NDA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213871
Priority or Standard	Priority
Submit Date(s)	August 25, 2020
Received Date(s)	August 25, 2020
PDUFA Goal Date	July 25, 2021
Division/Office	DDD/OII
Review Completion Date	January 13, 2022
Established/Proper Name	abrocitinib
(Proposed) Trade Name	CIBINQO
Pharmacologic Class	NME
Code name	
Applicant	Pfizer Inc.
Dosage form	Tablets
Applicant proposed Dosing Regimen	100mg or 200mg once daily
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	
Recommendation on Regulatory Action	CIBINQO is indicated for the treatment of adult patients with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, biologics or when use of those therapies is inadvisable.
Recommended Indication(s)/Population(s) (if applicable)	Recommended population are adults, 18 years and older (b) (4) (b) (4)
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Moderate to severe atopic dermatitis, (b) (4)
Recommended Dosing Regimen	100 mg PO QD (b) (4) If an adequate response is not achieved with CIBINQO 100 mg orally daily after 12 weeks, consider increasing dosage to 200 mg

	orally once daily. Discontinue therapy if inadequate response is seen after dosage increase to 200 mg once daily.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

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Office Director	Julie Beitz	Office of Immunology and Inflammation (OII)	Sections: All	Select one: ___ Authored _X_ Approved

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Glossary

AC	advisory committee
AD	Atopic Dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse events of special interest
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body Surface Area
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
CI	Confidence Interval
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
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
EASI	eczema area and severity index
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	Full Analysis Set
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
GLMM	Generalized Linear Mixed Model

GRMP	good review management practice
ICH	International Conference on Harmonisation
IGA	Investigator's global assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
JAK	Janus kinase
JTR	Jump-to-Reference
LOCF	Last Observation Carried Forward
LTE	Long-term extension
MACE	Major adverse cardiac event
MAR	Missing at Random
MCAR	Missing Completely at Random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	mixed-effect model with repeated measures
MTP	Multiplicity Testing Procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	Non-Responder Imputation
NRS	Numeric Rating Scale
OC	Observed Cases
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
PPAS	Per Protocol Analysis Set
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSAAD	Pruritus and Symptoms Assessment for Atopic Dermatitis
PSUR	Periodic Safety Update report
Q2W	Every two weeks
QD	Once daily
REMS	risk evaluation and mitigation strategy

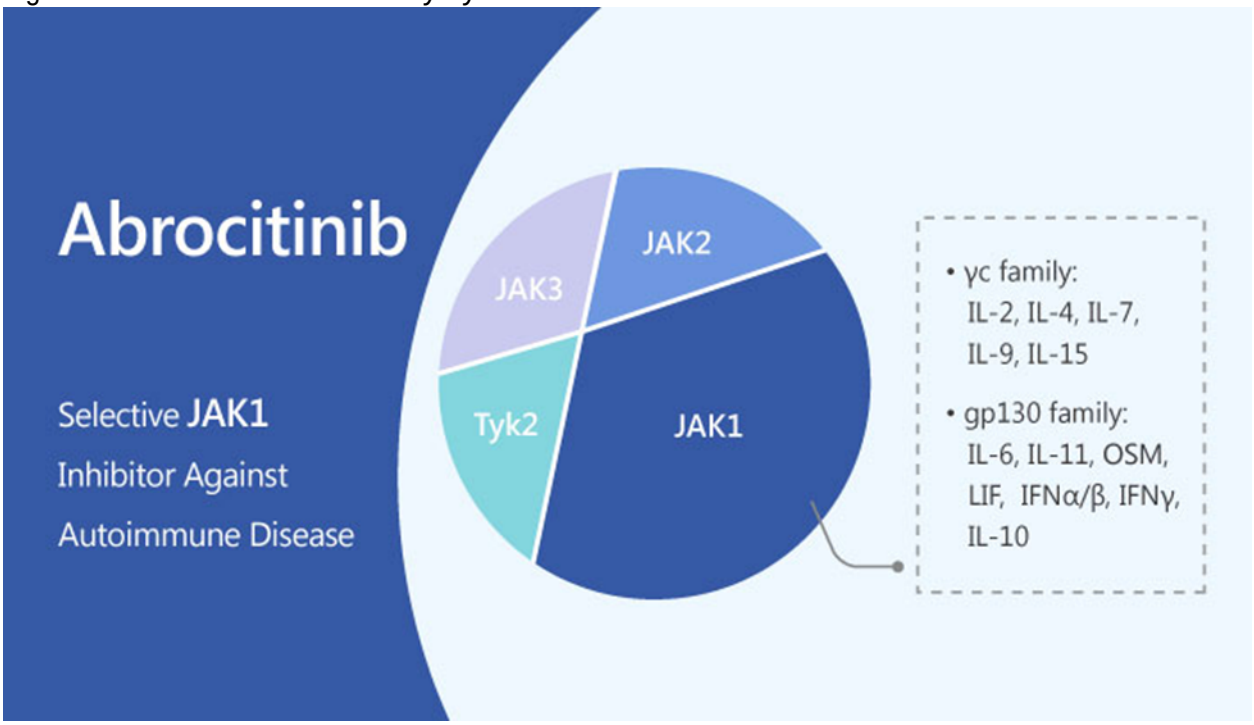
SAE	serious adverse event
SAP	statistical analysis plan
SDN	supplement designation number
SGE	special government employee
SOC	standard of care
TCS	Topical Corticosteroids
TEAE	treatment emergent adverse event
VTE	Venous thromboembolism event

1 Executive Summary

1.1. Product Introduction

Abrocitinib is an orally bioavailable small molecule that reversibly and selectively inhibits Janus Kinase (JAK) by blocking the ATP binding site. In the in vitro assays, according to Pfizer, abrocitinib has biochemical selectivity for JAK1 over the other three JAK isoforms JAK2 (28-fold), JAK3 (>340 fold) and TYK2 (43-fold) and even higher selectivity over the broader kinome.

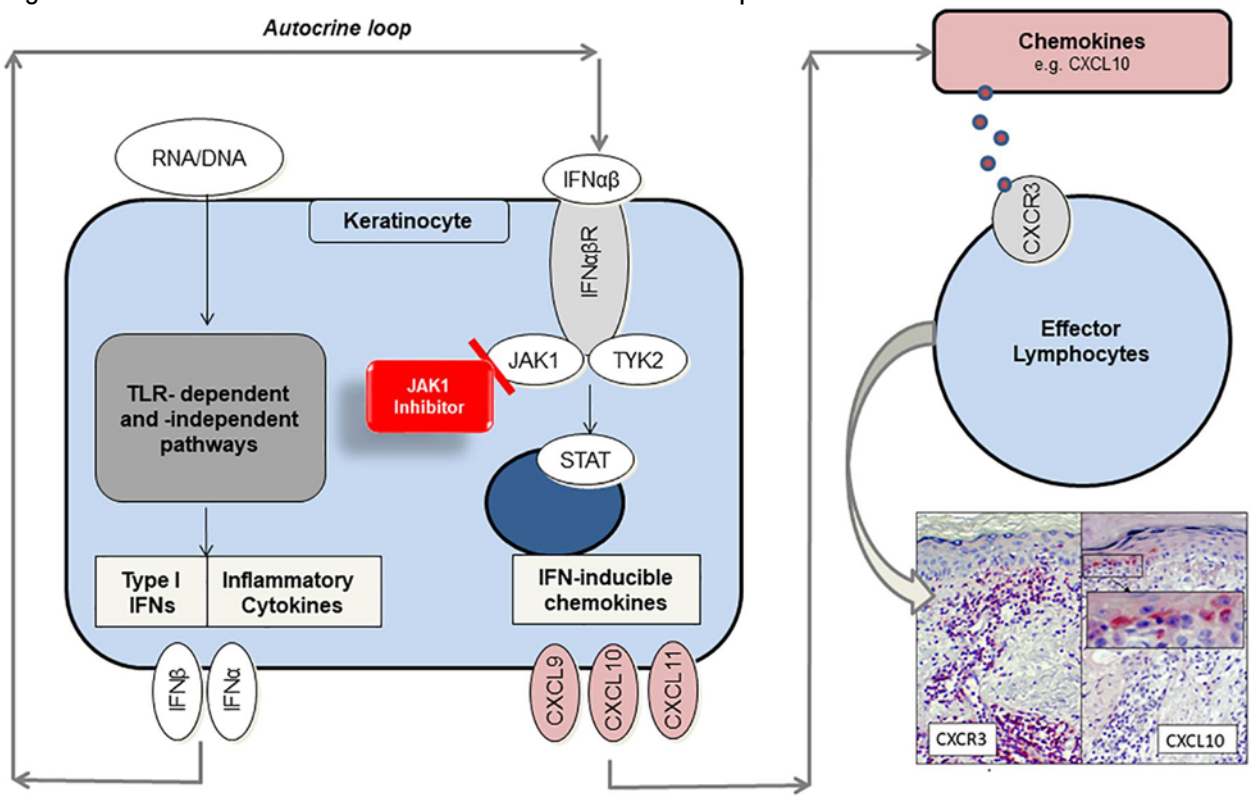
Figure 1: Inhibition of JAK Family by Abrocitinib



