose (mg)</th><th>Formulation</th><th>C_{max} (ng/mL)</th><th>t_{max} (h)</th><th>AUC_{last} (h·ng/mL)</th><th>AUC_{inf} (h·ng/mL)</th></tr>
<tr><td>Oral/ 200</td><td>Phase 2b tablet 2×100 mg</td><td>188</td><td>2</td><td>1090</td><td>1010</td></tr>
<tr><td>Oral/200</td><td>Phase 3 tablet 2×100 mg</td><td>298</td><td>1</td><td>1480</td><td>1540</td></tr>
<tr><td>Oral/200</td><td>Phase 3 tablet 200 mg</td><td>210</td><td>2</td><td>1210</td><td>1320</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Systemic exposures were similar between the tablet (2×100 mg) used in the Phase 2b and that used in Phase 3 trial (1×200 mg). Systemic exposure was higher following the Phase 3 tablet (2×100 mg) compared to Phase 2 tablet (2×100 mg).</td></tr>
<tr><td>Monkeys:</td><td></td></tr>
<tr><td>Study #: FK14151
IV PK in monkey</td><td>Single IV (1 mg/kg) dose (solution, AAC) in female cynomolgus monkeys
<table>
<tr><th>Route/Dose (mg/kg)</th><th>C_0 (ng/mL)</th><th>AUC_{last} (h·ng/mL)</th><th>AUC_{inf} (h·ng/mL)</th><th>CL (mL/min/kg)</th><th>V_{ss} (L/kg)</th><th>$t_{1/2}$ (h)</th></tr>
<tr><td>IV/1</td><td>7340</td><td>8140</td><td>9060</td><td>1.84</td><td>0.348</td><td>2.83</td></tr>
</table></td></tr>
<tr><td>Study #: PTG-B2-010
IV/oral PK in monkey</td><td>Single IV (1 mg/kg) and oral (2.5, 7.5 and 22.5 mg/kg) (solution, AAJ) in fasted male cynomolgus monkeys
<table>
<tr><th>Route/ Dose (mg/kg)</th><th>C_{max} (ng/mL)</th><th>t_{max} (h)</th><th>AUC_{last} (h·ng/ mL)</th><th>AUC_{inf} (h·ng/ mL)</th><th>CL (ml/min/kg)</th><th>V_{ss} (L/kg)</th><th>$t_{1/2}$ (h)</th><th>F (%)</th></tr>
<tr><td>IV/1</td><td>10119</td><td>-</td><td>-</td><td>12021</td><td>1.44</td><td>0.299</td><td>3.47</td><td>-</td></tr>
<tr><td>Oral/2.5</td><td>10.95</td><td>2</td><td>62.88</td><td>82.23</td><td>-</td><td>-</td><td>5.58</td><td>0.27</td></tr>
<tr><td>Oral/7.5</td><td>27.83</td><td>1</td><td>198</td><td>226</td><td>-</td><td>-</td><td>6.41</td><td>0.25</td></tr>
<tr><td>Oral/22.5</td><td>84.28</td><td>1.5</td><td>677</td><td>812</td><td>-</td><td>-</td><td>5.6</td><td>0.3</td></tr>
</table></td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>Study #: FK13680
Study #: FK14167
Study #: FK13893
Study #: FK13811</td><td>Binding of icotrokinra to plasma proteins, binding of icotrokinra in kidney tissues and blood-to-plasma ratios were generally comparable across species (mouse, rats, rabbits, monkeys and humans). Compared to human α1-acid glycoprotein, icotrokinra showed more binding to serum albumin.
Binding to antidrug antibody (ADA) was observed in rats, mice and monkeys. Free (unbound to ADA) icotrokinra was 6.2 to 21.3% of total icotrokinra exposure in the 6-month rat study and 15 to 114% in the 9-month monkey study.</td></tr>
<tr><td>Study #: FK14046</td><td>In a rat QWBA study with oral ^{14}C-icotrokinra, GI tract, kidney cortex, whole kidney, and on the bone surface showed the highest levels of radioactivity. After IV dosing of ^{14}C-icotrokinra in rats, total radioactivity was detected in more tissues compared to oral dosing, with highest levels in kidney and ear cartilage. The radioactivity detected in the brain was negligible following both oral and IV administrations.</td></tr>
<tr><td>Study #: FK13841
Study #: FK13750</td><td>The tissue distribution of icotrokinra was evaluated following single-dose IV, oral, or SC administration to male SD rats. Overall, kidney concentrations were higher than plasma, skin concentrations were similar to plasma, and there was negligible brain penetration.</td></tr>
<tr><td>Study #: FK 14075
Study #: PTG-B2-009</td><td>In a mass balance study of cynomolgus monkeys following single oral dose of icotrokinra, the radioactivity concentrations of icotrokinra in all tissues analyzed were BQL at 96 hours postdose or the QWBA analysis. The majority (62.2% in one animal and 84.1% in another) of the administered radioactive dose was recovered in excreta by 96 hours postdose. Following oral dosing of icotrokinra (nonradioactive), icotrokinra remained primarily in the colon contents (>98% of the detected icotrokinra), with much lower exposure (>100-fold difference) observed in the large intestinal tissue in male cynomolgus monkeys. Icotrokinra was basically absent (BQL) in the small intestine.</td></tr>
<tr><td>Study #: TOX16182</td><td>Icotrokinra was detected in all pup plasma samples from the icotrokinra-treated groups on both postnatal day 4 (PND4) and PND12 in the prenatal and postnatal development rat study. The concentration of icotrokinra in the pups was much lower than in dams. Although rat milk was not analyzed, icotrokinra present in the pups is most likely from lactational</td></tr>
</table>

Type of Study	Major Findings
	transfer. However, some contribution by placental transfer cannot be ruled out. ADA was detected in all pup samples.
Metabolism	
Study #: FK13680 Study #: FK13893 Study #: ADME-102294 Study #: FK13753	Icotrokinra appeared to be stable in vitro with $t_{1/2}$ of >24 hours for all species (mouse, rat, monkey and human) and matrices (plasma, kidney tissues, hepatocytes, and gastrointestinal matrices) tested.
Study #: PTG-B2-004 Study #: FK14612 Study #: FK14047 Study #: FK14053 Study #: FK14329 Study #: FK14499	In vitro and vivo metabolite profiling and identification was conducted in monkeys, rats and humans. <u>In vitro</u> In the fecal homogenate, 5 metabolites were identified in rats, monkeys and humans. Unchanged drug, M5, and M14 were identified in rat and monkey samples; unchanged drug, M6, M14, M25 and M26 were identified in human samples. Two out of the three metabolites that were only detected in human fecal homogenate were detected in in vivo fecal samples in monkeys. The remaining metabolite (M26) was likely degraded to M6. In the kidney tissue homogenate, parent drug, M6 and M12 were detected in rat, monkey and human samples. <u>In vivo</u> In plasma, urine and feces samples collected from rats, monkeys and humans, the main component detected was unchanged drug with small amounts of metabolites. (b) (4) [redacted] Most metabolites identified were derived via proteolytic hydrolysis (amide hydrolysis, deamidation) or N-acetylation of other metabolites.
Excretion	
Study #: FK13841 Study #: PTG-B2-025 Study #: FK13750 Study #: FK14047 Study #: FK 14075 Study #: PTG-B2-010 Study #: PTG-B2-009	Following oral administration of icotrokinra, unchanged drug was mostly excreted in feces in rats and monkeys. In mass-balance studies of rats and monkeys, the recoveries of oral ^{14}C-icotrokinra doses in feces were 97 and 67% for rats and monkey, respectively at 96 hours postdose. The radioactivity concentrations recovered in urine were 0.2 and 1% for rats and monkeys, respectively at 96 hours postdose. The elimination via bile was limited. The absorbed icotrokinra was mainly cleared by the kidneys.

Type of Study	Major Findings
TK data from general toxicology studies	
JNJ-77242113-AAC (IL-23R Antagonist): A 6-Month Oral (Gavage) Toxicity Study in Rats with a 1-Month Recovery Period and Male Fertility Evaluation (TOX14805)	Rat (6 months, oral) Total icotrokinra on Day 177: T_{max}: 0.5-8 hours AUC_{last} (hour·ng/mL): 1 mg/kg/day: 255 (M); 202 (F) 5 mg/kg/day: 659 (M); 495 (F) 20 mg/kg/day: 2250 (M); 547 (F) Accumulation: Substantial accumulation (between Day 177 and Day 1: 16-194 fold), likely due to the presence of ADA Dose proportionality: The systemic exposure generally increased with dose.
JNJ-77242113-AAC (IL-23R Antagonist): A 9-Month Toxicity Study by Oral Gavage in Cynomolgus Monkeys with a 1-Month Recovery Period (TOX14489)	Monkey (9 months, oral) Total icotrokinra on Day 273: T_{max}: 1-3 hours AUC_{0-24} (hour·ng/mL): 20 mg/kg/day: 296 (M); 4080 (F) 75 mg/kg/day: 4290 (M); 2280 (F) 200 mg/kg/day: 14400 (M); 12900 (F) Accumulation: Substantial drug accumulation between Day 91 and Day 1; no further accumulation between Day 273 and Day 91. Dose proportionality: The systemic exposure generally increased with dose, in a roughly dose proportional manner on Day 1.
TK data from reproductive toxicology studies	
JNJ-77242113-AAC (IL-23R Antagonist): A 6-Month Oral (Gavage) Toxicity Study in Rats with a 1-Month Recovery Period and Male Fertility Evaluation (TOX14805)	Male rats on Day 114 Total icotrokinra AUC_{0-24h}(hour·ng/mL): 1 mg/kg/day: 271 5 mg/kg/day: 901 20 mg/kg/day: 4170
An oral (gavage) study of the effects on fertility and early embryonic development to implantation in	Female rats on GD7 Total icotrokinra AUC_{last}(hour·ng/mL): 5 mg/kg/day: 1980 20 mg/kg/day: 5740 70 mg/kg/day: 12300

Type of Study	Major Findings
female rats (TOX14806)	
JNJ-77242113-AAC (IL-23R): Embryofetal toxicity study by the oral route (gavage) in the rat (TOX14673)	Female rats on GD17 Total icotrokinra $AUC_{0\text{-}24h}$ (hour·ng/mL): 70 mg/kg/day: 813 200 mg/kg/day: 4150 1000 mg/kg/day: 10900
JNJ-77242113-AAC (IL-23R): Embryofetal toxicity study by the oral route (gavage) in the rabbit (TOX14674)	Female rabbits on GD19 Total icotrokinra $AUC_{0\text{-}24h}$ (hour·ng/mL): 50 mg/kg/day: 203 200 mg/kg/day: 975 500 mg/kg/day: 5770
JNJ-77242113-AAC (IL-23R antagonist): An Oral (Gavage) Study of Pre- and Postnatal Development in CD® (Sprague Dawley) IGS Rats (TOX16182)	Female rats on LD 12 Total icotrokinra $AUC_{0\text{-}24h}$ (hour·ng/mL): 20 mg/kg/day: 3250 70 mg/kg/day: 4800 200 mg/kg/day: 4660

Type of Study	Major Findings
TK data from carcinogenicity studies	
JNJ-77242113-AAC (IL-23R antagonist): A 2-Year Oral Gavage Carcinogenicity Study in Sprague Dawley Rats (TOX15377)	Rats on Day 546 Total icotrokinra AUC_{0-24h} (hour·ng/mL): 5 mg/kg/day: 516 (M); 788 (F) 10 mg/kg/day: 514 (M); 1660 (F) 20 mg/kg/day: 580 (M); 2700 (F) Rats on Day 630 Total icotrokinra AUC_{0-24h} (hour·ng/mL): 5 mg/kg/day: 450 (M) 10 mg/kg/day: 868 (M) 20 mg/kg/day: 283 (M) Of note, males at 0, 5 and 10 mg/kg/day were terminated at Week 100 (Day 694), at 20 mg/kg/day were terminated at Week 94 (Day 657); and all female animals were terminated at Week 87 (Day 604).
JNJ-77242113-AAC (IL-23R antagonist): A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1-Tg (HRAS)2Jic Mice (TOX15455)	Mice on Day 182 Total icotrokinra AUC_{last} (hour·ng/mL): 50 mg/kg/day: 2780 (M); 1060 (F) 150 mg/kg/day: 1360 (M); 1930 (F) 500 mg/kg/day: 2780 (M); 6700 (F)

Source: From submission.
Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration–time curve from time zero to the last measurable concentration, AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; CL, clearance; F, bioavailability; $T_{1/2}$, half-life; T_{max}, time to Cmax; TK, toxicokinetic, Vss, volume of distribution at steady state

ADME Study Titles and Numbers

- An In Vitro Study to Assess the Transepithelial Transport of JNJ-77242113 and (b) (4) Across Caco-2 Cell Monolayers (FK14168).
- Assessment of P-gp-Mediated Transport of JNJ-77242113 and Potential Inhibition of P-Gp Activity by JNJ-77242113 (FK13809).
- Evaluation of the Pharmacokinetics of JNJ-77242113 Following Single Intravenous or Oral Administration to Male C57BL Mice (FK13751).
- Evaluation of the Pharmacokinetics of JNJ-77242113 Following Single Intravenous, Oral, or Subcutaneous Administration to Male Sprague Dawley Rats (FK13750).
- Pharmacokinetics of JNJ-77242113 in Male Dogs after Single Intravenous Administration of JNJ-77242113 at 0.5 mg/kg, after Single Oral Administration of a Solution Containing JNJ-77242113 at 10 mg/kg, and after Single Oral Administration of 1 or 2 Tablets Containing 100 mg JNJ-77242113 Each, without and with (b) (4) (FK13847).
- A Repeat Dose Pharmacokinetic and Tissue Distribution Study of JNJ-77242113 by Intravenous (Bolus) Injection in Female Cynomolgus Monkeys (FK14151).
- Oral Bioavailability of PN-235 After a Single Intravenous or Oral Dose to Male Cynomolgus Monkey (PTG-B2-010).
- PN-235: Single-Dose Oral Gavage Maximum Tolerability Study in Cynomolgus Monkeys (PTG-B2-001).
- Assessment of the Binding of JNJ-77242113 (PN-21235) to the Plasma Proteins From Human, Monkey, Rat, and Mouse, and in Isolated Human Plasma Protein Fractions Albumin and α-1-Acid Glycoprotein (FK13680).
- Free Fraction Determination of JNJ-77242113 in Rabbit Plasma (FK14167).
- Stability and Binding Assessment of JNJ-77242113 (PN-21235) in Kidney Tissue Homogenates From Human, Monkey, and Rat (FK13893).
- Assessment of the Whole Blood to Plasma Partitioning of JNJ-77242113 in Human, Monkey, Dog, and Rat (FK13811).
- The Tissue Distribution (Quantitative Whole Body Autoradiography) of Total Radioactivity in the Male Pigmented Rat Following IV or Oral Administration of [14C]-JNJ-77242113 (FK14046).
- A Pharmacokinetic and Excretion Balance Study of [14C]-JNJ-77242113 Following Single Administration to Cynomolgus Monkeys (FK14075).
- In Vitro Metabolic Stability of JNJ-77242113 in Hepatocytes of Rat, Monkey and Human (ADME-102294).
- Stability Assessment of JNJ-77242113 in Feces and Gut Mucosa From Human, Monkey, and Rat, as Well as in the Purified Enzymes Pepsin, Trypsin, Chymotrypsin, and Pancreatin (FK13753).
- Metabolite Identification of PN-235 in In Vitro Incubations With Rat, Cynomolgus Monkey, or Human Fecal Homogenate (PTG-B2-004).
- Profiling of JNJ-77242113 Renal Metabolism (FK14612).

- The Absorption, Metabolism, and Excretion of 14C-JNJ-77242113 in the Male Sprague Dawley Rat After a Single Oral or Intravenous Administration of 14C-JNJ-77242113 at 300 mg/kg or 2 mg/kg, respectively (FK14047).
- Metabolite Profiling and Identification in Samples Resulting From Metabolism and Excretion Experiment in the Intact Male Cynomolgus NHP After a Single Oral Administration of [14C]-JNJ-77242113 at 300 mg/kg (FK14053).
- In Vivo Metabolite Profile and Identification of JNJ-77242113 in Human Plasma and Urine From SAD/MAD (PN-235-01) (FK14329).
- The In Vivo Metabolite Profile and Identification of JNJ-77242113 in Plasma From Healthy Volunteers (FK14499).
- Pharmacokinetics of PN-235 in Cynomolgus Monkeys Following Once- or Twice-Daily Oral Administration for Five Days (PTG-B2-009).

5.5. Toxicology

5.5.1. General Toxicology

Pivotal repeat-dose toxicity studies were conducted in rats (6 months) and monkeys (9 months). No test article-related findings were identified. The NOAELs were the highest doses tested in both studies. The high dose tested in the chronic rat study was relatively low compared to the high doses tested in monkeys because substantial drug accumulation was noted in rats after repeated dosing.

Study Title/Number: JNJ-77242113-AAC (IL-23R Antagonist): A 6-Month Oral (Gavage) Toxicity Study in Rats With a 1-Month Recovery Period and Male Fertility Evaluation/ TOX14805

- The NOAEL for both general toxicity and male fertility was identified as the high dose, 20 mg/kg/day.
- Despite the presence of ADAs, inhibition of IL-23-induced IL-17A production was noted in mid dose and high dose rats (not in low dose rats) at Weeks 25 and 26.
- Despite the presence of ADAs, inhibition of IL-23R binding-dependent bioluminescence reporter activity was noted at Week 26 in high dose animals (but not in low-dose or mid-dose animals).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 1, 5, and 20 mg/kg/day, once daily

Route of administration:	Oral gavage
Formulation/Vehicle:	50 mM sodium phosphate buffer in deionized water, pH 7.5
Species/Strain:	Rats/CD® [Crl:CD®(SD)]
Number/Sex/Group:	30 animals/sex/group; 8 animals/sex for control and high dose groups in the recovery phase
Age:	Approximately 9 to 9.5 weeks at first dose
Satellite groups/ unique design:	No separate satellite groups: 10 animals/sex/group were terminated on Day 123 (4-month interim necropsy); 20 animals/sex/group were terminated on Days 182-184 (terminal necropsy). The remaining animals were terminated on Day 213 following a 1-month recovery period. To evaluate male fertility, 20 naïve females per group were mated with 20 treated males per group beginning on Day 64. These females were not dosed.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: Changes From Control

Parameter	Major Findings
Mortality	There were 3 early incidental deaths (one LD female, one MD female, and one HD male), but those were not considered test article-related.
Clinical Signs	No test article-related findings
Body Weights	No test article-related findings
Ophthalmoscopy	No test article-related findings
Hematology	No test article-related findings
Clinical Chemistry	No test article-related findings
Urinalysis	No test article-related findings
Gross Pathology	No test article-related findings
Organ Weights	No test article-related findings
Histopathology Adequate battery: Yes	No test article-related findings
Male fertility (mating, fertility, or pregnancy indices)	No test article-related findings
GD 13 uterine implantation (mean number of corpora lutea, uterine implantation sites, viable embryos, resorption sites, and pre- and post-implantation loss indices)	No test article-related findings

Parameter	Major Findings
Antidrug antibody (ADA) analysis	ADA positive: LD: 23/24 MD: 24/24 HD: 21/23 At Weeks 17, 21, and 26
Neutralizing antibody (NAb) analysis	NAb positive: HD: 15/16 at the end of recovery phase (no data for LD or MD)
Pharmacodynamic analysis	MD and HD: inhibition of IL-23-induced IL-17A production at Weeks 25 and 26.
IL-23 bioassay	HD: inhibition of IL-23R binding-dependent bioluminescence reporter activity at Week 26.

Source: from submission.
Abbreviations: LD: low dose; MD: mid dose; HD: high dose.

Study Title/Number: JNJ-77242113-AAC (IL-23R antagonist): A 9-Month Toxicity Study by Oral Gavage in Cynomolgus Monkeys With a 1-Month Recovery Period/TOX14489

- The NOAEL was identified as the high dose, 200 mg/kg/day.
- A dose-dependent reduction in T-cell-dependent antibody was noted at all doses for IgM responses and at mid dose and high dose for IgG responses. However, T-cell-dependent antibody responses were still noted at all doses (not completely suppressed), and no correlative immunosuppression findings were noted.
- Despite the presence of ADAs, inhibition of IL-23R signaling (IL-23-mediated IFN-γ production) and IL-23R signaling dependent bioluminescence reporter activity was observed in all doses.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 20, 75, and 200 mg/kg/day, once daily
Route of administration:	
Formulation/Vehicle:	Deionized water acidified with phosphoric acid, pH 3.0
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	4/sex/group; 2/sex/group for control and high dose in the recovery phase
Age:	2.5-4.1 years at first dose
Satellite groups/ unique design:	No separate satellite groups

Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes From Control

Parameter	Major Findings
Mortality	A control male was euthanized early on Day 57 following multiple episodes of prolapsed rectum. This incidence is not considered treatment related.
Clinical Signs	No test article-related findings
Body Weights	No test article-related findings
Ophthalmoscopy	No test article-related findings
ECG	No test article-related findings
Hematology	No test article-related findings
Clinical Chemistry	No test article-related findings
Urinalysis	No test article-related findings
Gross Pathology	No test article-related findings
Organ Weights	No test article-related findings
Histopathology Adequate battery: Yes	No test article-related findings
Immunophenotyping	No test article-related findings
T-cell-dependent antibody response	Dose dependent reduction in T-cell-dependent antibody responses [measured by the formation of keyhole limpet hemocyanin (KLH)-specific antibodies]: IgM responses: All doses on Days 169 through 190 IgG responses: MD and HD on Days 169 through 190
ADAs analysis	ADA positive: LD: 7/8 MD: 8/8 HD: 12/12 (Results updated in the amendment 1)
NAb analysis	NAb positive: None At the end of the recovery phase
Pharmacodynamic analysis	Inhibition of IL-23R signaling (inhibition of IL-23-mediated IFN-γ production): LD, MD and HD
IL-23 bioassay	Inhibition of IL-23R binding-dependent bioluminescence reporter activity on Day 273: LD, MD and HD

Source: From submission
Abbreviations: LD: low dose; MD: mid dose; HD: high dose

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title/Number: PN-235: Bacterial Reverse Mutation Assay/ PTG-B2-020

Key Study Findings:

- No significant increases in revertant colony numbers were noted in any of the bacteria strains at any dose level in the presence or absence of S9.
- Icotrokinra was not mutagenic under the study conditions.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains (TA98, TA100, TA1535, and TA1537) and *Escherichia coli* strain WP2 uvrA were treated with icotrokinra at a range of concentrations up to 5000 µg/plate, in the presence and absence of S9. No precipitation was observed. No bacterial toxicity was observed.
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study Title/Number: PN-235: In Vitro Human Lymphocyte Chromosome Aberration Assay/PTG-B2-021

Key Study Findings:

- There were no biologically significant increases in the frequencies of cells with structural chromosome aberrations at any dose level in the presence or absence of S9.
- There were no increases in the frequencies of endoreduplicated and/or polyploid cells.
- Icotrokinra was not clastogenic under the study conditions.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes were treated with icotrokinra at concentrations of 200, 300, and 500 µg/mL for 3 hours without S9, 200, 400, and 500 µg/mL for 3 hours with S9, and 50, 300, 400, and 500 µg/mL for 24 hours without S9. The high dose was set based on cytotoxicity.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/Number: In Vivo Mammalian Erythrocyte Micronucleus Assay and Mammalian Alkaline Comet Assay in Male Rats Following Oral Administration With JNJ-77242113 AAC/TOX14583

Key Study Findings:

- There was no significant decrease in the ratio between immature erythrocytes (polychromatic erythrocytes, PCEs) and mature erythrocytes (normochromatic erythrocytes, NCEs), which is indicative of bone marrow toxicity. There was no significant increase in the incidence of micronucleated PCEs.

- In both the kidney and colon comet evaluation, no significant increases in the percentage of tail DNA were observed for the test article groups.
- Icotrokinra was not clastogenic in the micronucleus assay and did not induce DNA damage in the comet assay, under the study conditions.

GLP compliance: Yes
Test system: Oral (gavage) doses of 0 (vehicle: deionized water acidified to pH 3.0 with phosphoric acid), 250, 500, 1000, and 2000 mg/kg/day icotrokinra were administered to male SD rats on three consecutive days (6/group for 250 and 500 mg/kg/day doses and 8/group for 1000 and 2000 mg/kg/day doses). The high dose was the limit dose per the ICH S2(R1) guidance. At 3 hr after the last dose, colon, kidney, and bone marrow were collected and processed for the comet and micronucleus evaluations, respectively.
Study is valid: Yes

5.5.3. Carcinogenicity

In a 2-year oral rat carcinogenicity study, oral (gavage) doses of 0 (vehicle: 0.85% phosphoric acid in deionized water), 5, 10, and 20 mg/kg/day icotrokinra were administered to SD rats. There was a treatment-related increase in mortality in male rats. The 2-year rat study was terminated early due to decreased survival. There were no significant icotrokinra-related neoplastic findings in either sex.

In a 6-month oral mouse carcinogenicity study, oral (gavage) doses of 0 (vehicle: 0.85% phosphoric acid in deionized water), 50, 150, and 500 mg/kg/day icotrokinra were administered to transgenic rasH2 mice. A positive control group (treated with intraperitoneal doses of 500 mg/kg urethane on Days 1, 4, and 7) was also included in the study. There was no icotrokinra-related effect on mortality. There were no significant icotrokinra-related neoplastic findings in either sex.

The full review for carcinogenicity studies is provided in the Appendix.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study Title/Number: An Oral (Gavage) Study of the Effects on Fertility and Early Embryonic Development to Implantation in Female Rats/TOX14806

Key Study Findings:
- There were no test article-related findings on mortality, clinical observations, body weight, or food consumption.
- There were no test article-related effects on reproductive performance (mating, fertility, and pregnancy indices), estrous cyclicity, intrauterine survival. There were no test article-related gross necropsy findings or effects on ovarian weights.
- The NOAEL for both female fertility and maternal toxicity was identified as the high dose, 70 mg/kg/day.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 5, 20, and 70 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	deionized water acidified with phosphoric acid, pH 3.0
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	20 females/group
Satellite groups:	No separate satellite groups
Study design:	Female rats were dosed from 21 days prior to mating, throughout mating and implantation, and to Gestation Day (GD) 7. Male rats were used for breeding purpose only and not treated with test article.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameter	Major Findings
Mortality	No test article-related findings
Clinical Signs	No test article-related findings
Body Weights	No test article-related findings
Necropsy findings *[Mating/fertility index, corpora lutea, preimplantation loss, etc.]*	No test article-related findings

Source: from submission

Embryo-Fetal Development

Study Title/Number: JNJ-77242113-AAC (IL-23R): Embryofetal Toxicity Study by the Oral Route (Gavage) in the Rat/TOX14673

Key Study Findings

- There were no treatment-related effects on maternal toxicity or embryofetal development at any dose level.
- No test article-related macroscopic observations or effects on cesarean section parameters were noted. No test article-related fetal external or visceral variations or malformations were observed.

- The NOAEL for both maternal toxicity and embryofetal toxicity was identified as the high dose, 1000 mg/kg/day, under the study conditions.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 70, 200, and 1000 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	50mM sodium phosphate buffer in deionized water, pH 7.5
Species/Strain:	Rat/Crl:CD(SD)
Number/Sex/Group:	22 females/group Sprague Dawley
Satellite groups:	No separate satellite groups
Study design:	Pregnant females were dosed during Gestation Days (GD) 6-17.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameter	Major Findings
Mortality	No test article-related findings
Clinical signs	No test article-related findings
Body weights	No test article-related findings
Necropsy findings Cesarean section data	No test article-related findings
Necropsy findings Offspring	No test article-related findings

Source: From submission.

Embryo-Fetal Development

Study Title/Number JNJ-77242113-AAC (IL-23R): Embryofetal Toxicity Study by the Oral Route (Gavage) in the Rabbit/TOX14674

Key Study Findings:

- Two high dose females aborted on GD 26.
- Slightly higher incidence of fused ribs was noted in the high dose group (one fetus each in three litters in the high dose group compared to one fetus in one litter in the control group). The mean litter proportion of this finding (2.55%) was also higher than the maximum mean value for rib anomaly in the (b) (4) historical control data (1.06% per litter).

- Based on abortions and fetal skeletal malformation (fused ribs) noted at high dose, the NOAEL for both maternal toxicity and embryofetal toxicity was identified as the mid dose, 200 mg/kg/day, under the study conditions.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 50, 200, and 500 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	50mM sodium phosphate buffer in deionized water, pH 7.5
Species/Strain:	Rabbit/HsdHra:(NZW) SPF New Zealand White
Number/Sex/Group:	20 females/group
Satellite groups:	No separate satellite groups
Study design:	Pregnant females were dosed GD 7 through 19.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameter	Major Findings
Mortality	MD: 1 female euthanized in extremis HD: 1 female found death on GD 18 Incidental deaths, due to dosing errors based on clinical observations (primarily abnormal breathing sounds) and necropsy findings (tan or dark red firm discoloration in the lungs).
Clinical signs	HD: 2 females aborted on GD 26
Body weights	HD: 8% lower compared to control, corresponding 5% lower mean food consumption during GD 7-20; not considered significant.
Necropsy findings Cesarean section data	No test article-related findings.
Necropsy findings Offspring	HD: higher incidence of fused ribs (1 fetus each in 3 litters) compared to control (1 fetus in 1 litter)

Source: from submission
Abbreviations: MD: mid dose; HD: high dose; GD: gestation day

Prenatal and Postnatal Development

Study Title/Number: JNJ-77242113-AAC (IL-23R Antagonist): An Oral (Gavage) Study of Pre- and Postnatal Development in CD® (Sprague Dawley) IGS Rats/TOX16182

Key Study Findings:

- One F0 dam was euthanized in extremis on LD 2. The moribundity was likely due to gavage error and/or aspiration related to gavage dosing.

- All F1 pups from the early-terminated dam were observed as cold with no milk band present and were terminated. The condition was likely due to F0 dam's clinical condition.
- The NOAEL was identified 200 mg/kg/day, the high dose, for F0 maternal toxicity, F1 neonatal, parental systemic, and reproductive toxicity, and for F2 developmental toxicity, under the study conditions.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 20, 70 and 200 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized water pH adjusted to 3.0±0.1 with either 0.85% phosphoric acid in water or 8.5% phosphoric acid in water
Species/Strain:	Rat/ Crl:CD(SD)
Number/Sex/Group:	22 females/group
Satellite groups:	3 females/group
Study design:	Time-mated female rats were dosed from Gestation Day (GD) 6 through Lactation Day (LD) 20.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F0 Dams	HD: 1 female euthanized in extremis on LD 2. The moribundity was likely due to gavage error and/or aspiration related to gavage dosing. No test article-related findings.
F1 Generation	HD: all pups from the early-terminated dam were observed as cold with no milk band present and were terminated. The condition was likely due to F0 dam's clinical condition. No test article-related findings.
F2 Generation	No test article-related findings.

Source: from submission
Abbreviations: HD: high dose; LD: lactation day

5.5.5. Other Toxicology Studies

Phototoxicity

The phototoxic potential of icotrokinra was assessed in an in vitro neutral red uptake phototoxicity assay (TOX14597, GLP). Icotrokinra was tested up to 100 µg/mL (solubility limit in the 1% phosphate buffer/Dulbecco's phosphate-buffered saline). In the definitive assays, the cells were exposed to 5 J/cm^2 of UVA and 19 mJ/cm^2 of UVB from a xenon arc solar simulator. Based on the mean photo effect (MPE) values (0.019 and -0.003 for assay 1 and 2, respectively), no phototoxic effect was observed. Icotrokinra did not show phototoxic potential in this in vitro test system.

Impurities

The reporting threshold (RT), identification threshold (IT), and qualification threshold (QT) as (b) (4) respectively, for (b) (4) impurities in the drug substance received Agency's concurrence in July 2024.

At the beginning of the development including toxicology studies and Phase 3 clinical trials, the drug substance was (b) (4) Subsequently, (b) (4) was used to manufacture drug substance for Phase 3 clinical trials. Since the (b) (4) resulted in higher levels of impurities, the impurities were qualified in a 1-month rat study (TOX16245, GLP). In the 1-month rat study (TOX16245), SD rats received oral (gavage) doses of 0 (vehicle: 0.85% phosphoric acid in deionized water), 70, and 200 mg/kg/day icotrokinra. The drug product contained actual impurities RRT (b) (4) and potential impurities RRT (b) (4). The impurities were well tolerated in rats. No icotrokinra- or impurity-related findings were observed up to the highest dose of 200 mg/kg/day icotrokinra.

The only potentially mutagenic compound identified is (b) (4). Based on the test results of representative batches of the intermediate (b) (4) the level of (b) (4) appeared to be below (b) (4) which is below the maximum allowable concentration (MACO) of (b) (4) for daily drug substance dose of 200 mg/day. After application of a downstream (b) (4), the level of (b) (4) in the final drug substance would be less than (b) (4) which is far below the MACO of (b) (4)

Five potential (b) (4) were identified: (b) (4) Based on the risk assessment conducted by the Applicant, the presence of these potential (b) (4) in the final drug substance appeared to be below (b) (4) of the applicable Acceptable Intake Limits.

Overall, there are no safety concerns related to excipients or impurities in the proposed oral drug product.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted a New Drug Application (NDA) 220149 for icotrokinra (Icotyde®) for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. Icotrokinra is a 13 amino acid peptide for oral administration that selectively binds to the IL-23 receptor (IL-23R) and competitively antagonizes the binding of IL-23. Icotrokinra inhibits IL 23/IL-23R-dependent release of proinflammatory cytokines.

This submission includes data from seven Phase 1 trials conducted in healthy subjects (PN-235-01, PSO1002, PSO1003, PSO1004, PSO1006, PSO1007, PSO1009), one Phase 2 trial (PSO2001) with long-term extension (PSO2002) in adult subjects with moderate to severe plaque PsO, and four Phase 3 trials (PSO3001, PSO3002, PSO3003, and PSO3004) in adult subjects with moderate to severe plaque PsO with studies PSO3001 and PSO3002 including adolescent subjects.

The proposed dosing regimen for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older and weighing at least 40 kg who are candidates for systemic therapy or phototherapy is icotrokinra 200 mg once daily (QD) as immediate release film-coated tablet.

Key review issues and comments are summarized in Table 3.

Table 3. Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The effectiveness of the icotrokinra is primarily supported by the statistically significant treatment effects for achieving PASI 90 and/or IGA 0/1 (with ≥2 grade improvement from baseline) in Phase 3 trials. In addition, the Phase 2 and Phase 3 exposure-response (E-R) analyses indicated that the 200 mg QD dose provided consistently high response rates across all quartiles of exposure (see Section 19.4.6).
Recommended dosage regimens	200 mg once daily (QD)
Dosage in patient subgroups (intrinsic factors)	Icotrokinra exposure is increased in patients with moderate (eGFR 30 to 59 mL/min/1.73 m2) or severe (eGFR 15 to 29 mL/min/1.73 m2) renal impairment relative to patients with normal renal function (see Section 6.3.2.3). It is recommended to monitor for icotrokinra potential adverse reactions when used in patients with moderate or severe renal impairment. Alternative dose/dosing regimen based on age (range: 12 to 87 years), body weight (range: 39 to 211 kg), sex, race (76% White, 20.1% Asian, and 1.7% Black),

Review Issues	Recommendations and Comments
	immunogenicity, mild (eGFR ≥60 to <90 mL/min/1.73 m^2) renal impairment or any degree of hepatic impairment is not needed (see Section 6.3.2.3).
Dosage in patient subgroups (extrinsic factors)	Icotrokinra AUC decreased by 43% and Cmax decreased by 59% following administration with a high-fat meal (1000 calories, 50% fat) (see Section 6.3.2.4). Therefore, icotrokinra 200 mg immediate release tablet should be taken upon waking on an empty stomach with water. After taking icotrokinra, patients should wait at least 30 minutes before eating food. Any dosage adjustment based on concomitant use of acid-reducing agents is not needed (see Section 6.3.2.4).
Clinical trial formulation	Icotrokinra Hydrochloride in film-coated tablet (Lot #G078)
To-be-marketed formulation	The to-be-marketed formulation will be the debossed clinical formulation used in phase 3 trials (Lot #G078)
Formulations bridging	Phase 1 oral solution was bridged successfully to Phase 2 immediate release film-coated tablet formulation (Lot #014) via a relative bioavailability (BA) trial. Phase 2 immediate release film-coated tablet formulation (Lot #G014) was bridged successfully to Phase 3 immediate release film-coated tablet clinical formulation (Lot # G078) via a relative BA trial (see Section 6.3.2.4).
Immunogenicity	Out of 2,083 evaluable subjects treated with icotrokinra 200 mg QD in phase 3 trials through Week 52, 199 (9.6%) developed treatment-emergent (TE) antidrug antibodies (ADAs) to icotrokinra. Out of the 199 subjects with positive TEADA, 119 (59.8%) had the lowest measurable titer of 1:50, 74 (37.2%) had titers between 100 and <1,000 and 6 (3%) had titer ≥1,000 with the highest titer being 1:6,400 in 1 subject. Among those positive for ADA to icotrokinra, none were positive for neutralizing antibodies (NAb) through Week 52. Based on pop-PK analysis, ADA-positive subjects had 1.2- and 1.3-fold higher Cmax and AUC of icotrokinra, respectively, compared to ADA-negative subjects. There is no impact of immunogenicity on efficacy (see Section 6.3.1.4).
Pharmacodynamics	Icotrokinra reduced serum levels of IL-17A, IL-17F, IL-19, IL-22 and β-defensin-2 relative to pretreatment levels in evaluated subjects with moderate-to-severe plaque psoriasis based on exploratory analysis of the pharmacodynamic markers. A decrease was observed in the expression of mRNA of its molecular targets IL-17A, IL-17F, IL-19, IL-22, IL-23A, and DEFB4A in lesional skin biopsies measured at baseline and up to 24 weeks post treatment in an exploratory analysis of subjects with moderate-to-severe plaque psoriasis. The relationship between these pharmacodynamic markers and the mechanism(s) by which icotrokinra exerts its clinical effects is not fully understood (see Section 6.3.1.1).
Cardiac electrophysiology	Exposure-Response analysis of single or multiple doses of icotrokinra in the first-in-human (FIH) trial PN-235-01 (doses of 10-1000 mg) showed that at 5-fold the maximum recommended dose of icotrokinra, clinically significant QTc interval prolongation was not observed (see Cardiac Safety IRT Consult Response, dated October 22, 2025, by Eliford N Kitabi, DARRTS).
Pharmacokinetics	Single dose In healthy subjects, following the administration of single doses of icotrokinra 10 to 1000 mg immediate release formulations, the median tmax was 2 hours (range 0.25-8 hours) under fasted conditions and the median half-life (t1/2) was 12 hours. In addition, a dose-proportional PK was demonstrated across 10-1000-mg dose range (see Section 6.3.1.2). Multiple doses Following the administration of multiple doses of icotrokinra up to 1000 mg once daily for 10 days in heathy subjects, steady state was achieved within 3 days with

Review Issues	Recommendations and Comments
	minimal accumulation, 0.7 to 1.6-fold for Cmax and 0.9 to 1.5-fold for AUC. The dose-proportional PK was maintained with once-daily dosing as well. The elimination t1/2 was 9 to 16 hours on Day 10. Approximately <0.001% excreted unchanged in urine and 37 to 81% recovered in feces across multiple dose range of 10 to 1000 mg once daily (see Section 6.3.1.2). Pop-PK analysis showed that the exposure in adults and adolescents with PsO was comparable following the administration of 200 mg QD.
Dose/exposure-response	The dose-ranging Study PSO2001 evaluate the clinical response following the administration of icotrokinra 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, and 100 mg BID. Results showed a dose response (D-R) relationship with a plateau at or near the highest dose studied of 100 mg BID. C_{avg} was the driver of clinical response compared to Ctrough, which supported the Phase 3 dosing regimen of 200 mg QD (see Sections 6.3.2.2 and 19.4.2.4). The 200 mg QD dose demonstrated consistently high response rates (PASI90 and IGA0/1) across all exposure quartiles compared to placebo in Phase 3 trials PSO3001, PSO3002, and PSO3004. The response rates remained stable with increasing exposure, indicating the dose is on the flat portion of the dose/exposure-response curve. Adolescents showed comparable or slightly higher PASI90 efficacy versus adults, with similar drug exposures between age groups (see Section 6.3.2.1). In addition, trial PSO3003 confirmed consistently high IGA0/1 response rates across exposure quartiles.
Exposure-Safety	Exposure-safety analysis found similar AE rates across all quartiles of icotrokinra exposure indicating lack of E-R for safety (see Sections 19.4.6.3 and 19.4.6.4).
Drug Interactions	In vitro, icotrokinra is not a CYP enzyme substrate, inhibitor, or inducer. Icotrokinra is not a substrate or inhibitor of P-gp or other major drug transporters at clinically relevant concentrations. Therefore, no clinically relevant drug interactions are expected (see Section 6.3.2.4).

Source: Reviewer's-generated table.
Abbreviations: PASI, psoriasis area and severity index; IGA, investigator's global assessment; QD, once daily; BID, twice daily; eGFR, estimated glomerular filtration rate; C_{max}, maximum drug concentration; AUC, area under the plasma concentration time profile; TE, treatment emergent; ADA, antidrug antibodies; NAb, neutralizing antibodies; IL, interleukin; DEFB4A, defensin beta 4A; t_{max}, time to maximum drug concentration; $t_{1/2}$, elimination half-life; E-R, exposure response; AE, adverse events; CYP, cytochrome P450; P-gp, p-glycoprotein; C_{avg}, average drug concentration, C_{trough}, predose drug concentration; pop, population; PK, pharmacokinetic; IRT, integrated review team

6.1.1. Recommendations

The Office of Clinical Pharmacology reviewed this submission and found it acceptable for approval.

6.1.2. Postmarketing Requirement/Postmarketing Commitment

See Section 13.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

6.2.1.1. Mechanism of Action and Pharmacodynamics

Icotrokinra is a 13 amino acid peptide that competitively antagonizes IL-23 binding to the IL-23 receptor (IL-23R). By blocking IL-23/IL-23R signaling, it inhibits the release of proinflammatory cytokines that contribute to chronic inflammation in immune-mediated diseases. Icotrokinra reduced serum levels of IL-17A, IL-17F, IL-19, IL-22 and β-defensin-2 relative to pretreatment levels in evaluated subjects with moderate-to-severe plaque psoriasis based on exploratory analysis of the PD markers. A decrease was observed in the expression of mRNA of its molecular targets IL-17A, IL-17F, IL-19, IL-22, IL-23A, and DEFB4A in lesional skin biopsies measured at baseline and up to 24 weeks post treatment in an exploratory analysis of subjects with moderate-to-severe plaque psoriasis. The relationship between these PD markers and the mechanism(s) by which icotrokinra exerts its clinical effects is not fully understood.

6.2.1.2. Clinical Pharmacokinetics of Icotrokinra

Following the administration of single doses of 10 to 1000 mg of icotrokinra in healthy subjects, the median t_{max} was 2 hours (range 0.25 to 8 hours) for the immediate release (IR) formulations under fasted conditions and the median half-life ($t_{1/2}$) was 12 hours. In addition, a dose-proportional PK was demonstrated across 10 to 1000 mg range. The PK parameters were comparable across Caucasian, Chinese, and Japanese populations.

Following the administration of multiple doses of icotrokinra up to 1000 mg once daily for 10 days, steady state was achieved within 3 days with minimal accumulation, 0.7- to 1.6-fold for C_{max} and 0.9 to 1.5-fold for AUC. The dose-proportional PK was maintained with once-daily dosing as well. The elimination $t_{1/2}$ was 9 to 16 hours on Day 10. Approximately <0.001% excreted unchanged in urine and 37 to 81% recovered in feces across multiple dose range.

Pop-PK analysis showed that the exposure in adults and adolescents with PsO is comparable following the administration of 200 mg QD.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen for adult and adolescent (12 to 18 years) subjects weighing at least 40 kg with moderate to severe PsO is 200 mg once daily (QD).

Therapeutic Individualization

No clinically significant differences in the pharmacokinetics of icotrokinra were observed based on age (range: 12 to 87 years), body weight (range: 39 to 211 kg), sex, race (76% White and

20.1% Asian), immunogenicity, mild (eGFR ≥60 to <90 mL/min/1.73 m^2) renal impairment or any degree of hepatic impairment. Therefore, alternative dosing regimens based on these intrinsic patient factors are not necessary (see Section 6.3.2.3).

Population PK analyses in adult and adolescent PsO subjects showed that CL/F and V/F of icotrokinra increased with increasing body weight and there was an inverse correlation between body weight and icotrokinra exposure levels. For example, subjects weighing ≥90 kg having a 17% lower AUC compared with subjects weighing <90 kg. However, the difference in exposure due to body weight was deemed clinically insignificant (see Section 6.3.2.3).

Renal Impairment

In renal impairment trial (PSO1007), icotrokinra exposure was elevated in patients with moderate (eGFR 30 to 59 mL/min/1.73 m^2) and severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment (RI) as compared to subjects with normal renal function following administration of a single dose of icotrokinra 200 mg. Specifically, C_{max} increased by 1.79- and 1.26-fold, respectively, while AUC_{last} increased by 2.4- and 2.6-fold, respectively. The Applicant indicated that the anticipated steady state exposures in moderate and severe RI patients are within the range of exposures found in the icotrokinra phase 3 psoriasis studies. Therefore, the Applicant proposed no dose adjustment in patients with moderate or severe renal impairment. The review team agreed that the standard dosing of icotrokinra 200 mg QD is recommended for patients with moderate or severe renal impairment with monitoring for potential adverse events in patients with eGFR <60 mL/min. (see Section 6.3.2.3).

In pop-PK analysis, mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2) did not impact the exposure to icotrokinra where C_{max} and AUC increased by 1.1- and 1.2-fold, respectively. Therefore, alternative dosing regimens based on mild renal impairment are not necessary (see Section 6.3.2.3).

Drug-Drug Interactions

There is low potential to of icotrokinra to modulate CYP enzymes and transporters in vivo. The PK or efficacy of icotrokinra were not meaningfully impacted by concomitant use of acid reducing agents (ARAs). In addition, the modulation of gastric pH by the concomitant use of ARAs is unlikely to impact the solubility and dissolution of icotrokinra in the small intestine and therefore is unlikely to impact its extent of absorption (see Section 6.3.2.4).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

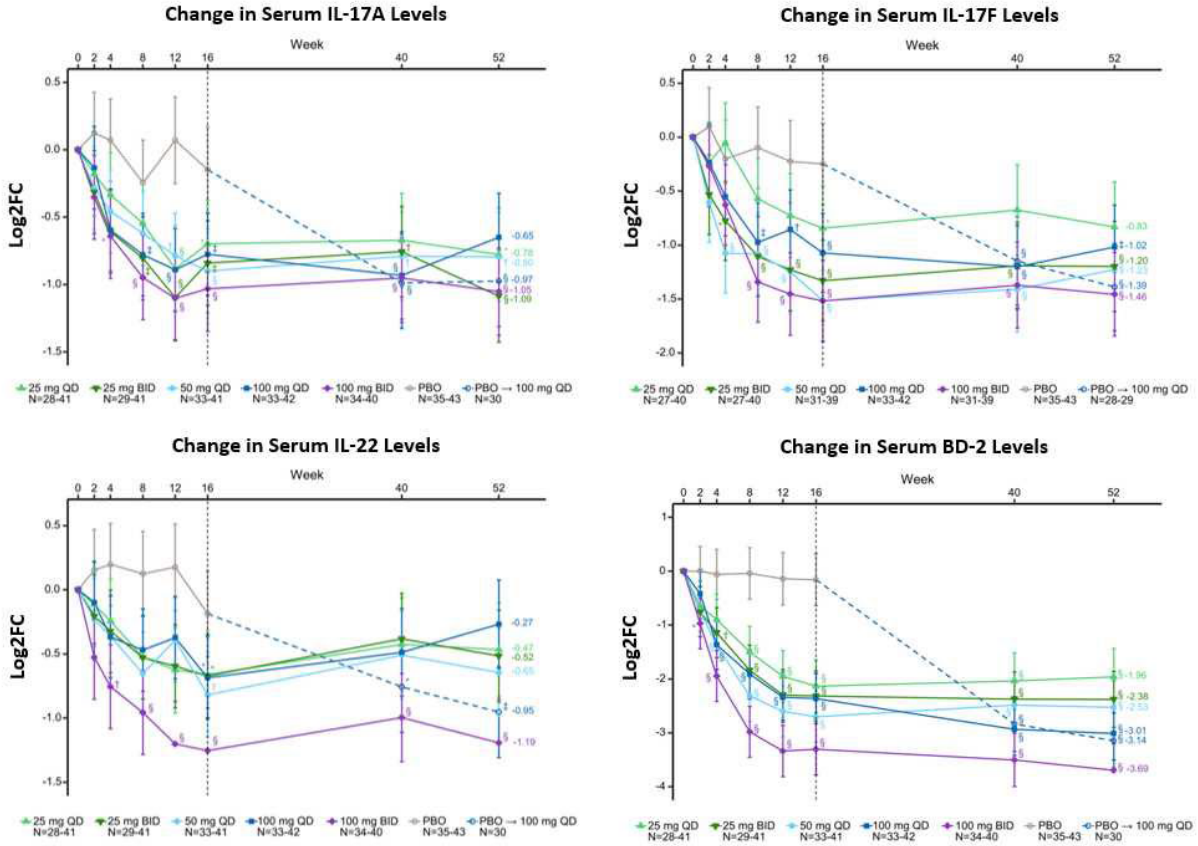
6.3.1.1. Pharmacology and Pharmacodynamics

Serum Biomarkers

Icotrokinra is a 13-amino-acid peptide that binds to the IL-23 receptor (IL-23R) with high affinity and competitively antagonizes the binding of IL-23. Icotrokinra inhibits the IL-23/IL-23R-dependent release of proinflammatory cytokines.

The PD effect of icotrokinra was evaluated in Phase 2 (Study PSO2001) and Phase 3 (Studies PSO3001 and PSO3002). In Phase 2 trial PSO2001 and long-term extension trial PSO2002, there was a reduction from baseline in IL-17A, IL-17F, IL-22, and BD-2 in all icotrokinra dosing groups (25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, and 100 mg BID) relative to placebo that sustained through Week 52, with the greatest reduction observed in the 100 mg BID dosing group, especially in IL-22 and BD-2 (Figure 1). Similar reductions in these biomarkers were observed in the placebo group from Week 16 to Week 52 after crossing over to icotrokinra 100 mg QD (see Section 19.4.2.4).

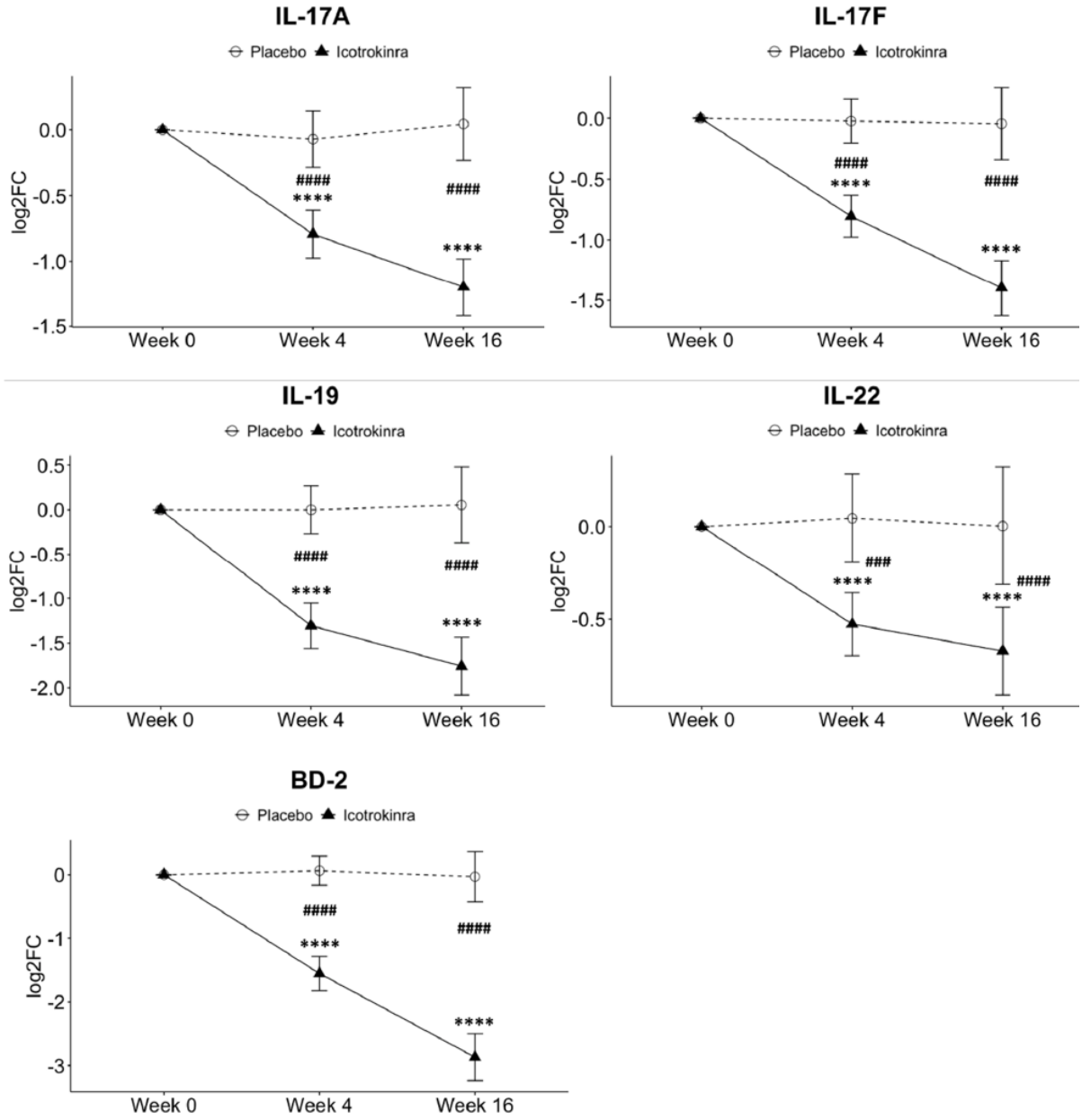
Figure 1. Change From Baseline in Serum Levels of IL-17A, IL-17F, IL-22, and BD-2 in Subjects Receiving Icotrokinra 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, and 100 mg BID or Placebo in Trials PSO2001 and PSO2002



Source: Summary of Clinical Pharmacology, Figure 12.
Abbreviations: BD-2, beta-defensin-2; BID, twice daily; FC, fold change; IL, interleukin; log2, logarithm to the base 2; PBO, placebo; QD, once daily.
A total of 24 subjects (9.4%) discontinued study intervention prior to Week 16. A higher percentage of subjects discontinued from study intervention in the placebo group and the 25 mg QD group compared with the other icotrokinra groups.
Estimated marginal means displayed. Error bars are model-based 95% confidence intervals.

In Phase 3 trial PSO3001, the PD effects of icotrokinra on serum IL-17A, IL-17F, IL-22, IL-19, and BD-2 were evaluated in a subset of subjects using Week 0, Week 4, and Week 16 samples from up to 167 subjects following the administration of icotrokinra 200 mg QD. Compared to placebo, icotrokinra decreased serum IL-17A, IL-17F, IL-22, IL-19, and BD-2 levels at Week 4 and Week 16 compared with baseline (Figure 2) (see Section 19.4.2.5.1).

Figure 2. Reduction of IL-17A, IL-17F, IL-19, IL-22, and BD-2 In Response to Icotrokinra and Placebo Treatment at Week 4 and Week 16 in Trial PSO3001



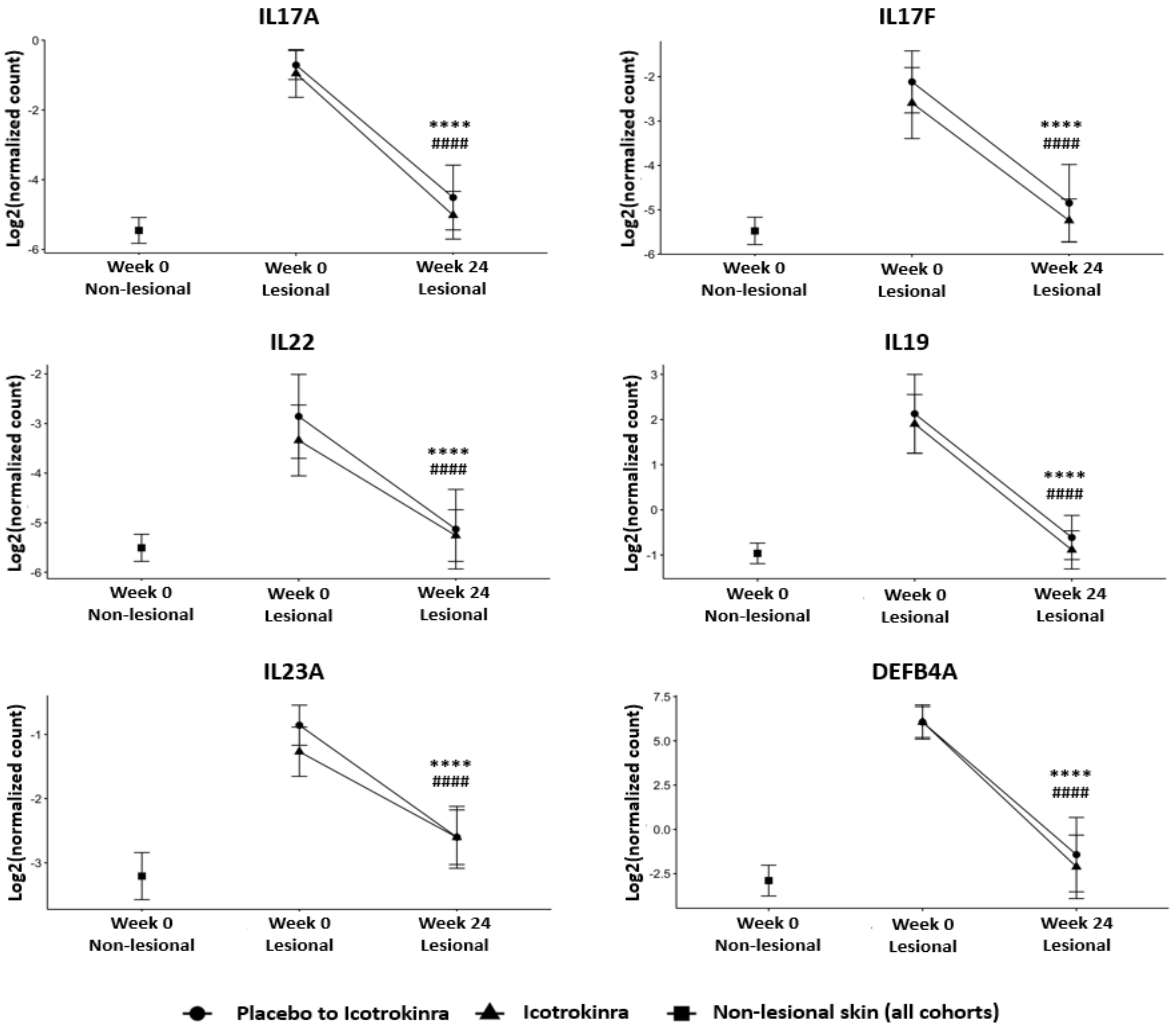
Source: Summary of Clinical Pharmacology, Figure 14.
Abbreviations: FC, fold change (post-treatment concentration divided by baseline concentration); IL, interleukin; BD-2, beta-defensin 2.
Points show mean value, whiskers show 95% confidence intervals. p-values from lmer model with interaction term shown for arm comparisons (#, Placebo vs. Icotrokinra) and pairwise estimation for within arm time effect (*, vs. W0). */# p<0.05, **/## p <0.01, ***/### p<0.001, ****/#### p<0.0001. n=115 (IL-22), 116 (IL-17A, IL-17F, IL-19 and BD-2) for ICO; n=54 (IL-22), n=53 (IL-17A, IL-17F, IL-19 and BD-2) for placebo.
Linear Model: log2FC ~WEEK*TREATMENT + log2(Baseline Value) + (1 | Subjects). This model framework assumes an approximately normal distribution of residuals can be achieved with log2 data transformations. P-value adjustment using "sidak" method.
No covariates were used in the model for IL-17A, IL-17F, and IL-22. SEX was added as a covariate in the model for IL-19 log2FC ~WEEK*TREATMENT + Sex + log2(Baseline Value) + (1 | Subjects). Sex and Ethnicity were added as covariates in the model for BD-2: log2FC ~WEEK*TREATMENT + Sex + Ethnicity+ log2(Baseline Value) + (1 | Subjects).
A post hoc procedure was used to calculate the marginal mean estimates of change from baseline and the 95% confidence intervals and p-values in comparison to a mu of zero. One-sample t-tests were performed for each log2-transformed measurement comparing baseline and measurement at Week 4 and Week 16 for both treatment groups. Additionally, independent two-sample t-tests were performed on the same log2(fold change) to test differences between treatment groups at baseline.
n=113-114 for icotrokinra; n=52-53 for placebo.

Skin Transcriptomic Biomarkers

In exploratory analysis in Phase 3 trials PSO3001 and PSO3002 skin biopsies were analyzed to assess the PD effects of icotrokinra on skin genes and pathways relevant to PsO and IL-23/Th17 pathway. In trial PSO3001, baseline non-lesional, baseline lesional, and Week 24 lesional (collected from the same lesional area as baseline) skin biopsies were used for analysis. Analysis of subjects on icotrokinra treatment and subjects on placebo crossed over to icotrokinra showed a reduction in the expression levels of DEFB4A, IL-17A, IL-17F, IL-19, IL-22, and IL-23A genes in lesional skin at Week 24 compared with those at Week 0 to a level similar to non-lesional skin (Figure 3) (see Section 19.4.2.5.1).

In an exploratory analysis in trial PSO3002, icotrokinra treatment reduced the expression levels of PsO-related IL17A, IL17F, IL22, IL19, IL23A, and DEFB4A genes in lesional skin at Week 16 compared with Week 0. The active controlled Deucravacitinib treatment group also showed reduced expression of these genes; however, to a lesser extent than icotrokinra at Week 16. In contrast, no substantial reduction was observed in the placebo group (see Section 19.4.2.5.2). This is an exploratory analysis with limited number of subjects; therefore, these PD results should be interpreted with caution.

Figure 3. Reduction of Psoriasis and IL-23/Th17 Pathway-Related Genes at Week 24 in Icotrokinra and Placebo Crossover to Icotrokinra Cohorts in Trial PSO3001



Source: Summary of Clinical Pharmacology, Figure 15.
Abbreviations: IL, interleukin; DEFB4A, human beta-defensin 2.
Points show mean values, whiskers show 95% CIs. p-values from linear mixed model with interaction term shown for pairwise estimation for within arm time effect (*, versus Week 0 lesional, icotrokinra cohort; #, versus Week 0 lesional, placebo crossover to icotrokinra cohort). ****/#### p<0.0001,
Linear Model: Counts ~ Week + Baseline value + (1 | Subjects) with p-value adjustment using "sidak" method.
Age was added as a covariate in the model for DEFB4A when compared lesional skin at Week 0 vs. lesional skin Week 24 and lesional skin at Week 24 and non-lesional skin at Week 0 in the icotrokinra treatment group but not in the placebo to icotrokinra group. In addition, Age was used as covariate in the model that compares icotrokinra group vs. placebo to icotrokinra group at Week 0 and Week 24 with lesional skin.
Ethnicity and Age was added as a covariate in the model for IL-17A and IL-19, respectively, when compared lesional skin at Week 24 and non-lesional skin at Week 0 in the icotrokinra treatment group but not in the placebo to icotrokinra group.
A post hoc procedure was used to calculate the marginal mean estimates of change from baseline and the 95% confidence intervals and p-values in comparison to a mu of zero. One-sample t-tests were performed for paired analysis. Additionally, independent two-sample t-tests were performed to test differences between treatment groups at baseline.

Overall, the relationship between these PD markers and the mechanism(s) by which icotrokinra exerts its clinical effects is not fully understood.

6.3.1.2. Pharmacokinetics in Healthy Adults Subjects

Single Dose PK

The single dose PK of icotrokinra in healthy subjects was evaluated in several clinical trials across the dose range of 10 to 1000 mg. Across all trials at a dose range of 100 to 300 mg, the PK of icotrokinra after single-dose administration in healthy subjects was comparable (Table 4). For additional details on study design and PK analysis, refer to Section 19.4.2.

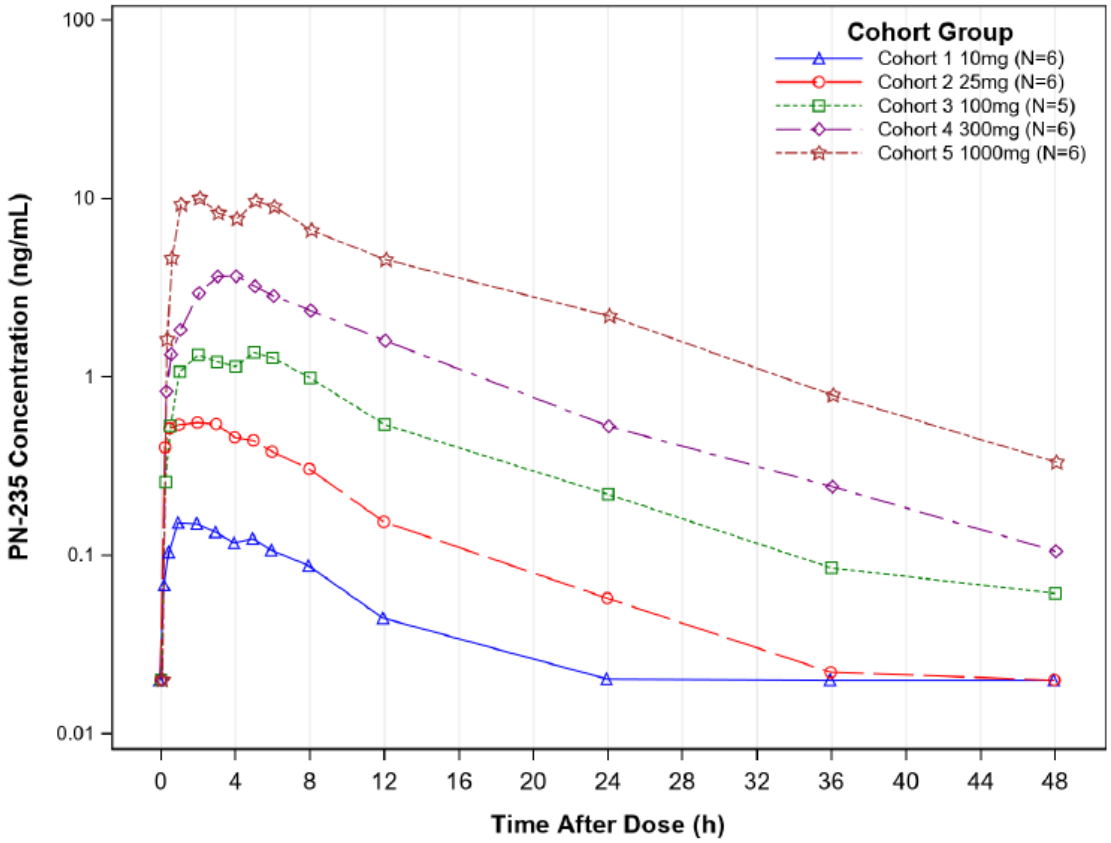
The median t_{max} following administration of icotrokinra IR tablet under fasted state occurs after approximately 2 (range 0.25 to 8) hours, and the median half-life ($t_{1/2}$) following single dose administrations was 12 hours. In addition, icotrokinra has approximately dose-proportional PK within the dose range of 10 to 1000 mg single doses (see Section 19.4.2.1.1). The PK parameters in healthy subjects were found to be consistent across all clinical trials, with no substantial differences observed between Caucasian (Studies PN-235-01, PSO1003, PSO1006, PSO1007 and PSO1009), Chinese (Study PSO1004), and Japanese (Study PSO1002) subjects (Table 4). Representative icotrokinra concentration versus time curves derived from trial PN-235-01 are shown in Figure 4.

Table 4. Summary of Icotrokinra PK Parameters in Healthy Subjects Following the Administration of Single Doses of Icotrokinra Immediate Release (IR) Tablet in a Fasted State

	Mean (SD), CV%; t_{max}: Median (Range)												
	100 mg					200 mg			300 mg				
Parameter	PN-235-01 Part 1 OS	PN-235-01 Part 2 Day 1 OS	PSO1002 Part 1 Phase 2 Tablet	PSO1003 Phase 2 Tablet	PSO1004 Phase 2 Tablet	PSO1006 1×200 mg Phase 3 Tablet	PSO1007 Phase 3 Tablet	PSO1009 Phase 3 Tablet	PN-235-01 Part 1 OS	PN-235-01 Part 2 Day 1 OS	PSO1002 Part 1 Phase 2 Tablet	PSO1002 Part 2 Phase 2 Tablet	PSO1004 Phase 2 Tablet
N	5	8	6	14	10	24[a]	8	15	6	8	6	6	10
C_{max} (ng/mL)	1.48 (0.4), 27.51	3.3 (3.8), 113.48	3.17 (1.03), 32.5	2.10 (0.942)	2.63 (1.02), 38.8	3.62 (1.48), 40.9	3.29 (1.47), 44.6	3.38 (1.81), 53.6	3.97 (1.9), 47.16	5.8 (5.6), 96.52	4.61 (2.38), 51.6	4.33 (2.12), 49.1	7.90 (5.85), 74.1
t_{max} (h)	3.0 (2.0; 6.0), 51.35	1.5 (0.3; 8.0), 105.16	2.00 (0.25; 5.00), 86.4	2.51 (0.25; 5.00)	1.00 (0.25; 5.00)	2.00 (0.25; 8.00)	2.00 (0.50; 6.02), 83.3	1.00 (0.50; 6.00), 92.2	4.0 (3.0; 8.0), 42.97	3.5 (1.0; 8.0), 57.13	4.00 (0.25; 6.00), 72.3	0.50 (0.50; 6.00), 147.6	1.00 (0.25; 8.00)
AUC_{last} (ng*h/mL)	19.3 (5.2), 26.72	-	27.0 (8.09), 30.0	21.9 (8.28)	19.5 (4.13), 21.2	42.0 (10.7), 25.6	37.9 (9.36), 24.7	34.3 (7.70), 22.4	49.5 (20.1), 40.52	-	49.6 (19.0), 38.3	45.3 (15.7), 34.6	62.3 (30.9), 49.5
AUC_{inf} (ng*h/mL)	20.7 (6.5), 31.33	-	27.5 (8.01), 29.2	22.3 (8.34)	19.9 (4.21), 21.2	44.8 (11.4), 25.5	38.7 (9.28), 24.0	36.7 (9.01)[b], 24.5	51.0 (20.6), 40.46	-	50.7 (18.8), 37.1	46.5 (15.7), 33.8	63.3 (30.9), 48.8

Source: Summary of Clinical Pharmacology, Table 19.
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; IR, immediate release; N, number of participants; OS, oral solution; PK, pharmacokinetic(s); SD, standard deviation; t_{max}, time to C_{max}
Trials PN-235-01, PSO1003, PSO1006, PSO1007 and PSO1009 included mostly Caucasian subjects.
Trial PSO1004 included Chinese subjects.
Trial PSO1002 included Japanese and Chinese subjects. PK data from Japanese subjects were reported.
Trial PSO1007 included PK data from the healthy subjects group that matched subjects with severe renal impairment.
Trial PSO1009 represent the PK data obtained following the administration of icotrokinra with 240 mL noncarbonated water.
[a] N=23 for AUC_{last} and AUC_{inf}.
[b] N=14.

Figure 4. Mean Plasma Concentration Time Profiles of Icotrokinra Following the Administration of Single Doses of Icotrokinra Oral Solution in Trial PN-235-01 – Log-Linear Scale

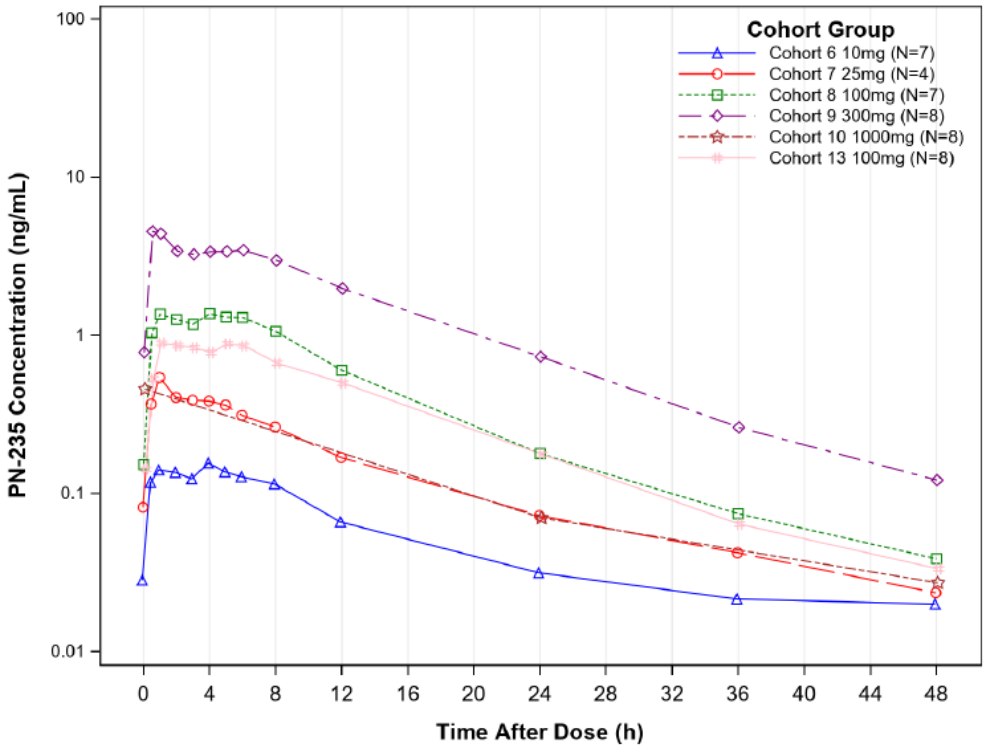


Source: Study PN-235-01 Report, Figure 14.2.15.

Multiple Dose PK

After repeated once-daily dosing of icotrokinra 10, 25, 100, 300, and 1000 mg oral solution for 10 days in Study PN-235-01, steady state was achieved within 3 days with minimum drug accumulation and dose proportional PK (Figure 5). The accumulation was 0.7 to 1.6-fold for C_{max} and 0.9 to 1.5-fold for AUC, with once daily dosing. The elimination $t_{1/2}$ was 9 to 16 hours on Day 10. Less than 0.001% of PN-235 was excreted intact in the urine and 37% to 81% of icotrokinra was recovered in the feces across the administered multiple doses of 10 to 1000 mg once daily (see Section 19.4.2.1.1).

Figure 5. Mean Plasma Concentration Time Profiles of PN-235 on Day 10 Following the Administration of Multiple Doses of PN-235 Oral Solution in Trial PN-235-01 – Log-Linear Scale



Source: Study PN-235-01 Report, Figure 14.2.15
Dosing in Cohort 10 (1000 mg once daily) was interrupted after one subject administered PN-235 was noted to have ventricular extrasystoles and a preliminary echocardiogram was misread as abnormal. Based upon this report, dosing in the entire cohort was stopped on Day 8. At the time dosing was interrupted, 8 subjects in Cohort 10 had completed 8 out of the planned 10 days of treatment, and 2 subjects had completed 7 days of treatment.

Formulations Bridging

Relative Bioavailability of Phase 2 IR Tablet to Phase 1 Oral Solution

The relative bioavailability of Phase 2 IR tablet formulation (Lot # G014) compared to oral solution was evaluated following the administration of a single 100-mg dose in the fasted state in trial PSO1003. The median t_{max} under fasted condition was 2.51 hours and 1 hour for the 100 mg IR tablet and 100 mg oral solution, respectively, without observed delay in absorption. The C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of icotrokinra increased by 6.4% (90% CI: 84% to 134.8%), 5.6% (90% CI: 90.5% to 123%), and 9.7% (90% CI: 94.4% to 127.4%), respectively, after the administration of 100 mg IR tablet in fasted state compared to 100 mg oral solution administered in fasted state. Although the upper limit of the 90% CI for C_{max} and $AUC_{0\text{-}inf}$ was outside the no effect boundary of 80% to 125%, this would not have any clinically meaningful effect due to lack of exposure response for safety and efficacy, suggesting relatively similar PK between icotrokinra IR tablet and oral solution when administered at the same dose of 100 mg (see Section 19.4.2.1.1).

Relative Bioavailability of Clinical IR Tablet to Phase 2 IR Tablet

The relative bioavailability of Phase 3 clinical IR tablet formulation (Lot #G078) compared to Phase 2 IR tablet was evaluated following the administration of a single 200-mg dose in the fasted state in trial PSO1006. The median t_{max} was 2 hours for both tablet formulations. The C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of icotrokinra decreased by 12% (90% CI: 74.2% to 104.4%), 5.8% (90% CI: 85% to 104.3%), and 5% (90% CI: 85.6% to 105.2%), respectively, after the administration of a single dose of 200 mg as clinical IR tablet in fasted state compared to a single dose of 200 mg icotrokinra as Phase 2 IR tablet (see Section 19.4.2.2.2). Although the lower limit of the 90% CI for C_{max} is outside the no effect boundary of 80% to 125%, this would not have any clinically meaningful effect due to lack of exposure response for safety and efficacy. These results suggest relatively comparable exposure between Phase 3 clinical IR tablet formulation (Lot # G078) and phase 2 IR tablet formulation (Lot #G014).These results suggest relatively comparable exposure between Phase 3 clinical IR tablet formulation (Lot # G078) and Phase 2 IR tablet formulation (Lot #G014).

The above provides evidence to support a bridge between the Phase 3 clinical IR tablet and solution.

6.3.1.3. Pharmacokinetics in Adult and Adolescent Subjects With Moderate to Severe PsO

The PK in subjects with PsO was determined using pop-PK analysis. The pop-PK model used PK data (IR formulations only) collected from trials PN-235-01, PSO1002, PSO1003, PSO1004, PSO1006, PSO2001, PSO2002, PSO3001, PSO3002, PSO3003, and PSO3004 conducted in healthy subjects and subjects with PsO. A one-compartment model with first-order absorption and first-order elimination was found to best describe the PK of icotrokinra in subjects with PsO. Refer to Section 19.4.5 for details regarding the population PK analysis.

The model-predicted PK parameters for the recommended dosage of 200 mg once daily in adults and adolescents (12 to <18 years) is shown in Table 5. Based on pop-PK analysis, the exposure in adults and adolescent was comparable.

Table 5. Predicted Geometric Mean (CV%) Icotrokinra Exposure in Adult and Adolescent Subjects With Moderate to Severe PsO Following the Administration of Icotrokinra 200 mg Once Daily

Parameter	Adolescents (N=69)	Adults (N=2043)	Overall (N=2112)
$C_{max,ss}$ (ng/mL)	2.84 (54.9)	2.6 (48.0)	2.6 (48.2)
$C_{avg,ss}$ (ng/mL)	1.48 (64.2)	1.34 (48.7)	1.34 (49.3)
$C_{trough,ss}$ (ng/mL)	0.525 (105.8)	0.482 (71.1)	0.483 (72.3)
$AUC_{0\text{-}24,ss}$ (h·ng/mL)	35.4 (64.2)	32.2 (48.7)	32.3 (49.3)

Source: Reviewer's generated table adapted from Population Pharmacokinetics and Exposure-Response Report, Table 5.
Abbreviations: $AUC_{0\text{-}24,ss}$, steady-state area under the concentration-time curve from 0 to 24 hours; $C_{avg,ss}$, average drug concentration at steady state; $C_{max,ss}$, steady-state maximum plasma icotrokinra concentration; $C_{trough,ss}$, steady-state trough concentration; CV, coefficient of variation; N, number of subjects; PsO, psoriasis

6.3.1.4. Immunogenicity

The evaluation of immunogenicity was based on data pooled from phase 3 trials PSO3001, PSO3002, PSO3003, and PSO3004 through Week 52. The immunogenicity assessment was based on subjects who were randomized to receive icotrokinra 200 mg QD from Week 0, subjects randomized to placebo and switched to icotrokinra 200 mg QD at Week 16, and subjects randomized to deucravacitinib 6 mg QD and switched to icotrokinra 200 mg QD at Week 24.

Out of 2,083 evaluable subjects treated with icotrokinra 200 mg QD through Week 52, 199 (9.6%) developed treatment-emergent (TE) antidrug antibodies (ADAs) to icotrokinra (Table 6). Out of the 199 subjects with positive TEADA, 119 (59.8%) had the lowest measurable titer of 1:50, 74 (37.2%) had titers between 100 and <1,000 and 6 (3%) had titer ≥1,000 with the highest titer being 1:6,400 in 1 subject.

Among those positive for ADA to icotrokinra, none was positive for neutralizing antibodies (NAb) through Week 52. However, 3.7% to 14% of ADA-positive samples across the four Phase 3 studies had icotrokinra concentrations greater than the NAb assay drug tolerance. Given the limited drug tolerance of the NAb assays, it is difficult to conclude that none of the ADA-positive patients developed NAb. In response to the Immunogenicity Consult, the Office of Pharmaceutical Quality Research (OPQR) had determined that the potential impact of the poor drug tolerance could lead to the underestimation of NAb positive samples; however, given the lack of observed clinical impact on efficacy or safety in the trials the importance of addressing the adequacy of the drug tolerance of the assay may not be needed. It is unlikely that these analytical deficiencies will significantly compromise patient safety given icotrokinra's low observed immunogenicity, the NAb assay's bias toward false positivity rather than false negativity, and lack of observed clinical impact on efficacy or safety in trials (see Immunogenicity Consult Response in DARRTS, dated 02/04/2026, by Dr. Bruce K Huang).

Table 6. Summary of Treatment-Emergent Antibodies to Icotrokinra Status Up to Week 52 in Pooled Phase 3 Studies

	77242113PSO3001[a]	77242113PSO3002[b]	77242113PSO3003[a]	77242113PSO3004[c]	
	JNJ-77242113	JNJ-77242113	JNJ-77242113	JNJ-77242113	Total[d]
Analysis set: Immunogenicity analysis set	664	731	296	392	2083
Subjects positive for antibodies to JNJ-77242113 at baseline[e]	3 (0.5%)	2 (0.3%)	1 (0.3%)	4 (1.0%)	10 (0.5%)
Baseline titers					
1:50	3 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)	10 (100.0%)
Subjects positive for antibodies to JNJ-77242113 at baseline who were treatment-boosted for antibodies to JNJ-77242113[f]	0	0	0	0	0
Subjects positive for antibodies to JNJ-77242113 at baseline who were not treatment-boosted for antibodies to JNJ-77242113[g]	3 (0.5%)	2 (0.3%)	1 (0.3%)	4 (1.0%)	10 (0.5%)
Baseline titers					
1:50	3 (100.0%)	2 (100.0%)	1 (100.0%)	4 (100.0%)	10 (100.0%)
Subjects positive for treatment-emergent antibodies to JNJ-77242113[h]	80 (12.0%)	57 (7.8%)	32 (10.8%)	30 (7.7%)	199 (9.6%)
Peak titers[i]					
1:50	63.8% (51/80)	56.1% (32/57)	56.3% (18/32)	60.0% (18/30)	59.8% (119/199)
1:100	11.3% (9/80)	17.5% (10/57)	9.4% (3/32)	16.7% (5/30)	13.6% (27/199)
1:200	13.8% (11/80)	14.0% (8/57)	6.3% (2/32)	3.3% (1/30)	11.1% (22/199)
1:400	8.8% (7/80)	5.3% (3/57)	12.5% (4/32)	6.7% (2/30)	8.0% (16/199)
1:800	1.3% (1/80)	7.0% (4/57)	3.1% (1/32)	10.0% (3/30)	4.5% (9/199)
1:1600	(0/80)	(0/57)	9.4% (3/32)	3.3% (1/30)	2.0% (4/199)
1:3200	(0/80)	(0/57)	3.1% (1/32)	(0/30)	0.5% (1/199)
1:6400	1.3% (1/80)	(0/57)	(0/32)	(0/30)	0.5% (1/199)
Peak titer group					
50-<100	63.8% (51/80)	56.1% (32/57)	56.3% (18/32)	60.0% (18/30)	59.8% (119/199)
100-<1000	35.0% (28/80)	43.9% (25/57)	31.3% (10/32)	36.7% (11/30)	37.2% (74/199)
≥1000	1.3% (1/80)	(0/57)	12.5% (4/32)	3.3% (1/30)	3.0% (6/199)
Subjects negative for treatment-emergent antibodies to JNJ-77242113[j]	584 (88.0%)	674 (92.2%)	264 (89.2%)	362 (92.3%)	1884 (90.4%)

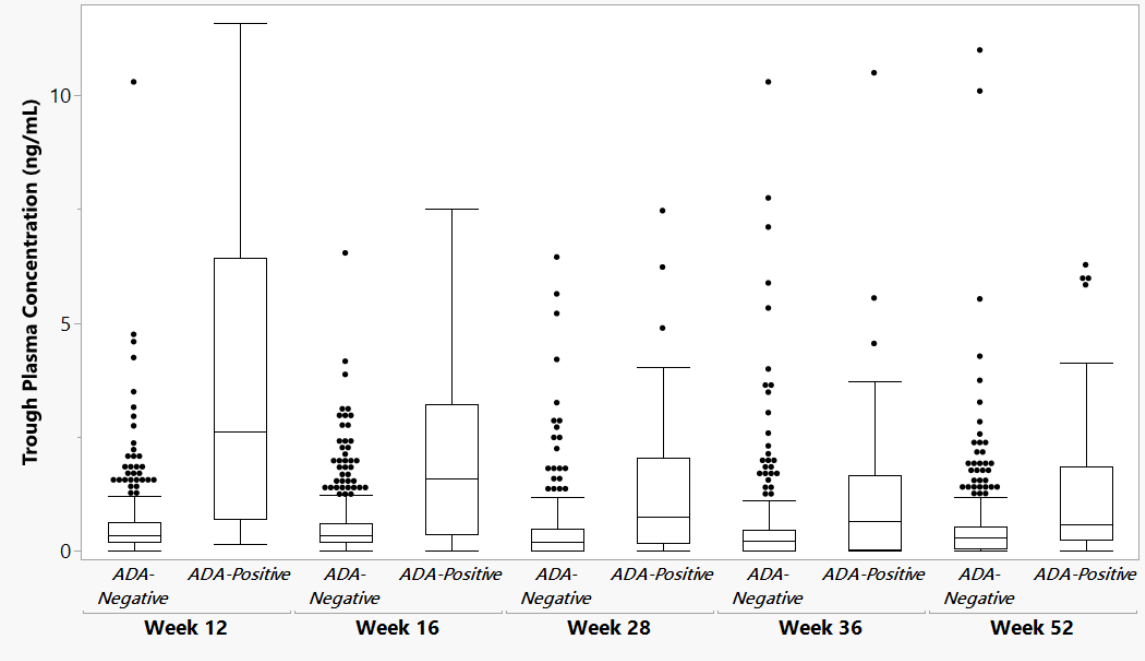
Source: Integrated Summary of Immunogenicity, Table 9.
Abbreviation: ADA, antidrug antibodies); JNJ-77242113, icotrokinra.
a Includes data for subjects randomized to JNJ-77242113 and received at least 1 dose of JNJ-77242113, and data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113 and had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113 through Week 52.
b Includes data for subjects randomized to JNJ-77242113 and received at least 1 dose of JNJ-77242113, data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113, and data after Week 24 for deucravacitinib subjects who switched over to receive JNJ-77242113 and had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113 through Week 44, with the last sample collected at Week 36.
c Includes data for subjects randomized to JNJ-77242113 and received at least 1 dose of JNJ-77242113 and data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113 and had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113 through Week 24.
d Includes data from four studies for subjects randomized to JNJ-77242113 and received at least 1 dose of JNJ-77242113, data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113, and data after Week 24 for deucravacitinib subjects who switched over to receive JNJ-77242113 and had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.
e Subjects positive for antibodies to JNJ-77242113 at baseline, regardless of status after first JNJ-77242113 administration.
f Subjects positive for treatment-boosted antibodies to JNJ-77242113 includes subjects who were positive at baseline and whose titers increased 4-fold at any time. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
g Includes subjects positive for antibodies to JNJ-77242113 at baseline but whose titers did not increase 4-fold after their first JNJ-77242113 administration, remained the same after treatment or ADA titers were reduced, or disappeared after JNJ-77242113 administration.
h Subjects positive for treatment-emergent antibodies to JNJ-77242113 includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
i Denominator is the number of subjects positive for treatment-emergent antibodies.
j Includes all subjects whose sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 at any time. In addition, subjects who were ADA positive at Week 16 on placebo treatment or Week 24 on deucravacitinib treatment were considered negative for treatment-emergent antibodies to JNJ-77242113.
Note: Includes data up to Week 52 for subjects in PSO3001, data up to Week 44 for subjects in PSO3002, data up to Week 52 for subjects in PSO3003, and data up to Week 24 for subjects in PSO3004.

Impact of Immunogenicity on PK

Plasma icotrokinra trough concentrations from pooled Phase 3 trials PSO3001 and PSO3003 through Week 52 showed an increase in the trough concentration of icotrokinra in ADA-positive subjects compared to ADA-negative subjects (Figure 6). Studies PSO3001 and PSO3003 were pooled together due to similar duration of study intervention up to Week 52. The increased trough concentrations observed in ADA-positive subjects were still within the observed range of trough concentrations in ADA-negative subjects. In addition, there was a trend toward increasing trough concentrations of icotrokinra with increasing ADA titer values (Figure 7).

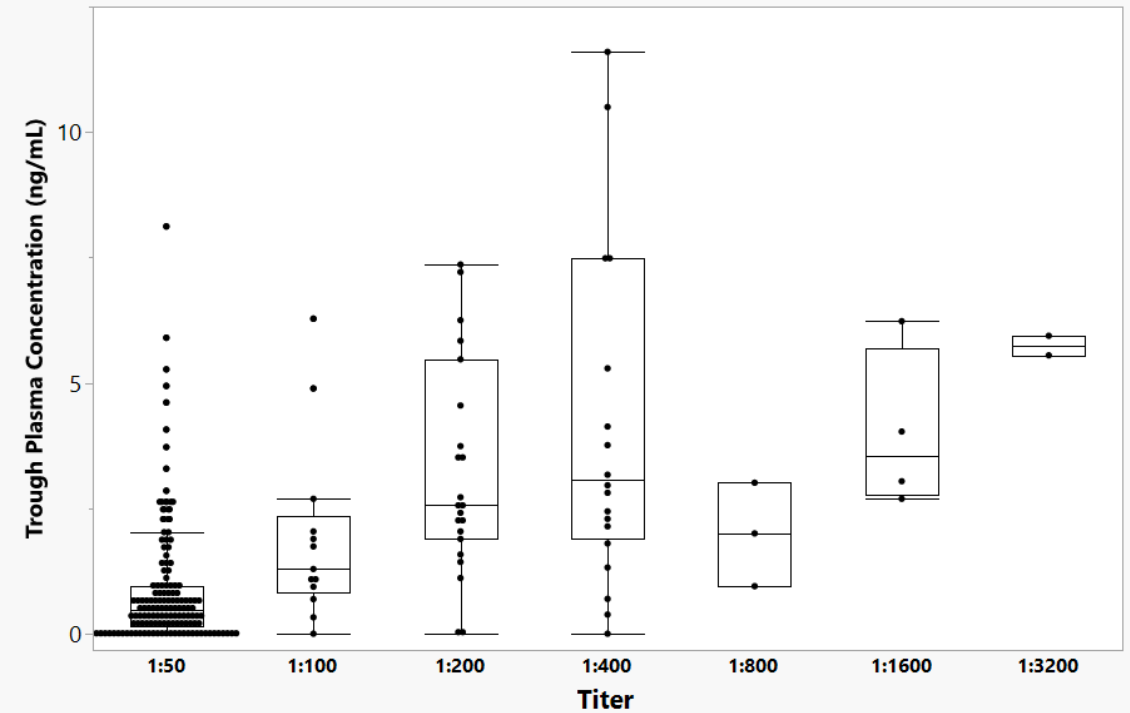
See Sections 19.4.2.5.2 and 19.4.2.5.4. for the impact of immunogenicity on the PK of icotrokinra in trials PSO3002 and PSO3004.

Figure 6. Boxplot of Pooled Trough Plasma Icotrokinra Concentrations From Week 12 Through Week 52 by Visit and Antibody Status Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trials PSO3001 and PSO3003



Source: Reviewer's generated figure using ADPC, ADIS, and ADSL datasets from Studies PSO3001 and PSO3003.
Abbreviations: ADA, antidrug antibody

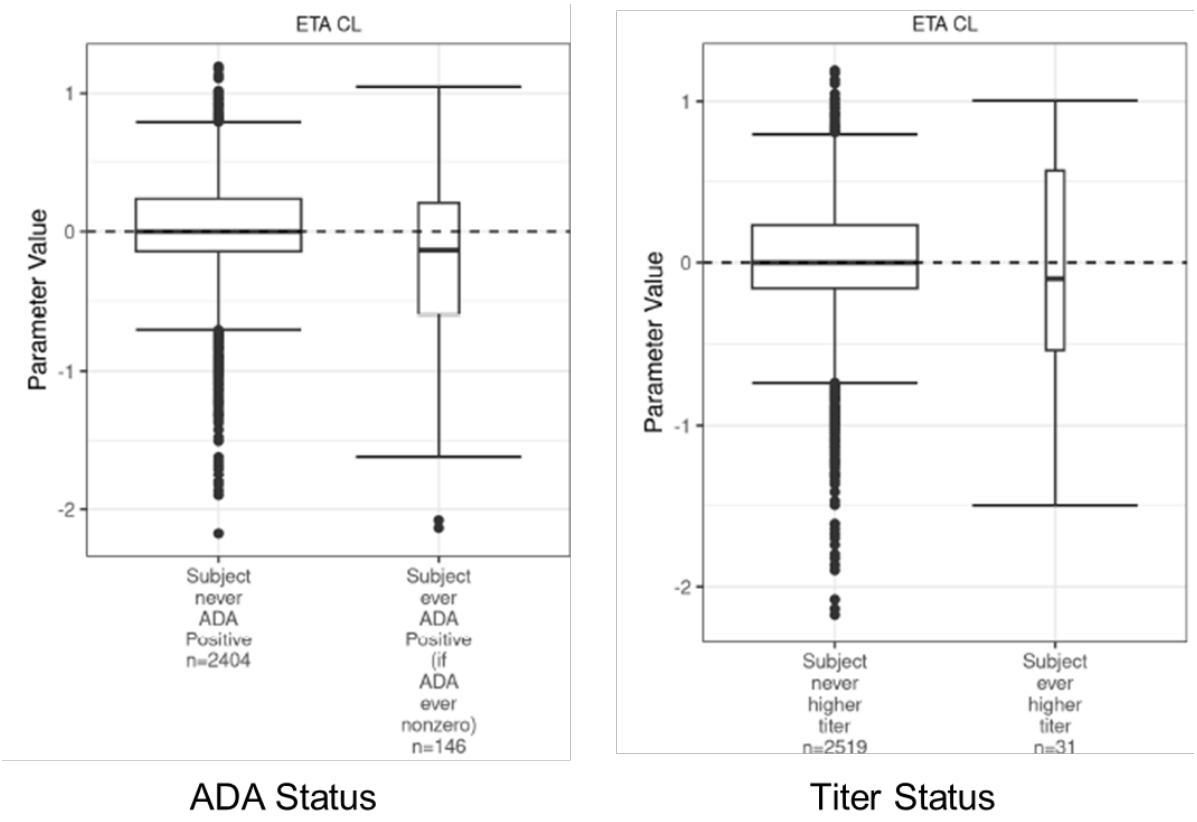
Figure 7. Impact of Titer on Trough Plasma Icotrokinra Concentrations Through Week 52 Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Pooled Trials PSO3001 and PSO3003



Source: Reviewer's generated figure using ADPC, ADIS, and ADSL datasets from studies PSO3001 and PSO3003.
There was 1 subject in trial PSO3001 with a titer of 1:6,400

Population PK analysis determined that ADA-positive subjects had lower CL/F and thus higher exposure compared with ADA-negative subjects or subjects with ADA titer of less than 100 (Figure 8). The pop-PK analysis using pooled Week 52 data from trials PSO3001, PSO3002, PSO3003, and PSO3004 showed that ADA-positive subjects had 1.2- and 1.3-fold higher model predicted C_{max} and AUC, respectively, compared to ADA-negative subjects (see Sections 6.3.2.3 and 19.4.5). In addition, subjects with ADA titer of ≥100 had a 1.5-fold higher C_{max} and a 2-fold higher AUC compared with subjects having ADA titer of <100 or who were ADA negative (see Section 6.3.2.3). These ADA-associated PK changes are not considered to be clinically relevant.

Figure 8. Icotrokinra Individual Predicted Clearance Versus ADA Status and Titer Categories in Pooled Phase 3 Studies



Source: Population PK/ER Report, p. 103.
Abbreviations: ADA, antidrug antibody; CL, clearance; n, number of subjects

Impact of Immunogenicity on Efficacy

The proportions of subjects who received icotrokinra 200 mg QD and achieved an IGA 0/1, IGA 0, PASI 75, PASI 90, or PASI 100 response at Week 16 were comparable between ADA-positive and ADA-negative subjects in pooled Phase 3 trials PSO3001, PSO3002, and PSO3004 (Table 7). Overall, 42 (70%) subjects that were ADA positive achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 16 compared 693 (67.9%) subjects who were ADA negative. In addition, 35 (58.3%) subjects who were ADA positive achieved a PASI 90 response at Week 16 compared to 543 (53.5%) subjects who were ADA negative.

There was no different in efficacy between subjects with low and high titer in pooled phase 3 trials PSO3001, PSO3002, and PSO3004. In the low titer (≥50 to <100) group, 32 (76.2%) subjects achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 16 compared 9 (52.9%) subjects who had high titer (≥100 to <100) (Table 7). Similarly, 32 (76.2%) subjects who had low titer achieved a PASI 90 response at Week 16 compared to 14 (82.4%) subjects who had high titer. Therefore, the development of antibodies to icotrokinra, regardless of titer, did not appear to be associated with a reduction in the efficacy of icotrokinra. Efficacy endpoints in Study PSO3003 were different from those in the other Phase 3

trials; therefore, this trial was excluded from this analysis. Results from trial PSO3003 demonstrated that immunogenicity did not impact the efficacy of icotrokinra (see Section 19.4.2.5.3).

Table 7. Clinical Responses at Week 16 by Antibodies to Icotrokinra Status Through Week 16 in Pooled Phase 3 Studies PSO3001, PSO3002, and PSO3004

	Antibodies to JNJ-77242113 Status				
			Peak Titers for Antibody Positive Subjects		
	Negative[b]	Positive[c]	≥50 to <100	≥100 to <1000	≥1000
Analysis set: Immunogenicity analysis set[a]	1020	60	42	17	1
IGA					
N	1020	60	42	17	1
IGA Score = 0 or 1 and a ≥2-grade improvement from baseline	693 (67.9%)	42 (70.0%)	32 (76.2%)	9 (52.9%)	1 (100.0%)
IGA Score = 0	360 (35.3%)	24 (40.0%)	18 (42.9%)	5 (29.4%)	1 (100.0%)
PASI					
N	1020	60	42	17	1
≥75% Improvement	748 (73.3%)	47 (78.3%)	32 (76.2%)	14 (82.4%)	1 (100.0%)
≥90% Improvement	546 (53.5%)	35 (58.3%)	27 (64.3%)	7 (41.2%)	1 (100.0%)
100% Improvement	304 (29.8%)	18 (30.0%)	13 (31.0%)	4 (23.5%)	1 (100.0%)

Source: Integrated Summary of Immunogenicity, Table 15.
Abbreviations: IGA, Investigator's Global Assessment; JNJ-77242113, icotrokinra; N, number of participants; PASI, Psoriasis Area and Severity Index.
[a] All participants who were randomized to and received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.
[b] Includes all subjects whose last sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 through Week 16.
c Includes all subjects who had at least 1 positive sample (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration through Week 16. In the instance that a subject had a positive sample at the reference baseline visit, the subject was considered positive only if the peak titer of the post-JNJ-77242113 treatment samples was at least a 4-fold higher (i.e., ≥4-fold) than the titer of the reference baseline sample.

Impact of Immunogenicity on Safety

The impact of immunogenicity on safety in Phase 3 trials was also evaluated among subjects randomized to receive icotrokinra 200 mg QD. Overall, the proportion of subjects with one or more treatment-emergent hypersensitivity reactions did not significantly differ between TE ADA-positive 11 (5.5%) and TE ADA-negative 58 (3.1%) subjects. The proportion of subjects with skin and subcutaneous tissue disorders did not significantly differ between TE ADA-positive 10 (5%) and TE ADA-negative 42 (2.4%) subjects (source: Integrated Summary of Immunogenicity, Table 20).

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. The effectiveness of the icotrokinra is primarily supported by the statistically significant treatment effects for achieving PASI 90 and/or IGA 0/1 (with ≥2 grade improvement from baseline) in Phase 3 psoriasis trials.

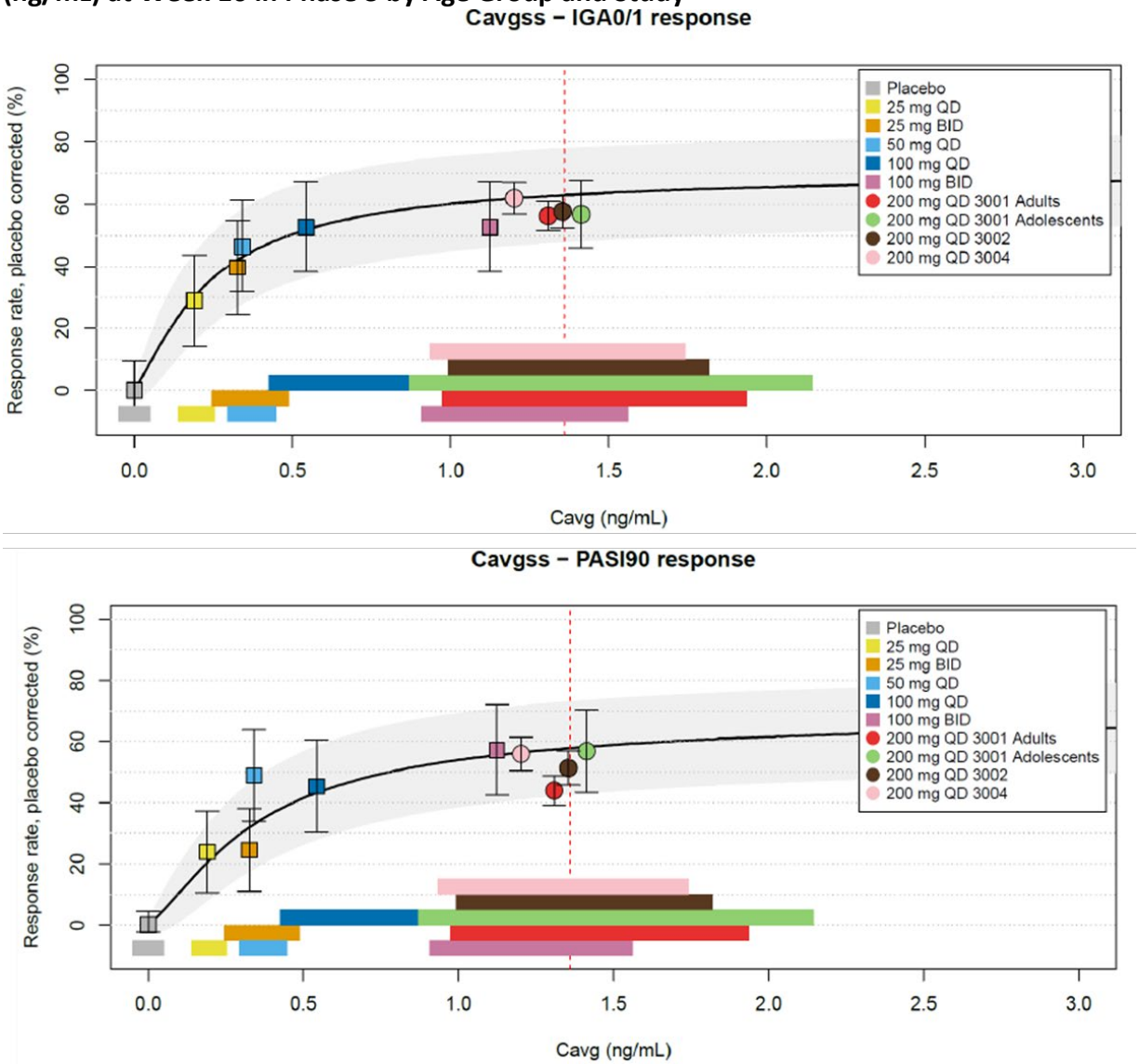
Exposure-Response Analysis

The response rates are on the flat portion of the exposure-response curve and there was no observed exposure-safety relationship. This supported the recommended dose of 200 mg QD for patients with moderate to severe PsO.

Supportive evidence of effectiveness from the clinical pharmacology program is derived from exposure-response analyses for efficacy. Based on the exposure-response analysis of Phase 3 trials, the icotrokinra 200 mg QD dose consistently provided high response rates across all quartiles of exposure when compared with placebo (Figure 9). The efficacy endpoints (PASI90 and IGA0/1) for the Phase 3 trials PSO3001, PSO3002, and PSO3004) versus the C_{avg} quartiles were similar with increasing exposure, suggesting that the response rates are on the flat portion of the exposure-response curve. In Study PSO3003, the IGA0/1 (overall) response rates were also consistently high across quartiles of exposure (see Sections 8.1 and 19.4.2.5.3). Adolescents may have comparable or better efficacy (in PASI90 score) compared with adults with overall similar exposures between adults and adolescents. Taken together, the 200 mg QD dosing regimen is effective for treating adults and adolescents who weight at least 40 kg with moderate to severe plaque PsO.

Refer to Section 19.4.6 for detailed E-R efficacy analyses and Section 7.1 for evaluation and definition of clinical endpoints.

Figure 9. Placebo-Corrected IGA0/1 and PASI90 Response Rates Versus Steady-state C_{avg} (ng/mL) at Week 16 in Phase 3 by Age Group and Study



Source: Population Pharmacokinetics and Exposure-Response Report (23 June 2025), Figures 11 and 12.
Abbreviations: IGA, investigator global assessment; PASI, psoriasis area and severity index; BID, twice daily; C_{avg}, average drug concentration; QD, once daily.
Horizontal colored bars represent 25th-75th percentile of PK post hoc steady-state exposure metrics. Boxes or circles and whiskers represent the observed, placebo-corrected, response rates and corresponding 95% CIs. Vertical dashed line represents simulated C_{avg} of 1.36 ng/mL for the 200 mg QD regimen based on Phase 1 and Phase 2 population PK model.

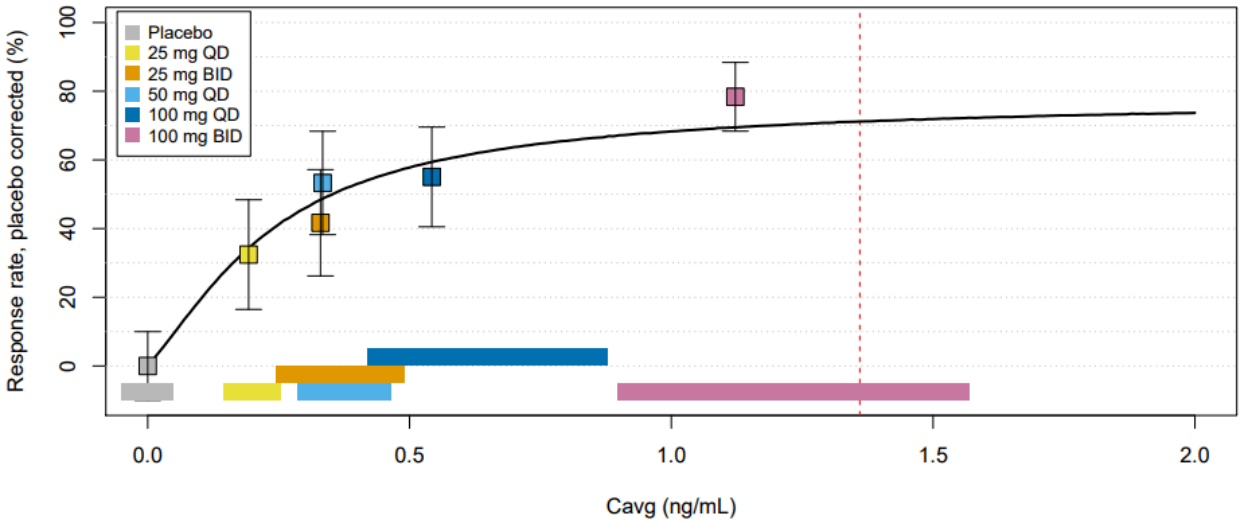
6.3.2.2. Is the Proposed Dosing Regimen Appropriate for the General Patient Population for Which the Indication is Being Sought?

Yes, from a clinical pharmacology perspective, the proposed dosing regimen of 200 mg QD is appropriate for the general PsO patient population. The proposed dosing regimen is supported by efficacy data as well as exposure-response analyses from Phase 3 trials PSO3001, PSO3002, PSO3003, and PSO3004.

Supportive Evidence for Dose-Selection for Phase 3 Studies

The selection of icotrokinra 200 mg QD dosing for the pivotal Phase 3 clinical trials PSO3001, PSO3002, PSO3003, and PSO3004 was based on the findings from a dose-ranging Phase 2 trial (PSO2001), modeled E-R analyses of efficacy data from the trial PSO2001, and human safety and tolerability data from the Phase 1 and Phase 2 trials (see Sections 19.4.2.4 and 19.4.6). In trial PSO2001, adult subjects with moderate to severe plaque PsO were randomized to receive icotrokinra immediate release film-coated tablet at various dosing regimens: 25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD, 100 mg BID, or placebo. The primary efficacy endpoint in Study PSO2001 was the proportion of subjects achieving PASI75 response at Week 16, defined as at least a 75% reduction from baseline in PASI total score, compared to placebo. The difference in the proportion of subjects achieving PASI75 response at Week 16 relative to placebo were as follows: 27.9% for 25 mg QD, 48.8% for 50 mg QD, 41.9% for the 25 mg BID, 55.8% for the 100 mg QD, and 69.4% for the 100 mg BID. Notably, the 100 mg BID dosing group demonstrated the highest treatment difference at Week 16 relative to placebo. Response plateaued at the highest administered dose (100 mg BID) and both a dose and an exposure-response modeling confirmed that the 100 mg BID dose resulted in the maximum efficacy across the doses studied in Phase 2 without evidence of dose-related safety or tolerability signals (Figure 10).

Figure 10. D/E-R Analyses: C_{avg} – PASI75 Response Rate at Week 16 in Phase 2 Study PSO2001



Source: Population Pharmacokinetics Report (March 25, 2024), Figure 3.
Abbreviations: E-R, exposure-response; C_{avg}, average icotrokinra concentration at steady-state; PASI, Psoriasis Area and Severity Index (PASI); QD, once daily; BID, twice daily
Black solid line represents model predicted response rate; red dashed line represents predicted median exposure metrics (Cavg=1.36ng/mL) of 200 mg QD regimen based on PopPK model from 1000 simulated subjects similar to those from the study; horizonal colored bars represent 25th-75th percentile of PK post hoc exposure metrics of each dosing regimen. The boxes and whiskers represent the observed, placebo-corrected, response rates and corresponding 95% confidence intervals.

Population PK and exposure-response analysis showed that average concentration (C_{avg}) of icotrokinra drives the efficacy and the 200 mg QD would provide comparable efficacy and C_{avg} exposure similar to 100 mg BID dose regimen (Figure 10). Therefore, to improve patients acceptability and compliance with the modified fasting requirements perspective (i.e.,

administration upon wakening on an empty stomach), a dose regimen of icotrokinra 200 mg QD was selected for the Phase 3 efficacy and safety trials.

According to the Applicant, pop-PK modeling and simulation from Phase 1 and Phase 2 data showed that with the 200 mg QD dose, the 90% prediction interval for the AUC of icotrokinra for adolescents with minimum weight of 40 kg would be within the range of the post hoc AUC in Study PSO2001. Therefore, the same dose regimen of 200 mg QD was used in adolescents and adults in Phase 3 PsO studies.

Selection of the Recommended Dosage for Patients With PsO

The icotrokinra 200 mg QD dose regimen was chosen as the recommended dose for patients with moderate to severe PsO based on the proportion of subjects achieving the coprimary endpoints IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 and PASI90 at Week 16 (Studies PSO3001, PSO3002, and PSO3004) and the proportion of subjects achieving the primary endpoint of IGA score of 0/1 (Scalp-Specific IGA score of 0/1) and ≥2-grade improvement from baseline at Week 16 (Study PSO3003). The 200 mg QD icotrokinra demonstrated a statistically significant improvement from baseline in IGA score of 0 or 1 and a ≥2-grade and PASI90 at Week 16 compared to patients who received placebo over 16 weeks (Table 8) (see Section 7.1). Based on these results, the 200 mg QD dosage is the recommended dosage for the treatment of moderate to severe PsO in adult and adolescent patients who weigh at least 40 kg. The pop-PK analysis of Phase 3 data from adult and adolescent subjects showed that exposures were comparable between adults and adolescents; therefore, the 200 mg QD dose is recommended dose for both adults and adolescents.

Table 8. Efficacy Results After Administration of Icotrokinra 200 mg Once Daily in Phase 3 Studies

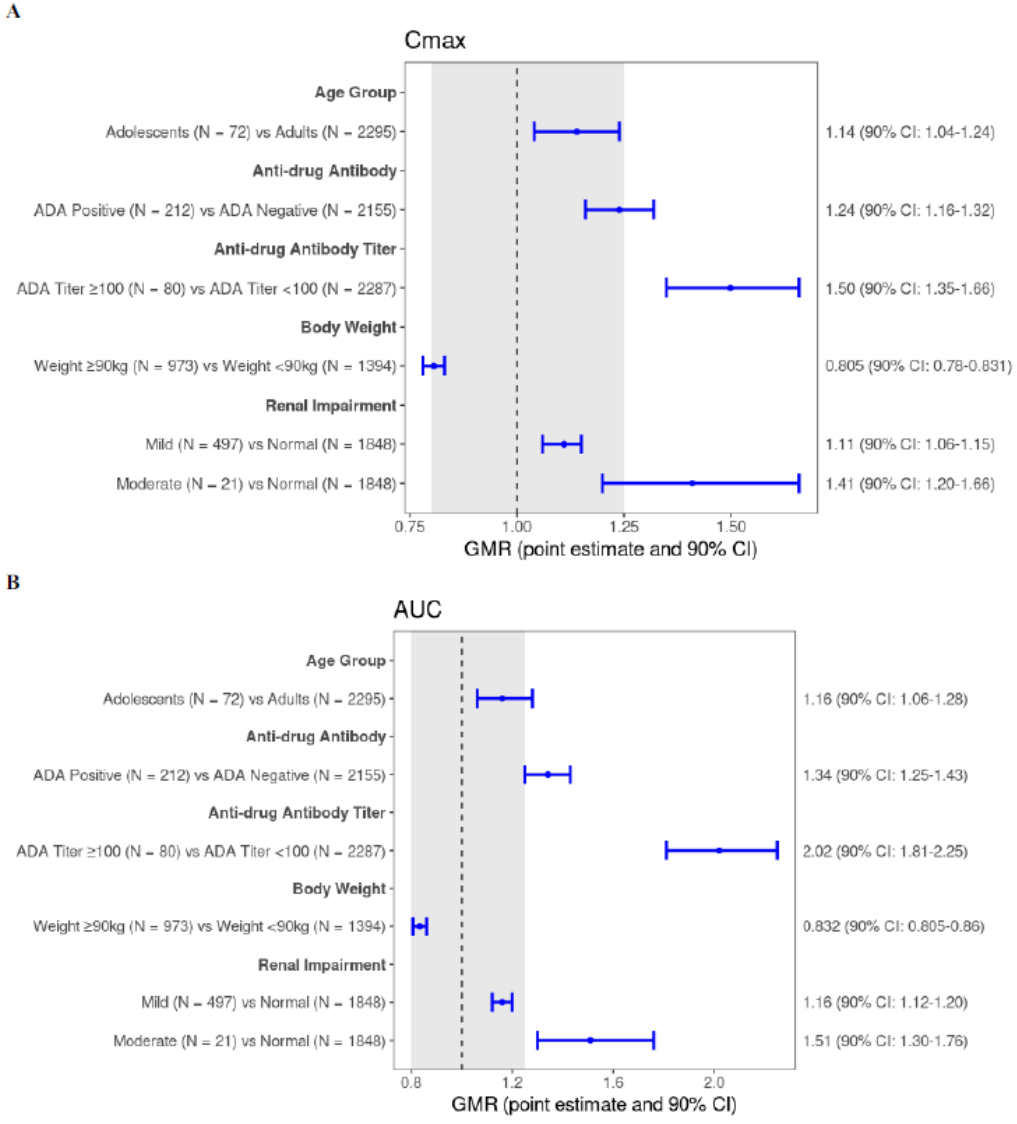
	PSO3001		PSO3002		PSO3003		PSO3004	
(Coprimary)	Icotrokinra	Placebo	Icotrokinra	Placebo	Icotrokinra	Placebo	Icotrokinra	Placebo
IGA 0/1 (Week 16)	64.7%	8.3%	68.5%	10.9%	56.7%	5.8%	70.5%	8.5%
Risk Diff. (95% CI)[a]	56.4% (50.4%, 61.7%)		57.6% (49.9%, 64.2%)		51.1% (42.1%, 58.8%)		62% (52.9%, 69.1%)	
PASI-90 (Week 16)	49.6%	4.4%	55%	3.8%			57.1%	1.2%
Risk Diff. (95% CI)[b]	45.1% (39.5%, 50.4%)		51.1% (44.5%, 57.3%)		Not included		56% (48.5%, 62%)	

Source: Reviewer's-generated table based in the primary Estimand results from phase 3 studies PSO3001 (Table 4), PSO3002 (Table 3), PSO3003 (Table 3) and PSO3004 (Table 3).
Abbreviations: IGA, investigator global assessment; PASI, psoriasis area and severity index; CI, confidence interval; Diff, difference
[a] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. For Study PSO3003, treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for special area involvement and BSA category using Mantel-Haenszel weights.
[b] Based on the Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

6.3.2.3. Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations Based on Intrinsic Patient Factors?

No alternative dosing regimens based on intrinsic patient factors (e.g., age, sex, body weight, immunogenicity, and renal impairment) are recommended (Figure 11). Monitoring for adverse reactions would be recommended in patients with moderate/severe renal impairment. Refer to Section 19.4.5 for detailed analysis regarding associations between subject covariates, PK parameters and exposure, and clinical outcomes.

Figure 11. Effects of Covariates on C_{max} and AUC From the Week 52 Population PK Model

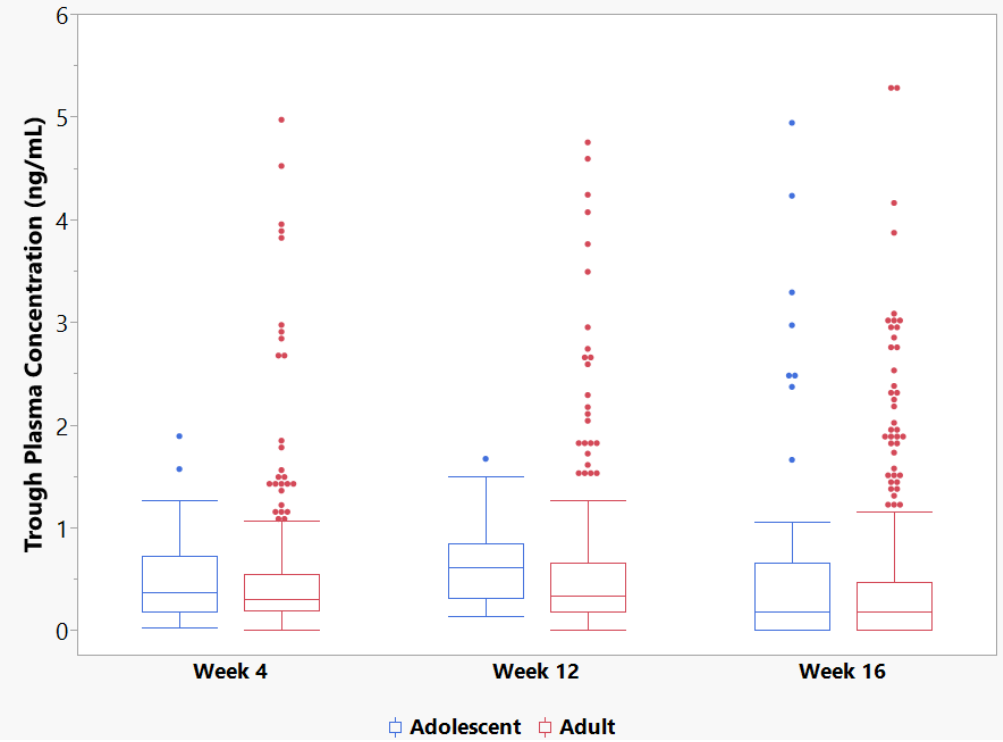


Source: Population PK and Exposure-Response Analysis Report, Figure 5.
Abbreviations: C_{max}, maximum plasma concentration; AUC, area under the plasma concentration time profile; GMR, geometric mean ratio; CI, confidence interval; N, number of subjects
Analysis at Week 52 in studies PSO3001 and PSO3003; Week 44 in study PSO3002; Week 24 in study PSO3004

Age

No dose adjustment is required based on age down to 12 years. Icotrokinra trough concentration following the administration of 200 mg QD in Phase 3 trial PSO3001 did not differ significantly between adults (N=551) and adolescent (N=56) subjects with PsO weighing at least 40 kg (Figure 12). In addition, there was no impact of age (12 to 87 years of age) on the PK of icotrokinra based on pop-PK analysis (Figure 11).

Figure 12. Box Plot of Trough Plasma Concentrations of Icotrokinra Through Week 16 by Age Group



Source: Reviewer-generated figure using ADPC data from Study PSO3001.

Sex

No dose adjustment is required based on sex. Population PK analysis determined that sex (67.7% male and 32.3% female) was not identified as a covariate affecting the apparent oral clearance (CL/F) and volume of distribution (V/F) of icotrokinra.

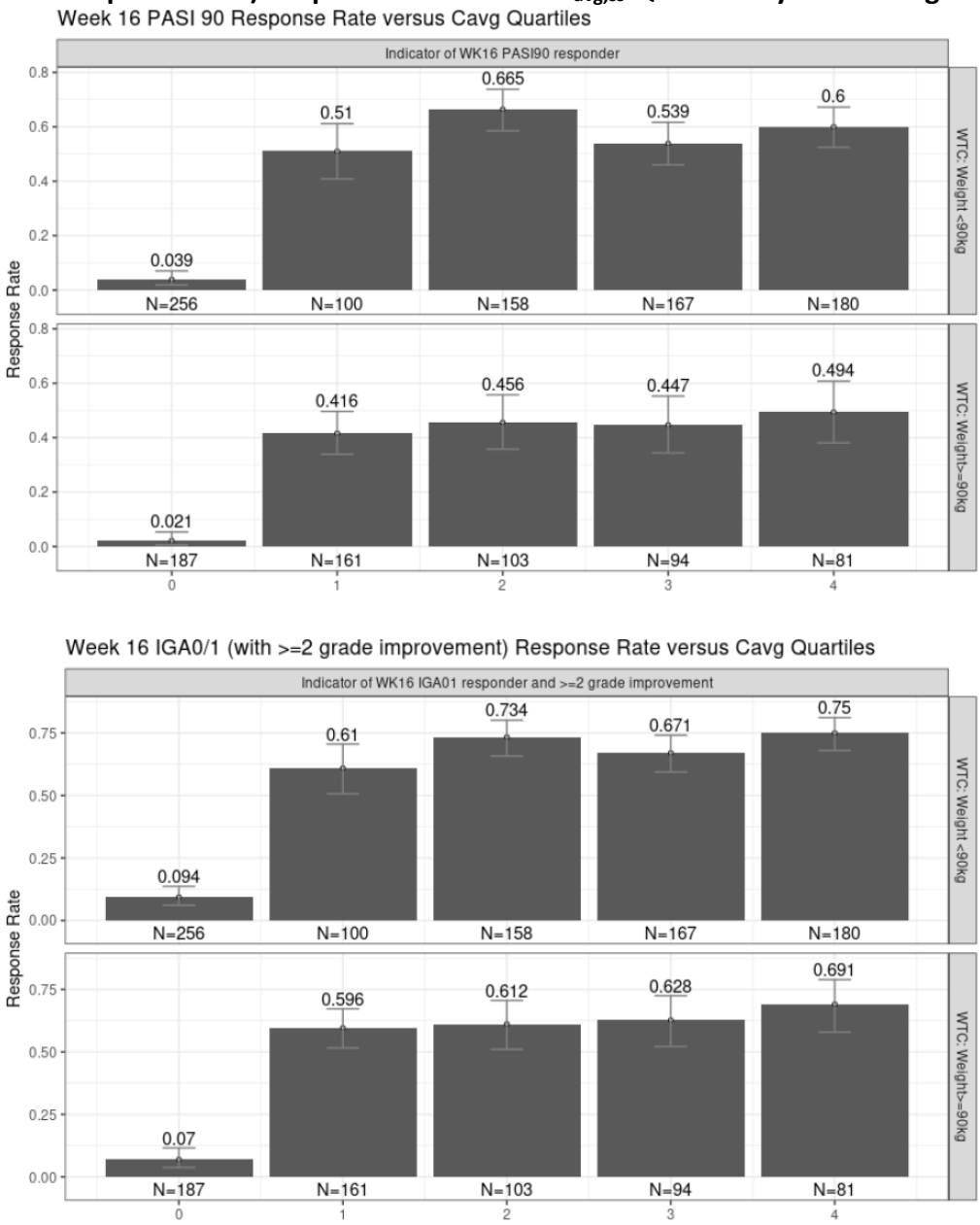
Body Weight

No dose adjustment is required based on body weight. Population PK analyses in adult and adolescent PsO subjects who weigh at least 40 kg showed that CL/F and V/F of icotrokinra increased with increasing body weight (see Section 19.4.5). The analysis demonstrated an inverse correlation between body weight and icotrokinra exposure levels. Body weight had an impact on exposure via standard allometric scaling conventions, with subjects weighing ≥90 kg having a 17% lower AUC compared with subjects weighing <90 kg (Figure 11). The observed

difference in exposure to icotrokinra attributed to body weight differences was deemed clinically insignificant.

The clinical responses (PASI90 and IGA0/1) were consistent across quartiles of exposure in adults with body weight both above and below 90 kg with slightly lower clinical response in subjects >90 kg (Figure 13). Due to the lack of apparent exposure-response by body weight subgroups, no dose adjustment is needed.

Figure 13. Pooled PSO3001, PSO3002, and PSO3004 Week 16 PASI90 and IGA0/1 (With ≥2 Grade Improvement) Response Rate Versus $C_{avg,ss}$ Quartiles by Adult Weight Group

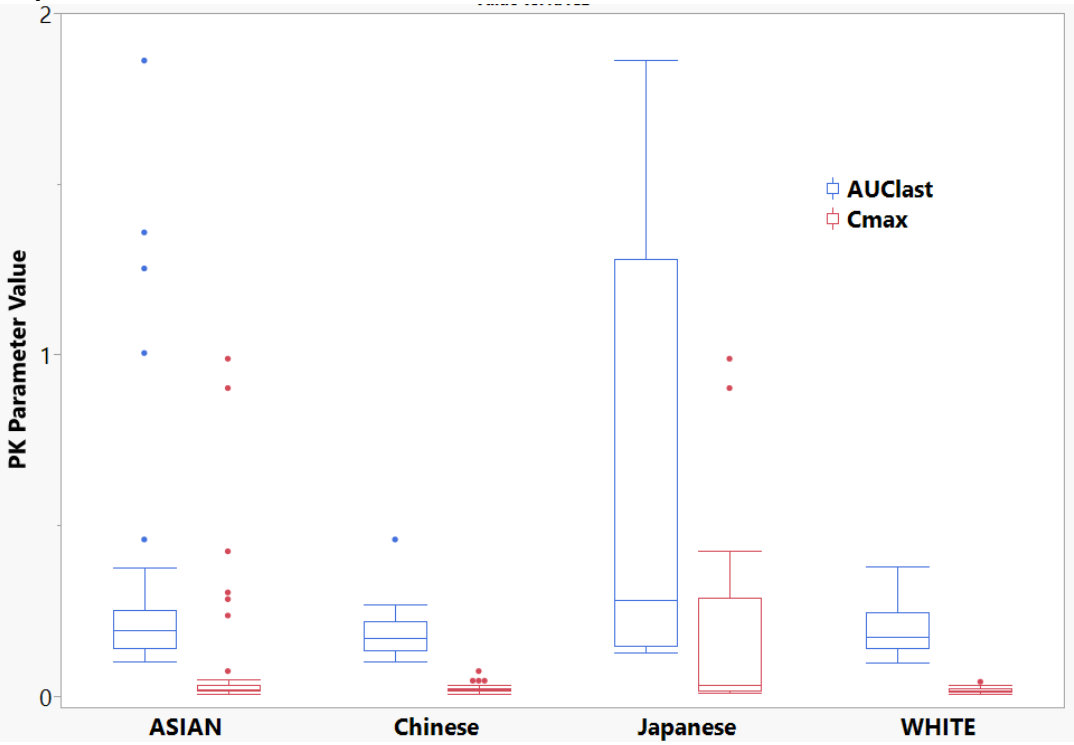


Source: Population PK/Exposure-Response Report, Figure 10.
Abbreviations: $C_{avg,ss}$, average drug concentration at steady state; N, number of participants; PK, pharmacokinetics; WK, Week

Race/Ethnicity

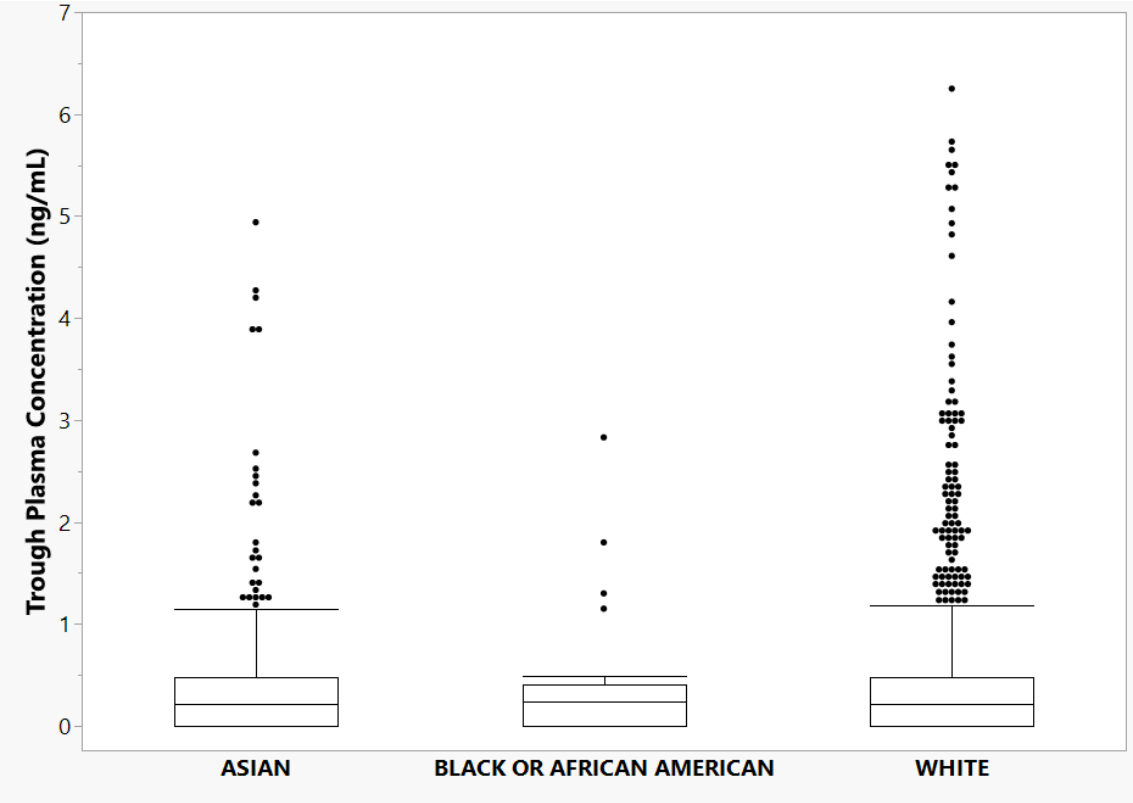
No dose adjustment is required based on race or ethnicity. A comparative PK analysis of icotrokinra was conducted across healthy Chinese (trials PSO1002 and PSO1004), Japanese (trial PSO1002), and White (Caucasian) (trial PN-235-01, and PSO1003) subjects following single oral administration of icotrokinra oral solution or immediate release tablet. There was relatively higher dose-normalized C_{max} and AUC_{last} in Japanese (N=18, 21%) subjects compared to Chinese (N=35, 40%) and White (N=34, 39%) subjects (Figure 14 and Table 4). However, the proportion of the observed dataset that fell within the Japanese population was relatively small as compared with White and Chinese populations. Thus, the finding of greater dose-normalized C_{max} and AUC among Japanese subjects should be interpreted with caution. In addition, the dose-normalized C_{max} and AUC_{last} are comparable between healthy White (N=34, 39%) and overall Asian (N=53, 61%) populations (Figure 14). The pooled trough plasma concentrations from the 4 phase 3 trials showed a comparable trough concentrations between Asian (N=340, 21%),White (N=1238, 76%), and Black or African American (N=23, 1.4%) populations (Figure 15).