Source: Pfizer online information on abrocitinib

In cellular settings, where JAK kinases signal in pairs, abrocitinib preferentially inhibits cytokine-induced STAT phosphorylation mediated by receptors utilizing JAK1 relative to receptors utilizing JAK2 only or JAK2/TYK2 pairs. The JAK-STAT signaling pathway is the common transduction pathway for Type 1 and Type 2 cytokine receptors in response to inflammatory and proliferative signals.

Figure 2: Mechanism of Action for JAK inhibition on Atopic Dermatitis



Source: Information on JAK inhibitor for atopic dermatitis (AAD.org)

The Pfizer clinical program evaluated the safety and efficacy of abrocitinib 100 mg and 200 mg tablets administered orally once daily used for the treatment of moderate-to-severe AD. The sponsor recommended doses for abrocitinib for the treatment of moderate-to-severe AD (b) (4) [redacted] For patients with moderate (b) (4) renal impairment, or patients receiving 1 or more concomitant medicinal products drugs that are strong CYP2C19 inhibitors (e.g., fluvoxamine), the sponsor dosing recommendation for abrocitinib is 50 mg QD or 100 mg QD.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Pfizer submitted an application for the treatment of moderate-to-severe atopic dermatitis in (b) (4) [redacted] adult subjects (18 years and older) with moderate-to-severe atopic dermatitis. Although efficacy of the 200 mg QD is better than the 100 mg QD, the safety issues which include serious infections, opportunistic infections, malignancies, retinal detachment,

thromboembolism, MACE, and laboratory abnormalities (i.e., thrombocytopenia, lipid abnormalities) is increased in the higher dose compared to the lower 100 mg dose. With the recent Agency review of safety issues in other JAK inhibitors in this class of drugs, this reviewer recommends approval of abrocitinib for a more limited indication of 3rd line treatment of moderate-to-severe atopic dermatitis at 100 mg QD in adults with the option of a 200 mg QD dose for those adults that are not responding to the 100 mg QD and for which they failed or are intolerant of other systemic options. This recommendation would be in line with other concurrent applications of JAK class products baricitinib and upadacitinib.

APPEARS THIS WAY ON ORIGINAL

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Pfizer Inc. has submitted a 505 (b)(1) application for abrocitinib (CIBINQO), a Janus kinase (JAK) inhibitor proposed for the treatment of (b) (4) moderate-to-severe atopic dermatitis (b) (4) Abrocitinib is proposed as an oral tablet (50 mg, 100 mg, 200 mg) that works by inhibiting JAK by blocking the ATP binding site, inhibiting cytokine induced STAT phosphorylation mediated by receptors utilizing JAK in response to inflammatory and proliferative signals in atopic dermatitis.

To establish the efficacy of oral dosed abrocitinib, Pfizer conducted two Phase 3, multi-centered, placebo-controlled, clinical trials with abrocitinib 100 mg QD, 200 mg QD, and placebo. These two clinical trials make up the monotherapy studies (B7451012 and B7451013). In addition, an open-label, randomized withdrawal, placebo-controlled study where subjects received 12-weeks of 200 mg QD, responders were then randomized to 200 mg QD or 100 mg QD, or matching placebo up to 52 weeks (B7451014). Another supportive study conducted was a 16-week active-controlled, 200 mg QD or 100 mg QD study (B7451029) with a comparator dupilumab (DUPIXENT) at 300 mg SQ every other week (Loading 600 mg SQ at baseline) and matching placebo, double dummy design.

In the B7451012 (MONO-1), the IGA 0 or 1 responder for 200 mg QD was 42.8%; 100 mg QD 23.7%; placebo 7.9% and the EASI-75 responder for 200 mg QD was 62.7%; 100 mg QD 39.7%; placebo 11.8%. In the B7451013 (MONO-2) IGA 0 or 1 responder for 200 mg QD was 38.1%; 100 mg QD 28.4%; placebo 9.1% and EASI-75 responder for 100 mg QD was 61.0%, 100 mg QD 44.5%; placebo 10.4%.

To establish the safety of abrocitinib, the 12-week monotherapy safety pool (MONO-1 and MONO-2) contained a total of 778 subjects; 314 subjects in the 100 mg QD group and 309 subjects in the 200 mg QD group (155 subjects in the Placebo group). Median age was 30-years-old; 15.9% were adolescents under the age of 18 years old. Most frequent reported adverse reactions were nausea, headaches, vomiting, dizziness, herpes simplex, abdominal pain, and increase in blood creatinine phosphokinase.

A safety pool of all placebo-controlled studies identified 1540 subjects (8.1% adolescents) in the placebo-controlled studies (MONO-1, MONO-2, B7451006 and B7451029) with abrocitinib doses of 100 mg QD and 200 mg QD and placebo (608 subjects exposed to abrocitnib 100 mg QD, 590 subjects exposed to 200 mg QD, and 342 subjects exposed to placebo). Significant safety events include serious infections (opportunistic infections, multidermatomal cutaneous herpes zoster infections, and serious herpetic infections), possible lymphoma and other malignancies, venous thromboembolic events (VTE) including pulmonary embolism (PE) and deep vein thrombosis (DVT), and retinal detachment was also

suspect in subjects exposed to abrocitinib. In addition, during the clinical trials subjects had dose-dependent increase in blood lipid parameters, reduction in absolute neutrophil counts, and thrombocytopenia (low platelet counts) that had a nadir at 4-weeks during treatment with abrocitinib.