Figure 14. Icotrokinra Dose-Normalized C_{max} and AUC_{last} After Single Oral Dose Administration of Icotrokinra 100, 300, or 1000 mg in Healthy Caucasian and Asian (Japanese and Chinese) Populations



Source: Viewer-generated Figure using ADPC dataset from trial PN-235-01, PSO1002, PSO1003, and PSO1004.
Trial PN-235-01 included subjects received a single dose of 100, 300, and 1000 mg. Only White population from Trial PN-235-01 were included in this analysis and 7 Asian subjects were excluded.
Trial PSO1002 included Japanese subjects dosed with icotrokinra 100 and 300 mg single doses and Chinese subjects dosed with icotrokinra 300 mg single dose.
Trial PSO1004 included Chinese subjects received a single dose of icotrokinra 100, 300, and 1000 mg.
Trial PSO1003 included subjects received a single dose of icotrokinra 100 mg in fasted state with 240 mL water (Treatment JD and Treatment JH).
Abbreviations: PK, pharmacokinetic; C_{max}, maximum concentration, AUC, area under the concentration-time profile

Figure 15. Icotrokinra Trough Concentration at Week 16 After the Administration of Icotrokinra 200 mg Once Daily in Phase 3 Trials Caucasian and Asian Populations with Moderate-to-Severe PsO



Source: Reviewer-generated Figure using ADPC dataset from trial PSO3001, PSO3002, PSO3003, and PSO3004.

In popPK analysis, race including 20.1% (N=514) Asian (2.9% [N=75] Japanese and 5.3% [N=135] Chinese), 1.7% (N=44) Black and 76% (N=1940) White was not identified as significant covariates affecting the clearance of icotrokinra (see Section 19.4.5).

Immunogenicity

No apparent impact of immunogenicity on safety and efficacy. Due to the similar duration of study intervention, data from phase 3 trials PSO3001 and PSO3003 were pooled for plasma icotrokinra concentration at Week 52. The trough plasma concentration of icotrokinra after the administration of icotrokinra 200 mg QD in Phase 3 trials increased in subjects who were ADA-positive compared to those who were ADA-negative (Figure 6). In addition, there was a trend toward increasing trough concentrations of icotrokinra with increasing ADA titer values (Figure 7) (see Section 6.3.1.4).

In pop-PK analysis, pot hoc C_{max} and AUC increased by 1.2- and 1.3-fold, respectively, in subjects with positive ADA compared with subjects who did not develop ADA (Figure 11). Subjects with peak ADA titer of ≥100 had a 1.5-fold higher C_{max} and a 2-fold higher AUC compared to subjects with peak ADA titers of <100 or who were ADA negative. The increase in exposure to

icotrokinra in ADA positive subjects or subjects with higher ADA titer is not considered as clinically meaningful.

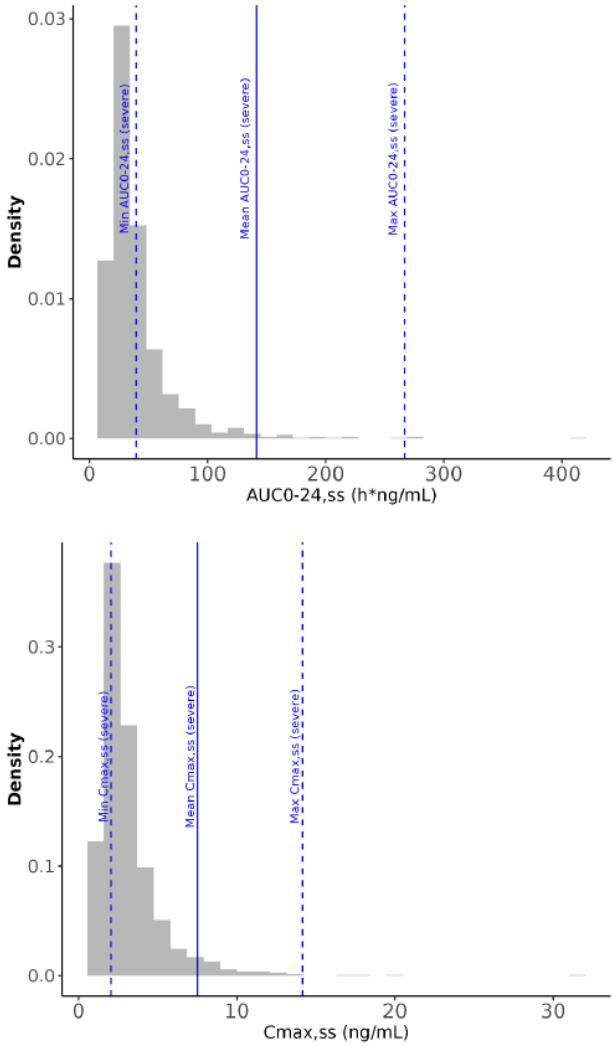
Renal Impairment

A dedicated renal impairment trial was conducted to evaluate the impact of moderate (eGFR 30 to 59 mL/min/1.73 m^2) and severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impairment on icotrokinra exposure compared to subjects with normal renal function (eGFR ≥90 mL/min/1.73 m^2) (trial PSO1007). Following the administration of a single dose of icotrokinra 200 mg, subjects with moderate renal impairment exhibited an approximate 1.79-, 2.41- and 2.47-fold increase in C_{max}, AUC_{last}, and AUC_{inf} of icotrokinra, respectively, compared to subjects with normal renal function. Similarly, subjects with severe renal impairment demonstrated 1.27-, 2.61-, and 2.78-fold increases in C_{max}, AUC_{last}, and AUC_{inf} of icotrokinra, respectively, compared to subjects with normal renal function (see Section 19.4.2.3).

According to the protocols for Phase 3 PSO3001, PSO3002, PSO3003, and PSO3004, subjects with eGFR <60 mL/min/1.73 m^2 were excluded from these clinical trials. In pop-PK analysis, mild (n=497) and moderate (n=21) renal impairment did not impact the exposure to icotrokinra where C_{max} and AUC increased by 1.1- and 1.16-fold, respectively, in subjects with mild RI and 1.4- and 1.5-fold, respectively, in subjects with moderate renal impairment. The median eGFR across all studies used in pop-PK analysis ranged from 87.7 to 119 mL/min/1.73 m^2 and median eGFR in phase 3 studies used in pop-PK analysis ranged from 89.8 to 96.9 mL/min/1.73 m^2 (see Section 19.4.5). Therefore, there is lack of adequate number of subjects across the wide range of renal function to support the prediction of the impact of moderate and severe renal impairment on the exposure to icotrokinra.

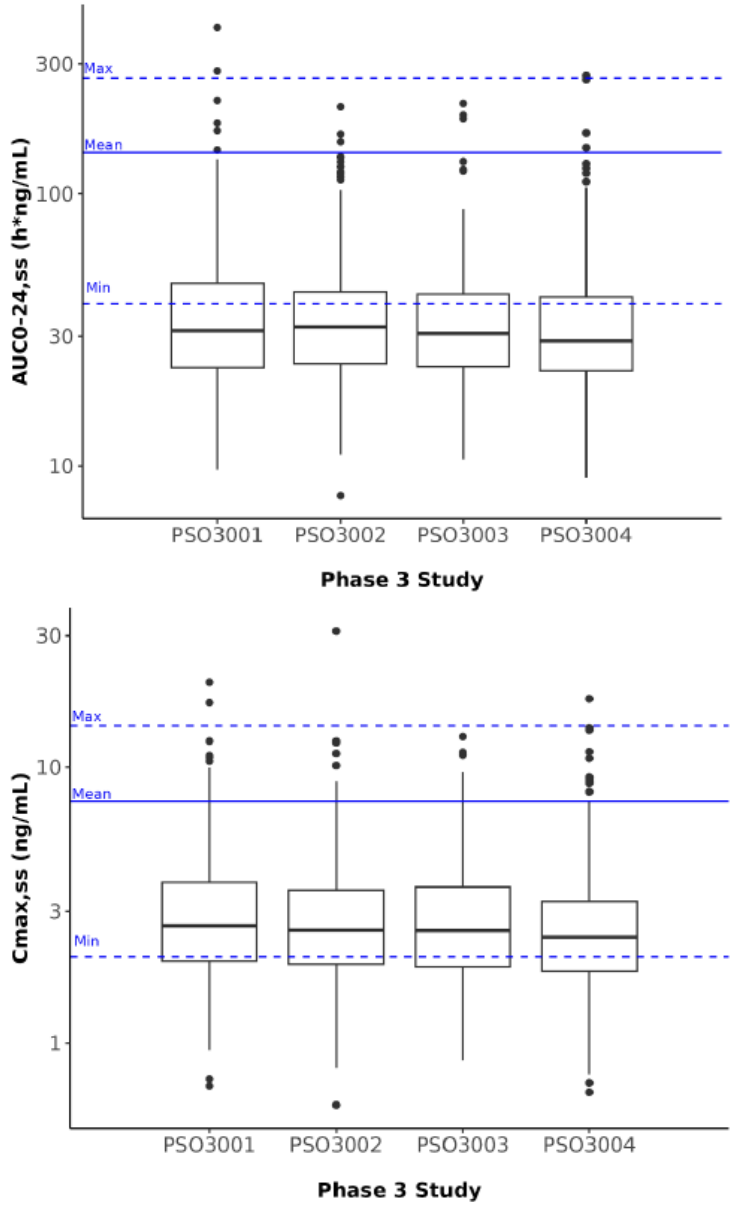
The Applicant anticipated that the steady state exposures in moderate and severe RI patients are within the range of exposures found in the icotrokinra phase 3 PsO trials (Figure 16 and Figure 17). Therefore, the Applicant has proposed no dose adjustments in patients with renal impairment.

Figure 16. Overlay of Icotrokinra Phase 3 Post Hoc Exposures (AUC and C_{max}) With Severe RI Exposures at Steady State



Source: Population PK and Exposure-Response Report, Appendix 8.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24,ss}$, steady-state area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; $C_{max,ss}$, steady-state maximum plasma icotrokinra concentration; max, maximum of steady-state PK metric from subjects with severe renal impairment in PSO1007; mean, mean of steady-state PK metric from subjects with severe renal impairment in PSO1007; min, minimum of steady-state PK metric from subjects with severe renal impairment in PSO1007; PK, pharmacokinetics; RI, renal impairment.
The blue solid and dashed lines are based on steady-state PK metrics from patients in PSO1007. The histogram represents the distribution of steady-state $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$ for patients in icotrokinra Phase 3 studies. The height of each bar corresponds to the frequency of values within each bin. The bins are defined by evenly spaced intervals along the x-axis, and the range of the histogram covers the full span of observed exposure values.

Figure 17. Overlay of Icotrokinra Phase 3 Post Hoc Exposures (AUC and C_{max}) by Study With Severe RI Exposures at Steady State (Semi-Log Scale)



Source: Population PK and Exposure-Response Report, Appendix 9.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24,ss}$, steady-state area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; $C_{max,ss}$, steady-state maximum plasma icotrokinra concentration; IQR, interquartile range; max, maximum of steady-state PK metric from subjects with severe renal impairment in PSO1007; mean, mean of steady-state PK metric from subjects with severe renal impairment in PSO1007; min, minimum of steady-state PK metric from subjects with severe renal impairment in PSO1007; PK, pharmacokinetics; RI, renal impairment.
The lower and upper hinges of the box plot correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5× IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5× IQR of the hinge. Data beyond the end of the whiskers are plotted individually.

The Agency conveyed to the Applicant that it was not acceptable to compare the mean/median exposure value in RI (particularly with the limited number of subjects and larger variability) with the range of exposures in Phase 3 trials which also applies to subjects with severe RI as the increase in exposure is relatively comparable between the moderate and severe RI groups (trial

PSO1007). Of note, subjects with eGFR < 60 mL/min/1.73 m^2 were excluded from the all phase 3 trials. Given these limitations and potential safety concerns with increased exposure, FDA initially recommend against administering icotrokinra to subjects with moderate or severe RI without dose adjustment. In response to an Information Request (dated 10/30/2025), the Applicant acknowledged the Agency's feedback but maintained that no dose adjustment is needed in patients with moderate or severe RI. The Applicant indicated that icotrokinra has a wide therapeutic safety margin based on the following justifications:

1. Icotrokinra has been studied across a wide range of doses in Phase 1 trials up to 1000 mg (e.g., Studies PN-235-01 [N=8] and PSO1004 [N=9]) with no dose-related adverse events were identified. In trial PSO1003, subjects received 50 mg of the high exposure delayed release tablet formulated with (b) (4) and no substantial AEs have been reported.
2. A Phase 2, randomized, placebo-controlled trial with 16 weeks of dosing in subjects with PsO (trial PSO2003) evaluated a 50-mg dose of icotrokinra using a delayed release tablet formulation with (b) (4) This dose resulted in icotrokinra exposures higher than that in subjects with moderate or severe renal impairment with the 200 mg IR formulation (Study PSO1007) without dose-dependent safety events identified and AE rates comparable to placebo treatment. Of note, trial PSO2003 is not included in this review because of lack of any regulatory utility due to the use of a different formulation. The mean $C_{max,ss}$ was 31.9 ng/mL (4.8-fold and 4.2-fold higher than moderate and severe RI patients, respectively). In addition, the highest observed concentration of 119 ng/mL was >8-fold higher than maximum predicted $C_{max,ss}$ for severe RI.
3. Analysis of Phase 3 subjects showed an exposure equal to or higher than the median severe RI exposure. The highest predicted Phase 3 $C_{max,ss}$ is 31.1 ng/mL which is more than 2-fold higher than highest predicted severe RI value of 14.1 ng/mL (Figure 16). According to the Applicant, there were similar proportions of AEs, SAEs, infections, and discontinuations between high and low exposure groups.
4. Direct comparison of Phase 3 subjects with and without moderate or severe RI showed similar rates of AEs, SAEs, and discontinuations between subgroups (Table 9).

Table 9. Number of Subjects With 1 or More Treatment-Emergent Adverse Events, Serious Adverse Events, or Adverse Events Leading to Study Agent Discontinuation Through Week 16 by Baseline Renal Impairment Status; Treated Subjects With a Baseline eGFR Measurement From Pooled Phase 3 Studies

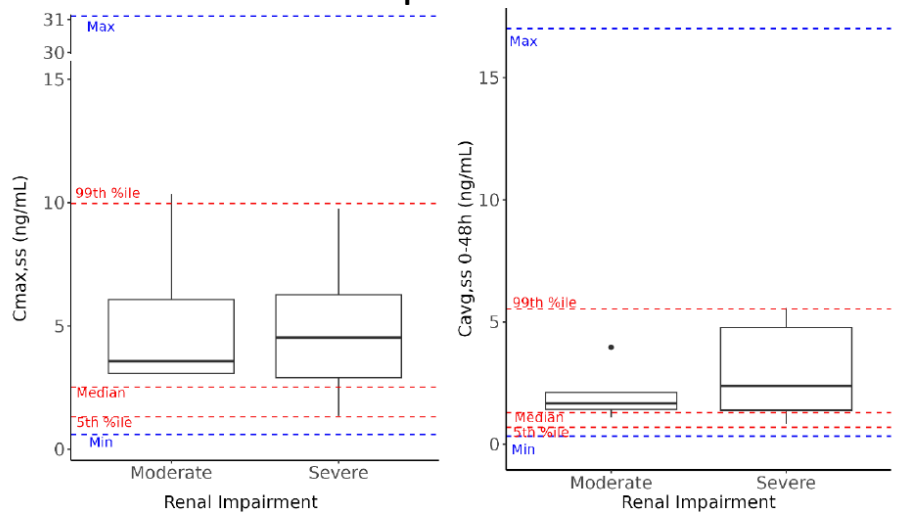
	Baseline Moderate to Severe Renal Impairment			
	Yes		No	
	Placebo	JNJ-77242113	Placebo	JNJ-77242113
Analysis set: Treated subjects with a baseline eGFR measurement	5	12	561	1281
Average duration of follow-up (weeks)	15.94	16.15	15.62	15.91
Subjects with 1 or more adverse events	1 (20.0%)	5 (41.7%)	294 (52.4%)	629 (49.1%)
Subjects with 1 or more serious adverse events	0	1 (8.3%)	12 (2.1%)	20 (1.6%)
Subjects with 1 or more adverse events leading to discontinuation of study agent	0	1 (8.3%)	17 (3.0%)	25 (2.0%)

Source: Applicant's response to Information request dated 10/30/2025, SDN 0018, Table 1.
Abbreviations: eGFR, estimated glomerular filtration rate; JNJ-77242113, icotrokinra

In consultation with the clinical review team, Table 9 demonstrated a higher rate of SAEs in subjects with higher baseline renal impairment and furthermore percentage discontinuation was also higher in subjects with renal impairment; but it could be argued that the condition of renal impairment at baseline may be a confounding factor for an SAE in and of itself due to comorbid medical conditions associated with renal impairment.

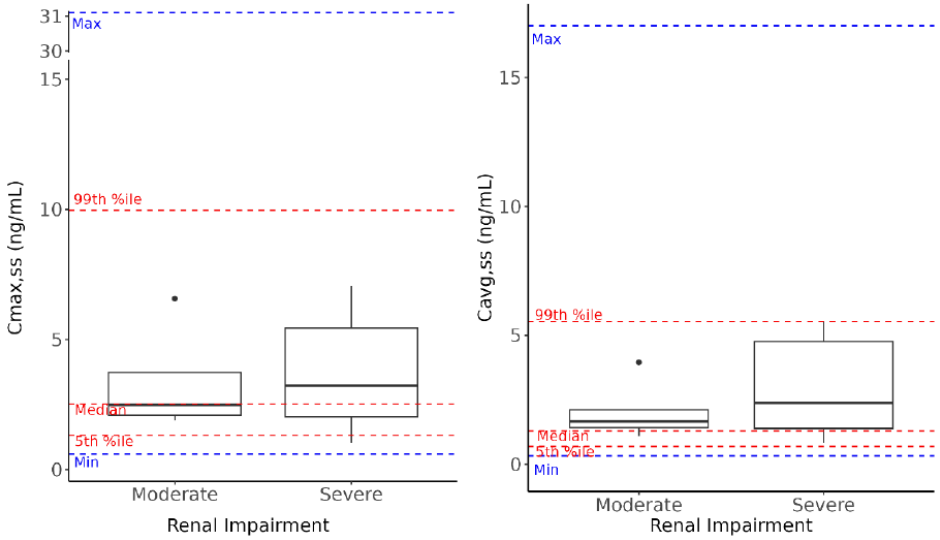
The safety analyses demonstrated that patients with moderate renal impairment experienced twice the infection rate of other patients, suggesting increased safety risk from overexposure at 200 mg QD (see Section 19.4.6). This would indicate that the same would be applicable in subjects with severe renal impairment. Despite the increased rate of infection that was similarly observed in moderate RI treated with placebo, the subject number is very limited (n=5) to conclude the increased risk is due to underlying disease rather than the drug. Given limited patients with moderate/severe RI, it is not possible to evaluate if those patients could present a steeper exposure-safety curve. Overall, the current data and analyses cannot rule out the possibility of an altered benefit-risk in PsO patients with moderate/severe RI. Considering icotrokinra is primarily renally cleared where an elevated PK and safety risk was observed in PsO patients with moderate RI (see Sections 19.4.6.3 and 19.4.6.4), FDA requested the Applicant to conduct pharmacokinetic modeling and simulation to identify appropriate dosing regimens (e.g., 100 mg QD, 200 mg QD, and 200 mg every other day [Q2D]) that achieve exposure matching with normal/mild renal impairment populations. In response to the information request (dated December 29, 2025), the Applicant provided simulated steady state concentrations of icotrokinra in subjects with moderate and severe renal impairment to compare with the observed concentrations of icotrokinra in Phase 3 PsO subjects following the administration of icotrokinra 100 mg QD, 200 mg QD, and 200 mg Q2D. Model-based simulations showed that the 200 mg Q2D and 100 mg QD dosing regimens in participants with moderate to severe renal impairment achieved $C_{avg,ss}$ concentrations within the range of exposures observed in Phase 3 psoriasis subjects with normal or mild renal impairment treated with the 200 mg QD dose (Figure 18 and Figure 19). The 200 mg QD dosing regimen achieved higher median exposures in moderate and severe renal impairment patients, but still within the overall exposure range of Phase 3 subjects (Figure 20).

Figure 18. Simulated $C_{max,ss}$ and $C_{avg,ss}$ Following 200 mg Q2D Dosing in Subjects With Moderate and Severe Renal Impairment



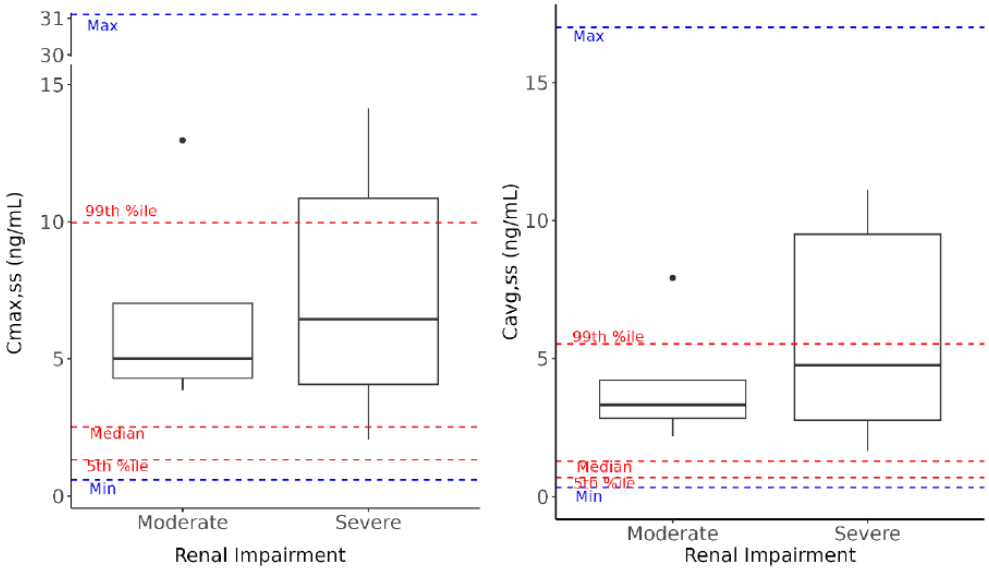
Source: Applicant's response to information requested (NDA 220149, SDN 0030, dated 12/29/2025, Figure 1).
$C_{avg,ss}$ was calculated as $AUC_{0\text{-}tau}/_{tau}$. Boxes represent the 25th, 50th (median), and 75th percentiles; whiskers reflect 1.5-fold the 25th and 75th percentiles; symbols reflect outliers. Red dashed lines indicate the 5th, 50th (median) and 99th percentiles of the values and blue dashed lines indicate the maximum and minimum values from the Phase 3 PsO population following 200 mg QD dosing predicted using the original population PK model.
Abbreviations: $C_{max,ss}$, maximum concentration at steady state; $C_{avg,ss}$, average concentration at steady state; Q2D, every other day; max, maximum; min, minimum; %ile, percentile

Figure 19. Simulated $C_{max,ss}$ and $C_{avg,ss}$ Following 100 mg QD Dosing in Subjects With Moderate and Severe Renal Impairment



Source: Applicant's response to information requested (NDA 220149, SDN 0030, dated 12/29/2025, Figure 2).
$C_{avg,ss}$ was calculated as $AUC_{0\text{-}tau}/_{tau}$. Boxes represent the 25th, 50th (median), and 75th percentiles; whiskers reflect 1.5 times the 25th and 75th percentiles; symbols reflect outliers. Red dashed lines indicate the 5th, 50th (median) and 99th percentiles of the values and blue dashed lines indicate the maximum and minimum values from the Phase 3 PsO population following 200 mg QD dosing predicted using the original population PK model.
Abbreviations: $C_{max,ss}$, maximum concentration at steady state; $C_{avg,ss}$, average concentration at steady state; QD, once daily; max, maximum; Min, minimum; %ile, percentile

Figure 20. Simulated $C_{max,ss}$ and $C_{avg,ss}$ Following 200 mg QD Dosing in Subjects With Moderate and Severe Renal Impairment



Source: Applicant's response to information requested (NDA 220149, SDN 0030, dated 12/29/2025, Figure 3).
$C_{avg,ss}$ was calculated as $AUC_{0\text{-}tau}/_{tau}$. Boxes represent the 25th, 50th (median), and 75th percentiles; whiskers reflect 1.5 times the 25th and 75th percentiles; symbols reflect outliers. Red dashed lines indicate the 5th, 50th (median) and 99th percentiles of the values and blue dashed lines indicate the maximum and minimum values from the Phase 3 PsO population following 200 mg QD dosing predicted using the original population PK model

Abbreviations: Cmax,ss, maximum concentration at steady state; Cavg,ss, average concentration at steady state; QD, once daily; Max, maximum; Min, minimum; %ile, percentile

Additionally, the Applicant conducted expanded safety analyses to assess whether patients with drug exposures similar to those expected in moderate or severe renally-impaired patients have increased safety risks. They divided Phase 3 psoriasis patients into "higher exposure" (≥1.64 ng/mL) and "lower exposure" (<1.64 ng/mL) groups, using $C_{avg,ss}$ of 1.64 ng/mL from Study PSO1007 as the cut-off since it represents the minimum drug level seen in moderate/severe renal impairment patients. The analysis included 751 higher-exposure participants from four Phase 3 studies with follow-up through the 120-day safety update. Results showed similar adverse event rates between higher exposure, lower exposure, and placebo groups at Week 16, and over long-term follow-up (808.8 patient-years), there was no increase in adverse events, serious adverse events, or treatment discontinuations in either exposure group. With 715 participants treated for at least 6 months and 537 for at least 1 year, the data demonstrated that patients with higher drug exposures comparable to those expected in renal impairment showed no increased safety risks compared to patients with lower exposures (Table 10), supporting the safety of standard dosing in moderate or severe renally-impaired patients.

Table 10. Summary of Treatment-Emergent Adverse Events, Serious Adverse Events, or Adverse Events Leading to Study Agent Discontinuation by Exposure Category and Period in the Four Phase 3 Studies

	Through Week 16			Through SUR Data Cut-off Date[a]	
		JNJ-77242113		JNJ-77242113	
	Placebo	Low C_{avg}	High C_{avg}	Low C_{avg}	High C_{avg}
Analysis set: Safety analysis set	568	831	465	1348	751
Average duration of follow-up (weeks)	15.63	15.83	16.08	53.96	56.16
Total subject-years of follow-up	170.1	252.0	143.3	1394.0	808.3
Subjects with events per 100 subject-years					
Adverse events	265.58 (295/111.1)	244.16 (420/172.0)	210.12 (216/102.8)	152.42 (967/634.4)	139.23 (531/381.4)
Serious adverse events	7.15 (12/167.8)	5.60 (14/250.2)	4.93 (7/142.1)	4.02 (55/1368.9)	4.55 (36/790.7)
Adverse events leading to discontinuation of study agent	10.11 (17/168.1)	7.19 (18/250.2)	5.63 (8/142.1)	2.67 (37/1386.4)	2.61 (21/803.8)

Source: Applicant's response to information requested (NDA 220149, SDN 0030, dated 12/29/2025, Table 4).
[a] Includes data for subjects randomized to JNJ-77242113, data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113, and data from 77242113PSO3002 after Week 24 for deucravacitinib subjects who switched over to receive JNJ-77242113.
Note: For 77242113PSO3001, data that occurred during the withdrawal period (on or after Week 28 and before retreatment) were excluded for subjects who were rerandomized to placebo at Week 24.
Note: Adverse events are coded using MedDRA Version 27.0.
Note: Crude pooling method was used to calculate the rates. Crude rates are calculated as (number of subjects with adverse events/total subject-years at risk)*100.
Note: Low Cavg is defined as Cavg lower than 1.64 ng/mL, the lowest simulated Cavg at steady state in participants with moderate to severe renal impairment. High Cavg is defined as Cavg ≥1.64 ng/mL.
Abbreviations: Cavg, average concentration; JNJ-72242113, icotrokinra

The review team agreed that the standard dosing of icotrokinra 200 mg QD could be used for patients with moderate or severe renal impairment with monitoring of potential adverse events in patients with eGFR <60 mL/min.

Hepatic Impairment

No dosage adjustment is recommended for patients with any degree of hepatic impairment (HI) (Child-Pugh score A to C). No formal PK hepatic impairment studies were conducted because it is unlikely that HI would impact the metabolism of icotrokinra. In pop-PK analysis, aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT), total bilirubin, albumin, and gamma glutamyl transferase (GGT) did not impact the CL/F and V/F of icotrokinra (see Section 19.4.5). In addition, Phase 3 studies excluded subjects with ALT and/or AST >2xULN laboratory results at screening and subjects with severe, progressive, or uncontrolled hepatic disorders.

6.3.2.4. Are There Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food Effect

Icotrokinra should be administered upon waking on an empty stomach with water. After taking Icotrokinra, subjects should wait at least 30 minutes before eating food.

Trial PSO1003 evaluated the impact of meal type and mealtime on the exposure to icotrokinra following the administration of a single dose of Icotrokinra 100 mg immediate release tablet (Lot # G014, Phase 2 formulation) in healthy adult subjects (see Section 19.4.2.2.1). In trial PSO1003, a high-fat meal decreased C_{max}, AUC_{last}, and AUC_{inf} of icotrokinra by approximately 66%, 58%, and 57%, respectively, and delayed t_{max} by 1.5 hour with comparison to the administration of icotrokinra in the fasted state (Figure 21). The high-fat meal consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 100 g of hashed brown potatoes (fried with butter), and 240 mL of whole milk (containing approximately: fat: 500 to 600 calories, carbohydrates: 250 calories, proteins: 150 calories, total: 900 to 1000 calories). Similarly, a low-fat meal decreased C_{max}, AUC_{last}, and AUC_{inf} of icotrokinra by approximately 52%, 47%, and 43%, respectively, and delayed t_{max} by 3 hours with comparison to fasted state. The low-fat meal consisted of 240 mL of milk (1% fat), one boiled egg, and one packet of flavored instant oatmeal made with water (containing approximately: fat: 100 to 125 calories, total: 400 to 500 calories). With respect to timing of the meals, similar reduction in systemic bioavailability was observed when taking icotrokinra 2 hours (~40%) or 1 hour (~50%) after a high-fat meal (approximately 1000 calories, 50% from fat) or when the tablet is taken 30 minutes (~40%) before a high fat-meal (Figure 21).

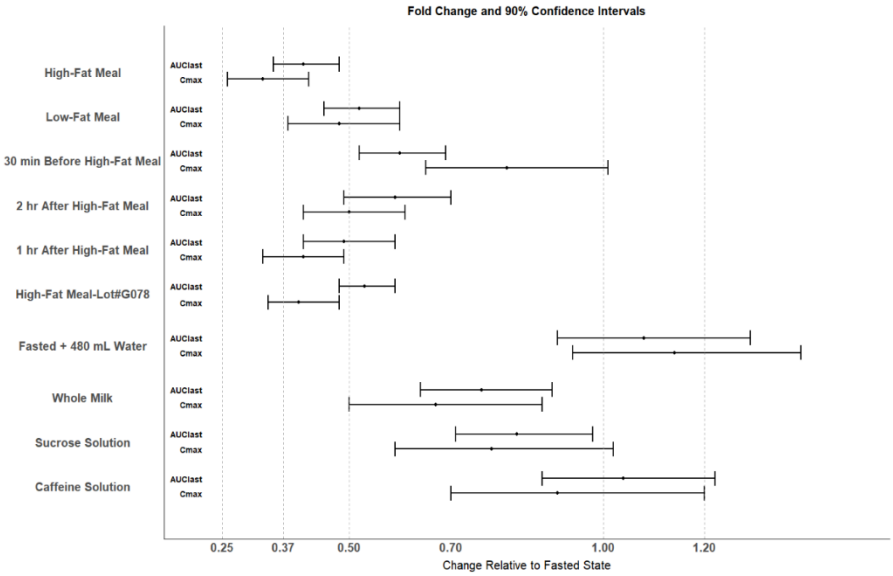
Trial PSO1006 evaluated the impact of high-fat meal on the exposure to icotrokinra following the administration of a single dose of icotrokinra 200 mg immediate release tablet (Lot # G078, clinical formulation) in healthy adult subjects (see Section 19.4.2.2.2). A high-fat meal decreased C_{max}, AUC_{last}, and AUC_{inf} of icotrokinra clinical formulation by approximately 59%, 47%, and 43% respectively, with comparison to the administration of icotrokinra in the fasted state (Figure 21). Results from trials PSO1003 and PSO1006 indicate that type of food showed minimal difference on the reduced absorption.

The Applicant evaluated the impact of the type of coadministered liquids on the bioavailability of icotrokinra 200 mg in trial PSO1009 (see Section 19.4.2.2.3). After fasting for at least 10 hours, the administration of icotrokinra with 240 mL whole milk or a sucrose solution decreased C_{max} by 33% and 22% and AUC_{last} by 24% and 16%, respectively, compared to when icotrokinra administered with 240 mL noncarbonated water (Figure 21). The administration of icotrokinra with 240 mL caffeine solution (Study PSO1009) or 480 mL noncarbonated water (Study PSO1003) did not impact the rate and extent of icotrokinra absorption compared to when

icotrokinra administered with 240 mL noncarbonated water after fasting for at least 10 hours (Figure 21).

In phase 3 trials, subjects were instructed to take the drug every day upon waking with 240 mL water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention). Accordingly, it is recommended that icotrokinra should be taken upon waking on an empty stomach with water at least 30 minutes before eating food.

Figure 21. Fold Change and 90% Confidence Intervals for the Impact of Meal Type and Mealtime on Exposure to Icotrokinra Following the Administration of a Single Dose of 100 mg in Immediate-Release Tablet Formulation



Source: Reviewer-generated figure based on the findings from trials PSO1003 and PSO1006.
Abbreviations: HF, high-fat, LF, low-fat.
Lot # G078 is the clinical formulation used in trial PSO1006.
Lot # G014 is phase 2 formulation used in trial PSO 1003 to assess the impact of high-fat meal, low-fat meal, 30-min before high-fat meal, 1 and 2 hours after a high-fat meal and fasted with 480 mL water.
The reference Fasted State represents the administration of icotrokinra 100 mg immediate release table with 240 mL after an overnight fasting of at least 10 hours.
Icotrokinra was administered under fasted or fed conditions, after at least 10 hours of fasting or within 10 minutes after completion of a high-fat or low-fat breakfast, but no more than 30 minutes after the start of breakfast. For the impact of mealtime on the exposure to icotrokinra, icotrokinra was administered 2 hours after completion of a high-fat breakfast (i.e., breakfast started 2.5 hours before study intervention intake), 1 hour after completion of a high-fat breakfast (i.e., breakfast started 1.5 hour before study intervention intake), or 30 minutes before the start of a high-fat breakfast. The breakfasts were ingested entirely within 30 minutes.
To compare the exposure to icotrokinra when in the presence of 240 mL of noncarbonated water, whole milk, sucrose solution or caffeine solution, icotrokinra 100 mg immediate release tablet (Lot # G078, phase 3 formulation) was administered after an overnight fasting of at least 10 hours. Intake of water was not allowed from approximately 1 hour before until approximately 1 hour after administration of icotrokinra except for the water or liquid used for icotrokinra administration), after which time, water was allowed ad libitum.
The high-fat breakfast consisted of (or its equivalent) 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 100 gm of hashed brown potatoes (fried with butter), and 240 mL of whole milk (containing approximately: fat: 500 to 600 calories, carbohydrates: 250 calories, proteins: 150 calories, total: 900 to 1000 calories). The low-fat breakfast consisted of (or its equivalent) 240 mL of milk (1% fat), 1 boiled egg, and 1 packet flavored instant oatmeal made with water (containing approximately: fat: 100 to 125 calories, total: 400 to 500 calories).

Drug-Drug Interactions

Drug-drug interaction (DDI) potential of icotrokinra was evaluated through in vitro studies focusing on CYP enzymes and transporter systems. In vitro assessments revealed that icotrokinra lacks inhibitory activity against several cytochrome P450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) and transporters (OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, BCRP, and BSEP). In addition, icotrokinra was not found as an inducer of CYP1A2, CYP2B6 and CYP3A4 in vitro (see Section 19.4).

At the highest C_{max} of 7.9 ng/mL (4.2nM) reported from Study PSO1004 following the administration of a single dose icotrokinra 300 mg immediate release tablet as Phase 2 formulation, there is low potential of icotrokinra to modulate CYP enzymes and transporters in vivo.

Acid-Reducing Agents

Icotrokinra is freely soluble in acidic pH (≥125 mg/mL at pH 1.2) and practically insoluble in basic pH (0.0623 mg/mL at pH 9.0). In addition, icotrokinra is a BCS Class 4 compound (low solubility, low permeability) with estimated low oral bioavailability (approximately <1%). Therefore, any reduction in the already limited absorption could result in clinically meaningful decreases in efficacy. Acid-reducing agents (ARAs) are commonly prescribed medications which may decrease the absorption of icotrokinra. FDA requested the Applicant to conduct a PK analysis using data from Phase 3 trials to compare the exposure to icotrokinra with and without the concomitant use of acid-reducing and to provide a summary of efficacy in subjects with and without the concomitant use of ARAs. In response to the FDA information request (dated 10/29/2025, SDN 0017), the Applicant's analysis demonstrated that a total of 87 (6.7%) of 1296 subjects exposed to icotrokinra in the Phase 3 trials (PSO3001, PSO3002, PSO3003 and PSO3004) received ARAs at least once during the 16-week period in the PK dataset. PK analysis at Week 4 and 16 showed comparable icotrokinra trough concentration between subjects who received ARAs and those who did not. The geometric mean trough concentration at Week 4 was 0.38 and 0.35 ng/mL and at Week 16 it was 0.44 and 0.39 ng/mL in those who received ARAs and those who did not, respectively (see Applicant's response to Information Request dated 10/29/2025, SDN 0017, in DARRTS). These results suggest that ARAs (including proton pump inhibitors) may not impact the PK of icotrokinra. The most common proton pump inhibitors used in phase 3 studies include omeprazole, pantoprazole, and esomeprazole.

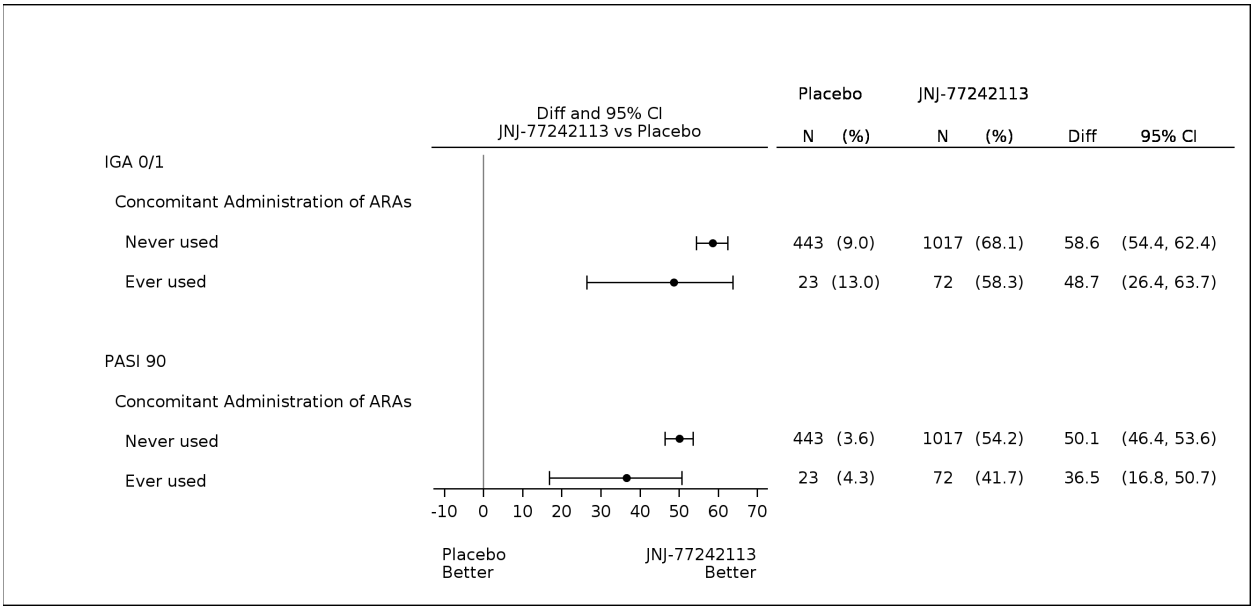
PopPK analysis was used to compare icotrokinra exposure with and without concomitant use of ARAs. The analysis was based on the total PK population (n=1296) who received at least one dose of icotrokinra from Week 0 to Week 16, including 87 patients who took ARAs (ARAs ever used) and 1209 patients who never took ARAs (ARAs never used). Analysis of the estimated icotrokinra $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ showed no meaningful differences in icotrokinra exposure between subjects with concomitant administration of ARAs compared with those without concomitant administration of ARAs (see the Applicant's response to information request dated 10/29/2025, SDN 0017, in DARRTS).

In order to determine the need for a drug interaction study with ARAs, FDA requested the Applicant to submit dissolution data and similarity (f2) value in different media (i.e., pH 1.2 versus pH 6.8 and pH 1.2 versus pH 4.5). In response to this information request (dated 10/29/2025, SDN 0016), there was a very rapid dissolution (100% within 10 minutes) at pH 1.2 (0.1M HCl) and pH 6.8 (0.05M sodium phosphate) and slower dissolution (83% within 30 minutes, >85% drug release at 45 minutes) at pH 4.5 (0.05M sodium acetate). Hence, the provided dissolution data showed no potential impact of ARAs on icotrokinra PK (see Applicant response to Information Requested dated 10/29/2025, SDN 0016).

Efficacy analysis of the coprimary endpoints (PASI 90 and IGA 0/1 at Week 16) in PsO Phase 3 studies (PSO3001, PSO3002, and PSO3004) was conducted when icotrokinra was concomitantly used with and without concomitant administration of ARAs. There were treatment differences of icotrokinra versus placebo in both populations (ARAs ever used and ARAs never used). A treatment difference of 58.6% (90% CI: 54.4%, 62.4%) in the IGA (Overall) Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 16 was observed in subjects never used ARAs and a treatment difference of 48.7% (90% CI: 26.4%, 63.7%) was observed in subjects ever used ARAs (Figure 22). In addition, there was a treatment difference of 50.1% (90% CI: 46.4%, 53.6%) in the PASI90 Score at Week 16 in subjects never used ARAs and 36.5% (90% CI: 16.8%, 50.7%) in subjects ever used ARAs. In trial PSO3003, there was a treatment difference of 48.8% (90% CI: 38.8%, 57.3%) in the IGA (Overall) Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 16 in subjects never used ARAs and 73.3% (90% CI: 41.4%, 92.2%) in subjects ever used ARAs (see Applicant's response to Information Request dated 10/29/2025, SDN 0017, in DARRTS). These point estimates were associated with high variability and wide CIs due to the small ample size of the ARAs ever used Group and no concreate conclusions can be made.

Overall, the PK or efficacy of icotrokinra were not meaningfully impacted by concomitant use of ARAs. In addition, the modulation of gastric pH by the concomitant use of ARAs is unlikely to impact the solubility and dissolution of icotrokinra in the small intestine and therefore is unlikely to impact its extent of absorption.

Figure 22. Proportion Difference and 95% CI in IGA (Overall) Score of 0 or 1 and a ≥2-Grade Improvement From Baseline and PASI 90 at Week 16 by Concomitant Administration of ARAs in Pooled Phase 3 Studies PSO3001, PSO3002 and PSO3004



Source: Applicant's response to information request dated 10/29/2025, SDN 0017, in DARRTS, Figure 2.
Abbreviations: IGA, investigator Global Assessment Score; PASI, psoriasis area and severity index; CI, confidence interval; Diff, difference; N, number of subjects; JNJ-77242113, icotrokinra.
Note: 95% confidence interval for difference in proportions was based on the Miettinen-Nurminen method using Mantel-Haenszel weights adjusted by study.
Note: Concomitant Administration of ARAs is defined by use at any time between Week 0 and Week 16. Acid-reducing agents were defined by ATC level 2 code of A02 "Drugs for acid-related disorders."

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

In support of the NDA, the Applicant submitted the following four Phase 3 trials, three Phase 2 trials, in addition to seven clinical pharmacology studies:

- Three Phase 3 controlled trials in subjects with moderate to severe plaque psoriasis (BSA≥10%, PASI ≥12, IGA≥3):
  - PSO3001 (included adolescent population ≥12 years to <18 years of age)
  - PSO3002 (included deucravacitinib 6 mg as an active comparator arm)
  - PSO3004 (included deucravacitinib 6 mg as an active comparator arm)
- One Phase 3 placebo-controlled trial in subjects with moderate-to-severe plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar)
  - PSO3003 (plaque psoriasis [BSA≥1%, IGA≥2] with at minimum moderate special area [scalp, genital and/or palmoplantar] involvement; included adolescent population ≥12 years to <18 years of age)

All four Phase 3 studies are ongoing to continue to collect safety and efficacy data for up to 3 years of icotrokinra exposure.

- Three Phase 2 placebo-controlled trials
  - PSO2001 (dose ranging).
  - PSO2002 (Long term extension for PSO2001).
  - PSO2003 (dose ranging).

The table below provides a summary of the aforementioned trials submitted for icotrokinra to treat moderate to severe psoriasis in adults who are candidates for systemic therapy or phototherapy, as well as a separate listing of clinical pharmacology studies.

Table 11. Clinical Trials Relevant to this NDA

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
	Controlled Studies to Support Efficacy and Safety						
PSO3001	Phase 3, randomized, PBO controlled, DB Randomized withdrawal at 28 weeks for icotrokinra responders (icotrokinra arm) OLE: 104 weeks	Icotrokinra: 200 mg oral tablet once daily Placebo: matching oral tablet once daily	Primary: • IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 • PASI 90 at Week 16	DB, PC period: 16 weeks RW period: 28 weeks OLE: 104 weeks	Planned 600 Actual 684	Adults and adolescents with moderate to severe plaque psoriasis	Centers: 138 Countries: 15
PSO3002	Phase 3, randomized, DB placebo and active controlled	Icotrokinra 200 mg oral tablet once daily Placebo: matching oral tablet once daily Deucravacitinib 6 mg oral tablet once daily	Primary: • IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 • PASI 90 at Week 16	DB, PC period: 16 weeks DB, AC period: 24 weeks OLE: 132 weeks	Planned 750 Actual 774	Adults with moderate to severe plaque psoriasis	Centers: 149 Countries: 13
PSO3003	Phase 3, randomized, DB placebo controlled	Icotrokinra: 200 mg oral tablet once daily Placebo: matching oral tablet once daily	Primary: • IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16	DB, PC period: 16 weeks OLE: 140 weeks Route of administration: Oral 200 mg tablet QD	Planned 300 Actual 311	Adults and adolescents with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar)	Centers: 69 Countries: 10

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO3004	Phase 3, randomized, DB placebo and active controlled	Icotrokinra 200 mg oral tablet once daily Placebo: matching oral tablet once daily Deucravacitinib 6 mg oral tablet once daily	Primary: • IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 • PASI 90 at Week 16	DB, PC period: 16 weeks DB, AC period: 24 weeks OLE: 132 weeks	Planned 675 Actual 731	Adults with moderate to severe plaque psoriasis	Centers 114 Countries 11
	Phase 2 Studies						
PSO2001	Randomized, double-blind, placebo-controlled, dose ranging, parallel group, multicenter, interventional study.	Number treated: Icotrokinra • 25 mg QD (N=43) • 50 mg QD (N=43) • 100 mg QD (N=43) • 25 mg BID (N=41) • 100 mg BID (N=42) • Placebo (N=43)	Primary: • PASI 75 at Week 16	16 Weeks	Planned 240 Actual 255	Adults with moderate to severe plaque psoriasis	Centers 60 Countries 10
PSO2002	Multicenter, long-term extension, dose-ranging study to evaluate efficacy and safety. Control randomization: Continued from PSO2001, with placebo arm receiving treatment	Number treated: Icotrokinra • 25 mg QD (N=35) • 50 mg QD (N=39) • 100 mg QD (N=40) • 25 mg BID (N=40) • 100 mg BID (N=38) • Placebo to 100 mg QD (N=35) **oral 25 and 100 mg tablets	To evaluate long-term clinical response of icotrokinra treatment. Primary: • PASI 75 at Week 36	36 weeks	Planned N/A Actual 227	Adults with moderate to severe plaque psoriasis	Centers 56 Countries 10

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO2003	Multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability.	Drug (established name): Icotrokinra Number treated: Icotrokinra with (b) (4) • 10 mg QD (N=31) • 50 mg QD (N=34) • Placebo (N=24) Duration: 16 weeks Route of administration: Oral 10 mg and 50 mg tablets	Primary: • PASI 75 at Week 16	16 Weeks	Planned 80 Actual 89	Adults with moderate to severe plaque psoriasis	Centers 34 Countries 6
Studies to Support Safety							
	Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
PN-235-01	Randomized DB placebo controlled single and multiple ascending dose	Part 1: SAD Cohort 1: PN-235, 10 mg Cohort 2: PN-235, 25 mg Cohort 3: PN-235, 100 mg Cohort 4: PN-235, 300 mg Cohort 5: PN-235, 1000 mg Part 2: MAD (q d for 10 days) Cohort 6: PN-235, 10 mg Cohort 7: PN-235, 25 mg Cohort 8: PN-235, 100 mg Cohort 9: PN-235, 300 mg Cohort 10: PN-235,	To assess the safety, tolerability, PK, PD, bioavailability of delayed-release tablet formulation of PN-235 relative to a solution, and effect of an (b) (4)	SAD: single doses MAD: q d for 10 days	Planned 102 Enrolled 107 Randomized 107 Completed 103	Healthy men and women of NCBP, aged 18-65 years inclusive	Aus

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
		1000 mg Cohort 13 (sigmoidoscopy assessments): PN-235, 100 mg Part 3: single dose of PN-235 on days 1, 8, 15, and 22 Cohort 11: PN-235, 25 mg oral solution PN-235, 25 mg DR tablet PN-235, 25 mg DR tablet with (b) (4) in fasted condition PN-235, 25 mg DR tablet with (b) (4) in fed					

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO1002-	Randomized, double-blind, placebo-controlled, single dose, and SAD study to investigate safety, tolerability, and PK. Healthy Japanese and Chinese participants aged 20 to 60 years, inclusive.	Parts 1 and 2: Icotrokinra 100 mg IR tablet (oral) Cohort 1: Icotrokinra 100 mg (1×100 mg) Cohort 2: Icotrokinra 300 mg (3×100 mg) Cohort 3: Icotrokinra 300 mg (3×100 mg) Placebo: Matching IR tablet without icotrokinra Part 3 Cohort 4: Icotrokinra 50 mg	To evaluate the safety, tolerability, and PK of icotrokinra after single dose and SAD administration as DR and IR tablet formulations, respectively, in healthy Japanese participants (Cohorts 1, 2, and 4). To evaluate the safety, tolerability, and PK of icotrokinra after single oral dose administration as an IR tablet formulation in healthy Chinese participants (Cohort 3).	Single dose	Treated: 36	Healthy Japanese and Chinese participants aged 20 to 60 years, inclusive.	JPN

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO1003	Single-dose, open-label, randomized, crossover, multipart, multicenter study.	Icotrokinra 100 mg, 30 mL (3.3 mg/mL solution, oral) Icotrokinra 100 mg (IR tablet, oral) Part 1: Single dose of 100 mg IR tablet formulation under fasted and fed (high-fat breakfast) conditions and 100 mg icotrokinra solution formulation under fasted conditions Part 2: 4-way crossover, single-dose Icotrokinra 10 mg (DR tablet, oral) Icotrokinra 25 mg (DR tablet, oral) Icotrokinra 100 mg (IR tablet, oral) Cohort 1: single dose of 2 DR tablet strengths of icotrokinra 10 mg and 25 mg with (b) (4) under fasted conditions	To assess the rate and extent of bioavailability of icotrokinra IR tablet formulation relative to an oral solution formulation under fasted conditions.	Single dose	Planned 114 Treated 100	Healthy men and women (non-childbearing potential) aged 18 to 60 years, inclusive.	BEL, NLD
PSO1004	Open-label, single-dose study to evaluate PK, safety, and tolerability.	Cohort 1: Icotrokinra 100 mg; 1×100 mg Cohort 2: Icotrokinra 300 mg; 3×100 mg	To assess the PK of icotrokinra following single oral administration.	Single dose	Planned: 30 Enrolled: N/A/ Randomized: 29 Completed:29	Healthy Chinese men and women, aged 18 to 55 years, inclusive.	CHN: 1

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO1006	single-dose, open-label, randomized, 3-way crossover study in healthy participants.	Group A: 1 Phase 3 200 mg icotrokinra tablet, fasted condition Group B: 1 Phase 3 200 mg icotrokinra tablet, fed (high-fat breakfast) condition Group C: 2 Phase 2 100 mg icotrokinra tablet, fasted condition	To assess the rate and extent of absorption and the bioavailability of icotrokinra when administered as Phase 3 IR tablet formulation relative to the Phase 2 IR tablet formulation under fasted conditions.	Single dose	Planned: 24 Enrolled:24 Randomized:24 Completed: 23	Healthy men and women (non-childbearing potential), aged 18 to 60 years, inclusive.	BEL: 1

Trial Number	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
PSO1007	Open-label, single-dose, parallel-group PK study.	Icotrokinra: 200 mg IR film-coated tablets (oral) Single dose 1 day	To evaluate the PK of icotrokinra after a single oral dose of 200 mg in adult participants with impaired renal function compared to adult participants with normal renal function.	Single dose	Planned 24-28 Completed 26	Healthy participants and participants with severe renal impairment or ESRD not on dialysis (Part A) and participants with moderate renal impairment (Part B), aged 18 to 80 years, inclusive.	DEU (2)
PSO1009	Open-label, randomized, crossover study to assess the effect of different types of coadministered oral liquids on the relative oral bioavailability of icotrokinra tablet formulation.	Icotrokinra: 200 mg IR tablet (oral), fasted condition Treatment A (reference): single dose with 240 mL of noncarbonated water. Treatment B (Test 1): single dose with 240 mL of caffeine solution. Treatment C (Test 2): single dose with 240 mL of whole milk. Treatment D (Test 3): single dose with 240 mL of sucrose solution	To evaluate the effect of different types of coadministered oral liquids on the relative bioavailability of the IR tablet formulation of icotrokinra.	Single dose	Planned 240 Completed 231	Healthy men and women (non-childbearing potential or of childbearing potential and practicing a highly effective method of contraception), aged 18 to 60 years, inclusive.	BEL (1)

Source:
Abbreviations:

7.2. Review Strategy

This application was submitted in electronic common technical document format and entirely electronic. The electronic submission included protocols, statistical analysis plans, clinical trial reports, and Statistical Analysis Software transport datasets in Study Data Tabulation Model and Analysis Data Model format. The clinical study reports and datasets in the initial submission were in the following network path:

Original submission: \\CDSESUB1\EVSPROD\nda220149\0001\m5

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. 77242113PSO3001 (ICONIC-LEAD)

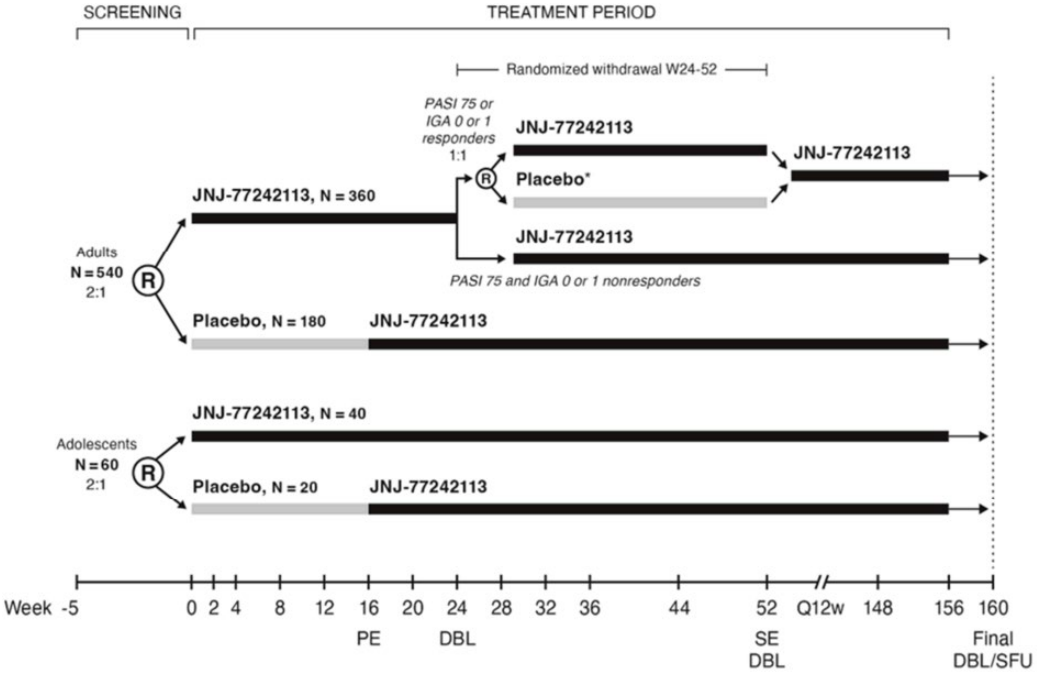
Trial Design

The Applicant conducted a randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 trial (77242113PSO3001; ICONIC-LEAD) in subjects ≥12 years of age with moderate-to-severe plaque psoriasis. The trial consisted of:

- A 5-week screening period
- A blinded placebo-controlled period from Week 0 to Week 16
- A randomized withdrawal and retreatment period from Week 24 through Week 52
- An open-label long-term extension period from Week 52 to Week 156.

The trial was designed to enroll and randomize approximately 600 subjects in a 2:1 ratio to icotrokinra 200 mg once daily or placebo. Randomization was performed separately for adult and adolescent subjects. Randomization of the adult group was further stratified by baseline weight category (≤90 kg, >90 kg) and geographic region. Randomization of the adolescent group was stratified by geographic region.

Figure 23. Trial Design Schematic for ICONIC-LEAD



Source: ICONIC-LEAD Clinical Study Report Synopsis, p. 6
* Participants will be retreated with JNJ-77242113 after a loss of ≥50% PASI improvement observed at Week 24.
Abbreviations: DBL=database lock; PE=primary endpoint; Q12W=once every 12 weeks; R=randomization; SE=secondary endpoint; SFU=safety follow-up visit

Key Inclusion Criteria

- ≥12 years of age at the screening visit
- Diagnosis of plaque psoriasis, with or without psoriatic arthritis (PsA), for at least 26 weeks prior to the first administration of study intervention.
- Total body surface area (BSA) ≥10% at screening and baseline.
- Total Psoriasis Area and Severity Index (PASI) ≥12 at screening and baseline.
- Total Investigator Global Assessment (IGA) ≥3 at screening and baseline.
- Candidate for phototherapy or systemic treatment for plaque psoriasis.

Study Endpoints

The coprimary efficacy endpoints were IGA 0/1 response, defined as achieving an IGA score of cleared (0) or minimal (1) and at least a two-grade improvement from baseline, at Week 16, and PASI-90 response, defined as achieving at least a 90% improvement from baseline in PASI total score, at Week 16.

Investigator's Global Assessment

Induration (I) (averaged over all lesions; may use the National Psoriasis Foundation Reference card for measurement)

- 0=no evidence of plaque elevation
- 1=minimal plaque elevation,=0.25 mm
- 2=mild plaque elevation,=0.5 mm
- 3=moderate plaque elevation,=0.75 mm
- 4=severe plaque elevation, >1 mm

Erythema (E) (average over all lesions)

- 0=no evidence of erythema, hyperpigmentation may be present
- 1=faint erythema
- 2=light red coloration
- 3=moderate red coloration
- 4=bright red coloration

Scaling (S) (averaged over all lesions)

- 0=no evidence of scaling
- 1=minimal; occasional fine scale over less than 5% of the lesion
- 2=mild; fine scale dominates
- 3=moderate; coarse scale predominates
- 4=severe; thick, scale predominates

Total Average=(I + E + S) / 3 (average will be calculated in the device but not displayed. Numeric result will be included in data transfer).
Physician's Static Global Assessment based upon above Total Average

- 0=Cleared, except for residual discoloration
- 1=Minimal – majority of lesions have individual scores for I + E + S / 3 that averages 1
- 2=Mild – majority of lesions have individual scores for I + E + S / 3 that averages 2
- 3=Moderate – majority of lesions have individual scores for I + E + S / 3 that averages 3
- 4=Severe – majority of lesions have individual scores for I + E + S / 3 that averages 4

Note: Scores should be rounded to the nearest whole number. If total ≤ 1.49, score=1; if total ≥1.50, score=2.

Psoriasis Area and Severity Index

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of the disease is calculated as follows.

In the PASI system, the body is divided into four regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20%, and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and

scaling, which are each rated on a scale of 0 to 4 (0=none, 1=slight, 2=moderate, 3=severe, and 4=very severe).
The scale for estimating the area of involvement for psoriatic lesions is outlined below.

- 0=no involvement
- 1=1% to 9% involvement
- 2=10% to 29% involvement
- 3=30% to 49% involvement
- 4=50% to 69% involvement
- 5=70% to 89% involvement
- 6=90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

- The neck is considered part of the head.
- The axillae and groin are part of the trunk.
- The buttocks are part of the lower extremities.

The PASI formula is:
$PASI=0.1\ (E_h + I_h + S_h)\ A_h + 0.3\ (E_t + I_t + S_t)\ A_t + 0.2\ (E_u + I_u + S_u)\ A_u + 0.4\ (E_l + I_l + S_l)\ A_l$
Where E=erythema, I=induration, S=scaling, and A=area

The multiplicity-controlled secondary efficacy endpoints were:

- Between the icotrokinra and the placebo group
  - Proportion of subjects who achieve an IGA score of cleared (0) at Week 16
  - Proportion of subjects who achieve a PASI-75 response at Week 4
  - Proportion of subjects who achieve a PASI-90 response at Week 8
  - Proportion of subjects who achieve a PASI-75 response at Week 16
  - Proportion of subjects who achieve a PASI-100 response at Week 16
  - Proportion of subjects (with a baseline scalp-specific IGA (ss-IGA) score ≥2) who achieve an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline at Week 16
  - Proportion of participants (with a baseline Psoriasis Symptom and Sign Diary (PSSD) symptom score >0) who achieve PSSD symptom score of 0 at Week 8
  - Proportion of subjects (with a baseline PSSD Itch score ≥4 points) who achieve at least a 4-point improvement from baseline in PSSD Itch score at Week 4
  - Proportion of subjects (with a baseline PSSD Itch score ≥4 points) who achieve at least a 4-point improvement from baseline in PSSD Itch score at Week 16
  - Proportion of subjects (among subjects with a baseline PSSD symptom score >0) who achieve PSSD symptom score of 0 at Week 16

- Between the icotrokinra group and the withdrawal group
  - Proportion of subjects (among PASI-75 responders randomized at Week 24) who achieve a PASI-75 response at Week 52
  - Proportion of subjects (among PASI-90 responders randomized at Week 24) who achieve a PASI-90 response at Week 52

- Time to loss of PASI-75 response through Week 52 among PASI-75 responders randomized at Week 24
- Time to loss of PASI-90 response through Week 52 among PASI-90 responders randomized at Week 24

Scalp-Specific Investigator Global Assessment *(ss-IGA)*

The ss-IGA instrument is used to evaluate the disease severity of scalp psoriasis. The lesions are assessed in terms of the clinical signs of redness, thickness, and scaliness which are scored as: absence of disease (0), very mild disease (1), mild disease (2), moderate disease (3), and severe disease (4).

Psoriasis Symptom and Sign Diary

The PSSD will be utilized in the adult and adolescent population and includes patient-reported outcomes (PRO) questionnaires designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit. There are two versions of the PSSD: a 24-hour recall version that asks the participant to answer the questions thinking about the last 24 hours and a 7-day recall version asking the participant to answer the questions thinking about the last 7 days. Both versions of the PSSD are self-administered PRO instruments and include 11 items in total, with 5 items covering symptoms (itch, pain, stinging, burning, and skin tightness) and 6 covering participant-observable signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding). A 0 to 10 numerical rating scale for severity is used. For both versions, two subscores will be derived each ranging from 0 to 100: the psoriasis symptom score and the psoriasis sign score. Additionally, for both versions, an item-level score will be derived for the PSSD itch item. The PSSD itch score will range from 0 to 10. For all scores, a higher score indicates more severe disease.

Statistical Analysis Plan

Analysis Sets

The SAP specified the following analysis sets:

- Enrolled: All subjects who signed the informed consent form (ICF).
- Randomized: All subjects who were randomized at Week 0 in the trial.
- Randomized at Week 24: All subjects who were re-randomized at Week 24 in the trial.
- Full Analysis Set (FAS): All subjects who were randomized at Week 0 in the trial.
- Per Protocol (PP): The per protocol analysis set (PP) includes a subset of subjects in the full analysis set (FAS) who were in general compliance with the protocol. Compliance is defined as subjects in FAS and meet the following criteria:
  - Had a total BSA ≥10% at the screening and baseline visit
  - Had a total PASI score ≥12 at the screening and baseline visit
  - Had a total IGA score ≥3 at the screening and baseline visit
  - Had an overall compliance of study treatment at least 80% and ≤120% prior to Week 16

  Subjects with intercurrent events (ICEs) 1 and 2 will be included in the per protocol

analysis set (see definition of these ICEs below).

- Safety Analysis Set: All randomized subjects who took at least 1 dose of study intervention.
- PK Analysis Set: All randomized subjects who received at least 1 dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
- Immunogenicity Analysis Set: All randomized subjects who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.

Estimands

The SAP specified the following as the main estimand for the coprimary endpoints:

- *Treatments*: Icotrokinra and placebo.
- *Population*: Subjects ≥12 years of age with moderate to severe plaque psoriasis.
- *Endpoints*: IGA response and PASI-90 response.
- *Intercurrent Events (ICEs) and Handling Strategies*: The SAP specified (1) discontinuation of treatment due to lack of efficacy, or due to an adverse event (AE) of worsening of psoriasis; (2) initiation of other medication or therapy that could improve psoriasis; and (3) discontinuation of treatment for other reasons than ICE (1) as ICEs. The SAP specified using a composite variable strategy for ICEs (1) and (2), where subjects who experience the ICEs are considered nonresponders, and a treatment policy strategy for ICE (3), where data collected after the ICE are used as-is in the analysis.
- *Population-level Summary Measure*: The SAP specified the difference in proportions between icotrokinra and placebo groups as the population-level summary.

For the key secondary efficacy endpoints at or prior to Week 16, the SAP specified that the estimands for the corresponding endpoints would be the same as the main estimand for the coprimary endpoints.

For the key secondary efficacy endpoints at Week 52, the SAP specified the following estimand:

- *Treatments*: Continuation of icotrokinra 200 mg QD versus withdrawal group (placebo).
- *ICEs and Handling Strategies:* Same ICEs (1)–(3) as those defined for the coprimary efficacy endpoints. In addition, the SAP defined ICE (4) as meeting criteria of loss of ≥50% Week 24 PASI improvement and specified using the composite variable strategy to handling ICE (4).
- *Endpoint:* See Table 12.
- *Population*: See Table 12.
- *Population-level Summary Measure*: See Table 12.

Table 12. Variables, Populations and Population-Level Summaries for Key Secondary Endpoints at Week 52

Variable	Population	Population Level Summary
Achieving a PASI-75 response at Week 52	Adult subjects with moderate to severe plaque psoriasis who are PASI-75 responders randomized at Week 24	Difference in proportions
Achieving a PASI-90 response at Week 52	Adult subjects with moderate to severe plaque psoriasis who are PASI-90 responders at Week 24	
Time to loss of PASI-75 through Week 52	Adult subjects with moderate to severe plaque psoriasis who are PASI-75 responders randomized at Week 24	Hazard ratio (HR) vs. placebo
Time to loss of PASI-90 through Week 52	Adult subjects with moderate to severe plaque psoriasis who are PASI-90 responders randomized at Week 24	

Source: ICONIC-LEAD Statistical Analysis Plan, p. 52
Note: For subjects, experiencing multiple ICEs, ICE (2) and (4) would override ICE (3)
Abbreviations: PASI, Psoriasis Area and Severity Index

Analysis Method

The SAP specified analyzing the coprimary endpoints using a two-sided (α=0.05) Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by age group (adults, adolescents), baseline weight category for adults (≤90 kg in adults, >90 kg in adults, adolescents), and geographic region (America, European Union, and Asia-Pacific). The difference in response rates between the icotrokinra group and the placebo group at Week 16 and their corresponding 95% confidence intervals (CIs) using the Miettinen-Nurminen method would be calculated adjusting for age group, baseline weight category for adults, and geographic region using Mantel-Haenszel (MH) weights.

Multiplicity Adjustment Plan

The SAP specified testing the coprimary endpoints first at the 5% significance level and proceeding to test the key secondary endpoints only if both the coprimary endpoints were statistically significant. Multiplicity was controlled across the key secondary endpoints by employing the serial gatekeeping procedure, where the key secondary endpoints were grouped into four tiers and all tests within a tier must be statistically significant based on Bonferroni-Holm's procedure to continue to the next tier. The tiers were defined in the SAP as shown in Table 13.

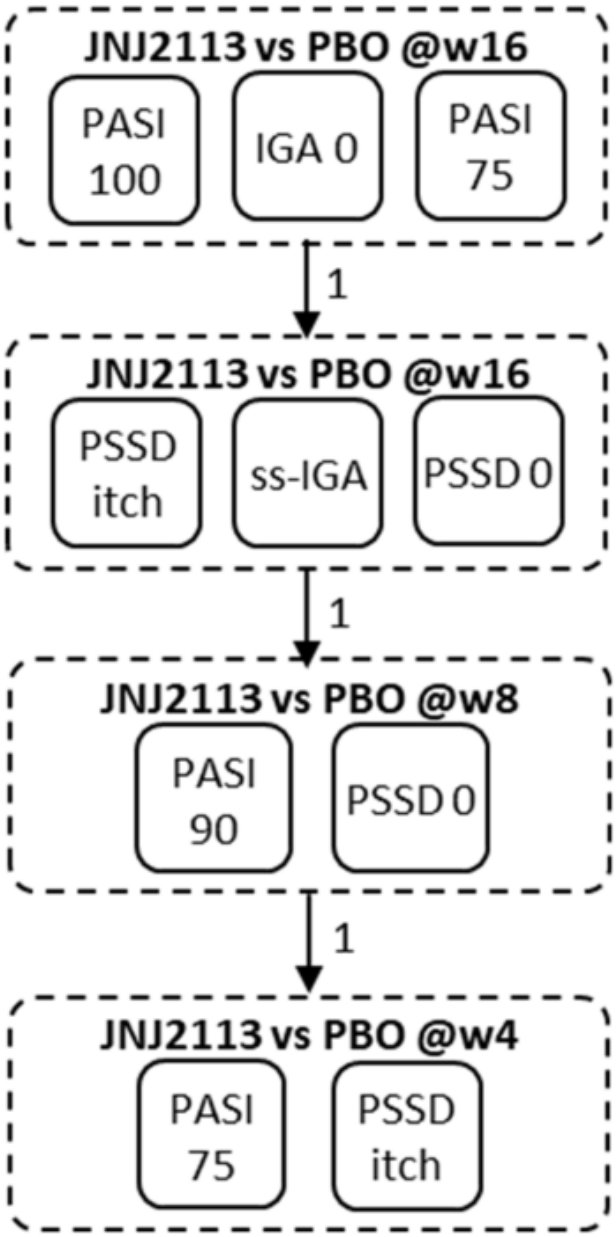
Table 13. Multiplicity Adjustment Procedure for Key Secondary Endpoints During the Placebo-Controlled Period – ICONIC-LEAD

Category	Endpoints
Tier 1	PASI-75 at Week 16
	PASI-100 at Week 16
	IGA score of 0 at Week 16
Tier 2	PSSD symptom score of 0 at Week 16
	≥4-point improvement from baseline in PSSD itch score at Week 16
	ss-IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 16
Tier 3	PASI-90 at Week 8
	PSSD symptom score of 0 at Week 8

Category	Endpoints
Tier 4	PASI-75 response at Week 4
	≥4-point improvement from baseline in PSSD itch score at Week 4

Source: ICONIC-LEAD Statistical Analysis Plan, pp. 13–14
Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp Specific Investigator's Global Assessment

Figure 24. Multiplicity Adjustment Procedure for the Key Secondary Endpoints During the Placebo-Controlled Period – ICONIC LEAD



Source: ICONIC-LEAD Statistical Analysis Plan, p. 14
Abbreviations: IGA, Investigator's Global Assessment; JNJ2113, icotrokinra; PASI, Psoriasis Area Severity Index; PBO, placebo; PSSD, Psoriasis Symptom and Sign Diary; W, week

Sensitivity and Supplementary Analysis

For the coprimary endpoints, the SAP specified a sensitivity analysis using fully conditional specification (FCS) logistic regression to impute missing PASI-90 and IGA 0 or 1 responses at Week 16, including treatment group, baseline score, response status through Week 16, age group, baseline weight category (for adults), and geographic region as covariates. Each imputed dataset was prespecified to be analyzed using a CMH test stratified by these same factors, with test statistics Wilson-Hilferty transformed and combined in SAS PROC MIANALYZE. Common risk differences and 95% confidence intervals were estimated using Mantel-Haenszel weights and the Sato variance estimator, adjusted for age group, baseline weight category, and geographic region.

The SAP also specified a tipping point analysis with Bernoulli draws to impute missing PASI-90 and IGA 0 or 1 response status at Week 16 after accounting for the ICEs. The tipping point analysis was prespecified to follow the following steps:

1. Some *p* would be assumed for each treatment group's response rate, which could vary by treatment group, to impute the response status (Yes/No) for subjects with a missing response based on a Bernoulli distribution. This would be repeated 200 times with seed=20240719 to generate 200 multiple imputations.
2. The common risk difference between icotrokinra and placebo would be calculated using Mantel-Haenszel stratum weights, adjusted for age group, baseline weight category (for adults), and geographic region for each imputed dataset. The resulting values would be combined to obtain an overall risk difference.
3. The results (with Wilson-Hilferty transformation) from the imputed datasets would then be combined to produce a p-value using Rubin's rule.

The analysis would be repeated for a range of values for *p* (e.g., 0% to 100% in increments of 10%, for the placebo group and the icotrokinra group, independently).

As supplementary analyses, the SAP prespecified that the coprimary endpoints would be analyzed once using the treatment policy strategy for all ICEs and once based on the per protocol population and the main estimand.

8.1.2. 77242113PSO3002 (ICONIC-ADVANCE 1) and 77242113PSO3004 (ICONIC-ADVANCE 2)

Trial Design

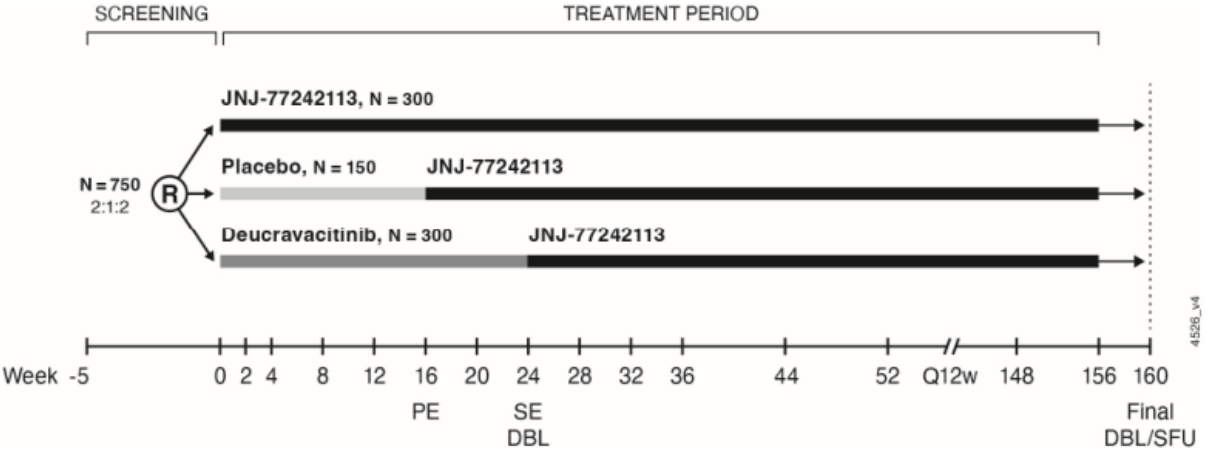
The Applicant conducted two randomized, multicenter, double-blind, placebo-controlled and active comparator-controlled, parallel-group Phase 3 trials (77242113PSO3002; ICONIC-ADVANCE 1 and 77242113PSO3004; ICONIC-ADVANCE 2) in adult subjects ≥18 years of age with moderate-to-severe plaque psoriasis. Both trials consisted of:

- A 5-week screening period
- A 16-week placebo-controlled period, which ran concurrently with a 24-week active comparator-controlled period from Week 0

- An open-label long-term extension period with icotrokinra from Week 16 (for placebo group) or Week 24 (for deucravacitinib group) through Week 156.

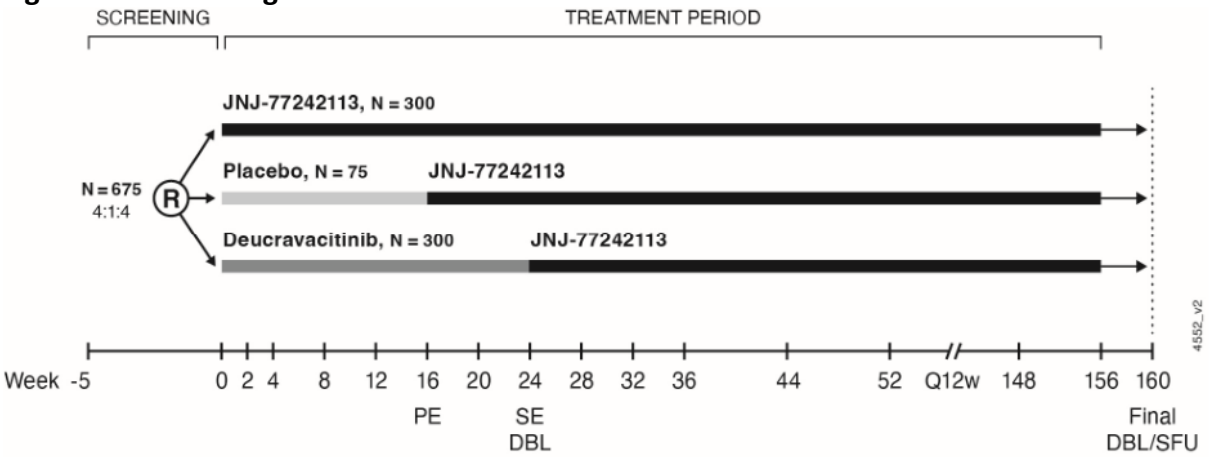
The trials were identically designed except for the randomization ratio. ICONIC-ADVANCE 1 was designed to enroll and randomize approximately 750 subjects in a 2:1:2 ratio to icotrokinra 200 mg once daily, placebo, or deucravacitinib 6 mg once daily. ICONIC-ADVANCE 2 was designed to enroll and randomize approximately 675 subjects in a 4:1:4 ratio to icotrokinra 200 mg once daily, placebo, or deucravacitinib 6 mg once daily. Randomization in both trials was stratified by baseline weight category (≤90 kg, >90 kg) and geographic region. Placebo subjects switched to icotrokinra 200 mg once daily at Week 16, while subjects in the deucravacitinib arm switched to icotrokinra 200 mg once daily at Week 24. Placebo was administered in all treatment groups to maintain blinding until Week 24.

Figure 25. Trial Design Schematic for ICONIC-ADVANCE 1



Source: ICONIC-ADVANCE 1 Clinical Protocol, p. 15
Abbreviations: DBL=database lock; PE=primary endpoint; Q12W=once every 12 weeks; R=randomization; SE=secondary endpoint; SFU=safety follow-up visit

Figure 26. Trial Design Schematic for ICONIC-ADVANCE 2



Source: ICONIC-ADVANCE 2 Clinical Protocol, p. 15
Abbreviations: DBL=database lock; PE=primary endpoint; Q12W=once every 12 weeks; R=randomization; SE=secondary endpoint; SFU=safety follow-up visit

Key Inclusion Criteria

- ≥18 years of age at the screening visit.
- Diagnosis of plaque psoriasis, with or without psoriatic arthritis (PsA), for at least 26 weeks prior to the first administration of study intervention.
- Total BSA ≥10% at screening and baseline.
- Total PASI ≥12 at screening and baseline.
- Total IGA ≥3 at screening and baseline.
- Candidate for phototherapy or systemic treatment for plaque psoriasis.

Trial Endpoints

In both trials, the coprimary efficacy endpoints were IGA 0/1 response, defined as achieving an IGA score of cleared (0) or minimal (1) and at least a two-grade improvement from baseline at Week 16, and PASI-90 response, defined as achieving at least a 90% improvement from baseline in PASI total score at Week 16. Table 14 lists the multiplicity-controlled secondary efficacy endpoints and their respective timepoints at which the comparisons – superiority, noninferiority or both – were specified to be conducted.

Table 14. Key Secondary Endpoint Analyses – ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2

Analysis	Comparison	
	Icotrokinra vs. Placebo	**Icotrokinra vs. Deucravacitinib**
Proportion of subjects with a PASI-75 response	At Weeks 4 and 16	At Weeks 16 and 24[a]
Proportion of subjects with a PASI-90 response	At Week 8	At Weeks 16 and 24[b]
Proportion of subjects with a PASI-100 response	At Week 16	At Weeks 16 and 24[b]
Proportion of subjects with an IGA score of cleared (0) or minimal (1) and at least 2-grade improvement from baseline	NA (coprimary endpoint)	At Weeks 16 and 24[a]
Proportion of subjects with an IGA score of cleared (0)	At Week 16	At Weeks 16 and 24[b]
Proportion of subjects with an ss-IGA score of absence of disease (0) or very mild disease (1) and at least a 2-grade improvement from baseline among subjects with a baseline ss-IGA score ≥2	At Week 16	NA
Proportion of subjects with a PSSD symptom score of 0 among subjects with a baseline PSSD symptom score >0	At Weeks 8 and 16	At Week 16[b]
Proportion of subjects with a ≥4-point improvement in PSSD Itch score among subjects with a baseline PSSD Itch score of ≥4 points	At Weeks 4 and 16	NA

Source: ICONIC-ADVANCE 1 Statistical Analysis Plan, p. 16
Abbreviations: NA=not applicable; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp Specific Investigator's Global Assessment
[a] Noninferiority tests with a noninferiority margin of 12% were prespecified to be performed before superiority tests.
[b] Only superiority tests were prespecified to be performed.

Statistical Analysis Plan

Analysis Sets

The SAP specified the following analysis sets:

- Enrolled: All subjects who signed the ICF.

- Randomized: All subjects who were randomized at Week 0 in the trial.
- Full Analysis Set (FAS): All subjects who were randomized at Week 0 in the trial.
- Per Protocol (PP): The per protocol analysis set (PP) includes a subset of subjects in the full analysis set (FAS) who were in general compliance with the protocol. Compliance is defined as subjects in FAS and meet the following criteria:
  - Had a total BSA ≥10% at the screening and baseline visit
  - Had a total PASI score ≥12 at the screening and baseline visit
  - Had a total IGA score ≥3 at the screening and baseline visit
  - Had an overall compliance of study treatment at least 80% and ≤120% prior to Week 16

Subjects with intercurrent events (ICEs) 1 and 2 will be included in the per protocol analysis set.

- Safety Analysis Set: All randomized subjects who took at least 1 dose of study intervention
- PK Analysis Set: All randomized subjects who received at least 1 dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra
- Immunogenicity Analysis Set: All randomized subjects who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra

Estimands

The SAP specified the following as the main estimand for the coprimary endpoints:

- *Treatments*: Icotrokinra and placebo.
- *Population*: Adult subjects ≥18 years of age with moderate to severe plaque psoriasis.
- *Endpoints*: IGA response and PASI-90 response.
- *Intercurrent Events (ICEs) and Handling Strategies*: The SAP specified (1) discontinuation of treatment due to lack of efficacy, or due to an adverse event (AE) of worsening of psoriasis; (2) initiation of other medication or therapy that could improve psoriasis; and (3) discontinuation of treatment for other reasons than ICE (1) as ICEs. The SAP specified using a composite variable strategy for ICEs (1) and (2), where subjects who experience the ICEs are considered nonresponders, and a treatment policy strategy for ICE (3), where data collected after the ICE are used as is in the analysis.
- *Population-Level Summary Measure*: The SAP specified the difference in proportions between icotrokinra and placebo groups as the population-level summary.

The SAP specified separate main estimands for the set of key secondary endpoints for which the comparisons were between the icotrokinra group and the placebo group and another set for which the comparisons were between the icotrokinra group and the deucravacitinib group – refer to Table 14. For the first set, the SAP specified that the main estimands have the same attributes as the coprimary estimands, except for the variable and population, which are presented in Table 15.

Table 15. List of Variables and Populations for the Main Estimands for the Key Secondary Endpoints Between Icotrokinra and Placebo – ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2

Variable Achieving a response based on:	Population
IGA score of 0 response at Week 16	Same as the primary estimand
PASI-75 response at Week 4	
PASI-90 response at Week 8	
PASI-75 response at Week 16	
PASI-100 response at Week 16	
ss-IGA score of 0 or 1 and a ≥2-grade improvement from baseline response at Week 16	Subjects with moderate to severe plaque psoriasis with a baseline ss-IGA score ≥2
PSSD symptom score of 0 response at Week 8	Subjects with moderate to severe plaque psoriasis and with a baseline PSSD symptom score >0
PSSD symptom score of 0 response at Week 16	
≥4-point improvement from baseline in PSSD itch score at Week 4	Subjects with moderate to severe plaque psoriasis and with a baseline PSSD itch score ≥4
≥4-point improvement from baseline in PSSD itch score at Week 16	

Source: ICONIC-ADVANCE 1 Statistical Analysis Plan, p. 30
Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp Specific Investigator's Global Assessment

For the other set of key secondary endpoints comparing icotrokinra and deucravacitinib, the SAP specified that the main estimands are identical to the coprimary estimand, except for the treatments, variable, and population.

Table 16. Variables and Populations for the Main Estimands for Key Secondary Endpoints Between Icotrokinra and Deucravacitinib – ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2

Variable Achieving a response based on:	Population
IGA score of 0 and 1 and a ≥2-grade improvement from baseline response at Week 16[a,b]	Same as the primary estimand
IGA score of 0 or 1 and a ≥2-grade improvement from baseline response at Week 24[a]	
IGA score of 0 response at Week 16[b]	
IGA score of 0 response at Week 24	
PASI-75 response at Week 16[a,b]	
PASI-75 response at Week 24[a]	
PASI-90 response at Week 16[b]	
PASI-90 response at Week 24	
PASI-100 response at Week 16[b]	
PASI-100 response at Week 24	
PSSD symptom score of 0 response at Week 16[a,b]	Subjects with moderate to severe plaque psoriasis and with a baseline PSSD symptom score >0

Source: ICONIC-ADVANCE 1 Statistical Analysis Plan, p. 31
[a] Noninferiority tests with a noninferiority margin of 12% were prespecified to be performed before superiority tests.
[b] Comparisons between deucravacitinib and placebo were prespecified to be performed to demonstrate assay sensitivity.
Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp Specific Investigator's Global Assessment

Analysis Method

The SAP specified analyzing the coprimary endpoints using a 2-sided (α=0.05) CMH chi-square test, stratified by baseline weight category for adults (≤90 kg in adults, >90 kg in adults,

adolescents) and geographic region (America, European Union, and Asia-Pacific). The difference in response rates between the icotrokinra group and the placebo group at Week 16 and their corresponding 95% confidence intervals (CIs) using the Miettinen-Nurminen method would be calculated adjusting for baseline weight category and geographic region using MH weights.

Multiplicity Adjustment Plan

The SAP specified testing the coprimary endpoints first at the 5% significance level and proceeding to test the key secondary endpoints only if both the coprimary endpoints were statistically significant. Multiplicity was controlled across the key secondary endpoints using a graphical testing approach, where the key secondary endpoints were organized into 11 tiers that were prespecified to be tested in a predetermined order using a graphical approach with Type I error propagation – see Figure 27. Within each tier, the Bonferroni-Holm procedure was specified to test endpoints with the assigned significance level. If any test within a tier was not significant, the assigned alpha for that tier was prespecified not to be passed down to subsequent tiers. The assigned alpha was prespecified to propagate to other tiers only if all hypotheses within the tier were rejected based on the Bonferroni-Holm procedure.

For comparisons between icotrokinra and deucravacitinib on IGA 0/1 response and PASI-75 response at Weeks 16 and 24, noninferiority testing (with a 12% margin) was prespecified to be performed before superiority testing, which was incorporated into the multiplicity adjustment procedure.

The tiers were defined in the SAP as shown in Table 17.

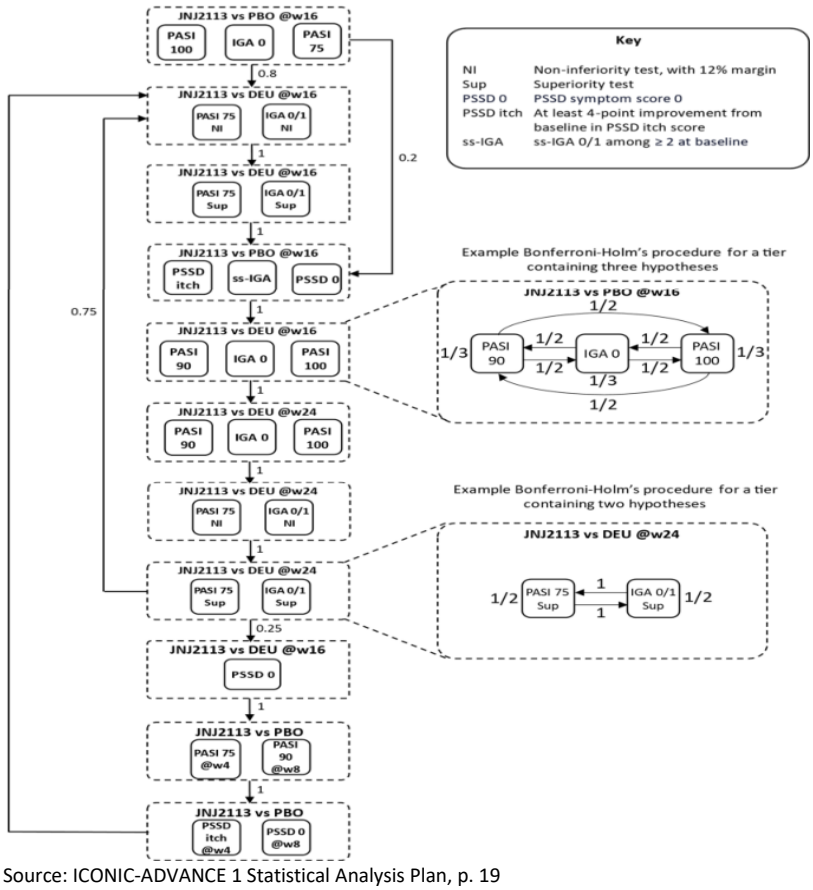
Table 17. Multiplicity Adjustment Procedure for Key Secondary Endpoints During the Placebo-Controlled Period – ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2

Tier	Endpoint	Treatments Compared
Tier 1	IGA score of 0 at Week 16	Icotrokinra and placebo at Week 16
	PASI-75 at Week 16	
	PASI-100 at Week 16	
Tier 2	IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 16	Icotrokinra and deucravacitinib at Week 16 (noninferiority)
	PASI-75 at Week 16	
Tier 3	IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 16	Icotrokinra and deucravacitinib at Week 16 (superiority)
	PASI-75 at Week 16	
Tier 4	ss-IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 16	Icotrokinra and placebo at Week 16
	PSSD symptom score of 0 at Week 16	
	≥4-point improvement from baseline in PSSD itch score at Week 16	
Tier 5	IGA score of 0 at Week 16	Icotrokinra and deucravacitinib at Week 16 and Week 24
	PASI-90 at Week 16	
	PASI-100 at Week 16	
Tier 6	IGA score of 0 at Week 24	
	PASI-90 at Week 24	
	PASI-100 at Week 24	

Tier	Endpoint	Treatments Compared
Tier 7	(Noninferiority) IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 24	
	(Noninferiority) PASI-75 at Week 24	
Tier 8	(Superiority) IGA score of 0 or 1 and ≥2-grade improvement from baseline at Week 24	
	(Superiority) PASI-75 at Week 24	
Tier 9	PSSD symptom score of 0 at Week 16	
Tier 10	PASI-75 at Week 4	Icotrokinra and placebo at early timepoints
	PASI-90 at Week 8	
Tier 11	PSSD symptom score of 0 at Week 8	
	≥4-point improvement from baseline in PSSD itch score at Week 4	

Source: ICONIC-ADVANCE 1 Statistical Analysis Plan, pp. 16–17
Abbreviations: IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp Specific Investigator's Global Assessment

Figure 27. Multiplicity Adjustment Procedure for the Key Secondary Endpoints During the Placebo-Controlled Period – ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2



Source: ICONIC-ADVANCE 1 Statistical Analysis Plan, p. 19
Abbreviations: DEU, deucravacitinib; IGA, Investigator's Global Assessment; JNJ2113, icotrokinra; NI, noninferiority test; PASI, Psoriasis Area Severity Index; PBO, placebo; PSSD, Psoriasis Symptom and Sign Diary; Sup, superiority test; ss-IGA, Scalp Specific IGA; w, week

<u>Reviewer Comment</u>: Regarding the active control comparisons, the Agency twice conveyed the comment – June 20, 2023 Type B End-of-Phase 2 Meeting and November 20, 2024 Advice Letter – that (b) (4) *and a formal*

(b) (4) *would not have regulatory utility.*

Sensitivity and Supplementary Analysis

For the coprimary endpoints, the SAP specified a sensitivity analysis using FCS logistic regression to impute missing PASI-90 and IGA 0 or 1 responses at Week 16, including treatment group, baseline score, response status through Week 16, age group, baseline weight category (for adults), and geographic region as covariates. Each imputed dataset was prespecified to be analyzed using a CMH test stratified by these same factors, with test statistics Wilson-Hilferty transformed and combined in SAS PROC MIANALYZE. Common risk differences and 95% confidence intervals were estimated using Mantel-Haenszel weights and the Sato variance estimator, adjusted for age group, baseline weight category, and geographic region.

The SAP also specified a tipping point analysis with Bernoulli draws to impute missing PASI-90 and IGA 0 or 1 response status at Week 16 after accounting for the ICEs. The tipping point analysis was prespecified to follow the following steps:

1. Some *p* would be assumed for each treatment group's response rate, which could vary by treatment group, to impute the response status (Yes/No) for subjects with a missing response based on a Bernoulli distribution. This would be repeated 200 times with seed=20240719 to generate 200 multiple imputations.
2. The common risk difference between icotrokinra and placebo would be calculated using Mantel-Haenszel stratum weights, adjusted for age group, baseline weight category (for adults), and geographic region for each imputed dataset. The resulting values would be combined to obtain an overall risk difference.
3. The results (with Wilson-Hilferty transformation) from the imputed datasets would then be combined to produce a p-value using Rubin's rule.

The analysis would be repeated for a range of values for *p* (e.g., 0% to 100% in increments of 10%, for the placebo group and the icotrokinra group, independently).

As supplementary analyses, the SAP prespecified that the coprimary endpoints would be analyzed once using the treatment policy strategy for all ICEs and once based on the per protocol population and the main estimand.

8.1.3. 77242113PSO3003 (ICONIC-TOTAL)

Trial Design

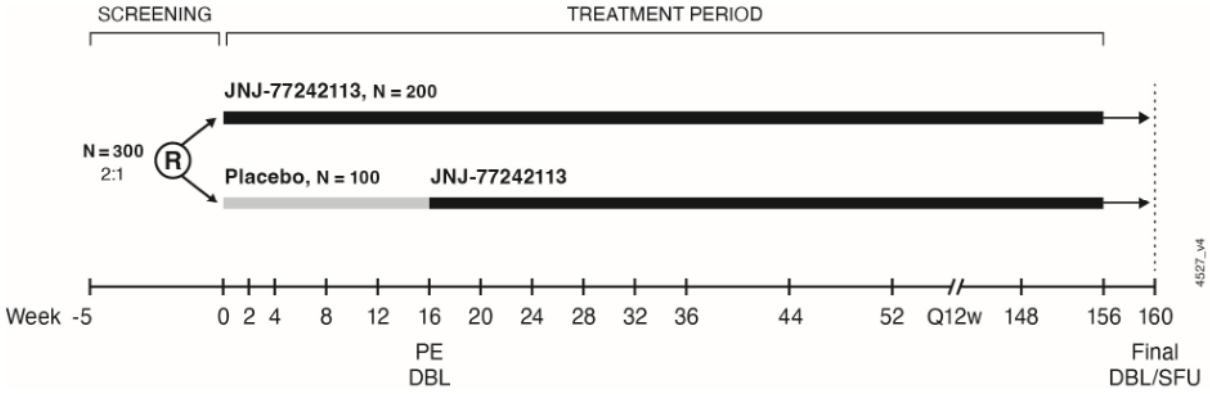
The Applicant conducted a randomized, multicenter, double-blind, placebo-controlled, parallel-group phase 3 trial (77242113PSO3003; ICONIC-TOTAL) in subjects ≥12 years of age with moderate-to-severe plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar). The trial consisted of:

- A 5-week screening period.
- A 16-week placebo-controlled period.
- A 140-week active treatment period.

- A 4-week safety follow-up period after discontinuation of study intervention or at the end of the treatment period.

ICONIC-TOTAL was designed to enroll and randomize approximately 300 subjects in a 2:1 ratio to icotrokinra 200 mg once daily or placebo. Randomization was stratified by special area involvement (with the order of baseline Physician's Global Assessment of hands and feet [hf-PGA] ≥3, Static Physician's Global Assessment of Genitalia [sPGA-G] ≥3, and Scalp-Specific Investigator Global Assessment [ss-IGA] ≥3), geographic region, and body surface area [BSA] category (<10%, ≥10%). Placebo subjects switched to icotrokinra 200 mg once daily at Week 16 and continued through Week 156.

Figure 28. Trial Design Schematic for ICONIC-TOTAL



Source: ICONIC-TOTAL Clinical Protocol, p. 16
Abbreviations: DBL=database lock; PE=primary endpoint; Q12W=once every 12 weeks; R=randomization; SFU=safety follow-up visit

Key Inclusion Criteria

- ≥12 years of age at the screening visit
- Diagnosis of plaque psoriasis, with or without PsA, for at least 26 weeks prior to the first administration of study intervention
- Candidate for phototherapy or systemic treatment for plaque psoriasis
- Need to meet criteria:
  - Total BSA ≥1% at screening and baseline, AND
  - IGA (overall) ≥2 at screening and baseline AND at least one of the following:
    - (Scalp) ss-IGA score ≥3 at screening and baseline, and/or
    - (Genitalia) sPGA-G ≥3 at screening and baseline, and/or
    - (Hands and feet) hf-PGA score ≥3 at screening and baseline

    Note for Population (a): The majority of participants will be required to have BSA involvement ≥10%. Enrollment will be closely monitored, and, in the lower BSA subpopulation (1% to 10%) stopped if a maximum of 40% is reached. This is to ensure the study includes a broad spectrum of disease and is consistent with prior study precedence.
- Failed to respond to at least 1 topical therapy (e.g., corticosteroids, calcineurin inhibitors, and/or vitamin D analogs) used for treatment of psoriasis.

- Confirmation of plaque psoriasis in a nonspecial area (i.e., areas excluding scalp, genital, palmoplantar) at screening and baseline.

Study Endpoints

Unlike the other three trials, ICONIC-TOTAL had IGA 0/1 response, defined as achieving an IGA score of cleared (0) or minimal (1) and at least a 2-grade improvement from baseline at Week 16, as the single primary efficacy endpoint.

The multiplicity-controlled secondary efficacy endpoints were:

- ss-IGA score of 0 or 1 at Week 16
- PSSI-90 at Week 16
- sPGA-G score of 0 or 1 at Week 16
- hf-PGA score of 0 or 1 at Week 16
- IGA (overall) score of 0 at Week 16
- PSSD symptom score of 0 at Week 16
- ≥4-point improvement in PSSD itch score from baseline at Week 16
- Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ) item 2 score of 0 or 1 at Week 16
- ≥4-point improvement in Scalp Itch NRS score from baseline at Week 16
- ≥4-point improvement in Genital Psoriasis Symptoms Score (GPSS) Genital Itch NRS score (Item 1 from the GPSS) from baseline at Week 16

Psoriasis Scalp Severity Index

The PSSI is a scalp-specific modification of the PASI based on the extent of involvement and the severity of erythema, infiltration, and desquamation. Involvement and severity of psoriasis on the PSSI is scored by physicians on a scale from 0 to 72, where 0=no psoriasis and higher scores indicate more severe disease.

Static Physician's Global Assessment of Genitalia

The sPGA-G is a 6-point scale to assess the severity of genital psoriasis at a given time point. The sPGA-G evaluates erythema, plaque elevation, and scale of genital psoriatic lesions. The severity of genital psoriasis is assessed as clear (0), minimal (1), mild (2), moderate (3), severe (4), and very severe (5).

Physician's Global Assessment of Hands and Feet

The hf-PGA assesses the severity of hand and foot psoriasis using a 5-point scale to score the plaques on the hands and feet as: clear (0), almost clear (1), mild (2), moderate (3), and severe (4).

Psoriasis Symptom and Sign Diary

The PSSD is utilized in the adult and adolescent populations and includes PRO questionnaires

designed to measure the severity of psoriasis symptoms and signs for the assessment of treatment benefit. There are 2 versions of the PSSD: a 24-hour recall version that asks the participant to answer the questions thinking about the last 24 hours and a 7-day recall version asking the participant to answer the questions thinking about the last 7 days. Both versions of the PSSD are self-administered PRO instruments and include 11 items in total, with 5 items covering symptoms (itch, pain, stinging, burning, and skin tightness) and 6 items covering participant-observable signs (skin dryness, cracking, scaling, shedding or flaking, redness, and bleeding). A 0 to 10 numerical rating scale for severity is used. For both versions, 2 subscores are derived each ranging from 0 to 100: the psoriasis symptom score and the psoriasis sign score. Additionally, for both versions, an item-level score is derived for the PSSD itch item. The PSSD itch score ranges from 0 to 10. For all scores, a higher score indicates more severe disease.

Scalp Itch Numeric Rating Scale

The Scalp Itch NRS is a single item instrument that evaluates the severity of scalp itch in adult and adolescent populations over the past 24 hours. The instrument uses an NRS score ranging from 0 (no scalp itch) to 10 (worst scalp itch imaginable).

Genital Psoriasis Symptoms Scale

The GPSS is a participant-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Each respondent was asked to answer the questions based on the psoriasis symptoms in his or her genital area. The overall severity for each individual genital psoriasis symptom is indicated by selecting the number from an NRS of 0 to 10 that best describes the worst level of each symptom in the genital area in the past 24 hours, ranging from 0 (no severity) to 10 (worst imaginable severity).

Genital Psoriasis Sexual Frequency Questionnaire

The GenPs-SFQ will be utilized in the adult population and is a 2-item participant-reported instrument used to assess the impact of genital psoriasis on the frequency of sexual activity in the last 7 days. Item 1 assesses overall frequency of sexual activity in the last 7 days (none/zero, once, or 2 or more times), and item 2 assesses how frequently genital psoriasis symptoms have limited the frequency of sexual activity in the last 7 days (never [0], rarely [1], sometimes [2], often [3], or always [4]).

Statistical Analysis Plan

Analysis Sets

The SAP specified the following analysis sets:

- Enrolled: All subjects who signed the ICF.
- Randomized: All subjects who were randomized at Week 0 in the trial.
- Full analysis set (FAS): All subjects who were randomized at Week 0 in the trial.

- Per protocol (PP): The per protocol analysis set (PP) includes a subset of subjects in the FAS who were in general compliance with the protocol. Compliance is defined as subjects in FAS and meet the following criteria:
  - Had a total BSA ≥1% at the screening and baseline visit, and had an IGA (overall) score ≥2 at the screening and baseline visit And at least one of the following:
    - ss-IGA score ≥3 at screening and baseline, and/or
    - sPGA-G≥3 at screening and baseline, and/or
    - hf-PGA score ≥3 at screening and baseline.
  - Had an overall compliance with study treatment at least 80% and ≤120% prior to Week 16. Subjects with intercurrent events (1) and (2) (see *Estimands*) will be included in the per protocol analysis set.
- Safety analysis set: All randomized subjects who took at least 1 dose of study intervention.
- PK Analysis set: All randomized subjects who received at least 1 dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
- Immunogenicity analysis set: All randomized subjects who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.

Estimands

The SAP specified the following as the main estimand for the primary endpoint

- *Treatments*: Icotrokinra and placebo.
- *Population*: Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar).
- *Endpoints*: Achieving an IGA (overall) score of 0 or 1 response at Week 16, where an IGA (overall) score of 0 or 1 responder is defined as a subject meeting an IGA (overall) 0 or 1 criteria at Week 16 and not experiencing either ICE (1) or ICE (2).
- *Intercurrent Events (ICEs) and Handling Strategies*: The SAP specified (1) discontinuation of treatment due to lack of efficacy, or due to an adverse event (AE) of worsening of psoriasis; (2) initiation of other medication or therapy that could improve psoriasis; and (3) discontinuation of treatment for other reasons than ICE (1) as ICEs. The SAP specified using a composite variable strategy for ICEs (1) and (2), where subjects who experience the ICEs are considered non-responders, and a treatment policy strategy for ICE (3), where data collected after the ICE are used as is in the analysis.
- *Population-Level Summary Measure*: The SAP specified the difference in proportions between icotrokinra and placebo groups as the population-level summary.

For the key secondary efficacy endpoints at Week 16, the SAP specified that the estimands for the corresponding endpoints would be the same as the main estimand for the primary endpoint, except for the variable and population – see Table 18.

Table 18. List of Variables and Populations for Key Secondary Endpoints – ICONIC-TOTAL

Estimands	Variable	Population
General Psoriasis and Special Area Psoriasis		
Sec 1	ss-IGA score of 0 or 1 response at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and a baseline ss-IGA score ≥3
Sec 2	PSSI-90 response at Week 16	
Sec 3	sPGA-G score of 0 or 1 response at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and a baseline sPGA-G score ≥3
Sec 4	hf-PGA score of 0 or 1 response at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and a baseline hf-PGA score ≥3
Sec 5	IGA (overall) score of 0 response at Week 16	Same as the primary estimand
Patient-Reported Outcomes		
Sec 6	PSSD symptom score of 0 response at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and a baseline PSSD symptom score >0
Sec 7	≥4-point improvement from baseline in PSSD Itch score at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and a baseline PSSD Itch score ≥4
Sec 8	GenPs-SFQ item 2 score of 0 or 1 response at Week 16	Adult subjects with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and with a baseline GenPs-SFQ item 2 score ≥2 and a baseline sPGA-G score ≥3
Sec 9	≥4-point improvement from baseline in Scalp Itch NRS score at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and with a baseline Scalp Itch NRS score ≥4 and a baseline ss-IGA score ≥3
Sec 10	≥4-point improvement from baseline in GPSS Genital Itch NRS score (Item 1 from the GPSS) at Week 16	Subjects ≥12 years of age with plaque psoriasis involving special areas (scalp, genital, and/or palmoplantar) and with a baseline GPSS Genital Itch NRS score (Item 1 from the GPSS) ≥4 and a baseline sPGA-G score ≥3

Source: ICONIC-TOTAL Statistical Analysis Plan, pp. 25-26.
Abbreviations: GenPs-SFQ, Genital Psoriasis Sexual Frequency Questionnaire; GPSS, Genital Psoriasis Symptoms Scale; hf-PGA, Physician's Global Assessment of hands and/or feet; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PSSD, Psoriasis Symptom and Sign Diary; PSSI, Psoriasis Scalp Severity Index; sPGA-G, static Physician's Global Assessment of Genitalia; ss-IGA, scalp-specific Investigator Global Assessment

Analysis Method

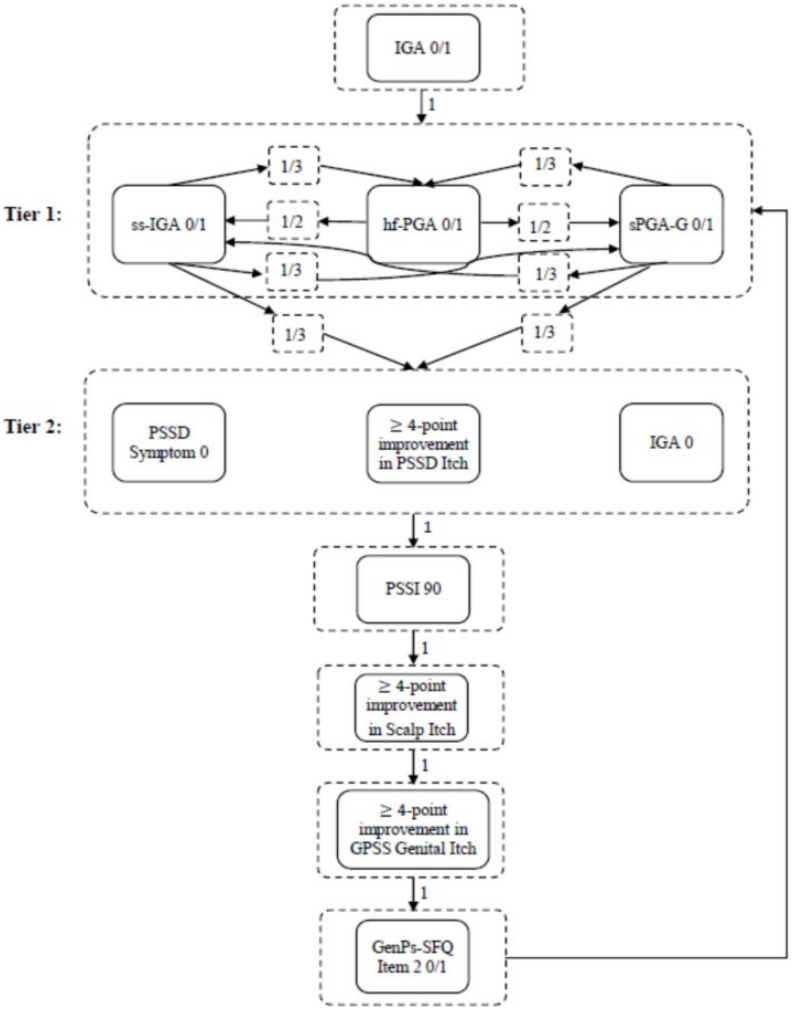
The SAP specified analyzing the primary endpoint using a two-sided (α=0.05) CMH chi-square test, stratified by special area involvement (baseline hf-PGA ≥3, sPGA-G ≥3, or ss-IGA ≥3), geographic region (America, European Union, and Asia-Pacific), and BSA category (<10%, ≥10%), if applicable. The difference in response rates between the icotrokinra group and the placebo group at Week 16 and their corresponding 95% confidence intervals (CIs) using the Miettinen-Nurminen method would be calculated adjusting for special area involvement and BSA category using MH weights.

Multiplicity Adjustment Plan

The SAP specified first testing the primary endpoint at the 0.05 level and proceeding to test the key secondary endpoints only if the primary endpoint was statistically significant. Multiplicity

was controlled across the key secondary endpoints using a graphical testing approach, where the key secondary endpoints were grouped into 2 tiers consisting of 3 endpoints each, and the remaining endpoints would be tested in a fixed sequence – see Figure 29. Within Tier 1, the truncated Bonferroni-Holm procedure was specified to test endpoints with the assigned significance level. In the truncated Bonferroni-Holm procedure, if ss-IGA 0/1 or sPGA-G 0/1 was statistically significant at its assigned alpha level, one-third of the assigned alpha would propagate to the endpoints in Tier 2. Within Tier 2, the Bonferroni-Holm procedure was specified to test endpoints with at an alpha level propagated from Tier 1. If any test within this tier was not significant, the other tests in the same tier could still be declared significant if they met the Bonferroni-Holm's thresholds, but the formal testing would stop and all p-values from subsequent tests would be considered nominal. If all tests in Tier 2 were statistically significant, the remaining endpoints would be tested per the fixed-sequence method.

Figure 29. Testing Procedure for the Primary Endpoint and Key Secondary Endpoints – ICONIC-TOTAL



Source: Statistical Analysis Plan, p. 14
Abbreviations: GenPs-SFQ, Genital Psoriasis Sexual Frequency Questionnaire; GPSS, Genital Psoriasis Symptoms Score; hf-PGA, Physician's Global Assessment of hands and feet; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; PSSI, Psoriasis Scalp Severity Index; sPGA-G, Static Physician's Global Assessment of Genitalia; ss-IGA, Scalp-Specific Investigator Global Assessment

Sensitivity and Supplementary Analysis

For the primary endpoint, the SAP specified a sensitivity analysis using FCS logistic regression to impute missing IGA 0 or 1 responses at Week 16, including treatment group, special area involvement, BSA category, baseline IGA (overall) score, and IGA (overall) 0 or 1 response status through Week 16 as covariates. Each of the 500 imputed datasets was prespecified to be analyzed using a CMH test stratified by these same factors, with test statistics Wilson-Hilferty transformed and combined in SAS PROC MIANALYZE. Common risk differences and 95% confidence intervals were estimated using Mantel-Haenszel weights and the Sato variance estimator, adjusting for special area involvement and BSA category for each imputed dataset.

The SAP also specified a tipping point analysis with Bernoulli draws to impute missing IGA 0 or 1 response status at Week 16 after accounting for the ICEs. The tipping point analysis was prespecified to follow the following steps:

1. Some *p* would be assumed for each treatment group's response rate, which could vary by treatment group, to impute the response status (Yes/No) for subjects with a missing response based on a Bernoulli distribution. This would be repeated 200 times with seed=20240719 to generate 200 multiple imputations.
2. The common risk difference between icotrokinra and placebo would be calculated using Mantel-Haenszel stratum weights, adjusting for special area involvement and BSA category for each imputed dataset. The resulting values would be combined to obtain an overall risk difference.
3. The results (with Wilson-Hilferty transformation) from the imputed datasets would then be combined to produce a p-value using Rubin's rule.

The analysis would be repeated for a range of values for *p* (e.g., 0% to 100% in increments of 10%, for the placebo group and the icotrokinra group, independently).

As a supplementary analysis, the SAP specified that the primary endpoint would be analyzed using the treatment policy strategy for all ICEs.

Protocol Amendments

Three trials had their protocols amended after trial initiation. ICONIC-ADVANCE 2 had one protocol amendment submitted approximately 7 weeks after trial initiation. ICONIC-TOTAL also had one protocol amended approximately 7 weeks after trial initiation. ICONIC-LEAD similarly had one protocol amendment approximately 15 weeks after trial initiation. ICONIC-ADVANCE 1 had two protocol amendments, both of which occurred before trial initiation.

Of the post-initiation amendments, only ICONIC-LEAD had a statistical change relevant to the assessment of efficacy regarding multiplicity control and analysis methods for key secondary endpoints. Protocol Amendment 2 (SDN 58) for ICONIC-LEAD, submitted on January 30, 2024, stated, "the multiplicity testing strategy will be devised based on the expected power and relative importance of the endpoints and will be performed via a graphical approach." The Applicant specified said graphical approach in a subsequent SAP. Protocol Amendment 2

further specified the intercurrent event handling for the key secondary endpoints (see Estimands above); that the same statistical method as that for the coprimary endpoints using the appropriate stratification factors will be used for analyzing the binary endpoints using the appropriate stratification factors (i.e., age group, baseline weight category for adults, and geographic region for endpoints during the placebo-controlled period and geographic regions and PASI-90 response status at Week 24 for Week 52 endpoints); and that the analyses related to the time-to-event endpoints during the randomized withdrawal period would be performed using the log-rank test stratified by geographic region and PASI-90 response status at Week 24.

8.1.4. Trial Results (ICONIC-LEAD, ICONIC-ADVANCE 1, ICONIC-ADVANCE 2, ICONIC-TOTAL)

Compliance With Good Clinical Practices

The Applicant states that all four pivotal phase 3 trials were conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archival of essential documents. However, during the review, the Applicant notified the Agency of GCP noncompliance issues regarding Site CB4-US10098 for ICONIC-ADVANCE 2. See Data Quality and Integrity.

Financial Disclosure

Refer to Section 19.2.

Subject Disposition

ICONIC-LEAD enrolled and randomized a total of 684 subjects from 138 investigational sites, with 456 randomized to icotrokinra and 228 randomized to placebo. Table 19 presents the subject disposition for the 16-week double-blind placebo-controlled treatment period. Approximately 5% of subjects discontinued the trial before Week 16. The most common reason for trial discontinuation was withdrawal by subject – approximately 2% on the icotrokinra arm and 5% on the placebo arm. Overall, trial discontinuation was higher in the placebo group than in the icotrokinra group (6% versus 4%).

Study treatment discontinuation occurred in approximately 5% of subjects overall before Week 16 to 4% on the icotrokinra arm and 6% on the placebo arm. The most common reasons for treatment discontinuation were withdrawal by subject (2% icotrokinra versus 1% placebo) and lack of efficacy (0.2% icotrokinra versus 4% placebo). Adverse events accounted for treatment discontinuation in 1% of icotrokinra subjects compared to 0.4% of placebo subjects.

Table 19. Subject Disposition for ICONIC-LEAD

Status	Icotrokinra	Placebo	Overall
Randomized	456	228	684
Discontinued trial (Week 16), n (%)	17 (3.7)	14 (6.1)	31 (4.5)
Lost to follow-up	3 (0.7)	1 (0.4)	4 (0.6)
Withdrawal by subject	11 (2.4)	11 (4.8)	22 (3.2)
Other	3 (0.7)	2 (0.9)	5 (0.7)
Discontinued study treatment (Week 16), n (%)	19 (4.2)	14 (6.1)	33 (4.8)
Adverse event	5 (1.1)	1 (0.4)	6 (0.9)
Lost to follow-up	3 (0.7)	1 (0.4)	4 (0.6)
Lack of efficacy	1 (0.2)	8 (3.5)	9 (1.3)
Noncompliance with study schedule	1 (0.2)	0	1 (0.1)
Physician decision	0	1 (0.4)	1 (0.1)
Pregnancy	1 (0.2)	0	1 (0.1)
Withdrawal by subject	8 (1.8)	3 (1.3)	11 (1.6)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, addisp.xpt
Abbreviations: n, number of subjects for the given category

ICONIC-ADVANCE 1 enrolled and randomized a total of 774 subjects from 149 investigational sites, with 311 randomized to icotrokinra, 156 to placebo, and 307 to deucravacitinib. Table 20 presents the subject disposition for the 16-week double-blind placebo- and active comparator-controlled treatment period. Approximately 6% of subjects discontinued the trial before Week 16. The most common reason for trial discontinuation was withdrawal by subject – approximately 2% on the icotrokinra arm, 6% on the placebo arm, and 4% on the deucravacitinib arm. Overall, trial discontinuation was highest in the placebo group (8%), followed by the deucravacitinib group (6%) and icotrokinra group (4%).

Study treatment discontinuation occurred in approximately 6% of subjects overall before Week 16 to 5% on the icotrokinra arm, 10% on the placebo arm, and 7% on the deucravacitinib arm. The most common reasons for treatment discontinuation were adverse events (2% icotrokinra versus 6% placebo versus 3% deucravacitinib) and withdrawal by subject (2% icotrokinra versus 1% placebo versus 1% deucravacitinib). Lack of efficacy accounted for treatment discontinuation in 0.3% of icotrokinra subjects, 2% of placebo subjects, and 1% of deucravacitinib subjects.

Table 20. Subject Disposition for ICONIC-ADVANCE 1

Status	Icotrokinra	Placebo	Deucravacitinib	Overall
Randomized	311	156	307	774
Discontinued study (Week 16), n (%)	12 (3.9)	12 (7.7)	19 (6.2)	43 (5.6)
Lost to follow-up	2 (0.6)	0	2 (0.7)	4 (0.5)
Withdrawal by subject	7 (2.3)	9 (5.8)	12 (3.9)	28 (3.6)
Other	3 (1.0)	3 (1.9)	5 (1.6)	11 (1.4)

Status	Icotrokinra	Placebo	Deucravacitinib	Overall
Discontinued study treatment (Week 16), n (%)	14 (4.5)	15 (9.6)	21 (6.8)	50 (6.5)
Adverse event	5 (1.6)	9 (5.8)	8 (2.6)	22 (2.8)
Death	0	0		0
Lost to follow-up	3 (1.0)	1 (0.6)	2 (0.7)	6 (0.8)
Lack of efficacy	1 (0.3)	3 (1.9)	4 (1.3)	8 (1.0)
Noncompliance with study drug	0	0	1 (0.3)	1 (0.1)
Physician decision	0	0	1 (0.3)	1 (0.1)
Protocol deviation	0	1 (0.6)	0	1 (0.1)
Withdrawal by subject	5 (1.6)	1 (0.6)	4 (1.3)	10 (1.3)
Other	0	0	1 (0.3)	1 (0.1)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, addisp.xpt
Abbreviations: n, number of subjects for the given category

ICONIC-TOTAL enrolled and randomized a total of 311 subjects from 69 investigational sites, with 208 randomized to icotrokinra and 103 randomized to placebo. Table 21 presents the subject disposition for the 16-week double-blind placebo-controlled treatment period. Approximately 6% of subjects discontinued the trial before Week 16. The most common reason for trial discontinuation was withdrawal by subject – approximately 3% on the icotrokinra arm and 8% on the placebo arm. Overall, trial discontinuation was higher in the placebo group than in the icotrokinra group (10% versus 4%).

Study treatment discontinuation occurred in approximately 6% of subjects overall before Week 16 to 4% on the icotrokinra arm and 11% on the placebo arm. The most common reasons for treatment discontinuation were adverse events (2% icotrokinra versus 4% placebo) and lack of efficacy (1% icotrokinra versus 5% placebo). Withdrawal by subject accounted for treatment discontinuation in 0.5% of icotrokinra subjects and 1% of placebo subjects.

Table 21. Subject Disposition for ICONIC-TOTAL

Status	Icotrokinra	Placebo	Overall
Randomized	208	103	311
Discontinued study (Week 16), n (%)	8 (3.8)	10 (9.7)	18 (5.8)
Lost to follow-up	2 (1.0)	0 (0.0)	2 (0.6)
Withdrawal by subject	6 (2.9)	8 (7.8)	14 (4.5)
Other	0 (0.0)	2 (1.9)	2 (0.6)
Discontinued study treatment (Week 16), n (%)	9 (4.3)	11 (10.7)	20 (6.4)
Adverse event	5 (2.4)	4 (3.9)	9 (2.9)
Lost to follow-up	0 (0.0)	1 (1.0)	1 (0.3)
Lack of efficacy	3 (1.4)	5 (4.9)	8 (2.6)
Withdrawal by subject	1 (0.5)	1 (1.0)	2 (0.6)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, addisp.xpt
Abbreviations: n, number of subjects for the given category

ICONIC-ADVANCE 2 enrolled and randomized a total of 731 subjects from 114 investigational sites, with 322 randomized to icotrokinra, 82 to placebo, and 327 to deucravacitinib. Table 22

presents the subject disposition for the 16-week double-blind placebo- and active comparator-controlled treatment period. Approximately 5% of subjects discontinued the trial before Week 16. The most common reason for trial discontinuation was withdrawal by subject – approximately 2% on the icotrokinra arm, 7% on the placebo arm, and 3% on the deucravacitinib arm. Overall, trial discontinuation was highest in the placebo group (10%), followed by the deucravacitinib group (4%) and icotrokinra group (3%).

Study treatment discontinuation occurred in approximately 6% of subjects overall before Week 16 to 5% on the icotrokinra arm, 10% on the placebo arm, and 6% on the deucravacitinib arm. The most common reasons for treatment discontinuation were adverse events (2% icotrokinra versus 2% placebo versus 2% deucravacitinib) and withdrawal by subject (1% icotrokinra versus 4% placebo versus 1% deucravacitinib). Lack of efficacy accounted for treatment discontinuation in 0.3% of icotrokinra subjects, 4% of placebo subjects, and 1% of deucravacitinib subjects. One death occurred in the icotrokinra group during the treatment period.

Table 22. Subject Disposition for ICONIC-ADVANCE 2

Status	Icotrokinra	Placebo	Deucravacitinib	Overall
Randomized	322	82	327	731
Discontinued study (Week 16), n (%)	11 (3.4)	8 (9.8)	14 (4.3)	33 (4.5)
Lost to follow-up	1 (0.3)	0	1 (0.3)	2 (0.3)
Withdrawal by subject	5 (1.6)	6 (7.3)	10 (3.1)	21 (2.9)
Other	3 (0.9)	2 (2.4)	3 (0.9)	8 (1.1)
Discontinued study treatment (Week 16), n (%)	15 (4.7)	8 (9.8)	18 (5.5)	41 (5.6)
Adverse event	5 (1.6)	2 (2.4)	5 (1.5)	12 (1.6)
Death	1 (0.3)	0	0	1 (0.1)
Lost to follow-up	3 (0.9)	0	4 (1.2)	7 (1.0)
Lack of efficacy	1 (0.3)	3 (3.7)	4 (1.2)	8 (1.1)
Noncompliance with study schedule	0	0	1 (0.3)	1 (0.1)
Physician decision	0	0	1 (0.3)	1 (0.1)
Withdrawal by subject	4 (1.2)	3 (3.7)	3 (0.9)	10 (1.4)
Other	1 (0.3)	0	0	1 (0.1)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, addisp.xpt
Abbreviations: n, number of subjects for the given category

Protocol Violations/Deviations

In ICONIC-LEAD, the two treatment arms had similar rates of major protocol deviations. The most common protocol deviations were receiving a wrong treatment or incorrect dose (3.7% for icotrokinra and 0.9% for placebo) and receiving a disallowed concomitant treatment (1.5% for icotrokinra and 3.1% for placebo). Fifteen subjects did not receive their randomized treatment during the 24-week placebo-controlled double-blind treatment period.

In ICONIC-ADVANCE 1, the rate of protocol deviations on the placebo arm was more than twice

as large as that on the icotrokinra arm – 4.8% on the icotrokinra arm and 11.5% on the placebo arm. The deucravacitinib arm had a similar rate (5.2%) of protocol deviations to the icotrokinra arm. The most common protocol deviations were entering the trial but not satisfying criteria (2.3% for icotrokinra, 4.5% for placebo, and 2.9% for deucravacitinib) and receiving a wrong treatment or incorrect dose (1.6% for icotrokinra, 3.8% for placebo, and 0.7% for deucravacitinib). Two subjects – one from each treatment arm – did not receive their randomized treatment during the 24-week placebo- and active comparator-controlled double-blind treatment period; the two subjects did not receive any treatment.

In ICONIC-TOTAL, the rate of protocol deviations on the placebo arm was more than twice as large as that on the icotrokinra arm – 4.3% on the icotrokinra arm and 10.7% on the placebo arm. The most common protocol deviations were entering the trial but not satisfying criteria (2.4% for icotrokinra and 3.9% for placebo) and receiving a disallowed concomitant treatment (1.4% for icotrokinra and 3.9% for placebo). All subjects received their randomized treatment during the 16-week placebo-controlled double-blind treatment period.

In ICONIC-ADVANCE 2, the three treatment arms had approximately similar rates of protocol deviations, with the placebo arm's being the largest (6.1%). The most common protocol deviations were entering the trial but not satisfying criteria (2.5% for icotrokinra, 2.4% for placebo, and 2.8% for deucravacitinib) and receiving a disallowed concomitant treatment (1.9% for icotrokinra, 2.4% for placebo, and 0.3% for deucravacitinib). All subjects received their randomized treatment during the 24-week placebo- and active comparator-controlled double-blind treatment period.

Demographic and Baseline Disease Characteristics

Table 23, Table 24, Table 25, and Table 26 present the demographics of ICONIC-LEAD, ICONIC-ADVANCE 1, ICONIC-TOTAL, and ICONIC-ADVANCE 2, respectively. Demographics and baseline disease characteristics were well-balanced in all four trials, although more subjects 65 years of age or older were randomized to icotrokinra (9.6%) than to placebo (4.9%) in ICONIC-TOTAL. All four trials enrolled more male subjects than female subjects.

In ICONIC-LEAD, approximately 72% of subjects were White, 24% Asian, and 1% Black or African American. More male subjects (65%) than female subjects (35%) were enrolled. Approximately 13% of subjects identified as Hispanic or Latino. The majority of subjects (75%) had a moderate IGA score at baseline. Demographics and baseline disease characteristics were generally well-balanced between treatment arms.

In ICONIC-ADVANCE 1, approximately 74% of subjects were White, 23% Asian, and 1.4% Black or African American. More male subjects (68%) than female subjects (32%) were enrolled. Approximately 17% of subjects identified as Hispanic or Latino. The majority of subjects (80%) had moderate IGA score at baseline. Demographic and baseline disease characteristics were well-balanced across the three treatment arms.

In ICONIC-TOTAL, approximately 78% of subjects were White, 20% Asian, and 1% Black or African American. More male subjects (64%) than female subjects (36%) were enrolled. Approximately 7% of subjects identified as Hispanic or Latino. At baseline, most subjects had moderate IGA (73%) and ss-IGA (64%) scores. At baseline, most subjects had moderate IGA (73%). The majority of subjects (81%) had moderate to severe ss-IGA scores at baseline, while smaller percentages had moderate to very severe sPGA-G scores (45%) and moderate to severe hf-PGA scores (23%) at baseline. The median (range) baseline BSA was 12.3 (1.0, 78.2). Notable demographic imbalances were observed, with a higher proportion of subjects ≥65 years of age randomized to icotrokinra compared to placebo (9.6% versus 4.9%). Imbalances were present in severe hf-PGA scores (8.2% icotrokinra versus 3.9% placebo) and in > 90 kg (34.1% icotrokinra versus 40.8% placebo).

In ICONIC-ADVANCE 2, approximately 83% of subjects were White, 12% Asian, and 3% Black or African American. The trial enrolled more male subjects (68%) than female subjects (32%). Approximately 14% of subjects were Hispanic or Latino. The majority of subjects (80%) had a moderate IGA score at baseline. Minor imbalances were observed in geographic distribution, with higher representation of Eastern European subjects in the placebo group (35.4%) compared to icotrokinra (29.2%) and deucravacitinib (33.3%) groups, and a higher proportion of Asian subjects in the placebo group (18.3%) compared to the icotrokinra (10.6%) and deucravacitinib (12.2%) groups.

Table 23. Demographic Characteristics and Baseline Disease Characteristics – ICONIC-LEAD (FAS[1])

Characteristic	Icotrokinra (N=456)	Placebo (N=228)	Total (N=684)
Age (years)			
Mean (SD)	42.4 (16.3)	43.2 (16.6)	42.6 (16.4)
Median	42.0	44.5	43.0
Min, Max	12, 85	12, 77	12, 85
Categories, n (%)			
12–17 years	44 (9.6)	22 (9.6)	66 (9.6)
18–44 years	208 (45.6)	92 (40.4)	300 (43.9)
45–64 years	165 (36.0)	89 (39.0)	253 (37.0)
≥65 years	40 (8.8)	25 (11.0)	65 (9.5)
Sex, n (%)			
Female	165 (36.2)	72 (31.6)	237 (34.6)
Male	291 (63.8)	156 (68.4)	447 (65.4)
Race, n (%)			
American Indian OR Alaska Native	0 (0.0)	1 (0.4)	1 (0.1)
Asian	110 (24.1)	57 (25.0)	167 (24.4)
Black OR African American	6 (1.3)	2 (0.9)	8 (1.2)
Multiple	1 (0.2)	0 (0.0)	1 (0.1)
Native Hawaiian OR Other Pacific Islander	2 (0.4)	0 (0.0)	2 (0.3)
Not Reported	5 (1.1)	2 (0.9)	7 (1.0)
Other	3 (0.7)	1 (0.4)	4 (0.6)
White	329 (72.1)	165 (72.4)	494 (72.2)

Characteristic	Icotrokinra (N=456)	Placebo (N=228)	Total (N=684)
Ethnicity, n (%)			
Hispanic OR Latino	61 (13.4)	27 (11.8)	88 (12.9)
Not Hispanic OR Latino	386 (84.6)	199 (87.3)	585 (85.5)
Not Reported	3 (0.7)	1 (0.4)	4 (0.6)
Unknown	6 (1.3)	1 (0.4)	7 (1.0)
Country, n (%)			
Argentina	19 (4.2)	7 (3.1)	26 (3.8)
Australia	6 (1.3)	4 (1.8)	10 (1.5)
Canada	44 (9.6)	27 (11.8)	71 (10.4)
China	67 (14.7)	34 (14.9)	1 01 (14.8)
Germany	64 (14.0)	37 (16.2)	101 (14.8)
Spain	13 (2.9)	5 (2.2)	18 (2.6)
United Kingdom	8 (1.8)	7 (3.1)	15 (2.2)
Hungary	12 (2.6)	7 (3.1)	19 (2.8)
Italy	1 (0.2)	0 (0.0)	1 (0.1)
Japan	2 (0.4)	5 (2.2)	7 (1.0)
Republic of Korea	7 (1.5)	2 (0.9)	9 (1.3)
Poland	107 (23.5)	43 (18.9)	150 (21.9)
Turkey	5 (1.1)	6 (2.6)	11 (1.6)
Taiwan	16 (3.5)	5 (2.2)	21 (3.1)
United States	85 (18.6)	39 (17.1)	124 (18.1)
Region, n (%)			
Australia and New Zealand	6 (1.3)	4 (1.8)	10 (1.5)
Eastern Asia	92 (20.2)	46 (20.2)	138 (20.2)
Eastern Europe	119 (26.1)	50 (21.9)	169 (24.7)
North America	129 (28.3)	66 (28.0)	195 (28.5)
Northern Europe	8 (1.8)	7 (3.1)	15 (2.2)
South America	19 (4.2)	7 (3.1)	26 (3.8)
Southern Europe	14 (3.1)	5 (2.2)	19 (2.8)
Western Asia	5 (1.1)	6 (2.6)	11 (1.6)
Western Europe	64 (14.0)	37 (16.2)	101 (14.8)
Weight at Baseline (kg)			
Mean (SD)	86.0 (21.6)	86.6 (23.5)	86.2 (22.2)
Median	84.5	84.5	84.5
Min, Max	41.0, 168.7	41.0, 199.6	41.0, 199.6
Categories, n (%)			
≤90 kg	274 (60.1)	136 (59.6)	410 (59.9)
>90 kg	182 (39.9)	92 (40.4)	274 (40.1)
Baseline BMI (kg/m^2)			
Mean (SD)	29.4 (19.13)	32.2 (21.63)	30.8 (20.37)
Median	25.5	29.0	26.5
Min, Max	3.8, 69.0	0, 99.0	0, 99.0
Categories, n (%)			
Normal (<25)	125 (27.4)	56 (24.6)	181 (26.5)
Obese (≥30)	179 (39.3)	88 (38.6)	267 (39.0)
Overweight (≥25 to <30)	151 (33.1)	83 (36.4)	234 (34.2)
Baseline PASI Score			
Mean (SD)	19.4 (7.1)	20.8 (8.1)	19.9 (7.5)
Median	17.4	18.1	17.5
Min, Max	12.0, 58.3	12.0, 56.0	12.0, 58.3

Characteristic	Icotrokinra (N=456)	Placebo (N=228)	Total (N=684)
IGA Score at Baseline, n (%)			
Moderate (=3)	341 (74.8)	173 (75.9)	514 (75.1)
Severe (=4)	115 (25.2)	55 (24.1)	170 (24.9)

Source: Statistical Reviewer's Analysis; adsl.xpt, adbdc.xpt
[1] Full analysis set (FAS): all randomized subjects.
Abbreviations: BMI, body mass index; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of subjects within given characteristic; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 24. Demographics and Baseline Disease Characteristics – ICONIC-ADVANCE 1 (FAS[1])

Characteristic	Icotrokinra (N=311)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=774)
Age (years)				
Mean (SD)	47.1 (13.2)	46.9 (12.8)	46.3 (13.9)	46.7 (13.4)
Median	47	46	47	47
Min, Max	18, 79	18, 76	18, 81	18, 81
Categories, n (%)				
18–44 years	139 (44.7)	69 (44.2)	136 (44.3)	344 (44.6)
45–64 years	140 (45.0)	69 (44.2)	137 (44.6)	346 (44.7)
≥ 65 years	32 (10.3)	18 (11.5)	34 (11.1)	84 (10.9)
Sex, n (%)				
Female	88 (28.3)	51 (32.7)	107 (34.9)	246 (31.8)
Male	223 (71.7)	105 (67.3)	200 (65.1)	528 (68.2)
Race, n (%)				
American Indian OR Alaska Native	1 (0.3)	1 (0.6)	1 (0.3)	3 (0.4)
Asian	69 (22.2)	34 (21.8)	77 (25.1)	180 (23.3)
Black OR African American	4 (1.3)	3 (1.9)	4 (1.3)	11 (1.4)
Native Hawaiian OR Other Pacific Islander	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)
Not Reported	2 (0.6)	0 (0.0)	3 (1.0)	5 (0.6)
Unknown	2 (0.6)	0 (0.0)	1 (0.3)	3 (0.4)
White	231 (74.3)	118 (75.6)	221 (72.0)	570 (73.6)
Ethnicity, n (%)				
Hispanic OR Latino	58 (18.6)	25 (16.0)	49 (16.0)	132 (17.1)
Not Hispanic OR Latino	250 (80.4)	129 (82.7)	257 (83.7)	636 (82.2)
Not Reported	2 (0.6)	2 (1.3)	0 (0.0)	4 (0.5)
Unknown	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.3)
Country, n (%)				
Argentina	24 (7.7)	15 (9.6)	17 (5.5)	56 (7.2)
Australia	5 (1.6)	3 (1.9)	3 (1.0)	11 (1.4)
Brazil	0 (0.0)	1 (0.6)	1 (0.3)	2 (0.3)
Canada	34 (10.9)	16 (10.3)	34 (11.1)	84 (10.9)
Germany	30 (9.6)	18 (11.5)	33 (10.7)	81 (10.5)
Spain	21 (6.8)	9 (5.8)	25 (8.1)	55 (7.1)
United Kingdom	2 (0.6)	2 (1.3)	5 (1.6)	9 (1.2)
Hungary	19 (6.1)	5 (3.2)	18 (5.9)	42 (5.4)
Japan	23 (7.4)	11 (7.1)	25 (8.1)	59 (7.6)
Republic of Korea	20 (6.4)	12 (7.7)	20 (6.5)	52 (6.7)
Poland	66 (21.2)	35 (22.4)	56 (18.2)	157 (20.3)
Taiwan	18 (5.8)	7 (4.5)	17 (5.5)	42 (5.4)
United States	49 (15.8)	22 (14.1)	53 (17.3)	124 (16.0)

Characteristic	Icotrokinra (N=311)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=774)
Region, n (%)				
Australia and New Zealand	5 (1.6)	3 (1.9)	3 (1.0)	11 (1.4)
Eastern Asia	61 (19.6)	30 (19.2)	62 (20.2)	153 (19.8)
Eastern Europe	85 (27.3)	40 (25.6)	74 (24.1)	199 (25.7)
North America	83 (26.7)	38 (24.4)	87 (28.3)	208 (26.9)
Northern Europe	2 (0.6)	2 (1.3)	5 (1.6)	9 (1.2)
South America	24 (7.7)	16 (10.3)	18 (5.9)	58 (7.5)
Southern Europe	21 (6.8)	9 (5.8)	25 (8.1)	55 (7.1)
Western Europe	30 (9.6)	18 (11.5)	33 (10.7)	81 (10.5)
Weight at Baseline (kg)				
Mean (SD)	86.9 (21.1)	88.2 (25.1)	87.7 (23.0)	87.5 (22.7)
Median	84.8	83.3	84.8	84.5
Min, Max	39.0, 166.0	43.0, 210.9	40.4, 180.0	39.0, 210.9
Categories, n (%)				
≤90 kg	189 (60.8)	92 (59.0)	185 (60.3)	466 (60.2)
>90 kg	122 (39.2)	64 (41.0)	122 (39.7)	308 (39.8)
Baseline BMI (kg/m^2)				
Mean (SD)	29.2 (6.3)	29.6 (8.1)	29.9 (7.3)	29.5 (7.1)
Median	28.3	28.3	28.8	28.5
Min, Max	16.3, 57.4	17.2, 82.6	16.4, 57.8	16.3, 82.6
Categories, n (%)				
Normal (<25)	80 (25.7)	42 (26.9)	80 (26.1)	202 (26.1)
Obese (≥30)	116 (37.3)	61 (39.1)	127 (41.4)	304 (39.3)
Overweight (≥25 to <30)	115 (37.0)	53 (34.0)	100 (32.6)	268 (34.6)
Baseline PASI Score				
Mean (SD)	20.3 (6.9)	19.2 (6.6)	20.4 (7.9)	20.1 (7.3)
Median	18.6	17.2	18.0	18.0
Min, Max	11.6, 48.6	12.0, 45.2	12.0, 62.4	11.6, 62.4
IGA Score at Baseline, n (%)				
Moderate (=3)	251 (80.7)	123 (78.8)	242 (78.8)	616 (79.6)
Severe (=4)	60 (19.3)	33 (21.2)	65 (21.2)	158 (20.4)

Source: Statistical Reviewer's Analysis; adsl.xpt, adbdc.xpt
[1] Full analysis set (FAS): all randomized subjects.
Abbreviations: BMI, body mass index; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of subjects within given characteristic; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 25. Demographics and Baseline Disease Characteristics – ICONIC-TOTAL (FAS[1])

Characteristic	Icotrokinra (N=208)	Placebo (N=103)	Total (N=311)
Age (years)			
Mean (SD)	45.3 (14.6)	43.5 (13.8)	44.7 (14.3)
Median	45	44	44
Min, Max	13, 82	12, 87	12, 87
Categories, n (%)			
12–17 years	3 (1.4)	3 (2.9)	6 (1.9)
18–44 years	100 (48.1)	50 (48.5)	150 (48.2)
45–64 years	85 (40.9)	45 (43.7)	130 (41.8)
≥ 65 years	20 (9.6)	5 (4.9)	25 (8.0)
Sex, n (%)			
Female	71 (34.1)	40 (38.8)	111 (35.7)
Male	137 (65.9)	63 (61.2)	200 (64.3)

Characteristic	Icotrokinra (N=208)	Placebo (N=103)	Total (N=311)
Race, n (%)			
Asian	41 (19.7)	20 (19.4)	61 (19.6)
Black OR African American	2 (1.0)	0 (0.0)	2 (0.6)
Multiple	1 (0.5)	0 (0.0)	1 (0.3)
Not Reported	3 (1.4)	1 (1.0)	4 (1.3)
White	161 (77.4)	82 (79.6)	243 (78.1)
Ethnicity, n (%)			
Hispanic OR Latino	16 (7.7)	5 (4.9)	21 (6.8)
Not Hispanic OR Latino	184 (88.5)	96 (93.2)	280 (90.0)
Not Reported	8 (3.8)	2 (1.9)	10 (3.2)
Country, n (%)			
Argentina	4 (1.9)	0 (0.0)	4 (1.3)
Canada	31 (14.9)	14 (13.6)	45 (14.5)
Germany	32 (15.4)	18 (17.5)	50 (16.1)
Spain	3 (1.4)	3 (2.9)	6 (1.9)
United Kingdom	2 (1.0)	0 (0.0)	2 (0.6)
Hungary	12 (5.8)	7 (6.8)	19 (6.1)
Republic of Korea	8 (3.8)	2 (1.9)	10 (3.2)
Poland	52 (25.0)	23 (22.3)	75 (24.1)
Taiwan	26 (12.5)	14 (13.6)	40 (12.9)
United States	38 (18.3)	22 (21.4)	60 (19.3)
Region, n (%)			
Eastern Asia	34 (16.3)	16 (15.5)	50 (16.1)
Eastern Europe	64 (30.8)	30 (29.1)	94 (30.2)
North America	69 (33.2)	36 (35.0)	105 (33.8)
Northern Europe	2 (1.0)	0 (0.0)	2 (0.6)
South America	4 (1.9)	0 (0.0)	4 (1.3)
Southern Europe	3 (1.4)	3 (2.9)	6 (1.9)
Western Europe	32 (15.4)	18 (17.5)	50 (16.1)
Weight at Baseline (kg)			
Mean (SD)	85.3 (20.2)	86.3 (25.7)	85.6 (22.1)
Median	83.8	85.7	84.0
Min, Max	45.4, 166.0	40.3, 246.0	40.3, 246.0
Categories, n (%)			
≤90 kg	133 (63.9)	59 (57.3)	192 (61.7)
>90 kg	71 (34.1)	42 (40.8)	113 (36.3)
Baseline BMI (kg/m^2)			
Mean (SD)	29.0 (6.6)	29.4 (8.1)	29.2 (7.1)
Median	28.3	27.6	28.2
Min, Max	17.1, 66.9	16.5, 77.8	16.5, 77.8
Categories, n (%)			
Normal (<25)	60 (28.8)	31 (30.1)	91 (29.3)
Obese (≥30)	78 (37.5)	37 (35.9)	115 (37.0)
Overweight (≥25 to <30)	65 (31.3)	33 (32.0)	98 (31.5)
Baseline PASI Score			
Mean (SD)	14.6 (7.6)	14.0 (7.0)	14.4 (7.4)
Median	13.4	13.8	13.6
Min, Max	1.8, 37.3	1.7, 41.8	1.7, 41.8

Characteristic	Icotrokinra (N=208)	Placebo (N=103)	Total (N=311)
IGA Score at Baseline, n (%)			
Mild (=2)	9 (4.3)	8 (7.8)	17 (5.5)
Moderate (=3)	153 (73.6)	73 (70.9)	226 (72.7)
Severe (=4)	46 (22.1)	22 (21.4)	68 (21.9)
ss-IGA Score at Baseline, n (%)			
Absent (=0)	13 (6.3)	7 (6.8)	20 (6.4)
Very Mild (=1)	6 (2.9)	0 (0.0)	6 (1.9)
Mild (=2)	22 (10.6)	11 (10.7)	33 (10.6)
Moderate (=3)	134 (64.4)	64 (62.1)	198 (63.7)
Severe (=4)	33 (15.9)	21 (20.4)	54 (17.4)
sPGA-G Score at Baseline, n (%)			
Clear (=0)	91 (43.8)	53 (51.5)	144 (46.3)
Minimal (=1)	6 (2.9)	3 (2.9)	9 (2.9)
Mild (=2)	13 (6.3)	5 (4.9)	18 (5.8)
Moderate (=3)	75 (36.1)	29 (28.2)	104 (33.4)
Severe (=4)	22 (10.6)	12 (11.7)	34 (10.9)
Very Severe (=5)	1 (0.5)	1 (1.0)	2 (0.6)
hf-PGA Score at Baseline, n (%)			
Clear (=0)	134 (64.4)	68 (66.0)	202 (65.0)
Almost Clear (=1)	8 (3.8)	4 (3.9)	12 (3.9)
Mild (=2)	18 (8.7)	8 (7.8)	26 (8.4)
Moderate (=3)	31 (14.9)	19 (18.4)	50 (16.1)
Severe (=4)	17 (8.2)	4 (3.9)	21 (6.8)
Baseline BSA			
Mean (SD)	16.6 (13.5)	14.8 (11.7)	16.0 (12.9)
Median	12.0	13.0	12.3
Min, Max	1.3, 78.2	1.0, 60.0	1.0, 78.2

Source: Statistical Reviewer's Analysis; adsl.xpt, adbdc.xpt
[1] Full analysis set (FAS): all randomized subjects.
Abbreviations: BMI, body mass index; BSA, body surface area; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of subjects within given characteristic; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Table 26. Demographics and Baseline Disease Characteristics – ICONIC-ADVANCE 2 (FAS[1])

Characteristic	Icotrokinra (N=322)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=785)
Age (years)				
Mean (SD)	45.9 (13.8)	48.4 (13.9)	45.6 (13.2)	46.1 (13.6)
Median	45.0	47.5	46.0	45
Min, Max	18, 84	21, 80	18, 86	18, 86
Categories, n (%)				
18–44 years	158 (49.1)	36 (43.9)	156 (47.7)	350 (47.9)
45–64 years	131 (40.7)	36 (43.9)	140 (42.8)	307 (42.0)
≥ 65 years	33 (10.2)	10 (12.2)	31 (9.5)	74 (10.1)
Sex, n (%)				
Female	104 (32.3)	27 (32.9)	104 (31.8)	235 (32.1)
Male	218 (67.7)	55 (67.1)	223 (68.2)	496 (67.9)

Characteristic	Icotrokinra (N=322)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=785)
Race, n (%)				
American Indian OR Alaska Native	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.3)
Asian	34 (10.6)	15 (18.3)	40 (12.2)	89 (12.2)
Black OR African American	9 (2.8)	2 (2.4)	11 (3.4)	22 (3.0)
Multiple	1 (0.3)	0 (0.0)	2 (0.6)	3 (0.4)
Native Hawaiian OR Other Pacific Islander	2 (0.6)	0 (0.0)	3 (0.9)	5 (0.7)
Not Reported	1 (0.3)	0 (0.0)	4 (1.2)	5 (0.7)
Unknown	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
White	274 (85.1)	65 (79.3)	265 (81.0)	604 (82.6)
Ethnicity, n (%)				
Hispanic OR Latino	42 (13.0)	12 (14.6)	48 (14.7)	102 (14.0)
Not Hispanic OR Latino	279 (86.6)	70 (85.4)	279 (85.3)	628 (85.9)
Unknown	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Country, n (%)				
Australia	9 (2.8)	2 (2.4)	9 (2.8)	20 (2.7)
Brazil	11 (3.4)	2 (2.4)	12 (3.7)	25 (3.4)
Canada	33 (10.2)	10 (12.2)	33 (10.1)	76 (10.4)
Germany	77 (23.9)	14 (17.1)	60 (18.3)	151 (20.7)
Spain	19 (5.9)	5 (6.1)	23 (7.0)	47 (6.4)
Hungary	12 (3.7)	5 (6.1)	11 (3.4)	28 (3.8)
Republic of Korea	7 (2.2)	3 (3.7)	13 (4.0)	23 (3.1)
Poland	79 (24.5)	24 (29.3)	90 (27.5)	193 (26.4)
Romania	3 (0.9)	0 (0.0)	8 (2.4)	11 (1.5)
Taiwan	16 (5.0)	4 (4.9)	13 (4.0)	33 (4.5)
United States	56 (17.4)	13 (15.9)	55 (16.8)	124 (17.0)
Region, n (%)				
Australia and New Zealand	9 (2.8)	2 (2.4)	9 (2.8)	20 (2.7)
Eastern Asia	23 (7.1)	7 (8.5)	26 (8.0)	56 (7.7)
Eastern Europe	94 (29.2)	29 (35.4)	109 (33.3)	232 (31.7)
North America	89 (27.6)	23 (28.0)	88 (26.9)	200 (27.4)
South America	11 (3.4)	2 (2.4)	12 (3.7)	25 (3.4)
Southern Europe	19 (5.9)	5 (6.1)	23 (7.0)	47 (6.4)
Western Europe	77 (23.9)	14 (17.1)	60 (18.3)	151 (20.7)
Weight at Baseline (kg)				
Mean (SD)	88.8 (20.1)	86.4 (18.8)	89.8 (21.4)	89.0 (20.6)
Median	87.0	85.0	86.7	86.6
Min, Max	46.1, 168.0	42.6, 138.0	49.0, 180.5	42.6, 180.5
Categories, n (%)				
≤90 kg	186 (57.8)	48 (58.5)	188 (57.5)	422 (57.7)
>90 kg	136 (42.2)	34 (41.5)	138 (42.2)	308 (42.1)
Baseline BMI (kg/m^2)				
Mean (SD)	29.9 (6.4)	29.5 (5.8)	29.9 (6.9)	29.8 (6.5)
Median	28.8	28.8	28.8	28.8
Min, Max	15.3, 50.9	18.4, 55.1	17.4, 57.7	15.3, 57.7
Categories, n (%)				
Normal (<25)	71 (22.0)	14 (17.1)	75 (22.9)	160 (21.9)
Obese (≥30)	140 (43.5)	38 (46.3)	135 (41.3)	313 (42.8)
Overweight (≥25 to <30)	111 (34.5)	30 (36.6)	115 (35.2)	256 (35.0)

Characteristic	Icotrokinra (N=322)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=785)
Baseline PASI Score				
Mean (SD)	19.9 (7.0)	20.1 (7.5)	19.6 (6.6)	19.8 (6.9)
Median	18.0	18.0	17.6	17.8
Min, Max	12.0, 50.8	10.8, 45.7	12.0, 51.6	10.8, 51.6
IGA Score at Baseline, n (%)				
Moderate (=3)	252 (78.3)	67 (81.7)	267 (81.7)	586 (80.2)
Severe (=4)	70 (21.7)	15 (18.3)	60 (18.3)	145 (19.8)

Source: Statistical Reviewer's Analysis; adsl.xpt, adbdc.xpt
[1] Full analysis set (FAS): all randomized subjects.
Abbreviations: BMI, body mass index; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of subjects within given characteristic; PASI, Psoriasis Area and Severity Index; SD, standard deviation

Efficacy Results – Primary Endpoint

Table 27 presents the results for the coprimary efficacy endpoints at Week 16 for all four pivotal trials. The endpoints were analyzed using the CMH chi-square test adjusted for the stratification factors at randomization. In all four trials, icotrokinra was statistically superior to placebo (p-values <0.0001).

Table 27. Results for Coprimary Efficacy Endpoints – ICONIC-LEAD, ICONIC-ADVANCE 1/2, ICONIC-TOTAL (FAS[1])

(Coprimary)	ICONIC-LEAD[a]		ICONIC-ADVANCE 1[b]		ICONIC-TOTAL		ICONIC-ADVANCE 2[b]	
	Icotrokinra (N=456)	Placebo (N=228)	Icotrokinra (N=311)	Placebo (N=156)	Icotrokinra (N=208)	Placebo (N=103)	Icotrokinra (N=322)	Placebo (N=82)
IGA 0/1 (Week 16)	64.7%	8.3%	68.5%	10.9%	56.7%	5.8%	70.5%	8.5%
Risk Difference (95% CI)[c]	56.4% (50.4%, 61.7%)		57.6% (49.9%, 64.2%)		51.1% (42.1%, 58.8%)		62.0% (52.9%, 69.1%)	
p-value[d]	<0.0001		<0.0001		<0.0001		<0.0001	
PASI-90 (Week 16)	49.6%	4.4%	55.0%	3.8%	Not included.		57.1%	1.2%
Risk Difference (95% CI)[c]	45.1% (39.6%, 50.4%)		51.1% (44.5%, 57.3%)				55.9% (48.5%, 62.0%)	
p-value[d]	<0.0001		<0.0001				<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adclrori.xpt, adpasiri.xpt
[1] Full analysis set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).
[a] For ICONIC-LEAD, randomization was stratified by age group, baseline weight category (≤90 kg, >90 kg) for adults, and geographic region.
[b] For ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2, randomization was stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.
[c] The risk difference and 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method were adjusted for the stratification factors at randomization.
[d] The p-value was based on the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors at randomization.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA 0/1, achievement of Investigator Global Assessment score of clear (0) or almost clear (1) with a ≥2-grade improvement from baseline; PASI-90, achievement of ≥90% improvement in Psoriasis Area Severity Index score from baseline

Table 28, Table 29, Table 30, and Table 31 summarize the numbers and rates of intercurrent events (ICEs) and missing data for the primary endpoints across the trials. The most consistent imbalance observed was the substantially higher rate of discontinuation of treatment due to lack of efficacy or worsening psoriasis (ICE 1) in placebo groups compared to icotrokinra groups, with differences ranging from 4.9-fold to 16.3-fold. Initiation of rescue therapy (ICE 2) was also consistently higher in placebo groups. These imbalances are expected, given the superior efficacy of icotrokinra, and support the primary efficacy findings. Missing data rates were generally low and balanced between groups (≤5% in most cases).

Table 28. Summary of Intercurrent Events and Missing Data Through Week 16 – ICONIC-LEAD (FAS[1])

Parameters	Icotrokinra (N=456)	Placebo (N=228)	Total (N=684)
Subjects with ICEs through Week 16, n (%)	20 (4.4)	16 (7.0)	36 (5.3)
ICE 1 – Discontinuation of treatment due to lack of efficacy, or due to an AE of worsening psoriasis	1 (0.2)	7 (3.1)	8 (1.2)
ICE 2 – Initiation of other medication or therapy that could improve psoriasis	1 (0.2)	3 (1.3)	4 (0.6)
ICE 3 – Discontinuation of treatment for other reasons than ICE 1	18 (3.9)	6 (2.6)	24 (3.5)
Missing IGA data at Week 16	17 (3.7)	6 (2.6)	23 (3.4)
Missing PASI data at Week 16	17 (3.7)	6 (2.6)	23 (3.4)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, adice.xpt, adclro.xpt, adpasi.xpt
[1] Full analysis set (FAS): all randomized subjects.
Subjects were counted only once in ICEs, based on whichever occurrence happened first.
After accounting for the ICEs, subjects with missing data were counted in the last row, therefore subjects with ICE 3 could also be counted in the last row if their observed data were missing.
Abbreviations: ICE, intercurrent event; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of corresponding subjects; PASI, Psoriasis Area and Severity Index

Table 29. Summary of ICEs and Missing Data Through Week 16 – ICONIC-ADVANCE 1 (FAS[1])

Parameters	Icotrokinra (N=311)	Placebo (N=156)	Deucravacitinib (N=307)	Total (N=774)
Subjects with ICEs through Week 16, n (%)	15 (4.8)	18 (11.5)	21 (6.8)	54 (7.0)
ICE 1 – Discontinuation of treatment due to lack of efficacy, or due to an AE of worsening psoriasis	2 (0.6)	7 (4.5)	5 (1.6)	14 (1.8)
ICE 2 – Initiation of other medication or therapy that could improve psoriasis	0 (0.0)	6 (3.8)	1 (0.3)	7 (0.9)
ICE 3 – Discontinuation of treatment for other reasons than ICE 1	13 (4.2)	5 (3.2)	15 (4.9)	33 (4.3)
Missing IGA data at Week 16	14 (4.5)	5 (3.2)	15 (4.9)	34 (4.4)
Missing PASI data at Week 16	14 (4.5)	5 (3.2)	15 (4.9)	34 (4.4)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, adice.xpt, adclro.xpt, adpasi.xpt
[1] Full analysis set (FAS): all randomized subjects.
Subjects were counted only once in ICEs, based on whichever occurrence happened first.
After accounting for the ICEs, subjects with missing data were counted in the last row, therefore subjects with ICE 3 could also be counted in the last row if their observed data were missing.
Abbreviations: ICE, intercurrent event; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of corresponding subjects; PASI, Psoriasis Area and Severity Index

Table 30. Summary of ICEs and Missing Data Through Week 16 – ICONIC-TOTAL (FAS[1])

Parameters	Icotrokinra (N=208)	Placebo (N=103)	Total (N=311)
Subjects with ICEs through Week 16, n (%)	7 (3.4)	10 (9.7)	17 (5.5)
ICE 1 – Discontinuation of treatment due to lack of efficacy, or due to an AE of worsening psoriasis	2 (1.0)	5 (4.9)	7 (2.3)
ICE 2 – Initiation of other medication or therapy that could improve psoriasis	0 (0.0)	3 (2.9)	3 (1.0)
ICE 3 – Discontinuation of treatment for other reasons than ICE 1	5 (2.4)	2 (1.9)	7 (2.3)
Missing IGA data at Week 16	6 (2.9)	3 (2.9)	9 (2.9)

Source: Statistical Analyst's Analysis (same as Applicant's Analysis); adsl.xpt, adice.xpt, adclro.xpt

[1] Full analysis set (FAS): all randomized subjects.

Subjects were counted only once in ICEs, based on whichever occurrence happened first.

After accounting for the ICEs, subjects with missing data were counted in the last row, therefore subjects with ICE 3 could also be counted in the last row if their observed data were missing.

Abbreviations: ICE, intercurrent event; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of corresponding subjects

Table 31. Summary of ICEs and Missing Data Through Week 16 – ICONIC-ADVANCE 2 (FAS[1])

Parameters	Icotrokinra (N=322)	Placebo (N=82)	Deucravacitinib (N=327)	Total (N=731)
Subjects with ICEs through Week 16, n (%)	15 (4.7)	8 (9.8)	18 (5.5)	41 (5.6)
ICE 1 – Discontinuation of treatment due to lack of efficacy, or due to an AE of worsening psoriasis	1 (0.3)	4 (4.9)	4 (1.2)	9 (1.2)
ICE 2 – Initiation of other medication or therapy that could improve psoriasis	3 (0.9)	0 (0.0)	2 (0.6)	5 (0.7)
ICE 3 – Discontinuation of treatment for other reasons than ICE 1	11 (3.4)	4 (4.9)	12 (3.7)	27 (3.7)
Missing IGA data at Week 16	11 (3.4)	4 (4.9)	11 (3.4)	26 (3.6)
Missing PASI data at Week 16	11 (3.4)	4 (4.9)	11 (3.4)	26 (3.6)

Source: Statistical Analyst's Analysis (Same as Applicant's Analysis); adsl.xpt, adice.xpt, adclro.xpt, adpasi.xpt

[1] Full analysis set (FAS): all randomized subjects.

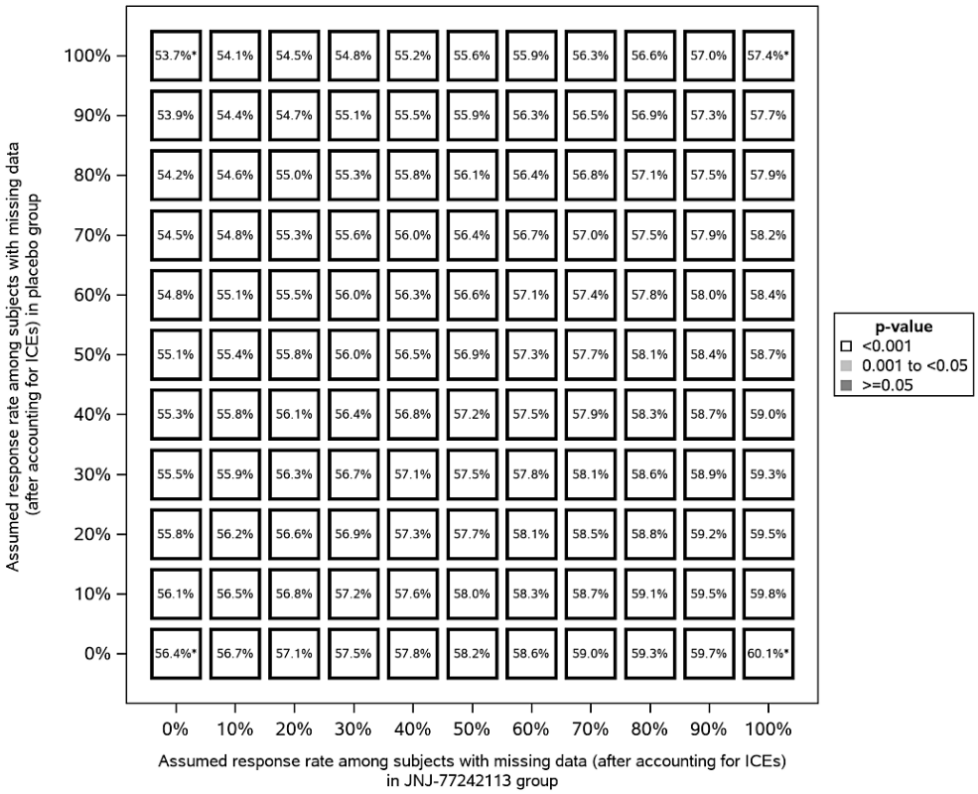
Subjects were counted only once in ICEs, based on whichever occurrence happened first.

After accounting for the ICEs, subjects with missing data were counted in the last row, therefore subjects with ICE 3 could also be counted in the last row if their observed data were missing.

Abbreviations: ICE, intercurrent event; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; n, number of corresponding subjects; PASI, Psoriasis Area and Severity Index

The Applicant conducted tipping point analyses for the primary efficacy endpoint (i.e., IGA 0/1 response) in ICONIC-TOTAL, and for the coprimary efficacy endpoints (i.e., IGA 0/1 response and PASI-90 response) in the remaining three trials. In all four trials, no tipping points were identified, and the results for the coprimary endpoints remained statistically significant, with p-values <0.001, even under the worst-case scenario, where all subjects on the icotrokinra arm with missing data at Week 16 were considered nonresponders and all such subjects on the placebo arm were considered responders.

Figure 30. Tipping Point Analysis for the Proportion of Subjects With an IGA Score of 0 or 1 and a ≥2-Grade Improvement From Baseline at Week 16 – ICONIC-LEAD (FAS[1])



Source: Clinical Study Report, p. 190

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

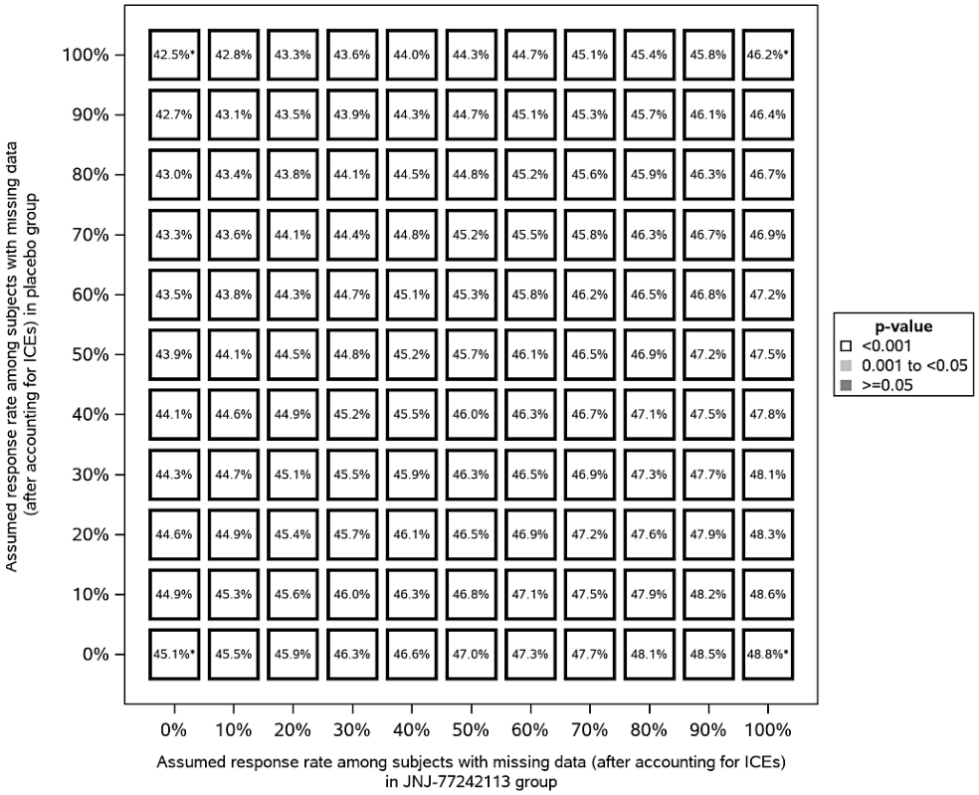
The treatment difference using Mantel-Haenszel weights adjusting for age group, baseline weight category for adult, and geographic region was calculated for each imputed dataset. The resulting values were combined to obtain an overall treatment difference.

The CMH chi-square statistic using the Wilson-Hilferty transformation was calculated for each imputed dataset. The resulting transformed values were combined to obtain an overall p-value.

For the asterisked scenarios, the estimates were based on a single imputed dataset using the corresponding assumed response rates.

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 31. Tipping Point Analysis for the Proportion of Subjects Achieving a PASI 90 Response at Week 16 – ICONIC-LEAD (FAS[1])



Source: Clinical Study Report, p. 233

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

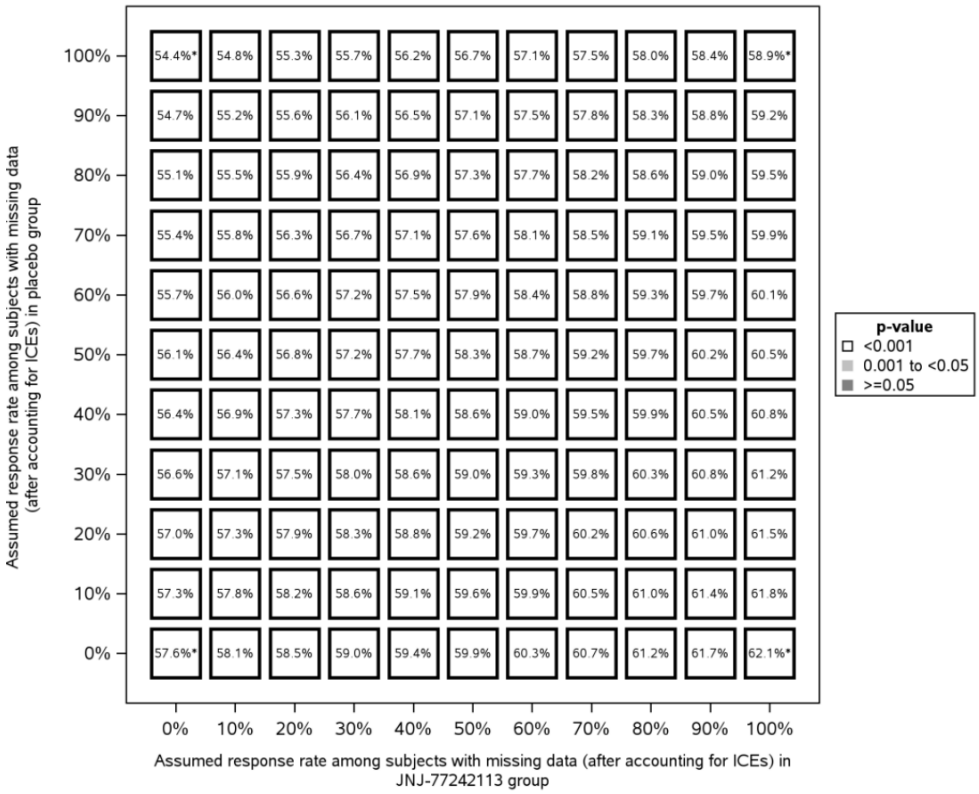
The treatment difference using Mantel-Haenszel weights adjusting for age group, baseline weight category for adult, and geographic region was calculated for each imputed dataset. The resulting values were combined to obtain an overall treatment difference.

The CMH chi-square statistic using the Wilson-Hilferty transformation was calculated for each imputed dataset. The resulting transformed values were combined to obtain an overall p-value.

For the asterisked scenarios, the estimates were based on a single imputed dataset using the corresponding assumed response rates.

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 32. Tipping Point Analysis for the Proportion of Subjects With an IGA Score of 0 or 1 and a ≥2-Grade Improvement From Baseline at Week 16 – ICONIC-ADVANCE 1 (FAS[1])



Source: Clinical Study Report, p. 136

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

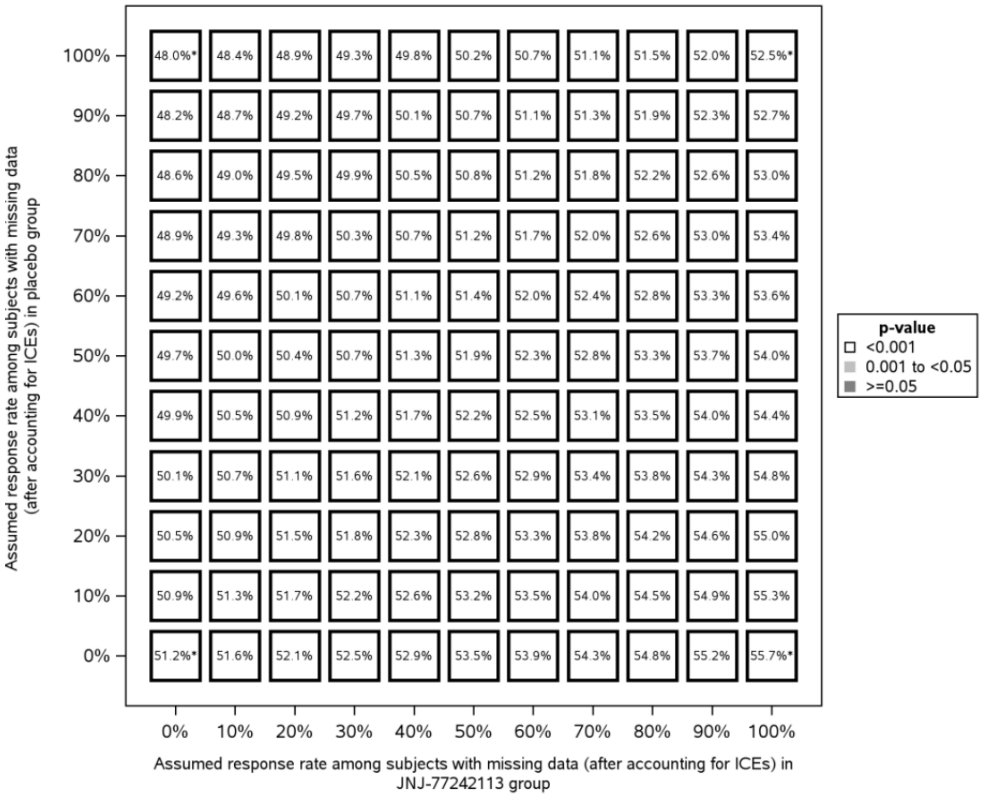
The treatment difference using Mantel-Haenszel weights adjusting for age group, baseline weight category for adult, and geographic region was calculated for each imputed dataset. The resulting values were combined to obtain an overall treatment difference.

The CMH chi-square statistic using the Wilson-Hilferty transformation was calculated for each imputed dataset. The resulting transformed values were combined to obtain an overall p-value.

For the asterisked scenarios, the estimates were based on a single imputed dataset using the corresponding assumed response rates.

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 33. Tipping Point Analysis for the Proportion of Subjects Achieving a PASI 90 Response at Week 16 – ICONIC-ADVANCE 1 (FAS[1])



Source: Clinical Study Report, p. 138

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

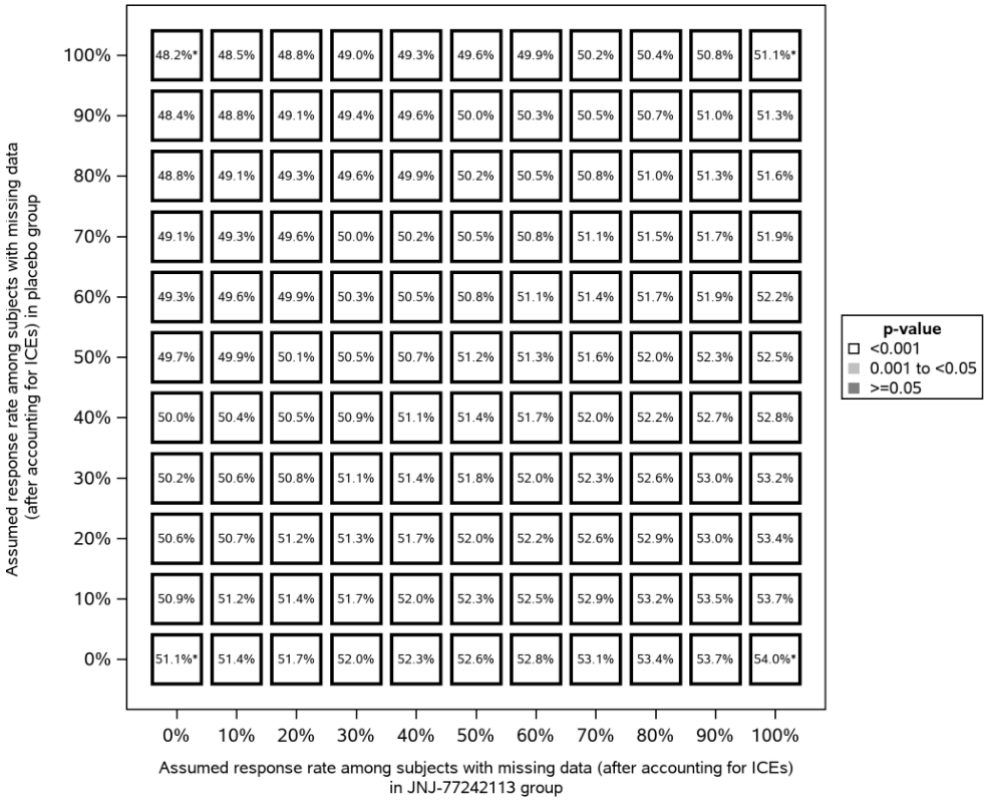
The treatment difference using Mantel-Haenszel weights adjusting for baseline weight category (≤ 90 kg, >90 kg) and geographic region was calculated for each imputed dataset. The resulting values were combined to obtain an overall treatment difference.

The CMH chi-square statistic using the Wilson-Hilferty transformation was calculated for each imputed dataset. The resulting transformed values were combined to obtain an overall p-value.

For the asterisked scenarios, the estimates were based on a single imputed dataset using the corresponding assumed response rates.

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 34. Tipping Point Analysis for the Proportion of Subjects With an IGA Score of 0 or 1 and a ≥2-Grade Improvement From Baseline at Week 16 – ICONIC-TOTAL (FAS[1])

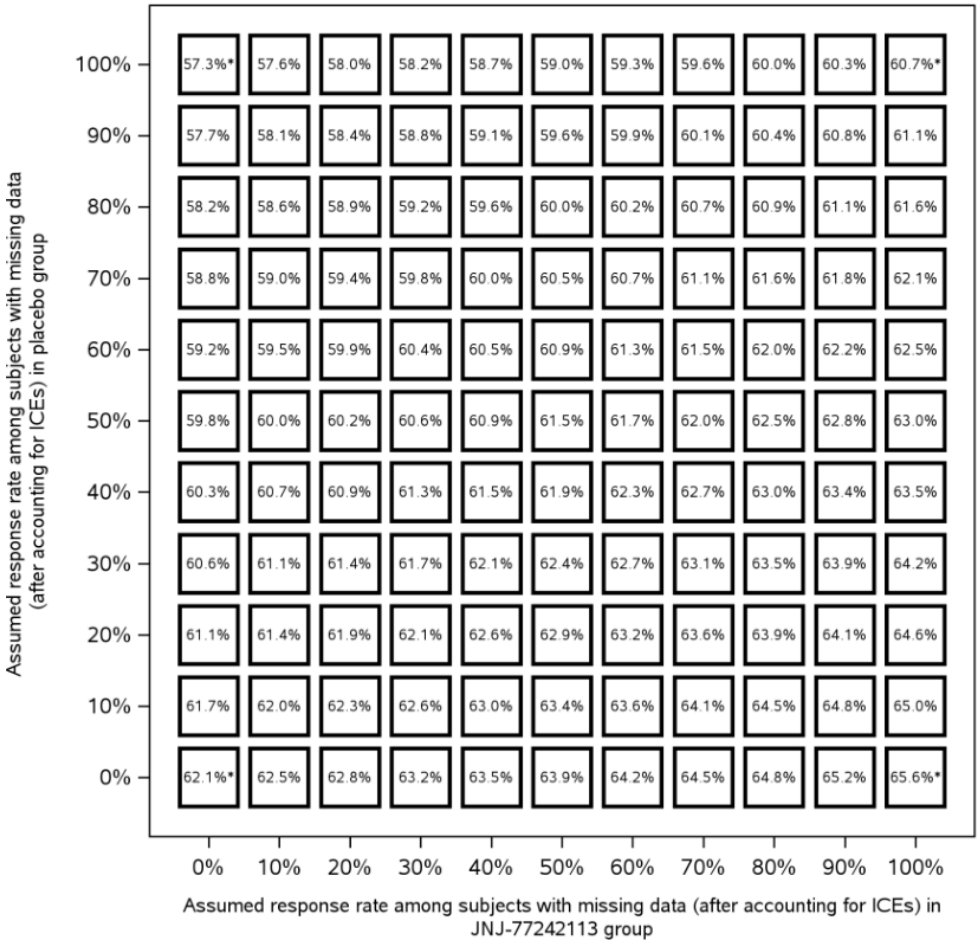


Source: Clinical Study Report, p. 144

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 35. Tipping Point Analysis for the Proportion of Subjects With an IGA Score of 0 or 1 and a ≥2-Grade Improvement From Baseline at Week 16 – ICONIC-ADVANCE 2 (FAS[1])

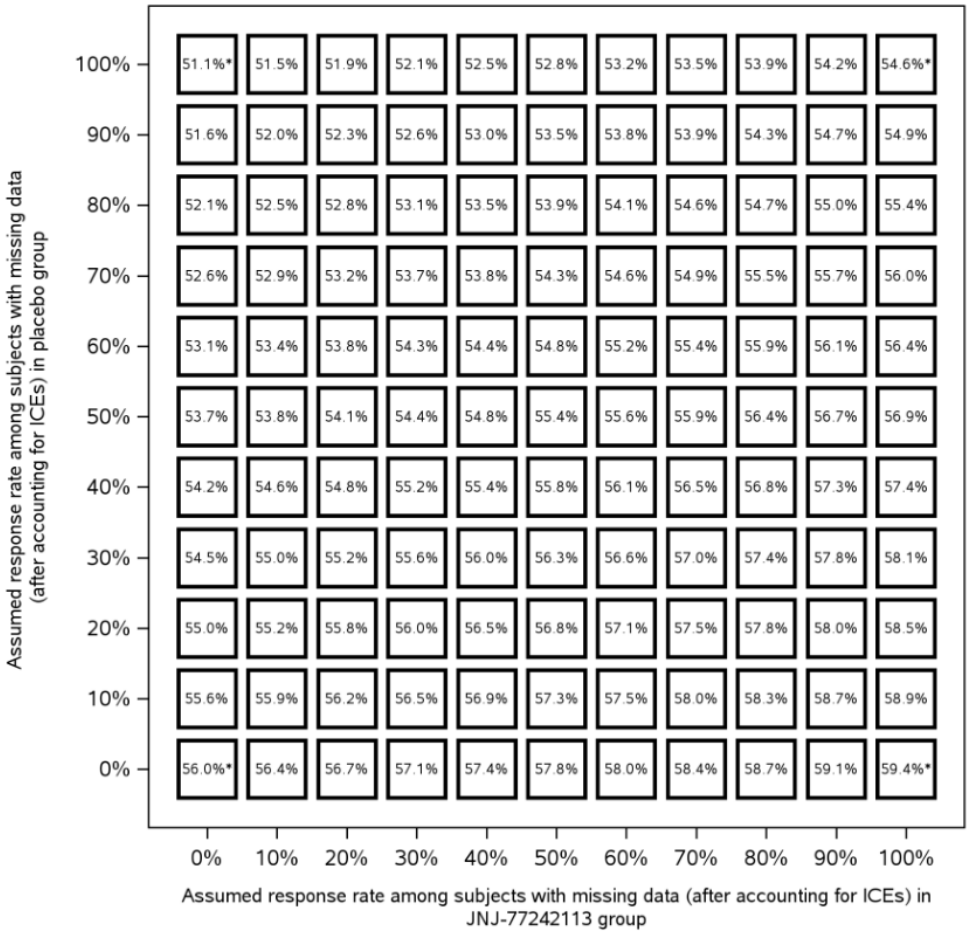


Source: Clinical Study Report, p. 129

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Figure 36. Tipping Point Analysis for the Proportion of Subjects Achieving a PASI 90 Response at Week 16 – ICONIC-ADVANCE 2 (FAS[1])



Source: Clinical Study Report, p. 130

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

Abbreviations: CMH, Cochran-Mantel-Haenszel; FAS, full analysis set; ICE, intercurrent event

Data Quality and Integrity

During the review, the Applicant notified the Agency of GCP noncompliance issues regarding Site CB4-US10098 for ICONIC-ADVANCE 2. The GCP noncompliance issues included a study coordinator having removed confidential patient source documentation, which was then returned to the site and participants were notified of patient privacy concerns via certified letters. Additional allegations included:

- Inaccurate discontinuation data for 7 of 8 participants during September–October 2025, which occurred after the January 2025 data cutoff date.
- Concerns regarding the reliability of patient-reported outcome data.

Site CB4-US10098 ranked 26th in enrollment for this study, reported no response for the primary endpoints (IGA and PASI-90) across all three treatment arms (control, treatment, and active comparator) and had lower adverse event reporting compared to the study average.

No issues related to data quality or integrity were identified in the remaining three trials.

Efficacy Results – Key Secondary Endpoints Comparing Icotrokinra to Placebo

Table 32 presents the placebo-controlled results for the key secondary efficacy endpoints up to and at Week 16 for ICONIC-LEAD, ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2, which share the same key secondary endpoints; Table 33 presents the placebo-controlled results for the key secondary efficacy endpoints up to and at Week 16 for ICONIC-TOTAL. The secondary endpoint results were supportive of the primary efficacy endpoints. The results for all but one secondary endpoint were statistically significant under the prespecified multiplicity adjustment procedure. In ICONIC-TOTAL, the key secondary efficacy endpoint of hf-PGA 0/1 (p=0.1441) was not statistically significant; however, it did not affect the statistical significance of the other key secondary efficacy endpoints per the prespecified multiplicity adjustment procedure.

Reviewer's Comment: A numerical difference of about 0.001 (i.e., 0.1%) was observed for a few confidence intervals between the Applicant's results and Statistical Reviewer's results. This discrepancy arose from the limited precision of the Applicant's grid search relative to the number of significant digits reported, rather than from any substantive numerical divergence. The Applicant implemented the stratified Miettinen-Nurminen method using a brute-force grid search[1], while the Statistical Reviewer used a bisection root-finding approach. In the stratified Miettinen-Nurminen method, each confidence limit is obtained by inverting a stratified score test – that is, by finding the value of the common difference in proportions (Δ) for which the Mantel Haenszel-weighted score statistic equals the critical value (i.e., $z_{0.025}$ or $z_{0.975}$). This root-finding problem can be solved either by using an iterative numerical solver such as the bisection method or by evaluating the function over a discrete grid. Because the Applicant's grid search evaluated the function at increments of 0.001, its located roots were inherently restricted to the thousandth. Consequently, small differences relative to the Statistical Reviewer's more precise estimates – computed using an iterative solver and later rounded to three decimal places for presentation – appeared as 0.001. Subsequent brute-force grid searches by the Statistical Analyst using a finer grid produced results consistent with those from the bisection method.

[1] https://pharmasug.org/proceedings/2025/SA/PharmaSUG-2025-SA-198.pdf

Table 32. Results for Key Secondary Efficacy Endpoints – ICONIC-LEAD, ICONIC-ADVANCE 1, and ICONIC-ADVANCE 2 (FAS[1])

	ICONIC-LEAD[a]		ICONIC-ADVANCE 1[b]		ICONIC-ADVANCE 2[b]	
Category	**Icotrokinra (N=456)**	**Placebo (N=228)**	**Icotrokinra (N=311)**	**Placebo (N=156)**	**Icotrokinra (N=322)**	**Placebo (N=82)**
IGA 0 (Week 16)	33.3%	1.3%	36.7%	1.9%	36.6%	1.2%
Risk Diff (95% CI)[c]	31.9% (27.2%, 36.6%)		34.8% (28.7%, 40.7%)		35.6% (28.5%, 41.7%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
PASI-100 (Week 16)	27.0%	0.4%	31.2%	1.3%	31.7%	1.2%
Risk Diff (95% CI)[c]	26.5% (22.4%, 30.8%)		29.9% (24.2%, 35.7%)		30.4% (23.6%, 36.0%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
PASI-75 (Week 16)	69.1%	11.0%	74.3%	11.5%	77.3%	9.8%
Risk Diff (95% CI)[c]	58.1% (51.9%, 63.6%)		62.7% (55.1%, 69.1%)		67.7% (58.3%, 74.5%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
ss-IGA 0/1 (Week 16)	72.3%	15.0%	72.4%	20.9%	73.7%	18.3%
Risk Diff (95% CI)[c]	57.0% (49.9%, 63.1%)		51.2% (41.8%, 59.4%)		55.5% (44.2%, 64.7%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
PSSD Symptom 0 (Week 16)	20.1%	1.0%	23.8%	2.8%	21.5%	0.0%
Risk Diff (95% CI)[c]	*19.2% (15.0%, 23.6%)		21.3% (15.3%, 27.2%)		21.5% (15.1%, 26.6%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
≥4-Point Improvement in PSSD Itch (Week 16)	58.0%	13.1%	61.8%	16.5%	60.1%	14.8%
Risk Diff (95% CI)[c]	45.2% (37.5%, 52.0%)		45.1% (35.2%, 53.5%)		46.3% (34.2%, 55.6%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
PSSD Symptom 0 (Week 8)	7.1%	1.4%	8.4%	2.1%	9.1%	1.4%
Risk Diff (95% CI)[c†]	5.7% (2.1%, 8.9%)		6.3% (1.8%, 10.4%)		7.5% (1.0%, 11.5%)	
p-value[d]	0.0030		0.0115		0.0322	
PASI-90 (Week 8)	21.5%	1.3%	19.9%	1.3%	25.2%	0.0%
Risk Diff (95% CI)[c]	20.1% (15.9%, 24.5%)		18.6% (13.5%, 23.5%)		25.1% (19.5%, 30.2%)	
p-value[d]	< 0.0001		< 0.0001		< 0.0001	
PASI-75 (Week 4)	14.9%	2.2%	12.2%	2.6%	16.1%	3.7%
Risk Diff (95% CI)[c]	*12.7% (8.9%, 16.6%)		9.6% (4.8%, 14.3%)		12.5% (5.2%, 18.0%)	
p-value[d]	< 0.0001		0.0006		0.0031	
≥4-point improvement in PSSD Itch (Week 4)	19.1%	5.1%	22.3%	7.0%	20.9%	4.9%
Risk Diff (95% CI)[c]	*14.1% (8.6%, 19.3%)		15.2% (7.7%, 22.1%)		15.7% (6.3%, 22.3%)	
p-value[d]	< 0.0001		0.0003		0.0039	

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, adbdc.xpt, adclrori.xpt, adpasiri.xpt, adpssdri.xpt, adbdc.xpt

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[a] For Trial PSO3001, randomization was stratified by age group, baseline weight category (≤90 kg, >90 kg) for adults, and geographic region.

[b] For Trial PSO 3002 and Trial PSO3004, randomization was stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

[c] The risk difference and 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method were adjusted for the stratification factors at randomization.

[d] The p-value was based on the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors at randomization.

* Geographic region was not included in the stratification factors for the calculation of the risk difference and its 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method.

[†] The risk difference and the 95% CI were calculated using Newcombe's exact method. The p-value was calculated using Fisher's exact test.

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary; ss-IGA, Scalp-Specific Investigator Global Assessment

Table 33. Results for Key Secondary Efficacy Endpoints – ICONIC-TOTAL (FAS[1])

	ICONIC-TOTAL	
Parameters (Week 16)	**Icotrokinra (N=208)**	**Placebo (N=103)**
ss-IGA 0/1[a,b]	65.9%	10.6%
Risk Diff (95% CI)	55.5% (44.8%, 64.4%)	
p-value	< 0.0001	
hf-PGA 0/1[e,h]	41.7%	26.1%
Risk Diff (95% CI)	16.7% (-6.2%, 36.8%)	
p-value	0.1441	
sPGA-G 0/1[d,e]	76.5%	21.4%
Risk Diff (95% CI)	55.4% (39.1%, 68.0%)	
p-value	< 0.0001	
PSSD Symptom 0[e,k]	16.2%	3.4%
Risk Diff (95% CI)	12.8% (5.5%, 19.4%)	
p-value	0.0025	
≥4-Point Improvement in PSSD Itch[i,j]	59.5%	13.5%
Risk Diff (95% CI)	45.2% (33.4%, 55.3%)	
p-value	< 0.0001	
IGA 0[i]	25.5%	1.0%
Risk Diff (95% CI)	24.8% (17.5%, 31.5%)	
p-value	< 0.0001	
PSSI-90[a,b]	57.5%	5.9%
Risk Diff (95% CI)	51.8% (41.7%, 60.3%)	
p-value	< 0.0001	
≥4-Point Improvement in Scalp Itch[b,c]	58.8%	8.6%
Risk Diff (95% CI)	50.2% (37.8%, 60.6%)	
p-value	< 0.0001	
≥4-Point Improvement in GPSS Genital Itch[e,f]	63.8%	12.9%
Risk Diff (95% CI)	49.8% (31.3%, 64.3%)	
p-value	< 0.0001	

	ICONIC-TOTAL	
Parameters (Week 16)	**Icotrokinra (N=208)**	**Placebo (N=103)**
GenPs-SFQ Item 2 0/1[e,g]	80.0%	36.0%
Risk Diff (95% CI)	43.2% (20.2%, 62.4%)	
p-value	0.0002	

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); adsl.xpt, adbdc.xpt, adclrori.xpt, adpssdri.xpt, adgpssri.xpt, adpssiri.xpt, adprori.xpt

[1] Full Analysis Set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[a] Among subjects with a baseline ss-IGA score ≥3 (167 in the icotrokinra arm vs. 85 in the placebo arm).

[b] The risk difference and 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method and the p-value based on the Cochran-Mantel-Haenszel test were adjusted for the geographic region and BSA category.

[c] Among subjects with a baseline ss-IGA score ≥3 and a baseline Scalp Itch NRS score ≥4 (131 in the icotrokinra arm vs. 58 in the placebo arm).

[d] Among subjects with a baseline sPGA-G score ≥3 (98 in the icotrokinra arm vs. 42 in the placebo arm).

[e] The risk difference and 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method and the p-value based on the Cochran-Mantel-Haenszel test were adjusted for the BSA category.

[f] Among subjects with a baseline sPGA-G score ≥3 and a baseline GPSS Genital Itch NRS score (item 1 from the GPSS) ≥4 (69 in the icotrokinra arm vs. 31 in the placebo arm).

[g] Among subjects with a baseline sPGA-G score ≥3 and a baseline GenPs-SFQ Item 2 score ≥2 (55 in the icotrokinra arm vs. 25 in the placebo arm).

[h] Among subjects with a baseline hf-PGA score ≥3 (48 in the icotrokinra arm vs. 23 in the placebo arm).

[i] The risk difference and 95% CI using the Mantel-Haenszel-weighted Miettinen-Nurminen method and the p-value based on the Cochran-Mantel-Haenszel test were adjusted for the special area involvement and BSA category.

[j] Among subjects with a baseline PSSD Itch score ≥4 (168 in the icotrokinra arm vs. 74 in the placebo arm).

[k] Among subjects with a baseline PSSD symptom score >0 (191 in the icotrokinra arm vs. 87 in the placebo arm).

Abbreviations: CI, confidence interval; FAS, full analysis set; GenPs-SFQ, Genital Psoriasis Sexual Frequency Questionnaire; GPSS, Genital Psoriasis Symptoms Score; hf-PGA, Physician's Global Assessment of hands and feet; N, number of subjects in treatment arm; sPGA-G, Static Physician's Global Assessment of Genitalia; ss-IGA, Scalp-Specific Investigator Global Assessment

Efficacy Results – Key Secondary Efficacy Endpoints Comparing Icotrokinra to Deucravacitinib

Table 34 and Table 35 present the results for the key secondary efficacy endpoints comparing icotrokinra to the active comparator (deucravacitinib) in ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2. Icotrokinra was statistically superior to deucravacitinib across all prespecified key secondary endpoints in both studies, with risk differences consistently being around or above 15%. ICONIC-ADVANCE 2 confirmed the statistical superiority of icotrokinra to deucravacitinib, replicating the findings from ICONIC-ADVANCE 1. However, for the endpoint of PSSD symptom score of 0 at Week 16, ICONIC-ADVANCE 2 showed a slightly smaller difference compared to ICONIC-ADVANCE 1; however, it remained statistically significant.

Table 34. Results for the Active Comparator-Controlled Key Secondary Efficacy Endpoints – ICONIC-ADVANCE 1 (FAS[1])

Parameters	**Icotrokinra (N=311)**	**Deucravacitinib (N=307)**
IGA Score of 0 or 1 and ≥2-Grade Improvement From Baseline (Week 16)	68.5%	50.2%
Risk Difference (95% CI)	18.3% (10.7%, 25.8%)	
p-value	<0.001	
IGA Score of 0 or 1 and ≥2 Grade Improvement From Baseline (Week 24)	74.0%	52.4%
Risk Difference (95% CI)	21.5% (14.2%, 28.7%)	
p-value	<0.001	

Parameters	Icotrokinra (N=311)	Deucravacitinib (N=307)
IGA Score of 0 (Week 16)	36.7%	15.6%
Risk Difference (95% CI)		21.0% (14.3%, 27.6%)
p-value	<0.001	
IGA Score of 0 (Week 24)	48.2%	20.5%
Risk Difference (95% CI)		27.7% (20.5%, 34.6%)
p-value	<0.001	
PASI 100 Response (Week 16)	31.2%	11.1%
Risk Difference (95% CI)		20.1% (13.9%, 26.4%)
p-value	<0.001	
PASI 100 Response (Week 24)	41.5%	16.0%
Risk Difference (95% CI)		25.5% (18.6%, 32.2%)
p-value	<0.001	
PASI 90 Response (Week 16)	55.0%	29.6%
Risk Difference (95% CI)		25.3% (17.7%, 32.6%)
p-value	<0.001	
PASI 90 Response (Week 24)	65.9%	41.4%
Risk Difference (95% CI)		24.5% (16.8%, 32.0%)
p-value	<0.001	
PASI 75 Response (Week 16)	74.3%	57.3%
Risk Difference (95% CI)		17.0% (9.6%, 24.2%)
p-value	<0.001	
PASI 75 Response (Week 24)	81.7%	63.8%
Risk Difference (95% CI)		17.8% (11.0%, 24.6%)
p-value	<0.001	
PSSD Symptom Score of 0 (Week 16)[2]	23.8%	9.2%
Risk Difference (95% CI)		14.5% (8.4%, 20.6%)
p-value	<0.001	

Source: Statistical Analyst's Analysis (similar to Applicant's Analysis); adsl.xpt, adbdc.xpt, adclrori.xpt, adpasiri.xpt, adpssdri.xpt

[1] Full analysis set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is). The risk difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≥90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. The p-value was based on Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≥90 kg, >90 kg) and geographic region.

[2] Among subjects with a baseline PSSD symptom score > 0 (286 in the icotrokinra arm vs. 272 in the deucravacitinib arm).

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary

Table 35. Results for the Active Comparator-Controlled Key Secondary Efficacy Endpoints – ICONIC-ADVANCE 2 (FAS[1])

Parameters	Icotrokinra (N=311)	Deucravacitinib (N=307)
IGA Score of 0 or 1 and ≥2-Grade Improvement From Baseline (Week 16)	70.5%	54.1%
Risk Difference (95% CI)		16.5% (9.3%, 23.6%)
p-value	<0.001	
p-value (Noninferiority)	<0.001	
IGA Score of 0 or 1 and ≥2 Grade Improvement From Baseline (Week 24)	68.3%	54.7%
Risk Difference (95% CI)		13.7% (6.4%, 20.9%)
p-value	<0.001	
p-value (Noninferiority)	<0.001	

Parameters	Icotrokinra (N=311)	Deucravacitinib (N=307)
IGA Score of 0 (Week 16)	36.6%	17.4%
Risk Difference (95% CI)	19.3% (12.6%, 25.9%)	
p-value	<0.001	
IGA Score of 0 (Week 24)	39.8%	20.8%
Risk Difference (95% CI)	19.0% (12.1%, 25.8%)	
p-value	<0.001	
PASI 100 Response (Week 16)	31.7%	14.1%
Risk Difference (95% CI)	17.6% (11.3%, 23.9%)	
p-value	<0.001	
PASI 100 Response (Week 24)	33.2%	15.9%
Risk Difference (95% CI)	17.3% (10.8%, 23.8%)	
p-value	<0.001	
PASI 90 Response (Week 16)	57.1%	33.9%
Risk Difference (95% CI)	23.2% (15.9%, 30.4%)	
p-value	<0.001	
PASI 90 Response (Week 24)	64.6%	43.1%
Risk Difference (95% CI)	21.5% (14.1%, 28.8%)	
p-value	<0.001	
PASI 75 Response (Week 16)	77.3%	60.6%
Risk Difference (95% CI)	16.9% (9.9%, 23.8%)	
p-value	<0.001	
p-value (Noninferiority)	<0.001	
PASI 75 Response (Week 24)	82.6%	66.1%
Risk Difference (95% CI)	16.6% (10.0%, 23.2%)	
p-value	<0.001	
p-value (Noninferiority)	<0.001	
PSSD Symptom Score of 0 (Week 16)[2]	21.5%	12.5%
Risk Difference (95% CI)	8.9% (2.9%, 15.0%)	
p-value	0.004	

Source: Statistical Analyst's Analysis (similar to Applicant's Analysis); adsl.xpt, adbdc.xpt, adclrori.xpt, adpasiri.xpt, adpssdri.xpt

[1] Full analysis set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is). The risk difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≥90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. The p-value was based on Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≥90 kg, >90 kg) and geographic region.

[2] Among subjects with a baseline PSSD symptom score > 0 (298 in the icotrokinra arm vs. 287 in the deucravacitinib arm).

Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; N, number of subjects in treatment arm; PASI, Psoriasis Area and Severity Index; PSSD, Psoriasis Symptom and Sign Diary

Table 36 presents the efficacy reanalysis results – primary and key secondary – for ICONIC-ADVANCE 2, excluding Site CB4-US10098 that was identified to have had GCP issues. Due to the site's sample size (n=8), its exclusion had a limited effect on the efficacy results, and the conclusions were unchanged.

Table 36. Efficacy Results in Adult Subjects with Moderate-to-Severe Plaque Psoriasis at Weeks 16 and 24 Excluding Site CB4-US10098 – ICONIC-ADVANCE 2 (FAS[1])

	Icotrokinra (N=320)	Placebo (N=81)	Deucravacitinib (N=322)	Difference, % (95% CI)	
Endpoint	n (%)	n (%)	n (%)	Difference from Placebo	Difference from Deucravacitinib
IGA 0 or 1 ("cleared" or "minimal") and a ≥2-grade improvement from baseline)					
Week 16[a]	227 (71%)	7 (9%)	177 (55%)	63% (53%, 70%)	16% (9%, 23%)
Week 24	220 (69%)		179 (56%)		13% (6%, 21%)
IGA 0 ("cleared")					
Week 16	118 (37%)	1 (1%)	57 (18%)	36% (29%, 42%)	19% (13%, 26%)
Week 24	128 (40%)		68 (21%)		19% (12%, 26%)
PASI 75					
Week 16	249 (78%)	8 (10%)	198 (62%)	68% (59%, 75%)	17% (10%, 23%)
Week 24	265 (83%)		216 (67%)		16% (9%, 23%)
PASI 90					
Week 16[a]	184 (58%)	1 (1%)	111 (35%)	57% (49%, 62%)	23% (16%, 30%)
Week 24	208 (65%)		141 (44%)		21% (14%, 29%)
PASI 100					
Week 16	102 (32%)	1 (1%)	46 (14%)	31% (24%, 36%)	18% (11%, 24%)
Week 24	107 (33%)		52 (16%)		17% (11%, 24%)
PSSD Symptom Score 0[b]					
N	296	70	282		
Week 16	64 (22%)	0	36 (13%)	22% (15%, 27%)	9% (3%, 15%)
PSSD Itch Score Improvement (≥4-point reduction from baseline)[c]					
N	256	60			
Week 16	154 (60%)	9 (15%)		46% (34%, 56%)	

Source: Statistical Analyst's Analysis, using adsl.xpt, adclrori.xpt, adpasiri.xpt and adpssdri.xpt.

[1] Full analysis set (FAS) is defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is). The risk difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≥90 kg, >90 kg) and geographic region using Mantel-Haenszel weights. The p-value was based on Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≥90 kg, >90 kg) and geographic region.

[a] Coprimary endpoints comparing icotrokinra to placebo.

[b] Includes subjects with baseline PSSD Symptom Score >0.

[c] Includes subjects with baseline PSSD Itch Score ≥4.

Abbreviations: CI, confidence interval; PASI, Psoriasis Area and Severity Index; IGA, Investigator's Global Assessment; PSSD, Psoriasis Symptoms and Signs Diary

Efficacy Results – Maintenance of Response

ICONIC-LEAD evaluated maintenance of efficacy for an additional 28 weeks (Weeks 24 to 52). Subjects randomized to icotrokinra and who were PASI-75 AND/OR IGA 0/1 responders at Week 24 were re-randomized in a 1:1 ratio to either continue icotrokinra or be withdrawn from therapy (i.e., placebo). Four key secondary efficacy endpoints were prespecified for the analysis at Week 52: PASI-75 at Week 52, PASI-90 at Week 52, time to loss of PASI-75, and time to loss of PASI-90.

For PASI-75 at Week 52, PASI-90 response status at Week 24 and geographic region were prespecified to be included in the analysis. During the review, 11 subjects were identified

whose PASI-90 response stratification variable at Week 24 used in the Applicant's Week 52 analysis did not match their Week 24 results – that is, they were mis-stratified in the Week 52 analysis. On September 26, 2025, FDA sent an information request (IR), asking the Applicant to identify the source of these discrepancies. Table 37 presents the Applicant's clarification on the source of mis-stratifications, based on the Applicant's October 9, 2025 response to the IR.

Table 37. Subjects With Week 24 PASI-90 Stratification Errors For Randomized Withdrawal Analyses

Subject ID	Investigator-Reported Week 24 PASI-90 Response	Analysis-Derived Week 24 PASI-90 Response	Applicant Clarification
(b) (6)	Y	N	Incorrectly entered as a PASI-90 responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	Y	N	Incorrectly entered as a PASI-90 responder in IWRS
	Y	N	Incorrectly entered as a PASI-90 responder in IWRS
	Y	N	Incorrectly entered as a PASI-90 responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	N	Y	Incorrectly entered as a PASI-90 non-responder in IWRS
	Y	N	The subject had ICE 2 (prohibited medication, topical tacalcitol) prior to Week 24 and considered PASI-90 non-responder at Week 24 in the analysis-derived result

Source: Applicant response to September 16, 2025 FDA information request
Abbreviations: ICE, intercurrent event; IWRS, interactive web response system; PASI, Psoriasis Area and Severity Index

Table 38 presents the original analysis results for the prespecified comparisons during the randomized withdrawal period in ICONIC-LEAD and the re-analysis results using the correct Week 24 responder statuses for the 11 subjects. The icotrokinra group showed higher maintenance rates than the randomized withdrawal group at Week 52. At Week 52, the icotrokinra group had not reached its median time to loss of PASI-75 or PASI-90 response. Correcting the investigator error in entering the 11 subjects' stratification factors decreased the risk-difference estimate and the confidence interval but did not alter the conclusions.

Table 38. Results for the Randomized Withdrawal Period – ICONIC-LEAD

Parameters	Icotrokinra (N=169)	Randomized Withdrawal (N=172)
PASI-75 Response		
Number of subjects who were PASI-75 responders[1] at Week 24	161	166
Proportion of subjects with PASI-75 at Week 52	89.4%	29.5%
Risk Difference (95% CI)[2]		59.6% (50.9%, 67.3%)
Misstratification-corrected Risk Difference (95% CI)[†]		59.4% (50.6%, 67.1%)
p-value[2†]	<0.001	
Median Time (Weeks) to Loss of PASI-75 Response	NC	16.9
Hazard Ratio (95% CI)[3]	0.08 (0.05, 0.13)	
p-value[3]	<0.001	
PASI-90 Response		
Number of subjects who were PASI-90 responders[4] at Week 24	128	129
Proportion of subjects with PASI-90 at Week 52	84.4%	20.9%
Risk Difference (95% CI)[5]		63.5% (53.1%, 72.0%)
p-value[5]	<0.001	
Median Time (Weeks) to Loss of PASI-90 Response	NC	10.1
Hazard Ratio (95% CI)[6]	0.13 (0.08, 0.20)	
p-value[6]	<0.001	

Source: Statistical Analyst's Analysis; adsl.xpt, adpasiri.xpt
[1] Among PASI-75 responders at Week 24.
[2] The risk difference and its 95% CI were based on the Miettinen-Nurminen method adjusting for Week 24 PASI-90 response status and geographic region using Mantel-Haenszel weights. The p-value was based on the CMH chi-square test stratified by investigator-reported Week 24 PASI 90 response status and geographic region.
† The risk difference and 95% CI were based on the Miettinen-Nurminen method adjusting for Week 24 PASI-90 response status (correcting investigator coding error) and geographic region using Mantel-Haenszel weights. The p-value was based on the CMH chi-square test stratified by Week 24 PASI 90 response status (corrected for investigator coding error) and geographic region.
[3] Among PASI-75 responders at Week 24. The hazard ratio and its 95% CI were based on the Cox regression model stratified by investigator-reported Week 24 PASI-90 response status and geographic region. The p-value was based on the log-rank test stratified by investigator-reported Week 24 PASI-90 response status and geographic region.
[4] Among PASI-90 responders at Week 24.
[5] The risk difference and its 95% CI were based on the Miettinen-Nurminen method adjusting for geographic region using Mantel-Haenszel weights. The p-value was based on the CMH chi-square test stratified by geographic region.
[6] Among PASI-90 responders at Week 24. The hazard ratio and its 95% CI were based on the Cox regression model stratified by geographic region. The p-value was based on the log-rank test stratified by geographic region.
Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis; initiation of other medication or therapy that could improve psoriasis; and/or loss of ≥50% Week 24 PASI improvement were considered non-responders for binary endpoints and considered an event of loss of PASI response for time-to-event endpoints. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is). After accounting for the ICEs, subjects with missing data were considered non-responders for binary endpoints and not imputed for time-to-event endpoints.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ICE, intercurrent event; N, number of subjects in treatment arm; NC, not calculable; PASI, Psoriasis Area and Severity Index

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

Efficacy on the coprimary endpoints of IGA 0/1 response and PASI-90 response at Week 16 was demonstrated in ICONIC-LEAD, ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2; efficacy on the primary endpoint of IGA 0/1 response at Week 16 was demonstrated in ICONIC-TOTAL. The risk-difference estimate for icotrokinra versus placebo for IGA 0/1 response was 56% in ICONIC-LEAD, 58% in ICONIC-ADVANCE 1, 51% in ICONIC-TOTAL, and 62% in ICONIC-ADVANCE 2. The risk-difference estimate for PASI-90 response was 45% in ICONIC-LEAD, 51% in ICONIC-ADVANCE 1, and 56% in ICONIC-ADVANCE 2.

Secondary and Other Endpoints

The secondary endpoint results were supportive of the primary endpoint results, with icotrokinra being statistically superior to placebo across multiple clinical measures including skin clearance assessments (IGA 0, PASI-75, PASI-100), scalp-specific assessments (ss-IGA 0/1), and patient-reported outcomes (PSSD symptom scores and itch improvements). Icotrokinra was statistically superior to placebo in all but one key secondary endpoint across all four trials.

In ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2, icotrokinra consistently demonstrated statistical superiority to deucravacitinib across all prespecified key secondary endpoints. In the special areas trial ICONIC-TOTAL, the key secondary endpoint of hf-PGA 0/1 was not statistically significant; however, this did not affect the statistical significance of other key secondary endpoints per the prespecified multiplicity adjustment procedure.

Subpopulations

Table 39, Table 40, Table 41, and Table 42 present the results for the primary efficacy endpoint of IGA 0/1 response at Week 16 by subgroup for the four trials. Table 43, Table 44, and Table 45 present the PASI-90 subgroup analysis results for ICONIC-LEAD, ICONIC-ADVANCE 1, and ICONIC-ADVANCE 2. Both sets of subgroup analyses generally demonstrated no substantial differences in treatment effect across demographic and baseline characteristic subgroups. Some imbalances were observed in subgroups with relatively small sample sizes, as reflected by wide confidence intervals indicating uncertainty (e.g., Hispanic/Latino subgroup in ICONIC-ADVANCE 2, multiple race subgroups, adolescent subgroup in ICONIC-TOTAL); it would be difficult to detect any meaningful difference in efficacy between these subgroups and their complements. Subjects in ICONIC-TOTAL with BSA ≥10% saw greater treatment effect than those with BSA <10%. The PASI-90 findings were consistent with the IGA 0/1 results.

Table 39. Results for the Primary Efficacy Endpoint of IGA 0/1 Response at Week 16 by Subgroup – ICONIC-LEAD (FAS[1])

Subgroup	Icotrokinra	Placebo	Difference from Placebo (95% CI)[2]
Overall	65% (295/456)	8% (19/228)	56% (50%, 62%)
[redacted]			
Female	68% (113/165)	14% (10/72)	55% (42%, 65%)
Male	63% (182/292)	6% (9/156)	57% (50%, 63%)
Race			
American Indian OR Alaska Native	0	0% (0/1)	NC
Asian	69% (76/110)	7% (4/57)	62% (49%, 72%)
Black OR African American	50% (3/6)	0% (0/2)	50% (-43%, 88%)
Native Hawaiian OR Other Pacific Islander	50% (1/2)	0	NC
White	64% (209/329)	9% (15/165)	54% (47%, 61%)
Not Reported	80% (4/5)	0% (0/2)	80% (-14%, 100%)
Unknown	67% (2/3)	0% (0/1)	67% (-59%, 99%)
Multiple	0% (0/1)	0	NC

Subgroup	Icotrokinra	Placebo	Difference from Placebo (95% CI)[2]
Ethnicity			
Hispanic OR Latino	59% (36/61)	11% (3/27)	48% (26%, 63%)
Not Hispanic OR Latino	66% (253/386)	8% (16/199)	58% (51%, 63%)
Not Reported	100% (3/3)	0% (0/1)	NC
Unknown	50% (3/6)	0% (0/1)	50% (-61%, 88%)
Age Group			
12–17 years	84% (37/44)	27% (6/22)	57% (32%, 76%)
18–44 years	62% (129/208)	9% (8/92)	53% (43%, 62%)
45–64 years	61% (100/164)	4% (4/89)	56% (47%, 65%)
≥65 years	73% (29/40)	4% (1/25)	68% (46%, 82%)
Weight			
≤90 kg	69% (189/274)	10% (13/136)	59% (51%, 66%)
<90 kg	58% (106/182)	7% (6/92)	52% (42%, 60%)
Baseline BMI			
Normal (<25 kg/m^2)	76% (95/125)	18% (10/56)	58% (43%, 70%)
Overweight (25–30 kg/m^2)	63% (95/151)	6% (5/83)	57% (46%, 66%)
Obese(≥30 kg/m^2)	59% (105/179)	5% (4/88)	54% (45%, 62%)
Baseline IGA Score			
Moderate (=3)	67% (229/341)	10% (18/173)	57% (49%, 63%)
Severe (=4)	57% (66/115)	2% (1/55)	56% (44%, 65%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt
[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).
[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.
Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; NC, not calculable

Table 40. Results for the Primary Efficacy Endpoint of IGA 0/1 Response at Week 16 by Subgroup – ICONIC-ADVANCE 1 (FAS[1])

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Overall	68% (213/311)	11% (17/156)	58% (50%, 64%)
[redacted]			
Female	76% (67/88)	10% (5/51)	66% (52%, 78%)
Male	65% (146/223)	11% (12/105)	54% (44%, 62%)
Race			
American Indian OR Alaska Native	100% (1/1)	0% (0/1)	NC
Asian	65% (45/69)	9% (3/34)	56% (38%, 70%)
Black OR African American	50% (2/4)	0% (0/3)	50% (-30%, 93%)
Native Hawaiian OR Other Pacific Islander	100% (2/2)	0	NC
White	69% (160/231)	12% (14/118)	57% (48%, 65%)
Not Reported	50% (1/2)	0	NC
Unknown	100% (2/2)	0	NC
Ethnicity			
Hispanic OR Latino	72% (42/58)	16% (4/25)	56% (34%, 72%)
Not Hispanic OR Latino	68% (170/250)	10% (13/129)	58% (49%, 65%)
Not Reported	50% (1/2)	0	50% (-61%, 99%)
Unknown	0% (0/1)	0	NC

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Age Group			
18–44 years	76% (106/139)	9% (6/69)	68% (56%, 76%)
45–64 years	59% (82/140)	12% (8/69)	47% (34%, 57%)
≥65 years	78% (25/32)	17% (3/18)	62% (31%, 80%)
Weight			
≤90 kg	70% (133/189)	12% (11/92)	58% (48%, 67%)
<90 kg	66% (80/122)	9% (6/64)	56% (43%, 66%)
Baseline BMI			
Normal (<25 kg/m^2)	73% (58/80)	17% (7/42)	56% (38%, 69%)
Overweight (25-30 kg/m^2)	70% (81/115)	9% (5/53)	61% (47%, 72%)
Obese(≥30 kg/m^2)	64% (74/116)	8% (5/61)	56% (42%, 66%)
Region			
Americas	59% (63/107)	13% (7/54)	46% (31%, 58%)
Asia Pacific	67% (44/66)	9% (3/33)	58% (38%, 71%)
European Union	77% (106/138)	10% (7/69)	67% (55%, 76%)
Baseline IGA Score			
Moderate (=3)	71% (178/251)	12% (15/123)	59% (50%, 66%)
Severe (=4)	58% (35/60)	6% (2/33)	52% (34%, 66%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt
[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).
[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.
Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; NC, not calculable

Table 41. Results for the Primary Efficacy Endpoint of IGA 0/1 Response at Week 16 by Subgroup – ICONIC-TOTAL (FAS[1])

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Overall	57% (118/208)	6% (6/103)	51% (42%, 59%)
[redacted]			
Female	48% (34/71)	13% (5/40)	35% (17%, 50%)
Male	61% (84/137)	2% (1/63)	60% (50%, 68%)
Race			
Asian	61% (25/41)	0% (0/20)	61% (41%, 76%)
Black OR African American	50% (1/2)	0	NC
Multiple	100% (1/1)	0	NC
Not Reported	33% (1/3)	0% (0/1)	33% (-81%, 91%)
White	56% (90/161)	7% (6/82)	49% (38%, 58%)
Ethnicity			
Hispanic OR Latino	63% (10/16)	0% (0/5)	62% (2%, 86%)
Not Hispanic OR Latino	55% (102/184)	6% (6/96)	49% (39%, 58%)
Not Reported	75% (6/8)	0% (0/2)	75% (-16%, 99%)
Age Group			
12-17 years	67% (2/3)	0% (0/3)	67% (-28%, 99%)
18-44 years	59% (59/100)	6% (3/50)	53% (39%, 64%)
45-64 years	58% (49/85)	7% (3/45)	51% (36%, 63%)
≥65 years	40% (8/20)	0% (0/5)	40% (-16%, 64%)

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Weight			
≤90 kg	58% (77/133)	7% (4/59)	51% (39%, 61%)
<90 kg	55% (39/71)	5% (2/42)	50% (34%, 63%)
Baseline BMI			
Normal (<25 kg/m^2)	57% (34/60)	6% (2/31)	50% (30%, 64%)
Overweight (25–30 kg/m^2)	62% (40/65)	9% (3/33)	52% (33%, 66%)
Obese(≥30 kg/m^2)	54% (42/78%)	3% (1/37)	51% (37%, 63%)
Region			
Americas	51% (37/73)	0% (0/36)	51% (38%, 63%)
Asia Pacific	59% (20/34)	0% (0/16)	59% (35%, 75%)
European Union	60% (61/101)	12% (6/51)	49% (33%, 61%)
Baseline IGA Score			
Mild (=2)	33% (3/9)	0% (0/8)	33% (-8%, 70%)
Moderate (=3)	60% (92/153)	7% (5/73)	53% (42%, 63%)
Severe (=4)	50% (23/46)	5% (1/22)	46% (21%, 62%)
Baseline BSA			
<10%	35% (26/74)	5% (2/38)	30% (13%, 43%)
≥10%	69% (92/134)	6% (4/65)	62% (51%, 72%)
Baseline ss-IGA Score			
Absence of Disease	15% (2/13)	14% (1/7)	1% (-43%, 36%)
Very Mild Disease	33% (2/6)	0	NC
Mild Disease	77% (17/22)	9% (1/11)	68% (31%, 87%)
Moderate Disease	57% (77/134)	5% (3/64)	53% (41%, 62%)
Severe Disease	61% (20/33)	5% (1/21)	56% (30%, 74%)
Baseline hf-PGA Score			
Clear	61% (82/134)	3% (2/68)	58% (48%, 67%)
Almost Clear	38% (3/8)	0% (0/4)	38% (-23%, 76%)
Mild	78% (14/18)	0% (0/8)	78% (35%, 94%)
Moderate	52% (16/31)	16% (3/19)	36% (5%, 58%)
Severe	18% (3/17)	25% (1/4)	-7% (-61%, 31%)
Baseline sPGA-G Score			
Clear	55% (50/91)	4% (2/53)	51% (38%, 62%)
Minimal	17% (1/6)	0% (0/3)	17% (-56%, 64%)
Mild	62% (8/13)	0% (0/5)	62% (-1%, 86%)
Moderate	60% (45/75)	7% (2/29)	53% (35%, 66%)
Severe	59% (13/22)	8% (1/12)	51% (13%, 74%)
Very Severe	100% (1/1)	100% (1/1)	NC

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt

[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; hf-PGA, Physician's Global Assessment of hands and/or feet; IGA, Investigator's Global Assessment; NC, not calculable; sPGA-G, static Physician's Global Assessment of Genitalia; ss-IGA, scalp-specific Investigator Global Assessment

Table 42. Results for the Primary Efficacy Endpoint of IGA 0/1 Response at Week 16 by Subgroup – ICONIC-ADVANCE 2 (FAS[1])

Subgroup	Icotrokinra	Placebo	Difference from Placebo (95% CI)[2]
Overall	70% (227/322)	9% (7/82)	62% (52%, 69%)
[redacted]			
Female	69% (72/104)	11% (3/27)	58% (38%, 71%)
Male	71% (155/218)	7% (4/55)	64% (52%, 72%)
Race			
American Indian OR Alaska Native	0% (0/1)	0	NC
Asian	74% (25/34)	7% (1/15)	67% (38%, 84%)
Black OR African American	56% (5/9)	0	56% (-31%, 86%)
Multiple	0% (0/1)	0	NC
Native Hawaiian OR Other Pacific Islander	100% (2/2)	0	NC
Not Reported	100% (1/1)	0	NC
White	71% (194/274)	9% (6/65)	62% (50%, 69%)
Ethnicity			
Hispanic OR Latino	40% (17/42)	25% (3/12)	16% (-19%, 41%)
Not Hispanic OR Latino	75% (209/279)	6% (4/70)	69% (60%, 76%)
Not Reported	100% (1/1)	0	NC
Age Group			
18-44 years	70% (110/158)	14% (5/36)	56% (38%, 67%)
45-64 years	72% (94/131)	3% (1/36)	69% (56%, 78%)
≥65 years	70% (23/33)	10% (1/10)	60% (19%, 79%)
Weight			
≤90 kg	75% (140/186)	13% (6/48)	63% (49%, 73%)
<90 kg	64% (87/136)	3% (1/34)	61% (47%, 70%)
Baseline BMI			
Normal (<25 kg/m^2)	82% (58/71)	14% (2/14)	67% (39%, 83%)
Overweight (25–30 kg/m^2)	77% (85/111)	13% (4/30)	63% (44%, 76%)
Obese(≥30 kg/m^2)	60% (84/140)	3% (1/38)	57% (45%, 67%)
Region			
Americas	54% (54/100)	8% (2/25)	46% (24%, 59%)
Asia Pacific	78% (25/32)	11% (1/9)	67% (28%, 86%)
European Union	78% (148/190)	8% (4/48)	70% (57%, 78%)
Baseline IGA Score			
Moderate (=3)	75% (190/252)	7% (5/67)	68% (58%, 75%)
Severe (=4)	53% (37/70)	13% (2/15)	40% (1%, 57%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt

[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; NC, not calculable

Table 43. Results for the Primary Efficacy Endpoint of PASI-90 Response at Week 16 by Subgroup – ICONIC-LEAD

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Overall	50% (226/456)	4% (10/228)	45% (40%, 50%)
[redacted]			
Female	54% (89/165)	10% (7/72)	44% (32%, 54%)
Male	47% (137/291)	2% (3/156)	45% (39%, 51%)
Race			
American Indian OR Alaska Native	-	0% (0/1)	NC
Asian	55% (60/110)	7% (4/57)	48% (34%, 58%)
Black OR African American	50% (3/6)	0% (0/2)	50% (-43%, 88%)
Native Hawaiian OR Other Pacific Islander	50% (1/2)	-	NC
White	49% (161/329)	4% (6/165)	45% (39%, 51%)
Not Reported	0% (0/5)	0% (0/2)	NC
Unknown	33% (1/3)	0% (0/1)	33% (-81%, 91%)
Multiple	0% (0/1)	-	NC
Ethnicity			
Hispanic OR Latino	31% (19/61)	7% (2/27)	24% (2%, 39%)
Not Hispanic OR Latino	53% (203/386)	4% (8/199)	49% (43%, 54%)
Not Reported	100% (3/3)	0% (0/1)	NC
Unknown	17% (1/6)	0% (0/1)	17% (-86%, 64%)
Age Group			
12-17 years	70% (31/44)	14% (3/22)	57% (32%, 74%)
18-44 years	50% (105/208)	3% (3/92)	47% (38%, 55%)
45-64 years	44% (72/164)	4% (4/89)	39% (30%, 48%)
≥65 years	45% (18/40)	0% (0/25)	45% (28%, 62%)
Weight			
≤90 kg	56% (153/274)	7% (9/136)	49% (41%, 56%)
<90 kg	40% (73/182)	1% (1/92)	39% (31%, 47%)
Baseline BMI			
Normal (<25 kg/m^2)	62% (78/125)	13% (7/56)	50% (36%, 61%)
Overweight (25–30 kg/m^2)	50% (75/151)	2% (2/83)	47% (38%, 56%)
Obese(≥30 kg/m^2)	41% (73/179)	1% (1/88)	40% (32%, 47%)
Baseline IGA Score			
Moderate (=3)	52% (177/341)	5% (9/173)	47% (40%, 53%)
Severe (=4)	43% (49/115)	2% (1/55)	41% (30%, 51%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt
[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).
[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.
Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; NC, not calculable; PASI, Psoriasis Area and Severity Index

Table 44. Results for the Primary Efficacy Endpoint of PASI-90 Response at Week 16 by Subgroup – ICONIC-ADVANCE 1

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Overall	55% (171/311)	4% (6/156)	51% (44%, 57%)
[redacted]			
Female	65% (58/88)	8% (4/51)	58% (44%, 70%)
Male	51% (113/223)	2% (2/105)	49% (41%, 56%)

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Race			
American Indian OR Alaska Native	0% (0/1)	0% (0/1)	NC
Asian	45% (31/69)	0% (0/34)	45% (32%, 57%)
Black OR African American	25% (1/4)	0% (0/3)	25% (-49%, 81%)
Native Hawaiian OR Other Pacific Islander	100% (2/2)	-	NC
White	58% (133/231)	5% (6/118)	52% (44%, 60%)
Not Reported	100% (2/2)	-	NC
Unknown	100% (2/2)	-	NC
Ethnicity			
Hispanic OR Latino	59% (34/58)	4% (1/25)	55% (35%, 69%)
Not Hispanic OR Latino	54% (136/250)	4% (5/129)	50% (43%, 57%)
Not Reported	50% (1/2)	0% (0/2)	50% (-61%, 99%)
Unknown	0% (0/1)	-	NC
Age Group			
18-44 years	60% (83/139)	1% (1/69)	58% (48%, 67%)
45-64 years	49% (69/140)	6% (4/69)	44% (32%, 53%)
≥65 years	59% (19/32)	6% (1/18)	54% (26%, 72%)
Weight			
≤90 kg	60% (113/189)	4% (4/92)	55% (46%, 63%)
<90 kg	48% (58/122)	3% (2/64)	44% (34%, 54%)
Baseline BMI			
Normal (<25 kg/m^2)	63% (50/80)	5% (2/42)	58% (43%, 69%)
Overweight (25-30 kg/m^2)	57% (65/115)	4% (2/53)	53% (40%, 63%)
Obese(≥30 kg/m^2)	48% (56/116)	3% (2/61)	45% (33%, 55%)
Region			
Americas	47% (50/107)	6% (3/54)	41% (28%, 52%)
Asia Pacific	45% (30/66)	0% (0/33)	46% (33%, 58%)
European Union	66% (91/138)	4% (3/69)	62% (51%, 70%)
Baseline IGA Score			
Moderate (=3)	56% (141/251)	4% (5/123)	52% (44%, 59%)
Severe (=4)	50% (30/60)	3% (1/33)	47% (30%, 61%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt

[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; NC, not calculable

Table 45. Results for the Primary Efficacy Endpoint of PASI-90 Response at Week 16 by Subgroup – ICONIC-ADVANCE 2

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Overall	57% (184/322)	1% (1/82)	56% (49%, 62%)
[redacted]			
Female	55% (57/104)	4% (1/27)	51% (34%, 62%)
Male	58% (127/218)	0% (0/55)	58% (51%, 65%)

Subgroup	Icotrokinra	Placebo	Difference From Placebo (95% CI)[2]
Race			
American Indian OR Alaska Native	0% (0/1)	-	NC
Asian	62% (21/34)	0% (0/15)	62% (38%, 78%)
Black OR African American	44% (4/9)	0% (0/2)	44% (-42%, 84%)
Multiple	0% (0/1)	-	NC
Native Hawaiian OR Other Pacific Islander	50% (1/2)	-	NC
Not Reported	0% (0/1)	-	NC
White	58% (158/274)	2% (1/65)	56% (48%, 62%)
Ethnicity			
Hispanic OR Latino	26% (11/42)	0% (0/12)	26% (-5%, 42%)
Not Hispanic OR Latino	62% (172/279)	1% (1/70)	60% (52%, 66%)
Not Reported	100% (1/1)	-	NC
Age Group			
18-44 years	55% (87/158)	0% (0/36)	55% (44%, 63%)
45-64 years	60% (79/131)	0% (0/36)	60% (49%, 69%)
≥65 years	55% (18/33)	10% (1/10)	44% (0%, 66%)
Weight			
≤90 kg	65% (120/186)	0% (0/48)	64% (56%, 71%)
<90 kg	47% (64/136)	3% (1/34)	44% (30%, 54%)
Baseline BMI			
Normal (<25 kg/m^2)	69% (49/71)	0% (0/14)	69% (42%, 80%)
Overweight (25-30 kg/m^2)	64% (71/111)	0% (0/30)	64% (51%, 73%)
Obese (≥30 kg/m^2)	46% (64/140)	3% (1/38)	43% (29%, 52%)
Region			
Americas	41% (41/100)	4% (1/25)	37% (15%, 49%)
Asia Pacific	59% (19/32)	0% (0/9)	59% (7%, 76%)
European Union	65% (124/190)	0% (0/48)	65% (58%, 72%)
Baseline IGA Score			
Moderate (=3)	60% (150/252)	1% (1/67)	58% (50%, 65%)
Severe (=4)	49% (34/70)	0% (0/15)	49% (21%, 62%)

Source: Statistical Analyst's Analysis; adsl.xpt, adclrori.xpt

[1] Full analysis set (FAS), defined as all randomized subjects. Subjects with an ICE of discontinuation of treatment due to lack of efficacy or due to an adverse event of worsening of psoriasis and/or initiation of other medication or therapy that could improve psoriasis were considered non-responders. The ICE of discontinuation of treatment for other reasons were handled using a treatment policy strategy (i.e., data after the ICE were used in the analysis as is).

[2] The risk difference and 95% CI were calculated using the exact method with continuity correction.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; NC, not calculable

Conclusions

All four trials were adequate and well-controlled trials that support the efficacy of icotrokinra for the treatment of moderate-to-severe plaque psoriasis. The results from all four trials were robust and consistent across subgroups and sensitivity analyses, although the endpoint of hf-PGA 0/1 in ICONIC-TOTAL was not statistically significant. In all four trials, the primary efficacy endpoints were statistically significant, and the key secondary efficacy endpoints supported the efficacy findings. In the active comparator trials, ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2, icotrokinra demonstrated statistical superiority to deucravacitinib in all prespecified key

secondary efficacy endpoints. Therefore, the Applicant provided substantial evidence of effectiveness for icotrokinra for the treatment of moderate to severe plaque psoriasis.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety of icotrokinra for the treatment of adults and pediatric patients 12 years of age and older who also weight at least 40 kg with moderate to severe plaque psoriasis who are candidates for systemic therapy and phototherapy was assessed primarily using pooled safety data from four Phase 3 trials (PSO3001, PSO3002, PSO3003, and PSO3004). The enrollment criteria varied by study and included adult subjects with moderate to severe plaque psoriasis, defined by a PASI ≥12, IGA ≥3, and BSA ≥10% who were candidates for phototherapy or systemic treatment. Study PSO3003 had inclusion criteria which differed to allow inclusion of subjects with psoriasis in special areas (scalp, genital, hand/foot) including a total BSA ≥1% at screening and baseline, and IGA (overall) ≥2 and at least one of the following: ss-IGA ≥3 and/or sPGA-G ≥3 and/or hf-PGA ≥3. For this study the majority of subjects were required to have BSA ≥10%, and the subpopulation was limited to a maximum of 40% of the population. Additionally, the age criterion was ≥12 years for Studies 3001 and 3003 to allow the enrollment of adolescents.

All four studies included a 16-week double blind placebo-controlled period which is the primary basis for the safety comparisons. Refer to Section 8.1.1 for details of trials pertinent to the evaluation of efficacy and safety. A Phase 2 dose ranging trial (PSO2001) and Phase 2 extension trial (PSO2002) provided additional supportive data, however the dosing regimens differed from the Phase 3 trial dosing regimens and therefore are not included in this safety analysis. Safety analyses from the Phase 3 studies included all randomized participants who received at least 1 administration of study intervention. Participants were analyzed based on the treatment they actually received, regardless of the treatment groups to which they were assigned. For the four Phase 3 studies, integrated datasets for the integrated summary of safety (ISS) as well as individual study datasets were used for review (including Study Data Tabulation Model [SDTM] and Analysis Data Model [ADaM]. This application was submitted in electronic common technical document format and included the Phase 3 protocols, statistical analysis plan, SAS transport datasets in the Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM) format. The datasets were in the following network path:

- NDA 220149: \\CDSESUB1\evsprod\NDA220149\0001

The review team analyzed short- and long-term pools of data to support the safety evaluation of icotrokinra in the target population (see below). The relevance of known and potential safety risks associated with IL-23 inhibitors was also considered while evaluating safety. Icotrokinra is an orally administered peptide that binds to the IL-23 receptor and antagonizes the binding of IL-23 and differs from other currently approved IL-23 inhibitors for the treatment of moderate to severe plaque psoriasis which are injectable monoclonal antibodies that target the p19 subunit of IL-23.

An observation of two gastrointestinal (GI) bleeding related deaths and two gastrointestinal related SAEs which occurred only in subjects receiving icotrokinra prompted further examination of GI-related serious adverse events and treatment emergent adverse events as well as a consultation with the Division of Gastroenterology. Pre-clinical safety signals had not indicated any risk of gastrointestinal bleeding in animal models that were evaluated. GI bleeding is not a known risk factor of systemic IL-23 inhibitors. CMC did not indicate any propensity for toxicity/irritation of the GI tract from the drug or formulation. The full evaluation is discussed in detail later in this review (8.2.4).

In attempts to attain reliable estimates of important safety parameters, the data from the Phase 3 clinical trials were pooled as follows:

The Placebo Controlled Safety Pool consists of data through Week 16 from all four Phase 3 trials (PSO3001, PSO3002, PSO3003, and PSO3004) for the double-blind comparison of icotrokinra to placebo.

The Active Controlled Safety Pool consists of data through Week 24 from two Phase 3 trials (PSO3002 and PSO3004) for the double-blind comparison of icotrokinra to deucravacitinib.

The open-label Extended Safety Pool consists of data from Week 16 to the safety data cut-off date or Week 156 in the four Phase 3 trials, for subjects continuing on icotrokinra or switching to icotrokinra from placebo. Subjects who completed the 16-week placebo-controlled period were eligible to continue on icotrokinra for up to 52 weeks of exposure.

Differing aspects of trial design influenced the ability to pool data beyond either Week 16, the placebo-controlled portion of all four studies, or week 24, the active controlled portion of PSO3002 and PSO3004. Adverse event rates in the Extended Safety Pool were exposure-adjusted to account for varying time on treatment. Subjects who switched from deucravacitinib to icotrokinra were not included this pool to avoid considering adverse events that might be attributed to the deucravacitinib active control. The 28-week randomized withdrawal period from Weeks 24 to 52 and the following long-term extension to Week 156 in PSO3001 was analyzed separately for both responders and nonresponders in the icotrokinra arm.

Lastly, the Adolescent Safety Pool was a separate analysis of the adolescent subgroup for the 16-week double-blind placebo-controlled period in PSO3001 and PSO3003.

While analyses using the Placebo Controlled Safety Pool are preferred to compare overall AEs, as well as laboratory assessments between treatment groups, rare events and events with long latency might not be seen. The Extended Safety Pool provides information on the total number of events (e.g., malignancies and deaths) that occurred in the controlled portion of the trials, as well as in the extended open-label safety portions of the trial. While acknowledging that the number of events in the extended safety pool is useful, the relationship to treatment cannot be

fully ascertained due to the open-label trial design. As such, there are limitations on the interpretation.

Primary safety analyses evaluated deaths, serious AEs (SAEs), AEs leading to discontinuation, treatment-emergent adverse events (AEs), adverse events of special interest (AESIs) and laboratory abnormalities in the Phase 3 trials. AESIs were determined based on the mechanism and targeted pathway of icotrokinra and include AEs seen with similar precedent immunomodulatory products such as injectable IL-23 inhibitors.

8.2.2. Review of the Safety Database

Overall Exposure

As of April 3, 2025, the last data cut-off date for the individual studies used for this application, the Phase 3 psoriasis development program included 2367 subjects ≥12 years of age who received at least one dose of icotrokinra 200 mg once daily. Of this total, 1849 were exposed for at least 26 weeks, and 648 were exposed for at least 52 weeks (Table 46). A total of 72 adolescent subjects ≥12 to <18 years of age, were exposed to icotrokinra; 71 were exposed for at least 26 weeks, and 45 were exposed for at least 52 weeks (Table 47).

Cumulatively through the safety cut-off date, there was a total of 1698 patient years (PY) of icotrokinra exposure.

The respective safety data cut-off dates for the pooled studies are as follows:

- PSO3001: 3-April-2025 (all subjects completed Week 52 visit)
- PSO3002: 3-April-2025 (all subjects completed the Week 44 visit)
- PSO3003: 19-Feb-2025 (all subjects completed the Week 52 visit)
- PSO3004: 6-Jan-2025 (all subjects completed the Week 24 visit)

Table 46. Duration of Treatment Exposure, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

Parameters	Pooled Icotrokinra to Icotrokinra N=1296	Pooled Placebo to Icotrokinra N=520	Pooled Deucravacitinib to Icotrokinra N=551	Pooled Total Icotrokinra N=2367
Duration of treatment, weeks				
Mean (SD)	45.4 (15.1)	37.2 (11.1)	18.8 (10.7)	37.4 (17.1)
Median (min, max)	51.3 (0.1, 73.3)	40.6 (0.3, 59.1)	19.7 (0.1, 37.1)	37.0 (0.1, 73.3)
Interquartile range	32.7 to 57.6	34.3 - 44.3	9.0 - 29.2	27.6 - 53.1
Total exposure (person-years)	1128.8	370.5	199	1698

Parameters	Pooled Icotrokinra to Icotrokinra N=1296	Pooled Placebo to Icotrokinra N=520	Pooled Deucravacitinib to Icotrokinra N=551	Pooled Total Icotrokinra N=2367
Subjects treated, by duration, n (%)				
<8 weeks	39 (3.0)	3 (0.6)	113 (20.5)	155 (6.5)
≥8 to <16 weeks	17 (1.3)	40 (7.7)	161 (29.2)	218 (9.2)
≥16 to <26 weeks	42 (3.2)	49 (9.4)	51 (9.3)	145 (6.1)
≥26 to <40 weeks	412 (31.8)	145 (27.9)	226 (41.0)	780 (33.0)
≥40 to <52 weeks	155 (12.0)	266 (51.2)	0	421 (17.8)
≥52 to <64 weeks	581 (44.8)	17 (3.3)	0	598 (25.3)
≥64 to <72 weeks	48 (3.7)	0	0	48 (2.0)
≥72 weeks	2 (0.2)	0	0	2 (0.1)

Source: adexsum.xpt; software: R.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Table 47. Duration of Treatment Exposure, Safety Population, Adolescent Subgroup, Pooled Trials PSO3001 and PSO3003

Parameters	Pooled Icotrokinra to Icotrokinra N=47	Pooled Placebo to Icotrokinra N=25	Pooled Total Icotrokinra N=72
Duration of treatment, weeks			
Mean (SD)	56.3 (3.3)	39.3 (6.7)	50.4 (9.4)
Median (min, max)	56.3 (45.9, 67.0)	40.6 (11.4, 45.6)	54.4 (11.4, 67.0)
Interquartile range	54.4 - 58.4	38.9 - 42.0	42.0 - 57.2
Total exposure (person-years)	50.7	18.8	69.6
Subjects treated, by duration, n (%)			
<16 weeks	0	1 (4.0)	1 (1.4)
≥16 to <26 weeks	0	0	0
≥26 to <40 weeks	0	9 (36.0)	9 (12.5)
≥40 to <52 weeks	2 (4.3)	15 (60.0)	17 (23.6)
≥52 to <64 weeks	44 (93.6)	0	44 (61.1)
≥64 weeks	1 (2.1)	0	1 (1.4)

Source: adexsum.xpt; software: R.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Per the Applicant's 120-day safety update, the 120-day safety update provided additional data through July 24, 2025 for a total of 2400 subjects exposed to icotrokinra. Of these, 2271 were exposed for at least 26 weeks and 1446 were exposed for at least 52 weeks.

Relevant Characteristics of the Safety Population

The icotrokinra psoriasis clinical trial safety population was predominantly (white, 75.5%) and (male, 67.0%). The icotrokinra psoriasis clinical trial safety population was predominantly (white, 75.5%) and (male, 67.0%). The median age was 45.0 years with 9.6% of the subjects at least 65 years old. Adolescents ages 12 to 18 years, comprised 3.6% (n=72) of the study population. The median body mass index (BMI) was 28.5 kg/m^2. The majority of the study population previously used prior psoriasis treatments including topical therapies, systemic therapies, including nonbiologic systemic or biologic therapies, and other systemic therapies and phototherapy.

Studies PSO3001, PSO3002, and PSO3004 required IGA≥3, PASI≥12, and BSA≥10% which reflect the pooled baseline scores for these study populations. Studies PSO3001, PSO3002, and PSO3304 had different enrollment criteria that PSO3003 which enrolled subjects with at least moderate "special area" (scalp, genital and/or hand/foot) psoriasis. Therefore, baseline demographics differ between the studies and are presented separately for PSO3003. Subjects in PSO3001, PSO3002, and PSO3004 had higher baseline IGA, all ≥3, higher baseline mean PASI scores 19.9), and higher mean BSA (25.8%). Subjects enrolled in PSO3003 included 5.5% with an IGA score of 2, baseline mean PASI of 14.4 and mean BSA of 16.0%.

Baseline disease characteristics in the adolescent subgroup were similar to the overall participant population except for psoriasis disease duration which was 5.2 years in the adolescent population versus 14.0 years in the adult population. The population appears to be representative of the U.S. target population based on race and age. Baseline demographics and disease characteristics were balanced across treatment groups in the Controlled Safety Pool, and concomitant medication use was generally similar across treatment groups (Table 48).

Table 48. Subject Populations, Randomized Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

Population	Pooled Icotrokinra N=1297 n (%)	Pooled Deucravacitinib N=634 n (%)	Pooled Placebo N=569 n (%)
Subjects randomized	1297 (100)	634 (100)	569 (100)
ITT population	1297 (100)	634 (100)	569 (100)
Safety population	1296 (99.9)	634 (100)	568 (99.8)
Per-protocol population	1280 (98.7)	626 (98.7)	560 (98.4)

Source: adsl.xpt; Software: R
The ITT population is referred to as the "Full Analysis Set" by the Applicant.
Abbreviations: ITT, intention-to-treat; N, number of subjects in treatment arm; n, number of subjects in specified subset of the treatment arm

Adequacy of the Safety Database

The demographics of the safety population are sufficiently representative of the target population. The clinical trial population is large enough to assess short-term safety in the general adult and pediatric psoriasis patient population, and the size of the database and duration of treatment reflects expected use in the patient population. Late developing adverse reactions that increase in severity or frequency over time such as overall malignancy, serious and opportunistic infections may not be represented from this population. At the time of this application, all 4 Phase 3 studies were ongoing to collect up to 3 years total exposure data to icotrokinra.

Pregnant and lactating females and pediatric subjects <12 years of age were excluded from clinical trials with icotrokinra, therefore the safety database is considered limited to assess the risks of icotrokinra use in specific populations including pregnant and lactating females, as well as pediatrics <12 years of age.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data quality and fitness were evaluated in conjunction with the Office of Computational Science (OCS) JumpStart team who audited results against the Applicant's study reports. The team confirmed that the adverse events matched to MedDRA version 27.0 for Trial PSO3001, PSO3002, PSO3003, PSO3004 Integrated Summary of Safety (ISS). Dataset modifications were required to update the subject level ADSL dataset as the presence of multiple treatment period dates/time variables caused JMP Clinical to attempt "Crossover Detection" in many reports, resulting in incorrect counts.

During the course of the review, multiple requests were sent to the Applicant requesting information and tables for adverse events of special interest (AESI) and laboratory abnormalities for subjects who did not switch treatment in order to better detect an association between drug use and an adverse event.

The team also collaborated with the Office of Scientific Investigations (OSI) to select sites for clinical inspections. See Section 4.1.

Categorization of Adverse Events

According to the Applicant, an adverse event (AE) was defined as any untoward medical occurrence in a clinical study subject administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per International Council on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. The sponsor collects AEs starting from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure.

For Trials 3001, 3002, 3003, and 3004, and the Integrated Summary of Safety (ISS), the Applicant defined treatment emergent adverse events (TEAEs) as events that occurred after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the trial if the last scheduled visit occurred at a later time. Nonetheless, analysis of the entire database beyond this defined scope was assessed for AEs.

The Applicant provided the following definition for serious adverse events (SAEs): An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose: results in death, is life-threatening (The

participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it was more severe), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a suspected transmission of any infectious agent via a medicinal product, is medically important (medical and scientific judgment must be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious).

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (e.g., all-cause mortality). Suspected unexpected serious AEs that are considered at least possibly related to study medication will be reported in an expedited manner to Health Authorities (including SUSARs to Eudravigilance according to EU CTR 536/2014 [EU CTR 2014]), IRBs, and Ethics Committees, as per local requirements.

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0. Each AE was coded to a system organ class (SOC) and preferred term (PT). Laboratory values were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0). The coding of adverse events and grading of laboratory values in the NDA submission appeared adequate and in general allowed for reasonable estimation of AE risks.

Investigators conducted assessments for AEs at study visits and recorded all observations and other data pertinent to the investigation on each subject treated or entered as a control. Data that was derived from source documents and reported on the case report form (CRF) had to be consistent with the source documents or discrepancies explained. For sites using the Applicant or designee electronic data capture tool, electronic CRFs were prepared for all data collection fields except for fields specific to SAEs and pregnancy, which were reported on the electronic SAE form and paper Pregnancy Surveillance Form, respectively. SAEs, whether related or not related to study drug, and pregnancies were required to be reported to the Medical Monitor within 24 hours of awareness of the event.

If limited information was initially available, follow-up reports were required. If an ongoing SAE changed its severity or relationship to study drug or if new information became available, the SAE report had to be updated and submitted within 24 hours to the Applicant (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs were required to be followed to “resolution or stabilization.”

The definitions of AE, TEAE, and SAE are acceptable. The method of categorizing severity, as well as assessment of causality were adequate. The Applicant's identification and presentation of AEs of special interest were reasonable.

Routine Clinical Tests

The Applicant's safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, concomitant medications, ECGs, clinical laboratory evaluation (chemistry, hematology, and urinalysis). Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Suicidality and depression were assessed using electronic Columbia–Suicide Severity Rating Scale (eC–SSRS) and eight-item Patient Health Questionnaire depression scale (PHQ-8). Subjects received a pretreatment evaluation for tuberculosis (TB). The schedules of safety assessments were similar among the trials.

8.2.4. Safety Results

Deaths

As of the 120-day safety update clinical data cut-off 24-July-2025 a total of 5 deaths were reported in the icotrokinra psoriasis development program. All 5 deaths occurred while on icotrokinra, 0 on placebo, and 0 in deucravacitinib-treated subjects.

The Applicant defined a fatal event as a death if it occurred following the first dose of study treatment through 30 days after the final dose of the study treatment or 30 days after a subject's participation in the study if the last scheduled visit occurred at a later time. Nonetheless, analysis of the entire database beyond this defined scope did not identify any additional deaths than what the Applicant reported.

Two of the five deaths occurred in the 16-week placebo-controlled period, with both subjects receiving icotrokinra. The 2 events were hematemesis (adjudicated as noncardiovascular death) and fatal myocardial infarction (adjudicated as a cardiovascular death). Three additional deaths occurred through the safety cut-off data, all in icotrokinra treated subjects. These events were malignancy (squamous cell carcinoma of the lung, adjudicated as a noncardiovascular death), gastrointestinal hemorrhage (adjudicated as a noncardiovascular death), and cocaine induced hypertensive cardiovascular disease.

Summaries of the deaths in the icotrokinra-treated subjects are provided below.

Week-16 Placebo-Controlled Period

Subject [redacted]: Upper Gastrointestinal Bleed and Death (Day 17). A 49-year-old male with a history of intellectual disability, parkinsonism due to haloperidol, bipolar disorder, ECG Q wave abnormal, obesity and hypertension received 200 mg of icotrokinra on Day 1. On Day 3, the participant started to experience worsening of generalized mobility, involuntary movements and progressive intense tremors and a serious adverse event

of tremor was reported. This event was assessed as severe and determined to be related to the study drug. It was reported that after receiving the study drug, the participant had lost the ability to perform self-care, such as drinking water alone, holding food and cutlery, and putting on slippers alone because the frequency and amplitude of the tremors had worsened. By Study Day 4, the participant was unable to walk independently due to generalized tremors, necessitating use of a wheelchair. The intensity of the tremors prevented him from maintaining daily activities of living. The participant did not inform of these symptoms as he occasionally had tremor crisis since the diagnosis of drug-induced parkinsonism. However, the symptoms reported on Study Day 3 were of a different level of severity than prior symptoms. In response to this event, the study intervention was interrupted on Study Day 12. After study drug interruption, the participant showed neurological improvement with a decrease in tremors, however, he was still unable to walk. No medications were reported for this event. On Day 17, the subject experienced 3 episodes of hematemesis, a seizure, and 2 cardiorespiratory arrests, resulting in death on the same day. The first dark-colored emetic episode occurred after an afternoon snack followed by 2 more episodes of dark-colored emesis followed by seizure and death. The fatal event as reported by the investigator was hematemesis and was considered related to the study intervention by the investigator. An autopsy report was not able to be obtained, however, a death certificate identified the cause of death as "Part I:A: Upper digestive hemorrhage B: Gastroesophageal varices rupture. Part II: psoriasis-Parkinson's Disease. The event was adjudicated as a noncardiovascular death, with cause of hemorrhage neither cardiovascular or stroke related.

Clinical Reviewer Comment: The subject's cause of death per the death certificate was determined to be from gastrointestinal bleeding from ruptured gastroesophageal varices. However, the subject history did not describe a history of liver disease, signs/symptoms of portal hypertension, or esophageal varices. Without an autopsy report, it is unclear how the diagnosis of gastroesophageal varices was determined. Gastroesophageal varices typically develop over a long period of time and study drug administration was 12 days, therefore the development of gastroesophageal varices is unlikely related to icotrokinra administration. However, a causal association between study drug and the event of death related to gastrointestinal bleeding cannot be ruled out. Additionally, the investigator considered study drug causally related to the event.

Subject (b) (6): Myocardial Infarction and Death (Day 35). A 63-year-old male with a history of hyperlipidemia, hypertension, right bundle branch block, concomitant amlodipine besilate/perindopril arginine use, and a BMI of 31.5 kg/m^2 who on Day 34 experienced chest pain during physical work, lost consciousness, had ventricular fibrillation, was cardioverted and transported to a hospital where 2 cardiac angiograms showed no large vessel occlusion or significant stenosis. On Day 35, during the second cardiac angiogram, he experienced ventricular fibrillation twice, bradycardia, hypotension, and asystole resulting in death. The fatal event of myocardial infarction was considered by the investigator to be not related to study intervention. The event was adjudicated as a cardiovascular death.

Clinical Reviewer Comment: The contribution of study drug is less likely given prior cardiac history and other cardiovascular risk factors including hypertension, hyperlipidemia and obesity. Psoriasis is associated with higher risk of CV events and stroke due to underlying systemic inflammation.

Post 16 Weeks Through Safety Cut-Off Date

Subject (b) (6): Squamous Cell Carcinoma of the Lung and Death (Day 412). A 70-year-old male, with a history of ischemic heart disease, hyperlipidemia, hypertension, Type 2 diabetes, obesity, deep vein thrombosis, abnormal chest x-ray finding in the left lower lung prior to study enrollment that was not considered significant by the investigator, former alcohol use, and smoking history (5 pack-years), was initially randomized to placebo and crossed over to icotrokinra on Day 113. On Day 368, the participant experienced abdominal pain, chest pain, cough and a deterioration in health requiring hospitalization and an SAE of squamous cell carcinoma of lung was reported. On Day 373, a CT scan of chest and abdomen revealed a primary nodule and metastatic nodules in the right lung, and numerous hypodense liver lesions consistent with metastases. On Day 412, the participant died due to squamous cell carcinoma of the lung. This fatal event was considered by the investigator to be not related to study intervention. The event was adjudicated as a noncardiovascular death due to malignancy.

Clinical Reviewer Comment: The contribution of study drug is unlikely as it was reported that there were abnormal chest x-ray findings prior to study enrollment which may have been a missed diagnosis given the presence of multiple metastases and advanced stage of the lung carcinoma at presentation.

Participant (b) (6): Gastrointestinal Hemorrhage and Death (Day 385). A 72-year-old male, with a history of hypertension, obesity, varicose veins, former smoking (7 packs every week for 23 years) and current alcohol use, was randomized to icotrokinra. Concomitant use of acetylsalicylic acid (75 mg daily since (b) (6)) and an unspecified anticoagulant was also reported. On Day 385, the participant was found dead at home with cause of death listed as gastrointestinal hemorrhage. It was reported that the participant had nausea for 2 days followed by vomiting which began the previous night, including episodes of black vomit. This was accompanied by loss of consciousness and sudden cardiac arrest. Chest compressions were initiated, and but had stopped by the time of emergency medical services arrival. Emergency medical services reported postmortem lividity and asystole on arrival. An autopsy was not performed.

Clinical Reviewer Comment: Acetyl salicylic acid use, along with use of alcohol and tobacco, are risk factors for the development of peptic ulcer disease. Gastric ulcers have also been associated with obesity and coronary artery disease. The presence of these confounding factors poses challenges to assessing and determining likeliness of study drug contribution to this event. However, a causal association between study drug and the event cannot be ruled out.

Participant (b) (6): Cocaine Toxicity induced hypertensive cardiovascular disease and Death (Day 252). A 48-year-old male, with history of gastroesophageal reflux disease, hypertension, obesity Class III (BMI 42.6 kg/m^2), psoriatic arthritis, and anemia, was initially randomized to placebo and crossed over to icotrokinra on Day 113. On Day 252, he was found deceased at home with evidence of decomposition. An autopsy was performed and a toxicology test was positive for cocaine toxicity. Hypertensive cardiovascular disease was considered as cause of death. Cocaine use and hypertension were included as contributing factors. Autopsy findings included cardiomegaly (560 g), coronary and aortic atherosclerosis, pulmonary congestion, cerebral swelling, cystitis with diverticula, and chronic kidney changes. The fatal event of toxicity to various agents (verbatim term: cocaine toxicity induced hypertensive cardiovascular disease) was considered by the investigator to be not related to study intervention.).

Clinical Reviewer Comment: The contribution of study drug is unlikely due to comorbid risk factors for cardiovascular disease, including hypertension and obesity, and substance use (cocaine) likely contributing to the fatal event.

Summary: A total of 5 deaths were reported in the icotrokinra psoriasis development program. All 5 deaths occurred in icotrokinra, and none in placebo or in deucravacitinib-treated subjects. The role of icotrokinra in the two deaths related to gastrointestinal bleeding are associated with multiple confounding factors present in these subjects for GI bleed, however, a causal association to the study drug cannot be ruled out. While both subjects had some general risk factors for GI bleed including presence of other comorbidities, alcohol and tobacco use, and in one subject, aspirin use, the possibility that icotrokinra use potentiated the risk of GI bleed is of interest. To examine the relationship between icotrokinra and GI bleed, other serious adverse events and treatment emergent adverse events were reviewed and are presented as a topic of special interest below. Two other deaths were cardiovascular related and had clear risk factors for cardiovascular disease and comorbid conditions. The squamous cell lung carcinoma related death may have had evidence of disease prior to enrollment, which may have been a missed diagnosis given the presence of multiple metastases and advanced stage of the lung carcinoma at presentation. This event is further discussed in Section 8.2.4 Adverse Events of Special Interest.

Serious Adverse Events

A number of serious adverse events are also protocol defined safety topics of special interest (AESI), which include malignancy, and possible Hy's Law. Other adverse events of interest specified in the submission include treatment-emergent LTBI reactivation, opportunistic infections and serious infections, positively adjudicated cardiovascular events (MACE, extended MACE, and other cardiovascular events), hepatic disorders reported as SAEs or that led to study treatment discontinuation, hypersensitivity reactions, anaphylactic reactions, suicidal ideation and behavior, and depression in subjects treated with icotrokinra. These adverse events of special interests are described in detail in Section 8.2.4 Adverse Events of Special Interest.

Serious TEAEs that occurred in the pooled 16-week placebo-controlled period are presented in the table below. The proportion of subjects with one or more SAEs was similar in the icotrokinra and placebo groups (1.5% versus 2.1%) through Week 16. No PT was reported as an SAE in >1 participant in the icotrokinra or placebo group. Most serious events were individual occurrences for both icotrokinra and placebo. Imbalances between icotrokinra and placebo were noted for SOC for Neoplasms, Cardiac Events, and Hepatobiliary Disorders, however, there did not seem to be any emerging pattern in reported events by preferred term within these categories. Analysis of SAEs in the open label period is also presented in Table 62. EAIRS were derived for the observed SAEs and did not show any increase over time.