The applicant's monotherapy and placebo-controlled safety pools had the same 124 adolescents [29 subjects 17 years old (12 200 mg, 9 100 mg, 8 placebo); 25 subjects 16 years old (8 200 mg, 9 100 mg, 8 placebo); 21 subjects 15 years old (8 200 mg, 11 100 mg, 2 placebo); 18 subjects 14 years old (7 200 mg, 8 100 mg, 3 placebo); 18 subjects 13 years old (7 200 mg, 7 100 mg, 4 placebo); 13 subjects 12 years old (7 200 mg, 5 100 mg, 1 placebo)] from 12 years to under the age of 18 years. This population made up only 15% of the monotherapy safety population (the adolescent population was the same for both pools). The Division had previously recommended at least 30% of the safety population be adolescents for adequate benefit/risk analysis. (b) (4)

The applicant submitted a completed Phase 3 clinical study, B7451036 (TEEN), a randomized, placebo-controlled study in adolescent subjects, during the 120-day safety update. This study added 285 new subjects to the adolescent safety population. The Division commented that this submission would (b) (4) increase the review time. The applicant asked the Agency not to review this study for this approval cycle. The applicant included the B7451036 (TEEN) study in the 120-day safety update to the ISS. The Division will not review the new submitted data (b) (4)

(b) (4) Pfizer has provided adequate evidence of safety and efficacy for the use of abrocitinib in adult subjects (18 years and older) with moderate-to-severe atopic dermatitis. The risk assessment includes the recent analysis of the tofacitinib PMR study which revealed safety signals for MACE and malignancy. In the opinion of this reviewer, the risk of abrocitinib exposure for atopic dermatitis patients in the context of significant adverse events is less than the benefits of treatment. This reviewer is recommending approval for the 100 mg QD dose in adults with moderate-to-severe atopic dermatitis who have failed or are intolerant of other systemic treatments prior to starting abrocitinib. In addition the 200 mg QD dose can be used for failure of the 100 mg QD dose in patients who have no other options or have failed other systemic treatments and have tried abrocitniib 100 mg QD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. • The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals, AD persists into the adult years. • AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhino-conjunctivitis, and food allergies.	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance in the affected individual may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning.
Current Treatment Options	• For the Applicant's target population, FDA approved the only systemic treatment for atopic dermatitis in DUPIXENT (dupilumab) on 28-MAR-2017. • Prior to this approval, the use of systemic steroids was the only other systemic treatment. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions.	Until recently, the medical needs of children (6 to < 12 years) with moderate-to-severe AD were not being adequately met by available therapies. DUPIXENT (dupilumab) was approved for use in patients 6 years and older with moderate-to-severe atopic dermatitis on May-2020. The addition of an oral product,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment. • Phototherapy is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. Its drawbacks include a potentially time intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. • Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	such as abrocitinib, to the armamentarium for the treatment of moderate-to-severe atopic dermatitis would represent an alternative to having injections or systemic steroids. Additionally, abrocitinib would represent a safe and effective alternative to the several systemic immunomodulating agents that are used off-label for treatment of this population. Actions for supplements for the AD population for baricitinib and upadacitinib are under review as of the writing of this review.
Benefit	• To establish efficacy in monotherapy, the clinical trials compared co-primary endpoints for abrocitinib to placebo: o IGA responder proportion of clear (0)or almost clear (1) with abrocitinib 100 mg QD was 26.6% and with 200 mg QD was 41.3%, compared to 7.8% with placebo. o EASI-75 responder proportion with abrocitinib 100 mg QD	The adult data for the use of abrocitinib in moderate-to-severe atopic dermatitis has been established in the clinical trials provided by Pfizer. Abrocitinib 100 mg PO QD appears to be safe and effective treatment for atopic dermatitis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	was 41.9% and with 200 mg QD was 62.3%, compared to 12.2% with placebo. • In addition, PP-NRS4 responders at Weeks 2, 4, and 12 were observed.	(b) (4) (b) (4)
Risk and Risk Management	• The applicant evaluated the safety and efficacy of oral abrocitinib for the treatment of moderate-to-severe atopic dermatitis in subjects 12 years and above. Common adverse events included nausea, vomiting, abdominal pain, herpes simplex, increase blood creatinine phosphokinase, dizziness, and headaches which showed dose dependency from 100 mg QD to 200 mg QD. Three deaths were reported for the placebo-controlled safety pool and none were likely related to study drug. Serious risk of venous thromboembolism (pulmonary embolism and deep venous thrombosis) was increased in the higher dose of abrocitinib. Infections and opportunistic infections were also increased, especially with herpes zoster, herpes simplex, and eczema herpeticum. Thrombocytopenia and lymphopenia are also seen on laboratory evaluation, which had a nadir at 4 weeks and did not lead to serious clinical outcome. Janus kinase inhibitors are known to be associated with many of these serious adverse reactions. Labeling for this drug product will include a boxed warning for the most serious adverse reactions. The Agency reviewed the safety of JAK inhibitors for multiple indications in the US market place. Evidence of increased safety issues for MACE and malignancy limits the use of JAK inhibitors for non-life-threatening disease.	The Agency recommended at least 750 subjects with 1-year exposure in the safety population and at least 225 (30%) of those subjects are in the adolescent population. The applicant provided 124 adolescent subjects in their placebo-controlled trials, with 25 of those subjects in the placebo arm. The evaluable adolescent subjects were limited. The risks for treatment with oral abrocitinib are significant considering the treatment options available currently. In conclusion, abrocitinib should be used as 3rd line therapy after subjects with moderate-to-severe atopic dermatitis have failed or are intolerant to systemic treatment. The higher 200 mg QD dose may be used for those adults who have failed 100 mg QD and have no other options available.

1.4. Patient Experience Data

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

☐	**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		6.1.1, 6.1.2, 7.1.2, 8.1.2
		X	Patient reported outcome (PRO)	6.1.1, 7.1.2, 8.1.1, 8.18
		X	Observer reported outcome (ObsRO)	6.1.1, 7.1.2, 8.1.2
		X	Clinician reported outcome (ClinRO)	6.1.1, 7.1.2, 8.1.1
		X	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)		
	X	Other: (Please specify): (DLQI, CDLQI, HADS, POED, PtGA, EQ-5D-%L, EQ-5D-Y, FACIT-F, Peds-FACIT-F, SF-36v2)		6.1.1, 7.1.2, 8.1.2, 8.18
☐	**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 was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis (AD) or commonly known as eczema, is a chronic, relapsing inflammatory skin condition characterized by dry, pruritic skin that occurs most frequently in children but also affects many adults. It is the leading non-fatal health burden attributable to skin disease, inflicts a substantial psychosocial burden on patients and their relatives, and increases the risk of food allergy, asthma, allergic rhinitis, other immune-mediated inflammatory diseases, and mental health disorders.[1] Clinical features of AD include skin dryness, erythema, oozing and crusting, and lichenification. Pruritis is a hallmark of the condition and responsible for much of the disease burden for patients and their families.

AD may have different endotypes, including race, ethnicity and age, and patients with and without filaggrin mutations. [2] In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals.[3] Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96%.[4] For 10-30% of individuals, AD persists into the adult years.[5]

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is like that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum

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[1] Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016 Mar;387(10023):1109-22.
[2] Czarnowicki T, He H, Drueger J, et al. AD endotypes and implications for targeted therapeutics. *J Aller Clin Immunol* 2019;143:1011.
[3] Weston WL and How W. Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis. Dellavalle RP, Levy ML, Fowler J, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed Sept. 15, 2020).
[4] Shaw TE et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. (2011) 131, 67-73.
[5] Eichenfield LF, et al. Guidelines of care for the management of atopic dermatitis. Section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol*. 2014;70:338-51.

corneum which permits the penetration of environmental allergens. The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[6]

Acute AD is associated with cytokines produced by T helper 2 type (Th2) cells (as well as other T-cell subsets and immune elements). These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in Th2 inflammation.[7] IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells.[8] IL-13 expression correlates with disease severity and flares.[4] IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex.[6] IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases. Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4Rα subunit.[9]

2.2. Analysis of Current Treatment Options

Food and Drug Administration (FDA)-approved or -licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 (PDE-4) inhibitors (topical), and IL-4 receptor antagonist (dupilumab).

Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[10] Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in

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[6] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. *J Allergy Clin Immunol*. 2014;134:769-79.
[7] Bao K and Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 immunity. *Cytokin*. 75 (2015) 25-37.
[8] May RD, Fung M. Strategies targeting the IL-4/IL-13 axes in disease. *Cytokin*. 2015;75:89-116.
[9] DUPIXENT package insert.
[10] Sidbury et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327-49.

children and adolescents is the risk of decreased linear growth during treatment. Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[11] Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate-to-severe AD and pimecrolimus for mild-to-moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors; a causal relationship has not been established. Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD).

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, lotions. Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease. They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principal treatment for mild disease. Although there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease. The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control the disease.[13]

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[11] Eichenfeld et al. Guidelines of care for the management of atopic dermatitis. Section 1. Management and treatment with topical therapies. *J Am Acad Dermatol*. 2014;71:116-32.

Dupilumab is currently indicated for use in patients > 6 years of age with moderate-to-severe atopic dermatitis (Supplement-17) who have failed topical therapies or when those therapies are inadvisable. Dupilumab is given by injection. New treatments, focused on oral therapies are needed in the armamentarium for the treatment of moderate-to-severe AD.

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts. However, long-term risks from phototherapy treatment of AD in children have not been evaluated. Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA).

Systemic immunomodulating agents are used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil).[12] Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Abrocitinib is not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pfizer opened the IND 123554 for PF-04965842 (abrocitinib) on 30-OCT-2014 with two Phase 1 studies (B7451001 and B7451004) in healthy subjects already completed. The 30-day safety IND was a Phase 2 study (B7451005) in subjects with moderate to severe psoriasis, not in atopic dermatitis. An End-of-Phase 2 meeting was held on 30-OCT-2017. The applicant was provided feedback on proposed Phase 3 endpoints and pruritus NRS scales. In addition, the Agency described labeling claims for active comparators and discussed the initial pediatric development plans. The applicant submitted a Breakthrough Designation Request which was granted on 7-FEB-2018. All Phase 3 study proposals were reviewed. The applicant requested a Pre-NDA meeting, but canceled the meeting after receiving the Agency's preliminary meeting comments. We reiterated that for safety, 750 subjects should be exposed to abrocitinib for at least 1 year and that of those subjects 30% (225) should be adolescent subjects.

A review of abrocitinib safety experience was done based on clinical trial submitted safety reports and liver injury reports. This was completed on 13-APR-2020. The applicant has requested a rolling submission and currently the Agency has received multiple submissions to this NDA.

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

4.1. Office of Scientific Investigations (OSI)

John Lee, M.D., of the Good Clinical Practice Assessment Branch, Division of Clinical Compliance Evaluation in the Office of Scientific Investigations authored the OSI review, which noted no GCP violations:

"Two clinical investigators were selected for good clinical practice (GCP) inspection. A remote regulatory assessment (RRA) was performed in lieu of an on-site GCP inspection for one of the two CI sites due to the on-going COVID-19 pandemic-related travel restrictions. Overall, no significant GCP violations were identified. Based on the results of the inspection and the RRA, the clinical data generated by the two CIs appear to be supportive of this NDA.

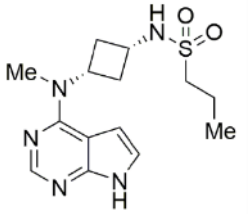
It should be noted that, at Site 1002 in Study B7451012 (Iftikhar Hussain; Tulsa, Oklahoma), the observations included violations of EASI (Eczema Area and Severity Index, 4 subjects) or pruritis NRS (Numerical Rating Scale, one subject) study eligibility criteria. The violations allowed subjects with disease severity scores that are not high enough to be enrolled in study. The violations were reported in the NDA for all 5 subjects. Enrolling subjects with less severe disease than that allowed by the protocol appeared to work against the demonstration of abrocitinib efficacy."

4.2. Product Quality

1) Drug Substance

Abrocitinib is a synthetic small molecule orally bioavailable Janus Kinase 1 inhibitor (JAK 1). It reversibly and selectively inhibits JAK1 by blocking the ATP binding site. This active ingredient has been classified as a new molecular entity and has been developed for the oral treatment of atopic dermatitis.

Abrocitinib is a white to slightly colored crystalline powder. It is non-hygroscopic with a melting point of ~189ºC, pKa of 5.3, and LogP of 1.66. Polymorph screening of abrocitinib have only shown a single anhydrous crystal form. It is insoluble to slightly soluble in common organic solvent. Abrocitinib has the chemical name, N-((1s,3s)-3-(methyl(7H-pyrrolo[2,3- d]pyrimidin-4-yl)amino)cyclobutyl)propane-1-sulfonamide, the molecular formula of $C_{14}H_{21}N_5O_2S$ with a molecular weight of 323.42g/mole, and the chemical structure presented below:



Abrocitinib for this application is manufactured by Pfizer Ireland Pharmaceuticals, Ringaskiddy, Cork, Ireland in accordance with current good manufacturing practices. The drug substance manufacturer is recommended for approval based on compliance history, acceptable profile codes and experience in the proposed responsibilities. This drug substance is tested and released according to a specification consistent with ICH Q3A, Q3C, and Q3D guidelines that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest of 24 months when stored at or below 30ºC + 2ºC and humidity of 75% + 5%. The applicant has provided sufficient stability data in support of the proposed retest period.

2) Drug Product

The drug product, CIBINQO (abrocitinib) Tablets, 50mg, 100mg, and 200mg has been developed for the treatment of moderate-to-severe atopic dermatitis (b) (4) CIBINQO tablets are intended for once a day oral administration. All strengths of CIBINQO are packaged as 30 tablets in 60-mL white high-density polyethylene bottles with white (b) (4) closure.

CIBINQO tablets are film-coated tablets each containing 50mg, 100mg, or 200mg of abrocitinib depending on the strength as the active ingredient and microcrystalline cellulose (NF), dibasic calcium phosphate anhydrous (USP), sodium starch glycolate (NF), magnesium stearate (NF), (b) (4) as inactive ingredients. Components used in the composition (b) (4) are all compendial materials. All strengths of the tablets are manufactured (b) (4) (b) (4) with identical quantitative composition and only differ in size. 50mg strength is a pink oval tablet debossed with "PFE" on one side and "ABR 50" on the other side. 100mg strength is a pink round tablet debossed with "PFE" on one side and "ABR 100" on the other side. 200mg strength is a pink oval tablet debossed with "PFE" on one side and "ABR 200" on the other side.

CIBINQO tablets are manufactured in accordance with the current good manufacture practices by a continuous manufacturing process and the use of a new emerging technology by Pfizer Manufacturing Deutschland GmbH, Freiburg, Germany.

The manufacturing process for the Abrocitinib tablet (b) (4)

The drug product manufacturing facility was evaluated through the 704(a)(4) based assessment in lieu of an onsite PAI. Based on the assessment of the records, the facility is recommended for approval for the stated function in this application.

CIBINQO tablets are tested and released against a specification consistent with ICH Q3B that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The applicant has submitted sufficient stability data in support of the proposed expiration dating period.

3) The OPQ Recommendation

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, purity, strength, and quality of the drug substances, abrocitinib, and the drug product, CIBINQO (abrocitinib) Tablets, 50mg, 100mg, and 200mg intended for oral administration.
- Labels/labeling issues have been satisfactorily addressed.
- The Office of Pharmaceutical Manufacturing Assessment has made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment has been granted.

Therefore, from the OPQ perspective, this NDA is recommended for APPROVAL with the expiration dating period of 24 months.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The applicant submitted a 505(b)(1) application for abrocitinib tablets for the treatment of moderate-to-severe atopic dermatitis (b) (4) Abrocitinib is a new molecular entity Janus kinase (JAK) inhibitor.

The applicant submitted the following nonclinical studies to support the NDA. Oral repeat dose toxicity studies in rats (up to 6 months in duration); oral repeat dose toxicity studies in monkeys (up to 9 months in duration); a battery of in vitro and in vivo genetic toxicity studies; a 2-year oral carcinogenicity study in rats; a 6-month oral carcinogenicity study in transgenic mice; fertility and early embryonic development studies in rats; embryofetal development studies in rats and rabbits; a pre- and postnatal development study in rats; and a juvenile animal toxicity study in rats. The applicant also submitted several studies to support the safety of several metabolites and potential impurities, including: in vitro cardiovascular safety studies of metabolites; in vitro genetic toxicity studies of potential impurities; and an in vivo repeat dose toxicity study of metabolites in rats.