Table 49. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (adjusted %)	Pooled Placebo N=568 n (adjusted %)	Risk Difference % (95% CI)
Any SAE	21 (1.5)	12 (2.1)	0.6 (2.2, 0.7)
Cardiac disorders (SOC)	3 (0.2)	0	0.2 (0.5, 0.6)
Acute myocardial infarction	1 (0.1)	0	0.1 (0.6, 0.5)
Coronary artery disease	1 (0.1)	0	0.1 (0.6, 0.4)
Myocardial infarction	1 (0.1)	0	0.1 (0.6, 0.4)
Gastrointestinal disorders (SOC)	2 (0.1)	0	0.1 (0.5, 0.5)
Pancreatitis	1 (0.1)	0	0.1 (0.6, 0.5)
Hematemesis	1 (0.1)	0	0.1 (0.6, 0.4)
Hepatobiliary disorders (SOC)	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Biliary dilatation	1 (0.1)	0	0.1 (0.6, 0.5)
Hypertransaminasemia	1 (0.1)	0	0.1 (0.6, 0.5)
Hepatitis	1 (0.1)	0	0.1 (0.6, 0.5)
Cholecystitis acute	0	1 (0.2)	0.2 (1.0, 0.1)
Infections and infestations (SOC)	2 (0.1)	2 (0.3)	0.2 (1.1, 0.2)
Gastroenteritis bacterial	1 (0.1)	0	0.1 (0.6, 0.5)
Infective exacerbation of chronic obstructive airways disease	1 (0.1)	0	0.1 (0.6, 0.4)
Arthritis bacterial	0	1 (0.2)	0.2 (1.0, 0.1)
COVID-19 pneumonia	0	1 (0.2)	0.2 (1.0, 0.1)
Sepsis	0	1 (0.2)	0.2 (1.0, 0.1)
Injury, poisoning and procedural complications (SOC)	1 (0.1)	4 (0.7)	0.6 (1.7, 0.1) *
Limb injury	1 (0.1)	0	0.1 (0.6, 0.5)
Concussion	0	1 (0.2)	0.2 (1.0, 0.1)
Craniofacial fracture	0	1 (0.2)	0.2 (1.0, 0.1)
Pelvic fracture	0	1 (0.2)	0.2 (1.0, 0.1)
Tendon rupture	0	1 (0.2)	0.2 (1.0, 0.1)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.1)	1 (0.2)	0.1 (0.9, 0.3)
Arthralgia	1 (0.1)	0	0.1 (0.6, 0.5)
Neck pain	0	1 (0.2)	0.2 (1.0, 0.1)

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (adjusted %)	Pooled Placebo N=568 n (adjusted %)	Risk Difference % (95% CI)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	6 (0.4)	1 (0.2)	0.2 (0.6, 0.8)
Adenocarcinoma of colon	1 (0.1)	0	0.1 (0.6, 0.5)
Pancreatic carcinoma	1 (0.1)	0	0.1 (0.6, 0.5)
Prostate cancer	1 (0.1)	0	0.1 (0.6, 0.5)
Benign neoplasm of bladder	1 (0.1)	0	0.1 (0.6, 0.4)
Breast cancer	1 (0.1)	0	0.1 (0.6, 0.4)
Keratoacanthoma	1 (0.1)	0	0.1 (0.6, 0.4)
Invasive ductal breast carcinoma	0	1 (0.2)	0.2 (1.0, 0.1)
Nervous system disorders (SOC)	2 (0.1)	1 (0.2)	0.0 (0.9, 0.4)
Subarachnoid hemorrhage	1 (0.1)	0	0.1 (0.6, 0.5)
Tremor	1 (0.1)	0	0.1 (0.6, 0.4)
Sciatica	0	1 (0.2)	0.2 (1.0, 0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	3 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Pulmonary embolism	1 (0.1)	0	0.1 (0.6, 0.5)
Chronic obstructive pulmonary disease	1 (0.1)	0	0.1 (0.6, 0.4)
Sleep apnea syndrome	1 (0.1)	0	0.1 (0.6, 0.4)
Acute respiratory failure	0	1 (0.2)	0.2 (1.0, 0.1)
Skin and subcutaneous tissue disorders (SOC)	1 (0.1)	1 (0.2)	0.1 (0.9, 0.3)
Diabetic foot	1 (0.1)	0	0.1 (0.6, 0.5)
Psoriasis	0	1 (0.2)	0.2 (1.0, 0.1)
Vascular disorders (SOC)	0	2 (0.3)	0.3 (1.3, 0.0) *
Hypertensive urgency	0	1 (0.2)	0.2 (1.0, 0.1)
Phlebitis superficial	0	1 (0.2)	0.2 (1.0, 0.1)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect**.**
Duration is 16 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

Table 50. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (adjusted EAIR)
Any SAE	27/535.0 (5.4)	11/364.9 (3.0)	46/916.4 (5.0)	57/1281.3 (4.5)
Cardiac disorders (SOC)	2/541.7 (0.4)	1/369.3 (0.3)	5/929.8 (0.5)	6/1299.1 (0.5)
Atrial fibrillation	2/541.7 (0.4)	0/370.0	2/930.2 (0.2)	2/1300.2 (0.2)
Coronary artery disease	0/541.8 (0.0)	0/370.0	1/929.9 (0.1)	1/1299.9 (0.1)
Myocardial infarction	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Angina unstable	0/541.8 (0.0)	1/369.3 (0.3)	0/930.3 (0.0)	1/1299.6 (0.1)
Acute myocardial infarction	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Gastrointestinal disorders (SOC)	1/541.8 (0.2)	0/370.0	3/929.6 (0.3)	3/1299.5 (0.2)
Hematemesis	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Gastric ulcer perforation	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Pancreatitis	0/541.8 (0.0)	0/370.0	1/929.5 (0.1)	1/1299.5 (0.1)
Hepatobiliary disorders (SOC)	0/541.8 (0.0)	0/370.0	3/928.7 (0.3)	3/1298.7 (0.2)
Hypertransaminasemia	0/541.8 (0.0)	0/370.0	1/929.5 (0.1)	1/1299.4 (0.1)
Biliary dilatation	0/541.8 (0.0)	0/370.0	1/929.5 (0.1)	1/1299.5 (0.1)
Hepatitis	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Infections and infestations (SOC)	5/541.2 (0.7)	1/369.9 (0.2)	7/928.7 (0.7)	8/1298.7 (0.6)
Infective exacerbation of chronic obstructive airways disease	2/541.8 (0.2)	0/370.0	3/929.6 (0.3)	3/1299.6 (0.3)
Pneumonia	3/541.7 (0.4)	0/370.0	3/930.2 (0.3)	3/1300.2 (0.2)
Diverticulitis	1/541.5 (0.2)	1/369.9 (0.2)	1/930.0 (0.1)	2/1299.9 (0.1)
Gastroenteritis bacterial	0/541.8 (0.0)	0/370.0	1/930.0 (0.1)	1/1300.0 (0.1)
Injury, poisoning and procedural complications (SOC)	11/537.8 (1.8)	3/369.0 (0.9)	12/925.4 (1.3)	15/1294.4 (1.2)
Meniscus injury	2/541.2 (0.3)	0/370.0	2/929.7 (0.2)	2/1299.7 (0.2)
Craniofacial fracture	2/541.1 (0.3)	0/370.0	2/929.6 (0.2)	2/1299.6 (0.2)
Thermal burn	1/541.6 (0.1)	0/370.0	1/930.1 (0.1)	1/1300.0 (0.1)
Foreign body in gastrointestinal tract	1/541.8 (0.1)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Procedural pain	0/541.8 (0.0)	1/369.5 (0.3)	0/930.3 (0.0)	1/1299.8 (0.1)
Limb injury	0/541.8 (0.0)	0/370.0	1/929.4 (0.1)	1/1299.4 (0.1)
Upper limb fracture	1/541.5 (0.2)	0/370.0	1/930.0 (0.1)	1/1300.0 (0.1)
Ligament rupture	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.0 (0.1)
Periprosthetic fracture	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Post procedural complication	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Toxicity to various agents	0/541.8 (0.0)	1/370.0 (0.3)	0/930.3 (0.0)	1/1300.3 (0.1)
Rib fracture	1/541.1 (0.2)	0/370.0	1/929.6 (0.1)	1/1299.5 (0.1)
Joint injury	1/541.1 (0.2)	0/370.0	1/929.6 (0.1)	1/1299.6 (0.1)
Lumbar vertebral fracture	0/541.8 (0.0)	1/369.5 (0.2)	0/930.3 (0.0)	1/1299.8 (0.1)
Clavicle fracture	1/541.7 (0.3)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (adjusted EAIR)
Musculoskeletal and connective tissue disorders (SOC)	2/541.5 (0.5)	2/368.3 (0.7)	3/929.0 (0.3)	5/1297.4 (0.4)
Intervertebral disc protrusion	0/541.8 (0.0)	1/369.2 (0.3)	0/930.3 (0.0)	1/1299.6 (0.1)
Osteoarthritis	1/541.5 (0.2)	0/370.0	1/930.0 (0.1)	1/1300.0 (0.1)
Spinal stenosis	0/541.8 (0.0)	1/369.1 (0.3)	0/930.3 (0.0)	1/1299.4 (0.1)
Back pain	1/541.8 (0.3)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Arthralgia	0/541.8 (0.0)	0/370.0	1/929.4 (0.1)	1/1299.3 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0/541.8 (0.0)	1/370.0 (0.2)	6/929.7 (0.6)	7/1299.7 (0.5)
Benign neoplasm of bladder	0/541.8 (0.0)	0/370.0	1/930.0 (0.1)	1/1299.9 (0.1)
Keratoacanthoma	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)
Breast cancer	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Pancreatic carcinoma	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of lung	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Adenocarcinoma of colon	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Prostate cancer	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)
Nervous system disorders (SOC)	5/540.6 (1.2)	1/369.6 (0.2)	7/929.1 (0.8)	8/1298.7 (0.6)
Syncope	2/541.2 (0.7)	0/370.0	2/929.7 (0.2)	2/1299.7 (0.1)
Tremor	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Cervical radiculopathy	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Transient ischemic attack	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Carotid artery dissection	1/541.3 (0.2)	0/370.0	1/929.8 (0.1)	1/1299.7 (0.1)
Status migrainosus	0/541.8 (0.0)	1/369.6 (0.2)	0/930.3 (0.0)	1/1299.9 (0.1)
Subarachnoid hemorrhage	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Product issues (SOC)	1/541.3 (0.2)	0/370.0	1/929.8 (0.1)	1/1299.8 (0.1)
Device loosening	1/541.3 (0.2)	0/370.0	1/929.8 (0.1)	1/1299.8 (0.1)
Renal and urinary disorders (SOC)	0/541.8 (0.0)	1/369.3 (0.3)	0/930.3 (0.0)	1/1299.7 (0.1)
Nephrolithiasis	0/541.8 (0.0)	1/369.3 (0.3)	0/930.3 (0.0)	1/1299.7 (0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	0/541.8 (0.0)	0/370.0	3/929.3 (0.3)	3/1299.3 (0.3)
Chronic obstructive pulmonary disease	0/541.8 (0.0)	0/370.0	1/929.8 (0.1)	1/1299.7 (0.1)
Sleep apnea syndrome	0/541.8 (0.0)	0/370.0	1/929.9 (0.1)	1/1299.9 (0.1)
Pulmonary embolism	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Skin and subcutaneous tissue disorders (SOC)	0/541.8 (0.0)	1/369.3 (0.2)	1/930.2 (0.1)	2/1299.4 (0.1)
Diabetic foot	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.1 (0.1)
Psoriasis	0/541.8 (0.0)	1/369.3 (0.2)	0/930.3 (0.0)	1/1299.6 (0.1)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (adjusted EAIR)
Vascular disorders (SOC)	2/541.7 (0.7)	0/370.0	2/930.2 (0.2)	2/1300.2 (0.1)
Poor peripheral circulation	1/541.8 (0.3)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Hypertension	1/541.7 (0.3)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk); SAE, serious adverse event; SOC, system organ class

Pooled data from PSO3002 and PSO3004 for the 24 week double blind placebo controlled period observed SAEs are presented in Table 51. Overall rates of SAEs were similar between icotrokinra and deucravacitinib. There were more events in SOC GI for deucravacitinib, and more hepatobiliary events for icotrokinra. Rates of other events were low and did not differ greatly between icotrokinra and deucravacitinib.

Table 51. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3002 and PSO3004, Double-Blind Active Comparator-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (adjusted %)	Pooled Deucravacitinib N=634 n (adjusted %)	Risk Difference % (95% CI)
Any SAE	18 (2.9)	20 (3.2)	-0.3 (-2.3, 1.7)
Cardiac disorders (SOC)	4 (0.6)	4 (0.6)	0.0 (-1.1, 1.1)
Atrial fibrillation	1 (0.2)	0	0.2 (-0.4, 0.9)
Acute myocardial infarction	1 (0.2)	0	0.2 (-0.4, 0.9)
Coronary artery disease	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.8)
Myocardial infarction	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.8)
Angina pectoris	0	1 (0.2)	-0.2 (-0.9, 0.4)
Tachycardia	0	1 (0.2)	-0.2 (-0.9, 0.4)
Bundle branch block left	0	1 (0.2)	-0.2 (-0.9, 0.4)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (adjusted %)	Pooled Deucravacitinib N=634 n (adjusted %)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)	1 (0.2)	4 (0.6)	-0.5 (-1.5, 0.3)
Hematemesis	1 (0.2)	0	0.2 (-0.4, 0.9)
Anal fistula	0	1 (0.2)	-0.2 (-0.9, 0.4)
Intestinal obstruction	0	1 (0.2)	-0.2 (-0.9, 0.4)
Pancreatitis	0	1 (0.2)	-0.2 (-0.9, 0.4)
Colitis ulcerative	0	1 (0.2)	-0.2 (-0.9, 0.4)
General disorders and administration site conditions (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Systemic inflammatory response syndrome	0	1 (0.2)	-0.2 (-0.9, 0.4)
Hepatobiliary disorders (SOC)	2 (0.3)	0	0.3 (-0.3, 1.1)
Biliary dilatation	1 (0.2)	0	0.2 (-0.4, 0.9)
Hypertransaminasemia	1 (0.2)	0	0.2 (-0.4, 0.9)
Infections and infestations (SOC)	3 (0.5)	5 (0.8)	-0.3 (-1.4, 0.7)
Infective exacerbation of chronic obstructive airways disease	3 (0.5)	0	0.5 (-0.1, 1.4)
Pneumonia	1 (0.2)	0	0.2 (-0.4, 0.9)
Lower respiratory tract infection	0	1 (0.2)	-0.2 (-0.9, 0.4)
Viral upper respiratory tract infection	0	1 (0.2)	-0.2 (-0.9, 0.4)
Campylobacter colitis	0	1 (0.2)	-0.2 (-0.9, 0.4)
Viral infection	0	1 (0.2)	-0.2 (-0.9, 0.4)
Wound infection	0	1 (0.2)	-0.2 (-0.9, 0.4)
Injury, poisoning and procedural complications (SOC)	3 (0.5)	2 (0.3)	0.2 (-0.7, 1.1)
Meniscus injury	1 (0.2)	0	0.2 (-0.4, 0.9)
Thermal burn	1 (0.2)	0	0.2 (-0.4, 0.9)
Limb injury	1 (0.2)	0	0.2 (-0.4, 0.9)
Head injury	0	1 (0.2)	-0.2 (-0.9, 0.4)
Wound dehiscence	0	1 (0.2)	-0.2 (-0.9, 0.4)
Metabolism and nutrition disorders (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Diabetes mellitus	0	1 (0.2)	-0.2 (-0.9, 0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	4 (0.6)	2 (0.3)	0.3 (-0.6, 1.3)
Benign neoplasm of bladder	1 (0.2)	0	0.2 (-0.4, 0.9)
Breast cancer	1 (0.2)	0	0.2 (-0.4, 0.9)
Keratoacanthoma	1 (0.2)	0	0.2 (-0.4, 0.9)
Pancreatic carcinoma	1 (0.2)	0	0.2 (-0.4, 0.9)
Malignant melanoma in situ	0	1 (0.2)	-0.2 (-0.9, 0.4)
Squamous cell carcinoma of the oral cavity	0	1 (0.2)	-0.2 (-0.9, 0.4)
Nervous system disorders (SOC)	1 (0.2)	2 (0.3)	-0.2 (-1.0, 0.6)
Tremor	1 (0.2)	0	0.2 (-0.4, 0.9)
Cerebrovascular accident	0	1 (0.2)	-0.2 (-0.9, 0.4)
Carotid arteriosclerosis	0	1 (0.2)	-0.2 (-0.9, 0.4)
Transient global amnesia	0	1 (0.2)	-0.2 (-0.9, 0.4)
Psychiatric disorders (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Depression	0	1 (0.2)	-0.2 (-0.9, 0.4)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (adjusted %)	Pooled Deucravacitinib N=634 n (adjusted %)	Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)	3 (0.5)	0	0.5 (-0.1, 1.4)
Chronic obstructive pulmonary disease	1 (0.2)	0	0.2 (-0.4, 0.9)
Sleep apnea syndrome	1 (0.2)	0	0.2 (-0.4, 0.9)
Pulmonary embolism	1 (0.2)	0	0.2 (-0.4, 0.9)
Skin and subcutaneous tissue disorders (SOC)	1 (0.2)	0	0.2 (-0.4, 0.9)
Diabetic foot	1 (0.2)	0	0.2 (-0.4, 0.9)
Surgical and medical procedures (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Coronary artery bypass	0	1 (0.2)	-0.2 (-0.9, 0.4)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

SAE: Malignancy

Week-16 Placebo-Controlled Period

Seven SAEs of malignancy were reported in icotrokinra-treated participants compared to one SAE of malignancy in placebo-treated participants during the 16-week placebo-controlled period. Of these SAEs, several cases had medical history suggestive of the malignancy being present prior to study enrollment. These include a case of prostate cancer in a 62-year-old male who had an elevated prostate specific antigen prior to study enrollment. Adenocarcinoma of the colon was reported in a 64-year-old female who reported symptoms of gastroenteritis and colitis prior to randomization, and the adenocarcinoma was diagnosed on study day 15. Invasive breast carcinoma was diagnosed in a 70-year-old female with history of fibrocystic breast disease, which may obscure mammography reading, on study day 14. Two keratocanthomas were identified in a 79-year-old male who had prior history of actinic keratosis and keratocanthoma on study day 63. Benign neoplasm of the bladder was reported in a 61-year-old with prior history of such neoplasm on study day 39. The details of these cases are reported below in Section 8.2.4.1.

Malignancies generally have a long development time and may not be adequately detected or identified in the time span of clinical trials in clinical development programs. There are some instances in which a drug either through target or off target effects, could act in a tumor promoting fashion. In the double blind placebo controlled period of the icotrokinra pooled phase 3 safety data, malignancy cases were reported. These cases did not form a cluster or

pattern by time to onset, organ system or type of malignancy; however, the 16 week placebo control period is a short administration time for potentiation of drug effect in tumor development. Therefore, the longer-term risk was estimated using the open label pool subjects who continuously received icotrokinra compared to subjects who initially received placebo and switched to icotrokinra. The associated EAIRs for each malignancy are reported below. Collectively, the EAIR rates do not suggest an increased risk of malignancy over time for the types of malignancies identified in the placebo control period.

8.2.4.1. Malignancy

Table 52. Adverse Events of Special Interest Assessment of Malignancy, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Malignancy Assessment	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
AE grouping related to AESI	2/541.6 (0.3)	1/370.0 (0.2)	8/929.6 (0.9)	9/1299.5 (0.7)
Keratoacanthoma	0/541.8 (0.0)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Breast cancer	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of skin	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Metastases to liver	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Pancreatic carcinoma	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Malignant melanoma in situ	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.2 (0.1)
Chronic lymphocytic leukemia	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of lung	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Adenocarcinoma of colon	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Prostate cancer	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)
Maximum severity				
Death	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Life-threatening	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Severe	0/541.8 (0.0)	0/370.0	2/930.3 (0.2)	2/1300.2 (0.2)
Moderate	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Mild	1/541.8 (0.2)	0/370.0	4/929.9 (0.4)	4/1299.9 (0.3)
Serious	0/541.8 (0.0)	1/370.0 (0.2)	5/930.1 (0.5)	6/1300.0 (0.5)
Deaths	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Resulting in treatment discontinuation	2/541.6 (0.3)	1/370.0 (0.2)	8/929.6 (0.9)	9/1299.5 (0.7)
Relatedness	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Number of subjects with adverse events with end dates on or before treatment end dates	1/0.6 (NA)	0/0.7 (NA)	3/2.1 (131.1)	3/2.8 (131.1)
Duration, days (from AE start date to AE end date)				
Mean (SD)	32.0 (NA)	NA	38.0 (14.9)	38.0 (14.9)
Median (min, max)	32.0 (32.0, 32.0)	NA	32.0 (27.0, 55.0)	32.0 (27.0, 55.0)
Interquartile range	32.0 to 32.0	NA	29.5 to 43.5	29.5 to 43.5

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Malignancy Assessment	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/0.7 (NA)	0/0.7 (NA)	3/2.4 (142.9)	3/3.1 (92.4)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/0.8 (NA)	1/0.7 (NA)	2/2.6 (91.7)	3/3.3 (70.6)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	NA	40.0 (NA)	54.5 (41.7)	49.7 (30.7)
Median (min, max)	NA	40.0 (40.0, 40.0)	54.5 (25.0, 84.0)	40.0 (25.0, 84.0)
Interquartile range	NA	40.0 to 40.0	39.8 to 69.2	32.5 to 62.0

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Severity scale as defined by the protocol.
Relatedness is determined by investigator.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk); SD, standard deviation

Narratives are presented below for several cases of interest.

Week-16 Placebo-Controlled Period

Subject (b) (6)

The subject is a 72 year old female with history of malignant melanoma and current smoker randomized to icotrokinra. On study day 110, she was evaluated by her dermatologist for an asymptomatic skin mole on the left posterior lateral distal thigh. The pathology report showed melanoma in situ. This was classified as a nonserious AE and the subject discontinued from the study.

Clinical Reviewer Comment: This event is unlikely to be related to icotrokinra administration due to prior history of melanoma which suggests preexisting risk factors for melanoma that may have contributed to development of melanoma in situ.

Participant (b) (6)

Forty-five-year-old male with no medical history and reporting regular alcohol and tobacco (30 pack year history) use was randomized to icotrokinra. On study day 26 the subject reported nausea. On study day 36 he developed night sweats, and metastases to the liver were reported. On Study Day 53, the participant visited hospital with complaints of night sweats, intermittent nausea, and stomach pain causing difficulty to work and he was sent home with diagnosis of urinary tract infection and liver mass. Subsequently, SAEs of pancreatic carcinoma (study day 60), Pulmonary embolism (study day 61), and acute myocardial infarction (study day 62) were reported. On study day 64, liver biopsy showed infiltration by a moderately differentiated adenocarcinoma with metastatic disease of the liver. The subject was discontinued from the study on study day 115.

Clinical Reviewer Comment: This event in unlikely related to icotrokinra due to history of alcohol and tobacco use and the relatively short time of drug administration to onset of the event in conjunction with advanced metastatic stage of pancreatic carcinoma at presentation.

Post 16 Weeks Through Safety Cut-Off Date

Participant (b) (6)

Subject is a 60-year-old male with medical history of pulmonary fibrosis and former alcohol and tobacco use, randomized to icotrokinra on (b) (6). The subject reported progressive fatigue in (b) (6). On study day 339, lymphocytosis was reported and phenotyping reported on study day 395 identified an abnormal B-cell population, subsequently B-cell small lymphocytic leukemia was diagnosed. The subject discontinued the study.

Clinical Reviewer Comment: This event is unlikely to be causally related to icotrokinra administration as a history of pulmonary fibrosis may be a risk factor for B-cell small lymphocytic leukemia as pulmonary fibrosis may be associated with chronic inflammation and shared genetic/cellular pathways that involve tissue damage, inflammation, and abnormal cell growth.[2]

Participant (b) (6)

Subject is a 43-year-old female without significant medical history and a current smoker (4 pack year history), who was initially randomized to deucravacitinib and switched to icotrokinra at

[2] Nicholson AG, Wotherspoon AC, Jones AL, Sheppard MN, Isaacson PG, Corrin B. Pulmonary B-cell non-Hodgkin's lymphoma associated with autoimmune disorders: a clinicopathological review of six cases. Eur Respir J. 1996 Oct;9(10):2022-5. doi: 10.1183/09031936.96.09102022. PMID: 8902461.

week 24 (study day 169). She experienced a fainting episode on study day 231 and was taken to an emergency ward where she received stitches for injury related to the fall. She was subsequently diagnosed with a serious adverse event of meningioma. A magnetic resonance imaging of the head with contrast on Day 246 revealed a lesion suggestive of meningioma on the superior surface of the cerebellar tentorium on the left side. She was referred for treatment on meningioma and discontinued the study.

Clinical Reviewer Comment: Attribution of icotrokinra is unknown, however as a confounding factor in assessment, this subject received deucravacitinib for 24 weeks prior to icotrokinra administration and is noted to have a history of smoking which is a risk factor for malignancy.

Participant (b) (6)

The subject is a 75-year-old male without past medical history and reported prior alcohol and tobacco (7 pack year history) was randomized to treatment with deucravacitinib and switched to icotrokinra to JNJ-77242113 at week 24 (study day 169). No medical history or family history was reported. On study day 62 while randomized to deucravacitinib a nonserious AE of mouth ulceration was reported. The subject was treated with paracetamol and on study day 64 the event was reported as resolved. On an unspecified date in (b) (6) (prior to the subject's first administration of icotrokinra on (b) (6)), an SAE of squamous cell carcinoma of the oral cavity was reported. The subject was hospitalized for surgical excision and subsequently study drug was discontinued.

Clinical Reviewer Comment: This event is unlikely to be related to icotrokinra administration due to presence of related signs and symptoms while on deucravacitinib randomization.

Participant (b) (6)

The subject is a 79 year old white male with medical history including diabetes mellitus, hypertension and basal cell carcinoma. The patient uses alcohol and is a former smoker. He was randomized to icotrokinra. On study day 209 SAE of squamous cell carcinoma was reported. The subject underwent Moh's surgery on study day 210 and was subsequently discontinued from the study due to this SAE.

Clinical Reviewer Comment: This event is unlikely related to icotrokinra administration as the subject had pre-existing history of basal cell carcinoma and use of tobacco and alcohol can increase risk for cancer.

Subject (b) (6)

The subject is a 71 year old male with medical history including neutropenia, hypertension and keratocanthoma. He was randomized to icotrokinra. On study day 206. Due to ongoing issues with neutropenia, the subject was referred to an oncologist who performed a bone marrow biopsy which revealed chronic lymphocytic leukemia. A non-serious AE was reported. The subject was asymptomatic, and no further details about treatment was provided. The subject discontinued due to this adverse event.

Clinical Reviewer Comment: Attribution of icotrokinra is unknown. The history of neutropenia may also indicate the process of progression to leukemia pre-dated the study enrollment.

Hepatic Events

Hepatic disorders reported as SAEs or that led to study treatment discontinuation (DAE) were identified in the submission as potential AESIs and individual narratives are discussed below. All cases began in the 16 week placebo controlled period.

Participant 77242113PSO3001-US100691004 (Potential Hy's Law)

Forty-five-year-old white male with unrelated medical history and alcohol and tobacco use was randomized to icotrokinra. At randomization, his liver enzymes were within normal ranges except for slightly elevated GGT. On Study Day 101 the subject presented with jaundice and dark urine and was diagnosed with hepatitis. His liver enzymes at that time were ALT 229 U/L (4.4× ULN; normal range 7 to 52 U/L), AST 84 U/L (2.2× ULN; normal range 13 to 39 U/L), ALP 327 U/L (3.1× ULN; normal range 34 to 104 U/L) and total bilirubin of 4.4 mg/dL (3.7× ULN; normal range 0.3 to 1.2 mg/dL). Subject was subsequently diagnosed with post-viral hepatitis due to Epstein Barr Virus (EBV). The subject's liver enzyme trended downward and returned to normal, and he resumed icotrokinra on Study Day 139.

Clinical Reviewer Comment: This event is unlikely related to icotrokinra due to diagnosis of EBV as source of transaminase elevations and normalization with resuming and continuation of study drug.

Participant [redacted] (b) (6) (SAE)

Subject is a 55-year-old male with past medical history of dyspepsia who was randomized to icotrokinra. The subject had a history of latent tuberculosis (LTBI) at screening and was receiving treatment with isoniazid at the start of study treatment. On study day 38 he developed transaminase elevations (ALT, AST and GGT) reported as a nonserious AE. On study day 38 he was noted to have further transaminase elevation, which triggered the reporting threshold for SAE of hypertransaminasemia and was attributed to isoniazid toxicity. Isoniazid was stopped on study day 35. The subject remained asymptomatic. Study drug was interrupted. On study day 59 liver enzymes were normalized and the subject resumed study drug on study day 96. He is continuing on the study at the safety cutoff date (study day 354).

Clinical Reviewer Comment: This event is unlikely related to icotrokinra administration as the subject was receiving isoniazid for LTBI prior to icotrokinra which was likely the cause of liver enzyme elevation and subject was able to continue on the study drug after resolution of liver enzyme elevation.

Subject [redacted] (b) (6) (SAE, DAE)

Forty-one-year-old white male with medical history of asthma, hyperlipidemia, and current alcohol use was randomized to icotrokinra. The subject had LTBI identified at screening and had elevated liver enzymes: ALT 1.2×ULN, ALP normal, AST normal, bilirubin normal, and GGT. The subject started treatment with isoniazid 300 mg oral once daily and vitamin B6 (10 mg oral once daily) Day -6. The subject received the first administration of icotrokinra with similar liver enzymes to screening values. On study day 30 the subject was noted to have AEs of ALT and AST mildly increased. An SAE of hepatitis began on Study Day 57 with marked elevations of liver enzymes on Study Day 57, routine study labs showed ALT 30.7× ULN, AST 17.2× ULN, ALP 2.1× ULN, bilirubin total 2.6× ULN, bilirubin direct 2.3 mg/dL, and GGT 8.1× ULN. On Study Day 58, treatment with isoniazid and vitamin B6 was stopped and the study drug was also withdrawn. On Study Day 59, the subject was hospitalized with abdominal pain, yellow skin, and dark urine; physical examination revealed yellowish skin and sclera. Upon admission, further laboratory tests indicated cholestasis, mixed hyperbilirubinemia, and markedly elevated transaminase levels. A serious adverse event of hepatitis (reported term: hepatitis due to unknown reason) was reported. During hospitalization, hepatoviral tests yielded negative results. A computed tomography (CT) scan of the abdominal cavity did not reveal any clinically significant abnormalities. On Study Day 59, oral prednisone was initiated, leading to a rapid reduction in transaminase levels and bilirubin levels; and there was improvement in the subject's clinical status. The participant received prednisone (oral) from Study Day 59 to Study Day 261. A liver biopsy was performed for suspected autoimmune hepatitis, which showed Grade 1 fibrosis and chronic hepatitis. The subject discontinued the study due to the event.

Clinical Reviewer Comment: This potential Hy's Law case is confounded by administration of isoniazid, possible pre-existing autoimmune hepatitis and hepatic fibrosis; icotrokinra is unlikely to have significant contribution to this case given the confounding factors.

The following event is a potential Hy's Law case that began on placebo but was unresolved at the time of switch to icotrokinra and resulted in discontinuation. The case is included here for completeness.

Participant [redacted] (b) (6) (DAE)

Subject is a 48-year-old female initially randomized to placebo, switched to icotrokinra at week 16. She developed elevated liver enzymes (AST, ALT and GGT) on study day 1 on placebo which remained elevated through switch to icotrokinra on study day 114. The subject discontinued the study on day 142 due to continued elevation of liver enzymes.

Clinical Reviewer Comment: This event is unlikely related to icotrokinra administration as the elevated live enzymes began on placebo and persisted through the time of switch to icotrokinra.

SAE Infections

Week-16 Placebo-Controlled Period

Participant (b) (6)

A 62-year-old male with history of diabetes mellitus, hypertension, and diabetic neuropathy was randomized to icotrokinra. On study day 55, the subject experienced a serious adverse event of diabetic foot ulcer requiring hospitalization. On study day 56 a nonserious event of chronic kidney disease was also reported. A second nonserious event of hyperkalemia was also reported on study day 59. The subject discontinued the study due to the adverse event of hyperkalemia.

Clinical Reviewer Comment: The event of diabetic foot ulcer is unlikely related to icotrokinra given the presence of signs of advanced sequelae of diabetes (neuropathy and chronic kidney disease).

Subject (b) (6)

The subject is a 42-year-old female with medical history including back pain, eczema, depression, and orthostatic hypotension and is a current smoker. She was randomized to icotrokinra. On study day 11 she experienced a nonserious AE of influenza-like illness. She was treated with salbutamol, guaifenesin, ibuprofen, paracetamol, and prednisone. She developed cough and significant dysphonia and was seen by ENT on study day 21 and diagnosed with laryngitis fungal by laryngoscopy. She was treated with fluconazole and nystatin and significantly improved. On study day 39, her symptoms recurred, and she was found to have recurrence of the fungal laryngitis. She received additional treatment with fluconazole and nystatin and discontinued study drug. The event was positively adjudicated as an opportunistic infection.

Clinical Reviewer Comment: Preceding influenza type illness along with steroid and antibiotic treatment may increase the risk for fungal infection and are potential confounding factors. Administration of icotrokinra which may have altered immune response to this infection could be a potential contributing factor.

Subject (b) (6)

The subject is a 57-year-old male with history of asthma and current tobacco and alcohol abuse. He was randomized to icotrokinra. The subject reported a 2-day history of cough, shortness of breath, and wheeze which worsened on study day 32. Viral PCR swab was positive for rhinovirus. An SAE of infectious exacerbation of COPD was reported. The subject received hydrocortisone (IV), azithromycin (IV), ceftriaxone (IV), ipratropium (inhalation), and salbutamol (inhalation). The subject recovered and continued in the study. Study drug was interrupted during the event.

Clinical Reviewer Comment: Increased infection risk is of concern with inhibition of IL-23 , however this is confounded by a history of asthma and smoking which may increase the risk of respiratory infection and may make the contribution of icotrokinra less likely in this event.

Subject (b) (6)

Subject is a 53-year-old with history of asthma and COPD, schizophrenia, sleep disorder and obstructive sleep apnea syndrome was randomized to icotrokinra. She developed several serious adverse events. She was noted to have nonserious events of nasopharyngitis on study days 3 and 28 which resolved. On study day 122, she was found agitated and cyanotic and was transported to hospital. Oxygen saturation was found to be approximately 20% and she was intubated for respiratory arrest. She was reported to have poorly controlled COPD and obstructive sleep apnea and was non-compliant with CPAP. On bronchoscopy she had copious sputum from the right middle and right lower lobe. CXR showed consolidation of the right lower lobe and right lower lobe collapse. The subject was also administered digoxin and amiodarone. Due to events of pneumonia and atrial fibrillation, study drug was withdrawn. She was noted to have another event of infective exacerbation of COPD on study day 144 attributed to non-optimized end stage COPD treatment and ongoing heavy smoking. She was treated with prednisolone and doxycycline. On study day 166, she received cephalexin for the infective exacerbation of COPD which resulted in an anaphylactic reaction for which she received epinephrine. This event was not considered to be related to study drug. Although it was previously reported that the subject discontinued study drug, it was reported that study was discontinued on study day 167.

Clinical Reviewer Comment: This series of events is unlikely related to icotrokinra administration due to history of OSA and poorly controlled COPD with reported noncompliance with medical treatment.

Post Week 16 Through Safety Reporting Period

Participant (b) (6)

Subject is a 56-year-old female with medical history including diabetes mellitus, cholecystitis and cholecystectomy who was initially randomized to deucravactinib and switched to icotrokinra at Week 24 (study day 169). On study day 263 she developed symptoms of pneumonia and was hospitalized on study day 267. The subject was treated with antibiotics and hydration for suspected bacterial pneumonia and subsequently resolved. Study drug was interrupted then resumed and the subject continued in the study.

Clinical Reviewer Comment: Increased infection risk is of concern with inhibition of IL-23, however this is confounded by a history of diabetes mellitus which also may impair the immune system and prior deucravacitinib administration also is a confounder.

Participant (b) (6)

Subject is a 65-year-old male with unremarkable medical history except for a 46-pack year history of smoking. He was randomized to icotrokinra and had a nonserious event of upper

respiratory tract inflammation on study day 250, and a nonserious event of nasopharyngitis on study day 322. On study day 327 due to worsening respiratory symptoms and fever he was hospitalized with pneumonia subsequently confirmed to be *Haemophilus influenzae* pneumonia. He was treated with antibiotics, recovered and continued study treatment.

Clinical Reviewer Comment: Increased infection risk is of concern with inhibition of IL-23, however this is confounded by a history of diabetes mellitus which also may impair the immune system and may make the contribution of icotrokinra less likely in this event.

Participant (b) (6)

The subject is a 65-year-old male with medical history of diabetes mellitus, hypertension and hypercholesterolemia who was randomized to icotrokinra. On study day 340 the subject presented with marked cough and congestion and was diagnosed with pneumonia reported as an SAE. He was hospitalized on study day 343 due to worsening symptoms. The subject was treated with antibiotics, steroids and inhaled salbutamol. The subject recovered and continued on the study.

Clinical Reviewer Comment: Increased infection risk is of concern with inhibition of IL-23, however this is confounded by a history of diabetes mellitus which also may impair the immune system and may make the contribution of icotrokinra less likely in this event.

Subject (b) (6)

The subject is a 74-year-old female with history of COPD and current cigarette smoker. She was randomized to icotrokinra. On study day 132 she reported 3 days of increased cough and shortness of breath along with chest tightness and wheezing, and an SAE of infective exacerbation of COPD was made, with hospitalization on study day 133. Study drug was interrupted, and the subject received treatment with budesonide, ipratropium, salbutamol, dexamethasone, benxonatate, guaifenesin. On study day 140 the event was considered resolved and she resumed study drug and continued on study.

Clinical Reviewer Comment: Increased infection risk is of concern with inhibition of IL-23, however this is confounded by a history of COPD and continued tobacco use which also may impair the immune system response to infection and may make the contribution of icotrokinra less likely in this event.

SAE: Positively Adjudicated Cardiovascular Events (MACE, Extended MACE, and Other Cardiovascular Events)

Week-16 Placebo-Controlled Period

Participant (b) (6)

Forty-nine-year-old white male with history of HTN, obstructive sleep apnea and prior fall with injury to coccyx was randomized to icotrokinra. He reported current use of alcohol and tobacco. On Study Day 11, the participant experienced a serious adverse event of subarachnoid

hemorrhage and was hospitalized on the same day. Prior to this event, the subject experienced non-serious events of headache on Study Day 7 and 8, and on Study Day 11 the participant received treatment with an unspecified muscle relaxant administered intramuscularly in the neck. The patient also reported dysarthria and hypoesthesia (feet). There was evidence of intervertebral disc disease at C2/C3 by CT and MRI. Angiography of the brain did not show aneurysm and transcranial doppler was normal. On Study Day 25 the events were reported as resolved. The subject discontinued from the study. The event of subarachnoid hemorrhage was positively adjudicated as a non-fatal stroke by an independent cardiac adjudication committee.

Clinical Reviewer Comment: The causality of icotrokinra is unknown however there is no known mechanism associated with IL-23 inhibition that would be related to vascular bleeding and there was a short period of study drug administration prior to onset of this event. There is no discussion in the narrative regarding the origin or cause of the subarachnoid hemorrhage and contributes to challenges in assessing causality to study drug.

Participant (b) (6)

The subject is a 45-year-old female with medical history of hypothyroidism, atrial fibrillation, and cardiac ablation, who was randomized to icotrokinra. On study day 64 she developed a nonserious event of supraventricular tachycardia. The event resolved with medical management. The subject continued in the study. An independent cardiac adjudication committee positively adjudicated the event of supraventricular tachycardia as arrhythmia (atrial fibrillation) requiring intervention.

Clinical Reviewer Comment: Preexisting history of atrial fibrillation requiring an ablation procedure is likely a key contributing factor in this event rendering icotrokinra administration less likely to be a contributing factor.

Subject (b) (6)

Fifty-two-year-old male with unremarkable medical history was randomized to icotrokinra. On study day 88 he experienced a nonserious adverse event of retinal vascular thrombosis and a related, nonserious adverse event of macular edema. The event of retinal vascular thrombosis was positively adjudicated as a cardiovascular event. The subject recovered and continued in the study.

Clinical Reviewer Comment: Attribution of icotrokinra is uncertain. There are lifestyle factors including age, smoking, obesity and sedentary lifestyle that may contribute to risk, as well as underlying inflammatory and metabolic disorders.

Subject (b) (6)

The subject is an 80-year-old male with history of BPH, anxiety, brain stem infarction, hypertension, hyperlipidemia, constipation, chronic gastritis, COPD, and CAD. He was randomized to icotrokinra. On study day 70 he reported AEs of dizziness and headache and was hospitalized for SAE of CAD. On study day 93 he again reported dizziness and headache that

were associated with elevated blood pressure. On study day 122 he underwent PTCA and a drug-eluting stent was inserted at the left anterior descending artery and the left circumflex artery. The subject improved and was discharged. He continued on study. On study day 212 he experienced a second unrelated SAE of foreign body in the gastrointestinal tract. He reported having "fish jaw" for lunch. A fish bone was observed in the distal stomach on CT scan. He responded to medical treatment and continued on study.

Clinical Reviewer Comment: The SAE of CAD is unlikely to be causally related to icotrokinra due to advanced age and presence of other cardiovascular risk factors.

Post 16 Weeks Through Safety Cut-Off Date

Participant (b) (6)

Sixty-eight-year-old male with medical history including obesity, varicose vein, hypertension, nocturia, dyspnea and alcohol and tobacco use was randomized to icotrokinra. The subject experienced 2 events of atrial fibrillation prior to randomization (study days -33, -5) and aortic aneurysm diagnosed on imaging (study day-6). On study day 134, another event of atrial fibrillation was reported. The subject underwent an unsuccessful cardioversion followed by elective pulmonary vein ablation which was successful in resolving the atrial fibrillation. On study day 265 the subject had surgical repair of the aortic aneurysm and continued the study.

Clinical Reviewer Comment: The events of atrial fibrillation and aortic aneurysm are not considered related to icotrokinra administration as they were present prior to study randomization.

Participant (b) (6)

Subject is a 16 year old male with unremarkable medical history randomized to icotrokinra and experienced an SAE of syncope on study day 355. The subject was visiting a relative in the hospital at the time of the event. He also reported a history of respiratory tract infection 1 week prior to the event. He was treated with intravenous fluids and recovered. Chest x-ray, ECG, and laboratory testing was normal. He continued in the study.

Clinical Reviewer Comment: Icotrokinra is unlikely to be related to this event as there is no mechanism related to cardiovascular changes that would result in syncope, and the subject was able to continue study drug. The investigator considered this event is unlikely related to icotrokinra due to preceding respiratory tract infection, response to fluids, and emotional stress which are likely contributing factors to a vasovagal reaction. In addition, the subject continued the study drug following the event without recurrence.

Participant (b) (6)

Subject is a 48 year old male with history of psoriatic arthritis and hypertension who was randomized to icotrokinra. On study day 381 he developed sore throat and fever and was diagnosed with tonsillitis. Due to worsening symptoms, he was hospitalized and diagnosed with

myocarditis. Study drug was interrupted. On study day 393, he improved and was discharged, and continued study drug.

Clinical Reviewer Comment: This event is unlikely related to icotrokinra as myocarditis is likely due to the preceding upper respiratory symptoms likely attributed to viral infection.

Participant (b) (6)

Forty-two-year-old male was with history of systemic scleroderma was randomized to icotrokinra. On study days 154, 221, and 290 he experienced worsening of circulation in his fingers as three separate SAE events, each requiring hospitalization.

Clinical Reviewer Comment: These events were considered unrelated to study drug due to his prior diagnosis of scleroderma.

Participant (b) (6)

Forty-six-year-old male with no past medical history and a current alcohol user, former smoker (25 pack years) was randomized to icotrokinra. On study day 126, an SAE of hypertension was reported and he was hospitalized. He developed symptoms of chest pain, weakness, and restlessness. He had a cardiac stress test performed which was stopped for severely elevated blood pressure. His electrocardiogram did not show signs of ischemia. He was started on antihypertensive medication and discharged in good condition.

The following nonserious AEs were also reported: atrioventricular block on study day 115, hypercholesterolemia on study day 122, hypertension on study day 127 for which he received ramipril. He continued on study drug without further recurrence of these events.

The SAE of hypertension was positively adjudicated to an event of non-fatal severe/accelerated hypertension leading to hospitalization without MI, HF, UA, Arrhythmia, ISA, Stroke, VTE or peripheral arterial thrombotic by an independent cardiac adjudication committee.

Clinical Reviewer Comment: Attribution of icotrokinra is difficult to ascertain as his history is confounded by alcohol and tobacco use which are risk factors for hypertension.

Participant (b) (6)

Subject is a 43-year-old male with history of hypertriglyceridemia and current smoker with 24 pack year history. He was initially randomized to placebo and received icotrokinra starting on Week 16 (study day 114). On study day 136 after switching to icotrokinra he developed unstable angina with ECG changes. Abnormal ECG findings were observed at the Week 16 study visit. The subject was treated with diltiazem and continued on study drug.

Clinical Reviewer Comment: This event is unlikely related to icotrokinra due to the presence of cardiovascular risk factors of hypertriglyceridemia and tobacco use, as well as presence of ECG changes prior to the event. Additionally, there was a short period of exposure to study drug prior to the event.

Participant (b) (6)

Subject is a 52-year-old male without past medical history randomized to icotrokinra. On study day 173 he developed diplopia and brachial paresis for which he was hospitalized for evaluation for stroke. Following imaging and neurology consultation the event was diagnosed as a transient ischemic attack (TIA) and an SAE was reported. A nonserious event of hypertension was also reported. The subject recovered but elected to discontinue the study. The event of transient ischemic attack was positively adjudicated as a transient ischemic attack by an independent cardiac adjudication committee.

Clinical Reviewer Comment: The contribution of icotrokinra is unknown. The subject had no reported medical history but had elevated blood pressure, which may be a risk factor for stroke, at the time of the event. Icotrokinra has no known effect on blood pressure and there is no known mechanism which would explain a relationship between study drug and this event.

Participant (b) (6)

The subject is a 49-year-old female with history of hyperlipidemia, hypertension, type 2 diabetes mellitus, coronary artery bypass, CAD and obesity as well as family history of early coronary artery disease. The subject was initially randomized to deucravacitinib and switched to icotrokinra at week 24 (study day 170). On study day 253 the subject experienced an SAE of chest pain and was hospitalized. ECG, chest x-ray, CT angiography of the thorax, echocardiogram and cardiac stress test were negative. The subject was treated medically, and on study day 256 the event was considered resolved. The subject continued on the study.

Clinical Reviewer Comment: Icotrokinra is unlikely to have contributed to this event due to pre-existing cardiac risk factors and history of CABG and is further confounded by prior administration of deucravacitinib.

Subject (b) (6)

The subject is a 48-year-old female with past medical history including seasonal allergy, headaches, spinal osteoarthritis (neck), hemorrhoids (occasional), irritable bowel syndrome, anxiety, menopausal symptoms, and COVID-19 as well as history of alcohol consumption. She was randomized to icotrokinra. On study day 176 she developed intense headache, along with pulsatile tinnitus and persistent trigeminal neuralgia on the right side, and a serious adverse event of carotid artery dissection was confirmed on head and neck angiograph. A nonserious adverse event of carotid artery thrombosis was also reported. The subject was followed as an outpatient and medically treated. On study day 288, repeat head and neck angiography revealed resolution of the carotid dissection. The subject continued on the study.

Clinical Reviewer Comment: Attribution of icotrokinra is uncertain in this event. There is no preclinical or clinical data to suggest vascular changes that would lead to carotid dissection from the icotrokinra program, and this is an isolated event. In addition, recognized risk factors for carotid artery dissection, which is a primary cause of stroke in young to middle-aged adults include underlying factors such as fibromuscular dysplasia, hypertension, migraine, genetic

connective tissue disease and minor neck trauma or strenuous activity may have not been diagnosed at the time of the event.

Subject (b) (6)

The subject is a 62-year-old male with medical history significant for hypercholesterolemia and hypertriglyceridemia who was randomized to icotrokinra. On study day 315 he developed numbness on the left side of his body and drooping of the left side of the mouth, which was accompanied by an elevated blood pressure reading. The symptoms resolved then recurred. Captopril was administered to reduce blood pressure and the subject presented to the emergency department where he was diagnosed with a nonserious adverse event of transient ischemic attack. No abnormalities were found on CT scan. Nonserious adverse events of transient ischemic attack (Study Day 314) and hypertension (Study Day 315) were reported. The subject was treated with acetylsalicylic acid. The event of TIA resolved. On study day 336 an additional event of carotid arteriosclerosis was also reported. The subject continued on study. The events of transient ischemic attack, hypertension, and carotid arteriosclerosis were positively adjudicated as cardiovascular events.

Clinical Reviewer Comment: These events are unlikely to be related to icotrokinra administration due to medical history of elevated cholesterol and triglycerides increasing risk of vascular event such as TIA and that the subject continued on study.

Subject (b) (6)

The subject is a 69-year-old female with medical history of basal cell carcinoma, hypercholesterolemia, and anxiety who was randomized to icotrokinra. On study day 139 she developed a nonserious adverse event of DVT. The subject was treated with apixaban. No risk factor for DVT were identified on diagnostic workup. The subject recovered and continued on the study.

Clinical Reviewer Comment: The subject did not have identified risk factors for DVT. However, contribution of icotrokinra is unlikely as she was able to resume and continue on study drug.

Subject (b) (6)

The subject is a 67-year-old male with medical history including hypertension and hyperlipidemia who was initially randomized to deucravacitinib and switched to icotrokinra at week 24 (study day 195). He experienced 2 SAEs on deucravacitinib, head injury from a fall (study day 94), and intestinal obstruction (study day 163). He was reported to have small bowel obstruction caused by a lack of peristalsis, mesenteric ischemia, and malrotation. He underwent exploratory laparotomy for volvulus and appendectomy. Postoperatively, he was found to have elevated troponins and a gastrointestinal bleed. An echocardiogram showed reduced left ventricular ejection fraction with appearance of takotsubo cardiomyopathy. On study day 166 a repeat echocardiogram showed improvement in the ejection fraction but persistent wall motion abnormalities. He was recommended to undergo evaluation for ischemia. The events of stress cardiomyopathy and troponin increased were positively adjudicated as a type 2

myocardial infarction by the cardiac adjudication committee. Following switch to icotrokinra, on study day 240 an SAE of cardiac failure was reported, and heart catheterization was recommended. The subject was treated medically and discharged. He continued on study.

Clinical Reviewer Comment: The SAE of cardiac failure which occurred following switch to icotrokinra is unlikely to be related due to events that preceded administration of icotrokinra leading to cardiomyopathy. The case is also confounded by administration of deucravacitinib for the first 24 weeks of the study, during which the initiating event of intestinal obstruction first presented. The event of cardiac failure presented after initiating treatment with icotrokinra but is unlikely related to icotrokinra treatment as the subject had evidence of myocardial ischemia and reduced ejection fraction prior to the start of icotrokinra treatment.

Serious GI Adverse Events

Week-16 Placebo-Controlled Period

Participant (b) (6)

Subject is a 19-year old female with no significant past medical history randomized to icotrokinra. On study day 51 she developed symptoms of bacterial gastroenteritis which required hospitalization. A stool culture was positive for *Shigella sonnei*, for which a source was not able to be identified. The subject was treated with ciprofloxacin and azithromycin and recovered.

Clinical Reviewer Comment: Shigella sonnei *is primarily acquired through the fecal-oral route, with transmission occurring via contaminated food, water, or direct person-to-person contact. A very low infectious dose of organisms can cause infection. The role of icotrokinra in the acquisition or severity of the infection is unknown.*

Participant (b) (6)

Subject is a 17 year old female with relevant medical history of obesity, sleeve gastrectomy and active weight loss due to the gastrectomy randomized to icotrokinra. On study day 92 she presented to the emergency department with sudden onset of abdominal pain and was diagnosed with pancreatitis. On study day 105 she was hospitalized for right upper quadrant pain, nausea and vomiting. Abdominal imaging confirmed pancreatitis and choledocholithiasis, for which the subject underwent cholecystectomy and recovered.

Clinical Reviewer Comment: Causality of icotrokinra is unlikely given the patient's medical history, recent weight loss and presence of gallstones.

Participant (b) (6)

The subject is a 51 year old male with unremarkable medical history who was initially randomized to placebo and switched to icotrokinra at week 16 (study day 113). On study day 203, the subject developed abdominal pain, chills, fatigue, anorexia and constipation. Diverticulitis was confirmed on abdominal CT scan. Due to persistent symptoms and re-hospitalization, the subject underwent a partial colectomy after repeat CT scan showed an

obstructing lesion in the sigmoid colon suggestive of long segment diverticulitis. He discontinued from the study and subsequently recovered from the event of diverticulitis.

Clinical Reviewer Comment: The presence of extensive changes in the bowel related to diverticulitis and relatively short administration period of icotrokinra make attribution to icotrokinra unlikely.

Participant (b) (6)

The subject is a 67 year old male with medical history significant for alcoholic liver disease, chronic pancreatitis, hepatic cirrhosis randomized to icotrokinra. On study day 56 the subject had elevated ALT, AST and GGT which was reported as a nonserious AE. On study day 63 the liver enzymes were reported as normal. On study day 69 an SAE of biliary dilatation following a CT scan which showed dilated common bile duct stone. A nonserious event of cholelithiasis was also reported. An endoscopic ultrasound and pathology were performed on Study Day 105. On study day 174 liver enzymes were normalized and the subject continued in the study.

Clinical Reviewer Comment: The event is unlikely related to icotrokinra due to the subject's medical history and long latency to develop cholelithiasis.

Post 16 Weeks Through Safety Cut Off Date

Participant (b) (6)

Subject is a 67 year old male with pertinent medical history of diabetes mellitus, dyslipidemia, obesity and alcohol use who was randomized to icotrokinra and presented with symptoms of abdominal pain on Study day 275. The patient was hospitalized and abdominal ultrasound showed presence of gallstones and hepatic steatosis, and he was diagnosed with acute necrotic cholecystitis.

Clinical Reviewer Comment: Given the subject's medical history and presence of gallstones, it is unlikely that icotrokinra contributed to this event.

Participant (b) (6)

Twenty-eight-year-old male with no reported medical history was randomized to deucravacitinib and switched to icotrokinra at Week 24 (study day 169). He developed an SAE of diverticulitis on study day 215. He was initially treated and responded to antibiotic therapy, however developed recurrent symptoms and was hospitalized for a second SAE of diverticulitis on study day 289. He was again treated with antibiotics and recovered. Diverticula were observed on colonoscopy. The subject recovered and continued study drug.

Clinical Reviewer Comment: Study drug attribution is unclear, as the subject had no risk factors for diverticulitis however lifestyle risk factors were not reported in the narrative, the event is confounded by prior administration of deucravacitinib in the 24-week period, and the subject was able to resume study drug without recurrence.

Participant (b) (6)

Subject is a 35 year old male with unremarkable medical history and use of alcohol and tobacco randomized to icotrokinra. On study day 336 the subject developed an anal fistula and underwent fistulotomy. The event resolved and the subject continued on the study.

Clinical Reviewer Comment: The subject had no known predisposing factors for development of anal fistula. The majority of anal fistulas result from incidental infection of cryptoglandular glands. However, as icotrokinra may predispose to infection due to inhibition of IL-23, therefore the contribution of study drug cannot be ruled out.

Participant (b) (6)

Subject is a 65-year-old female with history of perianal fistula, hypothyroidism, salivary gland adenoma, hypertension, diabetes mellitus, osteoarthritis, LTBI, and hemorrhoids with a 38 pack year smoking history. She was randomized to icotrokinra, and on study day 221 developed SAE of diverticulitis leading to hospitalization. CT of the abdomen confirmed presence of diverticula in the colon and signs consistent with diverticulitis. Study drug was interrupted and the subject responded to antibiotic treatment. The event of diverticulitis resolved and the subject resumed study treatment.

Clinical Reviewer Comment: This event is unlikely related to study drug as lifestyle factors and genetics are likely contributed to development of diverticula, and the subject was able to continue on study drug upon resolution of the event.

Participant (b) (6)

The subject is a 52 year old male with a past medical history of diverticulum intestinal, gastritis, and gastric ulcer who was initially randomized to deucravacitinib and switched to icotrokinra at week 24 (study day 179). On study day 240 he experienced SAE of serious adverse event of diverticulitis and was hospitalized due to acute inflammation of colonic diverticula. He received antibiotic treatment, recovered, and continued in the study.

Clinical Reviewer Comment: This event is unlikely related to study drug as lifestyle factors and genetics are likely contributed to development of diverticula, and the subject was able to continue study drug upon resolution of the event.

Participant (b) (6)

The subject is a 68-year-old white male with history of obesity, and current history of alcohol and tobacco use and no medications on study entry, was randomized to receive icotrokinra. On study day 271 the patient was hospitalized for an SAE of gastric ulcer perforation. The subject reported symptoms of diffuse peritonitis prior to pyloric perforation. The subject underwent laparotomy with repair of the pyloric perforation and irrigation and drainage of the abdominal cavity. In the postoperative period the subject developed cardiorespiratory failure necessitating a 2 day intensive care unit stay. The subject recovered but discontinued the study due the SAE. Additional information received via IR indicated the subject did not have any history of gastritis, gastric and/or intestinal ulcer, gastrointestinal bleeding, (e.g., hematemesis or melena), chronic

vomiting, chronic abdominal pain, thrombocytopenia, anemia, or *Helicobacter pylori*. There was no reported history of endoscopy, NSAID, or corticosteroid use.

Clinical Reviewer Comment: The role of icotrokinra in this event is unknown, however the subject had risk factors for gastric ulcer including obesity, and alcohol and tobacco use and a causal association between icotrokinra and the event cannot be ruled out.

SAE Other

SAEs that were reported either during the 16-placebo control period or the long term follow up period are summarized below. These events were related to events that were unlikely influenced by icotrokinra administration or clearly do to an underlying or pre-existing condition. There was no clear pattern to the events, and most were individual occurrences.

16-Week Placebo-Controlled Period

Accidental or injury related: Fracture due to MVA, arthralgia, tendon rupture due to gardening accident, rib fracture secondary to fall, ligament rupture requiring surgery, meniscus injury requiring surgery, fracture phalanges (foot) secondary to gardening accident related to pre-existing condition: sleep apnea (newly diagnosed while on study, however symptoms preceded study).

Post 16 Weeks

Accidental or injury related: Fracture bicycle accident, back pain lifting injury, fracture left upper limb due to fall, ACL tear (skiing), craniofacial fracture from fall, burn secondary to accident with boiling water.

Likely related to conditions pre-dating the study: planned hip replacement surgery, hip surgery to correct prosthesis osteoarthritis requiring hip replacement spinal stenosis requiring laminectomy (2 events), cervical radiculopathy, intervertebral disc protrusion, varicose vein surgery.

Individual events unlikely related to icotrokinra administration: retroarticular abscess, kidney stone, primary aldosteronism (initially received deucravacitinib), post colonoscopy hospitalization (procedure related), abdominal hernia, drug reaction secondary to treatment of pyelonephritis with sulfamethoxazole/trimethoprim, hepatitis E infection, alcoholism, worsening psoriasis (initial placebo randomization).

Other Event of Interest

Subject (b) (6)

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The subject is a 52-year-old male with history of cervical vertebral fracture, pain, depression, GERD and restless legs syndrome. He was randomized to receive icotrokinra. On study day 94, a nonserious AE of CIDP

was reported. He received treatment with immunoglobulin. Subsequently, it was clarified that the CIDP was not treatment emergent and the subject had been under evaluation for this condition prior to enrolling in the study. At this time an MRI of the brain showed cerebellar atrophy in proportion to cerebral. An EMG Electromyograph of the upper and lower extremities was done to evaluate generalized weakness, left hand atrophy and dysarthria. The EMG showed moderately severe polyneuropathy with motor demyelination and axonal damage in motor and sensory nerves. The subjects history, physical exam, and EMG are consistent with CIDP. The subject continued on study.

Dropouts and/or Discontinuations Due to Adverse Effects

During the placebo-controlled period, (Weeks 0 to 16) a similar proportion of icotrokinra-treated subjects (2.0%) discontinued treatment due to AEs compared to (3.0%) in the placebo group. In the icotrokinra group, AEs leading to treatment discontinuation in 2 or more subjects included diarrhea and headache.

At Week 16, the most common SOCs for AEs leading to discontinuation in icotrokinra-treated subjects were Neoplasms benign, malignant and unspecified (6, 0.4% icotrokinra versus 1, 0.2% placebo), and Gastrointestinal Disorders (4, 0.3% icotrokinra versus 1, 0.2% placebo). Overall rates of discontinuation are low and do not suggest a pattern related to icotrokinra administration.

Table 53. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Subjects with at least one AE leading to treatment discontinuation	26 (2.0)	17 (3.0)	1.0 (2.9, 0.5)
Cardiac disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.4)
Myocardial infarction	1 (0.1)	0	0.1 (0.6, 0.4)
Eye disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.5)
Vision blurred	1 (0.1)	0	0.1 (0.6, 0.5)
Visual field defect	1 (0.1)	0	0.1 (0.6, 0.5)
Gastrointestinal disorders (SOC)	4 (0.3)	1 (0.2)	0.1 (0.8, 0.6)
Diarrhea	2 (0.1)	0	0.1 (0.6, 0.5)
Constipation	1 (0.1)	0	0.1 (0.6, 0.5)
Nausea	1 (0.1)	0	0.1 (0.6, 0.5)
Aphthous ulcer	0	1 (0.2)	0.2 (1.0, 0.0) *
Hepatobiliary disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.5)
Hepatitis	1 (0.1)	0	0.1 (0.6, 0.5)
Infections and infestations (SOC)	1 (0.1)	3 (0.5)	0.4 (1.5, 0.1)
Laryngitis fungal	1 (0.1)	0	0.1 (0.6, 0.5)
Arthritis bacterial	0	1 (0.2)	0.2 (1.0, 0.1)
COVID-19 pneumonia	0	1 (0.2)	0.2 (1.0, 0.1)
Sinusitis	0	1 (0.2)	0.2 (1.0, 0.1)

Investigations (SOC)	0	2 (0.3)	0.3 (1.3, 0.0) *
Alanine aminotransferase increased	0	1 (0.2)	0.2 (1.0, 0.1)
Aspartate aminotransferase increased	0	1 (0.2)	0.2 (1.0, 0.1)
Blood glucose increased	0	1 (0.2)	0.2 (1.0, 0.1)
Gamma-glutamyltransferase increased	0	1 (0.2)	0.2 (1.0, 0.1)
Metabolism and nutrition disorders (SOC)	2 (0.2)	0	0.2 (0.5, 0.6)
Hyperkaliemia	1 (0.1)	0	0.1 (0.6, 0.5)
Hypertriglyceridemia	1 (0.1)	0	0.1 (0.6, 0.5)
Musculoskeletal and connective tissue disorders (SOC)	2 (0.1)	1 (0.2)	0.1 (0.9, 0.4)
Arthralgia	1 (0.1)	0	0.1 (0.6, 0.4)
Back pain	1 (0.1)	0	0.1 (0.6, 0.4)
Psoriatic arthropathy	1 (0.1)	1 (0.2)	0.1 (0.9, 0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	6 (0.4)	1 (0.2)	0.3 (0.6, 0.8)
Adenocarcinoma of colon	1 (0.1)	0	0.1 (0.6, 0.5)
Metastases to liver	1 (0.1)	0	0.1 (0.6, 0.5)
Prostate cancer	1 (0.1)	0	0.1 (0.6, 0.5)
Malignant melanoma in situ	1 (0.1)	0	0.1 (0.6, 0.5)
Breast cancer	1 (0.1)	0	0.1 (0.6, 0.4)
Keratoacanthoma	1 (0.1)	0	0.1 (0.6, 0.4)
Invasive ductal breast carcinoma	0	1 (0.2)	0.2 (1.0, 0.1)
Nervous system disorders (SOC)	3 (0.2)	1 (0.2)	0.1 (0.8, 0.5)
Subarachnoid hemorrhage	1 (0.1)	0	0.1 (0.6, 0.5)
Headache	2 (0.1)	1 (0.2)	0.0 (0.9, 0.4)
Psychiatric disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.5)
Anxiety	1 (0.1)	0	0.1 (0.6, 0.5)
Reproductive system and breast disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.5)
Erectile dysfunction	1 (0.1)	0	0.1 (0.6, 0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.1)	0	0.1 (0.6, 0.5)
Cough	1 (0.1)	0	0.1 (0.6, 0.5)
Skin and subcutaneous tissue disorders (SOC)	3 (0.3)	8 (1.4)	1.1 (2.5, 0.3) *
Erythrodermic psoriasis	1 (0.1)	0	0.1 (0.6, 0.5)
Urticaria	1 (0.1)	0	0.1 (0.6, 0.5)
Rash	0	1 (0.2)	0.2 (1.0, 0.1)
Psoriasis	1 (0.1)	7 (1.2)	1.1 (2.4, 0.4) *

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class

Subjects switched to icotrokinra from placebo following week 16, therefore analysis of subjects who switched from placebo was compared to subjects who remained on icotrokinra through the safety reporting date cut-off. For subjects receiving icotrokinra who remained on icotrokinra through the safety reporting cut-off, the distribution of AEs leading to discontinuation by PT or SOC was similar to that of the 16-week placebo-controlled period. For the pooled data, the rates for discontinuation were slightly higher for placebo treated subjects

than for those who received icotrokinra continuously. With longer exposure to icotrokinra through the safety reporting cut-off date, the EAIR of the AEs leading to treatment discontinuation were relatively consistent compared to the incidence rate at (52) weeks for subjects who were randomized and remained on the same treatment. The following table shows the number, proportion, and EAIRs of subjects who discontinued treatment due to an AE for the Phase 3 Safety pool at the time of pre-specified safety data cutoffs. Review of individual cases of discontinuation does not suggest a temporal pattern of discontinuation related to initiation of icotrokinra. The most common cases were related to worsening psoriatic arthropathy. There were other isolated cases of diarrhea, nausea and constipation that had confounding factors to attribution of icotrokinra in discontinuation.

SOC by PT – AEs Leading to Discontinuation

Table 54. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
Subjects with at least one AE leading to treatment discontinuation	7/541.3 (1.0)	7/369.7 (1.6)	32/927.6 (3.4)	39/1297.3 (3.0)
Cardiac disorders (SOC)	1/541.8 (0.1)	0/370.0	2/930.3 (0.2)	2/1300.3 (0.2)
Myocardial infarction	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Atrial fibrillation	1/541.8 (0.1)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Eye disorders (SOC)	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Vision blurred	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Visual field defect	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Gastrointestinal disorders (SOC)	2/541.8 (0.3)	0/370.0	5/929.8 (0.5)	5/1299.8 (0.4)
Diarrhea	0/541.8 (0.0)	0/370.0	2/929.8 (0.2)	2/1299.8 (0.2)
Nausea	1/541.8 (0.1)	0/370.0	2/930.3 (0.2)	2/1300.3 (0.2)
Constipation	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Gastric ulcer perforation	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
General disorders and administration site conditions (SOC)	1/541.8 (0.1)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Fatigue	1/541.8 (0.1)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Hepatobiliary disorders (SOC)	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Hepatitis	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
Infections and infestations (SOC)	2/541.7 (0.3)	4/369.8 (0.9)	3/930.1 (0.3)	7/1299.9 (0.5)
Pneumonia	1/541.8 (0.1)	1/370.0 (0.3)	1/930.3 (0.1)	2/1300.3 (0.2)
Lower respiratory tract infection	1/541.8 (0.1)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Subcutaneous abscess	1/541.7 (0.2)	0/370.0	1/930.2 (0.1)	1/1300.1 (0.1)
Laryngitis fungal	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Bronchitis	0/541.8 (0.0)	1/369.9 (0.2)	0/930.3 (0.0)	1/1300.2 (0.1)
Impetigo	0/541.8 (0.0)	1/369.9 (0.2)	0/930.3 (0.0)	1/1300.2 (0.1)
Diverticulitis	0/541.8 (0.0)	1/369.9 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Injury, poisoning and procedural complications (SOC)	0/541.8 (0.0)	1/370.0 (0.3)	0/930.3 (0.0)	1/1300.3 (0.1)
Toxicity to various agents	0/541.8 (0.0)	1/370.0 (0.3)	0/930.3 (0.0)	1/1300.3 (0.1)
Metabolism and nutrition disorders (SOC)	0/541.8 (0.0)	0/370.0	2/930.2 (0.2)	2/1300.1 (0.1)
Hyperkalemia	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.1 (0.1)
Hypertriglyceridemia	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Musculoskeletal and connective tissue disorders (SOC)	1/541.8 (0.1)	0/370.0	3/930.3 (0.3)	3/1300.3 (0.3)
Psoriatic arthropathy	1/541.8 (0.1)	0/370.0	2/930.3 (0.2)	2/1300.3 (0.2)
Arthralgia	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Back pain	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2/541.6 (0.3)	1/370.0 (0.2)	8/929.6 (0.9)	9/1299.5 (0.7)
Keratoacanthoma	0/541.8 (0.0)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Breast cancer	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of skin	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Metastases to liver	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Malignant melanoma in situ	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.2 (0.1)
Chronic lymphocytic leukemia	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of lung	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Adenocarcinoma of colon	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Prostate cancer	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)
Nervous system disorders (SOC)	0/541.8 (0.0)	0/370.0	3/930.3 (0.3)	3/1300.2 (0.2)
Headache	0/541.8 (0.0)	0/370.0	2/930.3 (0.2)	2/1300.2 (0.2)
Subarachnoid hemorrhage	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Psychiatric disorders (SOC)	0/541.8 (0.0)	0/370.0	1/929.8 (0.1)	1/1299.8 (0.1)
Anxiety	0/541.8 (0.0)	0/370.0	1/929.8 (0.1)	1/1299.8 (0.1)
Reproductive system and breast disorders (SOC)	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Erectile dysfunction	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Cough	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
System Organ Class Preferred Term	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
Skin and subcutaneous tissue disorders (SOC)	0/541.8 (0.0)	1/369.9 (0.2)	3/930.1 (0.3)	4/1300.0 (0.3)
Psoriasis	0/541.8 (0.0)	1/369.9 (0.2)	1/930.1 (0.1)	2/1300.1 (0.1)
Erythrodermic psoriasis	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Urticaria	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate (per 100 person-years); incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; PY, person-years (total exposure); py, person-years (at risk); SOC, system organ class

Adverse events leading to discontinuation for PSO3002 and PSO3004 24 week double blind placebo controlled period are presented in Table 55 for icotrokinra and deucravacitinib. Overall rates of discontinuation were similar between icotrokinra (2.5%) and deucravacitinib (3.0%). Overall rates of discontinuation were low for both treatments and did not differ by SOC class.

8.2.4.2. Adverse Events Leading to Discontinuation

8.2.4.3. SOC by PT – AEs Leading to Discontinuation

Table 55. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Pooled Trials PSO3002 and PSO3004, Double-Blind Active Comparator-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Subjects with at least one AE leading to treatment discontinuation	16 (2.5)	19 (3.0)	-0.5 (-2.4, 1.4)
Blood and lymphatic system disorders (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Thrombocytopenia	0	1 (0.2)	-0.2 (-0.9, 0.4)
Cardiac disorders (SOC)	2 (0.3)	1 (0.2)	0.2 (-0.6, 1.0)
Atrial fibrillation	1 (0.2)	0	0.2 (-0.4, 0.9)
Myocardial infarction	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.8)
Coronary artery disease	0	1 (0.2)	-0.2 (-0.9, 0.4)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Eye disorders (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Visual impairment	0	1 (0.2)	-0.2 (-0.9, 0.4)
Gastrointestinal disorders (SOC)	4 (0.6)	3 (0.5)	0.2 (-0.8, 1.2)
Diarrhea	2 (0.3)	0	0.3 (-0.3, 1.2)
Nausea	2 (0.3)	1 (0.2)	0.2 (-0.6, 1.0)
Constipation	1 (0.2)	0	0.2 (-0.4, 0.9)
Pancreatitis	0	1 (0.2)	-0.2 (-0.9, 0.4)
Abdominal pain	0	1 (0.2)	-0.2 (-0.9, 0.4)
Abdominal pain upper	0	1 (0.2)	-0.2 (-0.9, 0.4)
General disorders and administration site conditions (SOC)	1 (0.2)	5 (0.8)	-0.6 (-1.7, 0.2)
Fatigue	1 (0.2)	2 (0.3)	-0.2 (-1.0, 0.6)
Localized edema	0	1 (0.2)	-0.2 (-0.9, 0.4)
Noncardiac chest pain	0	1 (0.2)	-0.2 (-0.9, 0.4)
Systemic inflammatory response syndrome	0	1 (0.2)	-0.2 (-0.9, 0.4)
Infections and infestations (SOC)	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.7)
Lower respiratory tract infection	1 (0.2)	0	0.2 (-0.4, 0.9)
Pneumonia	1 (0.2)	0	0.2 (-0.4, 0.9)
Wound infection	0	1 (0.2)	-0.2 (-0.9, 0.4)
Investigations (SOC)	0	1 (0.2)	-0.2 (-0.9, 0.4)
Alanine aminotransferase increased	0	1 (0.2)	-0.2 (-0.9, 0.4)
Metabolism and nutrition disorders (SOC)	1 (0.2)	0	0.2 (-0.4, 0.9)
Hyperkalemia	1 (0.2)	0	0.2 (-0.4, 0.9)
Musculoskeletal and connective tissue disorders (SOC)	3 (0.5)	1 (0.2)	0.3 (-0.5, 1.3)
Psoriatic arthropathy	2 (0.3)	0	0.3 (-0.3, 1.2)
Back pain	1 (0.2)	0	0.2 (-0.4, 0.9)
Arthralgia	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	3 (0.5)	2 (0.3)	0.2 (-0.7, 1.1)
Breast cancer	1 (0.2)	0	0.2 (-0.4, 0.9)
Keratoacanthoma	1 (0.2)	0	0.2 (-0.4, 0.9)
Metastases to liver	1 (0.2)	0	0.2 (-0.4, 0.9)
Malignant melanoma in situ	0	1 (0.2)	-0.2 (-0.9, 0.4)
Squamous cell carcinoma of the oral cavity	0	1 (0.2)	-0.2 (-0.9, 0.4)
Nervous system disorders (SOC)	1 (0.2)	1 (0.2)	0.0 (-0.7, 0.8)
Headache	1 (0.2)	0	0.2 (-0.4, 0.9)
Dizziness	0	1 (0.2)	-0.2 (-0.9, 0.4)
Psychiatric disorders (SOC)	1 (0.2)	1 (0.2)	-0.0 (-0.8, 0.8)
Anxiety	1 (0.2)	1 (0.2)	-0.0 (-0.8, 0.8)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Skin and subcutaneous tissue disorders (SOC)	2 (0.3)	4 (0.6)	-0.3 (-1.3, 0.6)
Erythrodermic psoriasis	1 (0.2)	0	0.2 (-0.4, 0.9)
Urticaria	1 (0.2)	0	0.2 (-0.4, 0.9)
Dermatitis exfoliative generalized	0	1 (0.2)	-0.2 (-0.9, 0.4)
Pustular psoriasis	0	1 (0.2)	-0.2 (-0.9, 0.4)
Psoriasis	0	2 (0.3)	-0.3 (-1.1, 0.3)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 24 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class

Significant Adverse Events

According to the ICH guideline for industry E3 Structure and Content of Clinical Study Reports, significant adverse events include: marked hematological and the laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.

The majority of these adverse events is discussed in Section 8.2.4, SAEs.

Adverse Events of Special Interest

A number of the serious adverse events are also safety topics of special interest, and include Malignancy (Nonmelanoma skin cancer, malignancy other than nonmelanoma skin cancer), Possible Hy's Law, and Active TB events. These events were protocol defined as Adverse Events of Special Interest (AESIs). In addition to protocol defined AESIs, the following events were also identified as AESI and include: Treatment-emergent LTBI, Opportunistic Infections, Serious Infections, Cardiovascular Events (identified events underwent external adjudication to identify cardiovascular endpoints and positively adjudicated events were identified as MACE, Extended MACE, and Other Cardiovascular Events), Hepatic AEs (Serious and leading to discontinuation).These topics are presented with their subject narratives in the SAE section. LTBI, Hypersensitivity Reactions, Anaphylactic Reactions, and Suicidal Ideation and Behavior and Depression Excluding Suicidal Ideation and Behavior are discussed in the following section.

In addition to predefined categories of adverse events of interest, a review issue identified 2 events of gastrointestinal related death, both occurring on the icotrokinra treatment arm.

Therefore, a full assessment of events of gastrointestinal hemorrhage and related events was performed and the Division of Gastroenterology was consulted.

Active TB and LTBI Reactivation

As with other IL-23 inhibitors, the Phase 3 protocols specified a testing and treatment algorithm for active and LTBI. Subjects with LTBI were to have LTBI treatment initiated prior to or in parallel with receiving blinded study drug. Among the 2,498 subjects in the pooled PSO3001, PSO3002, PSO3003, and PSO3004, 173 subjects had LTBI identified by the testing algorithm at or prior to baseline. Of these 173 subjects, 50 (28.9%) completed LTBI prior to screening, 92 (53.2%) received concomitant LTBI treatment, and 31 (17.9%) received no LTBI treatment. Timing of LTBI identification (prior to or during screening) and treatment status was similar across treatment groups, and LTBI treatment status by treatment group reflected LTBI treatment requirements by study. There were no cases of active TB reported during icotrokinra administration, and there were no cases of active TB converted from LTBI reported in the study, and there were no positively adjudicated reactivated LTBI reported in the pooled Phase 3 studies.

There were subjects in the Phase 3 trials who tested positive for LTBI but did not go on to receive treatment and subsequently did not develop tuberculosis. There is insufficient information provided about subjects who tested positive for LTBI but did not receive LTBI treatment to assess whether there is bias in the decision not to treat to prevent active tuberculosis. Subjects who were LTBI positive but untreated may have had a lower risk assessment by the investigator for developing active tuberculosis. This data from untreated LTBI positive subjects does not substantially alter the interpretation of risk of developing active tuberculosis with IL-23 antagonism. The number of subjects who did not receive treatment also reflects a small number of subjects to make a risk assessment for the global population of psoriasis patients who may receive treatment with icotrokinra. Therefore, the recommendation for labeling will be to include testing for active and LTBI and initiate appropriate treatment in conjunction with initiating icotrokinra, and this recommendation will be reflected in labeling similar to other IL-23 antagonists.

Opportunistic Infections and Serious Infections

Opportunistic infections and serious infections are of interest due to potential modulation of immune response to infection by IL-23 inhibition. In the 16-week placebo-controlled period, there were 2 serious infection events in icotrokinra and 3 occurring in placebo. These event rates are low and extrapolation of risk of developing serious infections to the general population of psoriasis patients who may be treated with icotrokinra is difficult to estimate. The occurrence of these events does not suggest an increased risk for serious infections over placebo. These event rates are low and extrapolation of risk of developing serious infections to the general population of psoriasis patients who may be treated with icotrokinra is difficult to estimate. Infection event rates may increase over time and the risk may not be adequately assessed by the relatively short term placebo controlled treatment of 16 weeks in the Phase 3

program. However, given that the mechanism of action for icotrokinra is via IL-23 inhibition and resultant downstream modulation of cytokine and cellular responses which may potentially alter the response to infection, risk of opportunistic and serious infections is recommended for labeling in Section 5, Warnings and Precautions of the USPI.

Serious Infections

Table 56. Adverse Events of Special Interest Assessment of Serious Infections, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

Serious Infections Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
AE grouping related to AESI	2 (0.1)	2 (0.3)	0.2 (1.1, 0.2)
Gastroenteritis bacterial	1 (0.1)	0	0.1 (0.6, 0.5)
Infective exacerbation of chronic obstructive airways disease	1 (0.1)	0	0.1 (0.6, 0.4)
Arthritis bacterial	0	1 (0.2)	0.2 (1.0, 0.1)
COVID-19 pneumonia	0	1 (0.2)	0.2 (1.0, 0.1)
Sepsis	0	1 (0.2)	0.2 (1.0, 0.1)
Maximum severity			
Death	0	0	0.0 (0.7, 0.3)
Life-threatening	1 (0.1)	1 (0.2)	0.1 (0.9, 0.2)
Severe	1 (0.1)	1 (0.2)	0.1 (0.9, 0.3)
Moderate	0	0	0.0 (0.7, 0.3)
Mild	0	0	0.0 (0.7, 0.3)
Serious	2 (0.1)	2 (0.3)	0.2 (1.1, 0.2)
Deaths	0	0	0.0 (0.7, 0.3)
Resulting in treatment discontinuation	0	2 (0.3)	0.3 (1.3, 0.0) *
Relatedness	0	1 (0.2)	0.2 (1.0, 0.1)
Number of subjects with adverse events with end dates on or before treatment end dates	2/2 (NA)	0/2 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	29.0 (36.8)	NA	NA
Median (min, max)	29.0 (3.0, 55.0)	NA	NA
Interquartile range	16.0 to 42.0	NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/2 (NA)	0/2 (NA)	NA

Serious Infections Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/2 (NA)	2/2 (NA)	NA
Duration, days (from treatment end date to AE end date)			
Mean (SD)	NA	72.0 (14.1)	NA
Median (min, max)	NA	72.0 (62.0, 82.0)	NA
Interquartile range	NA	67.0 to 77.0	NA

Source: adae.xpt; software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Severity scale as defined by the protocol.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Relatedness is determined by investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; SD, standard deviation

Hypersensitivity and Anaphylactic Reactions

Orally administered peptides may result in immunogenicity. The assessment of the potential to cause hypersensitivity reactions focuses on identifying potential antidrug antibodies (ADA) and T-cell responses. This assessment requires a multitiered approach: in silico analysis for epitope prediction, in vitro assays (e.g., T-cell proliferation) to check for immune activation, and in vivo/clinical evaluation to measure safety and efficacy. The clinical data from the Phase 3 program with respect to potential hypersensitivity or anaphylactic reactions are summarized in Table 57.

Table 57. Adverse Events of Special Interest Assessment, Hypersensitivity Reactions, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

Hypersensitivity Reactions Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
AE grouping related to AESI	28 (2.2)	7 (1.3)	0.9 (0.6, 2.0)
Eczema	3 (0.3)	0	0.3 (0.4, 0.7)
Urticaria	3 (0.3)	0	0.3 (0.4, 0.7)
Rhinitis allergic	5 (0.4)	1 (0.2)	0.2 (0.6, 0.8)
Dermatitis allergic	2 (0.2)	0	0.2 (0.5, 0.6)
Perioral dermatitis	2 (0.2)	0	0.2 (0.5, 0.6)
Dermatitis acneiform	2 (0.1)	0	0.1 (0.5, 0.5)
Blepharitis allergic	1 (0.1)	0	0.1 (0.6, 0.5)
Drug hypersensitivity	1 (0.1)	0	0.1 (0.6, 0.5)
Eyelid oedema	1 (0.1)	0	0.1 (0.6, 0.5)
Hand dermatitis	1 (0.1)	0	0.1 (0.6, 0.5)
Swelling of eyelid	1 (0.1)	0	0.1 (0.6, 0.5)
Conjunctivitis allergic	1 (0.1)	0	0.1 (0.6, 0.5)
Dermatitis atopic	1 (0.1)	0	0.1 (0.6, 0.4)
Rash papular	1 (0.1)	0	0.1 (0.6, 0.4)
Eczema nummular	1 (0.1)	1 (0.2)	0.2 (1.0, 0.2)
Gingival swelling	0	1 (0.2)	0.2 (1.0, 0.0) *
Rash	1 (0.1)	2 (0.3)	0.3 (1.2, 0.1)
Dermatitis	1 (0.1)	2 (0.4)	0.3 (1.3, 0.0)
Maximum severity			
Death	0	0	0.0 (0.7, 0.3)
Life-threatening	0	0	0.0 (0.7, 0.3)
Severe	0	0	0.0 (0.7, 0.3)
Moderate	8 (0.6)	3 (0.6)	0.0 (1.0, 0.7)
Mild	20 (1.6)	4 (0.8)	0.8 (0.4, 1.7)
Serious	0	0	0.0 (0.7, 0.3)
Deaths	0	0	0.0 (0.7, 0.3)
Resulting in treatment discontinuation	1 (0.1)	1 (0.2)	0.1 (0.9, 0.4)
Relatedness	8 (0.6)	1 (0.2)	0.4 (0.4, 1.1)
Number of subjects with adverse events with end dates on or before treatment end dates	17/28 (53.7)	3/7 (40.8)	12.9 (29.2, 49.6)
Duration, days (from AE start date to AE end date)			
Mean (SD)	26.2 (16.7)	6.3 (4.2)	NA
Median (min, max)	25.0 (2.0, 62.0)	5.0 (3.0, 11.0)	NA
Interquartile range	15.0 to 31.0	4.0 to 8.0	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	7/28 (29.0)	3/7 (47.1)	-18.0 (55.9, 20.4)

Hypersensitivity Reactions Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	4/28 (17.3)	1/7 (12.1)	5.1 (37.3, 33.2)
Duration, days (from treatment end date to AE end date)			
Mean (SD)	85.5 (82.0)	37.0 (NA)	NA
Median (min, max)	50.0 (34.0, 208.0)	37.0 (37.0, 37.0)	NA
Interquartile range	46.0 to 89.5	37.0 to 37.0	NA

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Severity scale as defined by the protocol.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Relatedness is determined by investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; SD, standard deviation

Clinical Reviewer Comment: No TEAEs of hypersensitivity were reported as serious, all cases were mild or moderate. No TEAEs of anaphylaxis were reported from the clinical trials up to the 120-day safety cutoff date that were related to icotrokinra. One case reported of anaphylaxis was attributed to antibiotic administration following withdrawal of icotrokinra. Risk for hypersensitivity will be further informed by pharmacovigilance in the post-marketing setting.

Suicidal Ideation and Depression

Suicidal ideation and behavior were identified by C-SSR assessments and AEs identified by the investigator in the eCRF. The PHQ9 instruments was used to assess increase risk of depression. History of depression (6.8%) was prevalent at baseline in the study population. Rates of events were low. Through the safety cut-off date, suicidal ideation was reported in 3 subjects who received icotrokinra. Suicidal ideation was reported in 1 subject who received icotrokinra in the placebo control period. There were no episodes of suicidal behavior in either icotrokinra or placebo groups. In the 24 week active control period, suicidal ideation was reported in 1 subject in the icotrokinra and 1 subject in deucravacitinib treatment groups respectively, and no episodes of suicidal behavior in either group. No completed suicides were reported in the program. Depression event rates were low, less than 0.2% for either treatment group for either the 16 week placebo control period or the 24 week active control period. Shifts in PHQ-9 scores did not indicate an increase in depression in any treatment period.

Clinical Reviewer Comment: The data does not suggest an increased risk of suicidal ideation, suicidal behavior, or depression is associated with administration of icotrokinra.

Gastrointestinal-Related Events

In the icotrokinra phase 3 development program, 2 deaths attributed to gastrointestinal hemorrhage occurred in icotrokinra treated subjects, one following randomization in the placebo control period, and one after a longer period of dosing with icotrokinra in the extension period (Day 385). Additionally, there was one subject in the extension period who developed a GI SAE of gastric perforation, and a second SAE of lower GI bleeding was identified from the Day 120 safety update. The narratives of the 2 subjects with death and SAE due to GI hemorrhage are presented in Section 8.2.4.

Icotrokinra is a novel orally administered IL-23 receptor inhibitor, so while GI bleeding events are not recognized as adverse events in IL-23 inhibitors that are injectable, there was also consideration as to whether oral administration and presence of non-absorbed drug substance in the GI tract could have an effect in relationship to development of a GI bleed. There were no pre-clinical signals that suggested GI irritation or toxicity. The mechanism of inhibition of IL-23 is by competitive antagonism of the IL-23 receptor which differs from other IL-23 inhibitors which are monoclonal antibodies which bind the p19 subunit of IL-23 and block the binding of IL-23 to its receptor. Serious and treatment-emergent adverse events were reviewed to discern this potential signal of serious gastrointestinal events. Due to the complexity of this issue, a consult with the Division of Gastroenterology was sought.

Two GI bleeding related deaths were observed for icotrokinra. Review of SAEs did not show a trend for serious GI bleeding related cases in the placebo control period. The SAEs reported in this period for SOC GI were bacterial gastroenteritis, pancreatitis due to choledocholithiasis, and diverticulitis. In the post week 16 safety follow up period, there were 3 additional cases of diverticulitis, and one case of necrotizing cholangitis (secondary to choledocholithiasis). There was an additional case of SAE of gastric ulcer with perforation in the extension period. Although the subject reported general risk factors for gastric ulcer, the contribution of icotrokinra to the severity of this case should be considered given the GI bleed related deaths. One additional serious case of GI bleed was identified in Day 120 safety report. The subject reported lower GI bleeding on study day 502, reported with nonserious AEs of diverticulum and hemorrhoids. The clinical presentation was suggestive of colonic diverticular bleeding, which was presumptive given that no active bleeding or stigmata of bleeding was observed on colonoscopy or CT scan. Reviewing TEAEs in SOC GI, there is no trend in the data to suggest nonserious GI bleed related events. The most common events occurring on icotrokinra for the placebo control period were nausea, dry mouth, gastritis, abdominal discomfort, and dyspepsia. These events do not suggest any trend for less serious events suggestive of GI bleed. The following Gastrointestinal Tolerability table for the double blind placebo control period was created to specifically examine events related to GI tolerability.

Gastrointestinal Tolerability

Table 58. Adverse Events of Special Interest Assessment of Gastrointestinal Tolerability, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

Gastrointestinal Tolerability Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
AE grouping related to AESI	57 (4.4)	22 (3.9)	0.5 (1.7, 2.3)
Nausea	15 (1.2)	3 (0.5)	0.7 (0.4, 1.5)
Abdominal discomfort	4 (0.3)	0	0.3 (0.4, 0.8)
Chest pain	3 (0.2)	0	0.2 (0.5, 0.7)
Constipation	4 (0.3)	1 (0.2)	0.1 (0.7, 0.7)
Eructation	1 (0.1)	0	0.1 (0.6, 0.5)
Abdominal pain upper	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Feces soft	1 (0.1)	0	0.1 (0.6, 0.4)
Diarrhea	27 (2.0)	11 (2.0)	0.0 (1.6, 1.3)
Vomiting	4 (0.3)	2 (0.4)	0.0 (1.0, 0.4)
Abdominal distension	3 (0.3)	2 (0.3)	0.1 (1.0, 0.5)
Flatulence	1 (0.1)	1 (0.2)	0.1 (0.9, 0.2)
Abdominal pain	4 (0.3)	4 (0.7)	0.3 (1.5, 0.3)
Maximum severity			
Death	0	0	0.0 (0.7, 0.3)
Life-threatening	0	0	0.0 (0.7, 0.3)
Severe	0	0	0.0 (0.7, 0.3)
Moderate	11 (0.9)	5 (0.9)	0.0 (1.3, 0.8)
Mild	46 (3.5)	17 (3.0)	0.5 (1.4, 2.2)
Serious	0	0	0.0 (0.7, 0.3)
Deaths	0	0	0.0 (0.7, 0.3)
Resulting in treatment discontinuation	4 (0.3)	0	0.3 (0.4, 0.8)
Relatedness	26 (2.0)	6 (1.0)	0.9 (0.4, 2.0)
Number of subjects with adverse events with end dates on or before treatment end dates	44/57 (78.5)	17/22 (77.8)	0.7 (18.1, 24.2)
Duration, days (from AE start date to AE end date)			
Mean (SD)	15.2 (20.9)	12.5 (24.7)	NA
Median (min, max)	5.5 (1.0, 82.0)	5.0 (1.0, 103.0)	NA
Interquartile range	3.0 to 21.2	2.0 to 7.0	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	3/57 (4.4)	1/22 (4.6)	0.2 (18.3, 11.6)

Gastrointestinal Tolerability Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	11/57 (18.6)	3/22 (13.8)	4.8 (17.6, 20.1)
Duration, days (from treatment end date to AE end date)			
Mean (SD)	44.9 (46.1)	91.7 (103.7)	NA
Median (min, max)	32.0 (2.0, 113.0)	62.0 (6.0, 207.0)	NA
Interquartile range	5.0 to 86.0	34.0 to 134.5	NA

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Severity scale as defined by the protocol.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; SD, standard deviation

Clinical Reviewer Comment: In summary, there were 2 GI related deaths (one in the placebo controlled period and one in the extension period) and 2 GI related SAEs (one in the extension period and one as of the 120-day safety update report). Multiple confounding factors were present in each of the cases, and that there is no known pharmacologic mechanism associated with icotrokinra or other IL-23 antagonists that would support an increased risk of GI bleeding. However, a causal relationship with icotrokinra cannot be ruled out as these events only occurred in subjects who received icotrokinra. In general, the population of patients with plaque psoriasis is not considered to be at risk of mortality from GI bleeding. Due to the fact that causality cannot be completely ruled out, the clinical reviewer does not recommend that these cases be included in warnings and precautions, however due to the seriousness of the events, recommend they be included as rare and serious events observed in the Phase 3 clinical trial program under Section 6 of the PI. The events of upper gastrointestinal bleeding (1 case of upper gastrointestinal bleeding; fatal, 1 case of nonspecific hematemesis; fatal), lower gastrointestinal bleeding (1 case of rectal bleeding), and gastric ulcer perforation (1 case) are recommended to be included in the USPI in the ADVERSE REACTIONS, Clinical Trials Experience subsection as low frequency, serious adverse reactions.

Clinical Team Lead Comment: The clinical team lead acknowledges the multiple confounders and risk factors associated with each case of GI related death and GI related SAE of gastric ulcer perforation and lower gastrointestinal bleeding as described above. Agree with the primary clinical reviewer that a causal relationship with icotrokinra cannot be ruled out for each event. Furthermore, these events only occurred in subjects who received icotrokinra, and the subject population of patients with plaque psoriasis is not generally considered to be at risk for

mortality from GI bleeding events. As such, agree with the primary clinical reviewer and recommend inclusion of the events in Section 6 of the PI. Due to the fatalities, the clinical team lead's recommendation is to also include the events of GI related death as a warnings and precautions in Section 5 of the PI in addition to Section 6, noting that for Section 5 Warnings and precautions 'this section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug)… as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established' (21CFR201.57(c)(6)(i)).

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (TEAEs) are defined in the trials as events that occurred after the first dose of study treatment through 30 days after the final dose of the study treatment or subject's participation in the study if the last scheduled visit occurred at a later time. Adverse events were summarized by SOC and Preferred term for the double-blind placebo control period and are shown in the table below, along with the risk difference for active versus placebo. Rates of TEAEs were generally similar between icotrokinra and the placebo period for both SOC and preferred term for the 16-week double-blind controlled period.

Adverse events were summarized as both subject incidence rates and exposure-adjusted incidence rates per 100 PYs. The former provided the basis of assessment for the 16 week Controlled Safety Pool while the latter provided for a more adequate assessment of the long term safety data given the varied duration of exposure across different treatment groups. The exposure adjusted rates also enabled comparison of data across the short-term and long-term analysis sets. The table presenting the EAIR for subjects initially randomized to icotrokinra who continued icotrokinra treatment, and for subjects initially randomized to placebo and switched to icotrokinra for the extension period for observed TEAEs is presented below. Analysis of EAIR for the observed events did not suggest an increased risk of events over time.

Adverse events were pooled to provide data for ADR table for labeling. The review team pooled preferred terms (PTs) which were considered likely to describe the same AE to obtain a clearer understanding of the frequencies at which these events occurred. The following table describes the pooled terms and terms which met criteria of >1% in icotrokinra and >0.5% difference from placebo will be included as the ADR table for labeling.

SOC by PT

Table 59. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.2% of Subjects in Icotrokinra Arm, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Any AE	636 (49.0)	295 (52.0)	2.9 (7.9, 2.0)
Blood and lymphatic system disorders (SOC)	10 (0.8)	8 (1.4)	0.6 (2.0, 0.3)
Lymphadenopathy	3 (0.2)	1 (0.2)	0.1 (0.8, 0.5)
Neutropenia	2 (0.2)	3 (0.5)	0.4 (1.4, 0.1)
Cardiac disorders (SOC)	13 (1.0)	6 (1.0)	0.0 (1.3, 0.9)
Coronary artery disease	3 (0.2)	0	0.2 (0.5, 0.6)
Sinus bradycardia	4 (0.3)	1 (0.2)	0.2 (0.7, 0.8)
Ear and labyrinth disorders (SOC)	11 (0.9)	3 (0.5)	0.3 (0.8, 1.1)
Vertigo	6 (0.5)	0	0.5 (0.2, 1.0)
Deafness	2 (0.2)	0	0.2 (0.5, 0.6)
Tinnitus	2 (0.2)	0	0.2 (0.5, 0.6)
Gastrointestinal disorders (SOC)	86 (6.6)	35 (6.3)	0.4 (2.2, 2.7)
Nausea	15 (1.2)	3 (0.5)	0.7 (0.4, 1.5)
Dry mouth	6 (0.5)	0	0.5 (0.2, 1.0)
Toothache	5 (0.4)	0	0.4 (0.3, 0.9)
Gastritis	4 (0.3)	0	0.3 (0.3, 0.9)
Abdominal discomfort	4 (0.3)	0	0.3 (0.4, 0.8)
Dyspepsia	4 (0.3)	0	0.3 (0.4, 0.8)
Dental caries	2 (0.2)	0	0.2 (0.5, 0.6)
Barrett's esophagus	2 (0.2)	0	0.2 (0.5, 0.6)
Constipation	4 (0.3)	1 (0.2)	0.1 (0.7, 0.7)
Abdominal pain upper	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Diarrhea	27 (2.0)	11 (2.0)	0.0 (1.6, 1.3)
Vomiting	4 (0.3)	2 (0.4)	0.0 (1.0, 0.4)
Abdominal distension	3 (0.3)	2 (0.3)	0.1 (1.0, 0.5)
Gastroesophageal reflux disease	6 (0.5)	4 (0.7)	0.2 (1.3, 0.5)
Abdominal pain	4 (0.3)	4 (0.7)	0.3 (1.5, 0.3)
General disorders and administration site conditions (SOC)	34 (2.6)	10 (1.8)	0.8 (0.8, 2.1)
Fatigue	15 (1.0)	3 (0.5)	0.5 (0.5, 1.4)
Pyrexia	8 (0.6)	2 (0.4)	0.2 (0.7, 0.9)
Chest pain	3 (0.2)	0	0.2 (0.5, 0.7)
Peripheral swelling	2 (0.2)	0	0.2 (0.5, 0.6)
Oedema peripheral	2 (0.2)	3 (0.5)	0.4 (1.4, 0.1)
Hepatobiliary disorders (SOC)	6 (0.5)	4 (0.7)	0.2 (1.3, 0.6)
Cholelithiasis	2 (0.2)	0	0.2 (0.5, 0.6)
Hepatic steatosis	2 (0.2)	1 (0.2)	0.0 (0.8, 0.4)
Immune system disorders (SOC)	4 (0.3)	3 (0.5)	0.2 (1.2, 0.4)
Seasonal allergy	3 (0.3)	2 (0.3)	0.1 (1.0, 0.5)

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Infections and infestations (SOC)	311 (23.9)	148 (26.0)	2.1 (6.5, 2.1)
Nasopharyngitis	94 (7.4)	39 (6.9)	0.5 (2.2, 2.9)
Gastroenteritis	12 (0.8)	2 (0.3)	0.5 (0.5, 1.2)
Folliculitis	5 (0.4)	0	0.4 (0.3, 0.9)
Tinea pedis	4 (0.3)	0	0.3 (0.3, 0.9)
Gingivitis	3 (0.3)	0	0.3 (0.4, 0.7)
Periodontitis	2 (0.2)	0	0.2 (0.5, 0.6)
Bacteriuria	4 (0.3)	1 (0.2)	0.1 (0.7, 0.7)
Hordeolum	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Pneumonia	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Viral upper respiratory tract infection	8 (0.6)	3 (0.5)	0.1 (1.0, 0.8)
Cystitis	3 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Lower respiratory tract infection	2 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Upper respiratory tract infection	62 (5.0)	29 (5.1)	0.0 (2.4, 2.0)
Tonsillitis	3 (0.3)	2 (0.4)	0.1 (1.1, 0.4)
Pharyngitis	11 (0.9)	6 (1.0)	0.1 (1.4, 0.8)
Bronchitis	11 (0.9)	6 (1.1)	0.2 (1.4, 0.7)
Dengue fever	4 (0.3)	3 (0.5)	0.2 (1.2, 0.4)
COVID-19	18 (1.2)	8 (1.4)	0.2 (1.7, 0.8)
Pulpitis dental	6 (0.5)	4 (0.8)	0.3 (1.4, 0.4)
Influenza	13 (0.9)	7 (1.3)	0.3 (1.7, 0.7)
Sinusitis	8 (0.7)	6 (1.0)	0.3 (1.6, 0.5)
Urinary tract infection	16 (1.2)	10 (1.7)	0.6 (2.1, 0.5)
Gastroenteritis viral	5 (0.4)	6 (1.0)	0.6 (1.9, 0.1)
Oral herpes	5 (0.3)	7 (1.3)	0.9 (2.3, 0.2) *
Injury, poisoning and procedural complications (SOC)	32 (2.5)	18 (3.1)	0.6 (2.6, 0.9)
Skin laceration	4 (0.3)	0	0.3 (0.4, 0.8)
Limb injury	5 (0.4)	1 (0.2)	0.3 (0.6, 0.8)
Head injury	2 (0.2)	0	0.2 (0.5, 0.6)
Skin abrasion	2 (0.2)	0	0.2 (0.5, 0.6)
Muscle strain	2 (0.2)	1 (0.2)	0.0 (0.8, 0.5)

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Investigations (SOC)	88 (7.1)	37 (6.4)	0.7 (2.0, 3.0)
Blood alkaline phosphatase increased	5 (0.4)	0	0.4 (0.2, 1.0)
Blood glucose increased	7 (0.6)	2 (0.3)	0.3 (0.7, 1.0)
Blood potassium increased	3 (0.2)	0	0.2 (0.5, 0.7)
C-reactive protein increased	5 (0.4)	1 (0.2)	0.2 (0.6, 0.8)
Weight increased	5 (0.4)	1 (0.2)	0.2 (0.6, 0.8)
Blood uric acid increased	4 (0.3)	1 (0.2)	0.2 (0.7, 0.7)
Neutrophil count decreased	2 (0.2)	0	0.2 (0.5, 0.6)
Protein urine present	10 (0.9)	4 (0.7)	0.2 (1.0, 1.1)
Urinary occult blood positive	2 (0.2)	0	0.2 (0.5, 0.6)
Weight decreased	2 (0.2)	0	0.2 (0.5, 0.6)
White blood cell count increased	2 (0.2)	0	0.2 (0.5, 0.6)
Alanine aminotransferase increased	10 (0.9)	4 (0.7)	0.2 (1.0, 1.0)
White blood cell count decreased	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Gamma-glutamyltransferase increased	7 (0.6)	3 (0.5)	0.1 (1.0, 0.8)
Urine analysis abnormal	3 (0.2)	1 (0.2)	0.1 (0.8, 0.6)
Aspartate aminotransferase increased	11 (0.9)	5 (0.9)	0.0 (1.2, 0.9)
Bacterial test positive	3 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Blood creatine phosphokinase increased	9 (0.7)	4 (0.7)	0.0 (1.1, 0.8)
Blood creatinine increased	2 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Blood triglycerides increased	3 (0.2)	3 (0.5)	0.3 (1.3, 0.3)
Metabolism and nutrition disorders (SOC)	41 (3.1)	21 (3.7)	0.5 (2.6, 1.2)
Type 2 diabetes mellitus	3 (0.3)	0	0.3 (0.4, 0.7)
Hypercholesterolemia	3 (0.2)	0	0.2 (0.5, 0.6)
Hyperlipidemia	3 (0.3)	1 (0.2)	0.1 (0.8, 0.5)
Diabetes mellitus	3 (0.2)	1 (0.2)	0.1 (0.8, 0.5)
Increased appetite	2 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Hyperuricemia	5 (0.4)	3 (0.5)	0.1 (1.1, 0.6)
Hypertriglyceridemia	10 (0.8)	7 (1.2)	0.4 (1.7, 0.5)
Hyperglycemia	4 (0.3)	5 (0.9)	0.5 (1.7, 0.2)
Musculoskeletal and connective tissue disorders (SOC)	71 (5.1)	37 (6.6)	1.5 (4.1, 0.7)
Back pain	16 (1.1)	4 (0.7)	0.4 (0.8, 1.3)
Tendonitis	3 (0.2)	0	0.2 (0.5, 0.6)
Intervertebral disc disorder	2 (0.2)	0	0.2 (0.5, 0.6)
Musculoskeletal chest pain	2 (0.2)	0	0.2 (0.5, 0.6)
Arthralgia	19 (1.4)	7 (1.2)	0.1 (1.2, 1.2)
Psoriatic arthropathy	6 (0.4)	2 (0.3)	0.0 (0.9, 0.7)
Osteoarthritis	3 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Myalgia	6 (0.4)	3 (0.5)	0.1 (1.2, 0.5)
Rotator cuff syndrome	2 (0.2)	2 (0.3)	0.2 (1.1, 0.3)
Flank pain	2 (0.2)	2 (0.3)	0.2 (1.1, 0.3)
Pain in extremity	2 (0.2)	5 (0.9)	0.7 (1.9, 0.1) *
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	13 (1.0)	4 (0.7)	0.3 (0.9, 1.1)
Skin papilloma	3 (0.2)	2 (0.4)	0.2 (1.1, 0.3)

System Organ Class Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Nervous system disorders (SOC)	73 (5.7)	28 (4.9)	0.8 (1.6, 2.8)
Headache	51 (4.1)	19 (3.3)	0.7 (1.3, 2.4)
Migraine	4 (0.3)	0	0.3 (0.4, 0.8)
Hypoesthesia	5 (0.4)	1 (0.2)	0.2 (0.6, 0.7)
Syncope	2 (0.2)	0	0.2 (0.5, 0.6)
Dizziness	5 (0.4)	3 (0.5)	0.1 (1.2, 0.5)
Psychiatric disorders (SOC)	17 (1.3)	9 (1.6)	0.3 (1.8, 0.8)
Libido decreased	3 (0.2)	0	0.2 (0.5, 0.7)
Depression	2 (0.2)	0	0.2 (0.5, 0.6)
Anxiety	4 (0.3)	2 (0.3)	0.1 (1.0, 0.5)
Insomnia	6 (0.5)	5 (0.9)	0.4 (1.6, 0.3)
Renal and urinary disorders (SOC)	22 (1.7)	13 (2.3)	0.5 (2.2, 0.8)
Proteinuria	10 (0.9)	4 (0.7)	0.2 (1.0, 1.0)
Hematuria	5 (0.4)	3 (0.5)	0.2 (1.2, 0.4)
Reproductive system and breast disorders (SOC)	12 (1.0)	2 (0.4)	0.6 (0.4, 1.3)
Dysmenorrhea	3 (0.2)	0	0.2 (0.5, 0.7)
Respiratory, thoracic and mediastinal disorders (SOC)	37 (2.9)	11 (1.9)	0.9 (0.7, 2.3)
Cough	15 (1.2)	1 (0.2)	1.0 (0.2, 1.8) *
Rhinitis allergic	5 (0.4)	1 (0.2)	0.2 (0.6, 0.8)
Oropharyngeal pain	5 (0.4)	2 (0.4)	0.0 (0.9, 0.6)
Dyspnea	2 (0.2)	1 (0.2)	0.0 (0.8, 0.5)
Skin and subcutaneous tissue disorders (SOC)	80 (6.1)	43 (7.6)	1.5 (4.2, 1.0)
Eczema	3 (0.3)	0	0.3 (0.4, 0.7)
Urticaria	3 (0.3)	0	0.3 (0.4, 0.7)
Acne	5 (0.4)	1 (0.2)	0.2 (0.7, 0.7)
Night sweats	5 (0.4)	1 (0.2)	0.2 (0.7, 0.8)
Alopecia	2 (0.2)	0	0.2 (0.5, 0.6)
Dermatitis allergic	2 (0.2)	0	0.2 (0.5, 0.6)
Perioral dermatitis	2 (0.2)	0	0.2 (0.5, 0.6)
Dyshidrotic eczema	2 (0.2)	0	0.2 (0.5, 0.6)
Rosacea	4 (0.3)	1 (0.2)	0.1 (0.7, 0.7)
Dermal cyst	3 (0.3)	1 (0.2)	0.1 (0.7, 0.6)
Pruritus	15 (1.2)	8 (1.5)	0.3 (1.7, 0.7)
Psoriasis	10 (0.8)	18 (3.1)	2.4 (4.2, 1.0) *
Vascular disorders (SOC)	28 (2.2)	10 (1.7)	0.4 (1.1, 1.7)
Hypertension	22 (1.7)	7 (1.2)	0.4 (1.0, 1.6)
Peripheral coldness	2 (0.2)	0	0.2 (0.5, 0.6)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Preferred terms in the table are ordered by descending risk difference.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class

PT

Table 60. Subjects With Common Adverse Events Occurring at ≥0.5% Frequency by Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

Preferred Term	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Any AE	636 (49.0)	295 (52.0)	2.9 (7.9, 2.0)
Cough	15 (1.2)	1 (0.2)	1.0 (0.2, 1.8) *
Headache	51 (4.1)	19 (3.3)	0.7 (1.3, 2.4)
Nausea	15 (1.2)	3 (0.5)	0.7 (0.4, 1.5)
Fatigue	15 (1.0)	3 (0.5)	0.5 (0.5, 1.4)
Nasopharyngitis	94 (7.4)	39 (6.9)	0.5 (2.2, 2.9)
Gastroenteritis	12 (0.8)	2 (0.3)	0.5 (0.5, 1.2)
Hypertension	22 (1.7)	7 (1.2)	0.4 (1.0, 1.6)
Back pain	16 (1.1)	4 (0.7)	0.4 (0.8, 1.3)
Blood glucose increased	7 (0.6)	2 (0.3)	0.3 (0.7, 1.0)
Pyrexia	8 (0.6)	2 (0.4)	0.2 (0.7, 0.9)
Protein urine present	10 (0.9)	4 (0.7)	0.2 (1.0, 1.1)
Proteinuria	10 (0.9)	4 (0.7)	0.2 (1.0, 1.0)
Alanine aminotransferase increased	10 (0.9)	4 (0.7)	0.2 (1.0, 1.0)
Arthralgia	19 (1.4)	7 (1.2)	0.1 (1.2, 1.2)
Gamma-glutamyltransferase increased	7 (0.6)	3 (0.5)	0.1 (1.0, 0.8)
Viral upper respiratory tract infection	8 (0.6)	3 (0.5)	0.1 (1.0, 0.8)
Aspartate aminotransferase increased	11 (0.9)	5 (0.9)	0.0 (1.2, 0.9)
Diarrhea	27 (2.0)	11 (2.0)	0.0 (1.6, 1.3)
Blood creatine phosphokinase increased	9 (0.7)	4 (0.7)	0.0 (1.1, 0.8)
Upper respiratory tract infection	62 (5.0)	29 (5.1)	0.0 (2.4, 2.0)
Pharyngitis	11 (0.9)	6 (1.0)	0.1 (1.4, 0.8)
Bronchitis	11 (0.9)	6 (1.1)	0.2 (1.4, 0.7)
COVID-19	18 (1.2)	8 (1.4)	0.2 (1.7, 0.8)
Pruritus	15 (1.2)	8 (1.5)	0.3 (1.7, 0.7)
Influenza	13 (0.9)	7 (1.3)	0.3 (1.7, 0.7)
Sinusitis	8 (0.7)	6 (1.0)	0.3 (1.6, 0.5)
Hypertriglyceridemia	10 (0.8)	7 (1.2)	0.4 (1.7, 0.5)
Urinary tract infection	16 (1.2)	10 (1.7)	0.6 (2.1, 0.5)
Psoriasis	10 (0.8)	18 (3.1)	2.4 (4.2, 1.0) *

Source: adae.xpt; software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Coded as MedDRA preferred terms.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 61**. Subjects With Common Adverse Events Occurring at ≥1.3% Frequency by Preferred Term, Safety Population, Pooled Trials PSO3001, PSO3002, PS**O3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Preferred Term	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
Any AE	557/354.0 (157.5)	317/217.1 (150.9)	849/477.9 (177.6)	1166/695.1 (168.6)
Nasopharyngitis	114/508.8 (20.4)	64/346.4 (19.8)	177/849.8 (20.7)	241/1196.2 (20.5)
Upper respiratory tract infection	68/518.0 (12.9)	58/346.2 (17.3)	116/874.0 (13.4)	174/1220.1 (14.1)
Headache	25/532.8 (5.0)	11/364.1 (3.3)	66/893.8 (7.5)	77/1257.9 (6.1)
COVID-19	20/533.2 (3.2)	9/365.9 (2.9)	38/912.4 (4.0)	47/1278.3 (3.9)
Arthralgia	16/536.9 (2.7)	15/365.4 (4.3)	32/915.9 (3.4)	47/1281.3 (3.8)
Influenza	13/539.1 (2.1)	19/365.5 (5.8)	25/920.9 (2.6)	44/1286.5 (3.5)
Hypertension	13/538.8 (2.3)	9/367.3 (2.5)	34/915.2 (3.7)	43/1282.5 (3.4)
Urinary tract infection	16/537.4 (2.9)	11/364.8 (2.7)	29/916.7 (3.1)	40/1281.5 (3.1)
Diarrhea	5/538.8 (1.0)	5/367.1 (1.4)	32/908.8 (3.4)	37/1275.9 (3.0)
Hypertriglyceridemia	15/537.5 (3.8)	16/362.4 (4.4)	21/923.2 (2.4)	37/1285.5 (2.7)
Gastroenteritis	13/537.0 (2.2)	7/367.8 (2.6)	25/918.6 (2.7)	32/1286.5 (2.6)
Back pain	15/537.7 (2.9)	4/368.2 (1.5)	28/918.1 (3.0)	32/1286.3 (2.6)
Blood creatine phosphokinase increased	14/536.5 (2.9)	12/366.1 (3.3)	21/921.4 (2.3)	33/1287.5 (2.5)
Pharyngitis	16/536.6 (2.8)	5/367.7 (1.6)	26/920.4 (2.8)	31/1288.1 (2.4)
Bronchitis	12/538.3 (1.7)	7/367.1 (2.0)	23/919.9 (2.5)	30/1287.0 (2.4)
Cough	13/537.4 (2.0)	3/368.2 (0.9)	27/917.4 (3.0)	30/1285.6 (2.3)
Alanine aminotransferase increased	12/537.3 (2.3)	7/368.3 (2.0)	19/921.1 (2.1)	26/1289.4 (2.0)
Sinusitis	11/538.0 (1.5)	4/368.6 (1.3)	18/921.4 (1.9)	22/1290.0 (1.8)
Nausea	5/540.3 (0.9)	2/369.0 (0.5)	20/921.4 (2.2)	22/1290.5 (1.7)
Viral upper respiratory tract infection	9/540.2 (1.4)	4/368.5 (1.3)	17/925.6 (1.8)	21/1294.1 (1.7)
Fatigue	5/540.4 (0.6)	1/369.2 (0.2)	18/920.6 (1.9)	19/1289.8 (1.6)
Aspartate aminotransferase increased	9/537.9 (1.6)	3/369.1 (0.8)	17/921.4 (1.9)	20/1290.5 (1.5)
Pruritus	4/541.1 (0.5)	0/370.0	18/920.9 (1.9)	18/1290.9 (1.5)
Gamma-glutamyltransferase increased	11/538.4 (2.5)	4/369.0 (1.1)	15/924.2 (1.7)	19/1293.2 (1.4)
Myalgia	8/539.2 (1.2)	4/368.1 (0.9)	14/924.0 (1.5)	18/1292.0 (1.4)
Psoriasis	5/540.7 (0.8)	4/368.9 (0.7)	14/923.2 (1.5)	18/1292.0 (1.4)
Blood triglycerides increased	12/538.7 (2.9)	3/369.0 (0.9)	15/925.5 (1.7)	18/1294.5 (1.4)
Toothache	6/539.9 (1.4)	6/367.8 (1.5)	11/925.1 (1.2)	17/1292.9 (1.3)
Proteinuria	7/538.8 (1.4)	3/368.4 (0.8)	14/923.9 (1.6)	17/1292.3 (1.3)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.

Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Abbreviations: AE, adverse event; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PY, person-years (total exposure); py, person-years (at risk)

The following Adverse Reaction table was derived by combining terms from OCMQ, evaluating adverse events occurring in icotrokinra arm occurring at >1% and at greater rate than placebo by 0.5%. Adverse reactions of headache, nausea, cough, fungal infection, and fatigue are recommended for inclusion in labeling. The events that were identified are similar to those identified for other IL-23 inhibitors.

Table 62. Adverse Reactions That Occurred in ≥1% of Subjects in the TRADENAME Group and More Frequently Than in the Placebo Group in Trials 1, 2, 3, and 4 Through Week 16a

Adverse Reactions	TRADENAME N=1296 n (%)	Placebo N=568 n (%)
Headache	51 (4.1)	19 (3.3)
Nausea	15 (1.2)	3 (0.5)
Cough	15 (1.2)	1 (0.2)
Fungal infection[b]	14 (1.1)	0 (0)
Fatigue	15 (1.0)	3 (0.5)

Source:
[a] Percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions
[b] Fungal infection includes tinea pedis, tinea versicolor, onychomycosis, skin candida, oral candidiasis, urinary tract candidiasis, vulvovaginal candidiasis, fungal skin infection, genital infection fungal, ear infection fungal, laryngitis fungal.
Abbreviations:

Treatment-emergent adverse events by SOC and PT are presented in Table 63 for PSO3002 and PSO3004 24-week doubled blind placebo controlled period for icotrokinra and deucravacitinib. Overall rates of TEAEs were higher in deucravacitinib (65.3%) versus icotrokinra (57.6%). SOC of GI disorders was higher for deucravacitinib (12.8%) compared to icotrokinra (8.7%), as well as the SOC Infections and Infestations deucravacitinib (39.9%) versus icotrokinra (30.4%). The rates of other SOC and PTs were similar between the treatments.

Table 63. Subjects With Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 0.3% of Subjects in Icotrokinra Arm, Safety Population, Pooled Trials PSO3002 and PSO3004, Double-Blind Active Comparator-Controlled Period

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Any AE	364 (57.6)	414 (65.3)	-7.7 (-13.0, -2.3)*
Cardiac disorders (SOC)	9 (1.4)	9 (1.4)	0.0 (-1.4, 1.4)
Coronary artery disease	3 (0.5)	2 (0.3)	0.2 (-0.7, 1.1)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Gastrointestinal disorders (SOC)	55 (8.7)	81 (12.8)	-4.1 (-7.5, -0.7)*
Gastroesophageal reflux disease	5 (0.8)	1 (0.2)	0.6 (-0.2, 1.7)
Dry mouth	3 (0.5)	0	0.5 (-0.1, 1.4)
Diarrhea	18 (2.8)	16 (2.5)	0.3 (-1.5, 2.2)
Constipation	4 (0.6)	2 (0.3)	0.3 (-0.6, 1.3)
Toothache	4 (0.6)	5 (0.8)	-0.2 (-1.3, 0.9)
Nausea	5 (0.8)	7 (1.1)	-0.3 (-1.6, 0.9)
General disorders and administration site conditions (SOC)	25 (4.0)	29 (4.6)	-0.6 (-2.9, 1.6)
Fatigue	14 (2.2)	10 (1.6)	0.6 (-0.9, 2.3)
Chest pain	3 (0.5)	1 (0.2)	0.3 (-0.5, 1.2)
Pyrexia	6 (0.9)	8 (1.3)	-0.3 (-1.7, 0.9)
Infections and infestations (SOC)	192 (30.4)	253 (39.9)	-9.5 (-14.7, -4.2) *
Infective exacerbation of chronic obstructive airways disease	3 (0.5)	0	0.5 (-0.1, 1.4)
Pulpitis dental	5 (0.8)	2 (0.3)	0.5 (-0.4, 1.5)
Tinea versicolour	3 (0.5)	1 (0.2)	0.3 (-0.5, 1.3)
Bronchitis	7 (1.1)	5 (0.8)	0.3 (-0.9, 1.6)
Sinusitis	7 (1.1)	6 (0.9)	0.2 (-1.1, 1.4)
Pneumonia	3 (0.5)	2 (0.3)	0.2 (-0.7, 1.1)
Viral upper respiratory tract infection	4 (0.6)	4 (0.6)	0.0 (-1.1, 1.1)
Influenza	12 (1.9)	12 (1.9)	0.0 (-1.6, 1.6)
Bacteriuria	3 (0.5)	3 (0.5)	0.0 (-1.0, 1.0)
Pharyngitis	4 (0.6)	4 (0.6)	-0.0 (-1.1, 1.1)
Gastroenteritis	9 (1.4)	10 (1.6)	-0.2 (-1.6, 1.3)
Urinary tract infection	11 (1.7)	13 (2.0)	-0.3 (-1.9, 1.3)
COVID-19	17 (2.7)	22 (3.5)	-0.8 (-2.8, 1.2)
Folliculitis	4 (0.6)	9 (1.4)	-0.8 (-2.1, 0.4)
Oral herpes	4 (0.6)	12 (1.9)	-1.3 (-2.7, -0.0) *
Upper respiratory tract infection	34 (5.4)	49 (7.7)	-2.3 (-5.1, 0.4)
Nasopharyngitis	56 (8.9)	77 (12.1)	-3.3 (-6.7, 0.1)
Injury, poisoning and procedural complications (SOC)	28 (4.4)	29 (4.6)	-0.1 (-2.5, 2.2)
Skin laceration	4 (0.6)	1 (0.2)	0.5 (-0.3, 1.5)
Limb injury	4 (0.6)	1 (0.2)	0.5 (-0.3, 1.5)
Contusion	3 (0.5)	3 (0.5)	0.0 (-1.0, 1.0)
Investigations (SOC)	36 (5.7)	44 (6.9)	-1.3 (-4.0, 1.4)
Weight increased	3 (0.5)	0	0.5 (-0.1, 1.4)
Aspartate aminotransferase increased	4 (0.6)	3 (0.5)	0.2 (-0.8, 1.2)
Blood creatine phosphokinase increased	4 (0.6)	11 (1.7)	-1.1 (-2.5, 0.1)
Metabolism and nutrition disorders (SOC)	27 (4.3)	30 (4.7)	-0.4 (-2.8, 1.9)
Hyperglycemia	3 (0.5)	1 (0.2)	0.3 (-0.4, 1.2)
Hypercholesterolemia	3 (0.5)	3 (0.5)	0.0 (-0.9, 1.0)
Hypertriglyceridemia	5 (0.8)	8 (1.3)	-0.5 (-1.8, 0.7)

System Organ Class Preferred Term	Pooled Icotrokinra N=632 n (Adjusted %)	Pooled Deucravacitinib N=634 n (Adjusted %)	Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	62 (9.8)	48 (7.6)	2.3 (-0.8, 5.4)
Myalgia	9 (1.4)	3 (0.5)	1.0 (-0.1, 2.3)
Intervertebral disc protrusion	3 (0.5)	0	0.5 (-0.1, 1.4)
Arthritis	3 (0.5)	0	0.5 (-0.1, 1.4)
Back pain	13 (2.1)	11 (1.7)	0.3 (-1.3, 1.9)
Arthralgia	19 (3.0)	18 (2.8)	0.2 (-1.8, 2.1)
Psoriatic arthropathy	5 (0.8)	4 (0.6)	0.2 (-0.9, 1.3)
Osteoarthritis	3 (0.5)	2 (0.3)	0.2 (-0.7, 1.1)
Pain in extremity	4 (0.6)	3 (0.5)	0.2 (-0.8, 1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	8 (1.3)	3 (0.5)	0.8 (-0.3, 2.1)
Skin papilloma	3 (0.5)	1 (0.2)	0.3 (-0.5, 1.2)
Nervous system disorders (SOC)	41 (6.5)	43 (6.8)	-0.3 (-3.1, 2.5)
Headache	28 (4.4)	20 (3.2)	1.3 (-0.9, 3.5)
Hypoesthesia	3 (0.5)	0	0.5 (-0.1, 1.4)
Psychiatric disorders (SOC)	13 (2.1)	10 (1.6)	0.5 (-1.1, 2.1)
Insomnia	5 (0.8)	2 (0.3)	0.5 (-0.4, 1.5)
Anxiety	3 (0.5)	4 (0.6)	-0.2 (-1.2, 0.8)
Renal and urinary disorders (SOC)	13 (2.1)	14 (2.2)	-0.2 (-1.8, 1.5)
Hematuria	4 (0.6)	4 (0.6)	0.0 (-1.1, 1.1)
Respiratory, thoracic and mediastinal disorders (SOC)	25 (4.0)	24 (3.8)	0.2 (-2.0, 2.4)
Cough	11 (1.7)	9 (1.4)	0.3 (-1.1, 1.8)
Oropharyngeal pain	4 (0.6)	6 (0.9)	-0.3 (-1.5, 0.8)
Skin and subcutaneous tissue disorders (SOC)	56 (8.9)	80 (12.6)	-3.8 (-7.2, -0.4) *
Psoriasis	9 (1.4)	5 (0.8)	0.6 (-0.6, 2.0)
Dermal cyst	3 (0.5)	1 (0.2)	0.3 (-0.4, 1.2)
Pruritus	11 (1.7)	10 (1.6)	0.2 (-1.3, 1.7)
Night sweats	4 (0.6)	3 (0.5)	0.2 (-0.8, 1.2)
Dermatitis acneiform	3 (0.5)	4 (0.6)	-0.2 (-1.2, 0.8)
Rosacea	3 (0.5)	5 (0.8)	-0.3 (-1.4, 0.7)
Acne	3 (0.5)	23 (3.6)	-3.2 (-5.0, -1.6) *
Vascular disorders (SOC)	19 (3.0)	16 (2.5)	0.5 (-1.4, 2.4)
Hypertension	15 (2.4)	14 (2.2)	0.2 (-1.6, 1.9)

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 24 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SOC, system organ class

Laboratory Findings

Within the Week 16 placebo controlled period, there were no clinically meaningful changes in clinical laboratories assessed. The number of subjects who were within normal range at baseline and then had potentially clinically significant abnormalities were as expected for this population and did not represent any clinical signals of concern. Data were similar through the safety update period. Changes in hepatic enzymes are discussed in AESI narrative format in Section 8.2.4.

Hematology

Hematology was assessed by CTCAE toxicity grading. Within the Week 16 placebo controlled period, there were few hematology laboratory values with a maximum grade of 2, the majority were 0 or 1. There was one grade 3 value of lymphocyte count decreased in the 16 week period in a subject receiving icotrokinra. There was no change in pattern of CTCAE toxicity through the 120-day safety cut off compared to the initial NDA review for hematology parameters. The majority of hematology laboratory parameters were maximum CTCAE toxicity grade 0 or 1, similar to the NDA safety cut-off data. There was no pattern in shifts in hematology parameters from baseline to maximum CTCAE toxicity grade with most values being normal in the 16 week control period.

Chemistry

The following chemistry parameters were reviewed through the 120-day safety cut off: CPK, albumin, protein, glucose, sodium, calcium, magnesium, bicarbonate, chloride, creatinine, and urea nitrogen.

There was no change in pattern of CTCAE toxicity through the 120-day safety cut off compared to the initial NDA review for chemistry parameters. The majority of chemistry laboratory parameters were maximum CTCAE toxicity grade 0 or 1, similar to the NDA safety cut-off data. There was no pattern in shifts in chemistry parameters from baseline to maximum CTCAE toxicity grade.

Vital Signs

Vital signs comprised systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate. There were no clinically meaningful changes from baseline or shifts in vital signs.

Electrocardiograms (ECGs)

In the Phase 3 studies, ECGs were only performed at screening, Week 16, Week 52 and the early termination visit. The pooled double blind randomized controlled week 16 data for the Phase 3 studies did not show a clinically meaningful difference in ECG parameters In the pooled analysis of week 16 data, there were no clinically meaningful differences in ECG parameters in

Icotrokinra versus placebo administration over 16 weeks. There were no trends through the safety reporting period.

QT

ECGs were performed at screening, Week 16 and Week 52 in the Phase 3 studies. QT-IRT was consulted and reviewed the Applicant's QTc assessment, which included data from clinical study PN-235-01 and an integrated nonclinical risk assessment. The conclusion of this assessment was that there was an absence of QTc prolongation for icotrokinra. In addition, there was no effect in the concentration-QTc analysis that was reviewed.

Immunogenicity

Two types of ECLIA assays were implemented in the icotrokinra program. One for the detection of ADA and a noncell-based ECLIA assay for the identification of neutralizing antibodies against icotrokinra. Immunogenicity to icotrokinra did not have an impact on safety or efficacy, with similar response rates observed regardless of antibody status. The presence of antibodies and the associated titers were not associated with reduction in clinical efficacy or impacted safety of icotrokinra.

8.2.5. Analysis of Submission-Specific Safety Issues

Icotrokinra, an IL-23 receptor antagonist, is an orally administered peptide (once daily 200 mg dose). Icotrokinra binds to the IL-23 receptor and antagonizes the binding of IL-23.

Inhibition of the inflammatory cascade and downstream inhibition of the Th17 pathway and Th17 cell survival may increase the opportunity for infection in patients who receive IL-23 inhibitors by reducing mucosal defenses against bacteria and fungi. IL-23 is important in maintaining and expanding Th17 cell and therefore their differentiation and survival is reduced with IL-23 inhibition. Other impacts of IL-23 inhibition in risk of infection include reduction of effector cytokine, which reduces stimulation of epithelial cells and barrier defenses against pathogens. Reduction in Th17 response may specifically lower defense mechanisms against *Candida albicans* and *Staphylococcus aureus* infections. IL-23 inhibition can also alter innate and adaptive immune responses in the intestine leading to reduced mucosal defense.

There is ongoing debate about the role of IL-23 in malignancy. The role of IL-23 in the tumor microenvironment is complex, with both protumor and antitumor effects described. There are several pathways through which IL-23 can affect the tumor behavior. Activation of downstream cytokine pathways can inhibit tumor apoptosis and promote tumor proliferation; promotion of infiltration of immune cells that can have immunosuppressive function; stimulation of vascular endothelial growth factor and other proangiogenic factors; local inflammation and lymphocyte proliferation in the tumor microenvironment. There is a complex interaction in the inflammatory cytokines and cells involved in innate antitumor response, and therefore inhibition of IL-23 may have multiple influences in these processes.

Data from studies with IL-23 inhibition have generally demonstrated a favorable cardiovascular safety profile. Due to the significant downstream influence on inflammatory cytokines, potential for MACE events was reviewed in the program. MACE events are highly related to systemic inflammation, and patients with psoriasis are reported to have an approximately 50% increased relative risk of MACE events compared to the general population. Severe psoriasis increases the risk of myocardial infarction up to 3-fold. Eight percent of psoriasis patients are also recognized to have at least one cardiovascular risk factor and comorbidities of hypertension, diabetes, and dyslipidemia are prominent in this population.

Finally, the role of IL-23 inhibition is included as a risk factor for development of latent tuberculosis infection in other approved IL-23 inhibitor labels. Testing for latent TB infection has been standard clinical practice prior to initiation of biologic therapy for patients with psoriasis, largely initiated by experience with TNF inhibitors and their key role in formation and maintenance of granulomas, which are critical to containment of LTBI. Clinical data indicating reduced risk of LTBI reactivation have largely been retrospective review of programs that have included limited numbers of subjects with LTBI. Furthermore, clinical data from individuals identified as having IL-23 deficiency, which results from mutations in the IL-23 receptor gene, have impaired immune signaling and susceptibility to infection. Affected individuals may develop rare, severe infections such as Mendelian susceptibility to mycobacterial diseases or chronic mucocutaneous candidiasis.

The mechanism of action of IL-23 inhibition, and downstream effects on cellular and cytokine responses prompts evaluation of a set adverse events of safety interest for this review. Categories of Adverse events of interest for this program included: protocol/program derived AESIs include: malignancy, possible Hy's Law, and active tuberculosis. Other adverse events identified for regulatory review included: Treatment-emergent LTBI, opportunistic infections, serious infections, cardiovascular events, hypersensitivity reactions, anaphylactic reactions, Hepatic AEs leading to discontinuation of study intervention and serious hepatic AEs, depression, suicidal ideation and behavior.

In addition to protocol and program derived AESIs, a potential safety signal of gastrointestinal bleeding was identified in subjects who received icotrokinra in the Phase 3 studies. In the icotrokinra phase 3 development program, 2 deaths occurred in icotrokinra treated subjects, one following randomization in the placebo control period, and one after a longer period of dosing with icotrokinra in the extension period (Day 385). Additionally, there was one subject in the extension period who developed an gastrointestinal related SAE (perforated gastric ulcer with peritonitis), and a second SAE of lower GI bleeding (rectal hemorrhage) was identified from the Day 120 safety update. Nonclinical data submitted by the Applicant was reviewed and did not indicate signs of gastrointestinal toxicity in rats and monkeys with a 60-fold margin over human exposure.

The following were requested from the Applicant: 1) a summary table of the proportion of subjects who experienced gastrointestinal adverse events, as well as any data available from development programs with icotrokinra for ulcerative colitis and Crohn's disease programs; 2)

additional medical history for the subjects with deaths/SAEs. The Applicant responded with data from all current development programs including plaque psoriasis, ulcerative colitis, and psoriatic arthritis. Per the data submitted by the Applicant, across seven placebo-controlled studies in subjects with PsO (phase 2 and 3) and UC (phase 2) through Week 16 (with 1,762 icotrokinra-treated subjects and 698 placebo-treated subjects), a total of 7/1,762 (0.4%) subjects who received icotrokinra and 1/698 (0.1%) subjects who received placebo reported at least one of the adverse events (12 PTs above) identified for this query. Of these 7 subjects treated with icotrokinra, the reported AEs included gastritis (6), hematemesis (1), and the 1 subject who received placebo reported the AE of peptic ulcer (1).

The Applicant reported that no cases of the following selected AEs were reported in subjects who received icotrokinra through Week 16: peptic ulcer, gastrointestinal hemorrhage, melaena, feces discolored, hematochezia, gastrointestinal ulcer, gastrointestinal perforation, Mallory-Weiss syndrome, peritonitis, or thrombocytopenia. Furthermore, none of the selected AEs were identified at higher doses (300 mg, 400 mg, or 1,000 mg); thus, no dose-response relationship was identified by the Applicant.

The Division of Gastroenterology was consulted for evaluation of these cases and reported their recommendations in Division of Gastroenterology Consult Memo dated 23-Dec-2026. They reviewed potential identifiable clinical risk factors for GI bleed, as well as the known risk of GI bleeding in the psoriasis population. Consultant comments:

> Although the placebo sample size is small (as compared to the icotrokinra sample size), there is not an imbalance in the number of subjects who reported at least one of the specified GI related AEs between the icotrokinra and placebo arms in the seven placebo-controlled studies in subjects with psoriasis and UC. Of note, based on the results reported by the Applicant in response to the IR, there were no occurrences of serious GI events, including GI bleeding, gastrointestinal ulcer, or gastrointestinal perforation, across the placebo-controlled trials in the icotrokinra development programs other than the 2 deaths and 1 SAE of gastric ulcer perforation that are the focus of this consult. The analyses included in this response from the Applicant do not include data from the 120-day safety update.
>
> There remains uncertainty as to whether icotrokinra increases the risk of GI bleeding or other serious GI adverse events (e.g., ulcer perforation) as multiple confounding factors were present in each of the cases, and furthermore, there is no known pharmacologic mechanism associated with icotrokinra or other IL-23 antagonists that would support an increased risk of GI bleeding. However, there is some basis to believe that there is a causal relationship as these events only occurred in subjects that received icotrokinra, and the subject population (i.e., patients with psoriasis) is not considered to be at risk for GI bleeding or other serious GI adverse events.

Additional clinical information was provided on the 2 deaths and 2 SAEs and the role of icotrokinra in the events were re-evaluated based on additional clinical information on the cases submitted by the Applicant.

(b) (6) **(Death).** Additional information was provided on this case that attributed to subject's cause of death to bleeding from ruptured esophageal varices. Esophageal varices have a long developmental time, unlikely to develop in relationship to a short period of icotrokinra administration, and rupture of varices is most likely related to portal hypertension, and unlikely to be precipitated from icotrokinra administration. Therefore, upon further review, the subject's cause of death was unlikely to be related to icotrokinra administration.

(b) (6) **(Death).** Additional information was not obtained via the IR. Consultant's review of this case concluded that the subject's use of acetylsalicylic acid, alcohol, and tobacco are known risk factors for the development of peptic ulcer disease. Gastric ulcers have also been associated with obesity and coronary artery disease. Review of confounding factors in this case causality of death due to icotrokinra is not established.

(b) (6) **(SAE).** The incidence of the SAE with peptic ulcer and perforation represented a lower incidence in the sample size of the clinical trial population compared to the estimated incidence of GI perforation ins the general population. This subject was also noted to have multiple confounding factors for gastric ulcer, including obesity, and tobacco and alcohol use, therefore causality to icotrokinra administration cannot be established.

(b) (6) **(SAE).** Consultant review indicated that the likely source of lower GI bleed was from colonic diverticular bleeding, however, the source of the bleed could not be confirmed on imaging studies, including colonoscopy. Given suspected colonic diverticulosis as a source of GI bleed, the causality of icotrokinra is not established.

The rate of GI bleeding identified in the icotrokinra psoriasis program is consistent with the expected rate in the general population of similar size, however the rate of fatal GI bleeding exceeds the expected rate in the general population of the same size. Review of the literature does not indicate an increased risk of GI bleeding in the intended treatment population. In contrast with this population estimate, it is notable that all four of these cases occurred on icotrokinra treatment and serious GI events are not commonly reported in clinical trials in psoriasis patients.

In summary, there was one death attributed to upper gastrointestinal bleeding reported in the placebo control portion of the clinical studies. One additional death related to upper gastrointestinal bleed occurred in the extension period, and one SAE of acute gastric ulcer perforation with peritonitis in the extension period, and one SAE of lower

> gastrointestinal bleeding (rectal hemorrhage) was reported in the 120-day safety update.
>
> Given icotrokinra is a new molecular entity with mechanism of action through IL-23 receptor inhibition and differing mode of administration (oral), and the severity and imbalance of these events in administration of icotrokinra, the recommendation by the primary review team is to list the cases in Section 6 of the Prescribing Information as rare and serious events observed in the Phase 3 clinical trials.

A consult addendum by the Division of Gastroenterology was filed in DAARTs on March 12, 2026 at which time the Division of Gastroenterology concluded:

> There remains a significant amount of uncertainty regarding the relatedness of serious GI events to icotrokinra use. The additional data provided by the Applicant does not indicate the presence of a safety signal for serious GI bleeding with icotrokinra use across the psoriasis development program and the Applicant reports that the rates of serious GI bleeding and ulceration in the icotrokinra program are consistent with that expected in the psoriasis studies and registries (although there is some variation in reported rates in the literature). We also acknowledge the presence of multiple confounding factors in the four cases of serious GI events (i.e., upper GI bleeding, nonspecific hematemesis, 2 rectal hemorrhage, and gastric ulcer perforation), the clinical heterogeneity of the events (e.g., types of events, duration of therapy with icotrokinra), and the lack of a known pharmacologic mechanism associated with icotrokinra or other IL-23R antagonists.
>
> However, given the severity of the events (including two fatalities), the lack of data to better inform the potential risk(s) conferred by icotrokinra given that it is the first oral drug in class, as well as the uncertainty as to whether icotrokinra may increase the propensity for gastrointestinal irritation or bleeding in patients with underlying risks for bleeding or ulcers, it would be reasonable to include the events descriptively in Section 6 of the USPI. We recommend noting in the label that the cases were confounded and the subjects had underlying reasons for bleeding or ulcer perforation. In addition, we recommend noting in the label that a causal association between icotrokinra and these reactions has not been established. Alternatively, given that the rate of GI bleeding identified is lower than the expected rate in the general population, the presence of multiple confounding factors, and the clinical heterogeneity (e.g., types of events, duration of therapy with icotrokinra) in the four cases of serious GI events (i.e., upper GI variceal bleeding, nonspecific hematemesis, rectal hemorrhage, and gastric perforation), it would be reasonable not to describe the GI events in the label at this time.
>
> Postmarketing surveillance appears reasonable to further assess this unexpected potential risk.
>
> We also agree with the Applicant's proposal to implement enhanced pharmacovigilance

monitoring of serious GI adverse events including GI bleeding, ulceration, and perforation, and to establish an external, blinded adjudication committee to systematically review potential serious events.

Correction to DG's original consult memo:
DG would like to make a correction to our original response to Question 1 in the "DG Consult Memo," dated December 26, 2025, as noted by the changes in text identified in bold and strikeout shown below:

Question 1: Is this observation within the expected rate of fatal or serious upper GI bleed in this study population size, and specifically are there any concerns with 2 deaths and 1 SAE all occurring on active drug vs no cases on placebo?

Death from upper GI bleeding has been reported in the literature to occur with an annual incidence of approximately 80 to 150 per 100,000 population, with an estimated mortality rate of 2% to 10% (Stanley, 2019). Based on the pooled safety population of 1864 subjects across the four clinical trials of the phase 3 program in patients with psoriasis (1296 subjects who received icotrokinra and 568 subjects who received placebo), the two fatalities that were attributed to upper GI bleeding and the SAE of acute perforated ulcer with peritonitis represented 2/1864 (0.11%) subjects and 1/1864 (0.05%) subject, respectively. Therefore, the rate of GI bleeding identified in the icotrokinra PsO development program is lower than the expected rate in the general population. ~~of the same size; however, the rate of fatal GI bleeding exceeds the expected rate in the general population of the same size.~~

Refer to Section 8.2.4 Safety Results, Subsection Adverse Events of Special Interests, Subsection Gastrointestinal related events for assessment and recommendations by the primary clinical team.

Infections

As discussed, the mechanism of action of icotrokinra which involved inhibition of the IL-23 receptor and downstream effects on both cytokine and cellular immunity, icotrokinra may predispose to infection or influence the severity of an acquire infection.

In the pooled Phase 3 trials through Week 16, the number of reports of serious infections was similar in icotrokinra (0.1%) compared to placebo (0.3%). Serious infections (SAEs) reported for icotrokinra for this period include bacterial gastroenteritis and exacerbation of COPD (infective). The overall rate of infections and infestations (SOC), treatment-emergent adverse events was similar for icotrokinra (23.9%) versus placebo (26.0%).

There was adverse event of fungal laryngitis reported in a 42-year-old female, but there was significant confounding including prior illness and prior treatment with steroids. This event

resulted in discontinuation. The confounders limit ability to determine causality of study drug in this case and attribution of study drug cannot be ruled out.

Analysis of serious infections in the open-label extension did not show an increased risk for serious infections through the safety cut-off date. EAIRs did not indicate an increased risk over time. The data submitted for Phase 3 do not show a specific risk of serious infections resulting from administration of icotrokinra over time, however given the mechanism of action for IL-23 inhibition and potential risk of infection as well as label Warnings and Precautions for other IL-23 inhibitors, risk language for infection will be recommended for the label.

Table 64. Adverse Events of Special Interest Assessment of Serious Infections, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Serious Infections Assessment	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
AE grouping related to AESI	5/541.2 (0.7)	1/369.9 (0.2)	7/928.7 (0.7)	8/1298.7 (0.6)
Infective exacerbation of chronic obstructive airways disease	2/541.8 (0.2)	0/370.0	3/929.6 (0.3)	3/1299.6 (0.3)
Pneumonia	3/541.7 (0.4)	0/370.0	3/930.2 (0.3)	3/1300.2 (0.2)
Diverticulitis	1/541.5 (0.2)	1/369.9 (0.2)	1/930.0 (0.1)	2/1299.9 (0.1)
Gastroenteritis bacterial	0/541.8 (0.0)	0/370.0	1/930.0 (0.1)	1/1300.0 (0.1)
Maximum severity				
Death	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Life-threatening	2/541.8 (0.3)	0/370.0	3/929.7 (0.3)	3/1299.6 (0.3)
Severe	1/541.7 (0.2)	0/370.0	2/929.9 (0.2)	2/1299.9 (0.1)
Moderate	2/541.4 (0.3)	1/369.9 (0.2)	2/929.9 (0.2)	3/1299.8 (0.2)
Mild	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Serious	5/541.2 (0.7)	1/369.9 (0.2)	7/928.7 (0.7)	8/1298.7 (0.6)
Deaths	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Resulting in treatment discontinuation	1/541.8 (0.1)	1/369.9 (0.2)	1/930.3 (0.1)	2/1300.3 (0.2)
Relatedness	1/541.7 (0.2)	1/369.9 (0.2)	1/930.2 (0.1)	2/1300.2 (0.1)
Number of subjects with adverse events with end dates on or before treatment end dates	3/1.6 (NA)	0/0.3 (NA)	5/3.4 (159.6)	5/3.7 (129.4)
Duration, days (from AE start date to AE end date)				
Mean (SD)	17.3 (11.2)	NA	22.0 (21.0)	22.0 (21.0)
Median (min, max)	13.0 (9.0, 30.0)	NA	13.0 (3.0, 55.0)	13.0 (3.0, 55.0)
Interquartile range	11.0 to 21.5	NA	9.0 to 30.0	9.0 to 30.0
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/2.2 (NA)	0/0.3 (NA)	1/5.0 (19.7)	1/5.3 (19.7)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Serious Infections Assessment	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	1/2.2 (NA)	1/0.2 (NA)	1/4.9 (19.9)	2/5.2 (35.6)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	18.0 (NA)	62.0 (NA)	18.0 (NA)	40.0 (31.1)
Median (min, max)	18.0 (18.0, 18.0)	62.0 (62.0, 62.0)	18.0 (18.0, 18.0)	40.0 (18.0, 62.0)
Interquartile range	18.0 to 18.0	62.0 to 62.0	18.0 to 18.0	29.0 to 51.0

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Severity scale as defined by the protocol.
Relatedness is determined by investigator.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk); SD, standard deviation

Malignancies

Review of the 16-week placebo-controlled period revealed an imbalance for malignancy in subjects receiving icotrokinra compared to placebo. However, individual review of serious cases indicated that many subjects had pre-existing conditions for the malignancy or clinical signs that were missed diagnoses for malignancy identified on study. Refer to Section 8.2.4 for details of these serious cases. Analysis of malignancy events in the open label extension did not show an increased risk for malignancy through the safety cut-off date. EAIRs did not indicate an increased risk over time.

8.2.5.1. Malignancy

Table 65. Adverse Events of Special Interest Assessment of Malignancy, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Malignancy Assessment	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
AE grouping related to AESI	2/541.6 (0.3)	1/370.0 (0.2)	8/929.6 (0.9)	9/1299.5 (0.7)
Keratoacanthoma	0/541.8 (0.0)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Breast cancer	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of skin	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Metastases to liver	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Pancreatic carcinoma	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Malignant melanoma in situ	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.2 (0.1)
Chronic lymphocytic leukemia	1/541.8 (0.2)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Squamous cell carcinoma of lung	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Adenocarcinoma of colon	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Prostate cancer	0/541.8 (0.0)	0/370.0	1/930.2 (0.1)	1/1300.2 (0.1)
Maximum severity				
Death	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Life-threatening	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Severe	0/541.8 (0.0)	0/370.0	2/930.3 (0.2)	2/1300.2 (0.2)
Moderate	1/541.6 (0.2)	0/370.0	1/930.1 (0.1)	1/1300.1 (0.1)
Mild	1/541.8 (0.2)	0/370.0	4/929.9 (0.4)	4/1299.9 (0.3)
Serious	0/541.8 (0.0)	1/370.0 (0.2)	5/930.1 (0.5)	6/1300.0 (0.5)
Deaths	0/541.8 (0.0)	1/370.0 (0.2)	0/930.3 (0.0)	1/1300.3 (0.1)
Resulting in treatment discontinuation	2/541.6 (0.3)	1/370.0 (0.2)	8/929.6 (0.9)	9/1299.5 (0.7)
Relatedness	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Number of subjects with adverse events with end dates on or before treatment end dates	1/0.6 (NA)	0/0.7 (NA)	3/2.1 (131.1)	3/2.8 (131.1)
Duration, days (from AE start date to AE end date)				
Mean (SD)	32.0 (NA)	NA	38.0 (14.9)	38.0 (14.9)
Median (min, max)	32.0 (32.0, 32.0)	NA	32.0 (27.0, 55.0)	32.0 (27.0, 55.0)
Interquartile range	32.0 to 32.0	NA	29.5 to 43.5	29.5 to 43.5
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/0.7 (NA)	0/0.7 (NA)	3/2.4 (142.9)	3/3.1 (92.4)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Malignancy Assessment	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/0.8 (NA)	1/0.7 (NA)	2/2.6 (91.7)	3/3.3 (70.6)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	NA	40.0 (NA)	54.5 (41.7)	49.7 (30.7)
Median (min, max)	NA	40.0 (40.0, 40.0)	54.5 (25.0, 84.0)	40.0 (25.0, 84.0)
Interquartile range	NA	40.0 to 40.0	39.8 to 69.2	32.5 to 62.0

Source: adae.xpt; software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Severity scale as defined by the protocol.
Relatedness is determined by investigator.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; EAIR, exposure-adjusted incidence rate (per 100 person-years); MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk); SD, standard deviation

Potential Hy's Law Events and Hepatic AEs Leading to Discontinuation

Potential Hy's Law events and hepatic AEs that led to discontinuation are discussed in Section 8.2.4. There were 2 events in subjects receiving icotrokinra through the 16-week placebo control period, however both events were not confirmed as Hy's Law events and had significant confounding factors and were not attributed to icotrokinra administration. There were no additional events reported through the safety reporting period. There does not seem to be a relationship between icotrokinra administration and risk of elevated liver function tests.

Active Tuberculosis/LTBI

There were no cases of active TB reported through the safety cut-off date. Of 173 subjects identified to have LTBI at screening, 50 (28.9%) completed LTBI prior to screening, 92 (53.2%) received concomitant LTBI treatment, and 31 (17.9%) received no LTBI treatment. There were no cases of active TB reported during icotrokinra administration, and no cases of active TB

converted from LTBI reported through the safety cut off. Tuberculosis rates are increasing worldwide, and the potential for reactivation of latent TB has significant risk of morbidity and mortality for patients with psoriasis. The data submitted by the Applicant is insufficient at this time to waive standard language used for immunomodulatory biologics, including IL-23 inhibitors, for active TB and LTBI screening and treatment prior to initiation of icotrokinra. Standard language is therefore recommended for inclusion in the Warnings & Precautions section of the label for testing for active and/or latent tuberculosis and treatment prior to initiating icotrokinra.

MACE Events

The overlap of CV risk factors in the psoriasis population, underlying inflammation and CV risk, and the modification of the inflammatory cytokine cascade via IL-23 inhibition warrants examination of MACE events in the icotrokinra Phase 3 program. An adjudication committee reviewed and determined positively adjudicated MACE, extended MACE, and other cardiovascular events. MACE events include cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Extended MACE events include MACE events, hospitalization for unstable angina, and coronary revascularization.

In the 16-week placebo controlled period, there was an imbalance in adjudicate events with more events occurring on the icotrokinra arm. Review of the individual cases (see Section 8.2.4) demonstrated significant confounding factors and there was no clear attribution of cases to icotrokinra. Evaluation of EAIRs through the safety reporting period did not demonstrate an increased risk of icotrokinra for these events.

MACE

Table 66. Adverse Events of Special Interest Assessment of MACE, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

MACE Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
AE grouping related to AESI (positively adjudicated MACE)	3 (0.2)	0	0.2 (0.5, 0.7)
Myocardial infarction			
Acute myocardial infarction	1 (0.1)	0	0.1 (0.6, 0.5)
Coronary artery disease	1 (0.1)	0	0.1 (0.6, 0.5)
Hypertension	1 (0.1)	0	0.1 (0.6, 0.5)
Stroke			
Dysarthria	1 (0.1)	0	0.1 (0.6, 0.5)
Epidural hemorrhage	1 (0.1)	0	0.1 (0.6, 0.5)
Extradural hematoma	1 (0.1)	0	0.1 (0.6, 0.5)
Paresis	1 (0.1)	0	0.1 (0.6, 0.5)
Subarachnoid hemorrhage	1 (0.1)	0	0.1 (0.6, 0.5)
Syncope	1 (0.1)	0	0.1 (0.6, 0.5)
Cardiovascular death			
Myocardial infarction	1 (0.1)	0	0.1 (0.6, 0.4)

MACE Assessment	Pooled Icotrokinra N=1296 n (Adjusted %)	Pooled Placebo N=568 n (Adjusted %)	Risk Difference % (95% CI)
Maximum severity			
Death	1 (0.1)	0	0.1 (0.6, 0.4)
Life-threatening	1 (0.1)	0	0.1 (0.6, 0.5)
Severe	1 (0.1)	0	0.1 (0.6, 0.5)
Moderate	0	0	0.0 (0.7, 0.3)
Mild	0	0	0.0 (0.7, 0.3)
Serious	3 (0.2)	0	0.2 (0.5, 0.7)
Deaths	1 (0.1)	0	0.1 (0.6, 0.4)
Resulting in treatment discontinuation	2 (0.1)	0	0.1 (0.5, 0.5)
Relatedness	0	0	0.0 (0.7, 0.3)
Number of subjects with adverse events with end dates on or before treatment end dates	1/3 (NA)	0/0 (NA)	NA
Duration, days (from AE start date to AE end date)			
Mean (SD)	2.0 (NA)	NA	NA
Median (min, max)	2.0 (2.0, 2.0)	NA	NA
Interquartile range	2.0 to 2.0	NA	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/3 (NA)	0/0 (NA)	NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	1/3 (NA)	0/0 (NA)	NA
Duration, days (from treatment end date to AE end date)			
Mean (SD)	15.0 (NA)	NA	NA
Median (min, max)	15.0 (15.0, 15.0)	NA	NA
Interquartile range	15.0 to 15.0	NA	NA

Source: adae.xpt; software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Duration is 16 weeks.
Severity scale as defined by the protocol.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; CI, confidence interval; MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; SD, standard deviation

8.2.5.2. MACE

Table 67. Adverse Events of Special Interest Assessment of MACE, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
MACE Assessment	Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)	Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)	Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)	Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)
AE grouping related to AESI (positively adjudicated MACE)	0/541.8 (0.0)	0/370.0	3/930.4 (0.3)	3/1300.3 (0.2)
Myocardial infarction				
Acute myocardial infarction	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Coronary artery disease	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Hypertension	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Stroke				
Dysarthria	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Epidural hemorrhage	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Extradural hematoma	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Paresis	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Subarachnoid hemorrhage	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Syncope	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Cardiovascular death				
Myocardial infarction	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Maximum severity				
Death	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Life-threatening	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Severe	0/541.8 (0.0)	0/370.0	1/930.4 (0.1)	1/1300.3 (0.1)
Moderate	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Mild	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Serious	0/541.8 (0.0)	0/370.0	3/930.4 (0.3)	3/1300.3 (0.2)
Deaths	0/541.8 (0.0)	0/370.0	1/930.3 (0.1)	1/1300.3 (0.1)
Resulting in treatment discontinuation	0/541.8 (0.0)	0/370.0	2/930.3 (0.2)	2/1300.3 (0.2)
Relatedness	0/541.8 (0.0)	0/370.0	0/930.3 (0.0)	0/1300.3 (0.0)
Number of subjects with adverse events with end dates on or before treatment end dates	0/0.0 (NA)	0/0.0 (NA)	1/0.3 (380.5)	1/0.3 (380.5)
Duration, days (from AE start date to AE end date)				
Mean (SD)	NA	NA	2.0 (NA)	2.0 (NA)
Median (min, max)	NA	NA	2.0 (2.0, 2.0)	2.0 (2.0, 2.0)
Interquartile range	NA	NA	2.0 to 2.0	2.0 to 2.0
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/0.0 (NA)	0/0.0 (NA)	0/0.3 (0.0)	0/0.3 (0.0)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
MACE Assessment	**Pooled Icotrokinra to Icotrokinra PY=541.8 N=1240 n/py (Adjusted EAIR)**	**Pooled Placebo to Icotrokinra PY=370 N=520 n/py (Adjusted EAIR)**	**Pooled Icotrokinra to Icotrokinra PY=930.3 N=1296 n/py (Adjusted EAIR)**	**Pooled Total Icotrokinra PY=1300.3 N=1816 n/py (Adjusted EAIR)**
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	0/0.0 (NA)	0/0.0 (NA)	1/0.3 (376.5)	1/0.3 (376.5)
Duration, days (from treatment end date to AE end date)				
Mean (SD)	NA	NA	15.0 (NA)	15.0 (NA)
Median (min, max)	NA	NA	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)
Interquartile range	NA	NA	15.0 to 15.0	15.0 to 15.0

Source: adae.xpt; Software: R
Treatment-emergent AE defined as AEs that occurred after the start of initial administration of study intervention and/or AEs that were present at baseline but worsened in severity after the start of initial study intervention administration through up to 28 days after the last dose or treatment discontinuation.
MedDRA version 27.0.
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Adjusted EAIR based on Cochran-Mantel-Haenszel (CMH) weighted pooling.
Person-years calculated as the exposure time until the initial occurrence of the event for subjects who experienced an event, or the end of treatment for subjects who did not, among subjects as risk at the beginning of the study.
Severity scale as defined by the protocol.
Relatedness is determined by investigator.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; EAIR, exposure-adjusted incidence rate (per 100 person-years); MACE, major adverse cardiovascular events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; PY, person-years (total exposure); py, person-years (at risk); SD, standard deviation

Anaphylaxis and Hypersensitivity Reactions

Events that were categorized as hypersensitivity were primarily in the SOC Skin and Subcutaneous disorders and were events such as eczema and dermatitis. No events were categorized as serious or led to interruption of study drug. Most events were mild to moderate in severity.

Through the 16 week placebo controlled period the proportion of subjects with hypersensitivity reactions were similar in the icotrokinra (2.2%) and placebo (1.3%) groups. Events that were reported in more than one subject in the icotrokinra group included allergic rhinitis, eczema, urticaria, dermatitis acneiform, dermatitis allergic, and perioral dermatitis. Similar events were reported in the placebo group.

In the 24-week active controlled period rates of events in subjects with hypersensitivity reactions were icotrokinra (2.8%) and deucravacitinib (4.1%). Similar to the placebo control period, most events were in the SOC Skin and Subcutaneous disorders, and reported events were similar to the placebo control period. Through the safety cut-off date, all events that met the criteria for hypersensitivity in subjects who received icotrokinra were mild or moderate in severity.

There were no anaphylactic reactions related to icotrokinra for the 16-week placebo control period, the 24 week active control period, or the period through the safety cut-off date, with the exception of one reported case of anaphylaxis in a subject who had received icotrokinra, discontinued icotrokinra, and had an anaphylactic reaction to cephalexin 44 days after discontinuation of icotrokinra.

Depression, Suicidal Ideation and Behavior

Suicidal ideation and behavior were identified by C-SSR assessments and AEs identified by the investigator in the eCRF. The PHQ9 instruments was used to assess increase risk of depression. History of depression (6.8%) was prevalent at baseline in the study population. Rates of events were low. Through the safety cut-off date, suicidal ideation was reported in 3 subjects who received icotrokinra. Suicidal ideation was reported in 1 subject who received icotrokinra in the placebo control period. There were no episodes of suicidal behavior in either icotrokinra or placebo groups. In the 24 week active control period, suicidal ideation was reported in 1 subject in the icotrokinra and 1 subject in deucravacitinib treatment groups respectively, and no episodes of suicidal behavior in either group. No completed suicides were reported in the program. Depression event rates were low, less than 0.2% for either treatment group for either the 16 week placebo control period or the 24 week active control period. Shifts in PHQ-9 scores did not indicate an increase in depression in any treatment period. The data does not suggest an increased risk of suicidal ideation, suicidal behavior, or depression is associated with administration of icotrokinra.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Suicidal ideation and behavior were identified by the C-SSRS result. Additionally, investigators were to identify any related terms in the CRF. Through the 16-week placebo controlled period, suicidal ideation was reported in 0.1% (1 subject) who received icotrokinra. No suicidal behavior events were reported. Through the safety cutoff date, 2 additional subjects reported suicidal ideation. The number of subjects with suicidal ideation or behavior was low with associated low EAIRs.

Shifts from baseline in PHQ-9 scores were low and did not suggest that icotrokinra worsens depression in this subject group. There was no evidence via PHQ-9 assessment that icotrokinra increases the risk of depression in subjects with psoriasis.

8.2.7. Safety Analyses by Demographic Subgroups

Safety in the 16 week double blind placebo controlled period was examined by sex, age group, and race. Overall rates of AEs were similar between icotrokinra (49.0%) and placebo (52.0%). Rates of AEs were slightly higher in females compared to males who received icotrokinra but were similar to rates in the placebo group. Subjects who were less than 18 years of age had lower rates of AEs on icotrokinra treatment (45.4%) compared to placebo (72.2%). In the ≥18 to <45 years and ≥45 to <65 years rates of AEs were similar between icotrokinra and placebo. In the age group ≥65 years, AE rates were slightly higher than placebo but comparable to <65 year age group. There were no apparent differences by race or BMI, although some groups by race had small numbers of subject. Overall, there do not appear to be differences in adverse event rates by age, sex, BMI or race. This was observed for the 16 week double blind as well as the extension period with or without icotrokinra switch (icotrokinra to icotrokinra or placebo to icotrokinra).

Subgroup Analyses by Baseline Characteristics

Table 68. Overview of Adverse Events by Demographic Subgroups, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004, Double-Blind Placebo-Controlled Period

Characteristic	Pooled Icotrokinra N=1296 n/N_S (Adjusted %)	Pooled Placebo N=568 n/N_S (Adjusted %)	Risk Difference % (95% CI)
Any AE	636/1296 (49.0)	295/568 (52.0)	2.9 (7.9, 2.0)
Sex			
Female	235/428 (55.0)	113/190 (59.6)	4.6 (13.0, 3.9)
Male	401/868 (46.2)	182/378 (48.1)	1.8 (7.9, 4.2)
Age group 1, years			
<18	22/47 (45.4)	18/25 (72.2)	-26.8 (46.6, 2.5) *
≥18 to <45	275/605 (46.0)	134/247 (54.4)	8.4 (15.8, 0.9) *
≥45 to <65	277/519 (53.0)	119/238 (50.1)	2.9 (4.8, 10.6)
≥65	62/125 (48.3)	24/58 (41.7)	6.6 (9.0, 21.7)
Age group 2, years			
<45	297/652 (46.0)	152/272 (56.0)	-10.0 (17.0, 2.8) *
≥45 to <65	277/519 (53.0)	119/238 (50.1)	2.9 (4.8, 10.6)
≥65	62/125 (48.3)	24/58 (41.7)	6.6 (9.0, 21.7)
Age group 3, years			
<65	574/1171 (49.1)	271/510 (53.2)	4.1 (9.3, 1.1)
≥65	62/125 (48.3)	24/58 (41.7)	6.6 (9.0, 21.7)
Age group 4, years			
<75	627/1274 (49.2)	293/561 (52.3)	3.1 (8.1, 1.9)
≥75	9/22 (47.5)	2/7 (28.0)	19.4 (22.6, 48.4)
Age group 5, years			
≥12 to <18	22/47 (45.4)	18/25 (72.2)	-26.8 (46.6, 2.5) *
≥18	614/1249 (49.1)	277/543 (51.1)	1.9 (7.0, 3.1)
Age group 6, years			
<18	22/47 (45.4)	18/25 (72.2)	-26.8 (46.6, 2.5) *
≥18 to <65	552/1124 (49.2)	253/485 (52.2)	3.0 (8.4, 2.3)
≥65	62/125 (48.3)	24/58 (41.7)	6.6 (9.0, 21.7)

Characteristic	Pooled Icotrokinra N=1296 n/N_S (Adjusted %)	Pooled Placebo N=568 n/N_S (Adjusted %)	Risk Difference % (95% CI)
Race			
American Indian or Alaska Native	1/2 (0)	1/2 (100)	-100.0 (100.0, 58.7)
Asian	133/254 (52.5)	64/126 (50.6)	1.9 (8.5, 12.3)
Black or African American	4/21 (26.6)	4/7 (52.2)	-25.6 (62.4, 9.5)
Native Hawaiian or other Pacific Islander	4/6 (NA)	0/0 (NA)	NA
White	485/994 (48.6)	226/429 (52.8)	4.2 (9.8, 1.5)
Multiple	0/3 (NA)	0/0 (NA)	NA
Not reported	4/10 (43.2)	0/3 (0)	43.2 (30.0, 78.0)
Unknown	5/6 (100)	0/1 (0)	100.0 (12.3, 100.0)
Ethnicity			
Hispanic or Latino	85/177 (48.0)	33/69 (47.7)	0.3 (13.2, 13.7)
Not Hispanic or Latino	542/1098 (49.2)	261/493 (53.1)	3.8 (9.2, 1.5)
Not reported	5/13 (38.8)	1/5 (14.9)	23.9 (30.6, 59.1)
Unknown	4/8 (66.7)	0/1 (0)	66.7 (30.7, 91.2)
Is in United States			
United States	91/228 (40.0)	46/96 (48.1)	8.2 (19.9, 3.5)
Non-United States	545/1068 (51.1)	249/472 (52.7)	1.7 (7.1, 3.8)
Baseline BMI group, kg/m^2			
Normal (<25)	151/336 (45.9)	80/143 (56.1)	-10.2 (19.8, 0.3) *
Overweight (≥25 to <30)	215/443 (48.4)	100/199 (50.0)	1.6 (10.0, 6.8)
Obese (≥30)	267/511 (52.0)	113/223 (50.9)	1.1 (6.7, 9.0)
Missing	3/6 (44.4)	2/3 (74.1)	-29.6 (73.8, 40.8)

Source: adae.xpt; software: R
Duration is 16 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Confidence intervals for risk difference estimated with score-based method.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; BMI, body mass index; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; N_s, total number of subjects for each specific subgroup

Table 69. Overview of Adverse Events by Demographic Subgroups, Safety Population, Pooled Trials PSO3001, PSO3002, PSO3003, and PSO3004

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Characteristic	Pooled Icotrokinra to Icotrokinra N=1240 n/N_s (Adjusted %)	Pooled Placebo to Icotrokinra N=520 n/N_s (Adjusted %)	Pooled Icotrokinra to Icotrokinra N=1296 n/N_s (Adjusted %)	Pooled Total Icotrokinra N=1816 n/N_s (Adjusted %)
Any AE	819/1240 (66.1)	317/520 (60.8)	849/1296 (65.5)	1166/1816 (64.2)
Sex				
Female	293/413 (71.7)	117/176 (66.2)	302/428 (70.7)	419/604 (69.2)
Male	526/827 (63.4)	200/344 (58.0)	547/868 (63.0)	747/1212 (61.7)
Age group 1, years				
<18	34/47 (72.2)	16/25 (63.9)	34/47 (72.3)	50/72 (69.5)
≥18 to <45	359/580 (62.7)	141/227 (62.0)	371/605 (61.4)	512/832 (61.4)
≥45 to <65	348/493 (70.1)	129/213 (60.3)	362/519 (69.7)	491/732 (67.1)
≥65	78/120 (63.1)	31/55 (56.4)	82/125 (65.3)	113/180 (63.2)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Characteristic	**Pooled Icotrokinra to Icotrokinra N=1240 n/N_s (Adjusted %)**	**Pooled Placebo to Icotrokinra N=520 n/N_s (Adjusted %)**	**Pooled Icotrokinra to Icotrokinra N=1296 n/N_s (Adjusted %)**	**Pooled Total Icotrokinra N=1816 n/N_s (Adjusted %)**
Age group 2, years				
<45	393/627 (63.4)	157/252 (62.2)	405/652 (62.2)	562/904 (62.0)
≥45 to <65	348/493 (70.1)	129/213 (60.3)	362/519 (69.7)	491/732 (67.1)
≥65	78/120 (63.1)	31/55 (56.4)	82/125 (65.3)	113/180 (63.2)
Age group 3, years				
<65	741/1120 (66.3)	286/465 (61.3)	767/1171 (65.5)	1053/1636 (64.3)
≥65	78/120 (63.1)	31/55 (56.4)	82/125 (65.3)	113/180 (63.2)
Age group 4, years				
<75	808/1220 (66.3)	313/514 (60.7)	837/1274 (65.7)	1150/1788 (64.3)
≥75	11/20 (52.7)	4/6 (65.6)	12/22 (54.5)	16/28 (57.1)
Age group 5, years				
≥12 to <18	34/47 (72.2)	16/25 (63.9)	34/47 (72.3)	50/72 (69.5)
≥18	785/1193 (65.8)	301/495 (60.6)	815/1249 (65.3)	1116/1744 (64.0)
Age group 6, years				
<18	34/47 (72.2)	16/25 (63.9)	34/47 (72.3)	50/72 (69.5)
≥18 to <65	707/1073 (66.1)	270/440 (61.2)	733/1124 (65.2)	1003/1564 (64.1)
≥65	78/120 (63.1)	31/55 (56.4)	82/125 (65.3)	113/180 (63.2)
Race				
American Indian or Alaska Native	1/2 (0)	1/2 (0)	1/2 (42.9)	2/4 (42.9)
Asian	168/244 (68.9)	76/117 (64.8)	173/254 (68.1)	249/371 (67.1)
Black or African American	9/18 (54.1)	3/5 (55.0)	10/21 (48.3)	13/26 (48.9)
Native Hawaiian or other Pacific Islander	4/6 (NA)	0/0 (NA)	4/6 (66.7)	4/6 (66.7)
White	627/953 (65.7)	236/393 (59.9)	650/994 (65.4)	886/1387 (63.9)
Multiple	0/2 (NA)	0/0 (NA)	0/3 (0)	0/3 (0)
Not reported	5/9 (37.5)	1/2 (62.5)	6/10 (59.6)	7/12 (59.3)
Unknown	5/6 (100)	0/1 (0)	5/6 (84.4)	5/7 (71.1)
Ethnicity				
Hispanic or Latino	102/169 (60.9)	37/60 (61.5)	108/177 (61.1)	145/237 (61.1)
Not Hispanic or Latino	708/1052 (67.3)	276/454 (60.6)	730/1098 (66.5)	1006/1552 (64.8)
Not reported	5/11 (38.3)	4/5 (73.8)	7/13 (53.6)	11/18 (60.4)
Unknown	4/8 (66.7)	0/1 (0)	4/8 (50.9)	4/9 (43.6)
Is in United States				
United States	110/211 (52.5)	45/84 (53.3)	117/228 (51.4)	162/312 (51.8)
Non-United States	709/1029 (69.0)	272/436 (62.2)	732/1068 (68.5)	1004/1504 (66.7)

	Open-Label Period Week 16 to Data Cut-Off		Full Treatment Period Week 0 To Data Cut-Off	
Characteristic	Pooled Icotrokinra to Icotrokinra N=1240 n/N_s (Adjusted %)	Pooled Placebo to Icotrokinra N=520 n/N_s (Adjusted %)	Pooled Icotrokinra to Icotrokinra N=1296 n/N_s (Adjusted %)	Pooled Total Icotrokinra N=1816 n/N_s (Adjusted %)
Baseline BMI group, kg/m^2				
Normal (<25)	208/323 (65.2)	83/127 (65.2)	214/336 (63.8)	297/463 (64.0)
Overweight (≥25 to <30)	285/430 (65.8)	111/182 (60.7)	292/443 (65.8)	403/625 (64.5)
Obese (≥30)	323/482 (67.3)	122/210 (58.0)	339/511 (66.4)	461/721 (63.9)
Missing	3/5 (100)	1/1 (100)	4/6 (68.4)	5/7 (68.4)

Source: adae.xpt; software: R
Data cut-off is Week 24 for adults randomized to icotrokinra in Trial PSO3001 (who were evaluated for drug response at that point), and the safety data cut-off date or Week 156 for all other subjects.
Median duration of treatment is 44 weeks.
Pooled percentages based on Cochran-Mantel-Haenszel (CMH) adjusted proportions.
Abbreviations: AE, adverse event; BMI, body mass index; N, number of subjects in treatment arm; n, number of subjects with at least one event; NA, not applicable; N_s, total number of subjects for each specific subgroup

8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

For any product that produces immunosuppression and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

In a 6-month transgenic rasH2 mouse study, no drug-related tumors were observed at oral doses of icotrokinra up to 500 mg/kg/day (76 times the MRHD based on AUC comparison). In a 2-year rat carcinogenicity study, no drug-related tumors were observed at oral doses of 20 mg/kg/day (16 times the MRHD based on AUC comparison).

Icotrokinra was not genotoxic in an in vitro bacterial reverse mutation assay (the Ames test), an *in vitro* human lymphocyte chromosomal aberration assay, or an in vivo rat micronucleus and Comet assays.

Refer to Section 5.5.3 for a discussion of the carcinogenicity risk from Pharmacology/Toxicology perspective.

Data from the nonclinical and clinical development programs does not support the conclusion that icotrokinra is associated with increased risk of carcinogenesis. There was an imbalance of malignancies in the 16-week placebo controlled period, however, review of these cases indicate confounding factors in a number of the cases suggesting that the malignancy was present and

undiagnosed at the time of randomization. The imbalance in malignancies also demonstrated a short time period of icotrokinra administration, which makes icotrokinra contribution less likely given the long development time for most malignancies. Analysis of malignancy events in the open label extension did not show an increased risk for malignancy through the safety cut-off date. EAIRs did not indicate an increased risk over time.

Human Reproduction and Pregnancy

In male rats, icotrokinra had no adverse effect on mating, fertility or early embryonic development of their offspring at oral doses up to 20 mg/kg/day (114 times the MRHD based on AUC comparison).

In female rats, icotrokinra had no adverse effect on estrous cyclicity, mating, fertility, or early embryonic parameters at oral doses up to 70 mg/kg/day (335 times the MRHD based on AUC comparison).

The protocols for human clinical trials excluded pregnant females and required use of highly effective contraception by females with reproductive potential, as well as males with partners who are of reproductive potential while in the study. All female subjects promptly discontinued the study medication at the time of discovery of a positive pregnancy test.

The Applicant identified 5 maternal pregnancies and 6 paternal pregnancies in the Phase 3 program with exposure to icotrokinra.

Maternal pregnancy outcomes:

- 2/5 cases reported outcome as live healthy delivery.
- 1/5 cases reported elective abortion with possible embryo dysplasia
- 2/5 cases did not report pregnancy outcome

Paternal pregnancy outcomes:

- 2/8 cases reported as a live healthy delivery
- 1/8 reported spontaneous abortion randomized to icotrokinra
- 1/8 spontaneous abortion (initial randomization placebo; event 2 weeks after switch to icotrokinra)
- 1/8 elective/induced abortion (initial randomization to deucravacitinib and event 4.5 months after switch to icotrokinra
- 3/8 did not report outcomes

Pregnancy and Lactation

The animal reproduction studies did not identify a specific safety signal indicating an increased risk for embryo-fetal toxicity at clinical exposures. Animal reproduction data do not suggest a serious risk of developmental toxicity during pregnancy. Human data on icotrokinra exposure during pregnancy are insufficient to allow an assessment of a drug-associated risk of major

birth defects, miscarriage, or other adverse maternal or fetal outcomes. However, animal findings do not always predict findings in humans, therefore this is a need to collect data in humans exposed to icotrokinra in pregnancy. To obtain safety information related to the use of icotrokinra in pregnancy, DPMH recommends issuing a postmarketing requirement (PMR) for a descriptive pregnancy safety study. Together with the DPSS interim reports, DPMH recommends that the Applicant submit reports of icotrokinra utilization rates in females of reproductive potential (females aged 15 to 50 years) calculated yearly and cumulatively from the time of initial approval.

There are no available data on the presence of icotrokinra in human breast milk, the effects of icotrokinra on the breastfed infant or the effects on milk production. In the PPND study, the presence of icotrokinra in the plasma of newborn pups suggests transfer into rat milk. When a drug is present in animal milk, it is likely the drug will be present in human milk. Based on the lack of available clinical data and the anticipated use of icotrokinra in females of reproductive potential, which includes lactating females, DPMH recommends issuing a postmarketing requirement (PMR) for a clinical lactation study. The data obtained from a clinical lactation study would be helpful in determining the amount of icotrokinra in human breastmilk. If a clinical lactation study demonstrates a clinically important amount of icotrokinra in breast milk, further study to examine systemic exposure in the breastfed infant may be needed. DPMH discussed PMR and labeling recommendations with DDD on 11/18/2025 and there is concurrence on the recommendation.

The following PMRs are recommended (Refer to review by Kerry Shaab, MD dated 16-Dec-2025) by the Division of Pediatrics and Maternal Health:

1. Descriptive Pregnancy Safety Study:
   Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Icotyde (icotrokinra) during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.
2. Lactation Study:
   Perform a lactation study in lactating women who have received icotrokinra to measure concentrations of icotrokinra in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

Pediatrics and Assessment of Effects on Growth

The Applicant did not conduct an assessment of growth in the adolescent population. Approval of icotrokinra for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). Per the Food and Drug Administration Safety and Innovation Act (FDASIA), the Applicant submitted an Agreed Initial Pediatric Study Plan (iPSP) which was agreed with the Agency agreed with the iPSP (Agreement Letter dated 10-March-2023).

In this submission the Applicant requested 1) a waiver for the study of icotrokinra in infants and children <4 years of age with moderate to severe plaque psoriasis; 2) a plan to conduct a clinical study in adolescents 12 to <18 years of age concurrently or within the adult Phase 3 psoriasis study; 3) a deferral for children 4 to <12 years of age with pediatric psoriasis to allow for the safety data from adult and adolescent subjects with psoriasis to be evaluated and risk/benefit in adults and adolescents with psoriasis is established prior to proceeding with this study.

The Division presented the pediatric study plan to the Pediatric Review Committee (PeRC) on 20-January-2026, who agreed with the partial waiver and deferrals as requested. An assessment of the efficacy and safety of icotrokinra for the treatment of moderate to severe plaque psoriasis in pediatric patients 12 years of age and older who also weight at least 40 kg who are candidates for systemic therapy or phototherapy was conducted with the phase 3 trials under this NDA 220149.

The following PREA PMR is recommended with the recommended approval of this NDA 220149:

- Conduct a trial to evaluate the safety and pharmacokinetics of icotrokinra in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate a sufficient number of subjects exposed to icotrokinra at the highest proposed dosage for a minimum of 26 weeks to evaluate for safety and pharmacokinetics of icotrokinra in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no events of overdose reported in the Phase 3 program.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Icotrokinra is not marketed in any jurisdiction. Therefore, postmarketing safety data are not available.

Expectations on Safety in the Postmarket Setting

There are no significant safety concerns at this time that would impact the favorable risk/benefit assessment or require mitigation of risk with administration of icotrokinra in the postmarket setting. However, additional data are needed to characterize the safety profile of the proposed product in special populations (pregnant and lactating females and the pediatric population age ≥ 4 year of age to <12 years of age).

In addition, enhanced collection and reporting of safety data related to potential gastrointestinal adverse events will be needed. Refer to Section 12 of this review for the

postmarketing requirements and commitments.

8.2.11. Integrated Assessment of Safety

The safety profile for icotrokinra was adequately characterized in the drug development program. The primary safety database consisted of subjects from the Phase 3 Trials PSO3001, PSO3002, PSO3003, and PSO3004. All subjects treated with icotrokinra in the pooled safety analysis set received the proposed dose of 200 mg tablet orally administered once daily. 2367 subjects received at least one 200 mg oral dose of icotrokinra with 1849 subjects were treated for 6 months, and 648 received treatment for 1 year.

The review of the safety data did not reveal any contraindications to treatment with icotrokinra, and the Applicant proposed no contraindications for inclusion in Section 4 of product labeling. A total of five deaths occurred in subjects treated with icotrokinra in the 4 Phase 3 studies in the development program and none on placebo or deucravacitinib. Two of the deaths were gastrointestinal related bleeding events. Upon detailed review of the cases, there were multiple confounding factors in each case, however, the causality of icotrokinra could not be ruled out. Given the seriousness of the events and the occurrence of the events in participants exposed to icotrokinra treatment only , these events are recommended for inclusion in Section 6 of the USPI as serious events observed with icotrokinra administration in the Phase 3 program. Two other deaths were cardiovascular related and there were clear aspects of the subject's history that were related to the risk of the cardiovascular event. Psoriasis patients have an increased risk of cardiovascular events related to underlying systemic inflammation related to psoriasis. There was no suggestion of increased risk of CV events over times from examination of EAIR rates for CV events. The fifth death in the program had characteristics that suggested a missed diagnosis of malignancy prior to randomization. Review of reported malignancy events for the program did not suggest a pattern as to type or onset of malignancy. Review of EAIR rates for malignancies did not indicate an increased risk for malignancy subjects receiving icotrokinra over time.

In the pooled safety analysis set from the 16 week placebo controlled period, SAEs occurred in 1.5% of subjects in the icotrokinra group, and 2.1 % of subjects in the placebo group. From week 0 to 24, SAEs occurred in 2.9% of subjects in the icotrokinra group, and 3.2% of subjects in the deucravacitinib group (PSO3002 and PSO3004). Rates of observed SAEs did not increase over time and EAIRS did not demonstrate increased risk of specific observed SAEs over time. SAEs are described in more detail in Section 8.2.4 of this review.

In the pooled safety analysis set, the most common adverse reactions (AR) were headache (4.1%), nausea (1.2%), cough (1.2%), fungal infection (1.1%), and fatigue (1.0%). These ADRs are recommended for inclusion in the USPI Section 6.

As discussed in Section 8.2.9 of this review, through the 120-day safety review cutoff (07/24/2025) there were 13 pregnancies, 5 maternal pregnancies, and 8 partner pregnancies. 2/5 maternal pregnancy cases reported a live healthy delivery, 1/5 cases reported elective

abortion with possible embryo dysplasia, and 2/5 cases did not report pregnancy outcome. Of the paternal partner pregnancies, 2/8 reported a live healthy delivery, 1/8 reported spontaneous abortion (icotrokinra), 1/8 spontaneous abortion (2 weeks after switch to icotrokinra), 1/8 elective abortion (4.5 months after switch from placebo to icotrokinra), and 3/8 did not report outcomes. Because the available data are limited regarding use of icotrokinra in pregnant and lactating women, the Division of Pediatric and Maternal Health (DPMH) recommends a PMR that requires the Applicant to perform pregnancy and lactation studies to assess the safety of icotrokinra in pregnant and lactating women.

The clinical reviewer concludes that the safety data currently available are adequate and the benefit-risk of icotrokinra for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older who also weight at least 40 kg who are candidates for systemic therapy or phototherapy is acceptable. Recommended postmarketing risk management includes labeling (including prescribing information and a Medication Guide); labeling negotiations were ongoing at the time of the writing of this review. The maternal, fetal, and infant outcomes of women exposed to icotrokinra during pregnancy and lactation are recommended to be evaluated by pregnancy and lactation PMR studies.

8.3. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were large and consistent across trials and endpoints. The amount of missing data was relatively small (<5%) at Week 16 (i.e., the primary efficacy timepoint). For the handling of missing data, the Applicant conducted a tipping point analysis under the worst-case scenario (i.e., missing data for icotrokinra was imputed as non-responders and missing data for placebo was imputed as responders). In this extreme case, icotrokinra remained statistically superior to placebo ($p<0.001$) for both coprimary efficacy endpoints in all four pivotal trials.

There were no substantial differences in efficacy among subgroups. Approximately 81%, 89%, 90%, and 90% of subjects were 18 to 64 years of age in ICONIC-LEAD, ICONIC-ADVANCE 1, ICONIC-TOTAL, and ICONIC-ADVANCE 2, respectively; therefore, it would be difficult to detect any differences in efficacy between this subgroup and its complement (i.e., ≥65 years of age). In ICONIC-LEAD, 66 subjects (44 for icotrokinra versus 22 for placebo) were <18 years of age. In ICONIC-TOTAL, 6 subjects (3 for icotrokinra versus 3 for placebo) were <18 years of age. For [redacted], the treatment effect was slightly larger in males compared to females for IGA 0/1 response in all four trials; however, this was due to a larger placebo response rate in females compared to males.

During the review, the Applicant notified the Agency of GCP noncompliance issues regarding Site CB4-US10098 for ICONIC-ADVANCE 2. Analyses excluding the subjects at this site were conducted. Due to the site's sample size (n=8), its exclusion had a limited effect on the efficacy results, and the conclusions were unchanged.

8.4. Conclusions and Recommendations

To establish the effectiveness of icotrokinra, the Applicant submitted data from four randomized, multicenter, placebo-controlled, parallel-group, pivotal phase 3 trials (PSO3001, PSO3002, PSO3003, PSO3004). The trials enrolled subjects ≥18 years of age (PSO3002, PSO3004) and ≥12 years of age (PSO3001 and PSO3003). Trials PSO3001, PSO3002, and PSO3004 enrolled subjects who had plaque psoriasis with PASI score ≥12, IGA score ≥3, and BSA involvement of 10%. The coprimary efficacy endpoints for these three trials were IGA score of 0 or 1 plus a ≥2-grade improvement from baseline and PASI-90 at Week 16. PSO3003 had different inclusion criteria for psoriasis related to special areas, including Total BSA≥ 1% and IGA ≥2 and at least one of the following: ss-IGA score ≥3 and/or sPGA-G≥3 and/or hf-PGA≥3. The primary endpoint for PSO3003 was an IGA (overall) score of 0 or 1 plus a ≥2 grade improvement from baseline. The subpopulation of subjects with <10% total BSA was limited to 40% of the study population. In all four trials, icotrokinra was statistically superior to placebo (p-value <0.001) for the coprimary or primary efficacy endpoints at Week 16. In trials PSO3002 and PSO3004, which include deucravacitinib as an active comparator, icotrokinra was statistically superior to deucravacitinib for both coprimary endpoints.

The Applicant conducted a comprehensive assessment of the safety of icotrokinra in the target population. The size of the safety database and the safety evaluations are deemed adequate to characterize icotrokinra's safety profile.

Submitted safety and efficacy data support approval of this application for icotrokinra for the treatment of adults and pediatric patients 12 years of age and older who also weigh at least 40 kg with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting regarding this application was held.

10. Pediatrics

Refer to the following sections of this review for the proposed development program for icotrokinra in the pediatric population.

Section 3 and 13 for a discussion regarding the Pediatric Study Plan.

Section 13 Postmarketing Requirements and Commitments for the deferred pediatric studies, which are required under the Pediatric Research Equity Acti (PREA) (21 CFR 314.55 (b) and 601.27 (b).

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

The Applicant submitted proposed Prescribing Information (PI) and carton/container labels for Icotyde (icotrokinra) oral tablets. The review team provided recommendations regarding PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI, proposed patient package insert (PPI) and recommendation to convert it to the Medication Guide (MG), and carton/container. These comments are reflected in final labeling. Refer to the OPDP review by Jessica Chung, PharmD, MS and Eunice Chung-Davies, PharmD, MS (date 01/22/2026). In addition, Susan Hakeem provided comments regarding the proposed carton and container labels (Review dated 10/27/2025). Labeling negotiations are currently ongoing at the time of this writing of the review. Agreed upon labeling will be attached to the approval letter.

Other Prescription Drug Labeling

The Applicant submitted a proposed patient package insert (PPI). The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the PPI for Icotyde (icotrokinra) 200 mg tablet for oral administration. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Jessica Chung, PharmD, MS (dated 01/22/2026) DMPP for comments regarding the Medication Guide (MG).

12. Risk Evaluation and Mitigation Strategies (REMS)

Based on the known safety profile of this product, risk mitigation measures beyond labeling and a Medication Guide are not warranted at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 11.1. As no additional risk management strategies are required, the subsequent subsections are not applicable for this review and are omitted.

13. Postmarketing Requirements and Commitment

Clinical postmarketing requirements are intended to characterize the risk of icotrokinra use in special populations and address the long-term safety of this new molecular entity in the target population.

Icotrokinra triggers the Pediatric Research Equity Act (PREA) as a new active ingredient.

Required Pediatric Assessments: Pediatric Research Equity Act (PREA) (21 U.S.C 355c).

The pediatric study requirement for ages 0 to 4 years is waived because the necessary studies are impossible or highly impractical.

We are deferring submission of pediatric studies for ages 4 to less than 12 years for this application because this product is ready for approval for use in adults and pediatric patients 12 years of age and older who also weigh at least 40 kg who are candidates for systemic therapy or phototherapy and the pediatric studies for ages 4 to less than 12 years have not been completed.

Required Pediatric Assessment

Conduct a trial to evaluate the safety and pharmacokinetics of icotrokinra in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate a sufficient number of subjects exposed to icotrokinra at the highest proposed dosage for a minimum of 26 weeks to evaluate for safety and pharmacokinetics of icotrokinra in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Refer to the Approval Letter for the final PMRs with milestone dates.

The available safety data regarding icotrokinra use during pregnancy is limited. The study population as defined by the entry criteria excluded pregnancy and lactating females, and females planning to become pregnant or breastfeed during the trials. The Applicant reported that 5 pregnancies occurred in female subjects exposed to icotrokinra and 8 in female partners of male subjects exposed to icotrokinra during the development program for plaque psoriasis. However, no outcome information was available in 2 or the 5 pregnancies of female subjects or 3 out of 8 of the partners of male subjects. Therefore, the Applicant will be required to conduct the postmarketing assessments described below to characterize the drug associated risk.

Postmarketing Requirements Under 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Based on a review of the data in this submission, the following postmarketing requirements (PMRs) were conveyed to the Applicant:

Descriptive Pregnancy Safety Study

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Icotyde (icotrokinra) during pregnancy to assess risk of pregnancy and

maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

Refer to the Approval Letter for the final PMR with milestone dates.

Lactation Study

Perform a lactation study in lactating women who have received icotrokinra to measure concentrations of icotrokinra in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

Refer to the Approval Letter for the final PMR with milestone dates.

Pharmacovigilance Plan

The primary review team agrees with the Applicant's proposal to implement enhanced pharmacovigilance monitoring of serious and non-serious GI adverse events, both domestic and foreign, including but not limited to GI bleeding, ulceration, and perforation, and to establish an external, blinded adjudication committee to systematically review potential serious events. Refer to the Approval Letter for detailed description on this plan.

14. Division Director (DHOT) Comments

Not applicable.

15. Division Director (OCP) Comments

Not applicable.

16. Division Director (OB) Comments

Not applicable.

17. Division Director or Designated Signatory (Clinical) Comments

I agree with the review team recommendation to approve Icotyde (icotrokinra) for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older weighing at least 40 kg who are candidates for systemic therapy or phototherapy.

Icotrokinra is a new molecular entity (NME). It is a 13 amino acid peptide for oral administration that selectively binds to the IL-23 receptor (IL-23R) and competitively antagonizes the binding of IL-23. Icotrokinra inhibits IL 23/IL-23R-dependent release of proinflammatory cytokines.

For comparison, systemic IL 23 inhibitors available on the market for the treatment of psoriasis (guselkumab, risankizumab, ustekinumab and tildrakizumab) are monoclonal antibodies that bind IL-23 cytokine and prevent it from binding to the IL-23 receptor on T cells. Safety profile of IL-23 monoclonal antibodies is well established. It is anticipated that this new product safety profile will be comparable to systemic products' safety profile.

The product is the first IL-23 inhibitor in the oral dosage form. Being in oral form, icotrokinra accumulates in GI tract, kidneys and bone and is excreted almost unchanged in feces as shown in animal testing.

The Applicant submitted data from four adequate and well-controlled phase 3 clinical trials which enrolled 2367 adult and 72 adolescent subjects 12 years of age and older with moderate-to-severe plaque psoriasis. These data provided sufficient evidence of the effectiveness of icotrokinra for the indication. Superiority over placebo was established by the assessment of 2 co-primary endpoints in 3 of the studies at the end of placebo-controlled period at Week 16. The co-primary efficacy endpoints were:

- IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16.
- PASI 90 at Week 16.

Objective of the fourth study was to evaluated efficacy in the treatment of psoriasis with scalp, genitals, and hands and feet involvement; therefore, PASI 90 was not appropriate for capturing this outcome. The primary efficacy endpoint was:

- IGA (overall) score of 0/1 and a ≥2-grade improvement from baseline at Week 16.

Efficacy of icotrokinra in the treatment of psoriasis with scalp, genitals, and hands and feet involvement was evaluated by assessing pre-specified secondary endpoints. The results of these secondary endpoints are described in the labeling.

In addition, the data showed superiority of icotrokinra to an active comparator, deucravacitinib that would be also reflected in the labeling.

The safety database submitted by the Applicant provided sufficient evidence to allow for the determination that benefits of treatment outweigh the risks.

Overall, there were few serious adverse reactions identified in the safety database. Notable, there were a few cases of GI adverse events reported in patients on icotrokinra. None were reported in placebo or deucravacitinib arms.

One AR resulting in patient's death occurred during 16-week placebo-controlled phase. The diagnosis provided on patient's death certificate indicated that the person died from esophageal variceal bleeding, however this diagnosis was not confirmed since the autopsy was not performed, there was no previous history of esophageal varices and available lab data did not corroborate such a diagnosis. Therefore, the event is described in the labeling as upper gastrointestinal bleeding.

The event had several confounding factors and was a topic of lengthy discussion with the review team and consultants. Eventually, it was decided that the causality cannot be excluded, and the event should be described in Section 6.1. Of note, trial investigator assessed the case as related to investigational drug.

In addition, there were 3 more cases of GI adverse events that occurred while patients were on icotrokinra but outside of placebo-controlled phase; unspecified gastrointestinal bleeding resulting in death, gastric ulcer perforation and lower GI bleeding. Those cases were confounded as well and contained insufficient information to make a causality determination. After discussing with the review team, it was decided not to include them in the label.

Given the uncertainty around causality of GI adverse events, the applicant will be subject to enhanced pharmacovigilance to report all GI-related serious and non-serious, domestic and foreign, cases of gastrointestinal adverse events as 15-day reports as will be described in detail in approval letter.

To further define the product safety profile in the population that was not included in this development program, the Applicant will be required to conduct 3 studies:

One pediatric trial under PREA authority in pediatric subjects 4 years to 12 years of age, and 2 FDAAA studies to assess unexpected potential risks to pregnant women, fetuses, lactating woman and infants.

This approval adds a valuable treatment option to the armamentarium of available treatments for psoriasis.

18. Office Director (or Designated Signatory Authority) Comments

NDA 220149 for icotrokinra, an orally administered peptide that binds to the IL-23 receptor (IL-23R), was submitted on July 18, 2025. The proposed indication is for the treatment of moderate-to-severe plaque psoriasis (PsO) in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 200 mg administered orally once daily on an empty stomach.

I have carefully and thoroughly reviewed the data and information submitted in the NDA and considered the input and recommendations from the review team, including those from the signatory of the Division of Dermatology and Dentistry, detailed in Section 17 and the Division of Gastroenterology consult detailed in their consult review (dated March 12, 2026), as well as additional internal discussions. Given that the submission is summarized elsewhere in this document and other disciplines' review documents, here I will only review select aspects of the submission, pertinent to the labeling.

The review team concluded that substantial evidence of effectiveness has been demonstrated for icotrokinra for the proposed indication, based on data from four adequate and well-controlled phase 3 clinical trials (PSO3001, PSO3002, PSO3003, and PSO3004), as detailed elsewhere in this review. Further, information from the four trials supports the labeling claims in Section 14, Clinical Studies, of the proposed labeling, including claims of superiority to active comparator deucravacitinib. I agree with this assessment and conclusion.

The safety of icotrokinra was assessed primarily using integrated data from four phase 3 trials (PSO3001, PSO3002, PSO3003, PSO3004). The review team concluded that the Applicant conducted a comprehensive assessment of the safety of icotrokinra in the target population. The size of the safety database and the safety evaluations were adequate to identify treatment-emergent adverse reactions.

As part of the safety assessment, the review team identified one death attributed to upper gastrointestinal bleeding in a subject with underlying risk factor reported in the 16-week placebo control period of the clinical studies. One additional death related to non-specific upper gastrointestinal bleed occurred in the extension period, and one SAE of acute gastric ulcer perforation with peritonitis in the extension period, and one SAE of lower gastrointestinal bleeding (rectal hemorrhage) was reported in the 120-day safety update. Given that icotrokinra is a new molecular entity with mechanism of action through IL-23 receptor inhibition, oral route of administration, and the severity and imbalance of these events in administration of icotrokinra, the cross-discipline team leader recommended inclusion of this information in Section 5, Warnings and Precautions; based on the same information, the primary clinical reviewer recommended inclusion of these events in Section 6.1, Clinical Trails Experience of product labeling.

I agree with the review team that these cases were serious, and causal association cannot be reliably ruled out. However, I also note that the specifics of the cases indicate significant confounding, including underlying medical conditions, risk factors, and concomitant medications. While all cases have been adequately described elsewhere in this review and in the Division of Gastroenterology consult review, I will only reference one example. The fatal case reported during the 16-week placebo control period occurred five days (approximately 10 half-lives) after the icotrokinra was discontinued. The cause of death was listed as gastroesophageal varices rupture, a condition unlikely related to the use of icotrokinra. Based on the review of the information from the original NDA submission and additional responsive information provided by the Applicant, the review team and the Division of Gastroenterology consult team acknowledged the presence of multiple confounding factors in the four cases of serious GI events (i.e., upper GI bleeding, nonspecific hematemesis, rectal hemorrhage, and gastric ulcer perforation), the clinical heterogeneity of the events (e.g., types of events, duration of therapy with icotrokinra), and the lack of a known pharmacologic mechanism associated with icotrokinra or other IL-23R antagonists. They also concluded that there remains a significant amount of uncertainty regarding the relatedness of serious GI events to icotrokinra use. The Division of Gastroenterology consult team concluded that the additional information provided by the Applicant does not indicate the presence of a safety signal for serious GI bleeding with icotrokinra use across the psoriasis development program. Further, the reported gastrointestinal events occurred in a patient population where such events are not unexpected. In fact, based on the review of the same information, the gastroenterology consult team concluded that the rate of GI bleeding identified in the icotrokinra psoriasis development program is overall comparable to than the expected rate in the general population. Additional 2,041 person-years of icotrokinra safety data from the psoriasis program, including blinded data from the ongoing phase 3 psoriasis study PSO3006, and ongoing blinded psoriatic arthritis phase 3 studies PSA3001 and PSA3002, provided by the Applicant, reported no new cases of serious GI bleeding or ulcerative events. Further, nonclinical data submitted by the Applicant did not indicate signs of gastrointestinal toxicity in rats and monkeys with a 60-fold margin over human exposure.

Based on the above contextual information, I believe that describing the fatal case of upper GI bleeding that occurred in the context of a direct placebo and active control comparisons during the 16-week controlled period, may be reasonable, noting the significant confounding. However, in my assessment, the lack of reliable controlled comparisons during the open-label extension period, together with the significant amount of uncertainty regarding the relatedness of the serious GI events to icotrokinra use, inclusion of these cases from the open-label period in product labeling is not sufficiently justified to inform the safe or effective use of the product in product labeling and may potentially be confusing to prescribers.

Considering the reports of GI adverse events and the Division's concerns raised during the review, the Applicant proposed enhanced pharmacovigilance for targeted monitoring of serious GI adverse events including GI bleeding, ulceration, and perforation, and to establish an external, blinded adjudication committee to systematically review potential serious events in the post-market space and for future clinical development. This approach was found acceptable

to the Division of Dermatology and Dentistry review team and the GI consult team. Given the uncertainties with the causal association of icotrokinra of the observations, I also agree that this approach is reasonable and will be included as part of the action letter.

In sum, the review team concluded that based on the available safety and efficacy data, the overall benefit-risk profile is favorable and supports the approval of icotrokinra 200 mg for oral administration for the treatment of moderate to severe plaque psoriasis in adults and pediatric patients 12 years of age and older who also weight at least 40 kg who are candidates for systemic therapy or phototherapy. I agree with this assessment and conclusions.

The regulatory action for NDA 220149 is approval with the agreed upon labeling and enhanced pharmacovigilance for targeted monitoring of serious GI adverse events, as detailed in the action letter.

19. Appendices

19.1. References

Refer to review.

19.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PSO3001, PSO3002, PSO3003, PSO3004

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 1832 (PSO3001=572, PSO3002=627, PSO3003=241, PSO3004=392)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1832		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

19.3.1. Carcinogenicity Study Review

19.3.1.1. Study #1

Study Title: JNJ-77242113-AAC (IL-23R antagonist): A 2-Year Oral Gavage Carcinogenicity Study in Sprague Dawley Rats

Study no.:	TOX15377
Study report location:	SDN 1
Study initiation date:	May 19, 2022
Conducting laboratory and location:	(b) (4)
GLP compliance:	Y
Drug, lot #, and % purity:	JNJ-77242113-AAC, batch #:1000045290 (Week 1), A22BD0185 (beginning Week 2); purity: 95% (Week 1), 92.9% (beginning Week 2)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Multiples of human exposure

Reviewer Carcinogenicity Conclusion (negative/positive): Negative
ECAC Carcinogenicity Conclusion (negative/positive): Negative

Tumor Findings: No icotrokinra-related tumor findings were noted in the study. A complete list of tissues was examined histopathologically. No significant test article-related neoplastic findings were noted in this study.

Methods

Doses:	0, 5, 10 and 20 mg/kg/day (Group 1, 2, 3 and 4)
Frequency of dosing:	Once daily
Number/Sex/Group:	65/sex/group in Groups 1, 2, 3, and 4 for carcinogenicity evaluation; 5/sex in Group 1 and 11/sex/group in Groups 2, 3, and 4 for toxicokinetic [TK] and/or antidrug antibody [ADA] evaluation
Dose volume:	5 mL/kg
Formulation/Vehicle:	Phosphoric acid (0.85% or 8.5% in water)
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	SPRAGUE-DAWLEY
Age:	9 weeks at first dose

Comment on Study Design and Conduct:	None remarkable.
Dosing Comments (Dose Adjustments or Early Termination):	Males at 0, 5 and 10 mg/kg/day were terminated at Week 100, at 20 mg/kg/day were terminated at Week 94; and all female animals were terminated at Week 87.
Dosing Solution Analysis:	All study samples analyzed had mean concentrations within or equal to the protocol-specified acceptance criteria of ±10% of the theoretical concentrations, with each individual sample concentration within ±15%.

Observations and Results

Mortality

Males at 20 mg/kg/day declined to 20 animals on Day 623 (Week 89) and dosing was discontinued after Day 625 (Week 90) as per the criteria conveyed to the sponsor in an Advice Letter dated 1/4/2024. Males at 20 mg/kg/day declined to 15 animals on Day 657 (Week 94), and therefore the animals at 20 mg/kg/day were terminated on Day 658 (Week 94).

Males at 10 mg/kg/day declined to 15 animals on Day 692 (Week 99), and therefore the animals at 10 mg/kg/day were terminated on Day 694 (Week 100). Males at 0 mg/kg/day declined to 20 animals on Day 694 (Week 100), and therefore males at 0 and 5 mg/kg/day were terminated on Day 696 (Week 100).

Females at 0 mg/kg/day declined to 20 animals on Day 603 (Week 87) and therefore females in all groups were terminated on Day 604 (Week 87).

Based on the analysis conducted by the Agency statistical reviewer, Dr. Malick Mbodj, there was a statistically significant increase in mortality (trend test) across the vehicle control group and the three test article treated groups in male rats (P=0.0132). The pairwise comparisons also, showed a statistically significant increase in mortality in the 20 mg/kg/day group when compared to the vehicle control group in male rats (P=0.0154).

Table 70. Survival at the End of the Rat Study

Sex	Parameters	Group 1 (vehicle)	Group 2 (5 mg/kg/day)	Group 3 (10 mg/kg/day)	Group 4 (20 mg/kg/day)
Male	Survival number	22	17	15	15
	Survival rate	34%	26%	23%	23%
Female	Survival number	20	24	27	24
	Survival rate	31%	37%	42%	37%

Source: From submission.

Animals that died accidentally at the terminal sacrifice were included in the number of deaths in the analysis conducted by Dr. Malick Mbodj.

Clinical Signs

No test article-related findings in clinical signs were noted.

Body Weights

No test article-related changes in mean body weights were noted.

Feed Consumption

No test article-related changes in feed consumption were noted.

Gross Pathology

No test article-related findings in gross pathology were noted.

Histopathology

Peer review conducted: Yes
Historical control provided for tumor incidence: Yes
A complete list of tissues was examined histopathologically.

Neoplastic

The Agency statistical reviewer, Dr. Malick Mbodj, independently performed the tumor data analysis. No statistically significant differences in icotrokinra related tumor incidence were observed in rats of either sex in this study, according to the statistical criteria used by the Executive Carcinogenicity Assessment Committee (ECAC). The ECAC statistical criteria used to determine treatment related to common tumors is that the trend p-value should be less than 0.005 ($p<0.005$) and the pairwise p-value should be less than 0.01 ($p<0.01$). The statistical criteria used to determine treatment related rare tumors is that the trend p-value should be less than 0.025 ($p<0.025$) and the pairwise p-value should be less than 0.05 ($p<0.05$). Based on the statistical criteria used by the ECAC, there were no treatment related tumors in this oral carcinogenicity study.

Based on the analysis conducted by Dr. Malick Mbodj, the tumor type with p-values less than 0.05 for dose response relationship (trend comparison) and/or pairwise comparisons of vehicle control and treated groups were examined (see table below). Using the ECAC statistical criteria, neither trend nor pairwise comparison showed statistically significant increases in tumor incidence.

Table 71. Tumor Types With p-Values ≤0.05 for Dose Response Relationship or the Pairwise Comparisons

Treated Groups and Control Group in Rats

sex	Organ Name	Tumor Name	0 mg Cont (N=65) P - Trend	5 mg Low (N=65) P - C vs. L	10 mg Med (N=65) P - C vs. M	20 mg High (N=65) P - C vs. H
Male	hemolymphoreticular tissue	leukemia, granulocytic	0/65 (41) 0.0475@	0/65 (36) NC	0/65 (36) NC	2/65 (32) 0.1887

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.
@: not Statistically significant at 0.005 or 0.025 for common or rare tumor in dose response relationship.

Source: analysis from the statistical reviewer

Non-Neoplastic

No test article-related findings of non-neoplastic changes were noted.

Toxicokinetics

Total Icotrokinra

On Days 1, 63 (Week 9), 182 (Week 26), 364 (Week 52), and 546 (Week 78), blood samples were collected from icotrokinra-treated animals (males and females).

On Days 1 to 364, systemic exposure to total icotrokinra increased generally in a dose-proportional manner as dose increased in both sexes. On Days 546, systemic exposure to total icotrokinra remained constant as dose increased in males while systemic exposure generally in a dose-proportional manner increased as dose increased in females. On Day 630, systemic exposure to total icotrokinra remained constant as dose increased in males.

There were no consistent differences in systemic exposure to total icotrokinra between sexes up to Day 546. Female to male ratios ranged from 0.55 to 4.4 and from 0.61 and 4.7 for C_{max} and AUC_{0-24}, respectively.

Following repeat oral dosing of icotrokinra, accumulation of total icotrokinra was observed while the accumulation appeared to slightly decrease overtime.

Table 72. TK Parameters of Total Icotrokinra on Days 1, 63, 182, 364, 546 and 630

Day	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	t_{max} (hr)	t_{last} (hr)	AUC_{0-24} (hr*ng/mL)	AUC_{0-inf} (hr*ng/mL)
1	5	Female	2.94	0.5	24	20.8	NA[a]
		Male	2.12	1	24	20.4	NA[a]
1	10	Female	9.59	2	24	40.6	NA[a]
		Male	4.48	2	24	33.5	NA[a]
1	20	Female	30.3	2	24	83.0	95.9
		Male	6.91	2	24	43.5	NA[a]
63	5	Female	128	0.5	24	1980	NA
		Male	115	2	24	1730	NA
63	10	Female	154	1	24	2240	NA
		Male	280	2	24	3650	NA
63	20	Female	338	2	24	5160	NA
		Male	227	1	24	3400	NA
182	5	Female	118	0.5	24	1110	NA
		Male	55.6	2	24	756	NA
182	10	Female	122	8	24	1840	NA
		Male	267	2	24	2570	NA
182	20	Female	232	4	24	2580	NA
		Male	219	4	24	3330	NA
364	5	Female	102	0.558	24	973	NA
		Male	40.8	2	24	734	NA
364	10	Female	181	1	24	1790	NA
		Male	80.7	2	24	1100	NA
364	20	Female	236	0.5	24	2170	NA
		Male	127	2	24	1910	NA
546	5	Female	54.3	0.5	24	788	NA
		Male	91.3	2	24	516	NA
546	10	Female	155	1	24	1660	NA
		Male	47.4	2	24	514	NA
546	20	Female	210	2	24	2700	NA
		Male	50.7	2	24	580	NA
630	5	Male	22.2 ±3.54	2(2-4)	24(24-24)	450 ±90.0	NA
630	10	Male	54.6 ±51.8	2(1-2)	24(24-24)	868 ±792	NA
630	20	Male	22.9 ±8.72	1(1-2)	24(24-24)	283 ±30.2	NA
NA - Not applicable.							
[a] = AUC_{0-inf} was not reported due to insufficient plasma concentration-time data.							
Data represent mean ±SD for Day 630 (Median (Min – Max) for t_{max} and t_{last})							

Source: From submission
Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; Tlast, time of the last measurable drug concentration; T_{max}, time to C_{max}

Table 73. Summary of Accumulation Ratios of Total Icotrokinra on Days 63, 182, 364, 546, and 630

Day	Dose (mg/kg/day)	Sex	R_{Cmax}[a]	R_{AUC}[b]
63	5	Female	44	95
		Male	54	84
63	10	Female	16	55
		Male	63	110
63	20	Female	11	62
		Male	33	78
182	5	Female	40	53
		Male	26	37
182	10	Female	13	45
		Male	60	77
182	20	Female	7.6	31
		Male	32	77
364	5	Female	35	47
		Male	19	36
364	10	Female	19	44
		Male	18	33
364	20	Female	7.8	26
		Male	18	44
546	5	Female	18	38
		Male	43	25
546	10	Female	16	41
		Male	11	15
546	20	Female	6.9	33
		Male	7.3	13
630	5	Male	10	22
630	10	Male	12	26
630	20	Male	3.3	6.5
NA - Not applicable.				
[a] = R_{Cmax} = C_{max} repeated dosing/C_{max} Day 1.				
[b] = R_{AUC} = AUC_{0-24} repeated dosing/AUC_{0-24} Day 1.				

Source: from submission
Abbreviations: Rcmax, ratio of C_{max}; RAUC, ratio of AUC

Following repeat oral dosing of icotrokinra, the systemic exposure to total icotrokinra was higher compared to free (unbound to ADA) icotrokinra.

Antidrug Antibody

Blood samples were collected on Days 1, 63, 182, 364, 546, and 630.

All samples collected on Day 1 were negative for anti-icotrokinra antibodies. Anti- icotrokinra antibodies were detected in 9 out of 9 (100%) animals at 5 mg/kg/day, 6 out of 6 (100%)

animals at 10 mg/kg/day), and 11 out of 11 100% animals at 20 mg/kg/day. From all positive samples, the minimum specificity inhibition was 73.5%.

Discussion

The modeled clinical AUC value corresponding to 200 mg QD is 36.7 ng.h/mL. Since no icotrokinra-related tumor findings were noted in the study, the total AUC values (Day 546) at high dose are used to calculate the multiples of human exposure, which are 16 and 74 for males and females, respectively. The animal to human AUC ratio for males was below 25.

Table 74. Multiples to Human Exposure in the Rat Study

Dose	Sex	$AUC_{0\text{-}24h,ss}$ (ng·h/mL) (Total Icotrokinra)	Multiples of Human Exposure
20 mg/kg/day	Male	580	16
	Female	2700	74

Source: Analysis by the reviewer
Abbreviations: $AUC_{0\text{-}24h,ss}$, area under the concentration–time curve from 0 to 24 hours at steady state

Icotrokinra appeared to be highly immunogenic in rats. ADA was detectable in rats as early as 2 weeks postdose. In this study, ADA was present in all animals. The presence of ADA in rats introduced substantial variations in exposure within and across studies. In this study, the AUC ranged from 283 to 3400 ng·h/mL following repeat dosing in male rats at 20 mg/kg/day. Furthermore, the 2-year rat study was initially waived during the development of icotrokinra. Overall, the results of the 2-year rat study were considered acceptable.

19.3.1.2. Study #2

Study Title: JNJ-77242113-AAC (IL-23R antagonist): A 26-week Carcinogenicity Study by Oral Gavage in CByB6F1-Tg (HRAS)2Jic Mice

Study no.:	TOX15455
Study report location:	SDN 1
Study initiation date:	September 28, 2023
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	JNJ-77242113-AAC; lot#: A22BD0184 (93.4% purity) and A23BD0347 (93% purity)
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	Multiples of human exposure

Reviewer Carcinogenicity Conclusion (negative/positive): Negative
ECAC Carcinogenicity Conclusion (negative/positive): Negative

Tumor Findings: No icotrokinra-related tumor findings were noted in the study. A complete list of tissues was examined histopathologically. No significant test article-related neoplastic findings were noted in this study.

Methods

Doses:	0, 50, 150, and 500 mg/kg/day (Group 1, 2, 3 and 4)
Frequency of dosing:	Once daily
Number/Sex/Group:	25/sex/group in Groups 1, 2, 3, and 4 for carcinogenicity evaluation; 15/sex in Group 1 and 51/sex/group in Groups 2, 3, and 4 for TK and/or antidrug antibody [ADA] evaluation
Dose volume:	10 mL/kg
Formulation/Vehicle:	Phosphoric acid (0.85% or 8.5% in water)
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	9 weeks at initiation of dosing
Comment on Study Design and Conduct:	A positive control group was included (15/sex), in which IP doses of 500 mg/kg/day urethane were administered on Days 1, 4, and 7.
Dosing Comments (Dose Adjustments or Early Termination):	None remarkable.

Dosing Solution Analysis:	All study samples analyzed had mean concentrations within or equal to the protocol-specified acceptance criteria of ±10% of the theoretical concentrations, with each individual sample concentration within ±15%.

Observations and Results

Mortality

Based on the analysis conducted by the Agency statistical reviewer, Dr. Malick Mbodj, no statistically significant finding in dose response relationship was shown in the mortality in either male or female mice. The pairwise comparisons also showed no statistically significant changes in mortality rates between the treated groups, and the vehicle control group in either sex of mice.

Table 75. Survival at the End of the Mouse Study

Sex	Parameters	Group 1 (Vehicle)	Group 2 (50 mg/kg/day)	Group 3 (150 mg/kg/day)	Group 4 (500 mg/kg/day)
Male	Survival number	23	23	24	24
	Survival rate	92%	92%	96%	96%

Female	Survival number	25	24	24	21
	Survival rate	100%	96%	96%	84%

Source: From submission.

Animals that died accidentally at the terminal sacrifice were included number of deaths in the analysis conducted by Dr. Malick Mbodj.

Clinical Signs

No test article-related findings in clinical signs were noted.

Body Weights

No test article-related changes in mean body weights were noted. While the mean body weight was lower by 12% in males at 150 and 500 mg/kg/day, the decreases were not dose-dependent.

Feed Consumption

Feed consumption was not reported.

Gross Pathology

No test article-related findings in gross pathology were noted.

Histopathology

Peer Review Conducted: Yes
Historical Control Provided for Tumor Incidence: The historical data of microscopic finding was provided but the historical data of tumor incidence was not provided .

A complete list of tissues was examined histopathologically.

Neoplastic

The Agency statistical reviewer, Dr. Malick Mbodj, independently performed the tumor data analysis. No statistically significant differences in icotrokinra-related tumor incidence were observed in mouse of either sex in this study, according to the statistical criteria used by the ECAC. The ECAC statistical criteria used to determine treatment related common and rare tumors for the mouse study is that both trend and pairwise p-values should be less than 0.05 ($p<0.05$). Based on the statistical criteria used by the ECAC, there were no icotrokinra-related tumors in this oral carcinogenicity study.

In the positive control groups, there were statistically significant increases in the incidences of adenoma bronchioalveolar in the lung, hemangiosarcoma in the spleen in males and females;

and in the incidence of combined adenoma bronchioalveolar/carcinoma bronchioalveolar in the lungs in males. The findings in the positive control group were expected.

Non-Neoplastic

No test article-related non-neoplastic findings were noted.

In the nasal cavity, minimal to mild edema were noted in males at ≥50 mg/kg/day and females at 50 and 150 mg/kg/day) and neutrophilic inflammation was noted in males at 500 mg/kg/day and females at ≥150 mg/kg/day. The incidence and severity of edema did not appear to be dose-dependent while the findings of neutrophilic inflammation were dose-dependent. The incidences of these nasal cavity changes were within ranges of the Testing Facility historical control data (HCD) except for edema in males at 50 and 150 mg/kg/day.

While the incidence of edema exceeded the upper limit of the HCD, the findings were not dose-dependent. Therefore, the edema was not considered test article-related.

Similar exudative inflammatory changes (presence of eosinophilic proteinaceous fluid, fibrin, mucin, sloughed cells, and degenerate neutrophils within the nasal cavities) have been reported to occur in this mouse model, including vehicle control groups, without increased incidence of nasal tumors compared to animals without inflammatory changes (Paranjpe et al., 2017). The nasal inflammatory findings may have been related to oral gavage dosing which has been reported to lead to inflammatory changes in the nasal cavity due to gavage-related reflux in rodents (Damsch et al., 2011). In addition, the nasal inflammation was also thought to be related to a flooded cage incident and its associated wet environment. Taken together, the findings were not considered test article-related.

In the ear, mild to moderate neutrophilic inflammation was present in the middle ear canal that was observed in the tissue section trimmed for Zymbal's gland in 4 females at 500 mg/kg/day. The findings were considered due to the wet cage husbandry issue and not a test article-related effect.

In the thymus, minimal to moderate increased epithelial cellularity in a dose-dependent manner was observed in a single male at 500 mg/kg/day and in females in all groups including the vehicle control. It is unclear if the incidences were within HCD ranges due to the discrepancies in terminologies used in the study report and the historical data. The findings were not associated with any progression to epithelial tumors of the thymus.

References

Paranjpe MG, Belich JL, Richardson DR, et al. Exudative inflammatory lesions in the nasal cavities of the 26-week Tg.rasH2 Mice oral gavage carcinogenicity studies. Int. J. Toxicol. 2017;36(1):21–28.

Damsch S, Eichenbaum G, Tonelli A, et al. Gavage-related reflux in rats: identification, pathogenesis, and toxicological implications (review). Toxicologic Pathology. 2011;39(2):348–360.

Toxicokinetics

Blood samples were collected from TK animals On Day 1 and during Weeks 13 and 26 in all dose groups.

Total Icotrokinra

On Day 1, systemic exposure to total icotrokinra increased generally in a dose-proportional manner as dose increased in both sexes. On Day 87, systemic exposure to total icotrokinra did not increase as dose increased in females while systemic exposure to total icotrokinra increased in a less than dose-proportional manner as dose increased in males. On Day 182, systemic exposure to total icotrokinra increased in a less than dose-proportional manner as dose increased in females while systemic exposure to total icotrokinra did not increase as dose increased in males.

There were no consistent differences in systemic exposure to total icotrokinra between sexes.

Compared to systemic exposure on Day 1, slight accumulation of total icotrokinra was observed following repeat oral dosing of icotrokinra. However, no accumulation of total icotrokinra was observed when comparing systemic exposure of Days 182 to 87 in males at ≥150 mg/kg/day and in females at 50 mg/kg/day.

Table 76. TK Parameters of Total Icotrokinra on Days 1, 87, and 182

Day	Sex	Dose (mg/kg /day)	C_{max} (ng/mL)	t_{max} (hr)	t_{last} (hr)	AUC_{last} (hr*ng/mL)	AUC_{last}/Dose (hr*ng/mL /(mg/kg))	AUC_{0-INF} (hr*ng/mL)	AUC_{0-INF}/Dose (hr*ng/mL /(mg/kg))
1	Female	50	36.2	1	8	107[a]	2.14	108	2.16
		150	73.9	2	24	363	2.42	363	2.42
		500	123	2	24	836	1.67	836	1.67
1	Male	50	44.9	1	8	128[a]	2.55	142	2.84
		150	129	1	24	506	3.37	507	3.38
		500	238	2	24	1330	2.66	1330	2.66
87	Female	50	259	2	24	2450	48.9	NA	NA
		150	211	4	24	2150	14.3	NA	NA
		500	217	2	24	2020	4.05	NA	NA
87	Male	50	57.7	4	24	867	17.3	NA	NA
		150	166	2	24	1210	8.05	NA	NA
		500	393	2	24	2250	4.51	NA	NA
182	Female	50	182	4	24	1060	21.3	NA	NA
		150	549	2	24	1930	12.9	NA	NA
		500	363	8	24	6700	13.4	NA	NA
182	Male	50	267	24	24	2780	55.5	NA	NA
		150	212	2	24	1360	9.10	NA	NA
		500	382	1	24	2780	5.57	NA	NA

a =AUC_{last} is not equal to AUC_{0-24}, since t_{last} is not 24 hours.

Source: From submission.

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time zero to infinity; AUC_{last}, area under the concentration–time curve from time zero to the last measurable concentration; C_{max}, maximum plasma concentration; T_{last}, time of the last measurable drug concentration; T_{max}, time to C_{max}

Table 77. Summary of Accumulation Ratios of Total Icotrokinra on Days 87 and 182

Day	Sex	Dose Level (mg/kg/day)	R_{AUC}[a] (RATIO)	R_{Cmax}[b] (RATIO)
87	Male	50	6.8	1.3
		150	2.4	1.3
		500	1.7	1.7
87	Female	50	23	7.2
		150	5.9	2.8
		500	2.4	1.8
182	Male	50	22	6.0
		150	2.7	1.6
		500	2.1	1.6
182	Female	50	10	5.0
		150	5.3	7.4
		500	8.0	3.0
Day	**Sex**	**Dose Level (mg/kg/day)**	**R_{AUC}[c] (RATIO)**	**R_{Cmax}[d] (RATIO)**
182	Male	50	3.2	4.6
		150	1.1	1.3
		500	1.2	1.0
182	Female	50	0.43	0.70
		150	0.90	2.6
		500	3.3	1.7

a = $R_{AUC} = AUC_{last\ Day\ 87\ or\ 182}/AUC_{last\ Day\ 1}$.
b = $R_{Cmax} = C_{max\ Day\ 87\ or\ 182}/C_{max\ Day\ 1}$.
c = $R_{AUC} = AUC_{last\ Day\ 182}/AUC_{last\ Day\ 87}$.
d = $R_{Cmax} = C_{max\ Day\ 182}/C_{max\ Day\ 87}$.

Source: From submission.
Abbreviations: Rcmax, ratio of C_{max}; RAUC, ratio of AUC

Following repeat oral dosing of icotrokinra, the systemic exposure to total icotrokinra was generally higher compared to free (unbound to ADA) icotrokinra.

Antidrug Antibody (ADA)

Blood samples were collected during on Days 87, 182, and 189.

Anti-icotrokinra antibodies were detected in 51 out of 59 (86%) samples in the 50 mg/kg/day group, 51 out of 56 (91%) samples in the 150 mg/kg/day group, and 30 out of 40 (70%) samples in the 500 mg/kg/day group. ADA was observed in most animals of all groups.

Discussion

The modeled clinical AUC value corresponding to 200 mg QD is 36.7 ng.h/mL. Since no icotrokinra-related tumor findings were noted in the study, the total AUC values (Day 182) at high dose are used to calculate the multiples of human exposure, which are 76 and 183 for

males and females, respectively. The animal to human AUC ratios are greater than 50, which is acceptable.

Table 78. Multiples to Human Exposure in the Mouse Study

Dose	Sex	$AUC_{0\text{-}24h,ss}$ (ng.h/mL) (Total Icotrokinra)	Multiples of Human Exposure
500 mg/kg/day	Male	2780	76
	Female	6700	183

Source: analysis from the reviewer
Abbreviations: AUC0-24h,ss, area under the concentration–time curve from 0 to 24 hours at steady state

Overall Discussion and Conclusions

To evaluate the carcinogenic potential of icotrokinra, a 2-year oral rat carcinogenicity study and a 26-week oral rasH2 mouse carcinogenicity study were conducted. In both studies the tested doses were recommended by the ECAC. The 2-year rat study was terminated early due to decreased survival. The early termination was carried out based on the criteria conveyed to the sponsor. Of note, a waiver for the conduct of a 2-year rat study was granted previously but the sponsor conducted the study due to other regulatory considerations. The 6-month mouse study was completed as planned.

Both studies were considered adequately conducted. For both studies a complete list of tissues was examined histopathologically. Overall, there were no significant icotrokinra-related neoplastic findings in either study.

Icotrokinra was not carcinogenic when administered orally to SD rats once daily for 2 years or to rasH2 mice once daily for 6 months.

19.3.2. Multiples of Human Exposure Calculation

The multiples of human exposure based on AUC comparison between the NOAELs identified in pivotal toxicology studies and the maximum recommended human dose (MRHD, 200 mg QD) are shown in Table 79.

The Applicant provided modeled human steady-state exposure from the population PK/PD model in subjects with plaque psoriasis at 200 mg QD. It is a post hoc population PK modelling using data from the following clinical trials: PSO3001, PSO3002, PSO3003, and PSO3004. The clinical $AUC_{0\text{-}24h,ss}$ value is 36.7 ng·h/mL. This value was used for the calculation of exposure margins.

Table 79. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg/day)	AUC[a] (ng·h/mL)	Multiples of Human Exposure[b] (Based on AUC Comparison)
6-month rat study (Day 177)	Oral	20	547[C]	15
9-month monkey study (Day 273)	Oral	200	12900	351
2-year carcinogenicity study in rats (Day 546)	Oral	20	580	16
26-week carcinogenicity study in mouse (Day 182)	Oral	500	2780[C]	76
Fertility study in male rats (Day 114)	Oral	20	4170	114
Fertility study in female rats (GD7)	Oral	70	12300	335
Embryo-fetal development study in rats (GD 17)	Oral	Maternal: 1000	10900	297
		Embryo-fetal: 1000	10900	297
Embryo-fetal development study in rabbits (GD 19)	Oral	Maternal: 200	975	27
		Embryo-fetal: 200	975	27
Pre- and postnatal development study in rats (LD 12)	Oral	Maternal: 200	4660	127
		Developmental: 200	4660	127

Source: Analysis by the reviewer.
[a] The lower AUC value between males and females was used for the calculation.
[b] Compared with the estimated steady state human $AUC_{0\text{-}24h}$ value: 36.7 ng·h/mL.
[c] AUC_{Tlast} value.
Abbreviations: AUC, area under the concentration-time curve; GD, gestation day; LD, lactation day

19.3.3. Recommended Revisions to the Nonclinical Portions of Labeling

Recommended changes to the Applicant's proposed wording for the nonclinical and related sections of 8.1, 8.2, 12.1, and 13.1 of the label are provided below. It is recommended that the underlined wording be inserted into and the strikethrough wording be deleted.

INDICATIONS AND USAGE
TRADENAME is an interleukin-23 (IL-23) receptor antagonist (b) (4) -indicated for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy. (1)

1 INDICATIONS AND USAGE

TRADENAME is indicated for the treatment of moderate-to-severe plaque psoriasis in adults and pediatric patients 12 years of age and older who are candidates for systemic therapy or phototherapy (b) (4)

8.1 Pregnancy

Risk Summary

Available data (b) (4) pregnancy are insufficient to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. (b) (4)

In an animal reproduction study in rabbits (b) (4), oral administration of icotrokinra to pregnant rabbits during the period of organogenesis at a dose 157 times the maximum recommended human dose (MRHD) based on AUC comparison resulted in maternal body weight loss, low food consumption, late pregnancy loss , and an increased fetal incidence of fused ribs (b) (4) *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes The background risk of major birth defects and miscarriage for the indicated population is unknown. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

Data

Animal Data

(b) (4) -In an embryo-fetal development study, icotrokinra was administered to pregnant rats during the period of organogenesis at oral doses of 70, 200, and 1000 mg/kg/day. No maternal or embryo-fetal toxicity was observed at doses of up to 1000 mg/kg/day (297 times the MRHD based on AUC comparison). In another embryo-fetal development study, icotrokinra was administered to pregnant rabbits during the period of organogenesis at oral doses of 50, 200, and 500 mg/kg/day. Maternal body weight loss, low

food consumption, (b) (4) late pregnancy loss, and an increased fetal incidence of fused ribs were observed at 500 mg/kg/day (157 times the MRHD based on AUC comparison). No maternal or embryo-fetal toxicity was noted at doses of up to 200 mg/kg/day in rabbits (27 times the MRHD based on AUC comparison). (b) (4)

In a pre- and post-natal development study in rats, (b) (4) icotrokinra was administered to pregnant rats during pregnancy and lactation periods at oral doses of 20, 70, and 200 mg/kg/day. No maternal or developmental toxicity was noted in doses of up to 200 mg/kg/day (b) (4) (127 times the MRHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of icotrokinra in human milk, the effects on the breastfed infant, or on milk production. When administered to lactating rats, icotrokinra was detected in the plasma of nursing pups *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

Data

(b) (4)

In a pre- and post-natal development study in rats, icotrokinra was administered orally to pregnant rats during pregnancy and lactation periods (b) (4) -at doses up to 200 mg/kg/day (127 times the MRHD based on AUC comparison). Although not directly measured in rat milk, icotrokinra was detected in the plasma of nursing rat pups. No adverse developmental effects were observed on nursing pups.

12.1 Mechanism of Action

Icotrokinra is a peptide that selectively binds to the IL-23 receptor (IL-23R) with a dissociation constant of 7 pM (b) (4) and (b) (4) antagonizes the binding of IL-23. IL-23 is a naturally occurring cytokine that is involved in (b) (4) Icotrokinra inhibits the IL 23/IL-23R-dependent release of proinflammatory cytokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

(b) (4)

In a 6-month transgenic rasH2 mouse study, no drug-related tumors were observed at oral doses of icotrokinra up to 500 mg/kg/day (76 times the MRHD based on AUC comparison). In a 2-year rat carcinogenicity study, no drug-related tumors were observed at oral doses of up to 20 mg/kg/day (16 times the MRHD based on AUC comparison).

Icotrokinra was not genotoxic in an vitro bacterial reverse mutation (b) (4) assay (the Ames test), in an in vitro human lymphocyte chromosomal aberration assay, or ~~in~~ an in vivo rat micronucleus and Comet assays.

In male rats, icotrokinra had no adverse effect on mating, fertility or early embryonic development of their offspring at oral doses of up to 20 mg/kg/day (114 times the MRHD based on AUC comparison).

In female rats, icotrokinra had no adverse effect on estrous cyclicity, mating, fertility, or early embryonic parameters at oral doses of up to 70 mg/kg/day (335 times the MRHD based on AUC comparison).

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Summary of In Vitro Studies

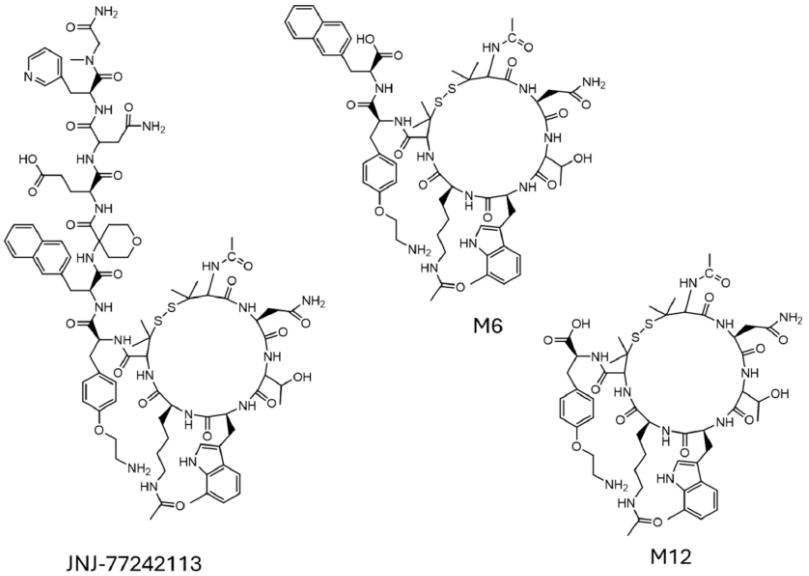
Clinical pharmacology-related in vitro studies are summarized in Table 80.

Icotrokinra is also referred to by the name JNJ-77242113 and PN-235. These names are used interchangeably.

Table 80. Summary of In Vitro Studies

Report Number/Objectives	Summary Findings and Key Conclusions
	Absorption
FK14168: To evaluate the permeability of JNJ-77242113 in Caco-2 cells monolayers in the absence or presence of (b) (4)	Caco-2 cell monolayers were incubated with two transport media, TM1 [Hanks Balanced Salt Solution (HBSS (+Ca/+Mg)) + 10mM Hepes, pH 7.4] used in the basolateral (acceptor) compartment and TM2 [HBSS (-Ca/-Mg) + 10mM Hepes + phenol red, pH 7.4] used in the apical (donor compartment) to avoid (b) (4) precipitation in the donor compartment but to still subject Caco-2 cells to divalent-cation-containing buffer. JNJ-77242113 (100 µM) was coincubated with (b) (4) for 30 and 120 minutes. Control compounds included ^{14}C-mannitol (low permeability marker), ^{3}H-atenolol (moderate permeability marker), ^{3}H-metformin (moderate permeability marker) and ^{3}H-propranolol (high permeability marker). 8, 10, 15 and 20mM) for 30 and 120 minutes. Control compounds included ^{14}C-mannitol (low permeability marker), ^{3}H-atenolol (moderate permeability marker), ^{3}H-metformin (moderate permeability marker) and ^{3}H-propranolol (high permeability marker). In the absence of the (b) (4), the apparent permeability ($P_{app, A to B}$) of JNJ-77242113 was 0.134×10^{-6} cm/s at 30 minutes incubation and 0.022×10^{-6} cm/s at 120 minutes incubation. (b) (4) of JNJ-77242113 (apparent permeability of 0.204×10^{-6} cm/s at 30 minutes incubation: 52% increase). However, higher concentrations of (b) (4) resulted in cell toxicity when incubated for 30 minutes, which confounded the permeability results. At 30 minutes incubation, the $P_{app, A to B}$ of the ^{3}H-propranolol was 6.45×10^{-6} cm/s and for the low and moderate permeability markers it was in the range of 0.0.765 to 1.57×10^{-6} cm/s. In the in vivo animal study (FK13784), a single oral dose 40 mg base-eq./kg JNJ-77242113 was administered to male P-gp Mdr 1a/b knock out and wild type mouse. Results indicate no or only minor P-gp effect on the absorption of JNJ-77242113. *JNJ-77242113 has low permeability across CaCo-2 cell monolayers.*
FK13809: to investigate whether JNJ-77242113 is a substrate of P-gp	The bidirectional permeability of ^{14}C-JNJ-77242113 was evaluated in triplicate in both LLC-PK1-MDR1 and Mock cells monolayers. Efflux ratios of ^{14}C-JNJ-77242113 at 1 µM concentration were 1 and 1.1 in the absence or presence of the P-gp inhibitor, valspodar (2µM), respectively. Over the concentration range studied (1-300M) in the absence of valspodar, permeability of ^{14}C-JNJ-77242113 was low and not saturable with no significant change in efflux ratio values (0.7 to 1.2) in LLC-PK1-MDR1 cells. Efflux ratios of ^{14}C-JNJ-77242113 were less than 2 in LLC-PK1-Mock cell monolayers. *JNJ-77242113 is not a P-gp substrate.*
	Distribution
FK13680: to evaluate the binding of JNJ-77242113 in human,	The binding of JNJ-77242113 (0.01, 0.1, and 1µM) to human plasma proteins ranged from 49.74% to 55.18% (F_u range from 49.7% to 55%).

Report Number/Objectives	Summary Findings and Key Conclusions
plasma and human purified plasma proteins albumin and α-1-acid glycoprotein (AAG).	In 4% albumin, 0.07% AAG, and 0.14% AAG, protein binding of 1µM JNJ-77242113 was 64%, 98%, and 91.5% respectively.
FK13811: to determine the whole blood to plasma partition ratio of JNJ-77242113 in pooled human	The ratio of JNJ-77242113 concentration in whole blood cells to the concentration in plasma was 0.49 to 0.61 across the tested JNJ-77242113 concentrations (2.5, 25, and 250 ng/mL) following incubation for 2 hours.
Metabolism	
ADME-102294: to determine the in vitro intrinsic clearance (CL_{int}) of JNJ-77242113 in pooled human cryopreserved hepatocytes	Following the incubation of 1µM JNJ-77242113 for up to 120 minutes with pooled human cryopreserved hepatocytes from 20 donors, the $t_{1/2}$ and CL_{int} of JNJ-77242113, were >371 minutes and <1.87 µL/min/10^6 cells, respectively.
FK13753: to evaluate the in vitro stability of JNJ-77242113 in feces and gut mucosa from human as well as the purified GI enzymes pepsin, trypsin, chymotrypsin, and pancreatin	JNJ-77242113 (50µM) was incubated, in duplicate for up to 24 hours, in human fecal homogenates (6.25% (w:v)) and duodenum, jejunum/ileum, and colon mucosa (20% (w:v)) from human. Stability of JNJ-77242113 (50µM) was also assessed in simulated gastric fluid (SGF) and the purified gastrointestinal (GI) enzymes (1 mg/mL) pepsin, trypsin, chymotrypsin, and pancreatin. Risperidone (10µM) and vapreotide (10µM) were used as the control compounds in the fecal stability assays. Aspirin (10µM) and vapreotide (10µM) were used as the control compounds in the mucosal stability assays. Insulin (25µM) and vapreotide (10µM) were used as the controls in the GI enzymes stability assays. JNJ-77242113 was stable in human feces, duodenum, jejunum/ileum, and colon mucosa and in each of the purified GI enzymes pepsin, trypsin, chymotrypsin, and pancreatin with mean $t_{1/2}$ value of >24 hours.
PTG-B2-004: to identify the in vitro metabolite(s) of JNJ-77242113 formed by the proteolytic enzymes in human fecal homogenate.	Following incubation of JNJ-77242113 (200µM) in human pooled fresh fecal homogenate (0.25 g/mL) at 37°C for up to 48 hours under anaerobic condition. The homogenate was centrifuged, and the supernatant was used as the fecal homogenate. A total of 5 metabolites were detected in human fecal incubations.
FK13893: to evaluate the in vitro stability and binding of JNJ-77242113 in human pooled kidney tissue homogenates	Following incubation of JNJ-77242113 (0.02, 0.2, and 2µM) in triplicate for 24 hours in human kidney tissue homogenates (20% (w:v)), the binding to human kidney tissues ranged from 92.97% to 96.74% with no concentration-dependent bindings. JNJ-77242113 was stable in human kidney tissue homogenates with $t_{1/2}$ >24 hours. Diclofenac (1µM) and lopinavir (1µM) were tested as the low and high binding controls, respectively, in the tissue homogenate binding assays. Vapreotide (5µM) was tested as the control compound in the tissue stability assay.
FK14612: to investigate the renal metabolism of JNJ-77242113 by	After incubating ^{14}C-JNJ-77242113 (20µM) for 24 hours with human kidney tissue homogenates (2 mg/mL proteins) for 24 hours, the main metabolites identified were M6 and M12 generated from the hydrolysis of the amid bond between 2Nal-THP and

Report Number/Objectives	Summary Findings and Key Conclusions
examining the drug profiles obtained from incubations with kidney homogenates	AEF-2Nal. Metabolites M6 and M12 represented 36% and 16% of the total drug related species, respectively. The unchanged JNJ-77242113 was 49% of drug related materials.  JNJ-77242113 M6 M12
	Drug-Drug Interaction
FK13675: to evaluate potential of JNJ-77242113 to inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 in pooled human cryopreserved hepatocytes	Using pooled human cryopreserved hepatocytes from 20 mixed [redacted] donors, the IC_{50} for the reversible inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 was >100µM. Maximum inhibition at the highest concentration tested (100µM) compared to vehicle control was less than 10% for all the isoforms, except CYP1A2 (19%) and CYP2E1 (30%).
FK14581: to evaluate the reversible inhibitory potential of JNJ-77242113 against CYP3A4	In cryopreserved human hepatocytes from a pool of 20 mixed-[redacted] donors, the IC_{50} for the inhibition of CYP3A4 by JNJ-77242113 (0.1 to 100 µM) was >100µM when measured in triplicate using testosterone as CYP3A4 substrate.
FK13809: to investigate whether JNJ-77242113 has potential for inhibiting P-gp activity	The transport inhibitory effect of JNJ-77242113 (1 to 600µM) on P-gp substrate [^{3}H] digoxin (10µM) was examined in Caco-2 cell monolayers. No inhibition of P-gp at the highest tested concentration of 600µM.
FK14279: to investigate whether JNJ-77242113 is a substrate and an inhibitor of several uptake or efflux transporters in intestine, liver, or kidney	The uptake of JNJ-77242113 (nominal concentrations of 0.25, 2.5 and 5µM) following incubation up to 30 minutes showed no difference between HEK293-OATP1B1, -OATP1B3, -OAT1 and -OCT2 and MDCK-II- OAT3, -MATE1, or -MATE2-K overexpressing cells and mock/parent cells without an effect of the positive control inhibitors on the uptake of JNJ-77242113. Of note, after incubating JNJ-77242113 (2.5 and 5µM) for 10 minutes with MDCK-II-OAT3 overexpressing cells, the dynamic range was 2.08 and 2.12, respectively, but the uptake was not reduced by more than 50% when coincubated with the selective

Report Number/Objectives	Summary Findings and Key Conclusions
	inhibitor (probenecid 300µM). In addition, at 0.25µM JNJ-77242113, the dynamic range was below 2. Therefore, JNJ-77242113 is not a substrate of OAT3. After incubating JNJ-77242113 (2.5 and 5µM) for 30 minutes with MDCK-II-MATE2-K overexpressing cells, the dynamic range was 4.09 and 4.03, respectively, but the uptake was not reduced by more than 50 % when coincubated with the selective inhibitor (pyrimethamine 100µM). However, uptake in mock cells reduced more than 3-fold after 30 minutes of incubation compared to the 10 minutes incubation. This decrease in function of time is not observed after incubation with MATE2-K cells. This phenomenon was not observed in all other investigated cell lines. Therefore, the results of the 30 minutes incubations should be interpreted carefully. The efflux ratios of JNJ-77242113 (nominal concentration of 2.5 and 5µM) following incubation for 240 minutes in transfected LLC-PK1-BCRP cells are 0.0154 and 0.0100, respectively and the efflux ratios with inhibitor are 0.0209and 0.0145, respectively, and it was comparable to LLC-PK1-mock cells. Suggesting that JNJ-77242113 is not a BCRP substrate. The potential for JNJ-77242113 to inhibit OAT1, OAT3, OCT2, MATE1, MATE2-K and BCRP was determined in uptake transporter inhibition assays using HEK293 (OATP1B1, OATP1B3,OAT1, OCT2) or MDCKII (OAT3, MATE1, MATE2-K) cells stably expressing the respective uptake transporter. JNJ-77242113 showed a maximum inhibition of OATP1B1 at 24.7µM (43.9%, IC_{50}=24.7µM), OATP1B3 at 24.2µM (48%, IC_{50}=24.2µM) and BSEP at 29.7µM (13.9%, IC_{50}=29.7µM). The IC_{50} for the inhibition of OAT1, OAT3, OCT2, MATE1, MATE2-K, BCRP was >22.5µM, >26.2µM, >22.7µM, >22.5µM, >22.2µM, >24.8µM *JNJ-77242113 is not a substrate or inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K and BCRP and it is not an inhibitor of BSEP*.
FK14481: to evaluate the effect of A23HD1353 (JNJ-77242113) as an inducer of human CYP1A2, CYP2B6 and CYP3A4.	In cryopreserved primary human hepatocyte cultures from 3 donors, A23HD1353 (0.1 to 90µM) was not an inducer of CYP1A2, CYP2B6 and CYP3A4 with maximum mRNA fold change of ≤1.78 across the three hepatocyte cultures with little or no effect (i.e., <2-fold change) on LDH release.

Report Number/Objectives	Summary Findings and Key Conclusions
ADME-102266: to evaluate the potential of JNJ-77242113 to activate human nuclear receptors PXR and AhR	DPX2 cells harboring hPXR and a luciferase reporter vector containing the promoter and enhancers from the CYP3A4 gene were utilized to assess human PXR activation. Human hepatoma cell line stably transformed with a luciferase reporter vector containing the promoter and enhancers from the CYP1A2 gene (1A2-DRE cell line) was utilized to assess human AhR activation. Positive controls include rifampicin 10µM was employed for DPX2 cells and omeprazole 100µM was used for 1A2-DRE cells. JNJ-77242113 (1 and 10µM) incubated with both cell lines for 24 hours did not exhibit activation of PXR or AhR, producing either 0% or 1% of the response exhibited by the positive controls at the concentrations tested. JNJ-77242113 (1 and 10µM) exhibited 0.97 and 1.15-fold increases in hPXR activation, respectively, and 1.20 and 1.13-fold increase in hAhR activation, respectively. *JNJ-77242113 at 1µM and 10µM did not activate hPXR or hAhR in vitro.*

Source: Reviewer's generated table based on in vitro studies.
Abbreviations: P_{app}, apparent permeability; BCRP, breast cancer resistance protein; P-gp, P-glycoprotein; MDR1, multidrug-resistant protein 1; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; CYP, cytochrome P450 enzymes; HLM, human liver microsomes; IC50, inhibitor concentration producing 50 % inhibition of enzyme activity; mRNA, messenger ribonucleic acid; MATE, multidrug and toxin extrusion protein; hPXR, human pregnane X receptor; hAhR, human aryl hydrocarbon receptor; BSEP, bile salt export pump; Caco-2, human colorectal adenocarcinoma cell line; TM, transport media; HBSS, Hanks Balanced Salt Solution; LLC-PK1, LLC-PK1, pig kidney derived cell line; Fu, fraction unbound; AAG, α-1-acid glycoprotein; Clint, intrinsic clearance; w:v, weight per volume; SGF, simulated gastric fluid; GI, gastrointestinal; $t_{1/2}$, half-life; MDCK-II, Madin-Darby canine kidney cells; HEK293, human embryonic kidney cells

19.4.2. Summary of Clinical Pharmacology Studies

As summary of the clinical pharmacology program for the development of icotrokinra is provided in Table 81. Icotrokinra is also referred to by the name JNJ-77242113 and PN-235. These names are used interchangeably.

Table 81. Summary of Clinical Pharmacology Program

Trial	Design and Objectives	Drug Product and Formulation	Dose Regimen
PN-235-01	Randomized, double-blind, placebo-controlled, single and multiple ascending doses to determine the safety, tolerability, PK, food effect, and PD of PN-235 in healthy adult subjects	• Oral solution: 0.33 to 33 mg/mL • Delayed release (DR) film-coated tablet (FCT) with and without (b) (4)	SAD: 10, 25, 100, 300, or 1000 mg oral solution in fasted state. MAD: 10, 25, 100, 300, or 1000 mg oral solution once daily (QD) for 10 consecutive days. Food Effect: DR tablet (b) (4) with an (b) (4) in fasted stated and with high-fat meal. Relative BA: (b) (4) DR tablet without (b) (4) compared to 25 oral solution in fasted state.
PSO1002	Randomized, double-blind, placebo-controlled, single dose study to evaluate the	• Immediate Release (IR) FCT (Lot # G014): 100 mg	Part 1: Single dose of 100 (1×100-mg tablet) and 300 mg (3×100-mg tablet)

Trial	Design and Objectives	Drug Product and Formulation	Dose Regimen
	safety, tolerability, and PK of JNJ-77242113 after SAD administration in Japanese and Chinese healthy adult subjects.	• DR FCT with (b) (4)	JNJ-77242113 IR FCT in Japanese subjects. Part 2: Single dose of 300 mg (3×100-mg tablet) JNJ-77242113 IR FCT in Chinese subjects. Part 3: Single dose of 50 mg (1×50-mg tablet) JNJ-77242113 DR FCT in Japanese subjects
PSO1004	Open-label, single-dose study conducted to evaluate the PK, safety, and tolerability of JNJ-77242113 in healthy Chinese adult subjects	IR FCT (Lot #G014): 100 mg	Single doses of 100 mg (1×100-mg tablet), 300 mg (3×100-mg tablet) and 1000 mg (10×100-mg tablet)
PSO1003	Part 1 was randomized, open-label, 3-way crossover, single-dose, study to evaluate the relative oral bioavailability of a JNJ-77242113 IR tablet phase 2 formulation (Lot # G014) versus an oral solution formulation, to evaluate the effect of food on the PK of a JNJ-77242113 IR tablet Phase 2 formulation, and to assess the safety and tolerability of single-dose oral administration of JNJ-77242113 in healthy subject. Part 4 consisted of Cohorts 5 and 6 each was a randomized, open-label, 4-way crossover, single-dose study in healthy subjects. Both cohorts in Part 4 evaluated the effect of different types of meals, the timing of a meal, and additional water intake on the bioavailability and PK of JNJ-77242113.	Oral Solution: 3.333 mg/mL IR FCT (G014): 100 mg	Relative bioavailability of IR tablet to oral solution: 100 mg single dose in fasted state. Food effect on IR FCT: 100 mg with high-fat meal, low-fat meal, 30 minutes before high-fat meal, 2 hours after completion of high-fat meal, 1 hours after completion of high-fat and with 480 mL water (fasted) in comparison to administration of the IR FCT in with 240 mL in fasted state.
PSO1006	Single-dose, open-label, randomized, 3-way crossover study to	• IR FCT (Lot # G014): 100 mg	Subjects received single oral dose of 200 mg (1×200-mg tablet) as clinical IR FCT (Lot #G078) in fasted and fed states

Trial	Design and Objectives	Drug Product and Formulation	Dose Regimen
	evaluate the relative oral bioavailability of JNJ-77242113 phase 3 clinical IR tablet formulation (Lot # G078) versus phase 2 IR tablet formulation (Lot # G014) and the impact of high-fat breakfast (1000 calories, 50% fat) on the PK of JNJ-77242113 clinical IR tablet formulation (Lot # G078) in healthy adult subjects	• IR FCT (Lot #G078): 200 mg	or a single oral dose of 200 mg (2×100-mg tablet) as phase 2 IR FCT (Lot #G014) in fasted state.
PSO1009	Randomized, open-label, single-dose, 4-way crossover study to evaluate the effect of caffeine solution, whole milk, and sucrose solution on the relative bioavailability of JNJ-77242113 IR FCT (Lot #G078), the clinical formulation, in healthy adult subjects	IR FCT (Lot #G078): 200 mg	Subjects received single oral dose of 200 mg (1×200-mg tablet) as clinical IR FCT (Lot #G078) in fasted state with 240 mL noncarbonated water, caffeine solution, whole milk, or sucrose solution.
PSO2001	Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study to evaluate the dose response of icotrokinra at Week 16 in adult subjects with moderate to severe plaque PsO.	• IR FCT (Lot # G14): 100 mg • IR FCT (G012): 25 mg	Subjects were randomized equally to received icotrokinra (25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD or 100 mg BID) or placebo.
PSO3001	Phase 3, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the clinical efficacy and safety of icotrokinra in subjects ≥12 years of age with moderate to severe plaque PsO	IR FCT (Lot #G078): 200 mg	Subjects received icotrokinra 200 mg QD or placebo QD
PSO3002	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, and deucravacitinib active comparator-controlled study to evaluate the clinical efficacy and safety	IR FCT (Lot #G078): 200 mg	Subjects received icotrokinra 200 mg QD or placebo QD

Trial	Design and Objectives	Drug Product and Formulation	Dose Regimen
	of icotrokinra in adults with moderate to severe plaque PsO		
PSO3003	Phase 3, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the clinical efficacy and safety of icotrokinra in subjects ≥12 years of age with at least moderate plaque PsO involving special areas (scalp, genital, and/or hand/foot)	IR FCT (Lot #G078): 200 mg	Subjects received icotrokinra 200 mg QD or placebo QD
PSO3004	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, and deucravacitinib active comparator-controlled study to evaluate the clinical efficacy and safety of icotrokinra in adults with moderate to severe plaque PsO	IR FCT (Lot #G078): 200 mg	Subjects received icotrokinra 200 mg QD or placebo QD

Source: Reviewer's generated table based on the complete reports of the listed studies.
Note, Lot # G014 is phase 2 formulation. Lot # G078 is the clinical formulation used in the four phase 3 studies. The to-be-marketed formulation is the IR FCT used in phase 3 studies but debossed.
Abbreviations: IR, immediate release; DR, delayed release; FCT, film-coated tablet; QD, once daily; BID, twice daily; PsO, psoriasis; SAD, single ascending dose; MAD, multiple ascending doses; PK, pharmacokinetic; PD, pharmacodynamic

19.4.2.1. Single Dose and Multiple Dose Studies in Healthy Subjects

19.4.2.1.1. Trial PN-235-01

Trial PN-235-01 was first-in-human, single-center, randomized, double-blind, placebo-controlled, single and multiple ascending dose study to determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of PN-235 in healthy adult subjects. This trial included three parts as follows.

Part 1: Single Ascending Dose (SAD) of PN-235 Oral Solution

A sequential single dose-escalation design with 5 cohorts of healthy adult subjects with 2 subjects received placebo and 6 subjects received PN-235 in each cohort. Subjects received a single dose of 10, 25, 100, 300, or 1000 mg oral solution (0.33 to 33 mg/mL) following an overnight fast of approximately 10 hours and remained fasted for approximately 4 hours after dosing. Blood samples were collected at pre-dose and up to 48 hours to evaluate the plasma concentrations of PN-235.

Part 2: Multiple Ascending Dose (MAD) of PN-235 Oral Solution

Part 2 includes 5 cohorts of healthy adult subjects with 2 subjects received placebo and 8 subjects received PN-235 in each cohort. Subjects received once daily doses of 10, 25, 100, 300, or 1000 mg PN-235 oral solution (0.33 to 33 mg/mL) for 10 consecutive days. On Day 1 and 10, subjects administered PN-235, or placebo following an overnight fasting of approximately 10 hours and remained fasted for approximately 4 hours after dosing. On other days, subjects fasted for approximately 2 hours before and after dosing.

For PK assessment, blood samples were collected at pre-dose and up to 24 hours after the first dose with pre-dose samples collected before the second (24 hours), third (48 hours) and fourth (72 hours) dose and a single sample 12 hours after the second dose (i.e., 36 hours after the first dose). Additional single pre-dose samples were collected on Days 6, 8, 9. Blood samples were collected up to 48 hours following the last dose on Day 10. For pharmacodynamic assessment, blood samples were collected at pre-dose and up to 24 hours following the administration of the first and last doses. For immunogenicity assessment, blood samples were collected at pre-dose and on Day 10 and end of study (Day 17). Urine samples were collected for 24 hours (Day 8 to Day 9 at the following times: 0 to 6 hours, 6 to 12 hours, and 12 to 24 hours). Fecal samples for assessment of fecal excretion were collected for 24 hours on Day 7 to 8.

Additional cohort (Cohort 13) of subjects who received 100 mg once daily was added to Part 2 for sigmoidoscopies and intestinal biopsies to allow measurement of the drug concentrations in the intestinal mucosa and evaluation of IL-23 receptor engagement in the tissue of interest as an exploratory endpoint. This additional Cohort 13 will not be discussed in this review.

Part 3: Oral Tablet Comparison and Effect of Food

This part was randomized, 4-way crossover to evaluate the oral bioavailability of a delayed-release oral tablet of PN-235 relative to the oral solution used in the SAD/MAD (Parts 1 and 2), the effect of an (b) (4) on the absorption of PN-235, and the effect of food on the delayed-release oral tablet with (b) (4) formulation. The delayed-release oral tablets with and without the (b) (4)

Subjects were randomized to receive 25 mg PN-235 on Day 1, 8, 15, and 22 with washout period of 5 days between treatments. Each subjects received the following treatments:

- 25 mg PN-235 as an oral solution in the fasted state.
- (b) (4) PN-235 as a delayed-release oral tablet without (b) (4) (Lot #G004) in the fasted state.
- (b) (4) PN-235 as a delayed-release oral tablet with an (b) (4) (Lot # G003) within 30 minutes of consuming a high fat, high calorie breakfast.
- (b) (4) PN-235 as a delayed-release oral tablet with an (b) (4) in a fasted state.

Subjects fasted for at least 10 hours before and for 4 hours after dosing, with the exception during the fed treatment when subjects received a standard high-fat meal prior to dosing. The high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes (one serving of approximately 114 g) and 240 mL of whole milk.

Blood samples were collected at predose and up to 48 hours to evaluate the plasma concentrations of PN-235.

Pharmacokinetic Results

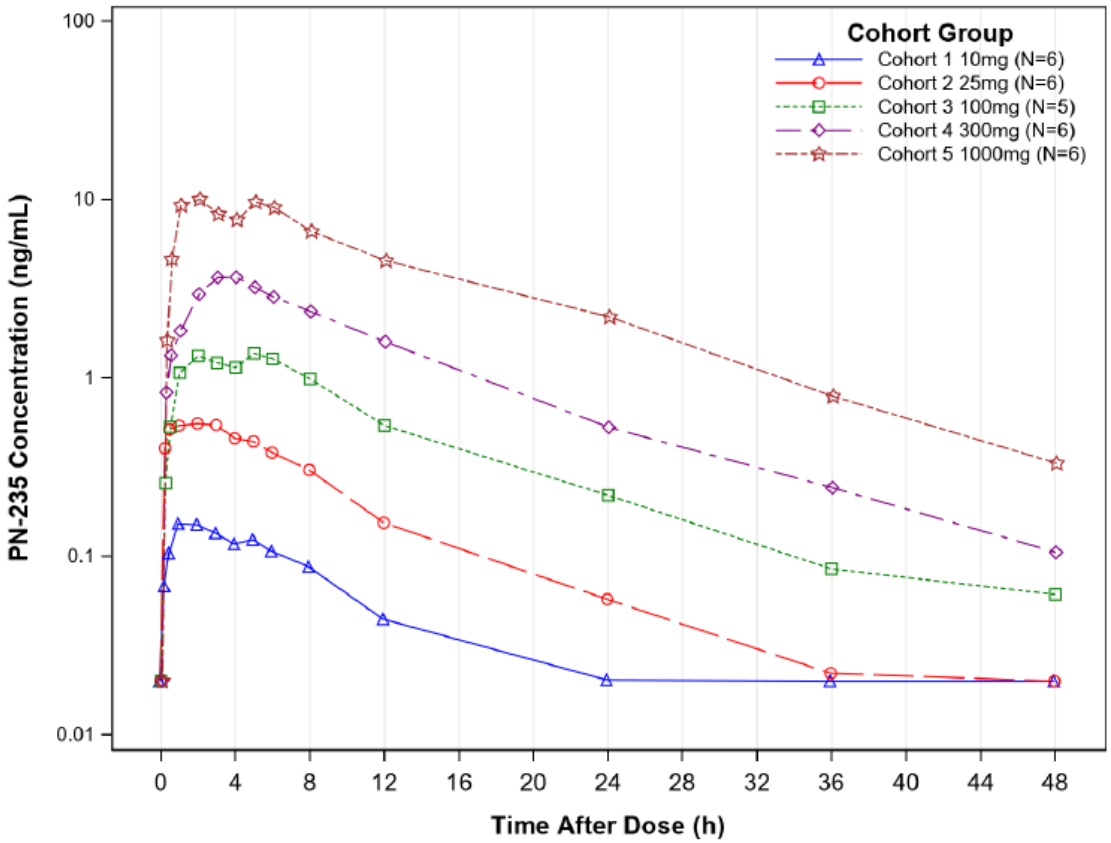
All study subjects (59.8% White and 35.5% Asian) were males with the exception of one female subject in Part 3.

Part 1: SAD

The mean plasma concentrations time profiles and a summary of PK parameters following the administration of single doses of PN-235 oral solution are provided in Figure 37 and Table 82. PN-235 has a median time to maximum concentration (t_{max}) of 1.5 to 4 hours and a mean elimination half-life ($t_{1/2}$) of 5 to 12 hours across the dose levels 10 to 1000 mg.

Results of the power model showed that PN-235 has approximately dose-proportional PK with slope parameter for AUC_{last} and $AUC_{0\text{-}inf}$ close to unity, 1.006 (90% confidence interval (CI): 0.922 to 1.09) for AUC_{last} and 0.972 (90% CI: 0.895 to 1.049) for AUC_{inf}, whereas the slope parameter for C_{max} was 0.881 (90% CI: 0.778 to 0.983).

Figure 37. Mean Plasma Concentration-Time Profiles of PN-235 Following the Administration of Single Doses of PN-235 Oral Solution in Trial PN-235-01 – Log-Linear Scale



Source: Study PN-235-01 Report, Figure 14.2.15

Table 82. Mean±SD Parameters of PN-235 Following the Administration of Single Doses of PN-235 in Trial PN-235-01

	Cohort 1 10 mg PN-235 (N=6)	Cohort 2 25 mg PN-235 (N=6)	Cohort 3 100 mg PN-235 (N=5)	Cohort 4 300 mg PN-235 (N=6)	Cohort 5 1000 mg PN-235 (N=6)
C_{max} (ng/mL)	0.17±0.09	0.79±0.5	1.48±0.4	3.97±1.9	12.2±5.7
T_{max} (h)[a]	2.5 (1.0, 5.0)	1.5 (0.5, 5.0)	3.0 (2.0, 6.0)	4.0 (3.0, 8.0)	3.5 (1.0, 6.0)
AUC_{last} (ng·h/mL)	1.3±0.74	6.1±2.9	19.3±5.2	49.5±20.1	152±24.0
AUC_{∞} (ng·h/mL)	1.6±0.73	6.5±2.8	20.7±6.5	51.0±20.6	156±23.5
$t_{½}$ (h)	5.0±0.5	8.5±2.4	11.7±5.4	9.6±1.3	8.7±1.3
CL/F (L/h)	7425±2632	4534±1954	5230±1688	7074±3691	6528±1047
Vz/F (L)	52450±18873	59891±43564	84257±30790	95604±43429	83403±23461

Source: Study PN-235-01 Report, Table 11
Abbreviations: AUC∞, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation.
[a] Median (min, max) reported

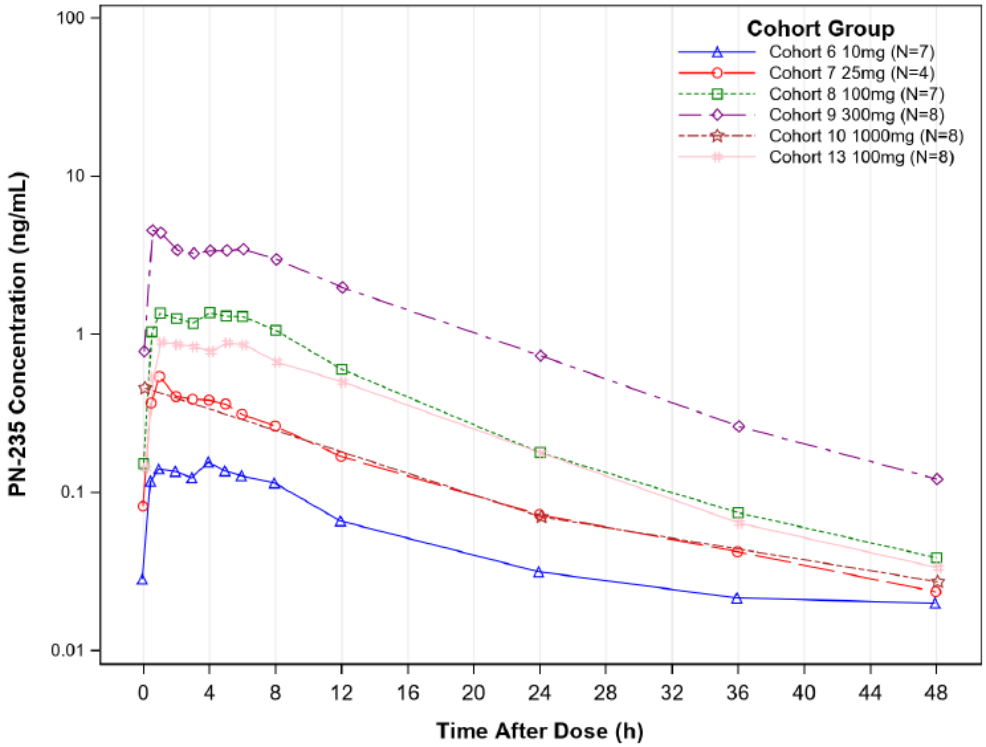
Part 2: MAD

The mean plasma concentrations time profiles and a summary of PK parameters following the administration of multiple doses of PN-235 are provided in Figure 38 and Table 83. The media t_{max} range from 1.5 to 5 hours on Day 1 and 1 to 6 hours on Day 10 after the administration of PN-235 once daily for 10 days with a $t_{1/2}$ of 9 to 16 hours on Day 10. The accumulation ratios following the administration of PN-235 10 to 1000 mg once daily were 0.9 to 1.5 based on AUC and 0.7 to 1.6 based on C_{max} (Table 83).

Results of the power model showed that PN-235 has dose-proportional PK with slope parameter for C_{max} and AUC_{0-24} close to unity. The slope parameter for AUC_{0-24} was 0.948 (90% CI: 0.861 to 1.035) on Day 1 and 0.932 (90% CI: 0.837 to 1.027) on Day 10. The slope parameter for C_{max} was 0.929 (90% CI: 0.811 to 1.047) on Day 1 and 0.931 (90% CI: 0.819 to 1.044).

Less than 0.001% of PN-235 was excreted intact in the urine. On the other hand, a notable fraction of PN-235 was stable in transit through the gastrointestinal tract and was detected in the feces (Table 84). PN-235 recovered in the feces was ranged from 37% at 10 mg (Cohort 6) to 81% at 1000 mg (Cohort 10) with high variability.

Figure 38. Mean Plasma Concentration-Time Profiles of PN-235 on Day 10 Following the Administration of Multiple Doses of PN-235 Oral Solution in Trial PN-235-01 – Log-Linear Scale



Source: Study PN-235-01 Report, Figure 14.2.15
Dosing in Cohort 10 (1000 mg once daily) was interrupted after one subject administered PN-235 was noted to have ventricular extrasystoles and a preliminary echocardiogram was misread as abnormal. Based upon this report, dosing in the entire cohort was stopped on Day 8. At the time dosing was interrupted, 8 subjects in Cohort 10 had completed 8 out of the planned 10 days of treatment, and 2 subjects had completed 7 days of treatment.