In a pivotal 6-month oral repeat dose toxicity study in rats, abrocitinib (doses: 0, 30, 45, and 70 mg/kg/day) decreased lymphocytes at all dose levels consistent with its intended pharmacological effect. Abrocitinib produced reversible, dose-related urinary crystals at doses ≥45 mg/kg/day. The NOAEL was 30 mg/kg/day, which corresponds to Day 182 AUC_{24} and C_{max} of 58500 ng·hr/mL and 9110 ng/mL, respectively. In a pivotal 39-week oral repeat dose toxicity study in monkeys, abrocitinib (doses: 0, 15, 35, and 75 mg/kg/day) decreased lymphocytes at all dose levels consistent with its intended pharmacological effect, but had no adverse effects. The NOAEL was 75 mg/kg/day, which corresponds to Day 273 AUC_{24} and C_{max} of 55200 ng·hr/mL and 5170 ng/mL, respectively.

Abrocitinib was not mutagenic in an in vitro reverse bacterial mutation assay. Abrocitinib was positive in an in vitro micronucleus assay and determined to be an aneugen in a follow-up study; however, it was not genotoxic in an in vivo micronucleus assay in rats.

In an oral carcinogenicity study in rats, abrocitinib (doses: 0, 3, 10, and 30 mg/kg/day) was administered once daily to rats for 104 weeks. Abrocitinib increased mortality in HD males, but not at lower doses or in females. At doses ≥10 mg/kg/day, abrocitinib significantly increased the incidence of benign thymoma in the thymus of female rats. No abrocitinib-related tumor findings were noted in males. In an oral carcinogenicity study in rasH2 transgenic mice, abrocitinib (female doses: 0, 10, 25, and 75 mg/kg/day; male doses: 0, 10, 20, and 60 mg/kg/day) was administered once daily to transgenic rasH2 mice for 6 months. Abrocitinib increased mortality in HD females, but not at lower doses or in males. No abrocitinib-related tumor findings were noted in mice.

In an oral fertility and early embryonic development study in rats, abrocitinib (doses: 0, 30, 45, and 70 mg/kg/day) produced dose-related adverse effects on female fertility and early embryonic development. No adverse effects were noted in males (male NOAEL: 70 mg/kg/day). In a second oral fertility and early embryonic development study in female rats with a 1-month recovery period, abrocitinib (doses: 0, 3, 10, and 70 mg/kg/day) displayed similar adverse effects on fertility and embryonic development at the HD as in the previous study; impaired fertility was reversible after a 1-month recovery. No adverse effects were noted at doses ≤10 mg/kg/day (female NOAEL: 10 mg/kg/day).

In an oral embryofetal development study in rats, abrocitinib (doses: 0, 10, 30, and 60 mg/kg/day) did not produce maternal toxicity (NOAEL: 60 mg/kg/day, corresponding to gestational day (GD) 17 AUC_{24} and C_{max} of 90000 ng·hr/mL and 6410 ng/mL, respectively). Abrocitinib increased the incidence of skeletal variations at doses ≥30 mg/kg/day, including the incidence of short 13th ribs, thickened ribs (HD only), and cervical arches with reduced ventral processes (HD only). Abrocitinib increased embryofetal lethality at the HD. The developmental NOAEL was 30 mg/kg/day, corresponding to a GD 17 AUC_{24} and C_{max} of 58300 ng·hr/mL and 4880 ng/mL, respectively. In an oral embryofetal development study in rabbits, abrocitinib (doses: 0, 10, 30, and 75 mg/kg/day), did not produce maternal toxicity or adverse developmental effects (maternal and developmental NOAEL: 75 mg/kg/day, corresponding to GD 19 AUC_{24} and C_{max} of 43000 ng·hr/mL and 16800 ng/mL, respectively).

In an oral pre- and postnatal development study in rats, abrocitinib (doses: 0, 10, 30, and 60 mg/kg/day) caused a high rate of total litter loss and markedly decreased F_1 survival at 60 mg/kg/day; consequently, no F_1 offspring were evaluated at the HD. Abrocitinib transiently reduced F_1 body weights from birth through weaning at the MD, but had no effect on F_1 offspring postnatal developmental, neurobehavioral, or reproductive performance (NOAEL: 30 mg/kg/day).

In an oral juvenile animal study in rats, abrocitinib (doses: 0, 5, 25, and 75 mg/kg/day; once daily from PND 10 to 63) produced dose-related adverse effects relating to development of the femur, tibia, and paws. At all dose levels, abrocitinib caused a reversible dose-related decrease in the primary spongiosa in the metaphysis of the proximal tibia and distal femur and irreversible dose-related small or misshapen femoral heads. At the MD and HD, abrocitinib irreversibly decreased femur size and caused paw malrotation and limb impairment; at the HD, paw fractures generally corresponded to limb impairment, a fractured tibia was noted in a single female, and effects noted at lower doses were increased in frequency and severity. Because adverse bone findings were noted at all dose levels, a NOAEL could not be established. Based on an unbound AUC comparison, the LD, MD, and HD are 1.1, 10, and 36 times the MRHD.

At clinically-relevant concentrations in vitro, the abrocitinib metabolites, M1 (PF-06471658), M2 (PF-07055087), and M4 (PF-07054874) did not inhibit $Na_v1.5$, $Ca_v1.2$, or hERG currents. The abrocitinib impurities (b) (4)

[redacted] were not mutagenic in bacterial reverse mutation assays. The abrocitinib impurities [redacted] were mutagenic in bacterial reverse mutation assays. The abrocitinib impurity [redacted] was weakly positive in bacterial reverse mutation assays and was genotoxic in vivo. [redacted] will be controlled using an ICH M7 [redacted] strategy. In an in vivo qualification study, abrocitinib (doses: 0, 30, and 30 [containing [redacted] mg/kg/day) was administered to rats by oral gavage once daily for 13 weeks; similar findings were noted between abrocitinib and impurity-spiked abrocitinib.

Abrocitinib tablets do not contain novel excipients; all excipients are present at the same or lower levels as previously approved oral drug products.

This NDA is approvable from a nonclinical perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this NDA.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Abrocitinib is a new molecular entity Janus kinase (JAK) inhibitor. In vitro, with ATP at the apparent Km, abrocitinib inhibits JAK1 (IC_{50}: 3.27 nM) with slight selectivity over JAK2 (IC_{50}: 30.3 nM), JAK3 (IC_{50}: 493 nM), and TYK2 (IC_{50}: 53.8 nM); with 1 mM ATP, abrocitinib inhibited JAK1 (IC_{50}: 29.2 nM) with greater selectivity over JAK2 (IC_{50}: 803 nM), JAK3 (IC_{50}: >10000 nM), and TYK2 (IC_{50}: 1250 nM). Additionally, except for JAK3, 1 µM abrocitinib did not have notable in vitro activity against a panel of kinases. These data support statements made in section 12.1 of labeling. Additionally, in various in vitro cell systems, abrocitinib inhibited cytokine-induced STAT phosphorylation more potently when JAK1-mediated. This is consistent with the selectivity of abrocitinib for JAK1 over other kinases.

In vitro, the abrocitinib metabolites, M1, M2, and M3 displayed similar inhibition of JAK1, JAK2, JAK3, and TYK2 compared to abrocitinib and similar (or greater) selectivity for JAK1 than abrocitinib; M4 did not have inhibitory activity in vitro. These data support statements made in section 12.1 of labeling.