Table 83. Mean±SD PK Parameters of PN-235 Following the Administration of Once Daily Doses of PN-235 in Trial PN-235-01

	Cohort 6 10 mg PN-235 (N=8)		Cohort 7 25 mg PN-235 (N=4)		Cohort 8 100 mg PN-235 (N=8)		Cohort 9 300 mg PN-235 (N=8)		Cohort 10 1000 mg PN-235 (N=8)		Cohort 13 100 mg PN-235 (N=8)	
	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10[a]	Day 1	Day 10
C_{max} (ng/mL)	0.14±0.06	0.19±0.1[c]	0.57±0.28	0.55±0.23	3.3±3.8	1.6±0.8[c]	5.8±5.6	5.3±2.1	16.6±26.3	–	1.1±0.4	1.2±0.7
T_{max} (h)[b]	4.0 (1.0, 8.0)	4.0 (0.5, 5.0)[c]	1.5 (0.5, 5.0)	1.0 (0.5, 1.0)	1.5 (0.3, 8.0)	6.0 (2.0, 8.0)[c]	3.5 (1.0, 8.0)	1.0 (0.5, 6.0)	5.0 (0.5, 6.0)	–	4.5 (1.0, 6.0)	2.0 (0.5, 12.0)
AUC_{24} (ng·h/mL)	1.4±0.4[c]	2.0±0.4[c]	4.7±0.9	5.2±1.5	21.8±13.9	17.7±5.8[c]	52.1±33.7	53.4±14.6	145±162	–	11.1± 3.5	12.7±5.6
AI AUC	–	1.5±0.3[d]	–	1.1±0.4	–	0.9±0.3[c]	–	1.2±0.4	–	–	–	1.2±0.4
AI C_{max}	–	1.6±1.0[c]	–	1.2±0.8	–	0.7±0.4[c]	–	1.2±0.5	–	–	–	1.1±0.5
$t_{½}$ (h)	–	10.6±5.0[c]	–	15.7±7.7	–	9.9±2.1[c]	–	8.9±1.7	–	–	–	10.1±4.1
CL/F (L/h)	–	5382±1453[c]	–	5211±1831	–	6319±2495[c]	–	6101±2098	–	–	–	9742±4996
Vz/F (L)	–	83917± 59422[c]	–	132494± 116359	–	88917± 32268[c]	–	76348± 24483	–	–	–	160150± 142981

Source: Study PN-235-01 Report, Table 14.
Abbreviations: AUC_{24}, area under the plasma concentration time profile from time zero to 24 hours; CL/F; apparent total body clearance; C_{max}, maximum observed plasma concentration; t_{max}, time to the maximum plasma concentration; $t_{½}$, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; AI, accumulation ratio; SD, standard deviation.
[a] Dosing in Cohort 10 was stopped on Day 8.
[b] Median (min, max) reported
[c] N=7
[d] N=6

Table 84. Urinary Excretion and Fecal Recovery of PN-235 Following Oral Administration on Day 10

Parameters	Cohort 6 10 mg (N=8)	Cohort 7 25 mg (N=4)	Cohort 8 100 mg (N=8)	Cohort 9 300 mg (N=8)	Cohort 10 1000 mg (N=8)
$A_{urine,24}$ (µg) [a]	0	0.06±0.07	0.70±1.2	1.21±1.5	5.20±2.7
% Excrete,urine, 24[b]	0	0.0002± 0.0003	0.0007± 0.0012	0.0004± 0.0005	0.0005± 0.0003
$A_{fecal,24}$ (µg) [c]	3717± 4981	10406± 7849	47041± 47121	170908± 124394	806682± 600770
% Recover,fecal, 24[d]	37±5	42±31	47±47	57±41	81±60

Source: Study PN-235-01 Report, Tables 19 and 20
[a] Amount excreted in urine over 24 hours (Day 8 and 9)
[b] Percentage excreted in urine over 24 hours (Day 8 and 9)
[c] Amount recovered in feces over 24 hours on Day 7-8
[d] Percentage recovered in feces over 24 hours on Day 7-8Abbreviations: Aurine.24, amount excreted in urine over 24 hours; Afecal,24, amount excreted in feces over 24 hours; PN-235, icotrokinra; N, number of subjects

Part 3: Delayed-Release Oral Tablet Comparison and Effect of Food

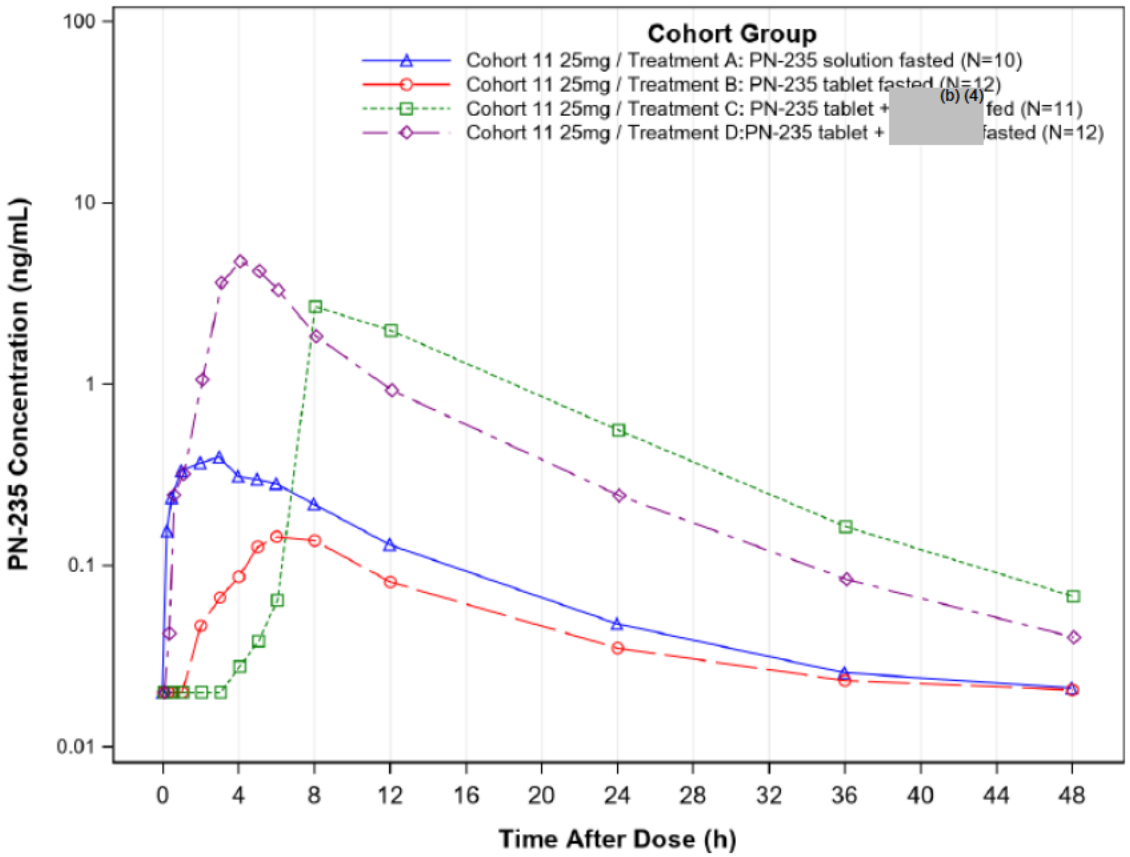
The mean PN-235 plasma concentration-time profile as an oral solution and as a delayed-release oral tablet is presented in Figure 39 and a summary of PK parameters is provided in Table 85.

There was a reduction in exposure with the delayed-release oral tablet without [(b) (4)] compared to the oral solution. The delayed-release tablet without an [(b) (4)] administered under fasted conditions had 6 hours delayed absorption with AUC_{last} ratio of 0.38 and C_{max} ratio of 0.34 relative to the oral solution (Table 86). The delayed-release oral tablet with [(b) (4)] administered under fasted conditions had AUC_{last} ratio of 8.05 and C_{max} ratio of 18.39 relative to the oral solution.

The [(b) (4)] improved the bioavailability of PN-235. The delayed-release tablet with [(b) (4)] had C_{max} ratio of 53.7 and AUC_{last} ratio of 21.29 relative to tablet without [(b) (4)] when both administered in fasted state (Table 86).

The administration of DR tablet with [(b) (4)] with a standard high-fat meal results in C_{max} ratio of 0.24 and AUC_{last} ratio of 0.63 relative to when administered in the fasted state (Table 86).

Figure 39. Mean Plasma Concentration-Time Profiles of PN-235 Following the Administration of Single Dose of PN-235 Oral Solution or Delayed-Release Tablet in Fasted or Fed State in Trial PN-235-01 – Log-Linear Scale



Source: Study PN-235-01 Report, Figure 14.2.15

Table 85. Mean±SD PK Parameters for PN-235 After Oral Administration as an Oral Solution, Delayed-Release Oral Tablets and Effect of Food in Trial PN-235-01

	Cohort 11 Treatment A PN-235 Solution Fasted (N=10)	Cohort 11 Treatment B PN-235 Tablet Fasted (N=12)	Cohort 11 Treatment C PN-235 Tablet + (b) (4) Fed (N=11)	Cohort 11 Treatment D PN-235 Tablet + (b) (4) Fasted (N=12)
C_{max} (ng/mL)	0.39±0.19	0.16±0.15	4.25±7.1	7.33±3.5
T_{max} (h)[a]	2.0 (1.0, 8.0)	8.0 (4.0, 12.0)	12.0 (5.0, 24.0)	3.5 (1.0, 6.0)
AUC_{last} (ng·h/mL)	4.5±2.0	2.0±1.6	45.0±60.6	37.6±19.8
AUC_{∞} (ng·h/mL)	5.1±2.0[b]	2.7±1.7[c]	70.1±75.5[d]	38.1±19.9
$t_{½}$ (h)	10.6±4.1[b]	11.0±4.1[c]	8.3±1.4[d]	8.7±1.7

Source: Study PN-235-01 Report, Table 17.
[a] Median (min, max) reported
[b] N=9
[c] N=10
[d] N=6
Abbreviations: C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC_{last}, area under the concentration-time profile from 0 to the last measured timepoint; AUC_{∞}, area under the concentration-time profile from 0 to infinity; $t_{1/2}$, elimination half-life; PN-235, icotrokinra; SD, standard deviation

Table 86. Statistical Analysis of PK Parameters of Delayed-Release Oral Tablet and Effect of Food on PN-235 Pharmacokinetics

	Treatment Comparison	N	Ratio of Geometric Mean	90% CI for Ratio of Geometric Mean
C_{max}	Treatment B vs A (B/A)	10	0.34	(0.177, 0.662)
	Treatment C vs A (C/A)	10	4.39	(2.246, 8.582)
	Treatment D vs A (D/A)	10	18.39	(9.523, 35.531)
	Treatment D vs B (D/B)	12	53.70	(28.761, 100.270)
	Treatment C vs D (C/D)	11	0.24	(0.126, 0.453)
AUC_{last}	Treatment B vs A (B/A)	10	0.38	(0.213, 0.671)
	Treatment C vs A (C/A)	10	5.06	(2.830, 9.052)
	Treatment D vs A (D/A)	10	8.05	(4.538, 14.285)
	Treatment D vs B (D/B)	12	21.29	(12.405, 36.540)
	Treatment C vs D (C/D)	11	0.63	(0.361, 1.096)
AUC_{∞}	Treatment B vs A (B/A)	7	0.46	(0.254, 0.848)
	Treatment C vs A (C/A)	5	6.67	(3.328, 13.374)
	Treatment D vs A (D/A)	9	7.23	(4.065, 12.852)
	Treatment D vs B (D/B)	10	15.59	(8.927, 27.221)
	Treatment C vs D (C/D)	6	0.92	(0.476, 1.788)

Source: Study PN-235-01 Report, Table 18.
Abbreviations: AUC∞, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; CI, confidence interval, Treatment A=oral solution fasted, Treatment B=tablet fasted, Treatment C=tablet + (b) (4) fed, Treatment D=tablet + (b) (4) fasted.
For evaluation of food effect, a mixed model with treatment and period as fixed effects and subject as random effect was performed on the natural log transformed C_{max}, AUC_{last}, and AUC_{∞} to evaluate the effect of a high fat meal. The 90% confidence intervals for the ratio of the geometric means of the fed to fasted state was estimated from the mixed model of the log transformed parameters.

Overall, administration of PN-235 as the delayed-release tablet without (b) (4) resulted lower exposure compared to the oral solution. Administration of PN-235 as a delayed-release tablet with the (b) (4) improved the bioavailability as noted by the higher C_{max} and AUC relative to the oral solution and the delayed-release tablet without the (b) (4)

Metabolite Profile and Identification of PN-235 in Plasma and Urine

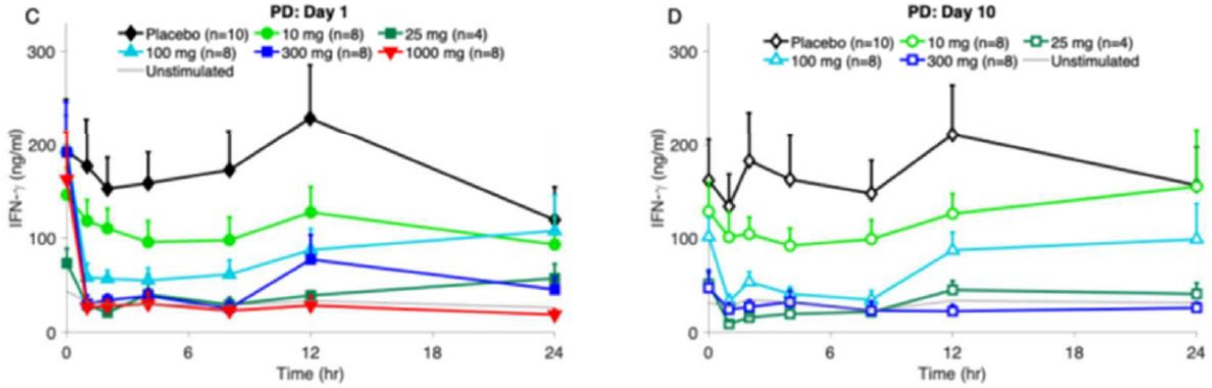
Metabolite profile of PN-235 in human plasma and urine was conducted after the administration of 300 mg once daily dose and 1000 mg single dose. Plasma samples were collected up to 240 hours for Cohort 9 (MAD dose 300 mg) and up to 192 hours for Cohort 10 (SAD dose 1000 mg) were selected for analysis. Urine samples of 0 to 6, 6 to 12 and 12 to 24 hours intervals collected on Day 8 for both Cohorts 9 and 10 were analyzed in this study. Unchanged PN-235 was the only drug related material in all plasma samples from both cohorts. No drug related materials were detected in the urine samples. Fecal samples were not available for analysis.

Pharmacodynamics Results

IL-23-Mediated IFN-γ Production

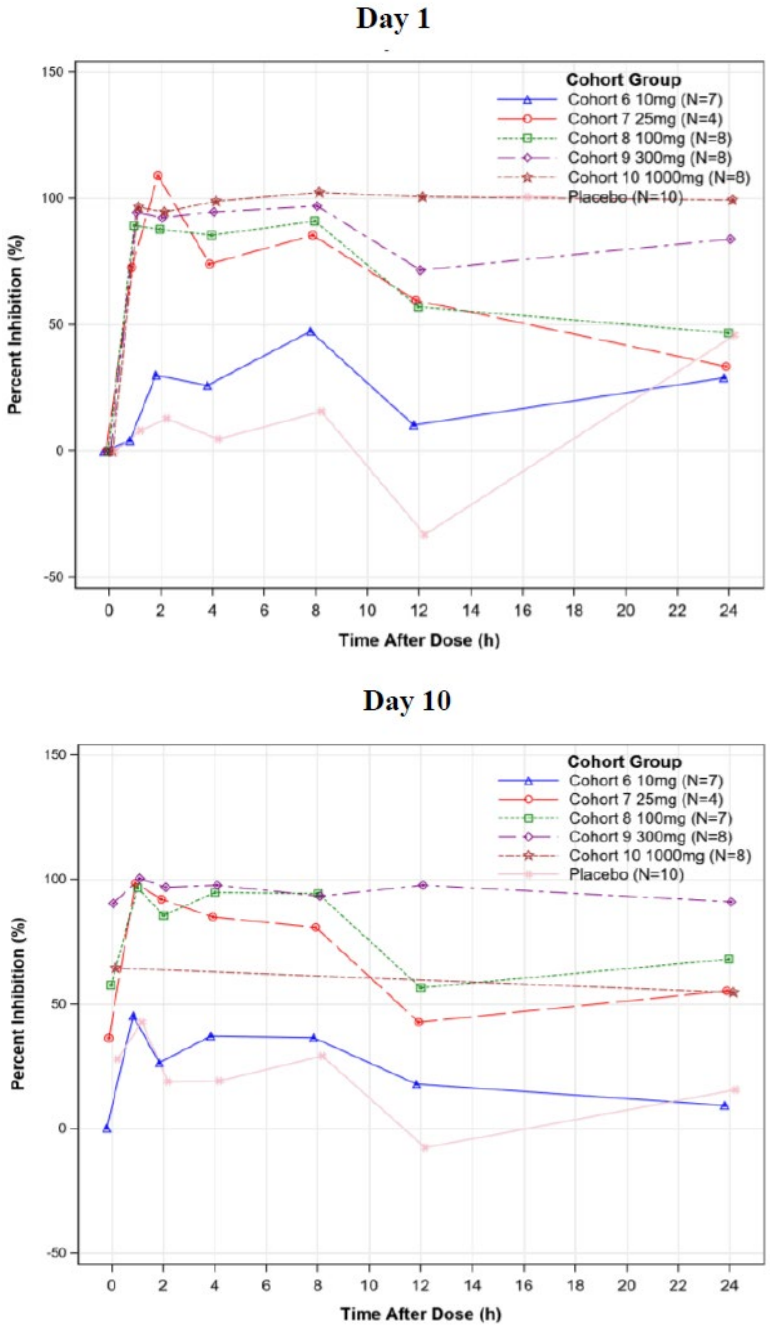
The effects of IL-23 on the production of interferon-γ (IFN-γ) from whole blood samples collected from healthy adult subjects enrolled in multiple-ascending dose part was determined. A decrease in the levels of IFN-γ in response to ex vivo IL-23 stimulation served as a PD readout for IL-23R inhibition by PN-235. On Day 1, there was a dose-dependent inhibition of IL-23-mediated IFN-γ release with approximately complete inhibition (100%) at PN-235 1000 mg that was sustained for at least 24 hours following the administration of the first dose. After the first 100 and 300-mg doses, there was approximately >75% inhibition in IFN-γ release which started to decline after approximately 8 hours post-dosing. The percentage inhibition from baseline in IFN-γ release was approximately 100% that lasted at least 8 hours and 20 hours following the last dose of 100 mg QD and 300 mg QD. The1000 mg cohort was not dosed on Day 10 (Figure 40 and Figure 41). Note that the 25 mg cohort only contained 4 subjects, and the baseline values (Figure 40) were lower in this cohort compared to the other cohorts and the low baseline values likely contribute to the low values seen in this cohort at all timepoints.

Figure 40. Mean+SE of Interferon-Gamma Following the Administration of Multiple Doses of PN-235 in Trial PN-235-01



Source: PK/PD analysis for effects of JNJ-77242113 (icotrokinra) on ex-vivo IL-23-stimulated interferon gamma from Phase 1 study PN-235-01, Figure 1
Abbreviations: IFN-γ, interferon-γ; SE, standard error

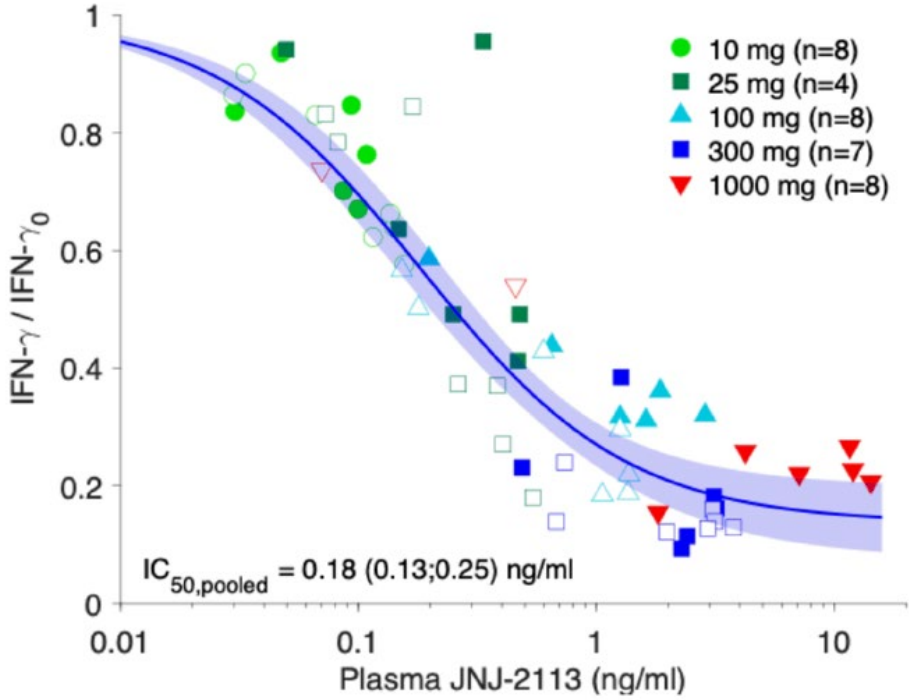
Figure 41. Median Percentage Inhibition of Interferon Gamma Release Versus Time on Day 1 and Day 10 Following Multiple Doses of PN-235



Source: Study PN-235-01 Report, Figure 10

PK/PD analysis using a direct effect model using data from Days 1 and 10 shows a consistent relationship between plasma concentrations of PN-235 and the concurrent PD effect, with an estimated IC_{50} of 0.18 ng/mL (95% CI: 0.13;0.25) for the pooled analysis (Figure 42).

Figure 42. PK/PD Relationship in Ex Vivo IL-23 Stimulated Whole Blood Assay in Healthy Subjects



Source: PK/PD analysis for effects of JNJ-2113 (icotrokinra, PN-235) on ex-vivo IL-23-stimulated interferon gamma from Phase 1 study PN-235-01, Figure 2.
Each symbol represents the mean PK and PD at an individual timepoint, with solid symbols being from Day 1 and open symbols from Day 10. Within each cohort and day, the early timepoints (near Cmax) are farther to the right and the later timepoints (near Ctrough) and further to the left. The solid curve shows the model fit to the data with the shading region representing the 95% CI. Note the model estimated curve and parameters were estimated using all of the individual subject data even though the figure shows the mean value in each group.
A direct effect model describing the relationship between plasma drug concentrations and PD was fit to the data using the equation: R(t)=1 – Emax*[C(t)/(C(t)+IC50)], where R(t) is the ratio IFNg(t)/IFNg0, C(t) is the plasma drug concentration, and the estimated parameters are Emax and IC50. Two subjects (one in the placebo group and one in the 300 mg cohort) had remarkably low stimulated IFN values at t=0 (orders of magnitude below both other subjects baseline values and subsequent values in the same subjects) leading to very high ratios of IFNg(t)/IFNg0 (>100 at some timepoints). The values for these subjects were excluded from the PK/PD analysis.
Abbreviations: IL, interleukin; PK, pharmacokinetic; PD, pharmacodynamic; IC50, PN-235 concentration that cause 50% inhibition in IFNg stimulation

The estimated IC_{50} values for all timepoints are presented in Table 87. The estimated IC_{50} at the initial timepoints on Day 1 tend to be modestly higher than the estimates at later timepoints on Days 1 and 10. The estimated IC_{50} beyond 4 hours are similar and suggests that there is no persistent IL-23 receptor inhibition beyond that predicted by the current drug concentration. According to the Applicant, the estimated IC_{50} values were not adjusted for the dilution (3X) in the whole blood assay and likely underestimate the true IC_{50} of PN-235. However, dilution is not important as it equally affects all timepoints and the PK/PD relationship is similar across the different timepoints.

Table 87. Estimated IC_{50} for PN-235 inhibition of IL-23-Stimulated IFNγ From Whole Blood Assay Following the Administration of Multiple Doses of PN-235 in Healthy Subjects Using PK/PD Data from Trial PN-235

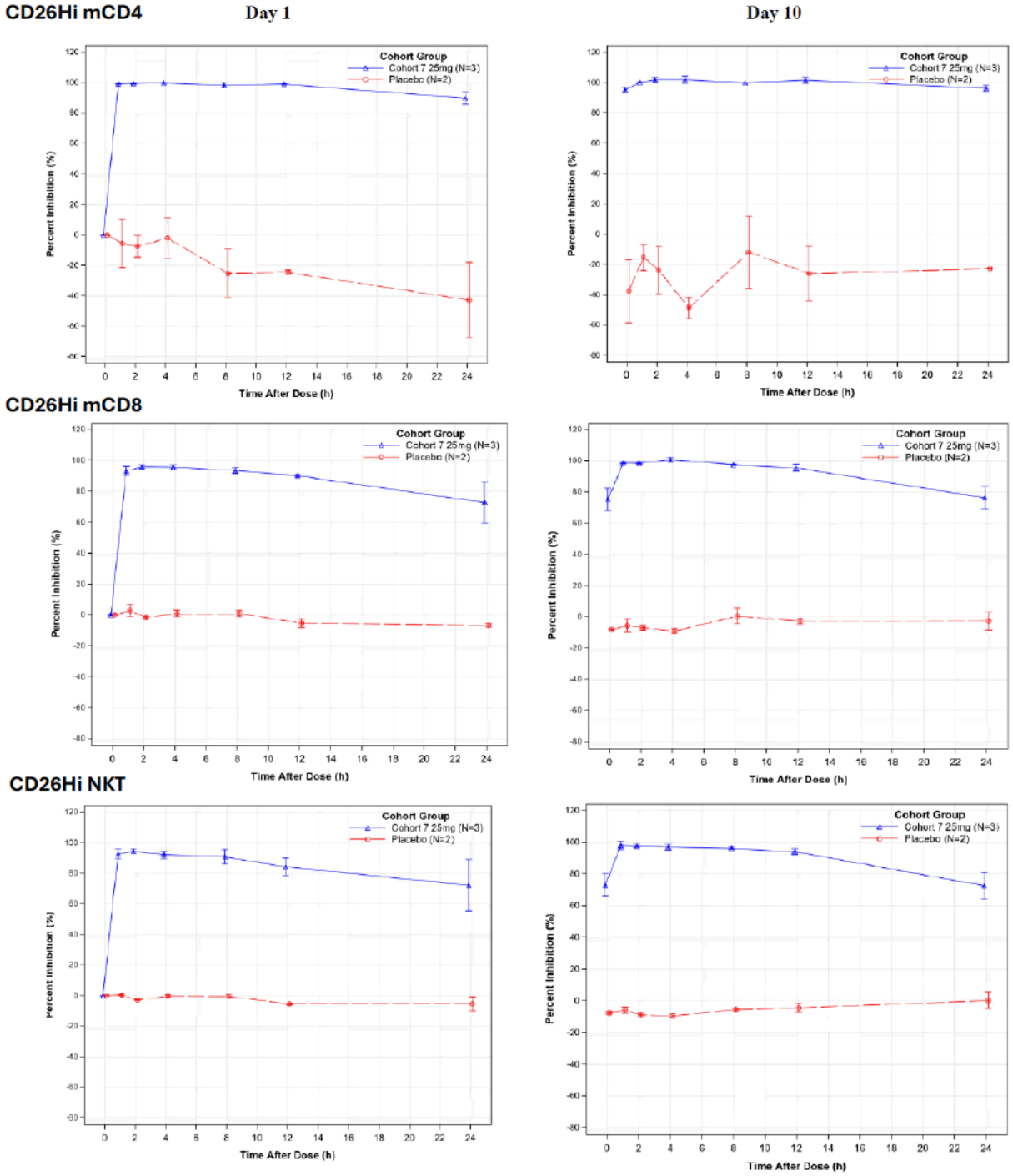
Hours after dosing	IC_{50} (ng/ml)	
	Day 1	Day 10
0	--	0.17 (0.093;0.30)
1	0.27 (0.16;0.47)	0.13 (0.063;0.27)
2	0.26 (0.13;0.51)	0.16 (0.070;0.36)
4	0.37 (0.11;1.2)	0.14 (0.063;0.29)
8	0.10 (0.077;0.38)	0.12 (0.06;0.23)
24	0.14 (0.058;0.35)	0.12 (0.044;0.35)

Source: PK/PD analysis for effects of JNJ-77242113 (icotrokinra) on ex-vivo IL-23-stimulated interferon gamma from Phase 1 study PN-235-01, Table 1
Abbreviations: IC50; PN-235 concentration that cause 50% inhibition in IFN-γ stimulation

IL-23 Mediated pSTAT3 Production

Signal transducer and activator of transcription 3 (STAT3) phosphorylation in response to IL-23 stimulation served as a PD marker for assessing the activity of PN-235 within three lymphocyte subsets ($CD26^{high}$ memory CD4 T cells, $CD26^{high}$ memory CD8 T cells, and $CD26^{high}$ natural killer T cells). A decrease in the IL-23 induced phosphorylation of STAT3 at tyrosine residue Y705 served as a readout of IL-23R inhibition by the PN-235 dosing regimen. The PD results showed almost complete inhibition of pSTAT3 (E_{max} close to 100%) with 25 mg PN-235 on $CD26^{high}$ memory CD4 T cells, $CD26^{high}$ CD8 T cells and $CD26^{high}$ NKT cells as compared to placebo (Figure 43). The inhibition of 80% of pSTAT3 was sustained for approximately 20 hours following the administration of the last dose on Day 10.

Figure 43. Mean (±SE) pSTAT3 Inhibition Versus Time at Day 1 and Day 10 Following Multiple Doses of PN-235 25 mg Once Daily in Trial PN-235-01



Source: Study PN-235-01 Report, Figure 11.
Abbreviations: pSTAT3, phosphorylated signal transducer and activator of transcription 3; CD, cluster of differentiation, Hi, high; m, memory; NKT, natural killer T cells; SE, standard error

Immunogenicity Results

None of the healthy subjects in Part 2 developed antidrug antibodies (ADA) following the administration of PN-235 10 to 1000 mg once daily for 10 days.

19.4.2.1.2. Trial PSO1002

This trial was a randomized, double-blind, placebo-controlled, single dose study to evaluate the safety, tolerability, and PK of JNJ-77242113 after SAD administration as an immediate release (IR) tablet (Lot # G014, phase 2 formulation) or delayed-release (DR) tablet formulations in Japanese and Chinese healthy adult subjects. This study consists of 3 parts with a total of 4 cohorts. In each cohort, 6 subjects received JNJ-77242113, and 3 subjects received placebo.

- Part 1 (Cohorts 1 to 2): A single dose of 100 (1×100-mg tablet) and 300 mg (3×100-mg tablet) JNJ-77242113 or placebo was administered as oral IR tablet(s) in Japanese subjects.
- Part 2 (Cohorts 3): A single dose of 300 mg (3×100-mg tablet) JNJ-77242113 or placebo was administered as oral IR tablets in Chinese subjects.
- Part 3 (Cohorts 4): A single dose of (b) (4) (1×50-mg tablet) JNJ-77242113 with (b) (4) or placebo was administered as oral DR tablet in Japanese subjects.

The (b) (4) dose in DR tablet formulated with (b) (4) was selected to account for the anticipated 8-fold increase in exposure to JNJ-77242113 when administered in DR tablet formulated with (b) (4). All study interventions were taken in the morning on Day 1 of each treatment period with 240 mL of noncarbonated water following an overnight fast of at least 10 hours. Water was allowed ad libitum beginning 2 hours after dosing. Standard meals were served beginning 4 hours after dosing.

Per the study protocol, subjects in this study should be male or female of non-childbearing potential; however, this study included male subjects (100%) only. Blood samples for PK assessment were collected predose and up to 48 hours after the administration of single dose of JNJ-77242113 in all study parts. Immunogenicity was evaluated predose and at end of treatment (Day 7).

Pharmacokinetic Results

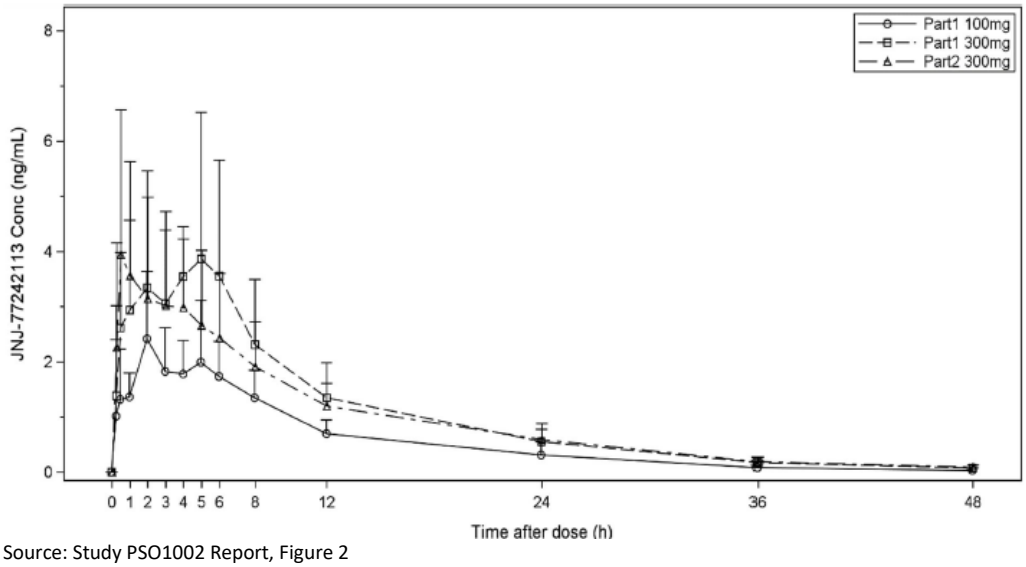
Part 1

The mean plasma concentration-time profiles of JNJ-77242113 after single-dose oral administration of 100 and 300 mg JNJ-77242113 as 100 mg IR tablet in Japanese subjects are provided in Figure 44. The PK parameters of JNJ-77242113 following single oral dose administration of in Japanese and Chinese subjects are listed in Table 88. Following a single-dose oral administration of 100 and 300 mg JNJ-77242113 as IR table(s) to healthy Japanese subjects (Part 1), there was less than dose-proportional PK based on AUC and C_{max}. The mean C_{max} and AUClast increased from 3.17 to 4.61 ng/mL and from 27 to 49.6 h·ng/mL, respectively, with approximately 1.45 to 1.84-fold between dose levels of 100 mg and 300 mg. The mean elimination $t_{1/2}$ was 8 to 9.2 hours and median t_{max} was 2 to 4 hours.

Part 2

Following a single-dose oral administration of 300 mg JNJ-77242113 as IR tablets to healthy Chinese subjects (Part 2), the mean elimination $t_{1/2}$ was 9 hours and median t_{max} was 0.5 hours (Table 88). In addition, there is comparable exposures of JNJ-77242113 as IR tablets between Japanese and Chinese subjects after a single-dose oral administration of 300 mg JNJ-77242113. Although the t_{max} is different between Japanese and Chinese subjects following the administration of 300 mg in Part 1 and 2 (median t_{max} of 4 hours in Japanese subjects and 0.5 hours in Chinese subjects), the range of t_{max} appears reasonable in the two populations. The range of t_{max} in Japanese subjects after 300 mg JNJ-77242113 is 0.25 to 6 hours and in Chinese subjects is 0.5 to 6 hours.

Figure 44. Mean (+SD) Plasma Concentration-Time Profile of JNJ-77242113 After the Administration of Single Doses of 100 or 300 mg JNJ-77242113 as Immediate Release Tablet in Japanese and Chinese Healthy Adult Male Subjects

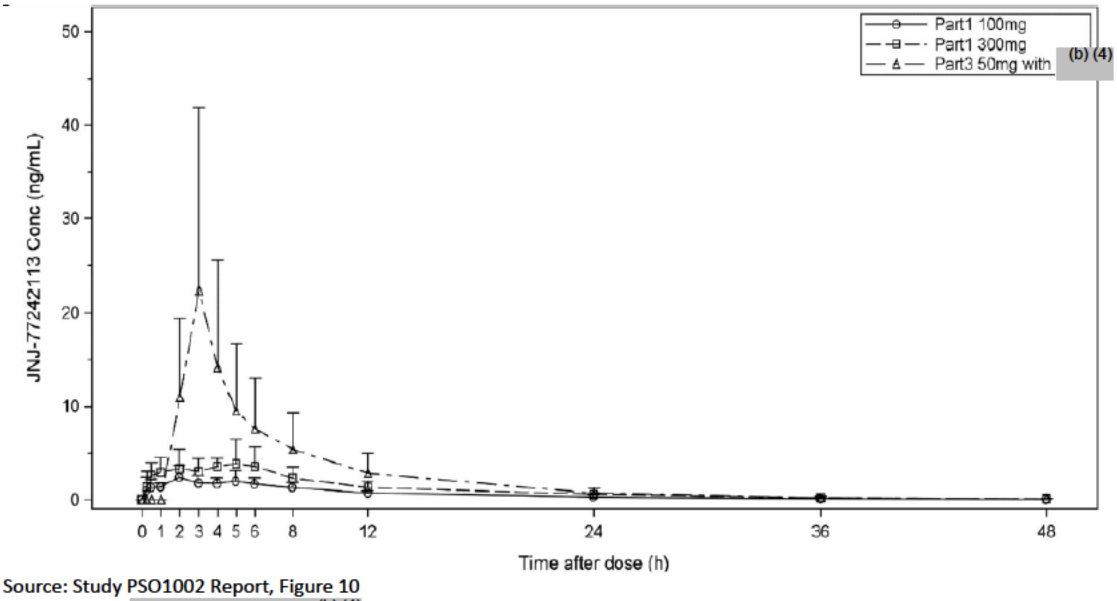


Source: Study PSO1002 Report, Figure 2
Part 1: Single dose of 100 and 300 mg JNJ-77242113 IR tablet in Japanese subjects.
Part 2: Single dose of 300 mg JNJ-77242113 IR tablets in Chinese subjects.

Part 3

After the administration of an oral single dose of 50 mg JNJ-77242113 as DR tablet in Japanese healthy male adult subjects (Part 3), the median t_{max} and t_{lag} of JNJ-77242113 were 3 hours and 1 hour, respectively, with mean $t_{1/2}$ of 7 hours (Figure 45 and Table 88). The administration of 50 mg JNJ-77242113 as DR tablet with [redacted] (b) (4) resulted in greater exposure compared to 300 mg (3×100 mg IR tablet) JNJ-77242113. For example, the mean C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ after the administration of 50 mg DR tablet with [redacted] (b) (4) in Japanese subjects were 26.1 ng/mL, 121 h·ng/mL and 122 h·ng/mL, respectively (Table 88). The mean C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ after the administration of 300 mg IR tablet in Japanese subjects were 4.61 ng/mL, 49.6 h·ng/mL and 50.7 h·ng/mL, respectively.

Figure 45. Mean (+SD) Plasma Concentration-Time Profile of JNJ-77242113 After the Administration of Single Doses of 50 mg JNJ-77242113 as Delayed Release Tablet and 100 or 300 mg JNJ-77242113 as Immediate Release Tablet in Japanese Healthy Adult Male Subjects



Source: Study PSO1002 Report, Figure 10
Abbreviations: (b) (4)
Part 1: Single dose of 100 and 300 mg JNJ-77242113 IR tablet in Japanese subjects.
Part 3: Single dose of 50 mg JNJ-77242113 DR tablet with (b) (4) in Japanese subjects.

Table 88. Summary of PK Parameters JNJ-77242113 After the Administration of Single Dose in Japanese and Chinese Healthy Adult Male Subjects

	Part 1		Part 2	Part 3
	100 mg	300 mg	300 mg	50 mg with (b) (4)
n	6	6	6	6
C_{max} (ng/mL)	3.17±1.03 (32.5)	4.61±2.38 (51.6)	4.33±2.12 (49.1)	26.1±16.7 (64.0)
C_{max}[dn] (ng/mL/mg)	0.0317±0.0103 (32.5)	0.0154±0.00793 (51.6)	0.0144±0.00708 (49.1)	0.522±0.334 (64.0)
t_{max} (h)	2.00 (0.25; 5.00)	4.00 (0.25; 6.00)	0.50 (0.50; 6.00)	3.00 (1.00; 3.00)
t_{lag} (h)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	1.00 (0.25; 2.00)
AUC_{last} (h*ng/mL)	27.0±8.09 (30.0)	49.6±19.0 (38.3)	45.3±15.7 (34.6)	121±85.0 (70.4)
AUC_{last}[dn] (h*ng/mL/mg)	0.270±0.0809 (30.0)	0.165±0.0633 (38.3)	0.151±0.0522 (34.6)	2.41±1.70 (70.4)
AUC_{inf} (h*ng/mL)	27.5±8.01 (29.2)	50.7±18.8 (37.1)	46.5±15.7 (33.8)	122±85.8 (70.6)
AUC_{inf}[dn] (h*ng/mL/mg)	0.275±0.0801 (29.2)	0.169±0.0626 (37.1)	0.155±0.0525 (33.8)	2.43±1.72 (70.6)
$t_{1/2}$ (h)	8.0±2.4 (30.1)	9.2±1.6 (17.2)	9.0±1.7 (19.0)	6.9±0.6 (9.4)
λ_z (1/h)	0.0915±0.0219 (23.9)	0.0774±0.0135 (17.5)	0.0789±0.0137 (17.3)	0.101±0.00978 (9.7)
CL/F (L/h)	3901±1087 (27.9)	6388±1524 (23.9)	6993±2022 (28.9)	583±314 (53.8)
V_z/F (L)	47081±26298 (55.9)	86050±26684 (31.0)	91426±30752 (33.6)	5672±2926 (51.6)

Source: Study PSO1002 Report, Table 19.
Abbreviations: AUCinf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation; λz, first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve; tlag, the time period between the time of dosing and the time of the first measurable (non-BQL) concentration; dn, dose-normalized (b) (4)
Median (range) for tmax and tlag and mean±SD (% CV) for other parameters.
Part 1 (Cohorts 1 to 2) in Japanese participants, a single dose of JNJ-77242113 or placebo was administered as oral IR tablet(s) to sequential cohorts (100 and 300 mg).
Part 2 (Cohort 3) in Chinese participants, a single dose of 300 mg JNJ-77242113 or placebo was administered as oral IR tablets.
Part 3 (Cohort 4) in Japanese participants, a single dose of 50 mg JNJ-77242113 with (b) (4) or placebo was administered as oral DR tablet.

Immunogenicity Results

None of subjects in Part 1 and 2 were positive for antibodies to JNJ-77242113. Immunogenicity assessment was not conducted in Part 3 following the administration of 50 mg as DR tablet in healthy Japanese subjects.

19.4.2.1.3. Trial PSO1004

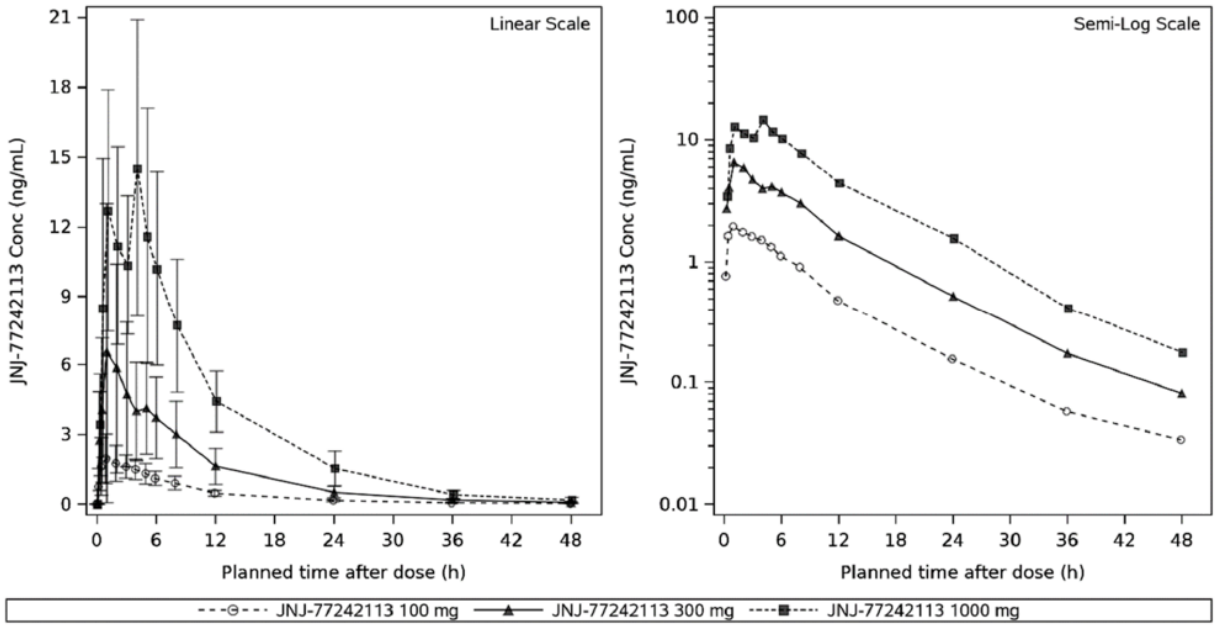
This is an open-label, single-dose trial conducted to evaluate the PK, safety, and tolerability of JNJ-77242113 in healthy Chinese adult subjects following the administration of single doses of 100 mg (1×100-mg tablet), 300 mg (3×100-mg tablet) and 1000 mg (10×100-mg tablet) JNJ-77242113 IR FCT (Lot #G014, phase 2 formulation).

Subjects fasted from food for at least 10 hours before drug administration and noncarbonated water was allowed up to 1 hour before study intervention administration. Water was allowed ad libitum beginning 2 hours after dosing. Standard meals were served beginning 4 hours after dosing. Blood samples for PK evaluation were collected predose and up to 48 hours after drug administration.

Pharmacokinetic Results

The mean plasma concentration-time profile of JNJ-77242113 after single oral administration of 100, 300, and 1000 mg in healthy Chinese adult subjects is shown in Figure 46 and the summary of PK parameters is provided in Table 89. Results from trial PSO1004 indicate that JNJ-77242113 has a t_{max} of 1 to 2 hours under fasting condition across the administered dose levels. The mean $t_{1/2}$ ranges from 7.1 to 8.6 hours. The C_{max} and AUC appear to increase in less than dose-proportional across the three doses of 100, 300, and 1000 mg, but they increase in approximately dose-proportional manner between 100 and 300 mg.

Figure 46. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After Single-dose Oral Administration of 100, 300 and 1000 mg of JNJ-77242113 as Immediate Release Film-Coated Tablet in Healthy Chinese Adult Subjects



Source: Summary of Clinical Pharmacology, Figure 7

Table 89. Summary of PK Parameters of JNJ-77242113 After Single-Dose Oral Administration of 100, 300 and 1000 mg of JNJ-77242113 as Immediate Release Film-Coated Tablet in Healthy Chinese Adult Subjects

	Mean (SD); t_{max}: Median (Range)		
Parameter	100 mg (N=10)	300 mg (N=10)	1000 mg (N=9)
C_{max} (ng/mL)	2.63 (1.02)	7.90 (5.85)	17.4 (6.07)
t_{max} (h)	1.00 (0.25; 5.00)	1.00 (0.25; 8.00)	2.00 (1.00; 4.00)
AUC_{last} (ng*h/mL)	19.5 (4.13)	62.3 (30.9)	159 (40.9)
AUC_{inf} (ng*h/mL)	19.9 (4.21)	63.3 (30.9)	161 (41.4)
$t_{1/2}$ (h)	8.6 (1.3)	8.4 (2.0)	7.1 (0.9)
CL/F (L/h)	5,235 (1,142)	5,588 (2,153)	6,506 (1,379)
V_z/F (L)	65,161 (17,294)	69,120 (35,032)	66,272 (16,276)

Source: Summary of Clinical Pharmacology, Table 5
Abbreviations: AUCinf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation.

19.4.2.2. Relative Bioavailability and Food/Liquid Effect Studies

19.4.2.2.1. Trial PSO1003

This was a single-dose, open-label, randomized, crossover, 4-part, multicenter trial in healthy adult subjects. Part 1 and Part 4 will be discussed in this review. Parts 2 and 3 utilized

exploratory formulations of JNJ-77242113 (i.e., delayed-release tablet) and they will not be discussed in this review. Part 2 evaluated the bioavailability of DR tablet formulations of JNJ-77242113 containing 2 different amounts of the (b) (4), relative bioavailability of DR tablet to IR tablet, and food effect on the DR tablet. Part 3 evaluated the bioavailability of JNJ-77242113 when administered at different strengths of DR tablets relative to an IR tablet formulation and the effect of food and timing of meal on the PK of DR tablet formulation of JNJ-77242113. JNJ-77242113 was supplied as an oral solution formulation (Lot #G005) (30 mL, 3.3 mg/mL) and 100 mg oral IR film-coated tablet (Lot # G014).

In Parts 1 and 4, no food was allowed for at least 4 hours postdose, except for Treatment JC in Cohort 5 (Part 4) (i.e., JNJ-77242113 administered 30 minutes before start of breakfast). The high-fat breakfast consisted of (or its equivalent) 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 100 g of hashed brown potatoes (fried with butter), and 240 mL of whole milk (containing approximately: fat: 500 to 600 calories, carbohydrates: 250 calories, proteins: 150 calories, total: 900 to 1000 calories). The low-fat breakfast consisted of (or its equivalent) 240 mL of milk (1% fat), 1 boiled egg, and 1 packet flavored instant oatmeal made with water (containing approximately: fat: 100 to 125 calories, total: 400 to 500 calories). For all treatments in Parts 1 and 4, approximately 4 hours after study intervention intake, a standard lunch was served at the study site.

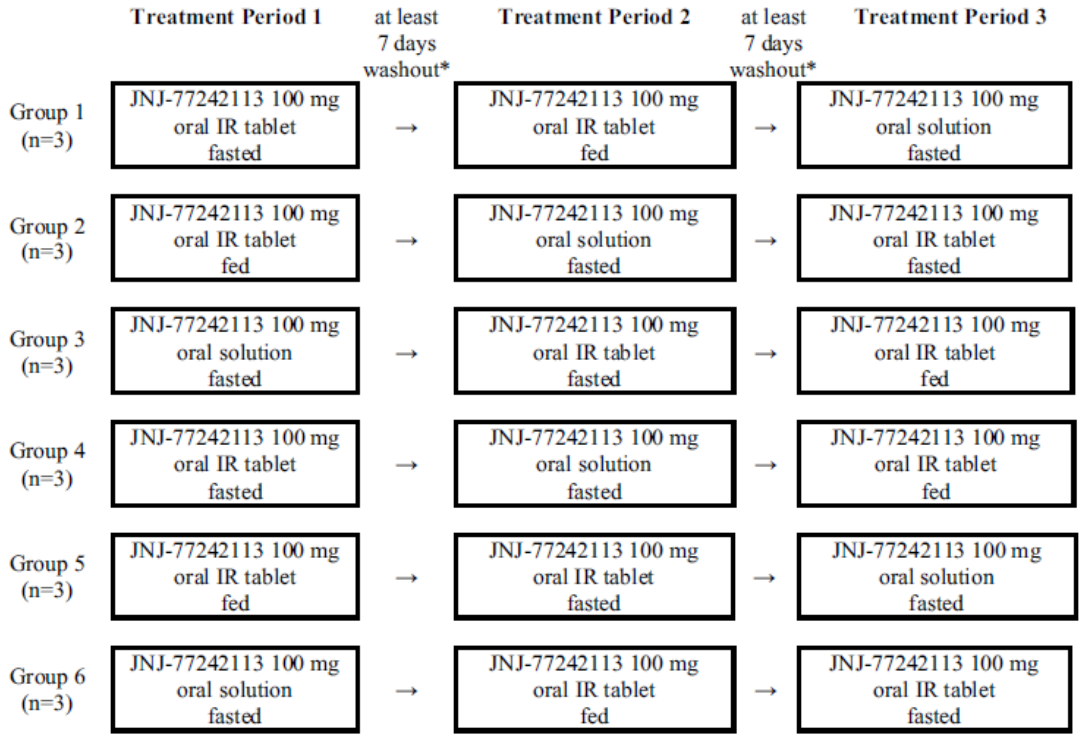
Part 1

Part 1 was randomized, open-label, 3-way crossover, single-dose, study to evaluate the relative oral bioavailability of a JNJ-77242113 IR tablet phase 2 formulation (Lot #G014) versus an oral solution formulation, to evaluate the effect of food on the PK of a JNJ-77242113 IR tablet phase 2 formulation, and to assess the safety and tolerability of single-dose oral administration of JNJ-77242113 in healthy subject. The design of Part 1 is depicted in Figure 47. The order of treatments was determined by randomization according to a classical 6-sequence, 3-period Williams design. There was at least 7 days washout between the three periods. JNJ-77242113 was administered orally as a single 100-mg dose (1×100 mg IR tablet) under both fasted and fed (high-fat breakfast) conditions and as a single 100-mg dose of a JNJ-77242113 solution formulation under fasted conditions. Blood samples for PK evaluation were collected at pre-dose and up to 48 hours after drug administration.

JNJ-77242113 was administered under fasted or fed conditions, after at least 10 hours of fasting or within 10 minutes after completion of a high-fat or low-fat breakfast, but no more than 30 minutes after the start of breakfast. The breakfasts were ingested entirely within 30 minutes. After administration of the solution treatment in Part 1 the vessel was not rinsed. The subjects drunk the entire oral vial contents followed by 240 mL of water.

The intake of water was restricted from approximately 1 hour before until approximately 1 hour after study intervention intake (except for the water used for administration of study intervention and breakfast), after which time, water was allowed ad libitum.

Figure 47. Schematic Overview of Part 1 in Study PSO1003



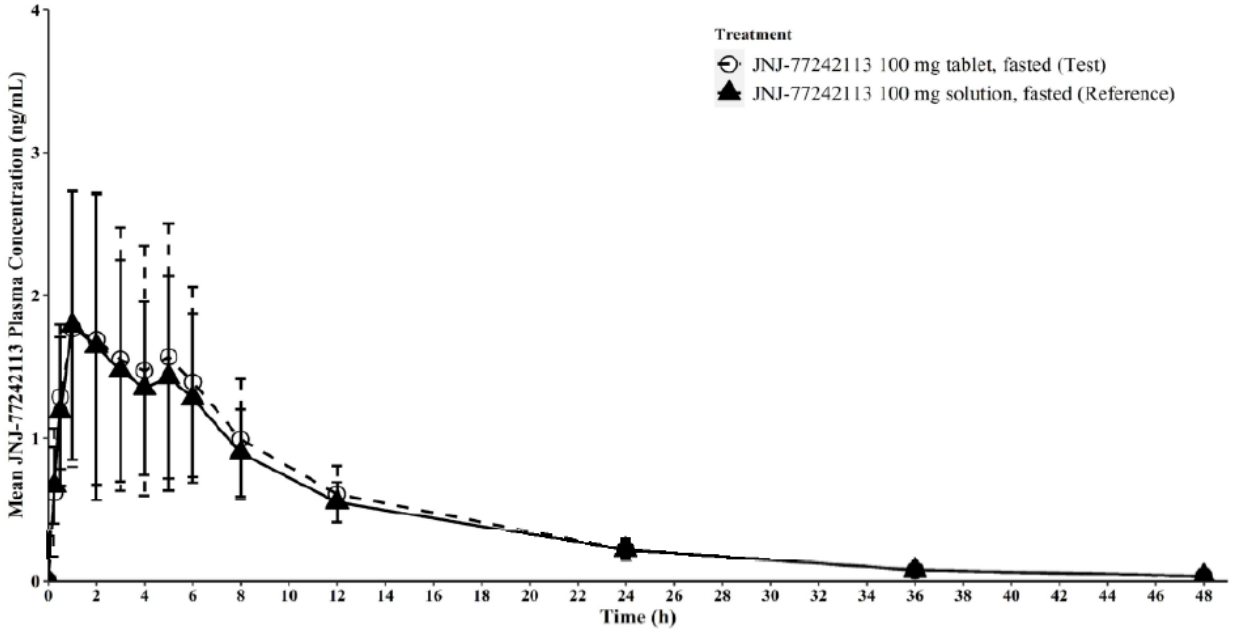
Source: Study PSO1003 Report, Figure 1.
*Day 1 of a treatment period, i.e., the day of study intervention administration, is the first day of the interdose period.
After administration of the solution treatment the vessel was not rinsed. The subject drunk the entire oral vial contents followed by 240 mL of water
Abbreviations: JNJ-77242113, icotrokinra; n, number of subjects; IR, immediate release

Pharmacokinetic Results from Part 1

Relative Bioavailability of IR Tablet to Oral Solution

The mean plasma concentration time-profile of JNJ-77242113 after the administration of 100 mg JNJ-77242113 IR tablet (Test) was comparable to that of 100 mg JNJ-77242113 oral solution (100 mg [30 mL, 3.3 mg/mL]; Reference), under fasted conditions (Figure 48). The median t_{max} under fasted condition was 2.51 hours and 1 hour for the 100 mg IR tablet and 100 mg oral solution, respectively, without observed t_{lag} (Table 90). The mean $t_{1/2}$ values were 8.7 hours and 8.9 hours, for oral IR tablet and oral solution, respectively.

Figure 48. Mean (SD) Plasma Concentration-Time Profiles After a Single Dose of 100 mg JNJ-77242113 IR Tablet Compared With Oral Solution (100 mg [30 mL, 3.3 mg/mL]) Under Fasting Conditions - Part 1 in Trial PSO1003 – Linear Scale



Source: Study PSO1003 Report, Figure 5
Abbreviations: IR, immediate release

Table 90. Summary of Mean (SD) PK Parameters After a Single Dose of 100 mg JNJ-77242113 IR tablet Under Fasted and Fed Conditions and After Oral solution (100 mg [30 mL, 3.3 mg/mL]) Under Fasted Condition in Part 1 in Trial PSO1003

PK Parameter	100 mg IR Tablet, Fasted	100 mg IR Tablet, Fed	100 mg Oral Solution, Fasted
N	14	14	14
C_{max} (ng/mL)	2.1 (0.942)	0.713 (0.33)	2.04 (1.06)
t_{max} (h)[a]	2.51 (0.25-5)	4 (2-6)	1.01 (0.25-5)
t_{lag} (h)	0 (0-0)	0 (0-0.5)	0 (0-0)
AUC_{24h} (ng·h/mL)	19.5 (7.67)	7.55 (2.52)	18.2 (6.55)
AUC_{last} (ng·h/mL)	21.9 (8.28)	8.98 (2.85)	20.5 (6.77)
$AUC_{0\text{-}inf}$ (ng·h/mL)	22.3 (8.34)	9.64 (2.87)	21.0 (6.72)
λz (1/h)	0.08 (0.008)	0.065 (0.017)	0.081 (0.014)
$t_{1/2}$ (h)	8.7 (0.9)	11.3 (3)	8.9 (1.9)

Source: Reviewer's generated table based on Study PSO1003 Report, Tables 19 and 20
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; AUC_{24h}, area under the plasma concentration time profile from time zero to the time 24 hours; CL/F; apparent total body clearance; C_{max}, maximum observed plasma concentration; T_{max}, time to the maximum plasma concentration; $t_{½}$, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation; tlag, time from administration to the time of first detected concentration in plasma; IR, immediate release
[a] Median (min, max) reported.

Statistical analysis of the PK parameters using least square geometric mean ratio (LSGMR) and its 90% confidence interval (CI) showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 increased by 6.39%, 5.59%, and 9.68%, respectively, after the administration of 100 mg IR tablet in fasted state compared to 100 mg oral solution administered in fasted state, suggesting relatively similar PK between 100 mg JNJ-77242113 IR tablet and 100 mg JNJ-77242113 oral solution (Table 91).

Table 91. Summary of the Statistical Analysis of the PK Parameters of JNJ-77242113 After Single Oral Administration of 100 mg JNJ-77242113 IR Tablet Compared With 100 mg Oral Solution (30 mL, 3.3 mg/mL) Under Fasted Conditions in Part 1 in Trial PSO1003

PK Parameter	Comparison	Geometric Mean	GMR (%) [90% CI (%)]	Intrasubject CV (%)
	Relative Bioavailability of IR Tablet to Oral Solution			
C_{max} (ng/mL)	100 mg IR tablet (Test) (N=14)	1.95	106.39 [83.95-134.83]	37.8
	100 mg oral solution (Reference) (N=14)	1.83		
AUC_{last} (ng·h/mL)	100 mg IR tablet (Test) (N=14)	21	105.59 [90.57-123.10]	24.0
	100 mg oral solution (Reference) (N=14)	19.9		
AUC_{0-inf} (ng·h/mL)	100 mg IR tablet (Test) (N=13)	21.8	109.68 [94.40-127.43]	22.5
	100 mg oral solution (Reference) (N=13)	19.9		
	100 mg IR tablet fed (Test) (N=14)	9.42		

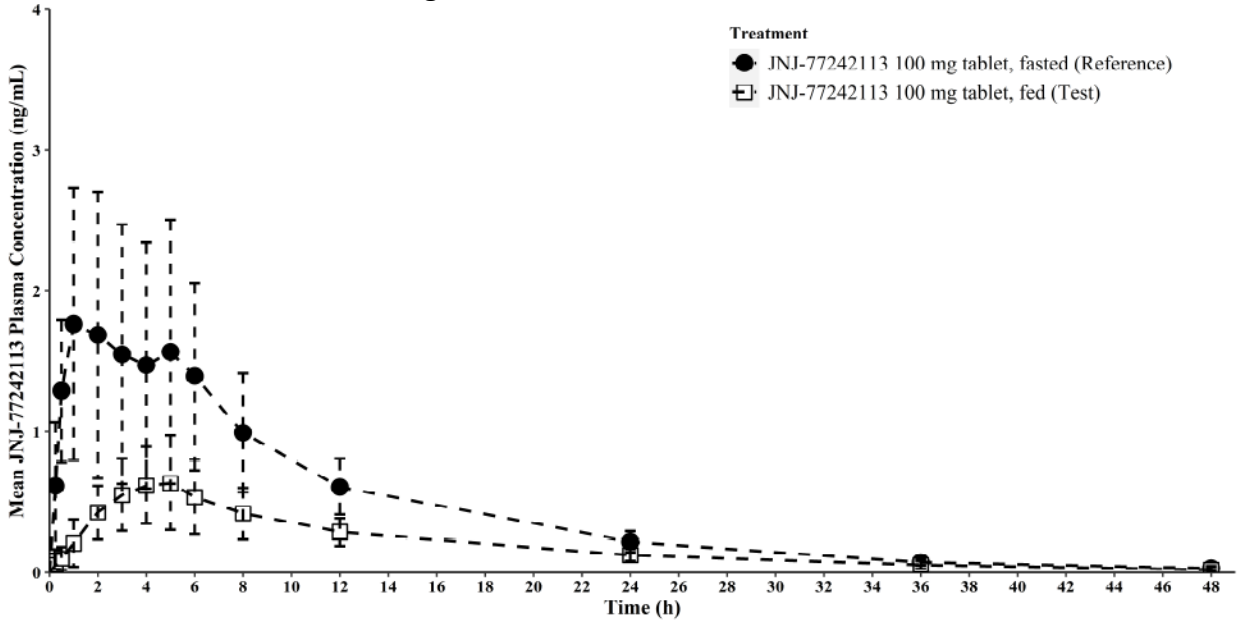
Source: Reviewer's generated table based on Study PSO1003 Report, Table 21.
Abbreviations: AUC_{0-inf}, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio, CV%, coefficient of variance percentage; CI, confidence interval; IR, immediate release
The least square means of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment (tablet fasted, solution fasted), sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the least square means of relative bioavailability: the tablet formulation (test) was compared to the solution formulation (reference), both under fasted conditions. Both the difference between the least square means and the 90% CIs were retransformed to the original scale.

Food Effect: Fasted Versus Fed Oral IR Tablet

In comparison to fasted state, the administration of a single dose 100 mg JNJ-77242113 IR tablet (phase 2 formulation) with a high-fat breakfast delayed t_{max} by 1.5 hours (median t_{max} of 4 hours in fasted state and 2.51 hours with high-fat meal) (Figure 49 and Table 90).

Statistical analysis showed that C_{max}, AUC_{last}, and AUC_{0-inf} of JNJ-77242113 decreased 66.5%, 58.4%, and 56.7%, respectively, after the administration of a single dose100 mg IR phase 2 tablet formulation with high-fat breakfast compared to a single dose of 100 mg IR tablet administered in fasted state (Table 92). Therefore, the exposure to JNJ-77242113 is lower under fed (high-fat breakfast) compared to fasted condition for oral IR tablet, suggesting that concomitant food would lower the extent of bioavailability of JNJ-77242113.

Figure 49. Mean (SD) Plasma Concentration-Time Profiles After a Single Dose of 100 mg JNJ-77242113 IR tablet Under Fasting and Fed Conditions - Part 1 in Trial PSO1003 – Linear Scale



Source: Study PSO1003 Report, Figure 6
Abbreviations: IR, immediate release

Table 92. Summary of the Statistical Analysis of the PK Parameters of JNJ-77242113 After Single Oral Administration of 100 mg JNJ-77242113 IR Tablet Under Fasted and Fed Conditions in Part 1 in Trial PSO1003

PK Parameter	Comparison	Geometric Means	GMR (%) [90% CI (%)]	Intra- subject CV (%)
C_{max} (ng/mL)	100 mg IR tablet fasted (Reference) (N=14)	1.95	33.51 [26.44-42.47]	37.8
	100 mg IR tablet fed (Test) (N=14)	0.652		
AUC_{last} (ng·h/mL)	100 mg IR tablet fasted (Reference) (N=14)	21	41.62 [35.70-48.52]	24.0
	100 mg IR tablet fed (Test) (N=14)	8.75		
$AUC_{0\text{-}inf}$ (ng·h/mL)	100 mg IR tablet fasted (Reference) (N=14)	21.8	43.29 [37.26-50.29]	22.5
	100 mg IR tablet fed (Test) (N=14)	9.42		

Source: Reviewer's generated table based on Study PSO1003 Report, Table 22.
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio, CV%, coefficient of variance percentage; CI, confidence interval; IR, immediate release
The least square means of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment (tablet fasted, tablet fed), sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the least square means, the tablets under fed conditions (test) were compared to the tablets under fasted conditions (reference). Both the difference between the least square means and the 90% CIs were retransformed to the original scale.

Part 4

Part 4 consisted of Cohorts 5 and 6 each was a randomized, open-label, 4-way crossover, single-dose study in healthy subjects. Both cohorts in Part 4 evaluated the effect of different types of meals (high-fat breakfast [total: 900 to 1000 calories] versus low-fat breakfast [total: 400 to 500 calories]), the timing of a meal, and additional water intake on the bioavailability and PK of 100 mg (1×100 mg IR tablet) JNJ-77242113. Within each cohort, subjects were randomly allocated in a 1:1:1:1 ratio to 1 of 4 treatment sequences based on a balanced 4-sequence,

4-period Williams design. There was at least 7 days washout between the four periods in each cohort and blood samples were collected predose and up to 48 hours postdose for PK assessment.

JNJ-77242113 was administered under fasted or fed conditions, after at least 10 hours of fasting or within 10 minutes after completion of a high-fat or low-fat breakfast, but no more than 30 minutes after the start of breakfast. For Treatment JE in Cohort 6 (Part 4), JNJ-77242113 was administered 2 hours after completion of a high-fat breakfast (i.e., breakfast started 2.5 hours before study intervention intake). For Treatment JF in Cohort 6 (Part 4), JNJ-77242113 was administered 1 hour after completion of a high-fat breakfast (i.e., breakfast started 1.5 hour before study intervention intake). For Treatment JC in Cohort 5 (Part 4), JNJ-77242113 was administered 30 minutes before the start of a high-fat breakfast. The breakfasts were ingested entirely within 30 minutes.

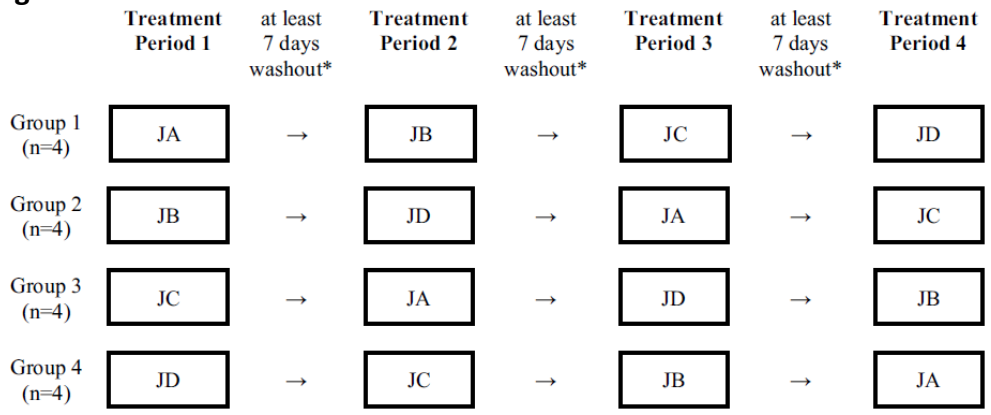
The intake of water was restricted from approximately 1 hour before until approximately 1 hour after study intervention intake (except for the water used for administration of study intervention and breakfast), after which time, water was allowed ad libitum.

Cohort 5

Each subject in Cohort 5 received the following treatments (Figure 50):

- JA: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (high-fat breakfast)
- JB: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (low-fat breakfast)
- JC: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 30 minutes before high-fat breakfast
- JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

Figure 50. Schematic Overview of Cohort 5 in Part 4 in Trial PSO1003



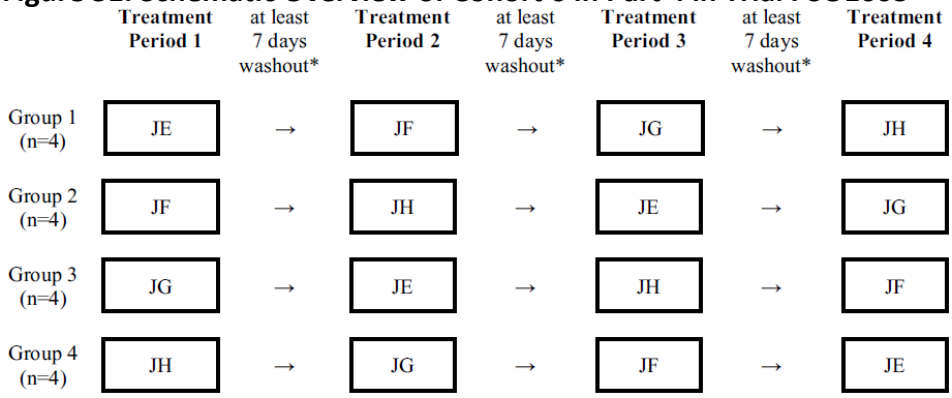
Source: Study PSO1003 Report, Figure 4.
*Day 1 of a treatment period, i.e., the day of study intervention administration, is the first day of the interdose period.
JA: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (high-fat breakfast).
JB: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (low-fat breakfast).
JC: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 30 minutes before high-fat breakfast.
JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted.

Cohort 6

Each subject in Cohort 6 received the following treatments (Figure 51):

- JE: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 2 hours after completion of high-fat breakfast.
- JF: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 1 hour after completion of high-fat breakfast.
- JG: single oral dose of 100 mg JNJ-77242113 IR tablet with 480 mL water, fasted.
- JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted.

Figure 51. Schematic Overview of Cohort 6 in Part 4 in Trial PSO1003



Source: Study PSO1003 Report, Figure 4.
*Day 1 of a treatment period, i.e., the day of study intervention administration, is the first day of the interdose period.
JE: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 2 hours after high-fat breakfast.
JF: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 1 hour after high-fat breakfast.
JG: single oral dose of 100 mg JNJ-77242113 IR tablet with 480 mL water, fasted.
JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted.

Pharmacokinetic Results from Part 4

A summary of PK parameters of JNJ-77242113 from all cohorts in part is provided in Table 93. The statistical analysis evaluating food effect on IR tablet in Part 4 is presented in Table 93.

Table 93. Summary of Mean (SD) PK Parameters After the Administration of a Single Dose of 100 mg JNJ-77242113 IR tablet with Different Meal Types and Mealtimes in Part 4 in Trial PSO1003

PK	Cohort 5				Cohort 6			
Parameter	JA	JB	JC	JD	JE	JH	JF	JG
N	13	13	13	13	14	14	15	15
C_{max} (ng/mL)	0.698 (0.255)	0.833 (0.298)	1.54 (0.986)	1.73 (0.607)	0.945 (0.297)	1.94 (0.884)	0.775 (0.304)	2.24 (0.923)
t_{max} (h)	5.00 (2-6)	4.00 (2-6)	1 (0.25-3)	1 (0.50-6)	5.00 (1-6)	1 (0.25-8)	5.00 (3-8)	3.00 (0.25-8)
t_{lag} (h)	0.00 (0-0.5)	0.50 (0.25-1)	0.00 (0-0)	0.00 (0-0)	0.50 (0-1)	0.00 (0-0.25)	0.50 (0-1.98)	0 (0-0.25)
AUC_{24h} (ng·h/mL)	7.81 (2.48)	8.86 (2.38)	11.0 (4.65)	17.9 (6.48)	9.37 (3.01)	17.1 (7.47)	7.74 (2.8)	18.7 (7.24)

AUC_{last} (ng·h/mL)	10.0 (3.10)	11.0 (2.88)	13.2 (5.09)	21.5 (7.25)	11.5 (3.81)	20.0 (8.6)	9.64 (3.4)	21.6 (8.08)
$AUC_{0\text{-}inf}$ (ng·h/mL)	11.3 (3.45)[a]	12.0 (3.27)[a]	14.3 (5.08)	22.7 (7.25)	12.6 (4.46)[a]	21.1 (8.9)	10.7 (3.65)	22.5 (8.24)
λz (1/h)	0.052 (0.01)[a]	0.055 (0.011)[a]	0.052 (0.014)	0.061 (0.017)	0.057 (0.014)[a]	0.062 (0.016)	0.051 (0.015)	0.064 (0.011)
$t_{1/2}$ (h)	13.9 (2.7)[a]	13.1 (2.7)[a]	14.3 (3.5)	12.0 (2.9)	12.9 (3.1)[a]	12.0 (3.2)	14.7 (4.2)	11.1 (2.0)

Source: Reviewer's generated table based on Study PSO1003 Report, Tables 44, 45, 46, and 47
Abbreviations: AUC0-inf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; AUC24h, area under the plasma concentration time profile from time zero to the time 24 hours; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation; tlag, time from administration to the time of first detected concentration in plasma.
Two participants in Part 4 Cohort 5 (1 participant each in Treatment JA and Treatment JB) and 2 participants in Part 4 Cohort 6 (2 participants in Treatment JE) had adjusted correlation coefficients (R2adj) <0.900. For these participants, AUC∞, λz, t1/2, R2adj were excluded from the descriptive statistics and for the inferential statistics only AUC∞ parameter was excluded. In Part 4 Cohort 5, for Treatment JA (2 participants) and for Treatment JB (1 participant), had %AUC∞,ex >20.00%. For these participants AUC∞, λz, t1/2, R2adj were excluded from the descriptive statistics and for the inferential statistics only AUC∞ parameter was excluded.
a Median (min, max) reported
Treatment JA: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (high-fat breakfast)
Treatment JB: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (low-fat breakfast)
Treatment JC: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 30 minutes before high-fat breakfast
Treatment JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted
Treatment JE: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 2 hours after completion of high-fat breakfast
Treatment JF: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 1 hour after completion of high-fat breakfast
Treatment JG: single oral dose of 100 mg JNJ-77242113 IR tablet with 480 mL water, fasted
Treatment JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

Table 94. Summary of the Statistical Analysis for PK Parameters of JNJ-77242113 After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted State (Reference) Compared to A Single Dose of 100 mg JNJ-77242113 IR tablet Administered With Different Meal Types and Mealtimes (Tests) in Part 4 in Trial PSO1003

PK Parameter	Comparison	Geometric Mean	GMR (%) [90% CI (%)]	Intrasubject CV (%)
High-Fat Breakfast + 240 mL Water [Treatment JA] vs. Fasted + 240 mL Water [Treatment JD]				
C_{max} (ng/mL)	Treatment JD (Reference) (N=13)	1.62	40.98 [32.99-50.91]	33.5
	Treatment JA (Test) (N=13)	0.663		
AUC_{last} (ng·h/mL)	Treatment JD (Reference) (N=13)	20.2	47.77 [41.45-55.05]	21.6
	Treatment JA (Test) (N=13)	9.65		
$AUC_{0\text{-}inf}$ (ng·h/mL)	Treatment JD (Reference) (N=10)	19.9	53.68 [45.67-63.08]	20.5
	Treatment JA (Test) (N=10)	10.7		
Low-Fat Breakfast + 240 mL Water [Treatment JB] vs. Fasted + 240 mL Water [Treatment JD]				
C_{max} (ng/mL)	Treatment JD (Reference) (N=13)	1.62	48.33 [38.91-60.04]	33.5
	Treatment JB (Test) (N=13)	0.782		
AUC_{last} (ng·h/mL)	Treatment JD (Reference) (N=13)	20.2	52.66 [45.69-60.69]	21.6
	Treatment JB (Test) (N=13)	10.6		
$AUC_{0\text{-}inf}$ (ng·h/mL)	Treatment JD (Reference) (N=10)	19.9	57.26 [48.81-67.18]	20.5
	Treatment JB (Test) (N=10)	11.4		

PK Parameter	Comparison	Geometric Mean	GMR (%) [90% CI (%)]	Intrasubject CV (%)
30 Minutes Before High-Fat Breakfast + 240 mL Water [Treatment JC] vs. Fasted + 240 mL Water [Treatment JD]				
C_{max} (ng/mL)	Treatment JD (Reference) (N=13)	1.62	81.46 [65.58-101.20]	33.5
	Treatment JC (Test) (N=13)	1.32		
AUC_{last} (ng·h/mL)	Treatment JD (Reference) (N=13)	20.2	60.68 [52.65-69.93]	21.6
	Treatment JC (Test) (N=13)	12.3		
AUC_{0-inf} (ng·h/mL)	Treatment JD (Reference) (N=10)	19.9	63.48 [54.11-74.48]	20.5
	Treatment JC (Test) (N=10)	12.6		
2 Hours After a High-Fat Breakfast + 240 mL Water [Treatment JE] vs. Fasted + 240 mL Water [Treatment JH]				
C_{max} (ng/mL)	Treatment JH (Reference) (N=14)	1.79	50.65 [41.79-61.38]	30.8
	Treatment JE (Test) (N=14)	0.904		
AUC_{last} (ng·h/mL)	Treatment JH (Reference) (N=14)	18.3	59.06 [49.76-70.10]	27.3
	Treatment JE (Test) (N=14)	10.8		
AUC_{0-inf} (ng·h/mL)	Treatment JH (Reference) (N=12)	19.1	60.07 [50.73-71.13]	24.8
	Treatment JE (Test) (N=12)	11.5		
1 Hours After a High-Fat Breakfast + 240 mL Water [Treatment JF] vs. Fasted + 240 mL Water [Treatment JH]				
C_{max} (ng/mL)	Treatment JH (Reference) (N=14)	1.79	41.16 33.92-49.93	30.8
	Treatment JF (Test) (N=14)	0.735		
AUC_{last} (ng·h/mL)	Treatment JH (Reference) (N=14)	18.3	49.77 41.89-59.12	27.3
	Treatment JF (Test) (N=14)	9.11		
AUC_{0-inf} (ng·h/mL)	Treatment JH (Reference) (N=12)	19.1	54.01 45.38-64.29	24.8
	Treatment JF (Test) (N=12)	10.3		
Fasted + 480 mL Water [Treatment JG] vs. Fasted + 240 mL Water [Treatment JH]				
C_{max} (ng/mL)	Treatment JH (Reference) (N=14)	1.79	114.88 94.69-139.36	30.8
	Treatment JG (Test) (N=14)	2.05		
AUC_{last} (ng·h/mL)	Treatment JH (Reference) (N=14)	18.3	108.71 91.51-129.15	27.3
	Treatment JG (Test) (N=14)	19.9		
AUC_{0-inf} (ng·h/mL)	Treatment JH (Reference) (N=12)	19.1	114.35 96.07-136.12	24.8
	Treatment JG (Test) (N=12)	21.8		

Source: Reviewer's generated table based on Study PSO1003 Report, Tables 48, 49, 50, 51, 52 and 53
Abbreviations: AUC0-inf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; Cmax, maximum observed plasma concentration; GMR, geometric mean ratio, CV%, coefficient of variance percentage; CI, confidence interval; IR, immediate release
All treatments were evaluated in a single statistical model. The least square means of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the least square means. Both the difference between the least square means and the 90% CIs were retransformed to the original scale.
Treatment JA: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (high-fat breakfast)
Treatment JB: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (low-fat breakfast)
Treatment JC: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 30 minutes before high-fat breakfast
Treatment JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted
Treatment JE: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 2 hours after completion of high-fat breakfast
Treatment JF: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 1 hour after completion of high-fat breakfast
Treatment JG: single oral dose of 100 mg JNJ-77242113 IR tablet with 480 mL water, fasted
Treatment JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

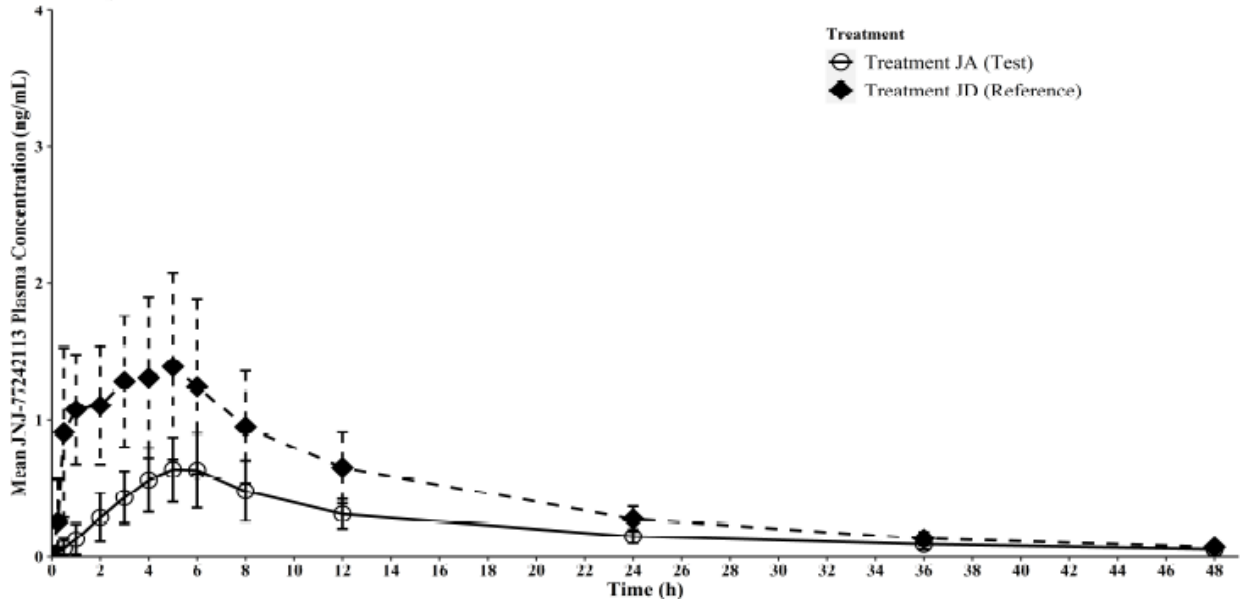
Results From Cohort 5 – Part 4

Effect of Meal Type: High-Fat Breakfast versus Fasted

The plasma concentrations of JNJ-77242113 were lower after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 240 mL water and high-fat breakfast compared to a single dose of 100 mg JNJ-77242113 IR tablet administered with 240 mL water in fasted state (Figure 52). The high-fat breakfast delayed t_{max} by 4 hours (median t_{max} of 5 hours with high-fat breakfast versus 1 hour in fasted state) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 59%, 52%, and 46%, respectively, after the administration of a single dose 100 mg IR tablet with high-fat breakfast and 240 mL water compared to a single dose of 100 mg IR tablet administered in fasted state with 240 mL water (Table 94). These results suggest that concomitant a high-fat meal would lower the bioavailability of JNJ-77242113 to a clinically relevant extent.

Figure 52. Mean (SD) Plasma Concentration-Time Profiles After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted State and After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet With High-Fat Breakfast in Part 4 in Trial PSO1003 – Linear Scale



Source: Study PSO1003 Report, Figure 22
Treatment JA: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (high-fat breakfast).
Treatment JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

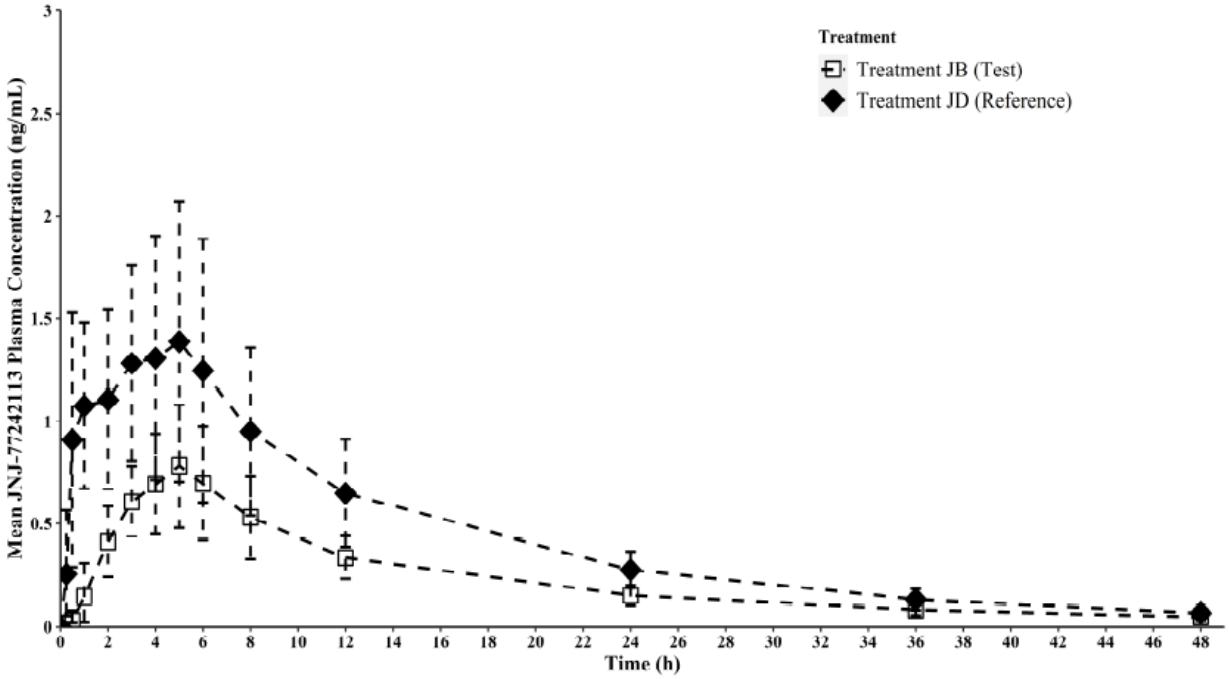
Effect of Meal Type: Low-Fat Breakfast Versus Fasted

The plasma concentrations of JNJ-77242113 were lower after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 240 mL water and low-fat breakfast compared to a single dose of 100 mg JNJ-77242113 IR tablet administered with 240 mL water in fasted state

(Figure 53). The low-fat breakfast delayed t_{max} by 3 hours (median t_{max} of 4 hours with low-fat breakfast versus 1 hour in fasted state) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 52%, 47%, and 43%, respectively, after the administration of a single dose 100 mg IR tablet with low-fat breakfast and 240 mL water compared to a single dose of 100 mg IR tablet administered in fasted state with 240 mL water (Table 94). These results suggest that concomitant low-fat meal would lower the extent of bioavailability of JNJ-77242113 to a clinically relevant extent.

Figure 53. Mean (SD) Plasma Concentration-Time Profiles After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted State and After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet With Low-Fat Breakfast in Part 4 in Trial PSO1003 – Linear Scale



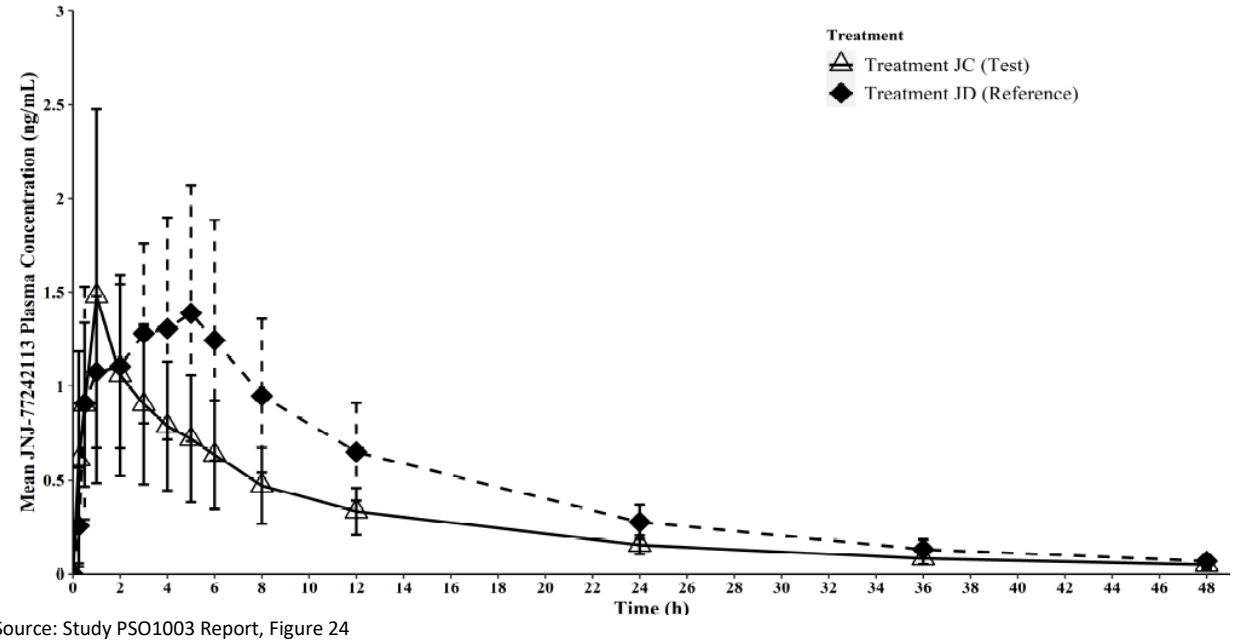
Source: Study PSO1003 Report, Figure 23
Treatment JB: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fed (low-fat breakfast)
Treatment JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

Effect of Mealtime: JNJ-77242113 Administered 30 Minutes Before High-Fat Breakfast Versus Administration in Fasted State

The plasma concentrations of JNJ-77242113 were slightly lower after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 240 mL water 30 minutes before a high-fat breakfast compared to a single dose of 100 mg JNJ-77242113 IR tablet administered with 240 mL water in fasted state (Figure 54). Both treatment groups have a comparable median t_{max} of approximately 1 hour without observed t_{lag} (t_{max} range is 0.25 to 3 hours when administered 30 minutes before high-fat breakfast and 0.5 to 6 hours when administered in fasted state) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 18.5%, 39%, and 36.5%, respectively, after the administration of a single dose 100 mg IR tablet with 240 mL water 30 minutes before a high-fat breakfast compared to a single dose of 100 mg IR tablet administered in fasted state with 240 mL water (Table 94). These results suggest that the administration of single dose of 100 mg JNJ-77242113 IR tablet 30 minutes before a high-fat meal does not impact the PK of JNJ-77242113 to a clinically relevant extent.

Figure 54. Mean (SD) Plasma Concentration-Time Profiles After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet 30 Minutes Before A High-Fat Breakfast and After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted State in Part 4 in Trial PSO1003 – Linear Scale



Source: Study PSO1003 Report, Figure 24
Treatment JC: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 30 minutes before high-fat breakfast.
Treatment JD: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted.

Results from Cohort 6 – Part 4

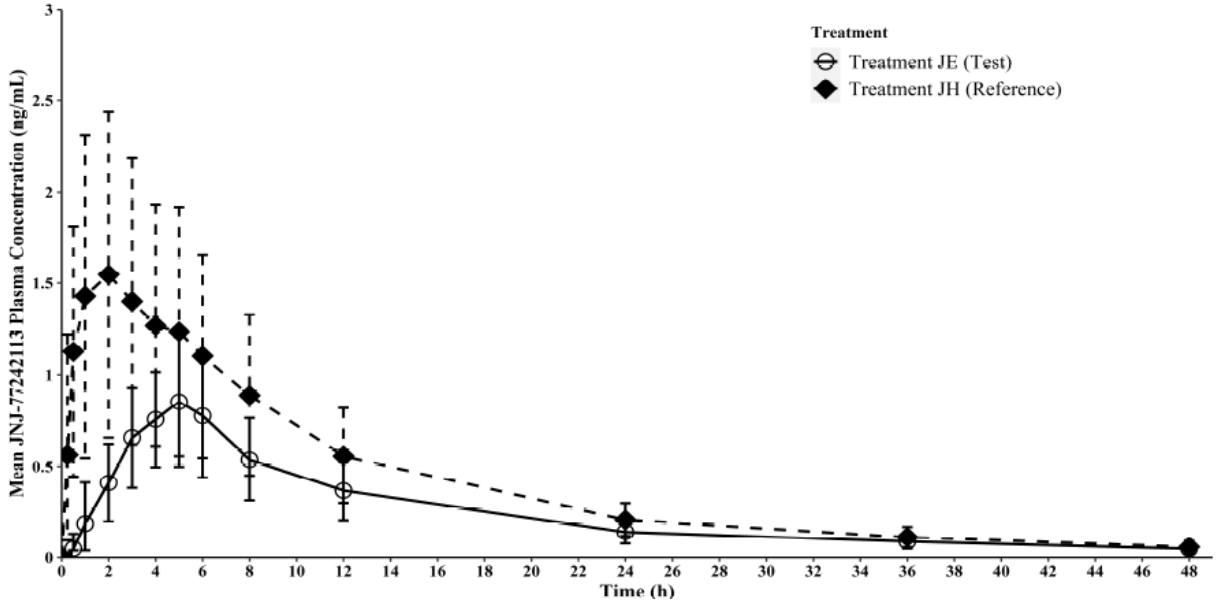
Effect of Mealtime: JNJ-77242113 Administered 2 Hours After High-Fat Breakfast Versus Administration in Fasted State

The plasma concentrations of JNJ-77242113 were lower after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 240 mL water 2 hours after a high-fat breakfast compared to a single dose of 100 mg JNJ-77242113 IR tablet administered with 240 mL water in fasted state (Figure 55). The administration of JNJ-77242113 IR tablet 2 hours after a high-fat breakfast delayed t_{max} by 4 hours (median t_{max} of 5 hours when administered 2 hours after a high-fat breakfast versus median t_{max} of 1 hour when administered in fasted state) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 49%, 41%, and 40%, respectively, after the administration of a single dose 100 mg IR tablet with 240 mL water 2 hours after a high-fat breakfast compared to a single dose of 100 mg IR tablet

administered in fasted state with 240 mL water (Table 94). These results suggest that the administration of single dose of 100 mg JNJ-77242113 IR tablet 2 hours after a high-fat meal impact the PK of JNJ-77242113 to a clinically relevant extent.

Figure 55. Mean (SD) Plasma Concentration-Time Profiles After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet 2 Hours After a High-Fat Breakfast and After the Administration of a Single Dose of 100 mg JNJ-77242113 IR tablet in Fasted State in Part 4 in Trial PSO1003 – Linear Scale



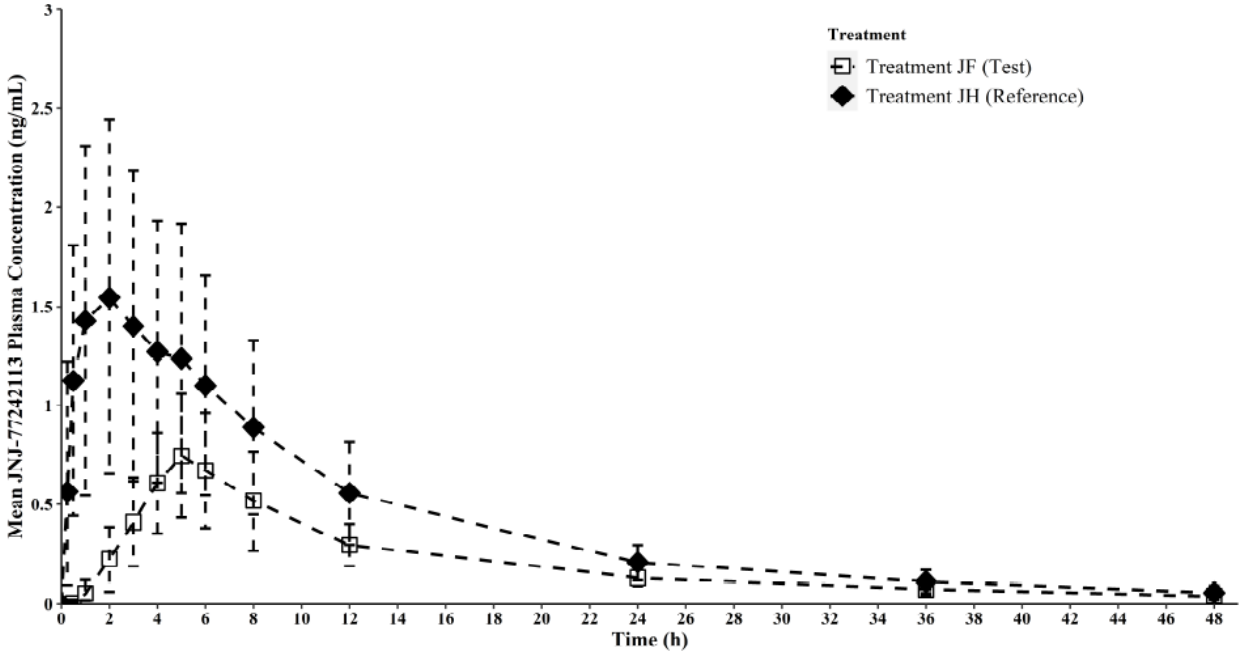
Source: Study PSO1003 Report, Figure 25
Treatment JE: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 2 hours after completion of high-fat breakfast.
Treatment JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

Effect of Mealtime: JNJ-77242113 Administered 1 Hour After High-Fat Breakfast Versus Administration in Fasted State

The plasma concentrations of JNJ-77242113 were lower after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 240 mL water 1 hour after a high-fat breakfast compared to a single dose of 100 mg JNJ-77242113 IR tablet administered with 240 mL water in fasted state (Figure 56). The administration of JNJ-77242113 IR tablet 1 hours after a high-fat breakfast delayed t_{max} by 4 hours (median t_{max} of 5 hours when administered 1 hour after a high-fat breakfast versus median t_{max} of 1 hour when administered in fasted state) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 59%, 50%, and 46%, respectively, after the administration of a single dose 100 mg IR tablet with 240 mL water 1 hours after a high-fat breakfast compared to a single dose of 100 mg IR tablet administered in fasted state with 240 mL water (Table 94). These results suggest that the administration of single dose of 100 mg JNJ-77242113 IR tablet 1 hour after a high-fat meal impact the PK of JNJ-77242113 to a clinically relevant extent.

Figure 56. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet 1 Hour After a High-Fat Breakfast and After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted State in Part 4 in Trial PSO1003 – Linear Scale



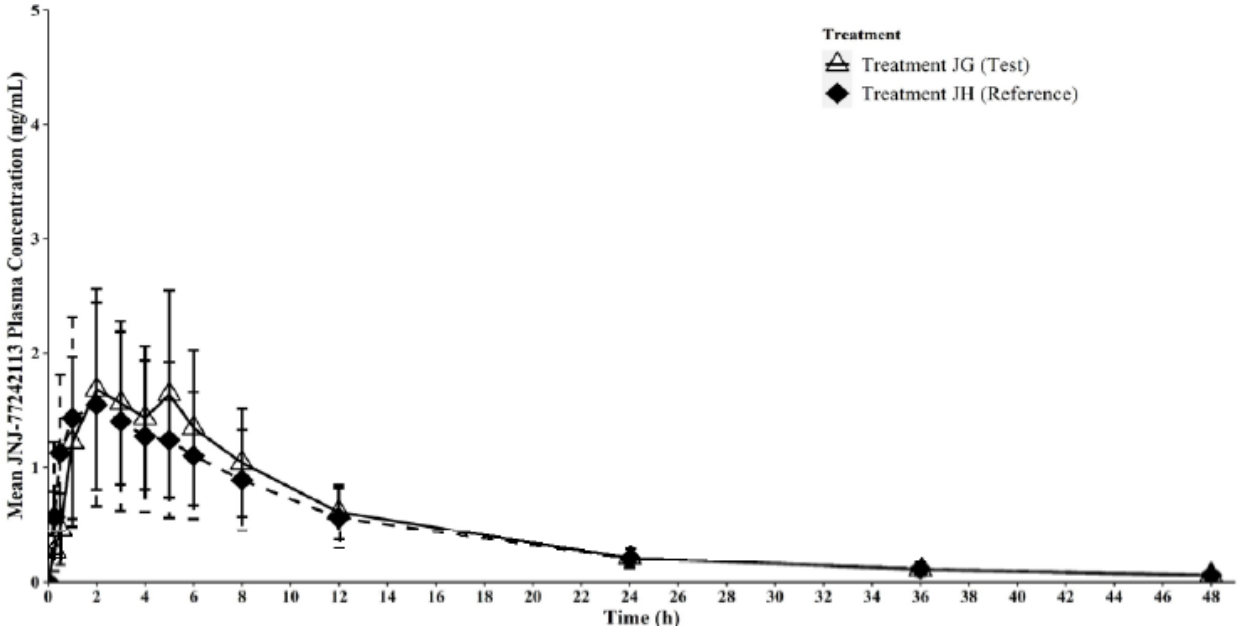
Source: Study PSO1003 Report, Figure 26.
Treatment JF: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, 1 hour after completion of high-fat breakfast.
Treatment JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted.

Effect of Additional Water: JNJ-77242113 Administered With 480 mL Water in Fasted State Versus Administration With 240 mL Water in Fasted State

The plasma concentrations of JNJ-77242113 were comparable after the administration of a single dose of 100 mg JNJ-77242113 IR tablet with 480 mL and 240 mL water following an overnight fasting of at least 10 hours (Figure 57). The administration of JNJ-77242113 IR tablet with 480 mL water delayed t_{max} by 2 hours (median t_{max} of 3 hours when administered with 480 mL water versus median t_{max} of 1 hour when administered with 240 mL water) (Table 93).

Statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 increased by 14.8%, 8.7%, and 14.3%, respectively, after the administration of a single dose 100 mg IR tablet with 480 mL water in fasted state compared to a single dose of 100 mg IR tablet administered in fasted state with 240 mL water (Table 94). These results suggest that the administration of JNJ-77242113 IR tablet with extra water is not anticipated to impact PK of JNJ-77242113.

Figure 57. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After the Administration of a Single Dose of 100 mg JNJ-77242113 IR Tablet in Fasted Stated With 480 mL Water and 240 mL Water in Part 4 in Trial PSO1003 – Linear Scale



Source: Study PSO1003 Report, Figure 27
Treatment JG: single oral dose of 100 mg JNJ-77242113 IR tablet with 480 mL water, fasted
Treatment JH: single oral dose of 100 mg JNJ-77242113 IR tablet with 240 mL water, fasted

19.4.2.2.2. Trial PSO1006

This was a single-dose, open-label, randomized, 3-way crossover trial to evaluate the relative oral bioavailability of JNJ-77242113 phase 3 clinical IR tablet formulation (Lot # G078) versus phase 2 IR tablet formulation (Lot # G014) and the impact of high-fat breakfast (1000 calories, 50% fat) on the PK of JNJ-77242113 clinical IR tablet formulation (Lot # G078) in healthy adult subjects. The design of trial PSO1006 is depicted in Figure 58. The order of treatments was determined by randomization according to a classical 6-sequence, 3-period Williams design. On Day 1 of each treatment period, all subjects received one of the following treatments:

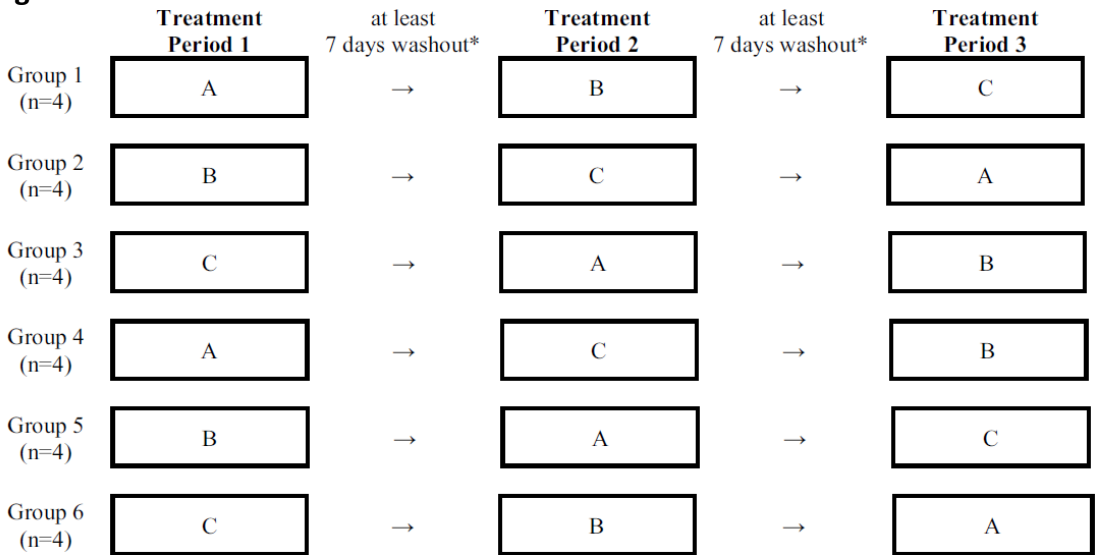
- Treatment A: A single oral dose of 200 mg (1×200 mg IR tablet) NJ-77242113 as clinical IR tablet (Lot #G078), fasted.
- Treatment B: A single oral dose of 200 mg (1×200 mg IR tablet) NJ-77242113 as clinical IR tablet (Lot #G078), fed.
- Treatment C: A single oral dose of 200 mg (2×100 mg IR tablet) NJ-77242113 as phase 2 IR tablet (Lot #G014), fasted

There was at least 7 days washout between treatment periods. Blood samples were collected up to 48 hours to evaluate the PK profile of JNJ-77242113.

In Treatment A and C, subjects fasted at least 10 hours before the administration of JNJ-77242113 with 240 mL water noncarbonated water. Water was not allowed from 1 hour before until 1 hour after JNJ-77242113 intake (except for the water used for JNJ-77242113 intake and

breakfast, if applicable), after which time, water was allowed ad libitum. For Treatment B, subjects started the high-fat breakfast (900 to 1,000 calories, 50% calories from fat) 30 minutes prior to JNJ-77242113 intake and the breakfast was ingested entirely within 30 minutes or less. JNJ-77242113 was administered with 240 mL noncarbonated water within 10 minutes after completion of a high-fat breakfast, but no more than 30 minutes after the start of breakfast, as applicable. For all treatments, no food was allowed for at least 4 hours postdose.

Figure 58. Schematic Overview of Trial PSO1006



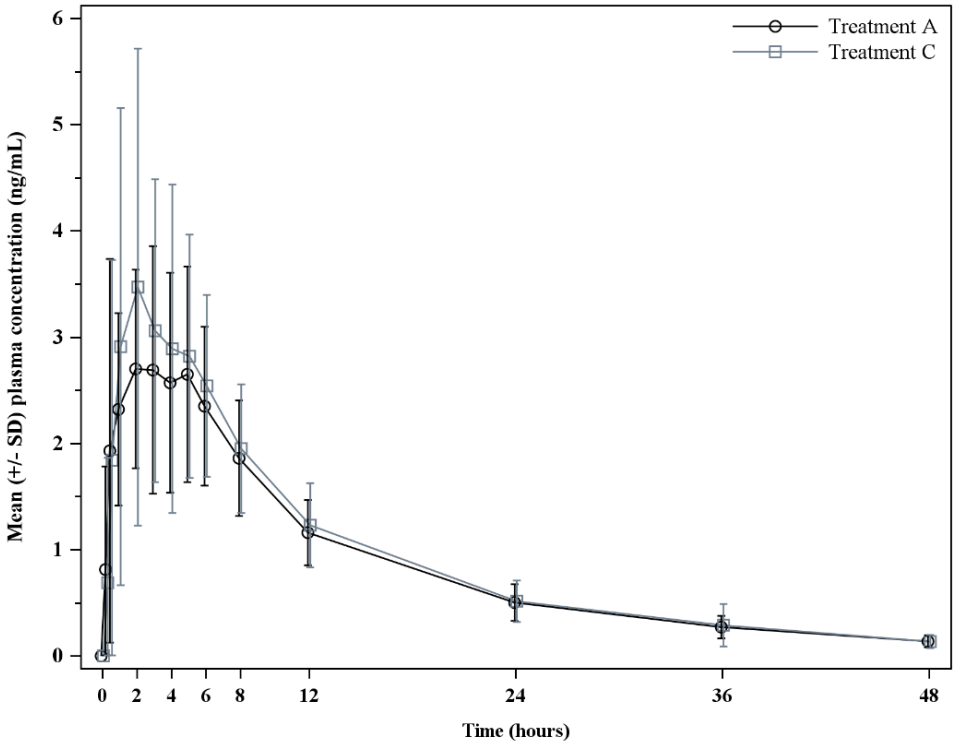
Source: Study PSO1006 Report, Figure 1
*Day 1 of a treatment period, i.e., the day of JNJ-77242113 administration, is the first day of the washout period.
A: A single oral dose of 200 mg JNJ-77242113 formulated as 1×200-mg Phase 3 IR tablet, fasted
B: A single oral dose of 200 mg JNJ-77242113 formulated as 1×200-mg Phase 3 IR tablet, fed
C: A single oral dose of 200 mg JNJ-77242113 formulated as 2×100-mg Phase 2 IR tablets, fasted

Pharmacokinetic Results

Relative Bioavailability of Phase 3 To-be-Marketed (Clinical) IR Tablet to Phase 2 IR Tablet

Overall, the mean plasma concentration time-profile of JNJ-77242113 after the administration of a single dose 200 mg (1×200 mg IR tablet) NJ-77242113 as clinical IR tablet (Lot #G078) was comparable to that after the administration of a single dose 200 mg (2×100 mg IR tablet) NJ-77242113 as Phase 2 IR tablet (Lot #G014) under fasted conditions (Figure 59). The median t_{max} was 2 hours for both tablet formulations without delay in absorption (Table 95). The mean $t_{1/2}$ values were 13 hours and 12.4 hours for clinical and Phase 2 IR tablets, respectively.

Figure 59. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After the Administration of a Single Dose of 200 mg JNJ-77242113 Clinical IR Tablet and After 200 mg JNJ-77242113 Phase 2 IR Tablet Both Under Fasted Conditions in Trial PSO1006



Source: Study PSO1006 Report, Figure 2.
Treatment A: a single oral dose of 200 mg JNJ-77242113 formulated as 1×200-mg Phase 3 IR tablet, fasted
Treatment C: a single oral dose of 200 mg JNJ-77242113 formulated as 2×100-mg Phase 2 IR tablets, fasted

Table 95. Summary of Mean (SD) PK Parameters of JNJ-77242113 After Administration of a Single Dose of 200 mg JNJ-77242113 Clinical IR Tablet Under Fasted and Fed Conditions and After 200 mg JNJ-77242113 Phase 2 IR Tablet Under Fasted Condition in Trial PSO1006

PK Parameters	200 mg JNJ-77242113 Clinical IR Tablet (Treatment A) (Fasted)	200 mg JNJ-77242113 Clinical IR Tablet (Treatment B) (Fed)	200 mg JNJ-77242113 Phase 2 IR Tablet (Treatment C) (Fasted)
N	24[a]	23[b]	23
C_{max} (ng/mL)	3.62 (1.48)	1.51 (0.753)	4.56 (3.05)
t_{max} (h)[c]	2 (0.25 - 8)	5 (3 - 6)	2 (0.25 - 5)
AUC_{24h} (ng·h/mL)	34.6 (9.09)	17.5 (6.05)	37.9 (12.9)
AUC_{last} (ng·h/mL)	42 (10.7)	22.7 (7.02)	45.3 (15.5)
$AUC_{0\text{-}inf}$ (ng·h/mL)	44.8 (11.4)	26.3 (8.01)	47.9 (16)
$t_{1/2}$ (h)	13 (4.1)	14.6 (4.9)	12.4 (3.5)
t_{lag} (h)	-	0.25 (0 - 0.5)	-

Source: Reviewer's generated table based on Study PSO1003 Report, Table 3.
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; AUC_{24h}, area under the plasma concentration time profile from time zero to the time 24 hours; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; SD, standard deviation; tlag, time from administration to the time of first detected concentration in plasma; IR, immediate release.
[a] n=23 for AUClast and $AUC_{0\text{-}inf}$
[b] n=19 for $t_{1/2}$ and n=18 for $AUC_{0\text{-}inf}$
[c] Median (min, max) reported

Statistical analysis of the PK parameters showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased by 12%, 5.8%, and 5%, respectively, after the administration of a single dose of 200 mg NJ-77242113 as clinical IR tablet in fasted state compared to a single dose of 200 mg NJ-77242113 as Phase 2 IR tablet (Table 96). These results suggest relatively comparable exposure between Phase 3 clinical IR tablet formulation (Lot #G078) and phase 2 IR tablet formulation (Lot #G014).

Table 96. Summary of the Statistical Analysis of the PK Parameters of JNJ-77242113 After a Single Dose of 200 mg JNJ-77242113 Clinical IR Tablet (Treatment A) and 200 mg JNJ-77242113 Phase 2 IR Tablet (Treatment C) Under Fasted Condition in Trial PSO1006

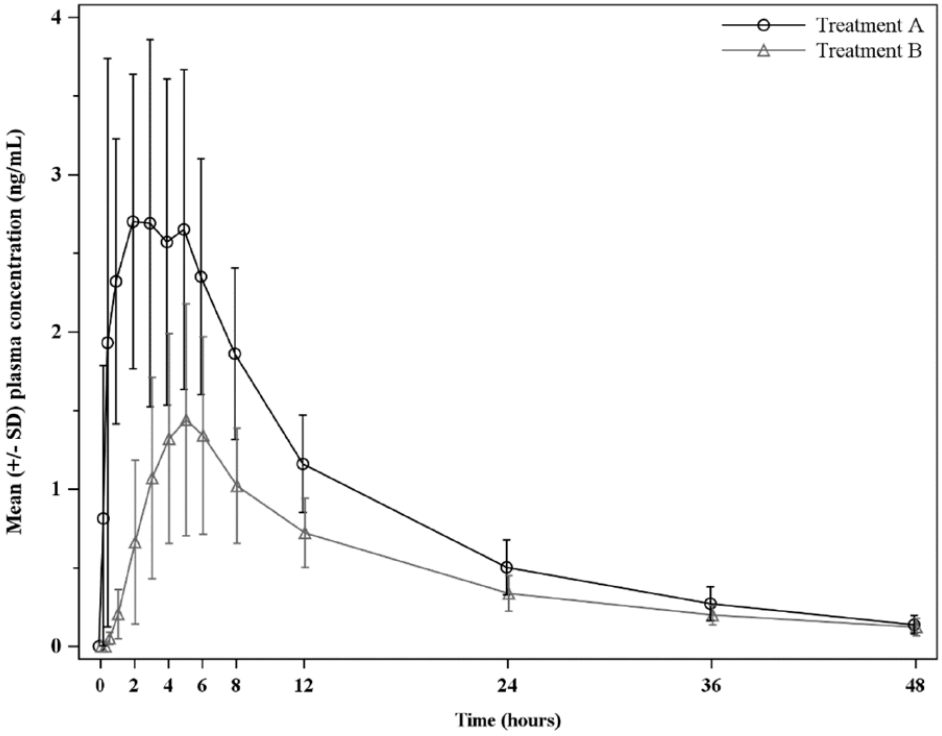
PK Parameter	Comparison	Geometric Means	GMR (%) [90% CI (%)]	Intra- subject CV (%)
C_{max} (ng/mL)	Clinical IR tablet (Test) (N=24)	3.4	88.08 [74.28-104.45]	35.6
	Phase 2 IR tablet (Reference) (N=23)	3.86		
AUC_{last} (ng·h/mL)	Clinical IR tablet (Test) (N=23)	41.1	94.2 [85.06-104.33]	20.5
	Phase 2 IR tablet (Reference) (N=23)	43.7		
$AUC_{0\text{-}inf}$ (ng·h/mL)	Clinical IR tablet (Test) (N=23)	43.8	94.9 [85.59-105.21]	20.7
	Phase 2 IR tablet (Reference) (N=23)	46.2		

Source: Reviewer's generated table based on Study PSO1003 Report, Table 4.
Abbreviations: AUC0-inf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; Cmax, maximum observed plasma concentration; GMR, geometric mean ratio, CV%, coefficient of variance percentage; CI, confidence interval; IR, immediate release.
All treatments were evaluated in a single statistical model. The least square means of the log transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the least square means. Both the difference between the least square means and the 90% CIs was retransformed to the original scale. The geometric mean ratios (GMRs) and 90% CIs were presented.

Food Effect: Fasted Versus Fed Using Phase 3 To-be-Marketed (Clinical) IR Tablet (Lot G078)

In comparison to fasted state, the administration of a single dose 200 mg JNJ-77242113 clinical IR tablet with a high-fat breakfast delayed t_{max} by 3 hours (median t_{max} of 2 hours in fasted state and 5 hours with high-fat meal) (Figure 60 and Table 95). In addition, statistical analysis showed that C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ of JNJ-77242113 decreased 59%, 47%, and 43%, respectively, after the administration of a single dose 200 mg clinical IR tablet with high-fat breakfast compared to a single dose of 200 mg clinical IR tablet administered in fasted state (Table 97). Therefore, the exposure to JNJ-77242113 is lower under fed (high-fat breakfast) compared to fasted condition for oral IR tablet, suggesting that concomitant food would lower the extent of bioavailability of JNJ-77242113.

Figure 60. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After the Administration of a Single Dose of 200 mg JNJ-77242113 Clinical IR Tablet Under Fasted and Fed Conditions in Trial PSO1006



Source: Study PSO1006 Report, Figure 3
Treatment A: a single oral dose of 200 mg JNJ-77242113 formulated as 1×200-mg Phase 3 IR tablet, fasted
Treatment C: a single oral dose of 200 mg JNJ-77242113 formulated as 2×100-mg Phase 2 IR tablets, fasted

Table 97. Summary of the Statistical Analysis of the PK Parameters of JNJ-77242113 After a Single Dose of 200 mg JNJ-77242113 Clinical IR Tablet Under Fasted (Treatment A) and Fed (Treatment B) Conditions in Trial PSO1006

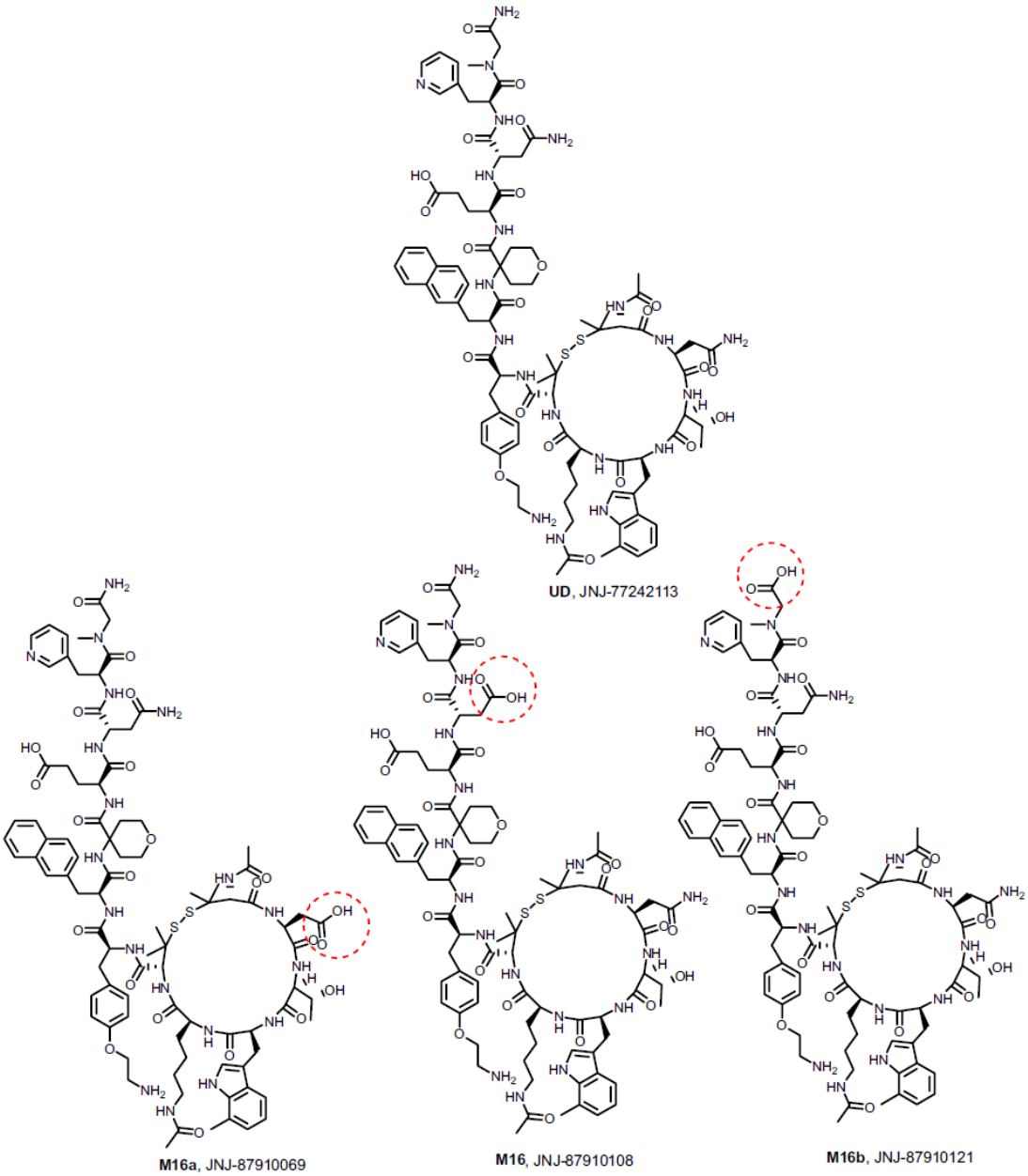
PK Parameter	Comparison	Geometric Means	GMR (%) [90% CI (%)]	Intra- subject CV (%)
C_{max} (ng/mL)	Clinical IR tablet, fed (Test) (N=14)	3.4	40.79 [34.39-48.37]	35.6
	Clinical IR tablet, fasted (Reference) (N=14)	1.39		
AUC_{last} (ng·h/mL)	Clinical IR tablet, fed (Test) (N=14)	41.1	53.5 [48.31-59.24]	20.5
	Clinical IR tablet, fasted (Reference) (N=14)	22		
AUC_{0-inf} (ng·h/mL)	Clinical IR tablet, fed (Test) (N=14)	43.8	57.45 [51.33-64.29]	20.7
	Clinical IR tablet, fasted (Reference) (N=14)	25.2		

Source: Reviewer's generated table based on Study PSO1003 Report, Table 4.
Abbreviations: AUC0-inf, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; Cmax, maximum observed plasma concentration; GMR, geometric mean ratio, CV%, coefficient of variance percentage; CI, confidence interval; IR, immediate release
All treatments were evaluated in a single statistical model. The least square means of the log transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the least square means. Both the difference between the least square means and the 90% CIs was retransformed to the original scale. The geometric mean ratios (GMRs) and 90% CIs were presented.

Metabolite Profiling

In plasma samples from 7 subjects in Trial PSO1006, three metabolites, M16a, M16 and M16b were identified (Figure 61). In all plasma samples, the unchanged JNJ-77242113 was the predominant species, accounting for >92.2% of the total drug related material, while the metabolites accounted for up to 3.7, 6 and 4.6% for M16a, M16 and M16b, respectively. (b) (4)

Figure 61. Structures of Metabolites Obtained in Human Plasma in Trial PSO1006



Source: Report FK14499: The In Vivo Metabolite Profile and Identification of JNJ-77242113 in Plasma from Healthy Volunteers.

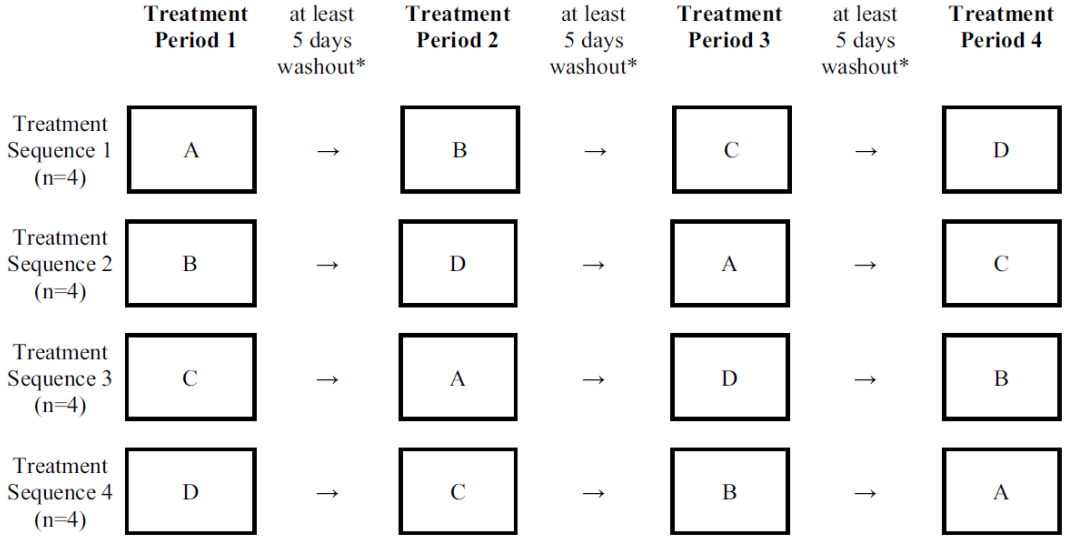
19.4.2.2.3. Trial PSO1009

This was a randomized, open-label, single-dose, 4-way crossover study to evaluate the effect of different types of coadministered oral liquids (including caffeine solution, whole milk, and sucrose solution) on the relative bioavailability of a JNJ-77242113 IR tablet clinical formulation (Lot #G078) in healthy adult subjects. Subjects were randomized in 1:1:1:1 ratio to 1 of 4 treatment sequences based on a balanced 4-sequence, 4-period design (Figure 62). There was at least 5 days washout between the treatment periods. On Day 1 of the treatment period, subjects received one of the following treatments:

- Treatment A (Reference): Single oral dose of 200 mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of noncarbonated water.
- Treatment B (Test 1): Single oral dose of 200 mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of caffeine solution.
- Treatment C (Test 2): Single oral dose of 200 mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of whole milk.
- Treatment D (Test 3): Single oral dose of 200 mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of sucrose solution.

JNJ-77242113 was administered after an overnight fasting of at least 10 hours. Intake of water was not allowed from approximately 1 hour before until approximately 1 hour after administration of JNJ-77242113 except for the water or liquid used for JNJ-77242113 administration), after which time, water was allowed ad libitum. For all treatments, approximately 4 hours after the administration of JNJ-77242113, a standard lunch (with water only) was served.

Figure 62. Schematic Overview of Trial PSO1009

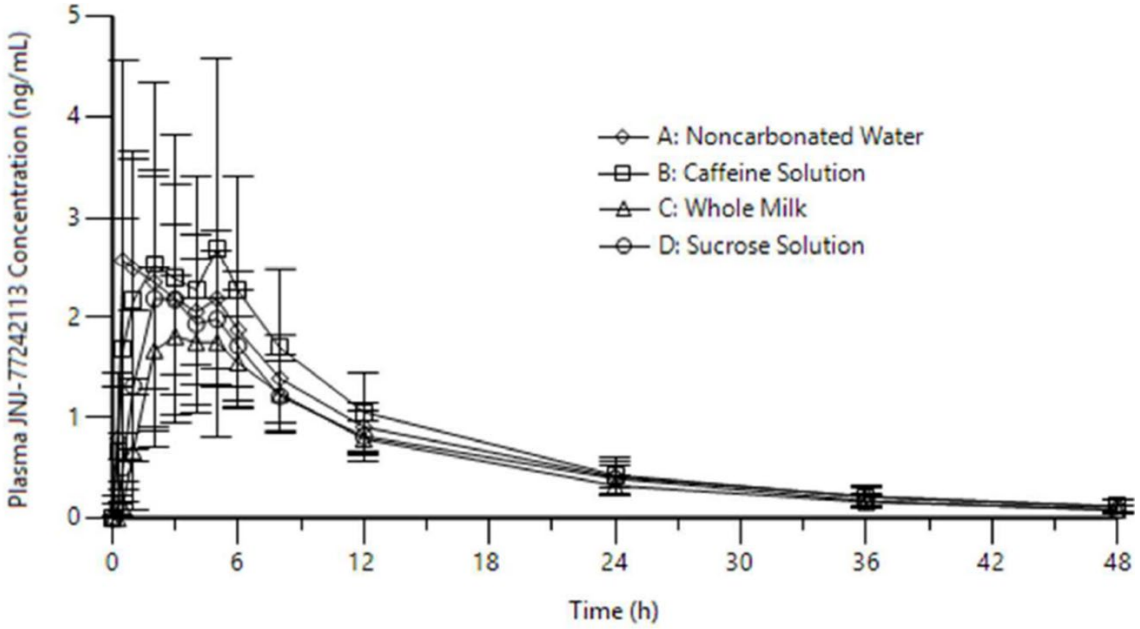


Source: Study PSO1009 Report, Figure 1
*Day1 of a treatment period, i.e., the day of study intervention administration is the first day of the washout period.
A: single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of noncarbonated water (Reference)
B: single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of caffeine solution (Test 1)
C: single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of whole milk (Test 2)
D: single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, and study intervention intake with 240 mL of sucrose solution (Test 3)

Pharmacokinetic Results

The plasma concentration time profiles and summary of PK parameters of JNJ-77242113 following the administration of a single dose of 200 mg JNJ-77242113 IR tablet after at least 10 hours overnight fasting with 240 mL of noncarbonated water, caffeine solution, whole milk, and sucrose solution are depicted in Figure 63 and Table 98. The t_{max} was delayed by approximately 2 hours following the administration of JNJ-77242113 with caffeine solution, whole milk, and sucrose solution compared to noncarbonated water. The mean $t_{1/2}$ of JNJ-77242113 in the 4 administration regimens was approximately 12 hours.

Figure 63. Mean (SD) Plasma Concentration-Time Profiles of JNJ-77242113 After the Administration of a Single Dose of 200 mg JNJ-77242113 IR Tablet With Noncarbonated Water, Caffeine Solution, Whole Milk, or Sucrose Solution in Fasted State in Trial PSO1009



Source: Study PSO1009 Report, Figure 2.
Abbreviations: IR, immediate release; SD, standard deviation

Table 98. Summary of PK Parameters of JNJ-77242113 After the Administration of a Single Dose of 200 mg JNJ-77242113 IR Tablet With Noncarbonated Water, Caffeine Solution, Whole Milk, or Sucrose Solution in Fasted State in Trial PSO1009

Parameter	Treatment A (Reference): With Noncarbonated Water	Treatment B (Test 1): With Caffeine Solution	Treatment C (Test 2): With Whole Milk	Treatment D (Test 3): With Sucrose Solution
n	15	15	14	16
C_{max} (ng/mL)	3.38 (1.81)	3.31 (2.12)	2.13 (0.621)	2.66 (1.38)
t_{max} (h)[a]	1.00 (0.50-6.00)	3.00 (0.25-6.00)	3.50 (1.00-6.00)	3.00 (1.00-6.00)
AUC_{last} (ng*h/mL)	34.3 (7.70)	37.6 (16.2)	26.3 (4.72)	29.4 (9.70)[c]
AUC_{∞} (ng*h/mL)	36.7 (9.01)[b]	39.9 (17.1)	27.9 (5.18)	30.8 (10.2)[c]
$t_{1/2}$ (h)	12.1 (3.1)[b]	12.6 (4.1)	11.9 (3.1)	10.9 (2.5)[c]
CL/F (L/h)	5,710 (1,183)[b]	5,756 (2,009)	7,438 (1,686)	7,236 (2,638)[c]
Vd_z/F (L)	96,225 (19,019)[b]	107,514 (64,199)	125,385 (33,607)	112,210 (45,666)[c]

Source: Study PSO1009 Report, Table 4
Abbreviations: AUC∞, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; Tmax, time to the maximum plasma concentration; t½, apparent elimination half-life; Vz/F, apparent volume of distribution during terminal phase; SD, standard deviation.
[a] median (minimum-maximum) presented for tmax
[b] n=14
[c] n=15

In comparison to the administration of a single dose 200 mg JNJ-77242113 IR tablet with 240 mL noncarbonated water (i.e., Reference), statistical analysis showed that C_{max} of JNJ-77242113 was decreased by 8% and AUC_{last} and $AUC_{0\text{-}inf}$ increased by approximately 4% when the single dose of 200 mg JNJ-77242113 IR tablet administered with 240 mL caffeine solution (Table 99). The C_{max} decreased by 33% and AUC_{last} and $AUC_{0\text{-}inf}$ decreased by 24% when the single dose of 200 mg JNJ-77242113 IR tablet administered with 240 mL whole milk. The C_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ decreased by 22%, 16.5%, and 18%, respectively when the single dose of 200 mg JNJ-77242113 IR tablet administered with 240 mL sucrose solution. According to the results from Study PSO1009, the exposure to JNJ-77242113 does not change significantly to a clinically relevant extent when the drug is administered with noncarbonated water, caffeine solution, whole milk, or sucrose solution.