Abrocitinib did not display activity at a panel of receptors, transporters, or ion channels at clinically relevant concentrations in vitro. Abrocitinib reversibly inhibited MAO-A (IC_{50}: 6 µM) in vitro. Abrocitinib bound to VEGFR2 (IC_{50}: 1.2 µM), but did not inhibit VEGFR2 function at clinically relevant concentrations in vitro.

Safety pharmacology

Neurological effects:
Male Wistar rats (6 per group) received a single oral dose of abrocitinib (doses: 0 [vehicle: (b) (4) in water], 75, 200, and 600 mg/kg). One hour post-dose, body temperature was recorded, and a functional observation battery was performed, followed by 30 minutes of locomotor activity measurement. No changes were noted in the functional observation battery. At the MD and HD, body temperature slightly decreased (by approximately 0.6°C). At all dose levels, locomotor activity decreased (by approximately 50%).

Respiratory effects:
Male Wistar rats (6 per group) received a single oral dose of abrocitinib (doses: 0 [vehicle: (b) (4) in water], 75, 200, and 600 mg/kg). Pulmonary parameters (respiratory rate, tidal volume, and minute volume) were assessed using whole body plethysmography for 4 hours post-dose. No adverse abrocitinib-related effects were noted.

Cardiovascular effects:
In vitro, abrocitinib did not produce clinically relevant inhibition of the hERG potassium current or the $Na_v1.5$ sodium current. Up to 300 µM abrocitinib produced 78% inhibition of the hERG current (IC_{50}: 95 µM) and 31% inhibition of the $Na_v1.5$ current.

Conscious unrestrained male cynomolgus monkeys (n=8) received oral doses of abrocitinib (doses: 0 [vehicle: (b) (4) in water], 15, 40, 80, or 150 mg/kg) in a cross-over study with a minimum washout period of 6 days. Cardiovascular parameters were monitored pre-dose through 22 hours post-dose, including arterial blood pressure, heart rate, and ECG (including RR, PR, QRS, QT, and QTc intervals). Emesis was noted at 80 and 150 mg/kg dose levels. Abrocitinib caused a dose-related increase in heart rate (up to 30 bpm increase at the HD).

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Single dose pharmacokinetics and oral bioavailability of PF-04965842 in rats following oral and intravenous administration / PF-04965842_13DEC12_123752	A single oral (3 mg/kg) or intravenous (1 mg/kg) dose of abrocitinib was given to male rats. Oral bioavailability of abrocitinib was 95.6%. Following intravenous dosing, mean clearance, volume of distribution, and half-life were 26.6 mL/min/kg, 1.04 L/kg, and 0.82 hours, respectively.
One day oral gavage or intravenous dose toxicokinetics/pharmacokinetics study of PF-04965842 in monkeys / 12MA052	A single oral (3 mg/kg) or intravenous (1 mg/kg) dose of abrocitinib was given to female and male monkeys. Oral bioavailability of abrocitinib was 9.8%. Following intravenous dosing, mean clearance, volume of distribution, and half-life were 30.8 mL/min/kg, 0.82 L/kg, and 0.52 hours.
Distribution	
Protein binding of PF-04965842-00 in human, monkey, and rat plasma / ADME-2012-001-0021	In vitro, 36.2%, 37.0%, and 38.3% of abrocitinib (2 µM) was unbound when incubated with human, monkey, and rat plasma, respectively.
Protein binding of PF-04965842 in mouse and rabbit plasma / PF-04965842_18Nov13_145025	In vitro, 19.1% and 55.2% of abrocitinib (2 µM) was unbound when incubated with rabbit and mouse plasma, respectively.
Protein binding of PF-06471658 in mouse, rat, rabbit, monkey and human plasma / YDP/067/273	In vitro, 62.8%, 55.3%, 37.2%, 63.5%, and 63.1% of M1 (2 µM) was unbound when incubated with mouse, rat, rabbit, monkey, and human plasma, respectively.
Protein binding of PF-07055087 in mouse, rat, rabbit, monkey and human plasma / YDP/067/275	In vitro, 59.7%, 54.5%, 45.5%, 66.3%, and 71.1% of M2 (2 µM) was unbound when incubated with mouse, rat, rabbit, monkey, and human plasma, respectively.
Protein binding of PF-07054874 in mouse, rat, rabbit, monkey and human plasma / YDP/067/274	In vitro, 95.2%, 76.2%, 58.7%, 93.8%, and 82.6% of M4 (2 µM) was unbound when incubated with mouse, rat, rabbit, monkey, and human plasma, respectively.
Quantitative Whole-Body Autoradiography of Male Long Evans Rats After a Single Oral Administration of [^{14}C]PF-04965842 / PF-04965842_06Mar18_024730	In male pigmented rats, a single 10 mg/kg oral dose of [^{14}C]abrocitinib was extensively distributed with highest concentrations in the uveal tract of the eye, liver, kidneys, and adrenal and salivary glands; distribution to the brain was minimal.
Metabolism	

Type of Study	Major Findings
Preliminary investigation of the in vitro and in vivo biotransformation of PF-04965842 in human and preclinical species / PF-04965842_28Nov12_140212	Abrocitinib metabolism was examined in vitro in rat, monkey, and human liver microsomes and hepatocytes and in vivo in rat and monkey plasma, urine, and bile. No unique human metabolites were noted. M4 was observed in vitro and in rat and monkey plasma, urine, and bile. M2 and M3 were not differentiated, but were noted in vitro and in rat plasma, urine, and bile. Note: See Excretion subsection for relevant findings regarding excretion of parent and metabolites.
Plasma pharmacokinetics of abrocitinib, M1, M2, and M4 in rats following multiple oral administrations / 8439720	Rats received abrocitinib (45 or 70 mg/kg/day in males and females, respectively) by oral gavage once daily for 5 days for pharmacokinetic assessment of plasma (on Day 5) and urine (on Day 4). Unchanged abrocitinib was M4 was the predominant metabolite, followed by M2; M1 exposure was very low in males and too low to calculate in females. Only M2 was detected in urine. AUC_{last} (ng·hr/mL): Abrocitinib: 48500 (male) and 164000 (female) M1: 22.7 (male) and not calculable for females M2: 1370 (male) and 662 (female) M4: 9720 (male) and 20500 (female)
Excretion	
Lacteal Excretion of PF-04965842 Following Administration of a Single Oral Dose to Rats / PF-04965842_24Apr18_095421	A single oral dose of abrocitinib (10 mg/kg) was given to lactating rats. Concentrations in milk were approximately 5 times higher than plasma. The C_{max} (at 1 hour post-dose) was 1710 and 8050 ng/mL in plasma and milk, respectively; the AUC_{0-t} was 4570 and 24200 ng·hr/mL in plasma and milk, respectively. These data support statements made in section 8.2 of labeling.
Preliminary investigation of the in vitro and in vivo biotransformation of PF-04965842 in human and preclinical species / PF-04965842_28Nov12_140212	In rats and monkeys, abrocitinib was not extensively excreted in the urine or bile; M4 was primarily excreted in the urine of rats and monkeys; M2 (and/or M3) was present at qualitatively similar levels in rat urine and bile; and M1 was present at trace levels in rat urine.

Type of Study	Major Findings
TK data from general toxicology studies A 6-Month Oral Gavage Toxicity and Toxicokinetic Study of PF-04965842 in Rats with a 12-Week Recovery Phase / 13MA056	<u>Rat @ NOAEL (30 mg/kg/day) on Day 182</u> t_{max}: 1.0 (female) and 1.8 hr (male) AUC_{24}: 140000 (female) and 142000 ng·hr/mL (male) C_{max}: 17000 (female) and 12700 ng/mL (male) Accumulation: None Dose proportionality: Exposure increased approximately dose proportionally on Days 1 and 182.
A 9-Month Oral Gavage Toxicity and Toxicokinetic Study of PF-04965842 in Cynomolgus Monkeys with a 12-Week Recovery Phase / 13MA055	<u>Monkey @ NOAEL (75 mg/kg/day) on Day 273</u> t_{max}: 5.7 (female) and 3.5 hr (male) AUC_{24}: 65500 (female) and 47500 ng·hr/mL (male) C_{max}: 4990 (female) and 5310 ng/mL (male) Accumulation: Yes, but only at the HD Dose proportionality: Exposure generally increased approximately dose proportionally.
TK data from reproductive toxicology studies An Oral (Gavage) Study of the Effects of PF-04965842 on Male and Female Fertility and Early Embryonic Development to Implantation in Rats / 17GR089	<u>Rat @ male fertility NOAEL (70 mg/kg/day; HD) on Day 12 of dosing</u> AUC_{24}: 142000 ng·hr/mL C_{max}: 12500 ng/mL (HD) Note: A female NOAEL could not be determined. Male AUC_{24} based on the male Day 182 AUC_{24} at 70 mg/kg/day in the 6-month oral repeat dose toxicity study, which had a similar C_{max} (12700 ng/mL)
Oral Female Fertility Study of PF-04965842 In Wistar Han Rats with 1-Month Reversibility / 18GR261	<u>Rat @ female fertility NOAEL (10 mg/kg/day; MD) on Day 10 of dosing</u> AUC_{24}: 11000 ng·hr/mL C_{max}: 2660 ng/mL
An Embryo-Fetal Development Study of PF-04965842 by Oral (Gavage) in Rats / 14GR073	<u>Rat @ developmental (10 mg/kg/day; LD) and maternal NOAEL (60 mg/kg/day; HD) on GD 17</u> AUC_{24}: 12900 (LD) and 90000 ng·hr/mL (HD) C_{max}: 2180 (LD) and 6410 ng/mL (HD)
An Embryo-Fetal Development Study of PF-04965842 by Oral (Gavage) in Rabbits / 14GR183	<u>Rabbit @ maternal and developmental NOAEL (75 mg/kg/day; HD) on GD 19</u> AUC_{24}: 43000 ng·hr/mL C_{max}: 16800 ng/mL
An Oral (Gavage) Juvenile (PND 10 Through 63) Toxicity Study of PF-04965842 in Wistar Han Rats With a 2-Month Recovery / 19GR039	<u>Rat @ LD (5 mg/kg/day) on PND 10 and 63</u> AUC_{24}: 12800 (PND 10) and 4270 ng·hr/mL (PND 63) C_{max}: 1250 (PND 10) and 988 ng/mL (PND 63) Note: A NOAEL could not be determined.

Type of Study	Major Findings
TK data from Carcinogenicity studies 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with PF-04965842 in Rats / 17MA056	Rat @ NOAEL (female: 3 mg/kg/day [LD]; male: 30 mg/kg/day [HD]) on Day 178 AUC_{24}: 3150 (LD) and 76000 ng·hr/mL (HD) C_{max}: 930 (LD) and 10700 ng/mL (HD)

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 6-Month Oral Gavage Toxicity and Toxicokinetic Study of PF-04965842 in Rats with a 12-Week Recovery Phase / 13MA056

- Abrocitinib produced dose-related reversible urinary crystals at the MD and HD.
- Abrocitinib decreased lymphocytes at all dose levels, consistent with its intended pharmacological effect.
- Based on the urinary crystals observed at higher doses, the NOAEL was 30 mg/kg/day, which corresponds to Day 182 AUC_{24} and C_{max} of 58500 ng·hr/mL and 9110 ng/mL, respectively.

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

Methods

Dose and frequency of dosing:	0, 30, 45, and 70 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in water
Species/Strain:	Rat/Wistar Han
Number/Sex/Group:	15
Age:	6-7 weeks old at dosing initiation
Satellite groups/ unique design:	5/sex/group for toxicokinetic assessment; 5/sex control and HD for 12-week recovery
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No abrocitinib-related findings.
Clinical Signs	Abrocitinib reversibly increased the incidence of skin sores and/or scabs at the MD and HD.
Body Weights	No adverse abrocitinib-related findings.

Ophthalmoscopy	No abrocitinib-related findings.
Hematology	Abrocitinib markedly decreased lymphocytes (by 64% to 70% in females and 71% to 82% in males) without a dose relationship.
Clinical Chemistry	No adverse abrocitinib-related findings.
Urinalysis	Dose-related reversible urinary crystals were noted in both sexes at the MD and HD.
Gross Pathology	Abrocitinib-related macroscopic findings were limited to a low incidence of small spleen (in all groups except MD males) and skin scabs (limited to MD and HD females).
Organ Weights	Abrocitinib decreased absolute and relative spleen and thymus weights at all dose levels in both sexes.
Histopathology Adequate battery: Yes	Abrocitinib reversibly decreased lymphoid cellularity in lymphoid tissues (spleen, thymus, gut-associated lymph tissue, and lymph nodes). This is consistent with its intended pharmacology.

MD: mid dose; HD: high dose.

Study title/ number: A 9-Month Oral Gavage Toxicity and Toxicokinetic Study of PF-04965842 in Cynomolgus Monkeys with a 12-Week Recovery Phase / 13MA055

- Abrocitinib-related findings were non-adverse and related to its pharmacology, including decreased circulating lymphocytes and decreased spleen and thymus weights and cellularity.
- The NOAEL was 75 mg/kg/day, which corresponds to Day 273 AUC_{24} and C_{max} of 55200 ng·hr/mL and 5170 ng/mL, respectively.

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

Methods

Dose and frequency of dosing:	0, 15, 35, and 75 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in water
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	4
Age:	2-4 years old at dosing initiation
Satellite groups/ unique design:	3/sex control and MD for 12-week recovery (reversibility was not assessed at the HD)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No abrocitinib-related findings.

Clinical Signs	No adverse abrocitinib-related findings.
Body Weights	No abrocitinib-related findings.
Ophthalmoscopy	No abrocitinib-related findings.
ECG	No abrocitinib-related findings.
Hematology	No adverse abrocitinib-related findings. Abrocitinib decreased lymphocytes (by 33% to 41.5% in females and 21.9% to 30.3% in males) without a dose relationship.
Clinical Chemistry	No adverse abrocitinib-related findings.
Urinalysis	No abrocitinib-related findings.
Gross Pathology	No abrocitinib-related findings.
Organ Weights	Abrocitinib decreased spleen (by up to 25.4%) and thymus (up to 44%) in females at all dose levels. Thymus weight decreased (up to 31.5%) in HD males; no effects were noted at lower doses or on spleen weights. These changes were related to the intended pharmacology and non-adverse.
Histopathology Adequate battery: Yes	Abrocitinib reversibly decreased lymphoid cellularity of the thymus and spleen in both sexes in a generally dose-related manner.
Immunophenotyping	Abrocitinib reversibly decreased NK cells at all dose levels (by 60.9% to 72.8% in females and 58.5% to 68.8% in males).
Serum Immunoglobulins	Abrocitinib reversibly decreased IgA at all dose levels, in a dose-related manner, in females (up to 41.6%) and in HD males (by up to 37.2%).
T Cell-Dependent Antibody Response	Abrocitinib reversibly decreased anti-KLH IgM and IgG titers in both sexes in a dose-related manner.

LD: low dose; MD: mid dose; HD: high dose; KLH: Keyhole limpet hemocyanin

5.5.2. Genetic Toxicology

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>
Study title/ number: PF-04965842 *Salmonella-E. Coli*/Mammalian Microsome Reverse Mutation Assay / 12GR326
Key Study Findings:

- Abrocitinib was not mutagenic under the conditions of the assay. These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA; up to 5000 µg/plate; ±S9
Study is valid: Yes

<u>In Vitro Assays in Mammalian Cells</u>
Study title/ number: PF-04965842 In Vitro Micronucleus Assay in TK6 Cells / 12GR325
Key Study Findings:

- Abrocitinib induced micronuclei in vitro after a 27-hour incubation without metabolic activation.