Table 99. Summary of the Statistical Analysis of the PK Parameters of JNJ-77242113 After the Administration of a Single Dose of 200 mg JNJ-77242113 IR Tablet With Noncarbonated Water (Treatment A), Caffeine Solution (Treatment B), Whole Milk (Treatment C), or Sucrose Solution (Treatment D) in Fasted State in Trial PSO1006

Parameter	Comparison	N		Geometric Means		GMR	90% CI	CV
		Test	Reference	Test	Reference	(%)	(%)	(%)
C_{max} (ng/mL)	B vs. A	15	15	2.80	3.04	91.98	70.09 - 120.72	
	C vs. A	14	15	2.04	3.04	67.01	50.80 - 88.40	46.3
	D vs. A	16	15	2.38	3.04	78.06	59.70 - 102.06	
AUC_{last} (ng*h/mL)	B vs. A	15	15	34.8	33.4	104.06	88.51 - 122.34	
	C vs. A	14	15	25.5	33.4	76.40	64.77 - 90.11	26.7
	D vs. A	15	15	27.9	33.4	83.54	71.06 - 98.22	
AUC_{∞} (ng*h/mL)	B vs. A	15	14	36.9	35.6	103.80	88.39 - 121.9	
	C vs. A	14	14	27.0	35.6	75.91	64.45 - 89.40	25.9
	D vs. A	15	14	29.2	35.6	82.02	69.84 - 96.32	

Source: Study PSO1009 Report, Table 5
Abbreviations: AUC∞, area under the plasma concentration time profile from time zero to infinity; AUClast, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; N, number of observations; GMR, geometric mean ratio; CI, confidence interval; CV: intrasubject coefficient of variation
All treatments were evaluated in a single statistical model. The LS means of the log-transformed primary PK parameters for each treatment were estimated with a linear mixed effects model, controlling for treatment, sequence, and period as fixed effects, and participant in sequence as a random effect. A 90% CI was constructed around the difference between the LS means of liquid effect: 1) intake with caffeine solution (Test 1) was compared to intake with water (reference), 2) intake with whole milk (Test 2) was compared to intake with water (reference), 3) intake with sucrose solution (Test 3) was compared to intake with water (reference). Both the difference between the LS means and the 90% CIs was retransformed to the original scale. The GMRs and 90% CIs were presented.
Treatment A (Reference): single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, with 240 mL of noncarbonated water.
Treatment B (Test 1): single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, with 240 mL of caffeine solution.
Treatment C (Test 2): single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, with 240 mL of whole milk.
Treatment D (Test 3): single oral dose of 200-mg JNJ-77242113 IR tablet, fasted, with 240 mL of sucrose solution.

19.4.2.3. Renal Impairment Study, Trial PSO1007

Study PSO1007 was an open-label, single-dose, parallel-group study to evaluate the impact of moderate and severe renal impairment (RI) on the exposure to icotrokinra compared to matched healthy adult subjects with normal renal function.

Part A included 8 subjects with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) or end stage renal disease (ESRD) (eGFR < 15 mL/min/1.73 m^2) not on dialysis, along with 8 matched control subjects with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2). Part B included 5 subjects with moderate renal impaired (eGFR 30 to 59 mL/min/1.73 m^2) along with 5 matched control subjects with normal renal function. The control subjects with normal renal function were matched to renally impaired subjects of the same sex, age (±10 years) and body weight (±10 kg).

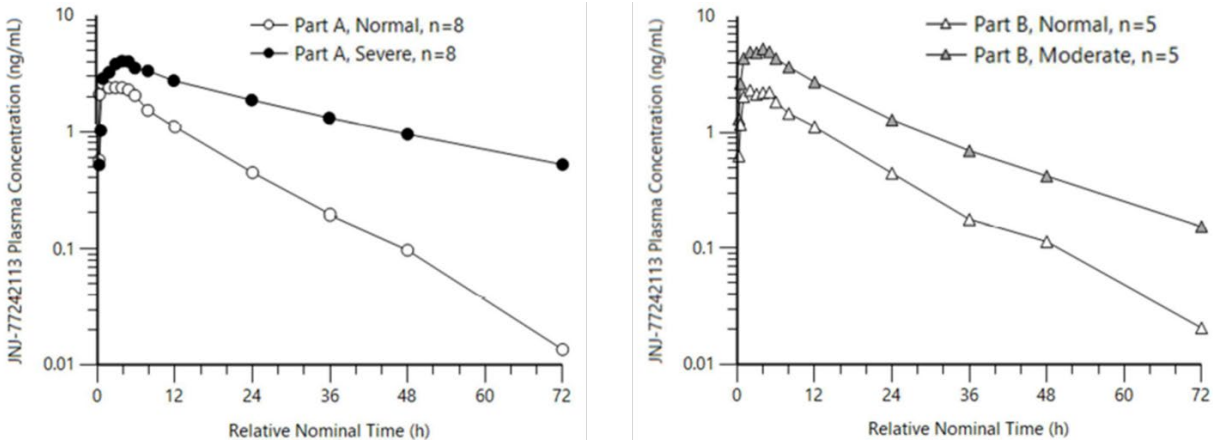
All subjects received a single oral dose of 200 mg icotrokinra IR tablet (Clinical formulation, Lot #G078) after fasting for at least 10 hours. Blood and urine samples were collected up to 72 hours postdosing for PK evaluation.

Pharmacokinetic Results

The mean plasma concentration-time profiles of icotrokinra following the administration of a single dose of 200 mg icotrokinra IR tablet in subjects with severe or moderate renal impairment and their match controls with normal renal function are depicted in Figure 64. A summary of PK parameters of icotrokinra in the three treatment groups is provided in Table 100. No subjects with ESRD (eGFR <15 mL/min) were enrolled in Part A of the study. The median t_{max} of icotrokinra was 3.5 hours in subjects with severe RI, 4 hours in subjects with moderate RI and 2 hours for the matched controls with normal renal function. The mean $t_{1/2}$ increased from 11 hours in the matched controls with normal renal function to 21 and 16.3 hours in subjects with severe and moderate RI, respectively.

The unchanged icotrokinra recovered in urine was 0.00323%, 0.00220%, 0.000525% and 0.000205% of the administered dose for severe RI, moderate RI, control subjects matching with severe RI and control subjects matching subjects with moderate RI, respectively (Table 100). The very low urinary recovery is the result of the low bioavailability (<1%) and renal metabolism of the parent compound, leading to low levels of unchanged drug in the urine. The renal clearance (CL_R) of unchanged icotrokinra was lower in healthy controls with normal renal function (0.0124 L/h and 0.0260 L/h) compared to subjects with moderate and severe RI impairment (0.0328 L/h and 0.0358 L/h, respectively) despite the higher CL/F in healthy controls.

Figure 64. Mean (SD) Plasma Concentration-Time Profiles of Icotrokinra After the Administration of a Single Dose of 200 mg Icotrokinra IR Tablet in Subjects With Severe or Moderate Renal Impairment and Their Match Controls with Normal Renal Function



Source: Study PSO1007 Report, Figures 2 and 3.

Table 100. Summary of PK Parameters of Icotrokinra After the Administration of a Single Dose of 200 mg Icotrokinra IR Tablet in Subjects With Severe or Moderate Renal Impairment and Their Matched Controls with Normal Renal Function

Parameter	Severe Renal Impairment	Normal Matched to Severe Renal Impairment	Moderate Renal Impairment	Normal Matched to Moderate Renal Impairment
N	8	8	5	5
C_{max} (ng/mL)	4.84 (3.21), 66.4	3.29 (1.47), 44.6	5.61 (3.82), 68.2	2.72 (0.49), 18
t_{max} (h)[a]	3.5 (0.92-8.02), 56.5	2 (0.50-6.02), 83.3	4 (0.5-5), 58.6	2 (1.00-5.03), 58.7
AUC_{24h} (ng·h/mL)	66.1 (42.3), 64	31.4 (9.36), 29.8	69.6 (39.9), 57.3	29.2 (5.43), 18.6
AUC_{last} (ng·h/mL)	116 (75.5), 64.8	37.9 (9.36), 24.7	95.0 (51.7), 54.4	36.5 (8.68), 23.8
$AUC_{0\text{-}inf}$ (ng·h/mL)	133 (97.2), 72.8 [a]	38.7 (9.28), 24	98.9 (53.2), 53.8	37.1 (8.69), 23.4
CL/F (L/h)	2,399 (1,629), 67.9 [a]	5,457 (1,386), 25.4	2,423 (1,007), 41.5	5,618 (1,214), 21.6
Vd/F (L)	67,040 (41,885), 62.5 [a]	85,759 (32,614), 38	56,156 (23,620), 42.1	85,014 (16,878), 19.9
$t_{1/2}$ (h)	21.1 (5.1), 24.1 [a]	10.6 (1.7), 16.3	16.3 (3.9), 24	10.7 (1.8), 17
Ae (ng)	6,450 (11,631)	1,050 (1,372)	4,410 (6,991)	410 (655)
Ae%dose (%)	0.00323 (0.00582)	0.000525 (0.000686)	0.00220 (0.00350)	0.000205 (0.000327)
CLR (L/h)	0.0358 (0.0405)[a]	0.0260 (0.0316)	0.0328 (0.0359)	0.0124 (0.0198)

Source: Reviewer's compiled table using Tables 6 and 8 from Summary of Clinical Pharmacology Studies.
Abbreviations: $AUC_{0\text{-}inf}$, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; AUC_{24h}, area under the plasma concentration time profile from time zero to 24 hours; CL/F; apparent total body clearance; Cmax, maximum observed plasma concentration; t_{max}, time to the maximum plasma concentration; t½, apparent elimination half-life; Vd/F, apparent volume of distribution during terminal phase; SD, standard deviation; Ae, amount excreted in urine; Ae%dose, percentage of the dose excreted in urine; CLR, renal clearance
Data presented as mean (SD), CV%; tmax: Median (Range), CV%
[a] N=7

Statistical analysis of PK parameters for icotrokinra showed that subjects with severe renal impairment have 1.26-, 2.6-, and 2.78-fold increase in the C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$, respectively, of icotrokinra compared to matched controls with normal renal function (Table 101). In addition, subjects with moderate renal impairment have 1.79-, 2.4-, and 2.46-fold increase in the C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$, respectively, of icotrokinra compared to matched controls with normal renal function.

Table 101. Statistical Analysis of PK Parameters of Icotrokinra After the Administration of a Single Dose of 200 mg Icotrokinra IR Tablet in Subjects With Severe or Moderate Renal Impairment and Their Matched Controls with Normal Renal Function

PK Parameter	Comparison	Geometric Means	GMR (%) [90% CI (%)]	Intrasubject CV (%)
	Severe Renal Impairment			
C_{max} (ng/mL)	Matched control (Reference) (N=8)	3.03	126.84 (73.58, 218.65)	68.2
	Severe RI (Test) (N=8)	3.85		
AUC_{last} (ng·h/mL)	Matched control (Reference) (N=8)	36.85	260.95 (166.65, 408.62)	54.4
	Severe RI (Test) (N=8)	96.15		
AUC_{0-inf} (ng·h/mL)	Matched control (Reference) (N=8)	37.66	278.33 (168.38, 460.07)	59.2
	Severe RI (Test) (N=7)	104.83		
	Moderate Renal Impairment			
C_{max} (ng/mL)	Matched control (Reference) (N=5)	2.68	179.01 (106.92, 299.71)	46
	Moderate RI (Test) (N=5)	4.8		
AUC_{last} (ng·h/mL)	Matched control (Reference) (N=5)	35.69	240.93 (154.67, 375.32)	39.1
	Moderate RI (Test) (N=5)	85.98		
AUC_{0-inf} (ng·h/mL)	Matched control (Reference) (N=5)	36.32	246.83 (158.85, 383.53)	38.8
	Moderate RI (Test) (N=5)	89.64		

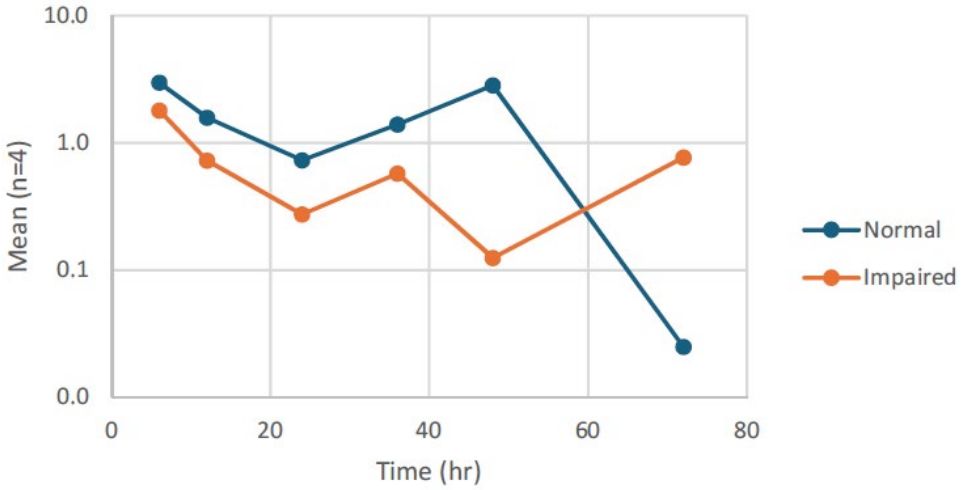
Source: Study PSO1007 Report, Tables 9 and 10.
Abbreviations: AUC_{0-inf}, area under the plasma concentration time profile from time zero to infinity; AUC_{last}, area under the plasma concentration time profile from time zero to the time of the last measurable concentration; C_{max}, maximum observed plasma concentration; N, number of observations; GMR, geometric mean ratio; CI, confidence interval; CV: intrasubject coefficient of variation
The primary PK parameters were C_{max}, AUC_{last}, and AUC_{0-inf} on the logarithmic scale. Log-transformed primary PK parameters were analyzed using various ANCOVA models with population (renal impairment group versus control group) as a fixed effect, as well as exploration. of age, body weight, and sex as continuous effects. The final models without covariates were retained for further analysis. For each group, the geometric means of the PK parameters were estimated and the GMRs with their 90% CI were obtained for participants with moderate renal impairment and participants with severe renal impairment/ESRD versus the control group, which were transformed back to the original scale.

Metabolite Profiling in Urine Samples

In vitro studies examined the renal metabolism of icotrokinra by analyzing its metabolite profile following in vitro incubations of the drug with kidney homogenates from humans (see Section 19.4.1). After incubating ^{14}C-icotrokinra with kidney homogenates from humans for 24 hours, the main metabolites identified were M6 and M12. The M6 metabolite constituted 36% and M12 constituted 16% of the total drug related species in humans.

In Study PSO1007, urine samples were collected from four subjects with normal renal function and four subjects with severe renal impairment (RI) for metabolite profiling by LC-MS analysis. M12, but not M6, and the unchanged icotrokinra were found in the urine samples from all subjects. A greater M12/unchanged drug was observed in subjects with normal renal function compared to those with sever renal impairment (Figure 65), indicating that the kidney metabolism was reduced in renally impaired patients which may explain the increase in renal clearance of icotrokinra in subjects with severe and moderate renal impairment.

Figure 65. Time Course of Peak Area Ratio of M12/Unchanged Icotrokinra Obtained by LC-MS Analysis of Human Urine from Trial PSO1007



Source: Report FK14612: Profiling of JNJ-77242113 renal metabolism, Figure 3.
Abbreviation: LC-MS, liquid chromatography-mass spectrometry

19.4.2.4. Dose-Ranging Study, Trials PSO2001 and PSO2002

Trial PSO2001 was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter study that evaluated the dose response of icotrokinra at Week 16 in adult subjects with moderate to severe plaque PsO. Subject in Study PSO2001 were randomized 1:1:1:1:1:1 to received icotrokinra (25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD or 100 mg BID) IR tablet or placebo. The primary efficacy endpoint was the proportion of subjects achieving PASI 75 response at Week 16, defined as at least a 75% reduction from baseline in PASI total score.

Eligible subjects at Week 16 in trial PSO2001 had the option to enroll in a 36-week long-term extension (LTE) study (Study PSO2002). Study PSO2002 was a multicenter, LTE, double-blind, dose-ranging, parallel-group study in which all subjects with moderate to severe plaque PsO were treated with icotrokinra. All subjects randomized to an icotrokinra in Study PSO2001 continued to receive the same dosing regimen. Subjects randomized to placebo in trial PSO2001 received icotrokinra 100 mg QD starting at Week 16 (LTE Week 0) of Study PSO2001 through the end of the treatment period in this study.

Icotrokinra IR tablets were supplied in two strengths, 25 mg (Lot G012) and 100 mg (Lot G014) administered after fasting for at least 10 hours under fasting conditions. Subjects administered icotrokinra in the morning and evening on an empty stomach with approximately 240 mL of noncarbonated water. Subjects abstained from food intake for at least 2 hours before taking icotrokinra and abstained from food and liquid intake for at least 30 minutes after taking icotrokinra. The trough concentrations of icotrokinra were evaluated at Weeks 0, 1, 2, 4, 8, 12, 16, 20, 24, 36, 40, and 52. Immunogenicity evaluation was conducted at Weeks 0, 2, 4, 8, 16, 20, 24, 36, 40, and 52. Serum biomarkers were measured at Weeks 0, 2, 4, 8, 12, 16, 40 and 52. Tape strips were collected from lesional and non-lesional skin at Week 0; lesional at Week 4

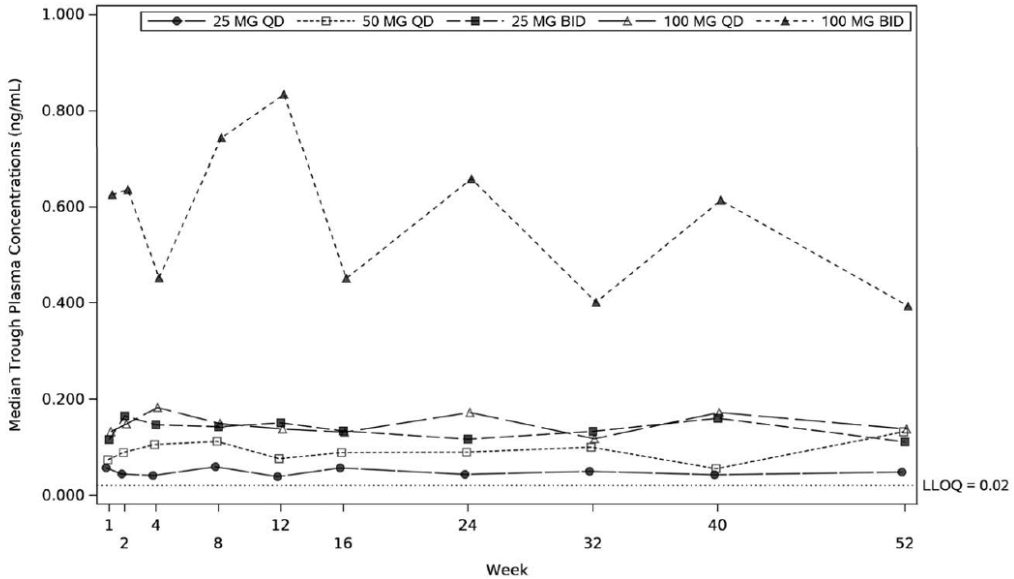
and Week 16. Ex vivo cytokine release blood sample were collected at Weeks 0, 2, 4, and 16. Icotrokinra was administered in the morning on an empty stomach with approximately 240 mL of noncarbonated water. Subjects abstained from food intake for at least 2 hours before taking icotrokinra and abstaining from food and liquid intake for at least 30 min after taking icotrokinra.

Pharmacokinetic Results From Trial PSO2001

The median plasma icotrokinra trough concentrations from Week 1 through Week 16 are provided in Figure 66. The median plasma drug concentrations increased in a dose-related manner, with no apparent drug accumulation consistent with icotrokinra short elimination half-life of approximately 9 to 12 hours and attainment of steady state conditions by Week 1 of treatment. The median trough plasma icotrokinra concentrations at Week 16 were 0.057, 0.089, 0.134, 0.132, 0.451 ng/mL and at Week 52 were 0.049, 0.133, 0.111, 0.138, 0.393 ng/mL following the administration of icotrokinra 25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD or 100 mg BID, respectively. Median trough plasma JNJ-77242113 concentrations were higher for the 25 mg and 100 mg BID dosing regimens versus the same total daily dose QD (Figure 66).

Body weight was not identified as a factor impacting the trough concentration of icotrokinra. The median trough concentration at Week 16 was 0.061, 0.077, 0.131, 0.150, and 0.576 ng/mL in subjects with body weight ≤90 kg and 0.047, 0.115, 0.138, 0.129, and 0.428 ng/mL in subjects with body weight < 90 kg following the administration of icotrokinra 25 mg QD, 50 mg QD, 25 mg BID, 100 mg QD and 100 mg BID, respectively.

Figure 66. Median Trough Plasma JNJ-77242113 Concentrations Through Week 52 (LTE Week 36) in Studies PSO2001 and PSO2002

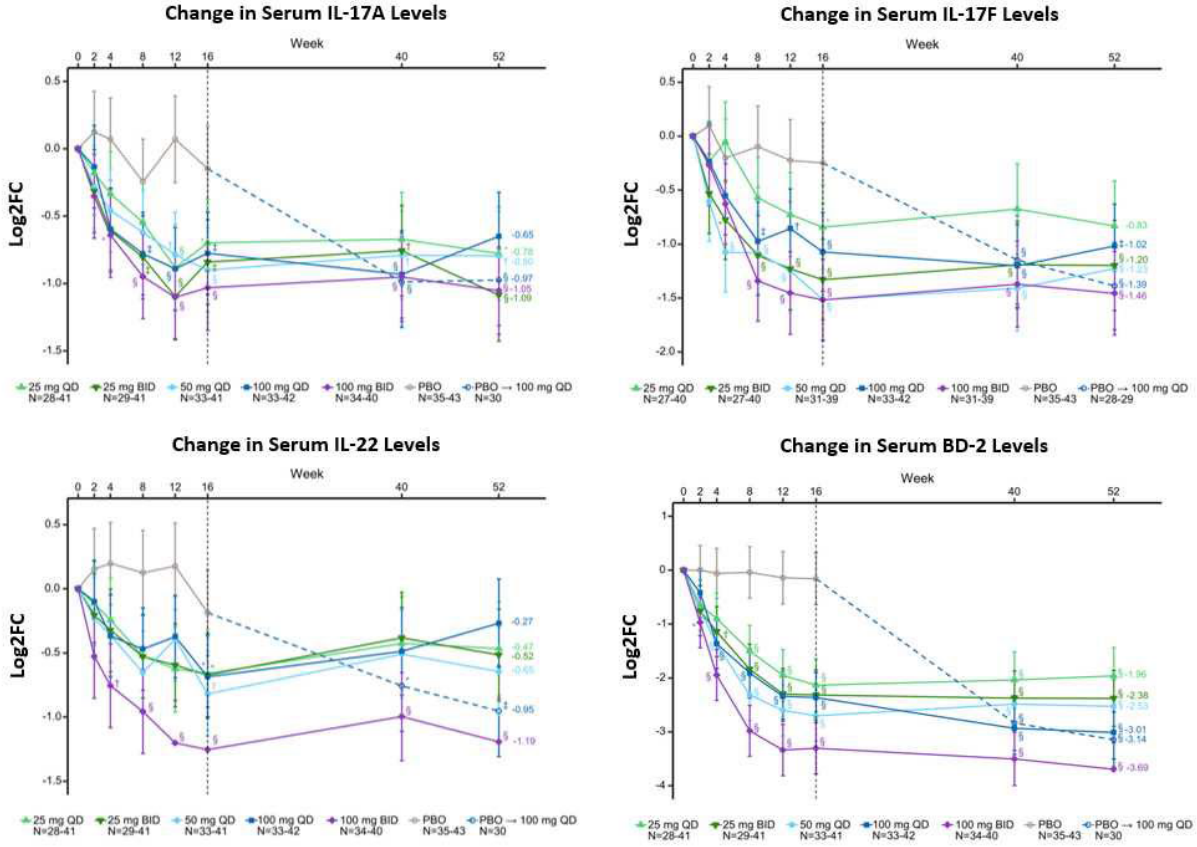


Source: Study PSO2001 Clinical Report, Figure 8.
Abbreviations: QD, once daily, BID, twice daily; LLOQ, lower limit of quantification

Pharmacodynamic Results

The PD effects of icotrokinra on serum IL-17A, IL-17F, IL-22, and BD-2 levels in subjects with moderate to severe PsO in trials PSO2001 and 2002 were assessed at Weeks 0, 2, 4, 8, 12, 16, 40, and 52. Overall, there is a reduction from baseline in IL-17A, IL-17F, IL-22, and BD-2 in all icotrokinra dose groups relative to placebo that was sustained through Week 52, with the greatest reduction observed in the 100 mg BID dosing group, especially in IL-22 and BD-2. Similar reductions in these biomarkers were observed in the placebo group from Week 16 to Week 52 after crossing over to 100 mg QD.

Figure 67. Change From Baseline in Serum Levels of IL-17A, IL-17F, IL-22, and BD-2 in Subjects Receiving Icotrokinra and Placebo in Trials PSO2001 and PSO2002



Source: Summary of Clinical Pharmacology, Figure 12.
Abbreviations: BD-2, beta-defensin-2; BID, twice daily; FC, fold change; IL, interleukin; log2, logarithm to the base 2; PBO, placebo; QD, once daily.
A total of 24 subjects (9.4%) discontinued study intervention prior to Week 16. A higher percentage of subjects discontinued from study intervention in the placebo group and the 25 mg QD group compared with the other icotrokinra groups.
Estimated marginal means displayed. Error bars are model-based 95% confidence intervals.
* Nominal p<0.05 for all treatments versus baseline.
† Nominal p<0.01 for all treatments versus baseline.
‡ Nominal p<0.001 for all treatments versus baseline.
§ Nominal p<0.0001 for all treatments versus baseline.

Efficacy Results

The primary endpoint was the proportion of subjects achieving PASI 75 at Week 16, defined as ≥75% improvement from baseline in PASI total score. The difference from placebo in the proportion of subjects achieving PASI 75 response at Week 16 relative to placebo were as follows: 27.9% for 25 mg QD, 48.8% for 50 mg QD, 41.9% for the 25 mg BID, 55.8% for the 100 mg QD, and 69.4% for the 100 mg BID (Table 102). Notably, the 100 mg BID dosing group demonstrated the highest proportion of subjects achieving PASI 75 response at Week 16 relative to placebo.

Table 102. Proportion of Subjects Achieving PASI 75 Response at Week 16 in Trial PSO2001

		JNJ-77242113				
	Placebo	25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID
Analysis set: Full analysis set	43	43	43	41	43	42
Subjects achieving ≥ 75% Improvement at Week 16[a]	4 (9.3%)	16 (37.2%)	25 (58.1%)	21 (51.2%)	28 (65.1%)	33 (78.6%)
Treatment difference (95% CI)[b]		27.9% (11.2%, 44.6%)	48.8% (31.9%, 65.8%)	41.9% (24.5%, 59.3%)	55.8% (39.3%, 72.3%)	69.4% (54.7%, 84.1%)
p-value[c]		0.002	< 0.001	< 0.001	< 0.001	< 0.001

Source: Study PSO2001 Report, Table 4
[a] Subjects with intercurrent event (ICE) 1 (discontinuation of study intervention due to lack of efficacy or due to an AE of worsening of psoriasis) and ICE 2 (initiation of a protocol-prohibited medication or therapy that could improve psoriasis) were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3 (discontinuation of study intervention due to other reasons). After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI were calculated adjusting for baseline weight category (≤90 kg, >90 kg) using Mantel-Haenszel (MH) weights.
[c] The p-values are based on Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline weight category (≤90 kg, >90 kg).

There was a higher proportion of subjects (81.5%) with PASI 75 at Week 16 in the highest trough concentration quartile (trough concentrations ≥0.306 ng/mL) (Table 103). There was no difference in proportion of subjects (46.2% to 53.8%) with PASI 75 at Week 16 at trough concentrations <0.306 ng/mL. There was no consistent trend in the proportion of participants who achieved clinical response at Week 16 by icotrokinra trough concentration quartiles.

Table 103. Percentage of Subjects Achieving PASI75 Response at Week 16 by Trough Plasma Icotrokinra (JNJ-77242113) Concentrations (ng/mL) Across All Icotrokinra Treatment Groups at Week 16 in Trial PSO2001

	Trough Plasma JNJ-77242113 Concentration Quartiles (ng/mL)			
Parameters	**<0.0638**	**≥0.0638 to <0.124**	**≥0.124 to <0.306**	**≥0.306**
N	26	26	26	27
Proportion subjects achieving PASI75 response at Week 16	50%	45.2%	53.8%	81.5%
Achieving IGA Score 0 or 1 at Week 16	53.8%	46.2%	57.7%	77.8%

Source: Adapted from Study PSO2001 Report, Figures 8 and 9.

Immunogenicity Results

The incidence of antidrug antibodies (ADA) in Study PSO2001 was low with 3 of 209 (1.4%) subjects in the 50 mg QD group were ADA positive at baseline who were negative thereafter. In

total, 8 out of 209 (3.8%) had one sample positive for ADA of low titer (1:50) in the 50 mg QD group (Table 104). There was no clear association between positive ADA results and dose level or time on treatment. All ADA-positive samples were negative for neutralizing antibodies (NAb).

Table 104. Summary of Treatment-Emergent Antibodies and Neutralizing Antibodies to JNJ-77242113 Status Through Week 16 in Study PSO2001

Immunogenicity Parameters	25 mg QD	50 mg QD	25 mg BID	100 mg QD	100 mg BID	Combined
Analysis set	42	43	41	42	41	209
Subjects positive for antibodies to icotrokinra at baseline [b]	0	3 (7%)	0	0	0	3 (1.4%)
Titer (1:50)	0	3	0	0	0	3
Subjects positive for antibodies to icotrokinra at baseline who were treatment-boosted for antibodies to icotrokinra [c]	0	0	0	0	0	0
Titer	0	0	0	0	0	0
Subjects positive for antibodies to icotrokinra at baseline who were not treatment-boosted for antibodies to icotrokinra [d]	0	3 (7%)	0	0	0	3 (1.4%)
Titer (1:50)	0	3	0	0	0	3
Subjects positive for treatment-emergent antibodies to icotrokinra [e]	1 (2.4%)	1 (2.3%)	0	3 (7.1%)	3 (7.3%)	8 (3.8%)
Titer (1:50)	1	1	0	3	3	8
Peak titer group						
>=50	1	1	0	3	3	8
>50-<100	0	0	0	0	0	0
>=100-<1000	0	0	0	0	0	0
>=1000	0	0	0	0	0	0
Subjects negative for treatment-emergent antibodies to icotrokinra [f]	41 (97.6%)	42 (97.7%)	41 (100%)	39 (92.9%)	38 (92.7%)	201 (96.2%)
Subjects evaluable for neutralizing Antibodies [g]	1 (2.4%)	1 (2.3%)	0	3 (7.1%)	3 (7.3%)	8 (3.8%)
Subjects positive for neutralizing antibodies at baselined [h]	0	0	0	0	0	0
Subjects positive for treatment-emergent neutralizing antibodies [i]	0	0	0	0	0	0

Source: Study PSO2001 Report, Tables 22 and 23.
[a] Includes all icotrokinra treatment columns (25 mg QD, 50 mg QD, 25 mg b.i.d, 100 mg QD, and 100 mg b.i.d).
[b] Subjects positive for antibodies to icotrokinra at baseline, regardless of status after first icotrokinra administration.
[c] Subjects positive for treatment-boosted antibodies to icotrokinra includes subjects who were positive at baseline and whose titers increased 2-fold at any time. Subjects with baseline positive samples without 2-fold increased titer after treatment not considered treatment-boosted.
[d] Includes subjects positive for antibodies to icotrokinra at baseline but whose titers did not increase 2-fold after their first icotrokinra administration, remained the same after treatment or ADA titers were reduced or disappeared after icotrokinra administration.
[e] Subjects positive for treatment-emergent antibodies to icotrokinra includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first icotrokinra administration through Week 16 or Follow-up Week 20 visit. Subjects with baseline positive samples and without 2-fold increased titer after treatment are not considered treatment-boosted.
[f] Excludes subjects who were treatment-emergent positive at any time through Week 16 or Follow-up Week 20 visit.
[g] An evaluable subject is a subject positive for treatment-emergent antibodies to icotrokinra with no detectable interference in the neutralizing antibody assay.
[h] Subjects positive for neutralizing antibodies at baseline regardless of antibodies to icotrokinra status after first icotrokinra administration.
[i] Subjects positive for neutralizing antibodies from treatment-emergent antibodies to icotrokinra positive subjects.

19.4.2.5. Phase 3 Trials

19.4.2.5.1. Trial PSO3001 (ICONIC-LEAD)

This is an ongoing multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the clinical efficacy and safety of icotrokinra in subjects ≥12 years of age with moderate to severe plaque PsO (with or without psoriatic arthritis) defined by a total BSA ≥10%, total PASI ≥12, and total IGA ≥3, who were candidates for phototherapy or systemic treatment. Randomization was separately performed for adult and adolescent subjects. Within the adult group, randomization was further stratified by baseline weight category (≤90 kg, >90 kg) and geographic region. Within the adolescent group, randomization was further stratified by geographic region. A total of 684 participants were randomized; 9.6% (66/684) were ≥12 to <18 years of age. For subjects ≥12 to <18 years of age, body weight must be ≥40 kg at baseline. Icotrokinra was provided as a 200 mg film-coated tablet for oral administration.

Subjects were randomized 2:1 to icotrokinra 200 mg QD or placebo in the following groups (Figure 68):

Adult Subjects

- Icotrokinra 200 mg QD Week 0 to Week 24
- Icotrokinra 200 mg QD Week 24 to Week 52
  - Adult subjects who received icotrokinra for 24 weeks and achieved clinical response (PASI 75 response or IGA 0/1) at Week 24 entered a randomized withdrawal period. Subjects in the randomized withdrawal period were randomized to receive icotrokinra 200 mg QD or transition to placebo from Week 24 to Week 52. Rerandomization was stratified by PASI 90 status and geographic region. Subjects who were rerandomized to placebo at Week 24 were retreated with icotrokinra 200 mg QD upon loss of ≥50% of their Week 24 PASI improvement or at Week 52 if loss of response was not observed. All subjects will be treated with JNJ-77242113 at Week 52.
  - Subjects who were both PASI 75 non-responders and IGA 0 or 1 non-responders at Week 24 continued to receive icotrokinra 200 mg QD through Week 52.
  - Icotrokinra 200 mg QD as an open-label long-term extension period from Week 52 to Week 156.

Placebo to Icotrokinra 200 mg QD

- Week 0 to Week 16: placebo QD
- Week 16 to Week 156: subjects crossed over to icotrokinra 200 mg QD

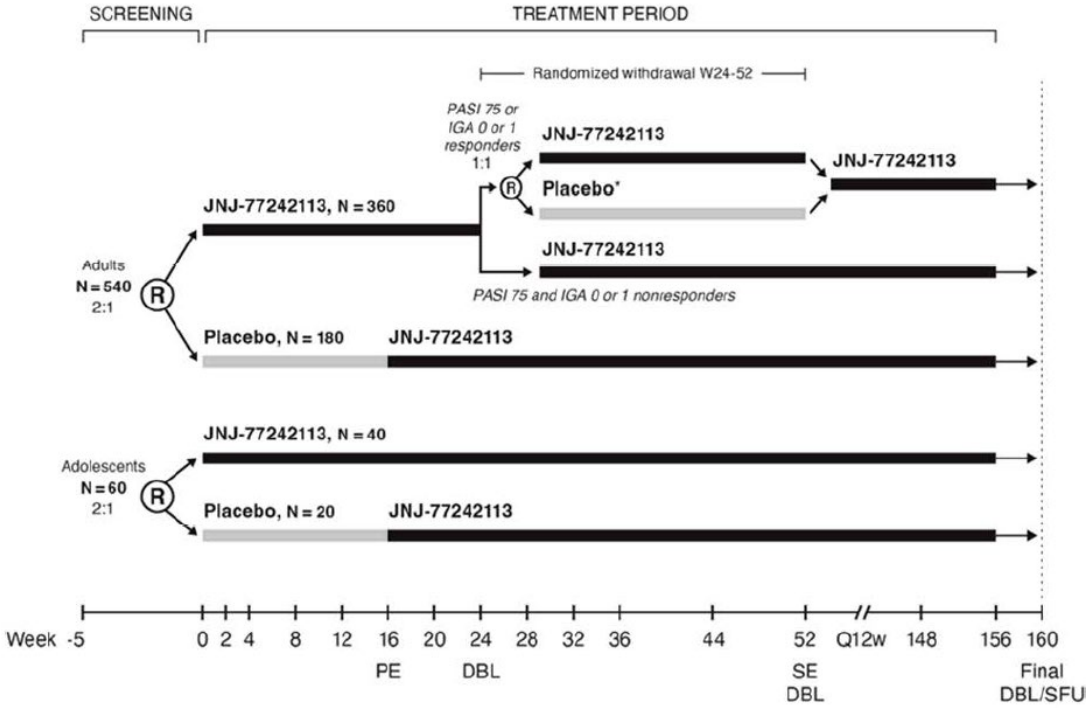
Adolescent Subjects

- Icotrokinra 200 mg QD
  - Week 0 to Week 52 followed by an open-label extension study to Week 156.
  - Adolescents did not participate in re-randomization regardless of their PASI score or IGA score at Week 24.

- Placebo to icotrokinra 200 mg QD
  - Week 0 to Week 16: placebo QD
  - Week 16 to Week 156: All subjects crossed to icotrokinra 200 mg QD through Week 156.

The primary efficacy endpoint was the proportion of subjects achieving IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 PASI 90 at Week 16. The trough plasma concentrations of icotrokinra and antibodies to icotrokinra were measured at Weeks 0, 4, 12, 16, 28, 36, and 52. Peak concentrations of icotrokinra were measured at Weeks 4 and 16. Serum biomarkers were measured at Weeks 0, 4, 16, 24, 28, 36, and 52. Skin biopsy was conducted on Weeks 0, 24, and 52.

Figure 68. Schematic Design of Trial PSO3001



Source: Study PSO3001 Report, Figure 1.
Abbreviations: DBL, database lock; PE, primary endpoint; Q12w, every 12 weeks; R, randomization; SE, secondary endpoint; SFU, safety follow-up visit

Subjects in Study PSO3001 must have discontinued IL-23 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and antitumor necrosis factor α biologic therapy at least 12 weeks or 5 half-lives, whichever is longer, prior to the first administration of icotrokinra. Subjects must have discontinued systemic medications for psoriasis including immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks prior to the first dose icotrokinra and must have discontinued topical therapies at least 2 weeks prior to the first dose of icotrokinra.

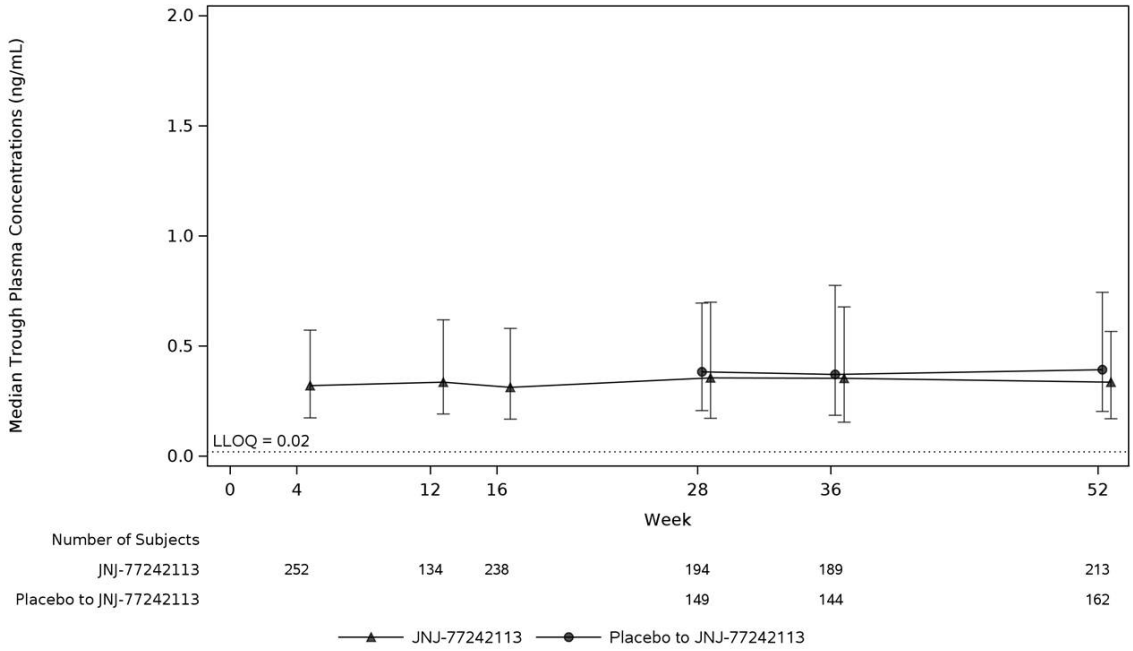
Adult and adolescent subjects administered icotrokinra upon waking with 240 mL water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention). Adolescent subjects who had difficulty swallowing the tablet, the

icotrokinra tablet was suspended in a glass of water and taken within 15 minutes followed by rinsing and swirling the glass with more water and swallow to ensure all the study intervention is taken. The total amount of water to be used for the dispersion of the tablet and rinsing should be at least 240 mL (about 8 oz or 1 cup).

PK and Efficacy Results

The median trough plasma concentrations at Week 16 were 0.3 ng/mL in adult subjects and 0.4 ng/mL in adolescent subjects (Figure 69). At Week 16, icotrokinra 200 mg QD consistently provided high clinical responses (PASI 90, IGA score of 0/1) across all 4 trough plasma concentration quartiles (Table 105). There was an increase in the clinical response from plasma concentration Quartile 1 (<0.2 ng/mL) to Quartile 2 (0.2 to <0.3 ng/mL) followed by a relative plateauing in the clinical response after Quartile 2.

Figure 69. Median (IQR) Trough Plasma Icotrokinra Concentrations Through Week 52 in Study PSO3001



Source: Summary of Clinical Pharmacology, Figure 13.
Abbreviations: JNJ-77242113, icotrokinra; IQR, interquartile range; LLOQ, lower limit of quantification

Table 105. Clinical Response at Week 16 by Trough Plasma Icotrokinra Concentration (ng/mL) Quartiles at Week 16 Among Subjects Randomized to Icotrokinra at Week 0 in Trial PSO3001

	Trough Plasma JNJ-77242113 Concentration Quartiles			
	<0.2 (N=99)[a]	0.2 to <0.3 (N=100)[a]	0.3 to <0.7 (N=100)[a]	≥0.7 (N=100)[a]
IGA				
N	99	100	100	100
IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16	58 (58.6%)	69 (69.0%)	70 (70.0%)	69 (69.0%)
IGA score of 0	30 (30.3%)	32 (32.0%)	35 (35.0%)	38 (38.0%)
PASI				
N	99	100	100	100
≥75% improvement	58 (58.6%)	80 (80.0%)	79 (79.0%)	69 (69.0%)
≥90% improvement	37 (37.4%)	56 (56.0%)	58 (58.0%)	53 (53.0%)
100% improvement	25 (25.3%)	27 (27.0%)	26 (26.0%)	31 (31.0%)

Source: Summary of Clinical Pharmacology, Table 10.
Abbreviations: IGA, Investigator's Global Assessment; N, number of samples; PASI, Psoriasis Area and Severity Index.
[a] All-randomized participants who received at least 1 complete dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
Subjects could have multiple samples collected at the same time window, and N is the number of the samples included in the summary.
The data from a subject who discontinued study intervention were excluded from that point onwards. In addition, the data from a subject who received an incomplete/incorrect or skipped dose based on the dose prior to the PK sample collection was excluded for that visit.

There was a significant clinical response in icotrokinra group compared to placebo in adult and adolescent populations. In adult and adolescent subjects, 295 (64.7%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline compared to placebo 19 (8.3%) with treatment difference of 56.4% (90% confidence interval [CI]: 50.4%, 61.7%) (Table 106). In addition, 226 (49.6%) achieved a PASI 90 response at Week 16 compared to placebo 10 (4.4%) with treatment difference of 45.1% (90% CI: 39.5%, 50.4%). In adolescent subjects only, 37 (84.1%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline compared to placebo 6 (27.3%) with treatment difference of 56.2% (90% CI: 33.2%, 74.1%). In addition, 31 (70.5%) of adolescent subjects achieved a PASI 90 response at Week 16 compared to placebo 3 (13.6%) with treatment difference of 45.1% (90% CI: 32.5%, 73%) (see Table 6 in the CSR for Study PSO3001), suggesting comparable efficacy between adult and adolescent subjects.

Table 106. Proportion of Adult and Adolescent Subjects Combined Achieving an IGA Score of Cleared (0) or Minimal (1) and a ≥2-Grade Improvement From Baseline and Proportion of Subjects Achieving a PASI 90 Response at Week 16 in Trial PSO3001

	Placebo	JNJ-77242113
Analysis set: Full analysis set	228	456
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	19 (8.3%)	295 (64.7%)
Treatment difference (95% CI)[b]		56.4% (50.4%, 61.7%)
p-value[c]		< 0.001
Subjects achieving a PASI 90 response at Week 16[a]	10 (4.4%)	226 (49.6%)
Treatment difference (95% CI)[b]		45.1% (39.5%, 50.4%)
p-value[c]		< 0.001

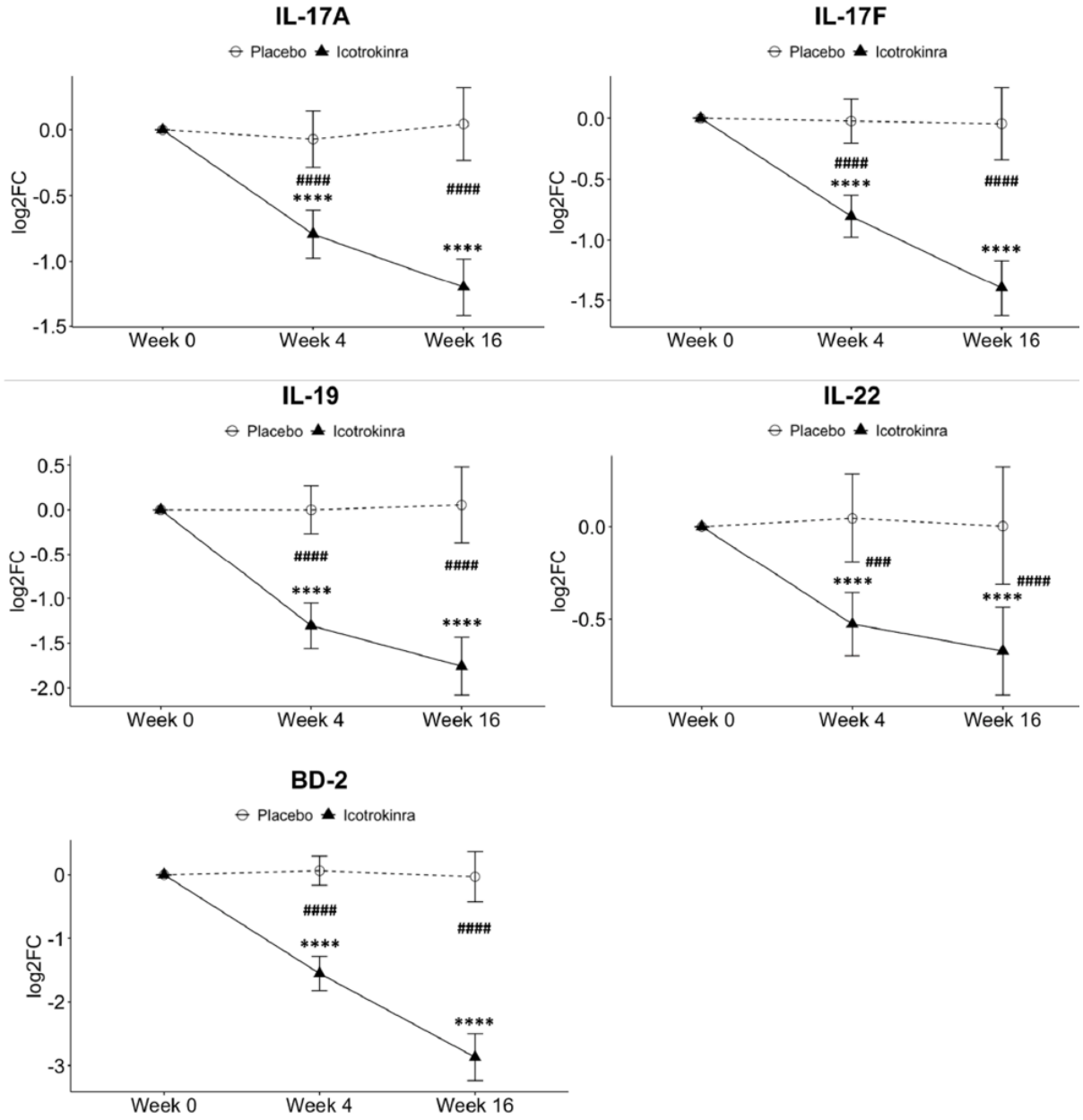
Source: Study PSO3001 Report, Table 4.
[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as nonresponders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for age group, baseline weight category for adult, and geographic region using Mantel-Haenszel weights.
[c] Based on the Cochran-Mantel-Haenszel chi-square test stratified by age group, baseline weight category for adults, and geographic region.

Pharmacodynamic Results

Serum Protein Biomarkers

The exploratory PD effects of icotrokinra on serum IL-17A, IL-17F, IL-22, IL-19, and BD-2 were evaluated in a subset of subjects using Week 0, Week 4, and Week 16 samples from up to 167 subjects in Study PSO3001. An independently procured serum from 30 healthy subjects (BioIVT, Hicksville, NY, USA) were also included as controls in the analysis. Compared to placebo, icotrokinra significantly decreased serum IL-17A, IL-17F, IL-22, IL-19, and BD-2 levels at Week 4 and Week 16 compared with baseline (Figure 70). Week 16 serum IL-17A, IL-17F, IL-22 and IL-19 levels were reduced to levels comparable to healthy control ($p \geq 0.05$). However, Week 16 serum BD-2 levels were still significantly elevated in psoriasis samples compared to healthy controls ($p < 0.0001$) (Source: Module 5.3.4.2, Translational Immunology Biomarker Exploratory Report (TIBER): Serum W0 and W16 Analysis for Study PSO3001, Table 10).

Figure 70. Reduction of IL-17A, IL-17F, IL-19, IL-22 and BD-2 In Response to Icotrokinra and Placebo Treatment at Week 4 and Week 16 in Trial PSO3001

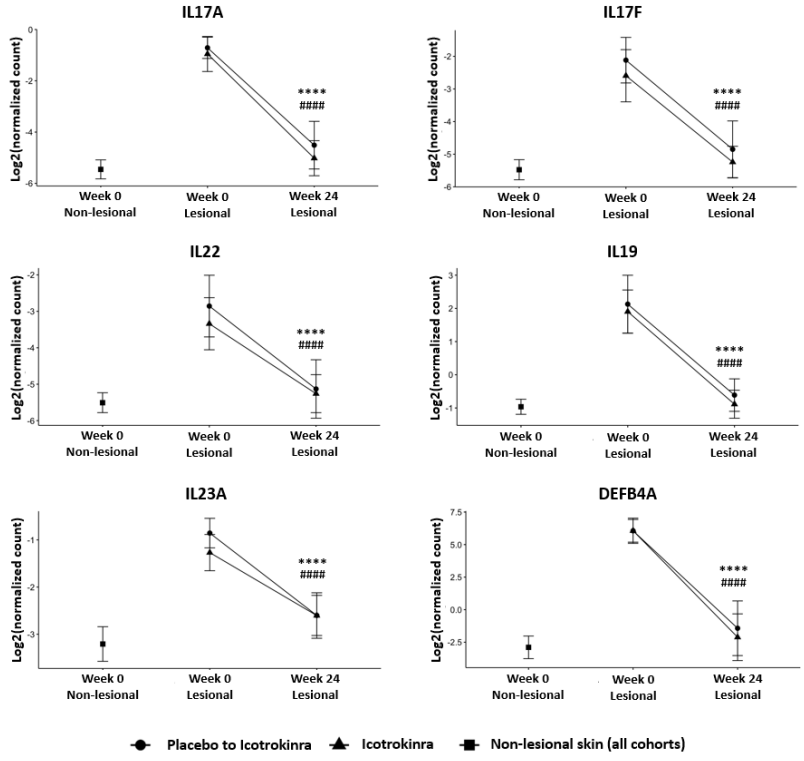


Source: Summary of Clinical Pharmacology, Figure 14.
Abbreviations: FC, fold change (post-treatment concentration divided by baseline concentration); IL, interleukin; BD-2, beta-defensin 2.
Points show mean value, whiskers show 95% confidence intervals. p-values from lmer model with interaction term shown for arm comparisons (#, Placebo vs. Icotrokinra) and pairwise estimation for within arm time effect (*, vs. W0). */# p<0.05, **/## p <0.01, ***/### p<0.001, ****/#### p<0.0001. n=115 (IL-22), 116 (IL-17A, IL-17F, IL-19 and BD-2) for ICO; n=54 (IL-22), n=53 (IL-17A, IL-17F, IL-19 and BD-2) for placebo.
Linear Model: log2FC ~WEEK*TREATMENT + log2(Baseline Value) + (1 | Subjects). This model framework assumes an approximately normal distribution of residuals can be achieved with log2 data transformations. P-value adjustment using "sidak" method.
No covariates were used in the model for IL-17A, IL-17F, and IL-22. SEX was added as a covariate in the model for IL-19 log2FC ~WEEK*TREATMENT + Sex + log2(Baseline Value) + (1 | Subjects). Sex and Ethnicity were added as covariates in the model for BD-2: log2FC ~WEEK*TREATMENT + Sex + Ethnicity+ log2(Baseline Value) + (1 | Subjects).
A post-hoc procedure was used to calculate the marginal mean estimates of change from baseline and the 95% confidence intervals and p-values in comparison to a mu of zero. One-sample t-tests were performed for each log2-transformed measurement comparing baseline and measurement at Week 4 and Week 16 for both treatment groups. Additionally, independent two-sample t-tests were performed on the same log2(fold change) to test differences between treatment groups at baseline.
n=113-114 for icotrokinra; n=52-53 for placebo.

Skin Transcriptomic Biomarkers

Exploratory skin biopsies (N=28 [icotrokinra cohort] and N=18 [placebo crossover to icotrokinra cohort]) were analyzed by bulk RNA-sequencing to assess the PD effects of icotrokinra on skin genes and pathways relevant to PsO and IL-23/Th17 pathway. Baseline nonlesional, baseline lesional, and Week 24 lesional (collected from the same lesional area as baseline) skin biopsies from 46 participants were used for paired analysis. Analysis of subjects on icotrokinra treatment and subjects on placebo crossed over to icotrokinra showed a significant reduction in the expression levels of DEFB4A, IL-17A, IL-17F, IL-19, IL-22, and IL-23A genes in lesional skin at Week 24 compared with those at Week 0 to a level similar to nonlesional (Figure 71).

Figure 71. Reduction of Psoriasis and IL-23/Th17 Pathway-Related Genes at Week 24 in Icotrokinra and Placebo Crossover to Icotrokinra Cohorts in Trial PSO3001

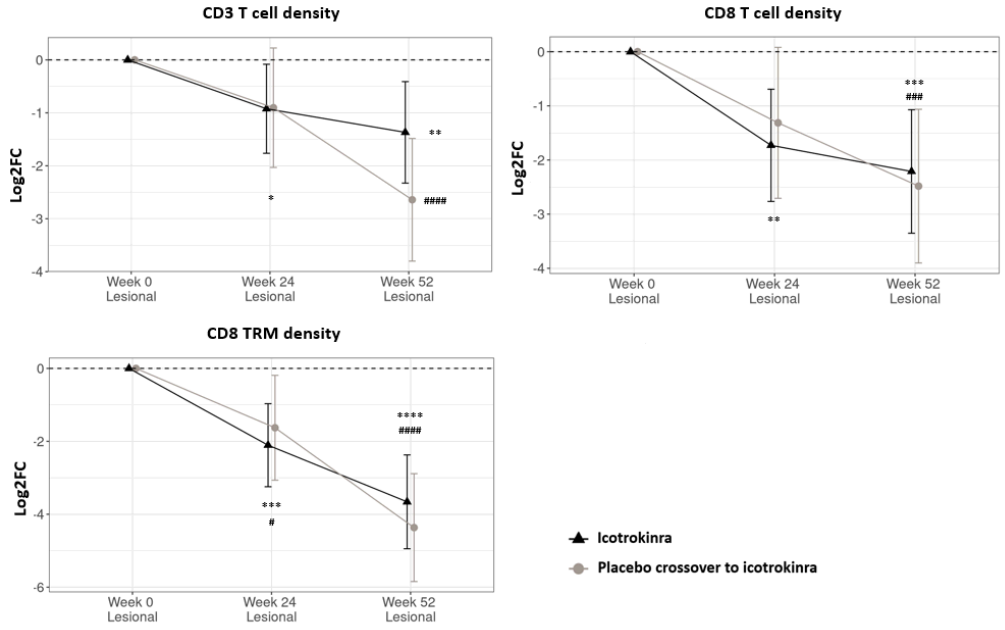


Source: Summary of Clinical Pharmacology, Figure 15.
Abbreviations: IL, interleukin; DEFB4A, human beta-defensin 2.
Points show mean values, whiskers show 95% CIs. p-values from linear mixed model with interaction term shown for pairwise estimation for within arm time effect (*, versus Week 0 lesional, icotrokinra cohort; #, versus Week 0 lesional, placebo crossover to icotrokinra cohort).
****/#### p<0.0001
Linear Model: Counts ~ Week + Baseline value + (1 | Subjects) with p-value adjustment using "sidak" method.
Age was added as a covariate in the model for DEFB4A when compared lesional skin at Week 0 vs. lesional skin Week 24 and lesional skin at Week 24 and non-lesional skin at Week 0 in the icotrokinra treatment group but not in the placebo to icotrokinra group. In addition, Age was used as covariate in the model that compares icotrokinra group vs. placebo to icotrokinra group at Week 0 and Week 24 with lesional skin. Ethnicity and Age was added as a covariate in the model for IL-17A and IL-19, respectively, when compared lesional skin at Week 24 and non-lesional skin at Week 0 in the icotrokinra treatment group but not in the placebo to icotrokinra group.
A post-hoc procedure was used to calculate the marginal mean estimates of change from baseline and the 95% confidence intervals and p-values in comparison to a mu of zero. One-sample t-tests were performed for paired analysis. Additionally, independent two-sample t-tests were performed to test differences between treatment groups at baseline.

Skin Histology Biomarker

PD effects of icotrokinra on skin epidermal thickness and skin T cell densities were assessed using Week 0, Week 24 and Week 52 skin biopsy samples. Exploratory analysis showed that baseline CD3 T cell, CD8 T cell and CD8 tissue resident memory T cell (TRM) densities were significantly greater in lesional skin compared to non-lesional skin (See Module 5.3.5.2., Skin Histology and Immunofluorescence Analysis for Study PSO3001, Figure 3). In addition, subjects received icotrokinra treatment and subjects on placebo crossover to icotrokinra cohort at Week 16 showed significant reduction in CD3 T cell, CD8 T cell and CD8 TRM densities at Week 24 and Week 52 lesional skin compared to Week 0 lesional skin (Figure 72). This is an exploratory analysis with limited number of subjects; therefore, the results from this skin transcriptomic biomarkers analysis will not be discussed further and it should be interpreted with caution.

Figure 72. Reduction of Skin Epidermal T-Cell Densities in Icotrokinra and Placebo Crossover to Icotrokinra Cohort in Trial PSO3001



Source: Applicant's response to information request (SDN 0009, dated 10/7/2025), Erratum 1 to Biomarker Skin Histology and Immunofluorescence Analysis Exploratory Report dated 17 June 2025, Figure 7.
Abbreviations: FC, fold change; CD, cluster of differentiation; TRM, tissue-resident memory T cells.
Points show mean, whiskers show 95% confidence intervals. * vs. Week 0 lesional (icotrokinra), # vs. Week 0 lesional (placebo crossover to icotrokinra cohort), */# p<0.05, **/## p<0.01, ***/### p<0.001, ****/#### p<0.0001. Icotrokinra cohort: n=32 (Week 0 non-lesional, Week 0 lesional and Week 24 lesional), n=18 (Week 52 lesional). Placebo crossover to icotrokinra cohort: n=18 (Week 0 non-lesional, Week 0 lesional and Week 24 lesional), n=15 (Week 52 lesional).

Immunogenicity Results

Incidence of ADA/NAb and Impact on Icotrokinra Trough Concentrations

The incidence of antibodies to icotrokinra through Week 52 was 80 (12%) in adults and 20 (30.8%) in adolescents (Table 107). Among subjects who were positive for antibodies to icotrokinra, 51 (63.8%) of the adult and 11 (55%) of adolescent subjects had the lowest

measurable titer (1:50). The highest measured titer was 1:6,400 in 1 adult subject and 1:400 in 3 (15%) adolescent subjects. All subjects with positive antibodies to icotrokinra through Week 52 were negative for NAb.

The median time to onset of ADA was 16.1 weeks (range, 4 to 52 weeks) of icotrokinra exposure for subjects in the icotrokinra group and 20.1 weeks (range, 11 to 36 weeks) of icotrokinra exposure for subjects in the placebo group who crossed over to icotrokinra at Week 16. There was no increased incidence of ADA in subjects retreated with icotrokinra after randomized withdrawal to placebo.

Table 107. Summary of Treatment-Emergent Antibodies to Icotrokinra Status Through Week 52 by Treatment Group and Population in Trial PSO3001

	Adults + Adolescent			Adolescents		
Parameter	**Placebo to Icotrokinra**	**Icotrokinra**	**Combined**	**Placebo to Icotrokinra**	**Icotrokinra**	**Combined**
Analysis set: Immunogenicity analysis set[a]	212	452	664	21	44	65
Subjects positive for antibodies to icotrokinra at baseline[b]	1 (0.5%)	2 (0.5%)	3 (0.5%)	0	0	0
Baseline titers 1:50	1	2	3			
Subjects positive for antibodies to icotrokinra at baseline who were treatment-boosted for antibodies to icotrokinra [c]	0	0	0	0	0	0
Subjects positive for antibodies to icotrokinra at baseline who were not treatment-boosted for antibodies to icotrokinra [d]	1 (0.5%)	2 (0.5%)	3 (0.5%)	0	0	0
Baseline titers 1:50	1	2	3			
Subjects positive for treatment-emergent antibodies to icotrokinra [e]	25 (11.8%)	55 (12.2%)	80 (12.0%)	3 (14.3%)	17 (38.6%)	20 (30.8%)
Peak titers[f]						
1:50	52.0% (13/25)	69.1% (38/55)	63.8% (51/80)	(0/3)	64.7% (11/17)	55.0% (11/20)
1:100	20.0% (5/25)	7.3% (4/55)	11.3% (9/80)	33.3% (1/3)	5.9% (1/17)	10.0% (2/20)
1:200	16.0% (4/25)	12.7% (7/55)	13.8% (11/80)	33.3% (1/3)	17.6% (3/17)	20.0% (4/20)
1:400	8.0% (2/25)	9.1% (5/55)	8.8% (7/80)	33.3% (1/3)	11.8% (2/17)	15.0% (3/20)
1:800	(0/25)	1.8% (1/55)	1.3% (1/80)			
1:6400	4.0% (1/25)	(0/55)	1.3% (1/80)			
Peak titer group						
50-<100	52.0% (13/25)	69.1% (38/55)	63.8% (51/80)	(0/3)	64.7% (11/17)	55.0% (11/20)
100-<1000	44.0% (11/25)	30.9% (17/55)	35.0% (28/80)	100.0% (3/3)	35.3% (6/17)	45.0% (9/20)
≥1000	4.0% (1/25)	(0/55)	1.3% (1/80)	(0/3)	(0/17)	(0/20)

	Adults + Adolescent			Adolescents		
Parameter	**Placebo to Icotrokinra**	**Icotrokinra**	**Combined**	**Placebo to Icotrokinra**	**Icotrokinra**	**Combined**
Subjects negative for treatment-emergent antibodies to icotrokinra [g]	187 (88.2%)	397 (87.8%)	584 (88.0%)	18 (85.7%)	27 (61.4%)	45 (69.2%)

Source: Study PSO3001 Report, Tables 43 and 44.

[a] All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.

[b] Subjects positive for antibodies to icotrokinra at baseline, regardless of status after first icotrokinra administration.

[c] Subjects positive for treatment-boosted antibodies to icotrokinra includes subjects who were positive at baseline and whose titers increased 4-fold at any time. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.

[d] Includes subjects positive for antibodies to icotrokinra at baseline but whose titers did not increase 4-fold after their first icotrokinra administration, remained the same after treatment or ADA titers were reduced or disappeared after icotrokinra administration.

[e] Subjects positive for treatment-emergent antibodies to icotrokinra includes all subjects who were positive (treatment- boosted or treatment-induced) at any time after their first icotrokinra administration. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.

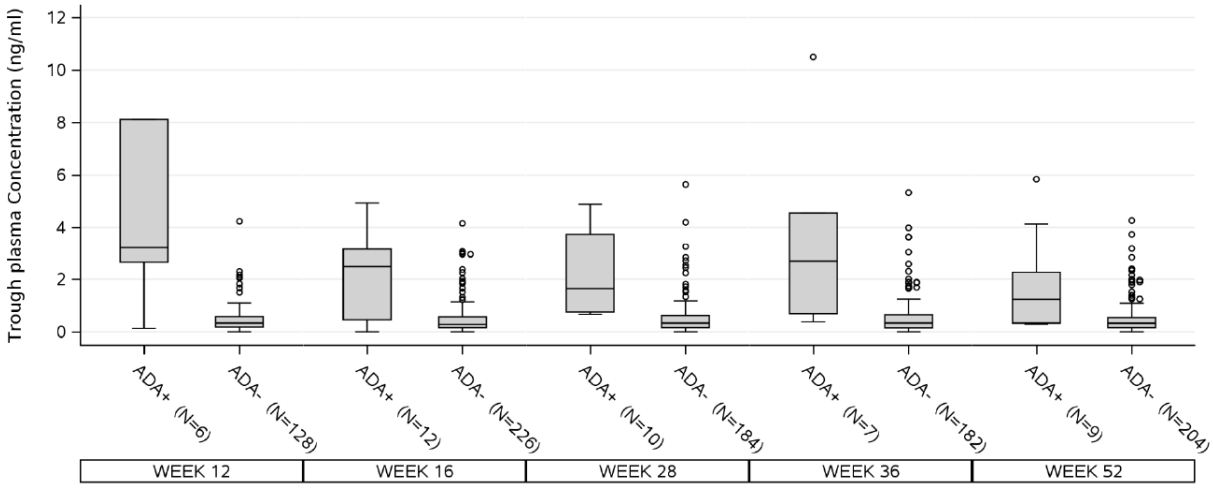
[f] Denominator is the number of subjects positive for treatment-emergent antibodies.

[g] Includes all subjects whose sample was negative and excludes subjects who were positive for antibodies to icotrokinra through Week 52. In addition, one subjects who were ADA positive at week 16 on placebo treatment were considered negative for treatment-emergent antibodies to icotrokinra

Source: Study PSO3001 Report, Tables 43 and 44.

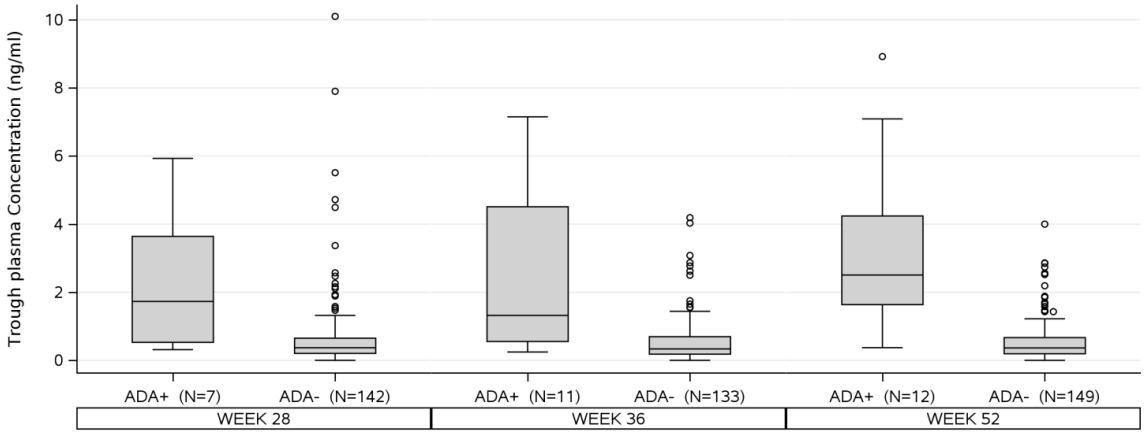
The median trough plasma concentrations over 52 weeks were generally higher in subjects who were ADA positive compared to subjects who were ADA negative with patrial overlapping in subjects who continued treatment with icotrokinra at Week 24 and developed antibodies to icotrokinra through Week 52 (Figure 73). The higher media trough concentrations of icotrokinra in subjects with positive ADA was observed from Week 28 through Week 52 among subjects who were randomized to placebo at Week 0 and crossed over to receive icotrokinra (Figure 73).

Figure 73. Boxplot of Median Trough Plasma Icotrokinra Concentrations (ng/mL) From Week 12 Through Week 52 and Antibody Status Among Icotrokinra Subjects Who Continued Treatment With Icotrokinra at Week 24 and Developed Antibodies to Icotrokinra Through Week 52 in Trial PSO3001



Source: Study PSO3001 Report, Figure GPKCONC22a
Abbreviations: ADA, antidrug antibody(ies); N, number of participants; PK, pharmacokinetic(s).
Note: All randomized subjects who received at least 1 complete dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra, excluding subjects who withdrew from treatment at Week 24.
Source: Study PSO3001 Report, Figure GPKCONC22a

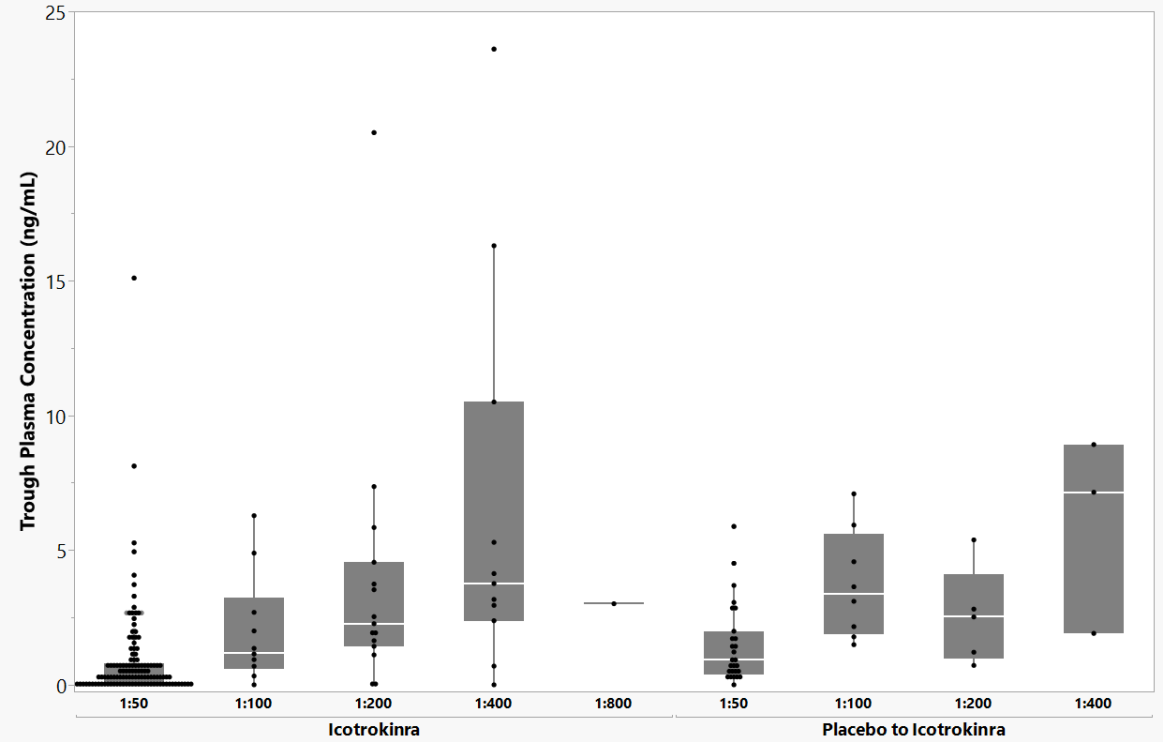
Figure 74. Boxplot of Trough Plasma Icotrokinra Concentrations (ng/mL) From Week 28 Through Week 52 by Visit and Antibody Status Among Subjects Who Were Randomized to Placebo at Week 0 and Crossed Over to Receive Icotrokinra in Trial PSO3001



Source: Study PSO3001 Report, Figure GPKCONC22a.
Abbreviations: ADA, antidrug antibody(ies); N, number of participants; PK, pharmacokinetic(s)
Source: Study PSO3001 Report, Figure GPKCONC22a.

The trough plasma concentrations of icotrokinra increased when the titer increases in subjects initially randomized to icotrokinra and continued treatment with icotrokinra for 52 weeks and subjects who were randomized to placebo at week 0 and crossed over to receive icotrokinra at Week 16 (Figure 75).

Figure 75. Boxplot of Median Trough Plasma Icotrokinra Concentrations and Titer Among Icotrokinra Subjects Who Continued Treatment With Icotrokinra at Week 24 and up to Week 52 and Subjects Who Were Randomized to Placebo at Week 0 and Crossed Over to Receive Icotrokinra in Trial PSO3001



Source: Reviewer's analysis using ADPC, ADIS, and ADSL data from Study PSO3001.

Impact of Developing ADA on Safety and Efficacy

The development of antibodies to icotrokinra did not have a clinically relevant impact on the efficacy of icotrokinra (Table 108). In adult and adolescent subjects who were randomized to icotrokinra at Week 0 and were ADA positive, 26 (70.3%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 52 compared 159 (65.4%) subjects who were ADA negative. Similarly, 28 (75.7%) subjects who were ADA positive achieved a PASI 90 response at Week 52 compared to 147 (60.5%) subjects who were ADA negative. Similar trend was also observed in subjects who were randomized to placebo at Week 0 and crossed over to icotrokinra at Week 16.

There was no difference in efficacy between subjects with low and high titer in the two treatment groups (Table 108). For example, in adult and adolescent subjects who were randomized to icotrokinra at Week 0 and had low titer (≥50 to <100), 17 (70.8%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 52 compared 9 (69.2%) subjects who had high titer (≥100 to <100). Similarly, 17 (70.8%) subjects who had low titer achieved a PASI 90 response at Week 52 compared to 11 (84.6%) subjects who had high titer. Similar trend was also observed in subjects who were randomized to placebo at Week 0 and crossed over to icotrokinra at Week 16.

Table 108. Clinical Responses at Week 52 by Treatment-Emergent Antibodies to Icotrokinra Status Through Week 52 Among Participants Who Continued Treatment With Icotrokinra at Week 24 in Trial PSO3001

	Antibodies to JNJ-77242113				
			Peak Titers for Antibody Positive Subjects		
	Negative[b]	Positive[c]	≥50 to <100	≥100 to <1000	≥1000
Analysis set: Immunogenicity analysis set[a]	430	62	37	24	1
Placebo to JNJ-77242113					
IGA					
N	187	25	13	11	1
IGA Score of 0 or 1 and a ≥2-grade improvement from baseline	143 (76.5%)	19 (76.0%)	10 (76.9%)	9 (81.8%)	0
IGA Score of 0	100 (53.5%)	13 (52.0%)	6 (46.2%)	7 (63.6%)	0
PASI					
N	187	25	13	11	1
≥75% Improvement	161 (86.1%)	23 (92.0%)	12 (92.3%)	10 (90.9%)	1 (100.0%)
≥90% Improvement	142 (75.9%)	20 (80.0%)	11 (84.6%)	9 (81.8%)	0
100% Improvement	89 (47.6%)	11 (44.0%)	5 (38.5%)	6 (54.5%)	0
JNJ-77242113					
IGA					
N	243	37	24	13	0
IGA Score of 0 or 1 and a ≥2-grade improvement from baseline	159 (65.4%)	26 (70.3%)	17 (70.8%)	9 (69.2%)	-
IGA Score of 0	97 (39.9%)	15 (40.5%)	11 (45.8%)	4 (30.8%)	-
PASI					
N	243	37	24	13	0
≥75% Improvement	187 (77.0%)	30 (81.1%)	19 (79.2%)	11 (84.6%)	-
≥90% Improvement	147 (60.5%)	28 (75.7%)	17 (70.8%)	11 (84.6%)	-
100% Improvement	90 (37.0%)	14 (37.8%)	10 (41.7%)	4 (30.8%)	-

Source: Study PSO3001 Report, Table 45.
Abbreviations: ADA, antidrug antibody(ies); IGA, Investigator's Global Assessment; JNJ-7242113, icotrokinra; N, number of participants; PASI, Psoriasis Area and Severity Index.
[a] All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113, excluding subjects who withdrew from treatment at Week 24.
[b] Includes all subjects whose last sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 through Week 52. In addition, 7 subjects who were ADA positive at Week 16 on placebo treatment were considered negative for treatment-emergent antibodies to JNJ-77242113.
[c] Includes all subjects who had at least 1 positive sample (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration through Week 52. In the instance that a subject had a positive sample at the reference baseline visit, the subject was considered positive only if the peak titer of the post-JNJ-77242113 treatment samples was at least a 4-fold higher (i.e., ≥4-fold) than the titer of the reference baseline sample.
Source: Study PSO3001 Report, Table 45.

There was no apparent relationship between the incidence of antibodies to icotrokinra and the occurrence of hypersensitivity reactions. The numbers of subjects with 1 or more hypersensitivity reactions were 3 (8.1%) in subjects with positive ADA and 8 (3.3%) in subjects with negative ADA. The number of subjects with skin and subcutaneous tissue disorders was 2 (5.4%) in subjects with positive ADA and 6 (2.5%) in subjects with negative ADA (Source: Integrated Summary of Immunogenicity, Table 16).

19.4.2.5.2. Trial PSO3002 (ICONIC-ADVANCE 1)

This is an ongoing multicenter, randomized, double-blind, parallel-group, placebo-controlled, and deucravacitinib active comparator-controlled study to evaluate the clinical efficacy and safety of icotrokinra in adults with moderate to severe plaque PsO (with or without psoriatic arthritis) defined by a total BSA ≥10%, total PASI ≥12, and total IGA ≥3, who were candidates for phototherapy or systemic treatment. Subjects were randomized 2:1:2 to icotrokinra, placebo, or deucravacitinib (Figure 76). The randomized subjects were further stratified by baseline weight category (≤90 kg, >90 kg) and geographic region. Icotrokinra was provided as a 200 mg film-coated tablet for oral administration. This study included the following treatment groups:

Icotrokinra

- Week 0 to Week 24: icotrokinra 200 mg QD and matching placebo for deucravacitinib once daily.
- Week 24 to Week 156: icotrokinra 200 mg QD.

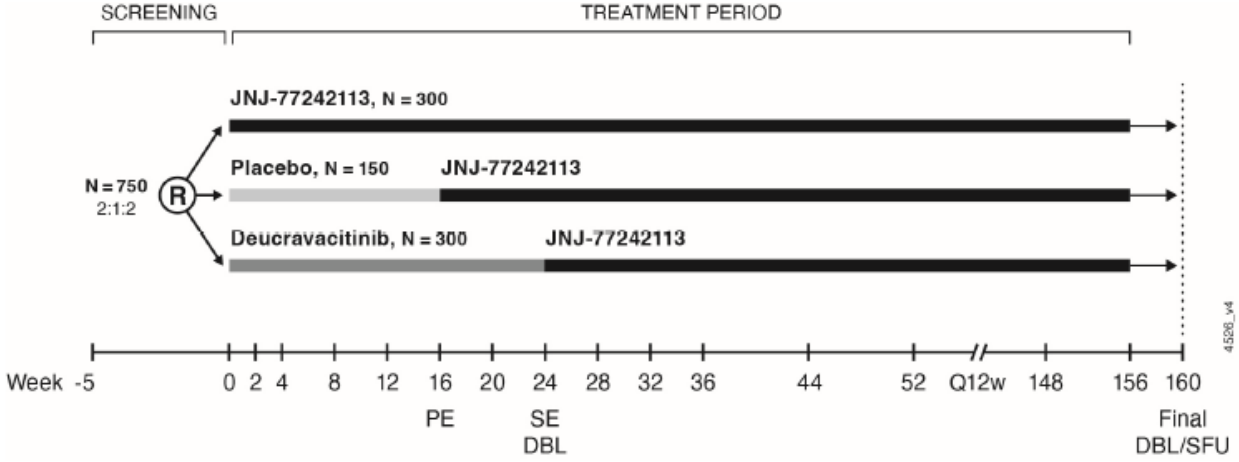
Placebo to Icotrokinra 200 mg QD

- Week 0 to Week 16: matching placebo for icotrokinra once daily and matching placebo for deucravacitinib once daily.
- Week 16 to Week 24: icotrokinra 200 mg QD and matching placebo for deucravacitinib once daily.
- Week 24 to 156: icotrokinra 200 mg QD.

Deucravacitinib

- Week 0 to Week 24: deucravacitinib 6 mg QD and matching placebo for icotrokinra once daily.
- Week 24 to Week 156: icotrokinra 200 mg QD.

Figure 76. Schematic Overview of Trial PSO3002



Source: Study PSO3002 Report, Figure 1.
Abbreviations: DBL, database lock; PE, primary endpoint; Q12w, every 12 weeks; R, randomization; SE, secondary endpoint; SFU, safety follow-up visit

The primary efficacy endpoint is the proportion of subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 and PASI 90 at Week 16.

Subjects must have discontinued IL-23 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and antitumor necrosis factor α biologic therapy at least 12 weeks or 5 half-lives, whichever is longer, prior to the first administration of study intervention. Participants must have discontinued systemic medications for psoriasis including immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks prior to the first dose of study intervention and must have discontinued topical therapies at least 2 weeks prior to the first dose of study intervention.

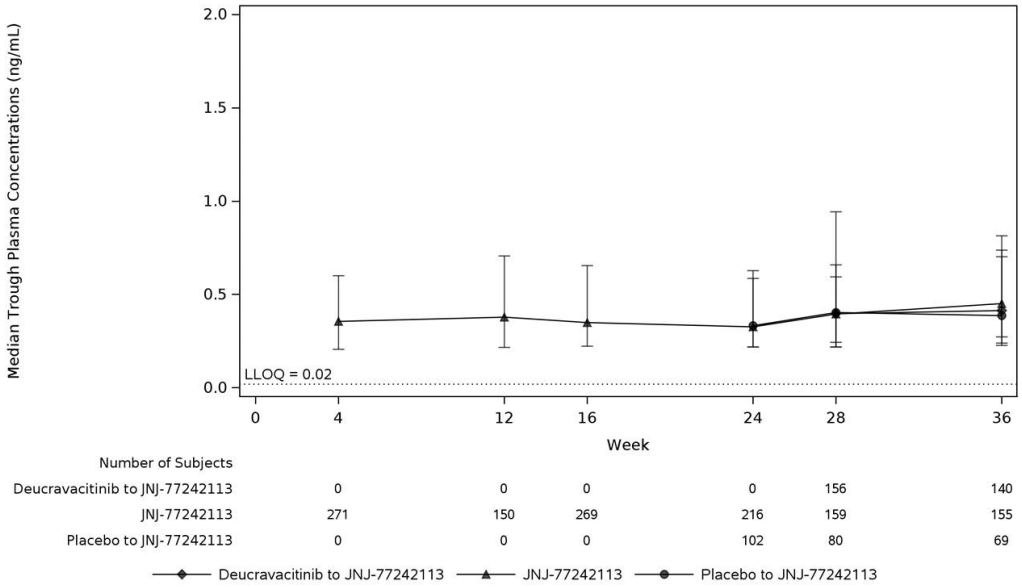
The trough plasma concentrations of icotrokinra and antibodies to icotrokinra were measured at Weeks 0, 4, 12, 16, 28, 36, and 52. Trough and peak concentrations of icotrokinra were measured at Weeks 4 and 16. Serum biomarkers were measured at Weeks 0, 4, 16, 24, 36, and 52. Skin biopsy was conducted on Weeks 0, 16, and 52. The available PK and immunogenicity results are through Week 36 and efficacy results are through Week 44. Safety data are summarized through Week 44.

Subjects administered icotrokinra upon waking with 240 mL water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention).

PK and Efficacy Results

The median trough plasma concentrations of icotrokinra over time through Week 36 remained stable without apparent drug accumulation in subjects who received icotrokinra 200 mg QD from Week 0 and subjects who received placebo or deucravacitinib at Week 0 then crossed over to icotrokinra 200 mg QD at Week 16 or 24, respectively (Figure 77).

Figure 77. Median (IQR) Trough Plasma Icotrokinra Concentrations Through Week 36 in Trial PSO3002



Source: Study PSO3002 Report, Figure 11.
Abbreviations: JNJ-77242113, icotrokinra; IQR, interquartile range; LLOQ, lower limit of quantification.

At Week 16, icotrokinra 200 mg QD consistently provided high clinical responses (PASI 90, IGA score of 0/1) across all 4 trough plasma concentration quartiles (Table 109). There was an increase in the clinical response from plasma concentration Quartile 1 (<0.2 ng/mL) to Quartile 2 (0.2 to <0.4 ng/mL) followed by a relative plateauing in the clinical response after Quartile 2.

Table 109. Clinical Response at Week 16 by Trough Plasma Icotrokinra Concentration Quartiles at Week 16 Among Subjects Randomized to Icotrokinra at Week 0 in Trial PSO3002

	Trough Plasma JNJ-77242113 Concentration Quartiles			
	<0.2 (N=67)[a]	0.2 to <0.4 (N=67)[a]	0.4 to <0.7 (N=67)[a]	≥0.7 (N=68)[a]
IGA				
N	67	67	67	68
IGA score=0 or 1 and a ≥2-grade improvement from baseline at Week 16	42 (62.7%)	52 (77.6%)	46 (68.7%)	50 (73.5%)
IGA score=0	18 (26.9%)	24 (35.8%)	29 (43.3%)	30 (44.1%)
PASI				
N	67	67	67	68
≥75% improvement	44 (65.7%)	55 (82.1%)	52 (77.6%)	55 (80.9%)
≥90% improvement	32 (47.8%)	44 (65.7%)	37 (55.2%)	40 (58.8%)
100% improvement	16 (23.9%)	21 (31.3%)	23 (34.3%)	23 (33.8%)

Source: Summary of Clinical Pharmacology, Table 13.
Abbreviations: IGA, Investigator's Global Assessment; N, number of samples; PASI, Psoriasis Area and Severity Index.
[a] All randomized subjects who received at least 1 complete dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
Subjects could have multiple samples collected at the same time window, and N is the number of the samples included in the summary.
The data from a subject who discontinued study intervention were excluded from that point onwards. In addition, the data from a subject who received an incomplete/incorrect or skipped dose(s) based on 2 previous doses prior to the PK sample collection or data from a subject who skipped dose prior to PK sample collection was excluded for that visit.
Source: Summary of Clinical Pharmacology, Table 13.

There was a significant clinical response in icotrokinra group compared to placebo. Following the administration of icotrokinra 200 mg QD, 231 (68.5%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline compared to placebo 17 (10.9%) with treatment difference of 57.6% (90% CI: 49.9%, 64.2%) (Table 110). In addition, 171 (55%) subjects in icotrokinra treatment arm achieved a PASI 90 response at Week 16 compared to placebo 6 (3.8%) with treatment difference of 51.2% (90% CI: 44.5%, 57.3%).

Table 110. Proportion of Subjects Achieving an IGA Score of Cleared (0) or Minimal (1) and a ≥2-Grade Improvement From Baseline and Proportion of Subjects Achieving a PASI 90 Response at Week 16 in Trial PSO3002

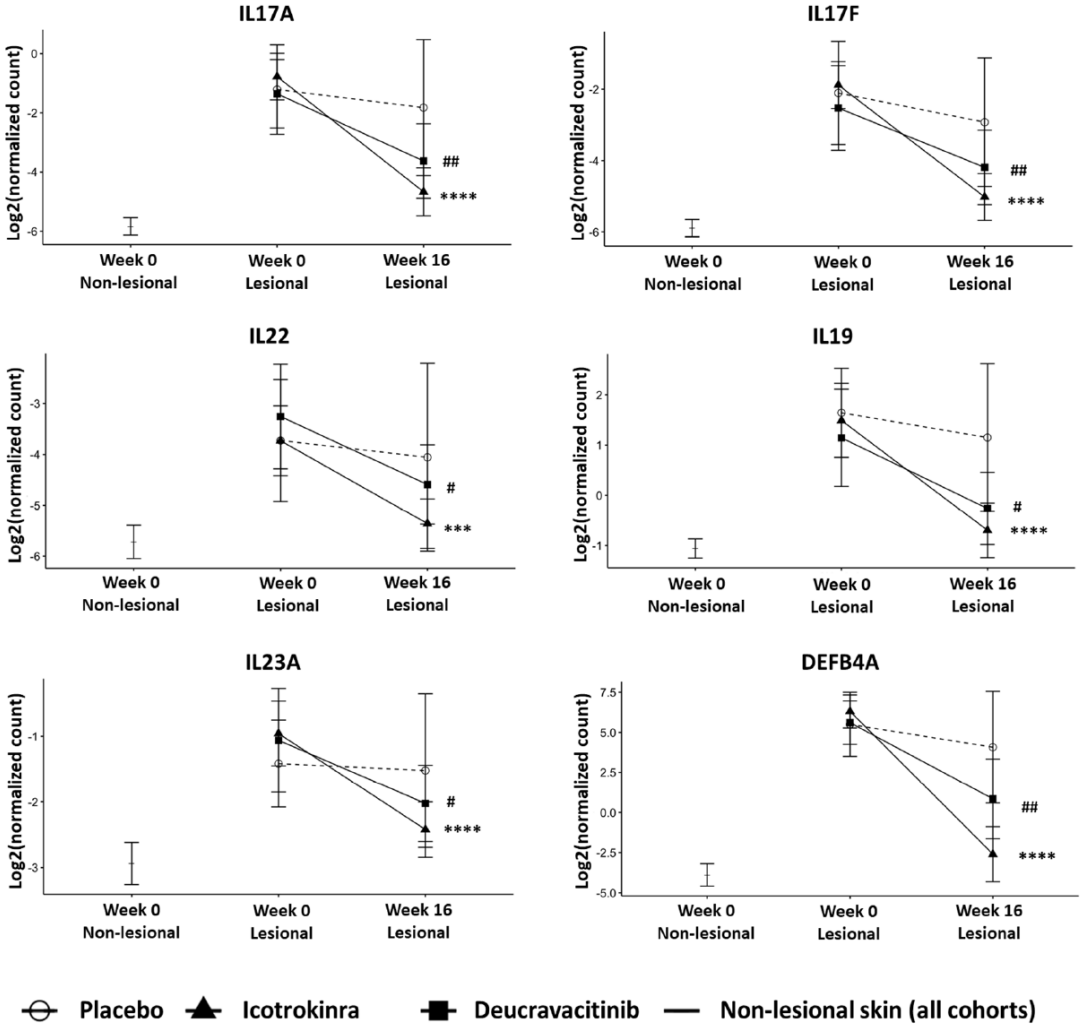
	Placebo	JNJ-77242113
Analysis set: Full analysis set	156	311
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	17 (10.9%)	213 (68.5%)
Treatment difference (95% CI)[b]		57.6% (49.9%, 64.2%)
p-value[c]		< 0.001
Subjects achieving a PASI 90 response at Week 16[a]	6 (3.8%)	171 (55.0%)
Treatment difference (95% CI)[b]		51.2% (44.5%, 57.3%)
p-value[c]		< 0.001

Source: Study PSO3002 Report, Table 3
[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights.
[c] Based on the Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.
Abbreviations: IGA, Investigator's Global Assessment; CI, confidence interval; PASI, Psoriasis Area and Severity Index

Pharmacodynamic Results

In an exploratory analysis, icotrokinra treatment significantly reduced the expression levels of PsO-related IL17A, IL17F, IL22, IL19, IL23A, and DEFB4A genes in lesional skin at Week 16 compared with Week 0 (Figure 78). Deucravacitinib treatment also significantly reduced expression of these genes to a lesser extent than icotrokinra at Week 16. In contrast, no significant reduction was observed in the placebo group. This is an exploratory analysis with limited number of subjects; therefore, these PD results should be interpreted with caution.

Figure 78. Reduction of PsO and IL-23/Th17 Pathway-Related Genes in Icotrokinra, Placebo, and Deucravacitinib Cohorts in Study PSO3002



Source: Summary of Clinical Pharmacology, Figure 20
Abbreviations: CI, confidence intervals; DEFB4A, gene that encodes beta-defensin 2; L, interleukin; PsO, psoriasis; TH17=T helper 17 cell.
Baseline non-lesional, baseline lesional, and Week 16 lesional (collected from the same lesional area as baseline) skin biopsies from 58 participants were used for paired analysis.
Linear Model: Counts ~ Week + (1 | Subjects) with p-value adjustment using "sidak" method. Baseline values or sex were used as covariate in different comparisons between treatment group or within the treatment group.
A post-hoc procedure was used to calculate the marginal mean estimates of change from baseline and the 95% confidence intervals and p-values in comparison to a mu of zero. One-sample t-tests were performed for paired analysis. Additionally, independent two-sample t-tests were performed to test differences between treatment groups at baseline.
Points show mean values; whiskers show 95% CIs. p-values from lmer model with interaction term shown for pairwise estimation for within arm time effect (*, versus Week 0 lesional, icotrokinra cohort; #, versus Week 0 lesional, deucravacitinib cohort).
Paired analysis, */# p<0.05, **/## p<0.01, ***/### p<0.001, ****/#### p<0.0001. n=30 (icotrokinra cohort), n=10 (placebo cohort), n=18 (deucravacitinib cohort).

Immunogenicity Results

Incidence of ADA/NAb and Impact on Icotrokinra Trough Concentrations

Positive antibodies to icotrokinra through Week 36 were observed in 57 (7.8%) subjects [25 (8.1%) subjects randomized to icotrokinra at Week 0, 16 (11.3%) subjects randomized to

placebo at Week 0 and crossed over to icotrokinra at Week 16, and 16 (5.7%) subjects randomized to deucravacitinib at Week 0 and crossed over to icotrokinra at Week 24) (Table 111). Among the subjects who were positive for antibodies to icotrokinra, 32 (56.1%) subjects had the lowest measurable titer (1:50). The highest measured titer was 1:800 in 4 (7%) subjects. Among the subjects who were positive for antibodies to icotrokinra through Week 36, the incidence of neutralizing antibodies was zero.

The median time to onset of ADA was 24.71 weeks (range 4.4 to 37 weeks) of icotrokinra exposure for subjects randomized to icotrokinra at Week 0, 12.21 weeks (range 7.7 to 20.1 weeks) of icotrokinra exposure for subject in the placebo to icotrokinra group who crossed over to icotrokinra at Week 16, and 12.14 weeks (range 3.7 to 13.1 weeks) of icotrokinra exposure for subjects in the deucravacitinib to icotrokinra group who switched to icotrokinra at Week 24. Since immunogenicity results are available up to Week 36 and the placebo to icotrokinra crossover was at Week 16, the ADA responses in this treatment group is inconclusive.

Table 111. Summary of Treatment-Emergent Antibodies to Icotrokinra Status Through Week 36 by Treatment Group in Trial PSO3002

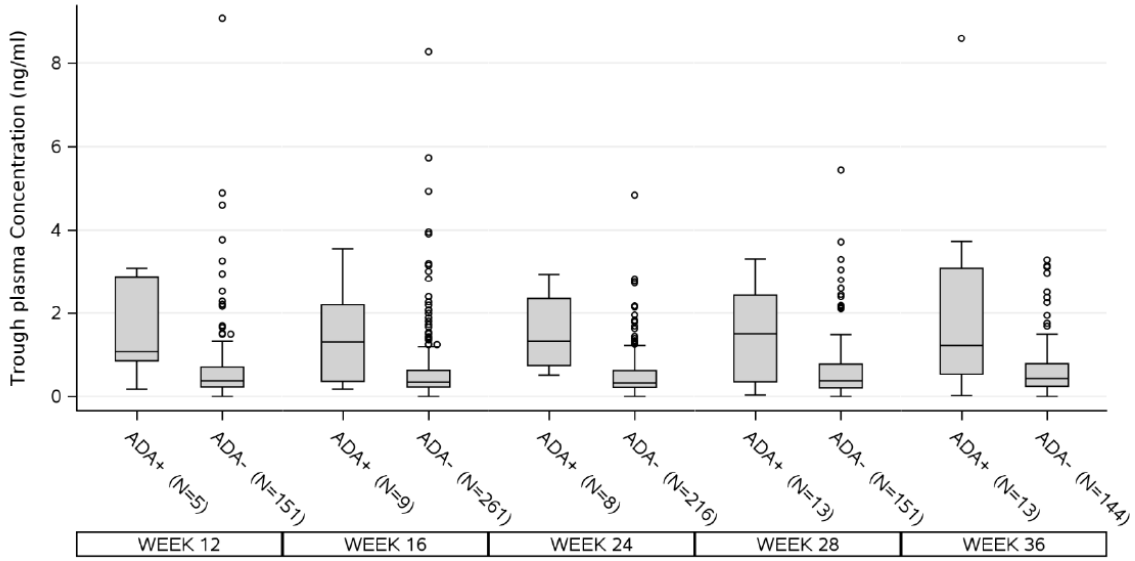
	Placebo -> JNJ-77242113	JNJ-77242113	Deucravacitinib--> JNJ-77242113	Combined
Analysis set: Immunogenicity analysis set[a]	141	309	281	731
Subjects positive for antibodies to JNJ-77242113 at baseline[b]	1 (0.7%)	0	1 (0.4%)	2 (0.3%)
Baseline titers				
1:50	1	-	1	2
Subjects positive for antibodies to JNJ-77242113 at baseline who were treatment-boosted for antibodies to JNJ-77242113[c]	0	0	0	0
Subjects positive for antibodies to JNJ-77242113 at baseline who were not treatment-boosted for antibodies to JNJ-77242113[d]	1 (0.7%)	0	1 (0.4%)	2 (0.3%)
Baseline titers				
1:50	1	-	1	2
Subjects positive for treatment-emergent antibodies to JNJ-77242113[e]	16 (11.3%)	25 (8.1%)	16 (5.7%)	57 (7.8%)
Peak titers[f]				
1:50	50.0% (8/16)	56.0% (14/25)	62.5% (10/16)	56.1% (32/57)
1:100	6.3% (1/16)	24.0% (6/25)	18.8% (3/16)	17.5% (10/57)
1:200	18.8% (3/16)	16.0% (4/25)	6.3% (1/16)	14.0% (8/57)
1:400	12.5% (2/16)	(0/25)	6.3% (1/16)	5.3% (3/57)
1:800	12.5% (2/16)	4.0% (1/25)	6.3% (1/16)	7.0% (4/57)
Peak titer group				
50-<100	50.0% (8/16)	56.0% (14/25)	62.5% (10/16)	56.1% (32/57)
100-<1000	50.0% (8/16)	44.0% (11/25)	37.5% (6/16)	43.9% (25/57)
>=1000	-	-	-	-
Subjects negative for treatment-emergent antibodies to JNJ-77242113[g]	125 (88.7%)	284 (91.9%)	265 (94.3%)	674 (92.2%)

Source: Integrated Summary of Immunogenicity, Table 5.
Abbreviations: ADA, antidrug antibody(ies); JNJ-77242113, icotrokinra.
[a] All randomized participants who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.
[b] Subjects positive for antibodies to icotrokinra at baseline, regardless of status after first icotrokinra administration.
[c] Subjects positive for treatment-boosted antibodies to icotrokinra includes subjects who were positive at baseline and whose titers increased 4-fold at any time. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[d] Includes subjects positive for antibodies to icotrokinra at baseline but whose titers did not increase 4-fold after their first icotrokinra administration, remained the same after treatment or ADA titers were reduced, or disappeared after icotrokinra administration.

[e] Subjects positive for treatment-emergent antibodies to icotrokinra includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first icotrokinra administration. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[f] Denominator is the number of subjects positive for treatment-emergent antibodies.
[g] Includes all subjects whose sample was negative and excludes subjects who were positive for antibodies to icotrokinra through Week 36. In addition, 2 subjects who were ADA positive at Week 24 on deucravacitinib treatment were considered negative for treatment-emergent antibodies to icotrokinra.

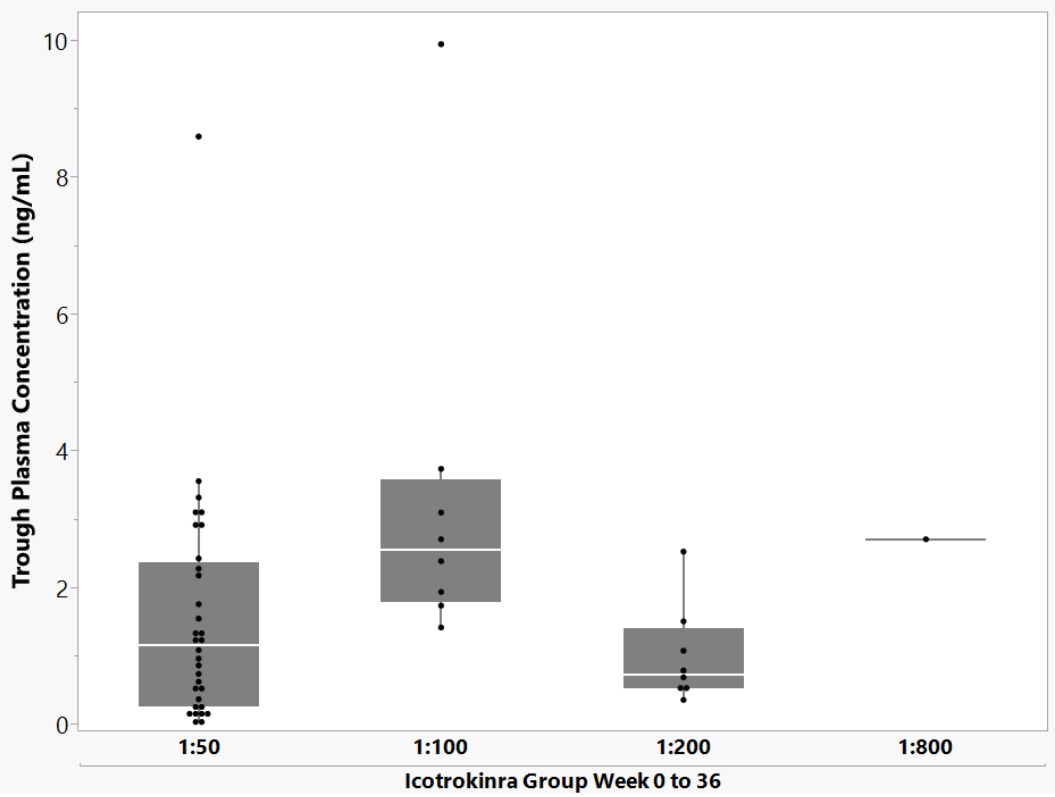
The median trough plasma concentrations over 36 weeks were generally higher in subjects who were ADA positive compared to subjects who were ADA negative with patrial overlapping in subjects who continued treatment with icotrokinra at Week 24 and developed antibodies to icotrokinra through week 36 (Figure 79). The impact of titer on the trough concentration of icotrokinra in subjects randomized to icotrokinra at Week 0 in Study PSO3002 is unclear due to the small number of subjects per titer group (Figure 80).

Figure 79. Boxplot of Trough Plasma Icotrokinra Concentrations From Week 12 Through Week 36 by Visit and Antibody Status Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3002



Source: Integrated Summary of Immunogenicity, Table 2.
Abbreviation: ADA, antidrug antibody

Figure 80. Impact of Titer on Trough Plasma Icotrokinra Concentrations From Week 12 Through Week 36 Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3002



Source: Reviewer's analysis using ADPC, ADIS, and ADSL data from Study PSO3002.

Impact of Developing ADA on Safety and Efficacy

The development of antibodies to icotrokinra and the titer of antibodies to icotrokinra did not have a clinically relevant impact on the efficacy of icotrokinra (Table 112). In subjects who were randomized to icotrokinra at Week 0 and were ADA positive, 21 (84%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 36 compared 211 (74.3%) subjects who were ADA negative. Similarly, 20 (80%) subjects who were ADA positive achieved a PASI 90 response at Week 36 compared to 201 (70.8%) subjects who were ADA negative. Similar trend was also observed in subjects who were randomized to placebo or deucravacitinib at Week 0 and crossed over to icotrokinra at Week 16 or 24, respectively.

There was no difference in efficacy between subjects with low and high titer in the two treatment groups (Table 112). In subjects who were randomized to icotrokinra at Week 0 and had low titer (≥50 to <100), 12 (85.7%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 36 compared 9 (81.8%) subjects who had high titer (≥100 to <100). Similarly, 11 (78.7%) subjects who had low titer achieved a PASI 90 response at Week 36 compared to 9 (81.8%) subjects who had high titer. Similar trend was also observed in subjects who were randomized to placebo or deucravacitinib at Week 0 and crossed over to icotrokinra at Week 16 or 24, respectively.

There was no apparent association between the incidence of antibodies to icotrokinra and the occurrence of hypersensitivity reactions. The number of subjects with 1 or more hypersensitivity reactions were 4 (16%) in subjects with positive ADA and 17 (6%) in subjects with negative ADA. The number of subjects with skin and subcutaneous tissue disorders was 2 (8%) in subjects with positive ADA and 10 (3.5%) in subjects with negative ADA (Source: Integrated Summary of Immunogenicity, Table 17).

Table 112. Clinical Responses at Week 36 by Antibodies to Icotrokinra Status Through Week 36 in Trial PSO3002

	Antibodies to JNJ-77242113 Status				
			Peak Titers for Antibody Positive Subjects		
	Negative[b]	Positive[c]	≥50 to <100	≥100 to <1000	≥1000
Analysis set: Immunogenicity analysis set[a]	674	57	32	25	-
Placebo -> JNJ-77242113					
IGA					
N	125	16	8	8	-
IGA score of 0 or 1 and a ≥2-grade improvement from baseline	94 (75.2%)	15 (93.8%)	7 (87.5%)	8 (100.0%)	-
IGA Score=0	60 (48.0%)	12 (75.0%)	6 (75.0%)	6 (75.0%)	-
PASI					
N	125	16	8	8	-
≥75% Improvement	103 (82.4%)	15 (93.8%)	7 (87.5%)	8 (100.0%)	-
≥90% Improvement	81 (64.8%)	14 (87.5%)	6 (75.0%)	8 (100.0%)	-
100% Improvement	49 (39.2%)	11 (68.8%)	6 (75.0%)	5 (62.5%)	-
JNJ-77242113					
IGA					
N	284	25	14	11	-
IGA score of 0 or 1 and a ≥2-grade improvement from baseline	211 (74.3%)	21 (84.0%)	12 (85.7%)	9 (81.8%)	-
IGA Score=0	147 (51.8%)	15 (60.0%)	10 (71.4%)	5 (45.5%)	-
PASI					
N	284	25	14	11	-
≥75% Improvement	241 (84.9%)	23 (92.0%)	13 (92.9%)	10 (90.9%)	-
≥90% Improvement	201 (70.8%)	20 (80.0%)	11 (78.6%)	9 (81.8%)	-
100% Improvement	136 (47.9%)	12 (48.0%)	7 (50.0%)	5 (45.5%)	-
Deucravacitinib -> JNJ-77242113					
IGA					
N	265	16	10	6	-
IGA score of 0 or 1 and a ≥2-grade improvement from baseline	199 (75.1%)	15 (93.8%)	10 (100.0%)	5 (83.3%)	-
IGA Score=0	104 (39.2%)	4 (25.0%)	2 (20.0%)	2 (33.3%)	-
PASI					
N	265	16	10	6	-
≥75% Improvement	222 (83.8%)	16 (100.0%)	10 (100.0%)	6 (100.0%)	-
≥90% Improvement	183 (69.1%)	11 (68.8%)	8 (80.0%)	3 (50.0%)	-
100% Improvement	93 (35.1%)	3 (18.8%)	2 (20.0%)	1 (16.7%)	-

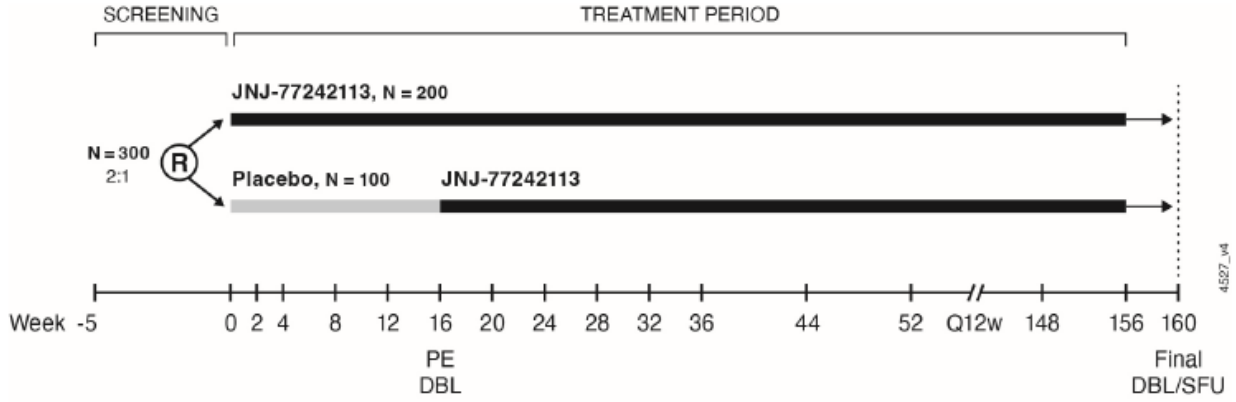
Source: Integrated Summary of Immunogenicity, Table 12.
Abbreviations: IGA, Investigator's Global Assessment; JNJ-77242113, icotrokinra; N, number of participants; PASI, Psoriasis Area and Severity Index.
[a] All randomized participants who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.
[b] Includes all subjects whose last sample was negative and excludes subjects who were positive for antibodies to icotrokinra through Week 36.
[c] Includes all subjects who had at least 1 positive sample (treatment-boosted or treatment-induced) at any time after their first icotrokinra administration through Week 36. In the instance that a subject had a positive sample at the reference baseline visit, the subject was considered positive only if the peak titer of the post- icotrokinra treatment samples was at least a 4-fold higher (i.e., ≥4-fold) than the titer of the reference baseline sample.
Note: Placebo to icotrokinra group only includes data after Week 16 for placebo subjects who crossed over to receive icotrokinra.
Note: Deucravacitinib to icotrokinra group only includes data after Week 24 for deucravacitinib subjects who switched to receive icotrokinra.
Source: Integrated Summary of Immunogenicity, Table 12.

19.4.2.5.3. Trial PSO3003 (ICONIC-TOTAL)

This is an ongoing multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the clinical efficacy and safety of icotrokinra in subjects ≥12 years of age with at least moderate plaque PsO (with or without psoriatic arthritis) involving special areas (scalp, genital, and/or hand/foot) defined by a total BSA ≥1% and IGA (overall) ≥2 and at least one of the following: ss-IGA score ≥3, sPGA-G ≥3, and/or hf-PGA score ≥3 who are candidate for phototherapy or systemic treatment for plaque psoriasis. Most subjects were required to have BSA involvement ≥10%. Enrollment was monitored, and, in the lower BSA subpopulation (1% to 10%) stopped if a maximum of 40% is reached. This is to ensure the study includes a broad spectrum of disease and is consistent with prior study precedence. Of note, 36% of participants enrolled in PSO3003 had a body surface area of 1% to 10%, and a baseline IGA score ≥2 was required.

Subjects were randomized 2:1 to icotrokinra 200 mg QD or placebo QD with blinded placebo-controlled treatment period (Week 0 to Week 16) and an open-label treatment period (Week 16 through Week 156) (Figure 81). A total of 311 subjects were randomized; 6 (1.9%) were ≥12 to <18 years of age. For subjects ≥12 to <18 years of age, body weight must be ≥40 kg at baseline. Icotrokinra was provided as a 200 mg film-coated tablet for oral administration.

Figure 81. Schematic Overview of Trial PSO3003



Source: Study PSO3003 Report, Figure 1.
Abbreviations: DBL, database lock; PE, primary endpoint; R, randomization; N, number of subjects, SFU, safety follow-up visit

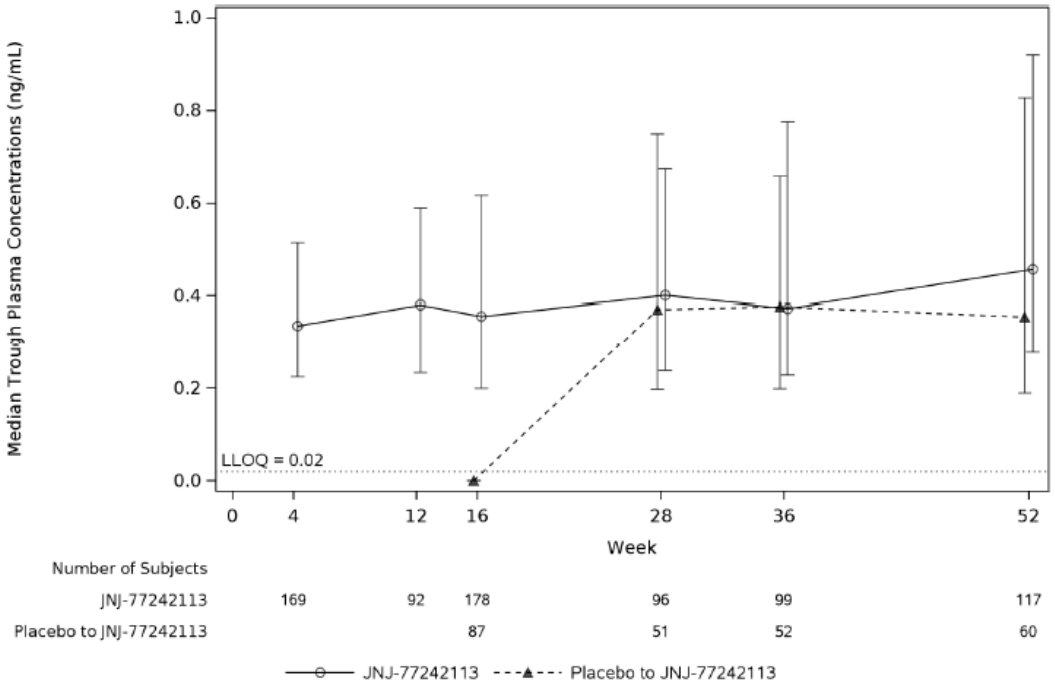
The primary efficacy endpoint is the proportion of subjects achieving IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16. The trough plasma concentrations of icotrokinra and antibodies to icotrokinra were measured at Weeks 0, 4, 12, 16, 28, 36, and 52. Trough and peak concentrations of icotrokinra were measured at Weeks 4 and 16. Serum biomarkers were measured at Weeks 0, 4, 16, 24, and 52. Skin biopsy was conducted on Weeks 0, 16, and 52. This study provides the results through Week 52.

PK and Efficacy Results

The median trough plasma concentrations of icotrokinra over time through Week 52 remained stable without apparent drug accumulation in subjects who received icotrokinra 200 mg QD

from Week 0 and subjects who received placebo at Week 0 then crossed over to icotrokinra 200 mg QD at Week 16 (Figure 82).

Figure 82. Median (IQR) Trough Plasma Icotrokinra Concentrations Through Week 52 in Trial PSO3003



Source: Study PSO3003 Report, Figure 14.
Abbreviations: JNJ-77242113, icotrokinra; IQR, interquartile range; LLOQ, lower limit of quantification

At Week 16, icotrokinra 200 mg QD consistently provided high clinical response rates (IGA score of 0/1, Scalp-Specific IGA score of 0/1) across all 4 trough plasma concentration quartiles (Table 113). The observed clinical response to icotrokinra is trough concentration independent with a proportion of subjects achieving the efficacy endpoint ranging from 55.6% to 63.6% across the trough concentration quartiles.

Table 113. Clinical Response at Week 16 by Trough Plasma Icotrokinra Concentration (ng/mL) Quartiles at Week 16 Among Subjects Randomized to Icotrokinra at Week 0 in Trial PSO3003

	Trough Plasma JNJ-77242113 Concentration Quartiles			
	<0.2 (N=44)[a]	≥0.2 to <0.4 (N=45)[a]	≥0.4 to <0.6 (N=44)[a]	≥0.6 (N=45)[a]
Participants treated with JNJ-77242113	44	45	44	45
IGA				
N	44	45	44	45
IGA score=0 or 1 and a ≥2-grade improvement from baseline at Week 16	28 (63.6%)	28 (62.2%)	27 (61.4%)	25 (55.6%)
IGA score=0	10 (22.7%)	15 (33.3%)	12 (27.3%)	12 (26.7%)
Participants treated with JNJ-77242113 and with a baseline ss-IGA score ≥3	32	38	38	36
ss-IGA				
N	32	38	38	36
ss-IGA score=0 or 1	23 (71.9%)	26 (68.4%)	27 (71.1%)	24 (66.7%)
ss-IGA score=0	14 (43.8%)	21 (55.3%)	21 (55.3%)	17 (47.2%)

Source: Summary of Clinical Pharmacology, Table 16.
Abbreviations: IGA, Investigator's Global Assessment; N, number of samples; ss-IGA, Scalp-Specific Investigator's Global Assessment.
[a] All randomized participants who received at least 1 complete dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
Quartiles are based on the PK Analysis Set with a trough sample at Week 16.
Participants could have multiple samples collected at the same time window, and N is the number of the samples included in the summary. The data from a participant who discontinued study intervention were excluded from that point onwards. In addition, the data from a participant who received an incomplete/incorrect or skipped dose based on the dose prior to the PK sample collection was excluded for that visit.

There was a significant clinical response rates in icotrokinra group compared to placebo. Following the administration of icotrokinra 200 mg QD, 118 (56.7%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline compared to placebo 6 (5.8%) with treatment difference of 51.5% (90% CI: 42.1%, 58.8%) (Table 114).

Table 114. Proportion of Subjects With an IGA (Overall) Score of 0/1 and a ≥2-Grade Improvement From Baseline at Week 16 in Trial PSO3003

	Placebo	JNJ-77242113
Analysis set: Full analysis set	103	208
Subjects achieving an IGA (overall) score of 0/1 and ≥2-grade improvement from baseline[a]	6 (5.8%)	118 (56.7%)
Treatment difference (95% CI)[b]		51.1% (42.1%, 58.8%)
p-value[c]		< 0.001

Source: Study PSO3003 Report, Table 3.
[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3. After accounting for the ICEs, subjects with missing data were considered as non-responders.
[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for special area involvement and BSA category using Mantel-Haenszel weights.
[c] The p-value was based on the Cochran-Mantel-Haenszel chi-square test stratified by special area involvement and BSA category.
Abbreviations: IGA, Investigator's Global Assessment; CI, confidence interval; JNJ-711242113, icotrokinra.

Incidence of ADA/NAb and Impact on Icotrokinra Trough Concentrations

The incidence of antibodies to icotrokinra through Week 52 was 10.8% (32 subjects) (Table 115). Among the subjects who were positive for antibodies to icotrokinra, 18 (56.3%) subjects had the lowest measurable titer (1:50). The highest measured titer was 1:3200 in 1 subject.

Among the subjects who were positive for antibodies to icotrokinra through Week 52, the incidence of neutralizing antibodies was zero. The median time to onset of ADA was 28 weeks (range 11.1 to 52.9 weeks) of icotrokinra exposure for subjects randomized to icotrokinra at Week 0, 13.14 weeks (range, 11.9 to 37.1 weeks) of icotrokinra exposure for subject in the placebo to icotrokinra group who crossed over to icotrokinra at Week 16.

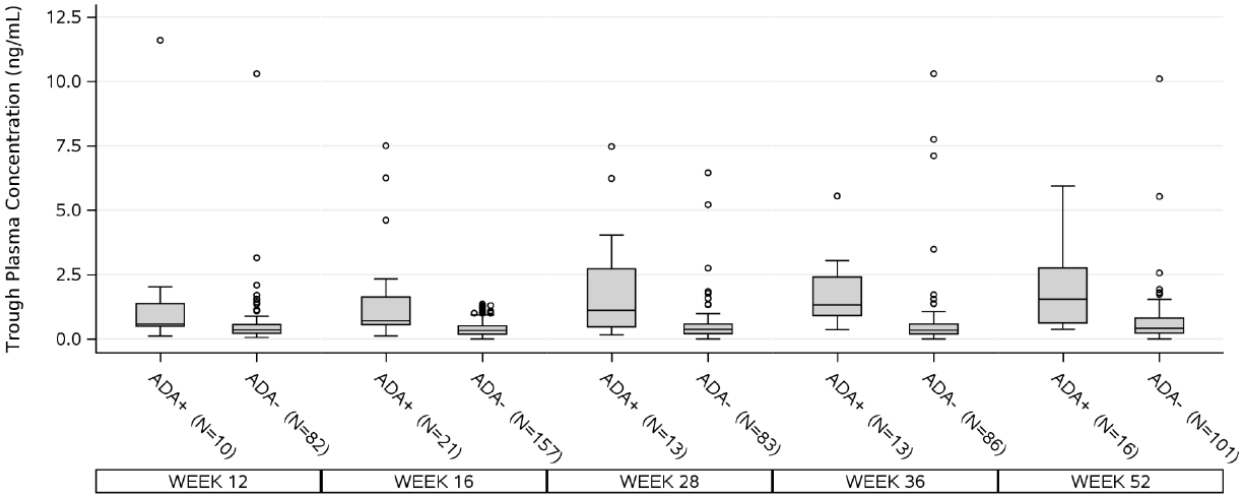
Table 115. Summary of Treatment-Emergent Antibodies to Icotrokinra Status Through Week 52 by Treatment Group in Trial PSO3003

		JNJ-77242113	
	Placebo -> JNJ-77242113	JNJ-77242113	Combined
Analysis set: Immunogenicity analysis set[a]	92	204	296
Subjects positive for antibodies to JNJ-77242113 at baseline[b]	0	1 (0.5%)	1 (0.3%)
Baseline titers			
1:50	0	1 (100.0%)	1 (100.0%)
Subjects positive for antibodies to JNJ-77242113 at baseline who were treatment-boosted for antibodies to JNJ-77242113[c]	0	0	0
Baseline titers			
Subjects positive for antibodies to JNJ-77242113 at baseline who were not treatment-boosted for antibodies to JNJ-77242113[d]	0	1 (0.5%)	1 (0.3%)
Baseline titers			
1:50	0	1 (100.0%)	1 (100.0%)
Subjects positive for treatment-emergent antibodies to JNJ-77242113[e]	9 (9.8%)	23 (11.3%)	32 (10.8%)
Peak titers[f]			
1:50	66.7% (6/9)	52.2% (12/23)	56.3% (18/32)
1:100	11.1% (1/9)	8.7% (2/23)	9.4% (3/32)
1:200	0.0% (0/9)	8.7% (2/23)	6.3% (2/32)
1:400	0.0% (0/9)	17.4% (4/23)	12.5% (4/32)
1:800	0.0% (0/9)	4.3% (1/23)	3.1% (1/32)
1:1600	22.2% (2/9)	4.3% (1/23)	9.4% (3/32)
1:3200	0.0% (0/9)	4.3% (1/23)	3.1% (1/32)
Peak titer group[f]			
50-<100	66.7% (6/9)	52.2% (12/23)	56.3% (18/32)
100-<1000	11.1% (1/9)	39.1% (9/23)	31.3% (10/32)
>=1000	22.2% (2/9)	8.7% (2/23)	12.5% (4/32)
Subjects negative for treatment-emergent antibodies to JNJ-77242113[g]	83 (90.2%)	181 (88.7%)	264 (89.2%)

Source: Integrated Summary of Immunogenicity, Table 6.
[a] All randomized participants who received at least 1 dose of icotrokinra and who had at least 1 sample obtained after the first dose of icotrokinra for the detection of antibodies to icotrokinra.
[b] Subjects positive for antibodies to icotrokinra at baseline, regardless of status after first icotrokinra administration.
[c] Subjects positive for treatment-boosted antibodies to icotrokinra includes subjects who were positive at baseline and whose titers increased 4-fold at any time. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[d] Includes subjects positive for antibodies to icotrokinra at baseline but whose titers did not increase 4-fold after their first icotrokinra administration, remained the same after treatment or ADA titers were reduced or disappeared after icotrokinra administration.
[e] Subjects positive for treatment-emergent antibodies to icotrokinra includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first icotrokinra administration. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[f] Denominator is the number of subjects positive for treatment-emergent antibodies.
[g] Excludes subjects who were treatment-emergent positive at any time.
Note: Placebo to icotrokinra column only includes data after Week 16 for placebo subjects who crossed over to receive icotrokinra.

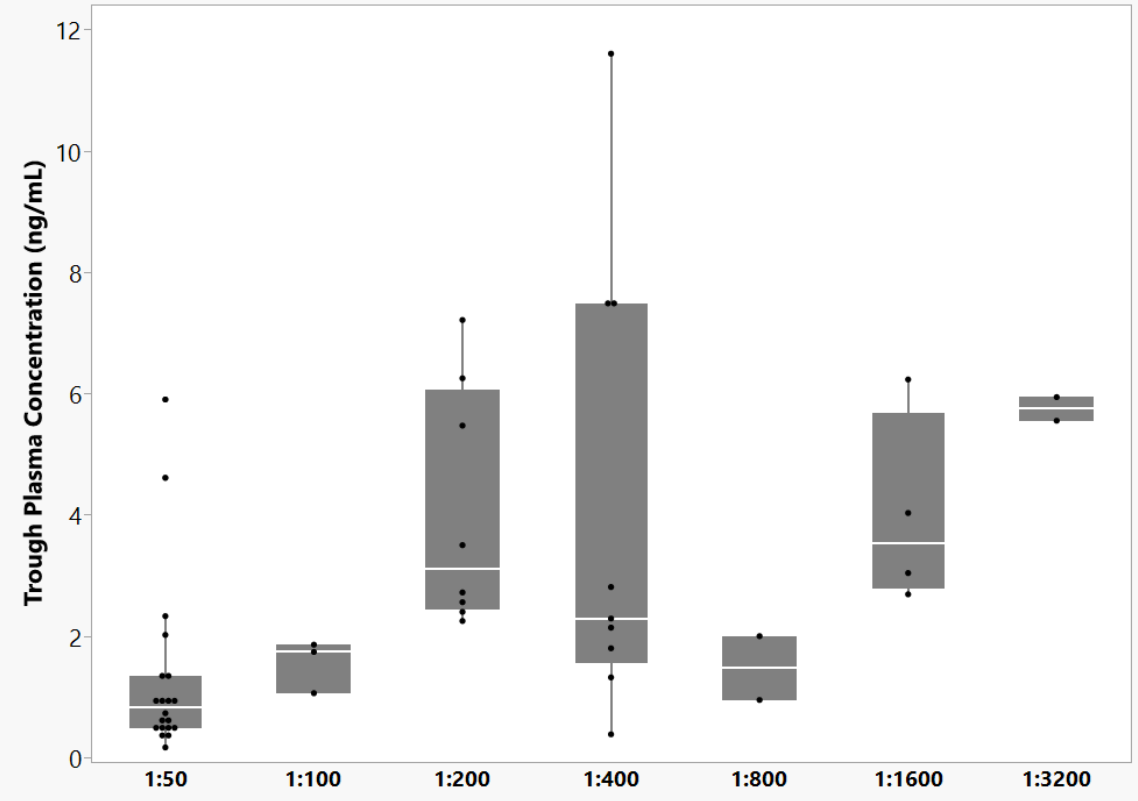
The median trough plasma concentrations over 52 weeks were generally higher in subjects who were ADA positive compared to subjects who were ADA negative with patrial overlapping (Figure 83). In addition, the trough plasma concentrations of icotrokinra increased when the titer increases in subjects randomized to icotrokinra at Week 0 and continued treatment with icotrokinra through Week 52 (Figure 84).

Figure 83. Boxplot of Trough Plasma Icotrokinra Concentrations from Week 12 Through Week 52 by Visit and Antibody Status Among Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3003



Source: Integrated Summary of Immunogenicity, Figure 3.
Abbreviations: ADA, antidrug antibodies; N, number of participants; PK, pharmacokinetic(s)

Figure 84. Impact of Titer on Trough Plasma Icotrokinra Concentrations Through Week 52 Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3003



Source: Reviewer's analysis using ADPC, ADIS, and ADSL data from Study PSO3003.

Impact of Developing ADA on Safety and Efficacy

The development of antibodies to icotrokinra and the titer of antibodies to icotrokinra did not have a clinically relevant impact on the efficacy of icotrokinra (Table 116). In subjects who were randomized to icotrokinra at Week 0 and were ADA positive, 19 (82.6%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 52 compared 120 (66.3%) subjects who were ADA negative. In subjects who were randomized to icotrokinra at Week 0 and had low titer (≥50 to <100), 9 (75%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 52 compared 8 (88.9%) subjects who had high titer (≥100 to <100) (Table 116). Similar trend was also observed in subjects who were randomized to placebo at Week 0 and crossed over to icotrokinra at Week 16.

There was no apparent association between the incidence of antibodies to icotrokinra and the occurrence of hypersensitivity reactions. The number of subjects with 1 or more hypersensitivity reactions were 2 (8.7%) in subjects with positive ADA and 8 (4.4%) in subjects with negative ADA. The number of subjects with skin and subcutaneous tissue disorders was 2 (8.7%) in subjects with positive ADA and 6 (3.3%) in subjects with negative ADA (Source: Integrated Summary of Immunogenicity, Table 18).

Table 116. Clinical Responses at Week 52 by Antibodies to Icotrokinra Status Through Week 52 in Study PSO3003

	Antibodies to JNJ-77242113				
		Peak Titers for Antibody Positive Subjects			
	Negative[b]	Positive[c]	≥50 to <100	≥100 to <1000	≥1000
Analysis set: Immunogenicity analysis set[a]	264	32	18	10	4
Placebo -> JNJ-77242113					
IGA (overall)					
N	83	9	6	1	2
IGA Score of 0 or 1 and a ≥2-grade improvement from baseline	57 (68.7%)	6 (66.7%)	3 (50.0%)	1 (100.0%)	2 (100.0%)
IGA Score = 0	36 (43.4%)	5 (55.6%)	3 (50.0%)	0	2 (100.0%)
ss-IGA					
Subjects with a baseline ss-IGA ≥3	67	8	6	1	1
ss-IGA Score = 0 or 1	48 (71.6%)	5 (62.5%)	3 (50.0%)	1 (100.0%)	1 (100.0%)
ss-IGA Score = 0	42 (62.7%)	4 (50.0%)	2 (33.3%)	1 (100.0%)	1 (100.0%)
JNJ-77242113					
IGA (overall)					
N	181	23	12	9	2
IGA Score of 0 or 1 and a ≥2-grade improvement from baseline	120 (66.3%)	19 (82.6%)	9 (75.0%)	8 (88.9%)	2 (100.0%)
IGA Score = 0	76 (42.0%)	15 (65.2%)	7 (58.3%)	6 (66.7%)	2 (100.0%)
ss-IGA					
Subjects with a baseline ss-IGA ≥3	147	17	7	9	1
ss-IGA Score = 0 or 1	106 (72.1%)	15 (88.2%)	6 (85.7%)	8 (88.9%)	1 (100.0%)
ss-IGA Score = 0	85 (57.8%)	11 (64.7%)	4 (57.1%)	6 (66.7%)	1 (100.0%)

Source: Integrated Summary of Immunogenicity, Table 13.
Abbreviations: IGA, Investigator's Global Assessment; JNJ-77242113, icotrokinra; N=number of participants; PASI, Psoriasis Area and Severity Index; ss-IGA, Scalp Specific Investigator's Global Assessment.
[a] All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.
[b] Includes all subjects whose last sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 through Week 52.
[c] Includes all subjects who had at least 1 positive sample (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration through Week 52. In the instance that a subject had a positive sample at the reference baseline visit, the subject was considered positive only if the peak titer of the post-JNJ-77242113 treatment samples was at least a 4-fold higher (i.e., ≥4-fold) than the titer of the reference baseline sample.
Note: Placebo->JNJ-77242113 column only includes data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113.

19.4.2.5.4. Trial PSO3004 (ICONIC-ADVANCE 2)

This is an ongoing multicenter, randomized, double-blind, parallel-group, placebo-controlled, and deucravacitinib active comparator-controlled study to evaluate the clinical efficacy and safety of icotrokinra in adults with moderate to severe plaque PsO (with or without psoriatic arthritis) defined by a total BSA ≥10%, total PASI ≥12, and total IGA ≥3, who were candidates for phototherapy or systemic treatment. Subjects were randomized 4:1:4 to icotrokinra, placebo, or deucravacitinib (Figure 85). The randomized subjects were further stratified by baseline

weight category (≤90 kg, >90 kg) and geographic region. Icotrokinra was provided as a 200 mg film-coated tablet for oral administration. This study included the following treatment groups:

Icotrokinra

- Week 0 to Week 24: icotrokinra 200 mg QD and matching placebo for deucravacitinib once daily.
- Week 24 to Week 156: icotrokinra 200 mg QD.

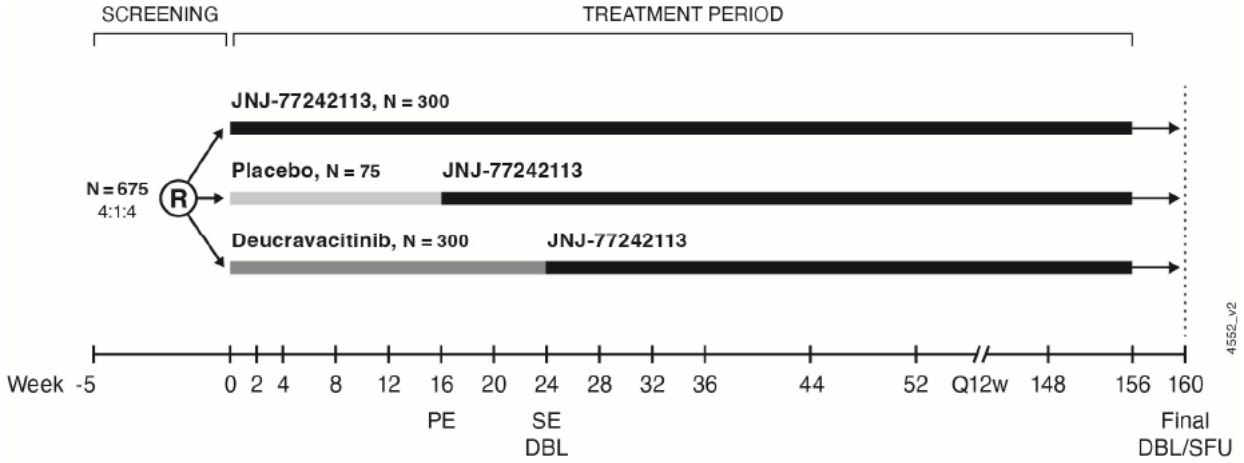
Placebo to Icotrokinra 200 mg QD

- Week 0 to Week 16: matching placebo for icotrokinra once daily and matching placebo for deucravacitinib once daily.
- Week 16 to Week 24: icotrokinra 200 mg QD and matching placebo for deucravacitinib once daily.
- Week 24 to 156: icotrokinra 200 mg QD.

Deucravacitinib

- Week 0 to Week 24: deucravacitinib 6 mg QD and matching placebo for icotrokinra once daily.
- Week 24 to Week 156: icotrokinra 200 mg QD.

Figure 85. Schematic Overview of Trial PSO3004



Source: Study PSO3004 Report, Figure 1.
Abbreviations: DBL, database lock; PE, primary endpoint; Q12w, every 12 weeks; R, randomization; SE, secondary endpoint; SFU, safety follow-up visit.

The coprimary efficacy endpoint is the proportion of subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16 and PASI 90 at Week 16.

Subjects must have discontinued IL-23 inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, and antitumor necrosis factor α biologic therapy at least 12 weeks or 5 half-lives, whichever is

longer, prior to the first administration of study intervention. Participants must have discontinued systemic medications for psoriasis including immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine) for at least 4 weeks prior to the first dose of study intervention and must have discontinued topical therapies at least 2 weeks prior to the first dose of study intervention.

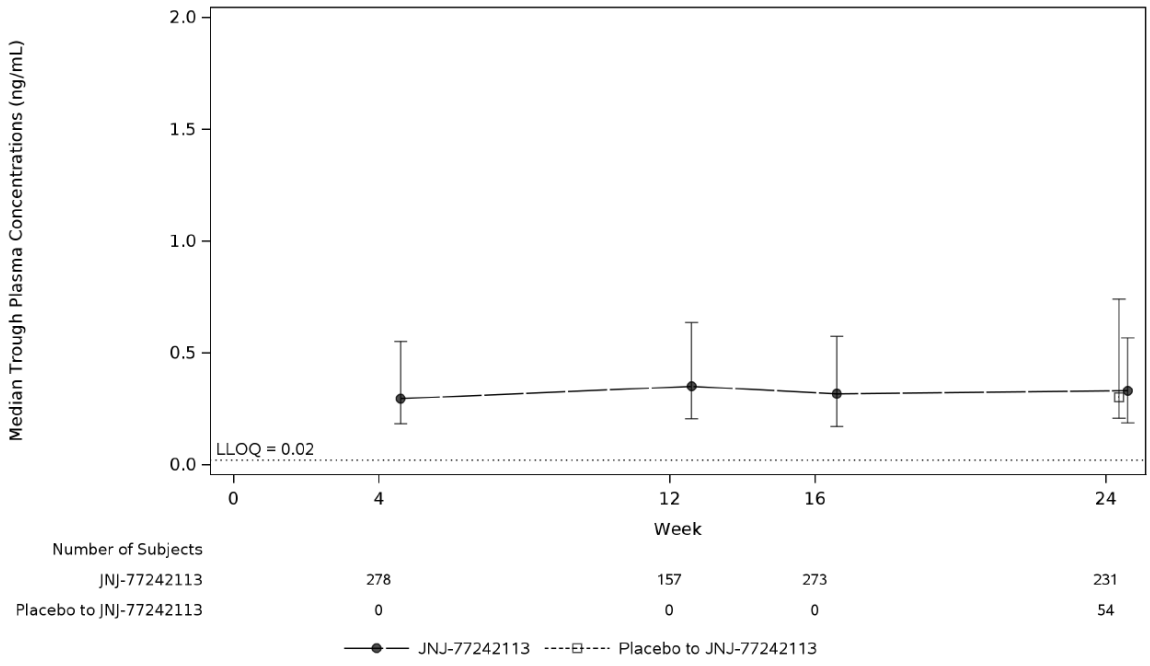
The trough plasma concentrations of icotrokinra and antibodies to icotrokinra were measured at Weeks 0, 4, 12, 16, 24, 28, 36, and 52. Trough and peak concentrations of icotrokinra were measured at Weeks 4 and 16.

Subjects administered icotrokinra upon waking with 240 mL water on an empty stomach (no food intake for at least 2 hours before and for at least 30 minutes after taking the study intervention).

PK and Efficacy Results

The median trough plasma concentrations of icotrokinra over time through Week 24 remained stable without apparent drug accumulation in subjects who received icotrokinra 200 mg QD from Week 0 and subjects who received placebo at Week 0 then crossed over to icotrokinra 200 mg QD at Week 16 (Figure 86).

Figure 86. Median (IQR) Trough Plasma Icotrokinra Concentrations Through Week 24 in Trial PSO3004



Source: Study PSO3004. Figure 11
Abbreviations: JNJ-77242113, icotrokinra; IQR, interquartile range; LLOQ, lower limit of quantification

At Week 16, icotrokinra 200 mg QD consistently provided high clinical responses (PASI 90, IGA score of 0/1) across all 4 trough plasma concentration quartiles (Table 117). There was an

increase in the clinical response from plasma concentration Quartile 1 (<0.2 ng/mL) to Quartile 2 (0.2 to < 0.3 ng/mL) followed by a relative plateauing in the clinical response after quartile 2 at plasma concentrations ≤0.3 ng/mL.

Table 117. Clinical Response at Week 16 by Trough Plasma Icotrokinra Concentration Quartiles at Week 16 in Trial PSO3004

	Trough Plasma JNJ-77242113 Concentration Quartiles			
	<0.2 (N=67)[a]	0.2 to <0.3 (N=69)[a]	0.3 to <0.6 (N=67)[a]	≥0.6 (N=70)[a]
Participants treated with JNJ-77242113	67	69	67	70
IGA				
N	67	69	67	70
IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16	40 (59.7%)	52 (75.4%)	58 (86.6%)	55 (78.6%)
IGA score of 0	22 (32.8%)	26 (37.7%)	28 (41.8%)	27 (38.6%)
PASI				
N	67	69	67	70
≥75% improvement	48 (71.6%)	57 (82.6%)	62 (92.5%)	59 (84.3%)
≥90% improvement	35 (52.2%)	39 (56.5%)	48 (71.6%)	44 (62.9%)
100% improvement	19 (28.4%)	21 (30.4%)	23 (34.3%)	25 (35.7%)

Source: Summary of Clinical Pharmacology, Table 17.
Abbreviations: IGA, Investigator's Global Assessment; N, number of samples; PASI, Psoriasis Area and Severity Index.
[a] All randomized subjects who received at least 1 complete dose of icotrokinra and had at least 1 valid blood sample drawn for PK analysis after their first dose of icotrokinra.
Subjects could have multiple samples collected at the same time window, and N is the number of the samples included in the summary.
The data from a subject who discontinued study intervention were excluded from that point onwards. In addition, the data from a subject who received an incomplete/incorrect or skipped dose(s) based on 2 previous doses prior to the PK sample collection or data from a subject who skipped dose prior to PK sample collection was excluded for that visit.

There was a significant clinical response in icotrokinra group compared to placebo. Following the administration of icotrokinra 200 mg QD, 227 (70.5%) subjects achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline compared to placebo 7 (8.5%) with treatment difference of 62.1% (90% CI: 52.9%, 69.1%) compared to placebo (Table 118). In addition, 184 (57.1%) subjects in icotrokinra treatment arm achieved a PASI 90 response at Week 16 compared to placebo 1 (1.2%) with treatment difference of 56% (90% CI: 48.5%, 62%) compared to placebo.

Table 118. Proportion of Subjects Achieving an IGA Score of Cleared (0) or Minimal (1) and a ≥2-Grade Improvement From Baseline and Proportion of Subjects Achieving a PASI 90 Response at Week 16 in Trial PSO3004

	Placebo	JNJ-77242113
Analysis set: Full analysis set	82	322
Subjects achieving an IGA score of 0 or 1 and a ≥2-grade improvement from baseline at Week 16[a]	7 (8.5%)	227 (70.5%)
Treatment difference (95% CI)[b]		62.1% (52.9%, 69.1%)
p-value[c]		< 0.001
Subjects achieving a PASI 90 response at Week 16[a]	1 (1.2%)	184 (57.1%)
Treatment difference (95% CI)[b]		56.0% (48.5%, 62.0%)
p-value[c]		< 0.001

Source: Study PSO3004 Report, Table 3

[a] Subjects with ICE 1-2 were assumed to be non-responders after the event. Observed data were used for subjects with ICE 3 after accounting for the ICEs, subjects with missing data were considered as non-responders.

[b] Treatment difference and 95% CI (using Miettinen-Nurminen method) were calculated adjusting for baseline weight category (≤90 kg, >90 kg) and geographic region using Mantel-Haenszel weights.

[c] Based on the Cochran-Mantel-Haenszel chi-square test stratified by baseline weight category (≤90 kg, >90 kg) and geographic region.

Immunogenicity Results

Incidence of ADA/NAb and Impact on Icotrokinra Trough Concentrations

The incidence of antibodies to icotrokinra through Week 24 was 7.7% (30 subjects). Among the subjects who were positive for antibodies to icotrokinra, 18 (60%) subjects had the lowest measurable titer (1:50) (Table 119). The highest measured titer was 1:1600 in 1 subject. Among the subjects who were positive for antibodies to icotrokinra through Week 24, the incidence of neutralizing antibodies was zero.

The median time to onset of ADA was 17.71 weeks (range 11 to 24.1 weeks) of icotrokinra exposure for subjects randomized to icotrokinra at Week 0 and 8.14 weeks (range 7.3 to 8.4 weeks) of icotrokinra exposure for subject in the placebo to icotrokinra group who crossed over to icotrokinra at Week 16. Since immunogenicity results are available up to Week 24 and the placebo to icotrokinra crossover was at Week 16, the ADA responses in this treatment group is inconclusive.

Table 119. Summary of Treatment-Emergent Antibodies to Icotrokinra Status Through Week 24 by Treatment Group in Trial PSO3004

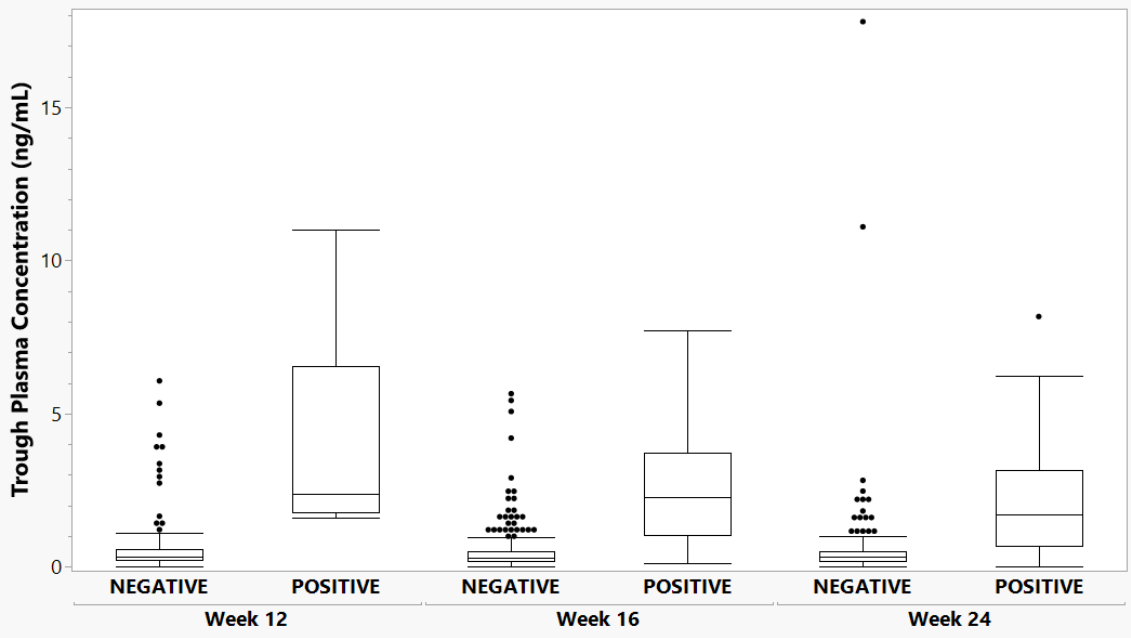
	Placebo -> JNJ-77242113	JNJ-77242113	Combined
Analysis set: Immunogenicity analysis set[a]	73	319	392
Subjects positive for antibodies to JNJ-77242113 at baseline[b]	1 (1.4%)	3 (1.0%)	4 (1.0%)
Baseline titers			
1:50	1	3	4
Subjects positive for antibodies to JNJ-77242113 at baseline who were treatment-boosted for antibodies to JNJ-77242113[c]	0	0	0
Subjects positive for antibodies to JNJ-77242113 at baseline who were not treatment-boosted for antibodies to JNJ-77242113[d]	1 (1.4%)	3 (1.0%)	4 (1.0%)
Baseline titers			
1:50	1	3	4
Subjects positive for treatment-emergent antibodies to JNJ-77242113[e]	8 (11.0%)	22 (6.9%)	30 (7.7%)
Peak titers[f]			
1:50	87.5% (7/8)	50.0% (11/22)	60.0% (18/30)
1:100	12.5% (1/8)	18.2% (4/22)	16.7% (5/30)
1:200	(0/8)	4.5% (1/22)	3.3% (1/30)
1:400	(0/8)	9.1% (2/22)	6.7% (2/30)
1:800	(0/8)	13.6% (3/22)	10.0% (3/30)
1:1600	(0/8)	4.5% (1/22)	3.3% (1/30)
Peak titer group[f]			
50-<100	87.5% (7/8)	50.0% (11/22)	60.0% (18/30)
100-<1000	12.5% (1/8)	45.5% (10/22)	36.7% (11/30)
≥1000	(0/8)	4.5% (1/22)	3.3% (1/30)
Subjects negative for treatment-emergent antibodies to JNJ-77242113[g]	65 (89.0%)	297 (93.1%)	362 (92.3%)

Source: Integrated Summary of Immunogenicity, Table 7.
Abbreviations: ADA, antidrug antibodies; JNJ-77242113, icotrokinra.
[a] All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.
[b] Subjects positive for antibodies to JNJ-77242113 at baseline, regardless of status after first JNJ-77242113 administration.
[c] Subjects positive for treatment-boosted antibodies to JNJ-77242113 includes subjects who were positive at baseline and whose titers increased 4-fold at any time. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted.
[d] Includes subjects positive for antibodies to JNJ-77242113 at baseline but whose titers did not increase 4-fold after their first JNJ-77242113 administration, remained the same after treatment or ADA titers were reduced, or disappeared after JNJ-77242113 administration.
[e] Subjects positive for treatment-emergent antibodies to JNJ-77242113 includes all subjects who were positive (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration. Subjects with baseline positive samples and without 4-fold increased titer after treatment are not considered treatment-boosted. One subject who tested positive for antibodies to JNJ-77242113 at Week 16 prior to receiving JNJ-77242113 administration is also included.
[f] Denominator is the number of subjects positive for treatment-emergent antibodies.
[g] Includes all subjects whose sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 through Week 24. In addition, one subject who was ADA positive at Week 16 on placebo treatment was considered negative for treatment-emergent antibodies to JNJ-77242113

The median trough plasma concentrations over 24 weeks were generally higher in subjects who were ADA positive compared to subjects who were ADA negative in subjects who were randomized to icotrokinra at Week 0 and continued treatment with icotrokinra at Week 24 (Figure 87). In addition, the trough plasma concentrations of icotrokinra increased when the

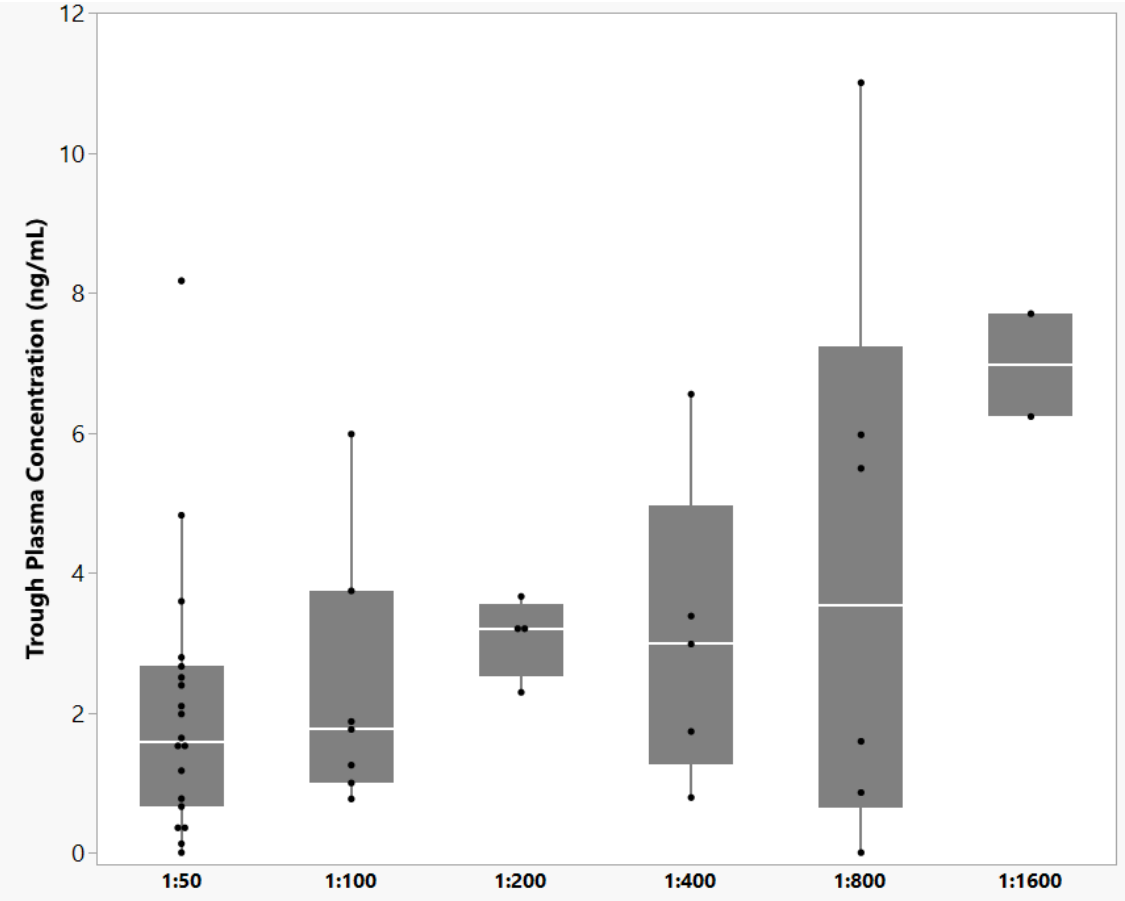
titer increases in subjects randomized to icotrokinra at Week 0 and continued treatment with icotrokinra through Week 24 (Figure 88).

Figure 87. Boxplot of Trough Plasma Icotrokinra Concentrations From Week 12 Through Week 24 by Visit and Antibody Status Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3004



Source: Reviewer's analysis using ADPC, ADIS, and ADSL data from Study PSO3002.

Figure 88. Impact of Titer on Trough Plasma Icotrokinra Concentrations From Week 12 Through Week 24 Among Icotrokinra Subjects Who Were Randomized to Icotrokinra at Week 0 in Trial PSO3004



Source: Reviewer's analysis using ADPC, ADIS, and ADSL data from Study PSO3002.

Impact of Developing ADA on Safety and Efficacy

The development of antibodies to icotrokinra and the titer of antibodies to icotrokinra did not have a clinically relevant impact on the efficacy of icotrokinra (Table 120). In subjects who were randomized to icotrokinra at Week 0 and were ADA positive, 18 (81.8%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 24 compared 202 (68%) subjects who were ADA negative. Similarly, 19 (86.4%) subjects who were ADA positive achieved a PASI 90 response at Week 24 compared to 189 (63.6%) subjects who were ADA negative. In subjects who were randomized to icotrokinra at Week 0 and had low titer (≥50 to <100), 10 (90.9%) achieved an IGA Score of 0 or 1 and a ≥2-Grade improvement from baseline at Week 24 compared 7 (70%) subjects who had high titer (≥100 to <100). Similarly, 8 (81.8%) subjects who had low titer achieved a PASI 90 response at Week 52 compared to 9 (90%) subjects who had high titer. Similar trend was also observed in subjects who were randomized to placebo at Week 0 and crossed over to icotrokinra at Week 16 (Table 120).

There was no apparent association between the incidence of antibodies to icotrokinra and the occurrence of hypersensitivity reactions. The number of subjects with 1 or more adverse events was 0 (0%) in subjects with positive ADA and 7 (2.4%) in subjects with negative ADA. The number of subjects with skin and subcutaneous tissue disorders was 0 (0%) in subjects with positive ADA and 6 (2%) in subjects with negative ADA (Source: Integrated Summary of Immunogenicity, Table 19)

Table 120. Clinical Responses at Week 24 by Antibodies to Icotrokinra Status Through Week 24 in Trial PSO3004

	Antibodies to JNJ-77242113				
			Peak Titers for Antibody Positive Subjects		
	Negative[b]	Positive[c]	≥50 to <100	≥100 to <1000	≥1000
Analysis set: Immunogenicity analysis set[a]	362	30	18	11	1
Placebo -> JNJ-77242113					
IGA					
N	65	8	7	1	-
IGA score of 0 or 1 and a ≥2-grade improvement from baseline	32 (49.2%)	5 (62.5%)	4 (57.1%)	1 (100.0%)	-
IGA Score=0	4 (6.2%)	0	0	0	-
PASI					
N	65	8	7	1	-
≥75% Improvement	35 (53.8%)	5 (62.5%)	4 (57.1%)	1 (100.0%)	-
≥90% Improvement	14 (21.5%)	3 (37.5%)	2 (28.6%)	1 (100.0%)	-
100% Improvement	3 (4.6%)	0	0	0	-
JNJ-77242113					
IGA					
N	297	22	11	10	1
IGA score of 0 or 1 and a ≥2-grade improvement from baseline	202 (68.0%)	18 (81.8%)	10 (90.9%)	7 (70.0%)	1 (100.0%)
IGA Score=0	120 (40.4%)	8 (36.4%)	4 (36.4%)	3 (30.0%)	1 (100.0%)
PASI					
N	297	22	11	10	1
≥75% Improvement	245 (82.5%)	21 (95.5%)	10 (90.9%)	10 (100.0%)	1 (100.0%)
≥90% Improvement	189 (63.6%)	19 (86.4%)	9 (81.8%)	9 (90.0%)	1 (100.0%)
100% Improvement	100 (33.7%)	7 (31.8%)	4 (36.4%)	2 (20.0%)	1 (100.0%)

Source: Integrated Summary of Immunogenicity, Table 14.
Abbreviations: IGA, Investigator's Global Assessment; JNJ-77242113, icotrokinra; N, number of participants; PASI, Psoriasis Area and Severity Index.
[a] All randomized participants who received at least 1 dose of JNJ-77242113 and who had at least 1 sample obtained after the first dose of JNJ-77242113 for the detection of antibodies to JNJ-77242113.
[b] Includes all subjects whose last sample was negative and excludes subjects who were positive for antibodies to JNJ-77242113 through Week 24. In addition, one subject who was ADA positive at Week 16 on placebo treatment was considered negative for treatment-emergent antibodies to JNJ-77242113.
[c] Includes all subjects who had at least 1 positive sample (treatment-boosted or treatment-induced) at any time after their first JNJ-77242113 administration through Week 24. In the instance that a subject had a positive sample at the reference baseline visit, the subject was considered positive only if the peak titer of the post-JNJ-77242113 treatment samples was at least a 4-fold higher (i.e., ≥4-fold) than the titer of the reference baseline sample.
Note: Placebo to JNJ-77242113 group only includes data after Week 16 for placebo subjects who crossed over to receive JNJ-77242113.

19.4.3. Bioanalytical Method Validation

19.4.3.1. Quantification of Icotrokinra in Human Plasma, Urine and Feces

Icotrokinra concentration in human plasma was quantified using LC-MS/MS assays developed and validated by [redacted] (Table 121). The initial assay which employed sample preparation consisted of protein precipitation followed by SPE was developed and validated by [redacted] (Method VAL442, Table 122). This initial assay was transferred to [redacted] where the chromatographic conditions were slightly modified to increase throughput (Method BA13692, Table 124). Both assays were cross-validated with quality control samples in study BA13692.

Following the transfer of development sponsorship to Janssen Research & Development, an assay for icotrokinra was implemented and validated at [redacted] (Method BA13914, Table 123).

The [redacted] method was again modified to increase the throughput with changes in sample preparation, equipment, and chromatography. The sample preparation was adapted to protein precipitation followed by evaporation of the supernatant and reconstitution.

The [redacted] assays were successfully cross-validated with quality control samples and a selection of study samples. [redacted] methods were cross-validated in study BA13914; [redacted] methods were cross-validated in studies BA13692 and SH-J01-R5448 (Table 126).

Later, the [redacted] assay was modified to improve chromatographic separation and partially validated with the original [redacted] assay in Method BA14082 (Table 123). The modified [redacted] assay was transferred to [redacted] with partial validation in Method BA14082. The original and modified [redacted] assays and the modified [redacted] and modified [redacted] assays were cross-validated with quality control samples and a selection of study samples in study [redacted]-J01-R5448 (Table 126).

Methods VAL446 and VAL447 were used to quantify icotrokinra in urine and feces, respectively, in Trial PN-235-01 (Table 125). In addition, Method VAL446 was used to quantify icotrokinra in urine in Trial PSO1007.

Overall, the performance of the bioanalytical methods and the cross validation between the analytical methos is acceptable.

Table 121. List of Bioanalytical Methods Used in Clinical Trials

Method	Bioanalytical Site	Matrix	Clinical Trials
VAL442	(b) (4)	Human Plasma (EDTA)	PN-235-01, PSO1002, PSO1003, PSO2001, PSO2002
BA13914 and BA14082		Human Plasma (EDTA)	PSO1006, PSO1007, PSO1009, PSO3001, PSO3002, PSO3003, PSO3004
BA13692 and BA14083		Human Plasma (EDTA)	PSO1004, PSO3001
VAL446		Human Urine	PN-235-01, PSO1007
VAL447		Human feces	PN-235-01

Source: Reviewer's generated table.
Abbreviations: EDAT, Ethylenediaminetetraacetic acid

Table 122. Performance of Bioanalytical Method VAL442

Parameters	Method VAL442 and Amendment 01
Analytical site	(b) (4)
Method description	Protein precipitation followed by SPE using a stable isotope labeled internal standard and LC-MS/MS
Matrix	human EDTA plasma
Calibration curve	8 calibration points 0.02 to 10 ng/mL
Cumulative accuracy (%bias)	-2.3% to 1.8%
Cumulative precision (%CV)	≤11.5%
Regression model and weighting	$1/x^2$ weighted linear regression
QC concentrations	
QC performance in blank human plasma	0.0200 (PQCLOQ) ng/mL 0.0600 (PQCL) ng/mL 0.750 (PQCM) ng/mL 7.50 (PQCH) ng/mL 100 (PQCOR) ng/mL
Cumulative accuracy (%bias)	-2.9 to 9.5%
Cumulative precision (%CV)	≤13.8%
Internal Standard	Stable isotope labelled internal standard (PN25503)
Selectivity	No interference observed in lots of blank humans EDTA plasma.
Matrix effect	No significant matrix effects were observed in 6 different matrix lots. – At PQCLOQ (0.02 ng/mL), bias: -13.5% to -5.5%; CV%: <10.9%
Specificity	
Hemolysis effect	One lot tested at PQCLOQ (0.02 nmol/L) in triplicate – %Bias: -2%; %CV: 11.7%
Lipemic effect	One lot tested at PQCLOQ (0.02 nmol/L) in triplicate – %Bias: 0%; %CV: 6.6%
Dilution linearity and hook effect	20-fold dilutions with dilution QC at 100 ng/ml (n=6). – %Bias: -6.9%; %CV: 1.8%

Parameters	Method VAL442 and Amendment 01
Bench-top/process stability	*Stability in human plasma samples for 4 hours at room temperature* – At PQCL (0.0600 ng/mL), bias: -9%, CV: 5% – At PQCH (7.5 ng/mL), bias: -5.2%, CV: 1.3% *Stability in human plasma samples for 24.25 hours at room temperature* – At PQCL (0.0600 ng/mL), bias: -5.7%, CV: 7.3% – At PQCH (7.5 ng/mL), bias: -5.7%, CV: 1.3% *Processed Samples for 168.5 hours at* 4°C – At PQCL (0.0600 ng/mL), bias: -0.7%, CV: 5% – At PQCH (7.5 ng/mL), bias: -4.5%, CV: 0.9% *Stability in human whole blood for 1 hour on ice* – At PQCL (0.0600 ng/mL), bias: -3.4%, CV: 4% – At PQCH (7.5 ng/mL), bias: -2.4%, CV: 1.4% *Stability in human whole blood for 1 hour at room temperature* – At PQCL (0.0600 ng/mL), bias: -3.5%, CV: 3.5% – At PQCH (7.5 ng/mL), bias: -1.7%, CV: 2.1%
Freeze-Thaw stability	*4 freeze/thaw cycles at -80°C* – At PQCL (0.0600 ng/mL), bias: -9.5%, CV: 4% – At PQCH (7.5 ng/mL), bias: -6.9%, CV: 0.5% *4 freeze/thaw cycles at -20°C* – At PQCL (0.0600 ng/mL), bias: -10%, CV: 3.2% – At PQCH (7.5 ng/mL), bias: -8.3%, CV: 1.5%
Long-term storage	*161 days at -80°C* – At PQCL (0.0600 ng/mL), bias: 4%, CV: 5.6% – At PQCH (7.5 ng/mL), bias: 6.8%, CV: 0.5% *161 days at -20°C* – At PQCL (0.0600 ng/mL), bias: 12.3%, CV: 4.5% – At PQCH (7.5 ng/mL), bias: 7.9%, CV: 3.3% *315 days at -20°C* – Not stable with %bias of -22% At PQCL (0.0600 ng/mL)
Stock solution stability	Stable for 80 days at 4ºC in LoBind tubes and for 89 days at 4ºC in polypropylene tubes The percentage differences between the baseline and stored solutions were within 10% for 80 (in LoBind tubes) and 89 days (in polypropylene tubes) at 4ºC. However, it fails to meet acceptance criteria for 316 days (in LoBind tubes) at 4ºC with % difference of -13.7%.
Working stock solution stability	Stable for 80 days at 4ºC in LoBind tubes Working solution stability in polypropylene tubes was not assessed. The percent differences between the baseline and stored solutions in LoBind tubes were within 10% for 84 days however fails to meet acceptance criteria for 316 days with % difference of -28.1%
Reinjection reproducibility	176.25 hours at *-4°C* – At PQCL (0.0600 ng/mL), %bias: 7%, CV: 3.9% – At PQCH (7.5 ng/mL), %bias: -0.5%, CV: 3%
Carry-over	Not significant
Recovery	– Analyte: 90.1% overall the concentrations 0.06, 0.75, and 7.5 ng/mL – Internal standard: 88.7%

Parameters	Method VAL442 and Amendment 01
In-Study Performance	The in-study performance was acceptable, including standard curve performance, QC performance, method reproducibility, ISR [trial PN-235-01: 181 (10% of 1000 + 6% of 1346 plasma samples), trial PSO1002: 33 (10%) plasma samples, trial PSO1003: 314 (10% of 1000 + 5% of 4283 plasma samples), trial PSO2001: 131 (10% of 1000 + 5% of 619 plasma samples), trial PSO2002: 101 (10% of 1000 + 5% of 125 plasma samples)], and sample analysis within the established stability period.

Source: Reviewer-generated table from Method VAL442 and Amendment 01.
Abbreviations: LC-MS/MS, liquid chromatography and mass spectroscopy; CV, coefficient of variation; QC, quality control, LLOQ, lower limit of quantification; EDTA, ethylenediaminetetraacetic acid; PQCLOQ, provisional quality control limit of quantification; PQCL, provisional quality control low concentration; PQCM, provisional quality control medium concentration; PQCH, provisional quality control high concentration; PQCOR, provisional quality control our-of-range concentration

Table 123. Performance of Bioanalytical Methods BA13914 and BA14082

Parameters	Method BA13914	BA14082 (Partial Validation)
Analytical site	(b) (4)	(b) (4)
Method description	Protein precipitation followed LC-MS/MS	Protein precipitation using a stable isotope labeled internal standard and LC-MS/MS
Matrix	Human EDTA plasma	
Calibration curve	9 calibration points – 0.0185 to 18.5 ng/mL for run IDs VA-1 through VA-12 – 0.0200 to 20.0 ng/mL for run ID VA-14	9 calibration points 0.0200 to 20.0 ng/mL
Cumulative accuracy (%bias)	– *For run IDs VA-1 through VA-12,* -2.0% to 1.8% – *For run ID VA-14,* -1.9% to 1.8%	-3.4% to 3%
Cumulative precision (%CV)	– *For run IDs VA-1 through VA-12,* ≤4.2% – *For run ID VA-14, ≤2.5%*	≤1.8%
Regression model and weighting	$1/x^2$ weighted linear regression	
QC concentrations		
QC performance in blank human plasma	*For run IDs VA-1 through VA-12* QC LLOQ: 0.0556 ng/mL QC Low: 5.56 ng/mL QC Mid: 13.9 ng/mL QC High: 139 ng/mL *For run ID VA-14* QC LLOQ: 0.06 ng/mL QC Low: 6 ng/mL QC Mid: 15 ng/mL QC High: 150 ng/mL	0.02 ng/mL (LLOQ), 0.06, 1.5, 6, 15, 150
Cumulative accuracy (%bias)	2.3% to 10.3% -1.8% to 3.3% (partial validation)	-2.2 to 4.8%
Cumulative precision (%CV)	≤5.4% ≤6.1% (partial validation)	≤7.6%
Internal Standard	Stable isotope labelled internal standard (PN25503)	Stable isotope labelled internal standard (PN25503)

Parameters	Method BA13914	BA14082 (Partial Validation)
Selectivity	– Response in at least 90% of the blank samples (including hemolytic and lipemic blank) at the retention time of icotrokinra was <20.0% of the mean response for JNJ-77242113 in the 6 samples spiked at 0.0185 ng/mL. – Response in at least 90% of the blank samples at the retention time of the internal standard was <5.0% of the mean response at the retention time of the internal standard in the 6 samples spiked at 0.0185 ng/mL.	– Response in all blank samples (including hemolytic and lipemic blank) at the retention time of icotrokinra was ≤20.0% of the mean response for Icotrokinra in the 6 samples spiked at 0.0200 ng/mL. Response in all blank samples at the retention time of the internal standard was ≤5.0% of the mean response at the retention time of the internal standard in the 6 samples spiked at 0.0200 ng/mL.
Matrix effect	No significant matrix effects were observed. – At 0.0556 and 13.9 ng/mL, %bias: ≤15%; CV%: ≤15%	No significant matrix effects were observed. At 0.06 and 15 ng/mL, %bias: ≤15%; CV%: ≤15%
Specificity	*Analyte from internal standard Interference* – For each replicate of the zero sample, the response (peak area) at the retention time of icotrokinra was ≤20.0% of its mean response in the 6 reference samples spiked at 0.0185 ng/mL. *Internal standard from interference* – For each replicate of the sample at 18.5 ng/mL, the response (peak area) at the retention time of PN25503 was ≤5% of its mean response in the 6 reference samples spiked at 0.0185 ng/mL. *Reference QC samples* – %Bias: ≤15%; CV%: ≤15%	*Analyte from internal standard Interference* – For each replicate of the zero sample, the response (peak area) at the retention time of icotrokinra was ≤20% of its mean response in the 6 reference samples spiked at 0.02 ng/mL. *Internal standard from interference* – For each replicate of the sample at 20 ng/mL, the response (peak area) at the retention time of PN25503 was ≤5% of its mean response in the 6 reference samples spiked at 0.02 ng/mL. *Reference QC samples* %Bias: ≤15%; CV%: ≤15%
Hemolysis effect	One lot tested, no significant effect	One lot tested at 0.06 and 15 ng/mL, no significant effect with %Bias: -2.1% to 3.5%, CV%: ≤4.3%
Lipemic effect	One lot tested, no significant effect	One lot tested at 0.06 and 15 ng/mL, no significant effect with %Bias: 0.9% to 2%, CV%: ≤5.5%
Dilution linearity and hook effect	10-fold dilutions were validated with dilution QC at 139 ng/mL – %Bias: -3.4%; %CV: 0.7%	-

Parameters	Method BA13914	BA14082 (Partial Validation)
Bench-top/process stability	*Stability in human whole blood for 2 hours at 0°C* – At 0.0556 ng/mL, %bias: 8.4%, CV: 3.5% – At 6.94ng/mL, %bias: 0%, CV: 0.3% *Stability in human whole blood for 2 hours at room temperature* – At 0.0556 ng/mL, %bias: -0.3%, CV: 0.7% – At 6.94ng/mL, %bias: -0.5%, CV: 2.5% *Stability in human plasma for at least 21 hours at room temperature* – At QC LLOQ (0.0556 ng/mL), %bias: -9.5%, CV: 1.1% – At QC Mid (13.9 ng/mL), bias: -6.7%, CV: 1% *Autosampler stability at least 144 at +4°C in processed sample* – At QC LLOQ (0.0556 ng/mL), %bias: -10.4%, CV: 2.5% – At QC Mid (13.9 ng/mL), %bias: -7.8%, CV: 2.3%	-
Freeze-Thaw stability	*5 freeze/thaw cycles at -70°C* – At QC LLOQ (0.0556 ng/mL), %bias: -10.7%, CV: 1.7% – At QC Mid (13.9 ng/mL), %bias: -6.4%, CV: 1.7% *4 freeze/thaw cycles at -70°C* at the overcurve level – At QC Mid (13.9 ng/mL), %bias: -9.5%, CV: 0.2% *5 freeze/thaw cycles at -20°C* – At QC LLOQ (0.0556 ng/mL), %bias: -8.8%, CV: 5.1% – At QC Mid (13.9 ng/mL), %bias: -6.8%, CV: 0.3% *4 freeze/thaw cycles at -20°Cat the overcurve level* – At QC Mid (13.9 ng/mL), %bias: -9.6%, CV: 0.1%	-
Long-term storage	*496 days at -70°C* – At QC LLOQ (0.0556 ng/mL), %bias: -3.7%, CV: 3.7% – At QC Mid (13.9 ng/mL), %bias: -12.3% to -5.4%, CV: ≤2% *496 days at -20°C* – At QC LLOQ (0.0556 ng/mL), %bias: -5.3%, CV: 6% – At QC Mid (13.9 ng/mL), %bias: -12.9% to 6%, CV: 1.3%	-

Parameters	Method BA13914	BA14082 (Partial Validation)
Stock solution stability	*At 0.0926 mg/mL* – 24 hours at room temperature, bias: -0.4%, CV: 1.5% – 27 days at -20°C, bias: -0.5%, CV: 1.2% *At 0.100 mg/mL* – 26 hours at room temperature, bias: -0.8%, CV: 0.9% – 135 days at -20°C, bias: 2.1%, CV: 0.9%	
Working stock solution stability	*PN25503 (internal standard)* – Stable for 24 hours at room temperature, %bias: 3.6%, CV: 9.7% – Stable for 330 days at -20°C, %bias: -4.1%, CV: 0.5%	-
Reinjection reproducibility	*161 hours at +4°C in processed sample (original calibration curve) at 0.0556, 5.56, and 13.9 ng/mL* – %bias: 8.3% to 11.5%%, CV≤2.2% *161 hours at +4°C in processed sample (reinjected calibration curve) at 0.0556, 5.56, and 13.9 ng/mL* – %bias: 11.4% to 11.8%%, CV≤1.8%	-
Carry-over	Not significant	No significant carry-over
Recovery	*Icotrokinra* 90.7% for QC LLOQ (0.0556 ng/mL) 91.2% for QC Low (5.56 ng/mL) 91.2% for QC Mid (13.9 ng/mL) *Internal standard at 13.9 ng/mL* 94.6%	-
In-Study Performance	The in-study performance was acceptable, including standard curve performance, QC performance, method reproducibility, ISR [trial PSO1006: 107 (10.9%) plasma samples, trial PSO1007: 42 (10.7%) plasma samples, trial PSO1009: 92 (10.9%) plasma samples, and trial PSO3001: 276 (10% of 1000 + 5% of 3480 plasma samples)], and sample analysis within the established stability period. No incurred sample reproducibility was assessed for Trials PSO3002, PSO3003, and PSO3004 because this was already done in a similar subject population in Trial PSO3001.	

Source: Reviewer-generated table based on Methods BA13914 and BA14082.
Abbreviations: LC-MS/MS, liquid chromatography and mass spectroscopy; CV, coefficient of variation; QC, quality control, LLOQ, lower limit of quantification; EDTA, Ethylenediaminetetraacetic acid

Table 124. Performance of Bioanalytical Methods BA13692 and BA14083

Parameters	Method BA13692 ((b) (4)-J01-R4518) and (b) (4)-J01-R4518A1	Method BA14083 (Partial Validation)
Analytical site	(b) (4)	(b) (4)
Method description	Protein precipitation followed by SPE using a stable isotope labeled internal standard and LC-MS/MS	Protein precipitation using a stable isotope labeled internal standard and LC-MS/MS
Matrix	Human EDTA plasma	Human EDTA plasma
Calibration curve	8 calibration points 0.0200 ng/mL to 10 ng/mL	8 calibration points 0.0200 ng/mL to 10 ng/mL

Parameters	Method BA13692 ((b) (4) -J01-R4518) and (b) (4) -J01-R4518A1	Method BA14083 (Partial Validation)
Cumulative accuracy (%bias)	-4.8 to 3.9%	-3.0 to 2.0%
Cumulative precision (%CV)	≤5.9%	≤4%
Regression model and weighting	$1/x^2$ weighted Linear regression	
QC concentrations		
QC performance in blank human plasma	LLOQ QC: 0.0200 ng/mL Low QC: 0.0600 ng/mL Mid QC 1: 0.750 ng/mL Mid QC 2: 3 ng/mL High QC: 7.50 ng/mL	LLOQ QC: 0.0200 ng/mL Low QC: 0.0600 ng/mL Mid QC 1: 0.750 ng/mL Mid QC 2: 3 ng/mL High QC: 7.50 ng/mL
Cumulative accuracy (%bias)	-8 to 0.9%	-1 to 1%
Cumulative precision (%CV)	≤9.3%	≤6.7%
Internal Standard	Stable isotope labelled internal standard (PN25503)	Stable isotope labelled internal standard (PN25503)
Selectivity	No interference observed in lots of blank humans EDTA plasma.	6 lots of blank human EDTA plasma were tested. No interferences were detected at the retention time of the compound or the internal standard.
Matrix effect	No significant matrix effects were observed in 6 different matrix lots for analyte at High QC, Mid QC 1, Mid QC2, and Low QC with CV% ≤3.9%	6 lots of blank human EDTA plasma were tested. No interferences were detected at the retention time of the compound or the internal standard.
Hemolysis effect	No obvious hemolysis effect was observed. One lot tested at Low QC (0.06 ng/mL) with %bias: -13.7%, CV%: ≤3.1% and at High QC (7.5 ng/mL) with %bias: -2.8%, CV%: ≤1.2%	No obvious hemolysis effect was observed. One lot tested at Low QC (0.06 ng/mL) with %bias: 1.3%, CV%: ≤3.3% and at High QC (7.5 ng/mL) with %bias: -2.4%, CV%: ≤3.9%
Lipemic effect	No obvious hyperlipidemic effect observed. One lot tested at Low QC (0.06 ng/mL) with %bias: -10.8%, CV%: ≤5.6% and at High QC (7.5 ng/mL) with %bias: -2.3%, CV%: ≤1%	No obvious hyperlipidemic effect observed. One lot tested at Low QC (0.06 ng/mL) with %bias: -2.3%, CV%: ≤1.8% and at High QC (7.5 ng/mL) with %bias: -1.5%, CV%: ≤1.4%
Dilution linearity and hook effect	150 ng/mL diluted 20-fold, %Bias: -6.7, CV%: ≤1.4%	

Parameters	Method BA13692 (b)(4)-J01-R4518) and (b)(4)-J01-R4518A1	Method BA14083 (Partial Validation)
Bench-top/process stability	*Stability in human whole blood for 2 hours at 0°C* – At Low QC (0.06 ng/mL): %bias: -3.8%, CV%: ≤5.5% – At High QC (7.5 ng/mL): %bias: -1.5%, CV%: ≤1.1% *Stability in human whole blood for 2 hours at room temperature* – At Low QC (0.06 ng/mL): %bias: -0.4%, CV%: ≤4.4% – At High QC (7.5 ng/mL): %bias: -0.4%, CV%: ≤1.6% *Stability in human plasma for at least 19 hours at room temperature* – At Low QC (0.06 ng/mL): %bias: -10.5%, CV%: ≤5.3% – At High QC (7.5 ng/mL): %bias: 1.5%, CV%: ≤0.9% *Stability in human plasma for at 7 days at -80°C* – At Low QC (0.06 ng/mL): %bias: -12.8%, CV%: ≤6.2% – At High QC (7.5 ng/mL): %bias: 0.7%, CV%: ≤1.5% *Autosampler stability at least 76 at +5°C in processed sample* – At Low QC (0.06 ng/mL), Mid QC 1 (0.75 ng/mL), Mid QC2 (3 ng/mL), and High QC (7.5 ng/mL): %bias: -5.7% to 1.3%, CV%: ≤3.2%	Process stability: Stable for at least 99 hours at autosampler temperature for High QC, Mid QC 1, Mid QC 2, and Low QC with %bias: -0.3% to 1.3%, CV%: ≤6.7%
Freeze-Thaw stability	*5 freeze/thaw cycles at -70°C* – At Low QC (0.06 ng/mL): %bias: -10.3%, CV%: ≤4.1% – At High QC (7.5 ng/mL): %bias: 1.6%, CV%: ≤0.8% *5 freeze/thaw cycles at -20°C* – At Low QC (0.06 ng/mL): %bias: -12.7%, CV%: ≤5.1% – At High QC (7.5 ng/mL): %bias: 0.4%, CV%: ≤1%	
Long-term storage	*798 days at -70°C* – At Low QC (0.06 ng/mL): %bias: -9%, CV%: 7.1% – At High QC (7.5 ng/mL): %bias: -7.1%, CV%: 1.4% *384 days at -20°C* – At Low QC (0.06 ng/mL): %bias: -12%, CV%: 5% – At High QC (7.5 ng/mL): %bias: -9.2%, CV%: 1%	

Parameters	Method BA13692 ((b) (4)-J01-R4518) and (b) (4)-J01-R4518A1	Method BA14083 (Partial Validation)
Stock solution stability	Stable for 23 hours at RT under light at 400 ng/mL, %bias: 6.2%, CV%: ≤2.5% Stable for 43 days at -20°C at 400 ng/mL, %bias: 7.6%, CV%: ≤3%	
Working stock solution stability	Stable for 23 hours at RT under light for ULOQ (200 ng/mL) and LLOQ (0.4 ng/mL), %bias: 2.4% to 5.5%, CV%: ≤6.9% Stable for 43 days at -20°C for ULOQ (200 ng/mL), %bias: 2.8%, CV%: ≤2.4% Stable for 50 days at -20°C for LLOQ (0.4 ng/mL), %bias: 3.6%, CV%: ≤2.2%	
Reinjection reproducibility	82 hours at autosampler temperature of 5°C – At Low QC (0.06 ng/mL), Mid QC 1 (0.75 ng/mL), Mid QC2 (3 ng/mL), and High QC (7.5 ng/mL): %bias: -2.9% to -1.5 %, CV%: ≤3.5%	Stable for 107 hours at autosampler temperature for High QC, Mid QC 1, Mid QC 2, and Low QC with %bias: -0.5% to 0.5%, CV%: ≤4.1%
Carry-over	Not significant, ≤ 19.9% for analyte and ≤ 5% for internal standard	No significant carry-over
Recovery	Total recovery of 101.4% (peak area) and 101% (peak area ratio) for the analyte at High QC, Mid QC 1, Mid QC 2, and Low QC. Total recovery of 101.5% (peak area) and 99.6% (peak area ratio) for internal standard at 10 ng/mL	Total recovery of 100.8% (peak area) and 101.7% (peak area ratio) for the analyte at High QC, Mid QC 1, Mid QC 2, and Low QC.
In-Study Performance	The in-study performance was acceptable, including standard curve performance, QC performance, method reproducibility, ISR [trial PSO1004: 60 (15%) plasma samples, trial PSO3001: 83 (10.5%) plasma samples], and sample analysis within the established stability period	

Source: Reviewer-generated table based on Methods BA13692 ((b) (4) J01-R4518), (b) (4)-J01-R4518A1, and Method BA14083.
Abbreviations: LC-MS/MS, liquid chromatography and mass spectroscopy; CV, co fficient of variation; QC, quality control; LLOQ, lower limit of quantification; EDTA, Ethylenediaminetetraacetic acid

Table 125. Performance of Bioanalytical Methods VAL447 and VAL446

Parameters	Method VAL447	Method VAL446
Analytical site	(b) (4)	(b) (4)
Method description	LC-MS/MS	LC-MS/MS
Matrix	Human feces	Human urine stabilized with 0.1% Triton-X and stored in polypropylene tubes
Calibration curve	8 calibration points 0.0200 ng/mL to 10 ng/mL	8 calibration points 0.0200 ng/mL to 200 ng/mL
Cumulative accuracy (%bias)	-2.5 to 2.3%	-3.8 to 4.5%

Parameters	Method VAL447	Method VAL446
Cumulative precision (%CV)	≤5.6%	≤7.5%
Regression model and weighting	$1/x^2$ weighted Linear regression	
QC concentrations		
QC performance in blank human plasma	FHQCLOQ: 0.0200 ng/mL FHQCL: 0.0600 ng/mL FHQCM 0.600 ng/mL FHQCH: 7.50 ng/mL FHQCOR: 50 ng/mL	UQCLOQ: 0.200 ng/mL UQCL: 0.600 ng/mL UQCM: 7.50 ng/mL UQCH: 150 ng/mL UQCOR: 1000 ng/mL
Cumulative accuracy (%bias)	0.1 to 8.5%	-2.8 to 5.5%
Cumulative precision (%CV)	≤15.8%	≤13.8%
Internal Standard	Stable isotope labelled internal standard (PN25503)	Stable isotope labelled internal standard (PN25503)
Selectivity	No interference observed in 2 different matrix lots	No interference observed in 6 different matrix lots
Matrix effect	No interference observed in 6 different matrix lots at 0.0200 ng/mL with %bias: -3.5% to 6.5%, CV%: ≤8.2%	No interference observed in 6 different matrix lots at 0.200 ng/mL with %bias: -4% to 6.5%, CV%: ≤9%
Dilution linearity and hook effect	50 ng/mL diluted 10-fold, %Bias: 2.6%, CV%: 6.6%	1000 ng/mL diluted 20-fold, %Bias: 0%, CV%: 3.3%
Bench-top stability	*Stability for 25 hours at room temperature* – At FHQCL (0.06 ng/mL): %bias: 6.3%, CV%: 7.5% – At FHQCH (7.5 ng/mL): %bias: 2.7%, CV%: 4.6%	*Stability for 24 hours at room temperature* – At UQCL (0.6 ng/mL): %bias: -10%, CV%: ≤6.2% – At UQCH (150 ng/mL): %bias: 0.7%, CV%: ≤1.1%
Freeze-Thaw stability	-	*4 freeze/thaw cycles at -80°C* – At UQCL (0.6 ng/mL): %bias: -2.8%, CV%: ≤7.3% – At UQCH (150 ng/mL): %bias: 1.3%, CV%: ≤2%
Long-term storage	*241 days at -80°C* – At FHQCL (0.06 ng/mL): %bias: 15%, CV%: 4.9% – At FHQCH (7.5 ng/mL): %bias: 5.9%, CV%: 4.9%	*270 days at -80°C* – At UQCL (0.6 ng/mL): %bias: 9.7%, CV%: 3.2% – At UQCH (150 ng/mL): %bias: 5.3%, CV%: 2.7%
Carry-over	Not significant	Not significant
In-Study Performance	The in-study performance was acceptable, including standard curve performance, QC performance, and sample analysis within the established stability period of 270 days at -80°C.	The in-study performance was acceptable, including standard curve performance, QC performance, and sample analysis within the established stability period

Source: Reviewer-generated table from Methods Method VAL447 and VAL446.
Abbreviations: LC-MS/MS, liquid chromatography and mass spectroscopy; CV, coefficient of variation; QC, quality control; LLOQ, lower limit of quantification; EDTA, Ethylenediaminetetraacetic acid; FHQCLOQ, full-historical quality control limit of quantification; FHQCL, full-historical quality control low concentration; FHQCM, full-historical quality control medium concentration; FHQCH, full-historical quality control high concentration; FHQCOR, full-historical quality control out-of-range

Table 126. Method Modifications and Cross-Validation

Methods	Details
Methods VAL442 (b) (4) and BA13692 (b) (4)	Method BA13692 ((b) (4)-J01-R4518 + (b) (4)-J01-R4518A1) used modified chromatographic to increase throughput. See Table 124 for the performance of calibration curve and QC for methods Method BA13692 and BA14083. For cross-validation, 18 spiked samples prepared at (b) (4), at three concentration levels (low, 0.0600 ng/mL; medium, 0.75 ng/mL; and high 7.5 ng/mL) were analyzed with (b) (4) method BA13692 with %bias of 9.5% to 11.5% and %CV ≤4%.
Methods VAL442 (b) (4) and BA13914 (b) (4)	Method BA13914 used a more sensitive instrument and chromatographic conditions. The sample preparation was adapted to a protein precipitation with evaporation of the supernatant and reconstitution. See Table 123 for the performance of calibration curve and QC for methods Method BA13914 and BA14082. For cross-validation, 18 spiked samples prepared at (b) (4), at three concentration levels (low, 0.0600 ng/mL; medium, 0.75 ng/mL; and high 7.5 ng/mL) were analyzed with (b) (4) method with %bias -14.6% to -4.5%. 30 study samples analyzed with both methods with 100% of the samples within ±20% difference.
Methods BA13914 (b) (4) and BA13692 (b) (4)	See Table 124 for the performance of calibration curve and QC for Methods BA13692 and BA14083. For cross-validation, 18 spiked samples prepared at (b) (4), at three concentration levels (low, 0.0600 ng/mL; medium, 6 ng/mL; and high 155 ng/mL) were analyzed with (b) (4) with %bias 0.7% to 4.3%, %CV ≤2.4%. 30 study samples analyzed with both methods with 100% of the samples within ±20% difference.
Methods BA13914 (b) (4) and BA14082 (b) (4)	This is a partial validation. The original method BA13914 (b) (4) was modified to enhance chromatographic separation and to adapt the temperature for the evaporation of the supernatant under method BA14082 (b) (4). See Table 123 for the performance of calibration curve and QC for methods Method BA13914 and BA14082. For cross-validation, 24 spiked samples prepared at 4 concentration levels (low, 0.0600 ng/mL; medium, 6 ng/mL; and high 155 ng/mL) were analyzed with both methods with 100% of the samples within ±20% difference. 30 study samples analyzed with both methods with 100% of the samples within ±20% difference.

Methods	Details
Method BA14082 (b) (4) and BA14083 (b) (4) and between Method BA13629 (b) (4) and BA14083 (b) (4)	Transfer of the validated method from (b) (4) ((b) (4) method number (b) (4) -NLSML-2924) to (b) (4) See Table 124 for the performance of calibration curve and QC for methods Method BA13692 and BA14083, respectively. For cross-validation between BA13629 ((b) (4) original method) and BA14083 ((b) (4) adapted method), 24 spiked samples prepared at (b) (4), at 4 concentration levels (0.06, 0.75, 3, and 7.5 ng/mL), were analyzed with assay BA13629 and BA14083 with %bias of -4.8% to -2.4% and CV% of ≤3.6%. In addition, 30 study samples were analyzed with both methods and 29 of 30 within ±20% difference. For Cross-validation between BA14082 ((b) (4) -NLSML-2924, adapted method) and BA14083 ((b) (4) adapted method), 24 spiked samples prepared at (b) (4), at 4 concentration levels (0.06, 1.5, 6, and 15 ng/mL) were analyzed using method BA14083 with %bias of 2.2% to +7.3% and CV% of ≤9.7%. In addition, 30/30 samples analyzed with both methods were within ±20% difference.

Source: Reviewer-generated table based on the cross-validation of the listed methods.
Abbreviations: QC, quality control; CV, coefficient of variation

19.4.3.2. Quantification of Serum Biomarkers

Biomarker assessments were performed using patient serum samples to assess disease related PD changes in psoriasis patients following treatment with icotrokinra or placebo. Assessments included the evaluation of IL-17A, IL-17F, IL-22, IL-19 and BD-2 levels in serum samples collected from Study PSO3001 at Week 0, Week 4 and Week 16. Healthy control samples were also included for comparison. Serum from normal healthy donors was purchased from (b) (4) and (b) (4). A total of 113 or 114 serum samples in the icotrokinra group and 52 or 53 serum samples in the placebo were used to measure the concentration of the biomarkers.

Serum IL-17A was measured with S-PLEX assay by Meso Scale Discovery (MSD). Serum IL-17F was measured using Single Molecule Counting (SMC) high sensitivity immunoassay by Millipore. IL-22 was measured with a custom SMC based assay by Millipore. Serum IL-19 was measured with ELISA by R&D Systems. BD-2 was measured with a custom assay by MSD. These assays were qualified internally. The performance of these assays kit is acceptable, and it is summarized in Table 127.

Table 127. Performance of Assay Kits for Quantification of Serum Biomarkers

Parameters	IL-17A	IL-17F	IL-19	IL-22	BD-2
Assay Kit	MSD S-PLEX IL-17A	MilliporeSigma SMC™ IL-17F	Human IL-19 Quantikine ELISA Kit; D1900	MilliporeSigma highly sensitive single molecule counting (SMC) assay kit	Qualification of MSD BD-2 assay kit
Assay Principles	S-PLEX achieves improved sensitivity through TURBO-TAG and TURBO-BOOST reagents, which generate more ECL signal than SULFO-TAG detection formats when combined with labeled antibodies. The streptavidin-coated plates deliver high sensitivity with consistent performance and excellent precision across batches	The SMC™ Human IL-17F immunoassay quantifies IL-17F in human plasma and serum using fluorescent sandwich immunoassay technology. Precoated paramagnetic beads with IL-17F-specific capture antibodies are combined with standards and samples in microplate wells, allowing IL-17F binding during incubation. After washing away unbound molecules, fluor-labeled detection antibodies are added to complete the immunosandwich by binding to captured IL-17F. Elution buffer releases the labeled antibody-protein complexes from beads, which are then transferred to a final microplate. The Erenna® or SMCxPRO™	This is a sandwich ELISA for human IL-19 detection. Samples are added to wells pre-coated with anti-IL-19 antibody, which captures any IL-19 present. After washing, HRP-conjugated detection antibody binds to captured IL-19. TMB substrate produces blue color proportional to IL-19 concentration. Sulfuric acid stops the reaction, turning the solution yellow. Absorbance is read at 450nm and 540nm to quantify IL-19 levels.	This IL-22 assay combines traditional sandwich ELISA methodology with specialized instrumentation for signal detection. A capture antibody bound to a plastic well surface binds to IL-22 protein and a fluorochrome-coupled detection antibody binds to the antibody-protein complex. The complete antibody-protein-antibody complex is transferred to a 384-well plate where fluorochrome signals are measured using imaging technology.	MSD assays enable rapid protein target measurement in small sample volumes using a custom sandwich immunoassay designed for Janssen. Pre-coated capture antibodies are immobilized on defined spots of MSD SECTOR plates. Samples and electrochemiluminescent-labeled detection antibodies (MSD SULFO-TAG™) are added during incubation periods to form antibody-analyte sandwiches. MSD buffer creates optimal conditions for electrochemiluminescence (ECL), and applied voltage causes captured labels to emit light proportional to analyte concentration. The instrument quantifies light intensity to provide precise analyte measurements for each sample.

Parameters	IL-17A	IL-17F	IL-19	IL-22	BD-2
		System detects and counts fluorescent molecules. The count directly correlates to IL-17F concentration, with unknown sample concentrations determined via standard curve interpolation.			
Standard curve range	0.059 to 240 pg/mL	0.098 to 100 pg/mL	31.25 to 2,000 pg/mL	0.24 to 250 pg/mL	9.8 to 5000 pg/mL
CV%	9-18.04%.	6.80-24.69%.	1-13.1% for Standards 1 through 9	2.24-16.46%	3.36-6.13%
Calibration curve recovery	94.48%-110.03%	90.22%-111.95%	93.0-104.8%	97.20 to 113.47%	93.98%-115.87%
CV%	5.12-8.4%	2.56-25.80%	0 to 20.3% for Standard 1 through 9 (2000 pg/mL-7.81pg/mL)	2.24 to 16.46%	1.44-6.89%
Calibrator curve fit	4-parameter logistic (or sigmoidal dose-response) model with a $1/Y^2$ weighing	4-parameter logistic (or sigmoidal dose-response) model	4-parameter logistic model	4-parameter logistic model	4-parameter logistic (or sigmoidal dose-response) model with a $1/Y^2$ weighing
Interassay Variability	Normal human serum samples (N=10) were tested for IL-17A levels on two subsequent days. The samples were frozen at -80°C in between the two measurements. The CV ranged from 0.68-13.44%.	Normal human serum samples (N=6) were tested for IL-17F levels on two subsequent days. The samples were frozen at -80°C in between the two measurements. The CV ranged from 0.47-17.82%.	Normal human serum samples (N=4) were tested for IL-22 levels on two separate runs. The CV ranged from 17.1-25.3%.	Normal human serum samples (N=6) were tested for IL-22 levels on either 7 or 8 different days. The CV ranged from 6.76 to 10.37%.	Normal human serum samples (N=16) were tested for IL-22 levels on two subsequent days. The CV ranged from 0.76-20.82%.

Parameters	IL-17A	IL-17F	IL-19	IL-22	BD-2
Endogenous levels (background)	0.10-1.41pg/mL	0.64-4.79 pg/mL	Healthy samples were 38-279 pg/mL.	1.64-116.32 pg/mL in healthy subjects and 3.79 – 28.1 pg/ml in psoriasis	Healthy samples were 111.38-16768.36 pg/mL
Freeze thaw stability	One freeze-thaw cycle at -80°C. The %CV ranged from 0.68-13.44%	4 freeze-thaw cycle at -80°C. The %CV ranged from 5.95-17.5%.	4 freeze-thaw cycle at -80°C for 24 hours. The CV ranged from 1.39-5.82%.	4 freeze-thaw cycle at -80°C. The %CV ranged from 2.60 to 7.81%.	4 freeze-thaw cycle at -80°C for 24 hours. The %CV ranged from 1.39-5.82%
Spike recovery	At 0.59 to 240 pg/mL was 100±25%.	At 0.313 to 5 pg/mL was 100±25% with the exception of two normal subjects and one Psoriatic arthritis donor having recoveries of 127.27%, 125.67% and 128.14 % for the 5 pg/mL IL-17F spike	At 9.8 to 39.1 pg/mL was 77% to 186%.	At 5 to 60 pg/mL was 83.47 to 102.14%.	At 9.8 to 39.1 pg/mL was 77% to 186%.
Dilution linearity	Samples were diluted up to 1:64. At least 75% of the samples passed the acceptable recovery criteria at all dilutions tested	Samples were diluted up to 1:10. At least 75% of the samples passed the acceptable recovery criteria at all dilutions tested	Samples were diluted up to 1:160. At least 75% of the samples passed the acceptable recovery criteria at dilutions tested.	Samples were diluted up to 1:16. At least 75% of the samples passed the acceptable recovery criteria at dilutions tested. One donor demonstrated poor dilution linearity, having over-recovered for dilutions greater than a 2-fold dilution.	The samples were diluted up to 1:160. At least 75% of the samples passed the acceptable recovery criteria at dilutions tested.

Source: Reviewer-generated table based on the methos validation reports for the listed serum biomarkers.
Abbreviations: IL, interleukin; CV, coefficient of variation; HRP, horseradish peroxidase; TMB, 3,3',5,5'-tetramethylbenzidine; BD-2, β-defensin-2

19.4.4. Model Risk Assessment

The pharmacometrics analyses were focused on assessing the appropriateness of dosing in moderate-to-severe PsO patients, especially in those with substantial exposure increase in patients with moderate/severer RI where kidney is the main route of elimination for the absorbed drug (Table 128).

Table 128. FDA – Assessment of Model Risk

Parameters	Details
Question of interest	Is the proposed dosage appropriate for moderate-to-severe PsO patients, including adolescents and adults, and patients with moderate/severe RI?
Context of use	PopPK was used to evaluate the patient factors on exposure and generate individual exposure for E-R analysis. E-R analyses were conducted to understand exposure dependent changes in efficacy and safety in patients.
Decision consequence	Low/Medium • Benefit/risk in the overall ITT inclusive of adults and adolescents taken 200 mg QD is supported by 4 Ph3 studies. • Patients with moderate/severe renal impairment experienced twice the infection rate of other patients, suggesting increased safety risk from overexposure at 200 mg QD. Dosage adjustment to achieve equivalent exposure may reduce this safety risk. Exposure of moderate/severe renal impaired patients without dosage adjustment remains in the exposure range of phase 3 studies.
Model influence	Low: E-R analyses serve as supportive evidence for the studied dosage in ITT including adolescents and adults. Medium: Given limited data in PsO patients with moderate/severe RI, popPK can be used to propose alternative dosages in these patients based on exposure matching to those with normal/mild RI.
Model risk	Low/Medium

Source: FDA analysis.
Abbreviations: PsO, psoriasis, popPK, population PK, E-R, exposure-response, ITT, intent-to-treat population, RI, renal impairment

The overall model risk is considered low-to-medium. In line with the determined model risk and specific objectives, following model evaluation/additional analysis was conducted for the respective methodologies as outlined in Table 129.

Table 129. FDA – Model Evaluation/Additional Analysis

Methodology	Objective	Model evaluation	Section
PopPK	• Characterize PK profile of icotrokinra • Evaluate patient factors that substantially impact PK • Predict individual exposure for subsequent E-R analysis	Standard model evaluation	19.4.5
Exposure-efficacy	• Characterize E-R relationship • Evaluate if age/weight impact E-R	• Standard model evaluation for PASI90 and IGA0/1 response	19.4.6.1; 19.4.6.2

Methodology	Objective	Model evaluation	Section
Exposure-safety	• Characterize E-R relationship • Evaluate risk in subgroup (i.e., ADA+ with high titers, patients with moderate/severe RI) due to overexposure	• Standard model evaluation for AEs, SAEs, infections, and AE leading to discontinuations. • Independent analysis to assess safety risk in patient subgroups	19.4.6.3-19.4.6.5

Source: FDA analysis.
Abbreviations: E-R, exposure-response, ADA, antidrug antibodies, AEs, adverse events, SAEs, serious adverse events

19.4.5. Population PK Analysis

19.4.5.1. Executive Summary

The FDA's Assessment

Icotrokinra PK was adequately described by a linear 1-compartment population PK model with first-order absorption and first-order elimination. Significant covariates with their respective impact on dosage are listed as follows:

- Exposures were comparable between adults and adolescents, supporting same flat dosage.
- Food significantly decreased bioavailability when taken with food, supporting icotrokinra taken under fasting condition.
- ADA positivity resulted in 1.3-fold higher AUC, with participants having ADA titer ≥100 showing 2-fold higher AUC, where no change in efficacy and safety was observed.
- Mild renal impairment (RI) no meaningful impact, while moderate resulted in 1.5-fold higher AUC which coincided with a higher incidence of infection. The impact on safety in patients with moderate/severe RI is unclear given that the drug is primarily renally eliminated and number of patients are limited.

In conclusion, the proposed recommended dosage for adults and adolescents were supported by population PK analysis where more frequent monitoring for adverse reactions is recommended in patients with moderate/severe RI.

19.4.5.2. PPK Assessment Summary

Table 130. PPK Assessment Summary

General Information	
Objectives of PPK Analysis	To update the population PK model from Phase 1/2 data, quantify population PK parameters including typical values and random variability estimates using pooled Phase 1/2/3 data, describe PK characteristics after oral administration, support E-R analysis through individual exposure metrics derivation, and evaluate demographic/disease factors contributing to PK variability in PsO patients.
Study Included	PN-235-01, PSO1002, PSO1003, PSO1004, PSO1006, PSO2001, PSO2002, PSO3001, PSO3002, PSO3003, and 3PSO3004 (IR formulation only)

Dose(s) Included		10 mg to 1000 mg in Phase 1 studies; 25 mg QD, 50 mg QD, 100 mg QD, 25 mg BID, 100 mg BID in Phase 2 studies; 200 mg QD in Phase 3 studies.
Population Included		N=2551 140 healthy participants (5.5%) and 2411 PsO patients (94.5%).
Population Characteristics (Table 131)	General	Age: median 45 years (range 12-87 years); Body weight: median 84.1 kg (range 39-211 kg); [redacted]: 67.7% male, 32.3% female; Race: 76% White (including Hispanic/non-Hispanic), 20.1% Asian, 1.7% Black, 1% Other, 1.1% Unknown/Not reported.
	Organ Impairment	Hepatic impairment categories not provided; Phase 3 studies excluded participants with ALT/AST >2×ULN. Renal impairment (RI) categorized by CrCL (non-indexed eGFR calculated by MDRD): Normal (≥90 mL/min): 2,019 participants; Mild (60-89 mL/min): 503 participants; Moderate (30-59 mL/min): 19 participants; Severe (<30 mL/min): 1 participant.
	Pediatrics (if any)	Pediatrics 12 to <18 years: 72 participants (2.8%). Age: median 15.5 years (range 12-17 years) Weight: median 65.5 kg (range 40.3-130.2 kg)
No. of Patients, PK Samples, and BLQ		2,551 patients with 12,299 plasma icotrokinra concentration records. BLQ samples: 7.3% of total samples were below the limit of quantification (0.02 ng/mL).
Sampling Schedule	Rich Sampling	Phase 1 studies: Baseline, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48 hours for single-dose; extended to 264 hours for multiple-dose studies.
	In ITT Population	Phase 2/3 studies: Baseline, Week 1, 2, 4, 8, 12, 16, 20 (PSO2001); Baseline, Week 4, 8, 16, 24, 36, 40 (PSO2002); Phase 3: Baseline, Week 4, 12, 16, 24, 28, 36, 52, 64, 112, 156.
Covariates Evaluated	Static	Age, adult vs. adolescent, sex, race, ethnicity, Japanese vs. non-Japanese, Chinese vs. non-Chinese, East Asian region, body weight, BSA, serum creatinine, CRCL, eGFR, albumin, AST, ALT, ALP, total bilirubin, total protein, GGT, LDH, creatine kinase, diabetes mellitus history, psoriasis history, psoriatic arthritis history.
	Time-varying	ADA positivity (time varying, last observation carried forward), meal timing (length of time between meal intake and dose administration).

Final Model	**Summary**	**Acceptability [FDA's Comments]**
Software and Version	NONMEM Version 7.5.1	Yes
Estimation Algorithm	First-Order Conditional Estimation with Interaction (FOCE-I) method.	Yes
Model Structure	1-compartment model with first-order absorption, first-order elimination, fixed standard allometric exponents (0.75 for CL/F, 1 for V/F), lag time (TLAG), and food effects on bioavailability (F) and absorption rate constant (ka)	Yes

Final Model	Summary	Acceptability [FDA's Comments]
Model Parameter Estimates	Table 132	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All parameters reliably estimated with RSE <30%. IIV for CL/F (52.6%) and V/F (61.6%) were moderate. ETA shrinkage for CL/F (21%) and V/F (26%) were acceptable (<30%), indicating reliable estimation. High shrinkage for ka (60%) limits interpretation of associated covariate effects.	Yes
BLQ for Parameter Accuracy	BLQ samples (7.3% of total) were treated as missing and not imputed.	Yes
GOF, VPC	Goodness-of-fit plots showed no apparent bias with IPRED values distributed uniformly along identity line and CWRES centered around zero. Visual predictive check demonstrated final model adequately captured mean concentration-time profiles and associated variability across studies and treatment groups. (Figure 89, Figure 90)	Yes

Final Model	Summary	Acceptability [FDA's Comments]
Significant Covariates and Clinical Relevance (Figure 11)	Significant covariates on CL/F: ADA titer ≥100 (decreased CL/F), eGFR (positive impact), body weight effects via allometric scaling (fixed exponents). Food effects: decreased F by 44% (fed) and 25% (modified fasting), decreased ka when fed. Body weight effect on exposure is not clinically meaningful. Food effects support taking the drug under fasting condition. ADA and renal impairment (RI) are not considered clinically meaningful.	FDA does not agree that RI is not clinically meaningful. The impact on safety for moderate/severe RI is unclear given limited number of patients. The infection rate was doubled in patients with moderate RI compared to other patients on 200 mg QD icotrokinra (refer to 19.4.6.5 for details).

Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	No clinically significant differences in the pharmacokinetics of icotrokinra were observed based on age (range: 12 to 87 years), body weight (range: 39 to 211 kg), sex, race (76% White and, 20.1% Asian, 1.7% Black), ethnicity, immunogenicity, mild (eGFR ≥60 to <90 mL/min/1.73 m^2, [calculated according to Chronic Kidney Disease Epidemiology Collaboration]) renal impairment. The effect of mild (Child-Pugh Class A) to severe (Child-Pugh Class C) hepatic impairment on icotrokinra pharmacokinetics is unknown. Hepatic impairment is unlikely to affect icotrokinra elimination since the drug is not metabolized hepatically. However, patients with severe hepatic impairment were not studied in clinical trials.	Yes

Source:
Abbreviations:

Table 131. Demographic and Baseline Characteristics of Pooled Study Data

Variable Labels	1002	1003	1004	1006	2001/ 2002	3001	3002	3003	3004	Total
N	18	69	29	24	210	669	571	297	664	2551
Sex, n (%)										
Male	18 (100)	51 (73.9)	21 (72.4)	19 (79.2)	150 (71.4)	434 (64.9)	389 (68.1)	192 (64.6)	452 (68.1)	1726 (67.7)
Female	0 (0)	18 (26.1)	8 (27.6)	5 (20.8)	60 (28.6)	235 (35.1)	182 (31.9)	105 (35.4)	212 (31.9)	825 (32.3)
Age category, n (%)										
Adults	18 (100)	69 (100)	29 (100)	24 (100)	210 (100)	603 (90.1)	571 (100)	291 (98)	664 (100)	2479 (97.2)
Adolescents	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	66 (9.9)	0 (0)	6 (2)	0 (0)	72 (2.8)
Past/current history of psoriasis, n (%)										
No	18 (100)	69 (100)	29 (100)	24 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	140 (5.5)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	210 (100)	669 (100)	571 (100)	297 (100)	664 (100)	2411 (94.5)
Past/current history of Diabetes Mellitus, n (%)										
No	0 (0)	69 (100)	0 (0)	24 (100)	180 (85.7)	0 (0)	508 (89)	263 (88.6)	595 (89.6)	1639 (64.2)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	30 (14.3)	669 (100)	63 (11)	34 (11.4)	69 (10.4)	865 (33.9)
N missing (%)	18 (100)	0 (0)	29 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	47 (1.8)
Past/current history of Psoriatic Arthritis, n (%)										
No	18 (100)	69 (100)	29 (100)	24 (100)	191 (91)	0 (0)	482 (84.4)	248 (83.5)	586 (88.3)	1647 (64.6)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	19 (9)	669 (100)	89 (15.6)	49 (16.5)	78 (11.7)	904 (35.4)
Race, n (%)										
White	0 (0)	62 (89.9)	0 (0)	23 (95.8)	152 (72.4)	484 (72.3)	434 (76)	232 (78.1)	553 (83.3)	1940 (76)
Black	0 (0)	3 (4.3)	0 (0)	0 (0)	5 (2.4)	7 (1)	9 (1.6)	2 (0.7)	18 (2.7)	44 (1.7)
Asian	18 (100)	4 (5.8)	29 (100)	1 (4.2)	43 (20.5)	164 (24.5)	119 (20.8)	58 (19.5)	78 (11.7)	514 (20.1)
Other	0 (0)	0 (0)	0 (0)	0 (0)	6 (2.9)	4 (0.6)	5 (0.9)	1 (0.3)	9 (1.4)	25 (1)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.9)	10 (1.5)	4 (0.7)	4 (1.3)	6 (0.9)	28 (1.1)
Ethnicity, n (%)										
Hispanic or Latino	0 (0)	0 (0)	0 (0)	0 (0)	15 (7.1)	83 (12.4)	100 (17.5)	20 (6.7)	93 (14)	311 (12.2)
Not Hispanic or Latino	18 (100)	0 (0)	29 (100)	24 (100)	192 (91.4)	575 (85.9)	466 (81.6)	267 (89.9)	570 (85.8)	2141 (83.9)
Unknown	0 (0)	69 (100)	0 (0)	0 (0)	3 (1.4)	11 (1.6)	5 (0.9)	10 (3.4)	1 (0.2)	99 (3.9)

Variable Labels	1002	1003	1004	1006	2001/ 2002	3001	3002	3003	3004	Total
Japanese, n (%)										
Non-Japanese	6	69	29	24	194	662	531	297	664	2476
	(33.3)	(100)	(100)	(100)	(92.4)	(99)	(93)	(100)	(100)	(97.1)
Japanese	12	0 (0)	0 (0)	0 (0)	16	7 (1)	40 (7)	0 (0)	0 (0)	75
	(66.7)				(7.6)					(2.9)
Chinese, n (%)										
Non-Chinese	12	69	0 (0)	24	210	569	571	297	664	2416
	(66.7)	(100)		(100)	(100)	(85.1)	(100)	(100)	(100)	(94.7)
Chinese	6	0 (0)	29	0 (0)	0 (0)	100	0 (0)	0 (0)	0 (0)	135
	(33.3)		(100)			(14.9)				(5.3)
East Asian Region, n (%)										
Non-East Asian	0 (0)	69	0 (0)	24	172	533	469	248	613	2128
		(100)		(100)	(81.9)	(79.7)	(82.1)	(83.5)	(92.3)	(83.4)
East Asian	18	0 (0)	29	0 (0)	38	136	102	49	51	423
	(100)		(100)		(18.1)	(20.3)	(17.9)	(16.5)	(7.7)	(16.6)
Antidrug antibody positive, n (%)										
ADA negative	18	69	29	24	166	628	553	286	631	2404
	(100)	(100)	(100)	(100)	(79)	(93.9)	(96.8)	(96.3)	(95)	(94.2)
ADA positive	0 (0)	0 (0)	0 (0)	0 (0)	44	41	18	10	33 (5)	146
					(21)	(6.1)	(3.2)	(3.4)		(5.7)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0)
Highest antidrug antibody Titer, n (%)										
ADA titer <100	18	69	29	24	209	663	564	291	652	2519
or negative	(100)	(100)	(100)	(100)	(99.5)	(99.1)	(98.8)	(98)	(98.2)	(98.7)
ADA titer ≥100	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	6 (0.9)	7 (1.2)	5 (1.7)	12	31
									(1.8)	(1.2)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)	1 (0)
Weight (kg)										
Mean (SD)	65.6	80.2	63.3	78.0	88.2	86.3	87.0	85.3	88.6	86.5
	(9.72)	(10.8)	(7.84)	(8.94)	(20.1)	(22.3)	(22.4)	(20.3)	(20.5)	(21.2)
Median	62.6	78.2	62.0	79.7	85.0	84.6	84.0	84.0	86.2	84.1
Range	(53.8;	(62.7;	(50.3;	(59.8;	(47.8;	(41.0;	(39.0;	(40.3;	(42.6;	(39.0;
	89.4)	113)	78.0)	91.3)	174)	200)	211)	166)	180)	211)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.3)	1 (0.2)	5 (0.2)
Age (years)										
Mean (SD)	29.0	44.7	32.7	48.2	44.3	42.6	47.2	45.0	46.2	44.9
	(8.51)	(13.4)	(7.83)	(12.4)	(12.2)	(16.4)	(13.2)	(14.4)	(13.7)	(14.4)
Median	26.0	49.0	33.0	55.0	45.0	43.0	47.0	44.0	45.0	45.0
Range	(21.0;	(19.0;	(19.0;	(23.0;	(19.0;	(12.0;	(18.0;	(12.0;	(18.0;	(12.0;
	50.0)	60.0)	44.0)	60.0)	73.0)	85.0)	79.0)	87.0)	86.0)	87.0)
Body surface area (m^2)										
Mean (SD)	1.77	1.99	1.71	1.95	2.07	2.03	2.05	2.02	2.07	2.04
	(0.15)	(0.17)	(0.135)	(0.152)	(0.263)	(0.301)	(0.298)	(0.275)	(0.275)	(0.285)
Median	1.74	1.95	1.71	1.98	2.04	2.04	2.03	2.01	2.06	2.03
Range	(1.55;	(1.69;	(1.51;	(1.60;	(1.44;	(1.31;	(1.28;	(1.31;	(1.33;	(1.28;
	2.11)	2.50)	1.94)	2.15)	3.03)	3.27)	3.36)	2.85)	3.15)	3.36)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)	0 (0)	5 (1.7)	1 (0.2)	8 (0.3)

Variable Labels	1002	1003	1004	1006	2001/ 2002	3001	3002	3003	3004	Total
Serum creatinine (µmol/L)										
Mean (SD)	81.3	75.5	63.8	80.4	74.9	72.3	74.9	73.5	75.4	74.2
	(8.43)	(13.6)	(11.3)	(15.5)	(13.8)	(13.8)	(14.0)	(14.6)	(15.7)	(14.5)
Median	81.3	73.0	63.0	78.7	75.0	72.0	74.0	73.0	75.0	74.0
Range	(68.1;	(49.0;	(42.0;	(53.9;	(41.0;	(39.0;	(41.0;	(36.2;	(40.7;	(36.2;
	101)	108)	93.0)	110)	114)	116)	146)	125)	262)	262)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)
Creatinine clearance (mL/min)										
Mean (SD)	110	121	128	108	135	138	129	131	133	132
	(16.4)	(26.6)	(22.5)	(22.5)	(38.3)	(47.0)	(43.6)	(40.9)	(43.2)	(43.1)
Median	111	115	123	106	129	133	124	124	127	126
Range	(90.0;	(84.3;	(86.5;	(68.4;	(61.4;	(51.1;	(46.4;	(51.9;	(25.8;	(25.8;
	154)	200)	175)	148)	340)	471)	470)	392)	368)	471)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)
Estimated glomerular filtration rate (mL/min/1.73 m²)										
Mean (SD)	86.4	95.0	120	87.9	94.9	99.2	91.2	95.4	92.9	94.9
	(12.5)	(19.3)	(18.4)	(18.0)	(18.5)	(24.0)	(17.4)	(21.3)	(18.5)	(20.6)
Median	87.7	92.4	119	89.2	92.8	96.9	89.8	91.5	90.7	92.7
Range	(56.1;	(61.2;	(83.9;	(54.0;	(52.0;	(49.6;	(42.0;	(53.9;	(18.3;	(18.3;
	103)	162)	159)	119)	148)	244)	150)	216)	166)	244)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)
Albumin (g/L)										
Mean (SD)	46.4	43.9	44.0	44.1	46.6	45.6	45.1	45.4	45.3	45.4
	(2.75)	(3.20)	(2.38)	(1.91)	(2.57)	(2.73)	(2.91)	(2.76)	(2.59)	(2.77)
Median	47.0	44.0	43.7	44.0	46.0	46.0	45.0	45.0	45.0	45.0
Range	(41.0;	(36.8;	(39.3;	(40.8;	(39.0;	(37.0;	(34.0;	(35.0;	(34.0;	(34.0;
	50.0)	53.0)	48.4)	47.6)	53.0)	54.0)	70.0)	53.0)	53.0)	70.0)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)
Aspartate transaminase (U/L)										
Mean (SD)	19.2	19.5	15.4	20.5	24.0	22.3	23.3	22.7	23.1	22.7
	(4.60)	(5.82)	(3.78)	(8.57)	(12.9)	(9.53)	(11.0)	(8.89)	(9.12)	(9.92)
Median	17.5	19.0	14.0	18.5	21.0	20.0	21.0	21.0	21.0	20.5
Range	(13.0;	(9.00;	(10.0;	(11.0;	(10.0;	(8.00;	(8.00;	(9.00;	(10.0;	(8.00;
	28.0)	43.0)	26.0)	55.0)	108)	97.0)	131)	79.0)	82.0)	131)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)
Alanine transaminase (U/L)										
Mean (SD)	19.6	22.9	14.2	19.2	27.8	26.1	26.6	27.4	25.9	26.1
	(10.7)	(10.6)	(5.65)	(12.2)	(17.7)	(17.8)	(15.6)	(16.6)	(14.6)	(16.1)
Median	18.0	21.0	13.0	15.0	23.0	22.0	22.0	23.0	22.0	22.0
Range	(8.00;	(7.00;	(6.00;	(5.00;	(6.00;	(6.00;	(5.00;	(6.00;	(6.00;	(5.00;
	45.0)	65.0)	29.0)	60.0)	114)	149)	126)	98.0)	108)	149)
N missing (%)	0 (0)	1 (1.4)	0 (0)	0 (0)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)	3 (0.1)
Alkaline phosphatase (U/L)										
Mean (SD)	63.9	70.8	55.5	69.9	81.1	86.5	82.0	79.6	80.1	81.5
	(11.7)	(19.3)	(13.5)	(19.9)	(21.7)	(47.6)	(25.3)	(29.3)	(22.8)	(32.4)
Median	63.5	67.0	53.3	74.5	79.0	78.0	79.0	74.0	76.0	77.0
Range	(41.0;	(31.0;	(29.1;	(27.0;	(29.0;	(20.0;	(32.0;	(31.0;	(32.0;	(20.0;
	87.0)	140)	85.0)	96.0)	151)	785)	210)	356)	186)	785)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0 (0)	1 (0)

Variable Labels	1002	1003	1004	1006	2001/ 2002	3001	3002	3003	3004	Total
Total bilirubin (µmol/L)										
Mean (SD)	17.8 (4.15)	11.3 (5.01)	7.91 (2.77)	9.40 (4.54)	8.80 (4.52)	9.20 (4.47)	9.25 (4.99)	8.51 (4.37)	9.35 (5.48)	9.24 (4.93)
Median	18.0	10.0	7.55	8.55	8.00	8.55	8.00	8.00	8.00	8.00
Range	(13.7; 25.6)	(5.13; 28.0)	(3.84; 14.7)	(3.42; 22.2)	(1.50; 27.0)	(3.00; 38.0)	(3.00; 39.0)	(1.50; 30.0)	(3.00; 51.0)	(1.50; 51.0)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	18 (2.7)	12 (2.1)	0 (0)	24 (3.6)	54 (2.1)
Total protein (g/L)										
Mean (SD)	71.0 (2.68)	71.8 (6.44)	67.4 (3.97)	67.2 (2.57)	71.3 (4.22)	72.3 (4.36)	71.7 (4.31)	72.0 (4.29)	72.0 (4.06)	71.8 (4.35)
Median	71.5	72.0	67.1	67.0	71.0	72.0	72.0	72.0	72.0	72.0
Range	(66.0; 75.0)	(59.0; 87.0)	(61.1; 80.2)	(63.0; 73.0)	(57.0; 85.0)	(55.0; 87.0)	(57.0; 84.0)	(61.0; 84.0)	(58.0; 83.0)	(55.0; 87.0)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)	2 (0.1)
Gamma glutamyl transferase (U/L)										
Mean (SD)	19.4 (11.6)	20.1 (16.0)	18.7 (11.6)	25.1 (16.2)	31.0 (24.7)	31.1 (40.3)	31.3 (31.3)	31.6 (28.7)	32.4 (39.3)	30.9 (34.8)
Median	15.5	14.0	14.0	20.0	23.5	20.0	22.0	22.0	23.0	22.0
Range	(9.00; 60.0)	(6.00; 104)	(9.00; 49.0)	(9.00; 69.0)	(5.00; 165)	(5.00; 507)	(7.00; 300)	(6.00; 220)	(5.00; 692)	(5.00; 692)
N missing (%)	0 (0)	1 (1.4)	0 (0)	0 (0)	0 (0)	2 (0.3)	0 (0)	0 (0)	0 (0)	3 (0.1)
Lactate dehydrogenase (U/L)										
Mean (SD)	144 (18.1)	181 (23.7)	137 (19.2)	162 (25.8)	181 (33.7)	169 (29.6)	173 (32.7)	165 (26.3)	174 (31.4)	171 (31.0)
Median	136	177	138	158	178	165	170	163	171	168
Range	(124; 176)	(137; 235)	(98.0; 174)	(97.0; 228)	(75.0; 323)	(76.0; 294)	(84.0; 315)	(94.0; 245)	(66.0; 349)	(66.0; 349)
N missing (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.4)	0 (0)	3 (1)	7 (1.1)	13 (0.5)
Creatine kinase (U/L)										
Mean (SD)	NA (NA)	136 (98.9)	74.2 (19.4)	146 (162)	150 (231)	135 (232)	125 (115)	136 (178)	145 (186)	136 (187)
Median	-	113	68.0	106	108	95.0	96.0	96.0	107	100
Range	(NA)	(33.0; 781)	(42.0; 128)	(41.0; 846)	(9.00; 2672)	(29.0; 3617)	(22.0; 1364)	(23.0; 2510)	(19.0; 2657)	(9.00; 3617)
N missing (%)	18 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.2)	0 (0)	0 (0)	20 (0.8)

Source: popPK and ER report (Table 2).
Abbreviations: SD-standard deviation

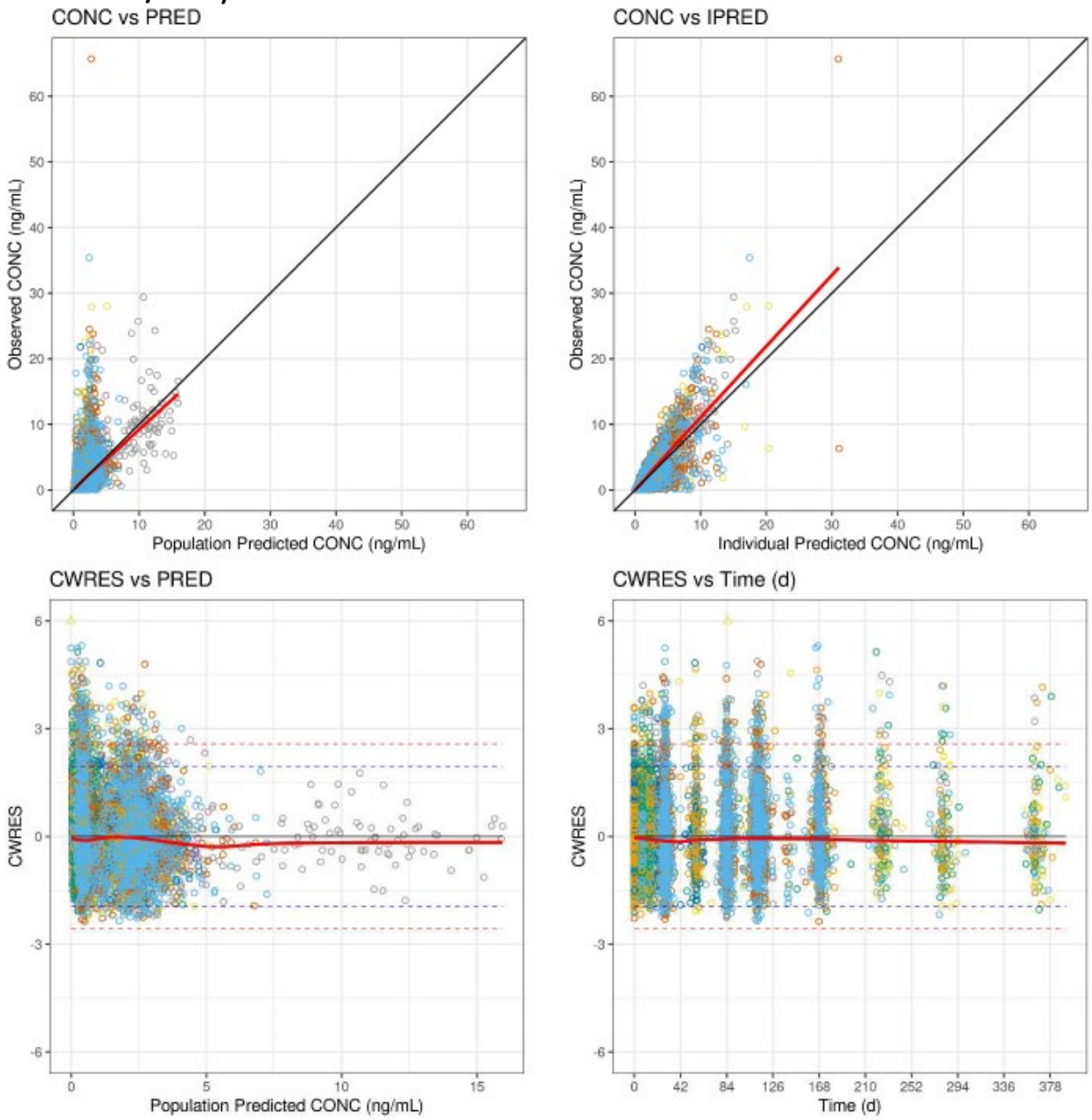
Table 132. Parameter Estimates and SE From Final Population PK Model

Parameters	Estimate	Shrinkage (%)
CL/F (L/h)	6,550 (2)	
BWT on CL/F	0.75, fixed	
ADAHT on CL/F	0.366 (11)	
EGFR on CL/F	0.225 (21)	
V/F (L)	92,800 (3)	
BWT on V/F	1, fixed	
ka (1/h)	2.62 (14)	

Parameters	Estimate	Shrinkage (%)
Tlag (h)	0.129 (16)	
Food on F (scaling factor vs. fasted)	0.559 (3)	
Modified Fasting on F (scaling factor vs. fasted)	0.755 (9)	
Food on ka (scaling factor vs. fasted)	0.111 (20)	
IIV of CL/F (%)	52.6 (5)	21
IIV of V/F (%)	61.6 (6)	26
IIV of ka (%)	84.7 (12)	60
Correlation between IIV of CL/F and V/F	0.727	--
Proportional residual error (CV%)	48.1% (2)	10

Source: popPK and ER report (Table E1). ADAHT=antidrug antibody titer ≥100 (1=yes, 0=no). Modified Fasting=fasted overnight and not had food for at least 30 minutes after dose administration.
CL/F=6550×(BWT/90)^0.75×(EGFR/90)^0.225×0.366^ADAHT. V/F=92800×(BWT/90).
Abbreviations: CL/F : apparent clearance, BWT: body weight, EGFR: estimated glomerular filtration rate, V/F: apparent volume, Ka: absorption rate, Tlag: lag time, IIV: inter-individual variability.

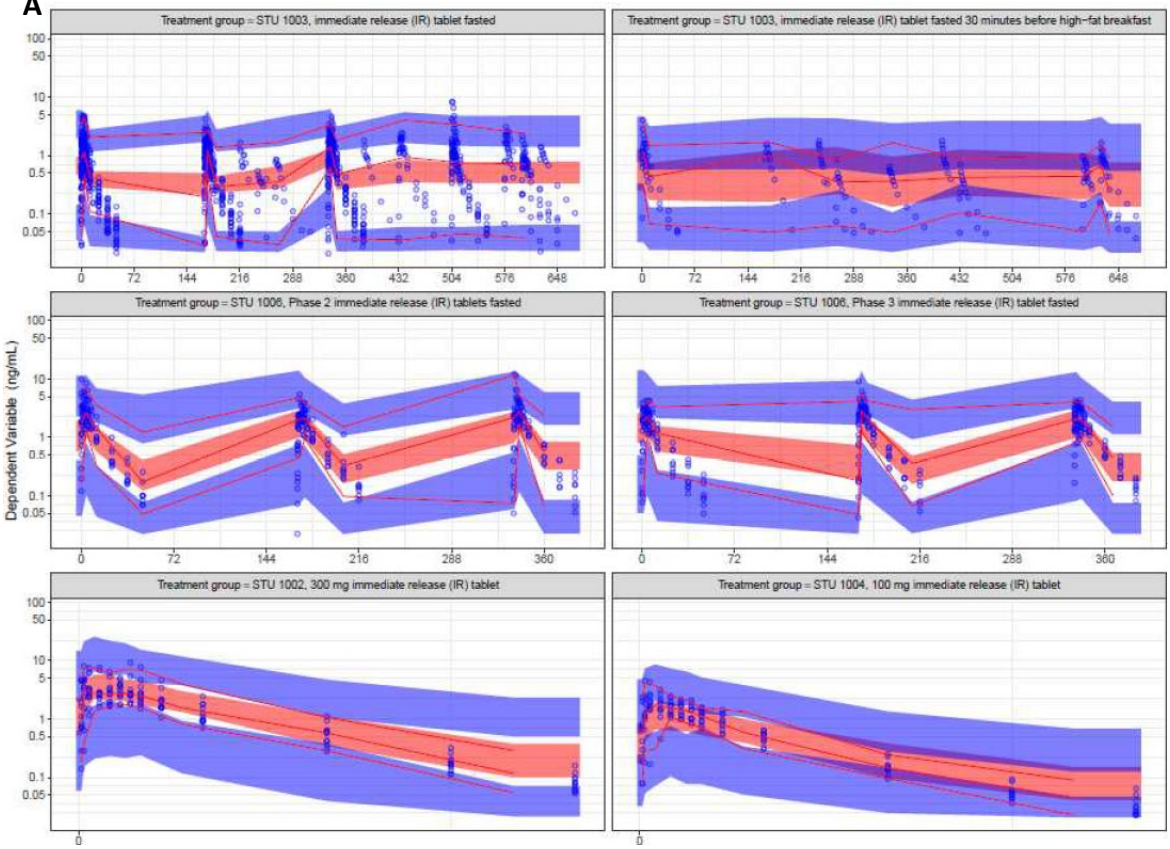
Figure 89. Goodness-of-Fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED)

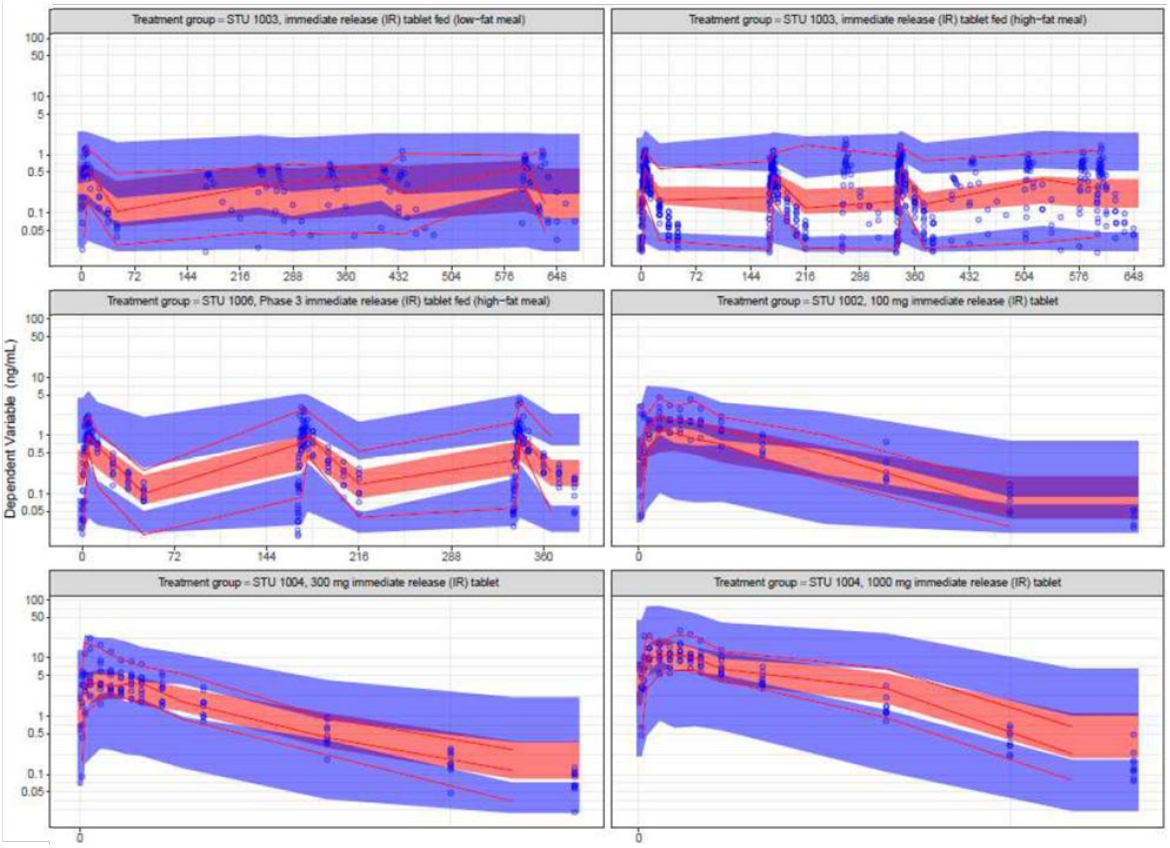


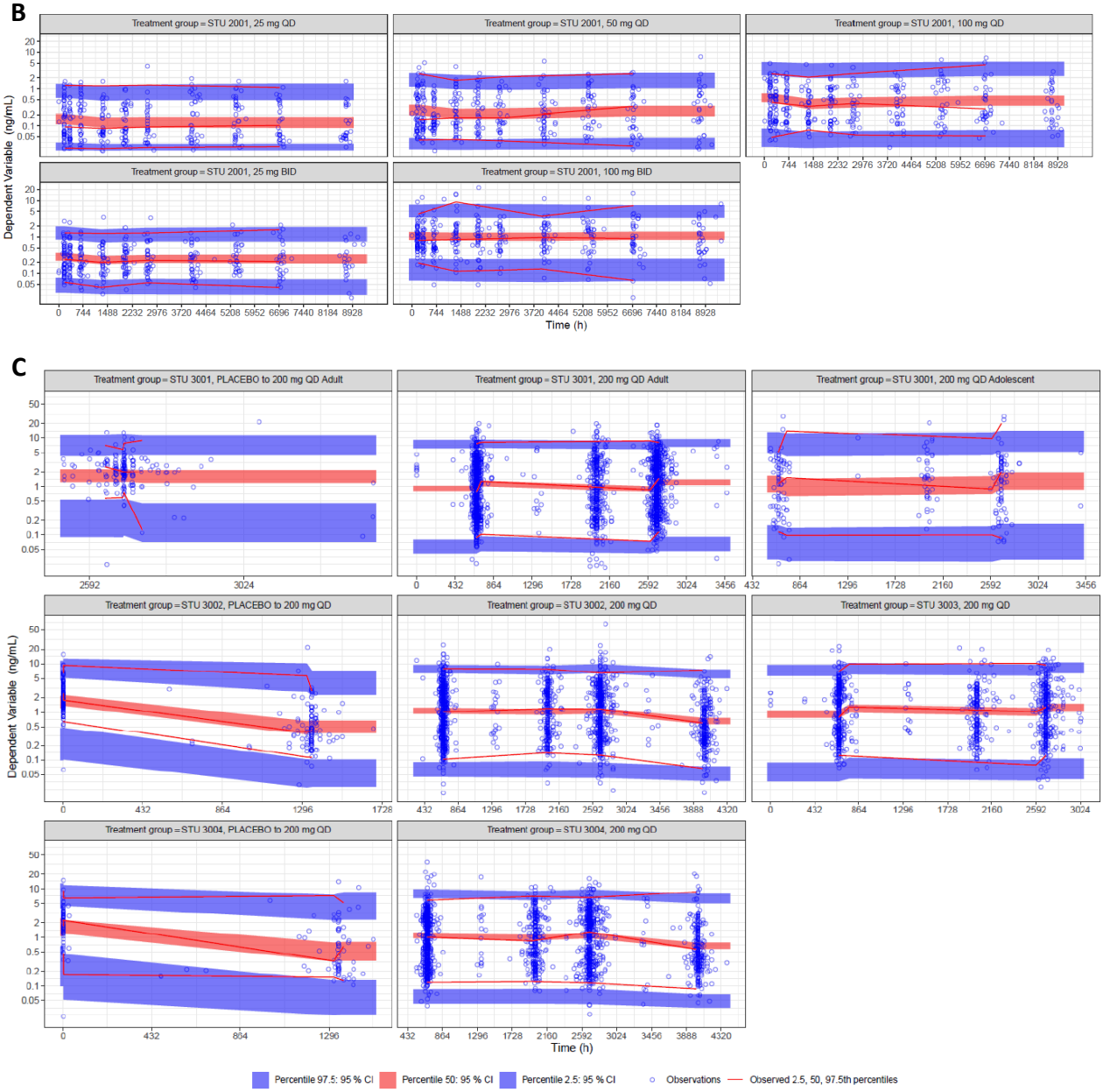
Source: popPK and ER report (Figure 3).
Abbreviations: PRED, population prediction, IPRED, individual prediction, CONC, concentration, CWRES, conditional weighted residuals

Figure 90. Prediction-Corrected VPC of Final Population PK Model, Stratified by Study and Treatment Group—(A) Phase 1, (B) Phase 2, (C) Phase 3

A




Treatment group = STU 1003, immediate release (IR) tablet fed (low-fat meal)
Treatment group = STU 1003, immediate release (IR) tablet fed (high-fat meal)
Treatment group = STU 1006, Phase 3 immediate release (IR) tablet fed (high-fat meal)
Treatment group = STU 1002, 100 mg immediate release (IR) tablet
Treatment group = STU 1004, 300 mg immediate release (IR) tablet
Treatment group = STU 1004, 1000 mg immediate release (IR) tablet
Dependent Variable (ng/mL)
100
50
10
5
1
0.5
0.1
0.05
0
72
144
216
288
360
432
504
576
648



Source: popPK and ER report (Figure 4).

The FDA's Assessment

The population PK analysis is adequate.

19.4.6. Exposure-Response Analysis

19.4.6.1. ER (Efficacy) Executive Summary

The FDA's Assessment

The E-R analysis explored relationships between icotrokinra exposure and achieving PASI90 (≥90% improvement from baseline in PASI) at Week 16, and IGA0/1 (an IGA score of cleared [0] or minimal [1]) with ≥2 grade improvement from baseline at Week 16 in Phase 3 studies. The observed response aligned with the predicted response by Phase 2 E-R models and indicated plateau response at the proposed recommended dosage of 200 mg QD. There was no apparent E-R relationship observed in body weight subgroups or age subgroups (i.e., adults versus adolescents).

19.4.6.2. ER (Efficacy) Assessment Summary

Table 133. ER (Efficacy) Assessment Summary

General Information		
Goal of ER analysis		To explore the relationship between exposure to icotrokinra and achieving PASI90 (≥90% improvement from baseline in PASI) at Week 16, and IGA0/1 (an IGA score of cleared [0] or minimal [1]) with ≥2 grade improvement from baseline at Week 16, the coprimary efficacy endpoints of Phase 3 studies PSO3001, PSO3002, and PSO3004. To explore the relationship between exposure to icotrokinra and achieving IGA0/1 with ≥2 grade improvement from baseline at Week 16 in participants with at least moderate plaque psoriasis involving special areas (scalp, genital, and/or hand/foot), the primary efficacy endpoint of Phase 3 study PSO3003.
Study included		PSO3001, PSO3002, PSO3004 pooled for analysis (similar endpoints and study populations); PSO3003 analyzed separately (different population - special areas psoriasis).
Endpoint		Primary endpoints: PASI90 and IGA0/1 at Week 16 for PSO3001/3002/3004; IGA0/1 with ≥2 grade improvement at Week 16 for PSO3003.
No. of patients (total, and with individual PK)		1864 patients (1296 treated with icotrokinra and 568 treated with placebo)
Population characteristics	General	Age: median 45 years (range 12-87 years); Weight: median 85.0 kg (range 39-246 kg); n=1422 (76.3%) male; Race: n=1613 (86.5%) White including Hispanic and non-Hispanic, n=514 (27.6%) Asian, n=33 (1.8%) Black, n=20 (1.1%) Other, n=24 (1.3%) Unknown/Not reported.
	Pediatrics (if any)	Pediatrics 12 to <18 years: 72 participants (3.9%). Age: median 15.5 years (range 12-17 years) Weight: median 65.5 kg (range 40.3-130.2 kg)
Dose(s) included		200 mg QD
Exposure metrics explored (range)		Cavg,ss: median 1.29 ng/mL (5th-95th percentile: 0.690-3.21 ng/mL) across Phase 3 studies.

Covariates evaluated	Age group (adult vs. adolescent), body weight (<90 kg vs. ≥90 kg), baseline disease severity, sex, race, ethnicity.

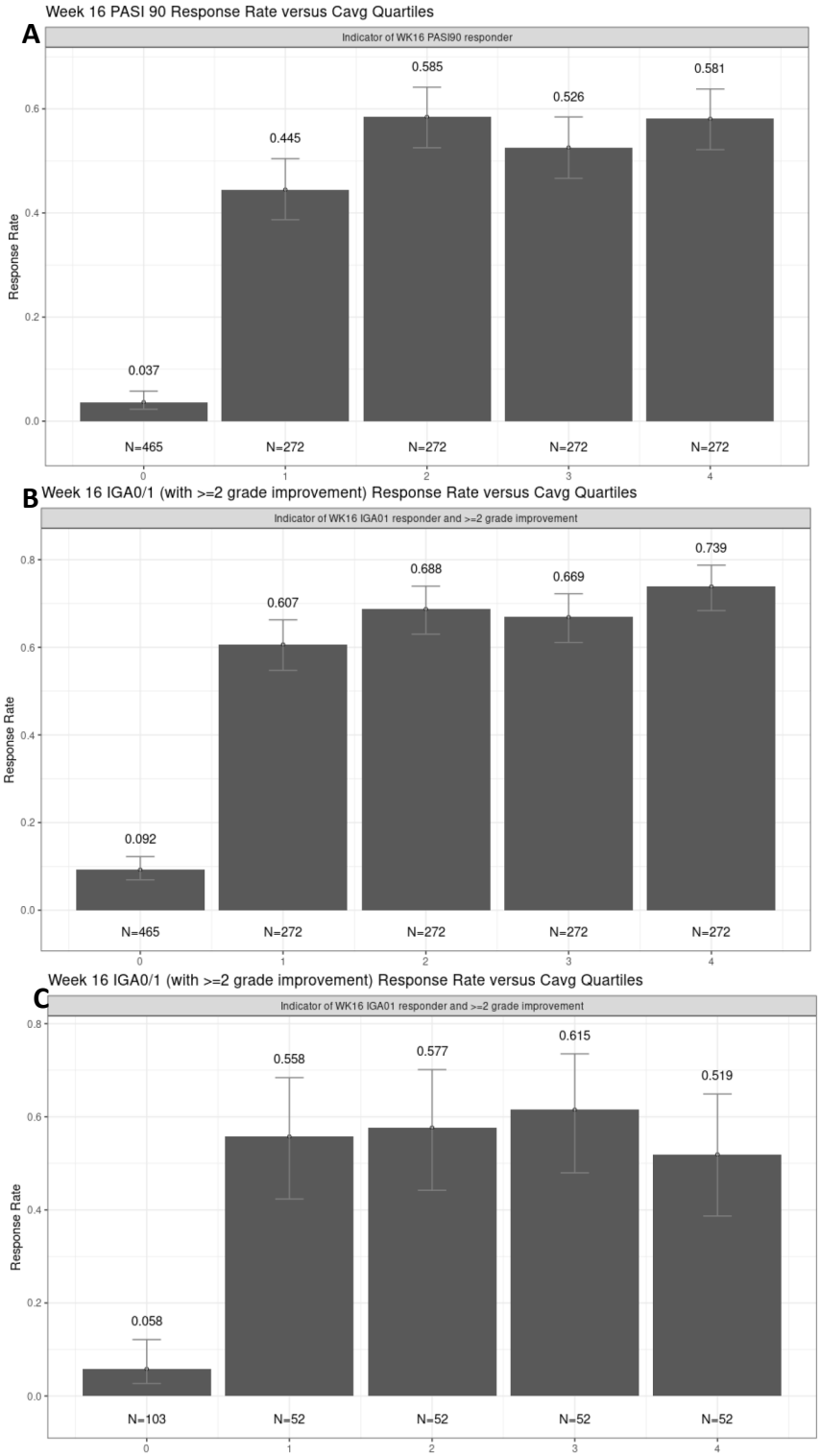
Final Model Parameters	**Summary**	**Acceptability [FDA's Comments]**
Model structure	Emax model	**Yes**
Model parameter estimates	Table 134	Yes
Model evaluation	Phase 2 E-R model adequately captured Phase 3 data, with observed Phase 3 response rates falling within confidence bounds derived from Phase 2 data in overlay analysis (Figure 9).	Yes The model fixing the same Emax for different PASI responses was acceptable for PASI90 and PASI75 but not PASI 100 which shows overprediction.
Covariates and clinical relevance	No apparent E-R relationship in body weight subgroups (<90 kg vs. ≥90 kg) or age subgroups (adults vs. adolescents) as confidence intervals overlapped across exposure quartiles for both endpoints (Figure 13).	Yes
Simulation for specific population	Phase 2 E-R modeling predicted 200 mg QD would provide comparable efficacy to 100 mg BID (Figure 9).	Yes
Visualization of E-R relationships	Figure 91	Yes
Overall clinical relevance for ER	Flat E-R relationship indicates therapeutic window achieved.	Yes

Table 134. Parameter Estimates From Phase 2 ER Model of PASI and IGA Response With $C_{avg,ss}$

Parameters	**PASI response**	**IGA0/1 response**
Logit of placebo response	-2.15 (24%)	-1.97 (23%)
Difference in logit between Y<=1 and Y=0	1.07 (14%)	1.39 (11%)
Difference in logit between Y<=2 and Y<=1	0.818 (15%)	---
Emax	4.25 (14%)	3.71 (17%)
EC50 (ng/mL)	0.23 (44%)	0.219 (45%)

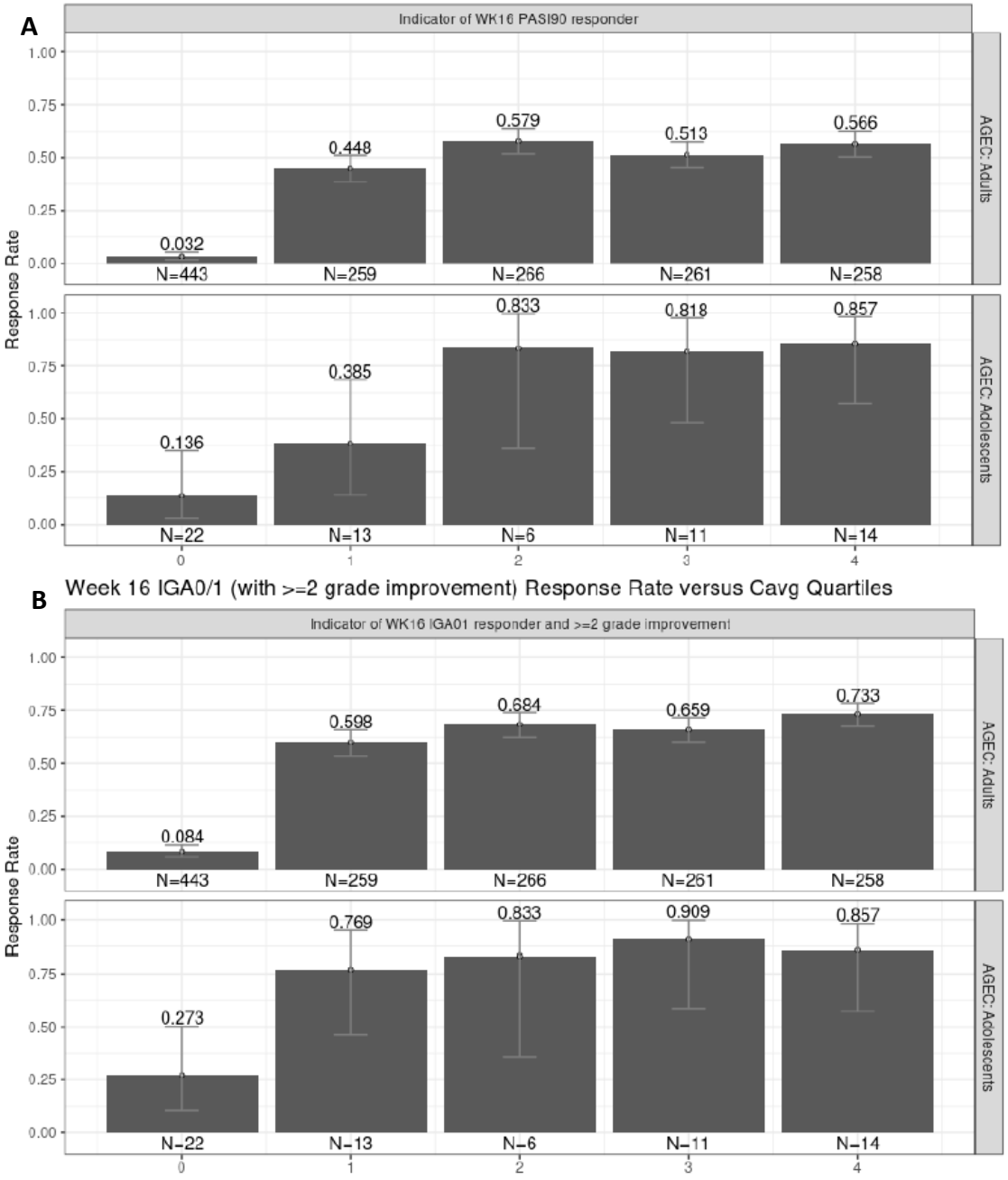
Source: popPK report of Ph1 and 2 studies (Appendix 7). The ordered categorical variable was defined as: Y values of 0, 1, 2, 3 correspond to PASI 100, PASI 90 response, PASI 75 response achieved, and PASI75 response not achieved in PASI model, Y values of 0, 1, 2 correspond to IGA score of 0, 1, or ≥2 in IGA model.
Abbreviations: Emax: maximum drug effect achievable, EC50: concentrations for 50% of maximum effect

Figure 91. Week 16 PASI90 and IGA0/1 (With ≥2 Grade Improvement) Response Rate Versus $C_{avg,ss}$ Quartiles in PsO Patients



Source: PopPK and ER report (Figure 7, 8). A: PASI90 response in Study PSO3001, PSO3002, and PSO3004, B: IGA0/1 response in Study PSO3001, PSO3002, and PSO3004, C: IGA0/1 response in Study PSO3003.
Abbreviations: IGA, investigator's global assessment; PASI, psoriasis area and severity index

Figure 92. Pooled PSO3001, PSO3002, and PSO3004 Week 16 PASI90 (A) and IGA0/1 (With ≥2 Grade Improvement, B) Response Rate Versus $C_{avg,ss}$ Quartiles by Age Group



Source: PopPK and ER report (Figure 29).
Abbreviations: IGA, investigator's global assessment; PASI, psoriasis area and severity index

19.4.6.3. ER (Safety) Executive Summary

The FDA's Assessment

The exposure-safety analysis evaluated relationships between icotrokinra exposure and rates of adverse events (AEs), serious adverse events (SAEs), infections, and discontinuation due to AEs

through Week 16 in pooled Phase 3 studies PSO3001, PSO3002, PSO3003, and PSO3004. All evaluated AE rates were similar across quartiles of icotrokinra exposure and comparable to placebo. No apparent exposure-safety relationship was identified. Data in PsO patients with moderate/severe RI were limited to evaluate if the exposure-safety relationship aligned with patients with normal/mild RI. Given the increased exposure and incidence of infection observed, FDA recommends more frequent monitoring for adverse reactions in patients with moderate/severe RI.

19.4.6.4. ER (Safety) Assessment Summary

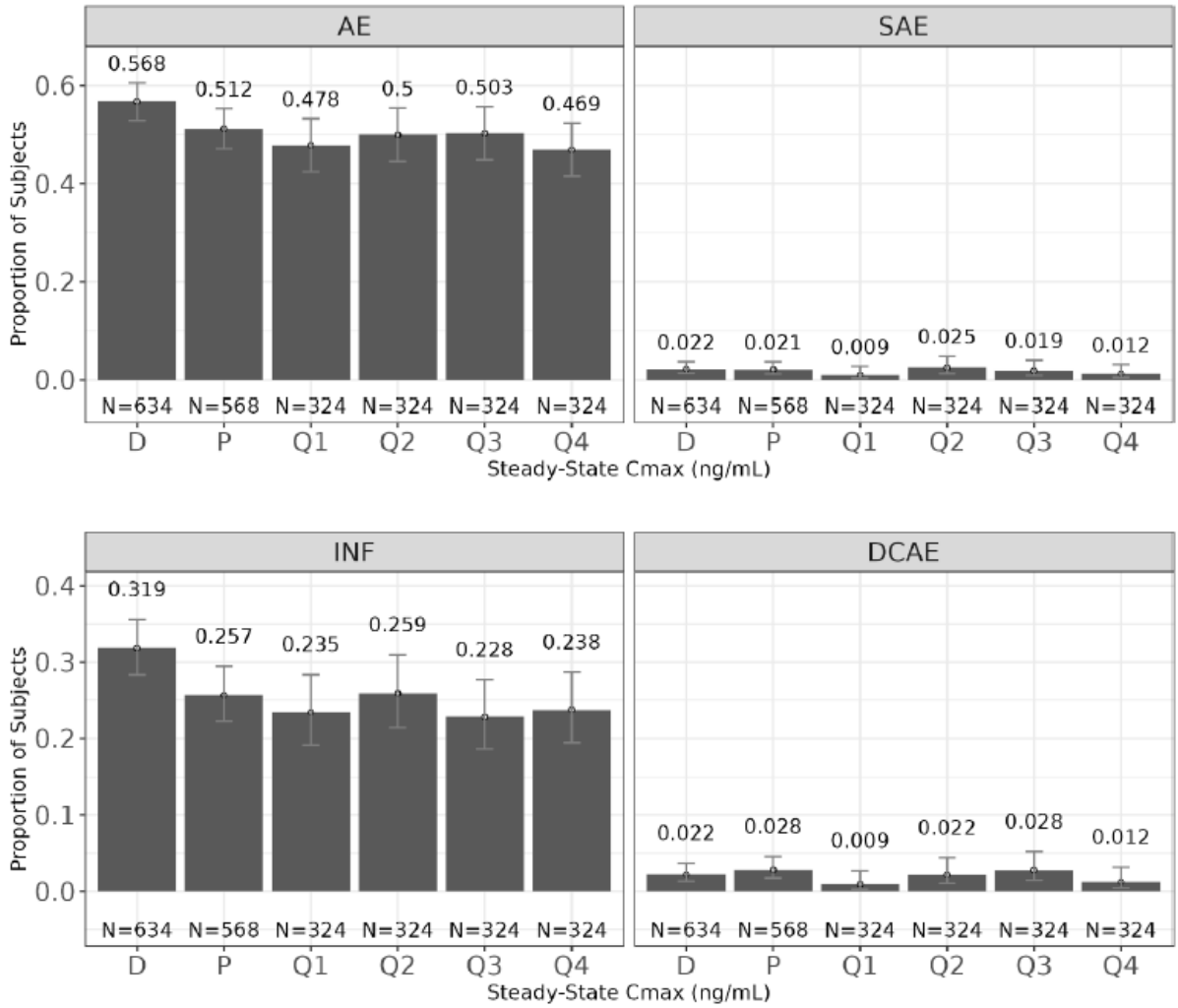
Table 135. ER (Safety) Assessment Summary

General Information		
Goal of ER analysis		To explore any relationship between exposure to icotrokinra and rates of AEs, SAEs, infection, and discontinuation due to AEs through Week 16 in PSO3001, PSO3002, PSO3003, and PSO3004.
Study included		Pooled data from PSO3001, PSO3002, PSO3003, and PSO3004 for exposure-safety analysis.
Endpoint		TEAEs, SAEs, infections, and discontinuation due to AEs through Week 16.
No. of patients (total, and with individual PK)		1,864 patients (1,296 patients treated with icotrokinra, 568 patients treated with placebo), and 634 patients treated with deucravacitinib (as reference).
population characteristics	General	Same as 19.4.6.2
	Organ impairment	Same as 19.4.6.2
	Pediatrics (if any)	Same as 19.4.6.2
	Geriatrics (if any)	Patients ≥65 years: 183 participants (9.8%); ≥75 years: 29 participants (1.6%).
Dose(s) included		200 mg QD
Exposure metrics explored (range)		Cavg,ss quartiles: Q1 (<0.96 ng/mL), Q2 (≥0.96 to <1.29 ng/mL), Q3 (≥1.29 to <1.86 ng/mL), Q4 (≥1.86 ng/mL). Cmax,ss quartiles: Q1 (<1.90 ng/mL), Q2 (≥1.90 to <2.57 ng/mL), Q3 (≥2.57 to <3.60 ng/mL), Q4 (≥3.60 ng/mL).
Covariates evaluated		Age group (adult vs. adolescent), body weight (<90 kg vs. ≥90 kg), baseline disease severity, sex, race, ethnicity.

Final Model Parameters	**Summary**	**Acceptability [FDA's Comments]**
model structure	No formal parametric ER model was fitted for safety endpoints due to absence of meaningful exposure-safety relationships	Yes
Covariates and clinical relevance	N/A given absence of E-R for safety	Yes
Visualization of significant E-R relationships	**No significant exposure-safety relationships across exposure quartiles, which is comparable to placebo** (Figure 93).	Yes

Final Model Parameters	Summary	Acceptability [FDA's Comments]
Overall clinical relevance for ER	No meaningful exposure-safety relationship identified, supporting the safety profile of icotrokinra 200 mg once daily across the observed exposure range.	FDA generally agrees. However, PsO patients with moderate/severe RI were limited to evaluate E-R relationship in this subgroup.

Figure 93. Studies PSO3001, PSO3002, PSO3003, and PSO3004 Rates of Adverse Events, Serious Adverse Events, Infections, and Discontinuations Due to Adverse Events Through Week 16 by Steady-State C_{max} Quartile



Source: PopPK and ER report (Figure 31).
Abbreviations: D, deucravacitinib; P, placebo; AE, adverse event; SAE, serious adverse event; INF, infections; DCAE, discontinuation due to adverse events

The FDA's Assessment

The E-R analysis is adequate. Despite a lack of ER observed, considering the increase in exposure and incidence of infections, FDA recommends more frequent monitoring for adverse reactions in PsO patients with moderate/severe RI. Refer to Section 19.4.6.5 for details.

19.4.6.5. Reviewer's Independent Analysis

Considering the PK elevation in ADA+ patients and patients with renal impairment, PK, efficacy, and safety were tabulated in these patient subgroups (Table 136, Table 137). In ADA+ patients with high titers, a prominent increase in exposure was observed, which presented similar rate of efficacy response and AEs. In patients with moderate RI, an increased rate of infections was observed, which accompanied a substantial PK alteration. Given limited patients with moderate/severe RI, it is not possible to evaluate if those patients could present a steeper exposure-safety curve.

Despite the increased rate of infection that was similarly observed in moderate RI treated with placebo, the subject number is very limited (n=5) to conclude that the increased risk is due to underlying disease rather than the drug.

Overall, the current data and analyses cannot rule out the possibility of an altered benefit-risk in patients with PsO and moderate/severe RI. Considering icotrokinra is primarily renally cleared where an elevated PK and safety risk was observed in patients with PsO and moderate RI, FDA recommended more frequent monitoring for adverse reactions in patients with moderate/severe RI.

Table 136. PK, Efficacy, Safety in Patient Subgroups of Interest – Subgroup A

		Icotrokinra		
Parameters	**Placebo n=568**	**ADA- n=1217**	**ADA+ & Titer<100 n=50**	**ADA+ & Titer≥100 n=28**
C_{max} (ng/mL)	--	2.6 (53%)	3.4 (68%)	4.9 (67%)
C_{avg} (ng/mL)	--	1.3 (54%)	2.0 (79%)	3.6 (71%)
C_{trough} (ng/mL)	--	0.45 (82%)	0.86 (113%)	2.5 (81%)
IGA0/1	8.6%	66%	78%	61%
PASI90	3.4%	52%	58%	46%
AEs	51%	49%	42%	50%
Infections	26%	24%	20%	21%

Source: FDA analysis.
A: patient subgroup by ADA.
Values were presented as geometric mean (CV%) for PK, and % for efficacy/safety events. Response rate was not placebo corrected. RI was categorized by non-indexed eGFR derived by MDRD equation. The analysis was conducted using E-R dataset.
Abbreviations:

Table 137. PK, Efficacy, Safety in Patient Subgroups of Interest – Subgroup B

	Placebo			Icotrokinra		
Parameters	Normal n=406	Mild RI n=105	Moderate RI n=5	Normal n=1035	Mild RI n=244	Moderate RI n=9
C_{max} (ng/mL)	--	--	--	2.6 (55%)	3.2 (49%)	3.8 (59%)
C_{avg} (ng/mL)	--	--	--	1.3 (58%)	1.7 (51%)	2.2 (54%)
C_{trough} (ng/mL)	--	--	--	0.45 (91%)	0.66 (78%)	0.99 (60%)
IGA0/1	9.6%	8.6%	20%	65%	71%	78%
PASI90	3.2%	5.7%	0%	51%	55%	67%
AEs	51%	55%	40%	48%	50%	56%
Infections	26%	24%	60%	24%	23%	56%

Source: FDA analysis.
B: patient subgroup by renal function.
Values were presented as geometric mean (CV%) for PK, and % for efficacy/safety events. Response rate was not placebo corrected. RI was categorized by non-indexed eGFR derived by MDRD equation. The analysis was conducted using E-R dataset.
Abbreviations: C_{max}, maximum concentration at steady state; C_{avg}, average concentration at steady state; C_{trough}, trough concentration at steady state; IGA, investigator's global assessment; PASI, psoriasis area and severity index; AE, adverse event

19.4.6.6. Overall Benefit-Risk Evaluation Based on E-R Analyses

The FDA's Assessment

The E-R analyses support a favorable benefit-risk profile for icotrokinra 200 mg once daily. The efficacy analysis demonstrated consistently high response rates across exposure quartiles for both PASI90 and IGA0/1 endpoints, indicating that the selected dose achieves responses near plateau in adults as well as pediatrics 12 years and older. The exposure-safety analysis showed no meaningful relationship between increasing exposure and safety events, with AEs comparable to placebo.

Overall, the consistent efficacy responses together with the absence of exposure-safety relationships support the appropriateness of the 200 mg once daily dosing regimen for treating moderate to severe plaque psoriasis in both adults and pediatrics 12 years and older. More frequent monitoring for adverse reactions was recommended in patients with moderate/severe RI considering the increased safety risk observed.

19.5. Additional Clinical Outcome Assessment Analyses

There were no additional clinical outcome assessment analyses conducted.

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MARY E KIM
03/17/2026 08:32:19 AM