- In a subsequent mechanistic study using Fluorescent In Situ Hybridization, abrocitinib was identified as an in vitro aneugen. These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: TK6 cells; up to 204 µg/mL (4-hour incubation, -S9), 175 µg/mL (4-hour incubation, +S9), or 43.6 µg/mL (27-hour incubation, -S9)
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title/ number: In Vivo Rat Bone Marrow Micronucleus Assay with PF-04965842 / 12GR327
Key Study Findings:

- Abrocitinib did not induce bone marrow micronuclei at doses up to 600 mg/kg/day (corresponding to a Day 1 AUC_{0-24} and C_{max} of 649000 ng·hr/mL and 35400 ng/mL, respectively). These data support statements made in section 13.1 of labeling.

GLP compliance: Yes
Test system: Rat, bone marrow micronuclei; two consecutive days of oral dosing of 0 (vehicle), 100, 300, or 600 mg/kg/day; assessments on the second day of dosing
Study is valid: Yes

Other Genetic Toxicity Studies
Ten abrocitinib impurities (up to 5000 µg/plate; ±S9) were evaluated for genotoxic potential in traditional in vitro bacterial reverse mutation assays using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA. The GLP studies were conducted using both plate incorporation and preincubation methods; exploratory non-GLP studies used the plate incorporation method. (b) (4) (study #20171491; GLP), (b) (4) (b) (4) (study #20171440; GLP), (b) (4) (study #20171525; GLP), (b) (4) (study #20171457; GLP), (b) (4) (study #20171507; GLP), (b) (4) (study #20GR050; non-GLP), and (b) (4) (study #18GR278; non-GLP) were not mutagenic.

(b) (4) (study #20171473; GLP) and (b) (4) (study #20GR051; non-GLP) were mutagenic. (b) (4) (study #18GR277; non-GLP) was weakly positive in bacterial reverse mutation assays. In a subsequent in vivo study (#AF66CZ.170 (b) (4)), Big Blue transgenic mice were given (b) (4) (doses: 0, 100, 300, and 600 mg/kg/day) by oral gavage once daily for 28 days. (b) (4) was genotoxic at all dose levels. (b) (4) (b) (4) will be controlled using an ICH M7 (b) (4) strategy.

5.5.3. Carcinogenicity

In a 6-month oral carcinogenicity study in transgenic rasH2 mice, abrocitinib (female doses: 0 [(b) (4) in water], 10, 25, and 75 mg/kg/day; male doses: 0, 10, 20, and 60 mg/kg/day) was orally administered once daily. Abrocitinib significantly

increased mortality in females at the HD, but not lower doses or in males. No abrocitinib-related clinical signs or effects on body weight or body weight gain were noted. Positive controls (a single intraperitoneal dose of N-methyl-N-nitrosourea [75 mg/kg]) produced expected results. No abrocitinib-related tumor findings were noted. These data support statements made in section 13.1 of labeling.

In a 2-year oral carcinogenicity study in rats, abrocitinib (doses: 0 [(b) (4) (b) (4) in water], 3, 10, and 30 mg/kg/day) was orally administered once daily. Abrocitinib increased mortality and decreased body weight in HD males, but not at lower doses or in females. Abrocitinib increased the incidence of skin scabs and/or scabs in MD and HD males and of skin sores in HD females. Abrocitinib increased the incidence of thymic mass or large thymus in MD and HD females, corresponding to the below tumor findings. No abrocitinib-related tumor findings were noted in male rats. Although the trend for benign thymoma in female rats did not meet the statistical criteria for common tumors ($p<0.005$), there was a clear, statistically significant increase in the incidence of thymomas in MD and HD females that exceeded historical controls. These data support statements made in section 13.1 of labeling.

Refer to Appendix 16.4.3 for full carcinogenicity study reviews.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Study title/ number: An Oral (Gavage) Study of the Effects of PF-04965842 on Male and Female Fertility and Early Embryonic Development to Implantation in Rats / 17GR089
Key Study Findings

- No abrocitinib-related effects were noted in males. The NOAEL was 70 mg/kg/day, which corresponded to an AUC_{24} of 142000 ng·hr/mL (based on the Day 182 AUC_{24} for male rats given 70 mg/kg/day in the 6-month repeat dose toxicity study, which had a similar C_{max} [12700 ng/mL] as the current study) and C_{max} of 12500 ng/mL.
- In HD females, abrocitinib markedly decreased fertility and conception indices and decreased corpora lutea and implantation sites. These data support statements made in sections 8.3 and 13.1 of labeling.
- In females, abrocitinib caused a dose-related increase in post-implantation loss and decrease in viable embryos. A NOAEL could not be established for females because of adverse effects at all dose levels.

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

Methods

Dose and frequency of dosing:	0, 30, 45, and 70 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in water
Species/Strain:	Rat/Wistar Han
Number/Sex/Group:	20
Satellite groups:	None
Study design:	Females were dosed beginning 2 weeks prior to mating (with naïve males) and continuing through gestation day (GD) 7. Males were dosed beginning 4 weeks prior to mating (with naïve females) and continuing for approximately 9 weeks. Cesarean sections were performed on surviving animals on GD 14.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No abrocitinib-related effects.
Clinical Signs	No adverse abrocitinib-related effects.
Body Weights	MD & HD: Females had lower mean body weight during the postdosing period (GD 7-14). This appeared related to an abrocitinib-related decrease in viable embryos.
Necropsy findings	Males: No abrocitinib-related effects. Females: Dose-related increase in post-implantation loss and decrease in mean viable embryos at all dose levels. HD females: Corpora lutea and implantation sites were decreased; fertility and conception indices were markedly decreased.

MD: mid dose; HD: high dose

Study title/ number: Oral Female Fertility Study of PF-04965842 in Wistar Han Rats with 1-Month Reversibility / 18GR261

Key Study Findings

- Similar effects on HD female fertility were noted as in the previous study. However, these effects were reversible at the end of recovery. These data support statements made in sections 8.3 and 13.1 of labeling.
- Abrocitinib did not produce systemic toxicity (maternal NOAEL: 70 mg/kg/day, corresponding to an AUC_{24} and C_{max} of 157000 ng·hr/mL and 12600 ng/mL, respectively).
- Because no adverse effects were noted at the MD, the developmental NOAEL was 10 mg/kg/day, corresponding to an AUC_{24} and C_{max} of 11000 ng·hr/mL and 2660 ng/mL, respectively.

Conducting laboratory and location	Pfizer Worldwide Research & Development, Groton, CT
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 3, 10, and 70 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) in water
Species/Strain:	Rat/Wistar Han
Number/Group:	20 females
Satellite groups:	20 control and HD females for 28-day recovery
Study design:	Females (except recovery) were dosed beginning 2 weeks prior to mating (with naïve males) and continuing through gestation day (GD) 7. Recovery females were dosed for 21 days without mating, then kept for 1 month and mated (with naïve males). Cesarean sections were performed on surviving animals on GD 14.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	No abrocitinib-related effects.
Clinical Signs	No adverse abrocitinib-related effects.
Body Weights	No adverse abrocitinib-related effects.
Necropsy findings	HD: Increased post-implantation loss; decreased viable embryos; decreased corpora lutea and implantation sites; and markedly decreased fecundity and fertility indices.

HD: high dose

Embryo-Fetal Development

Study title/ number: An Embryo-Fetal Development Study of PF-04965842 by Oral (Gavage) in Rats / 14GR073

Key Study Findings

- Abrocitinib did not produce maternal toxicity (NOAEL: 60 mg/kg/day, corresponding to a GD 17 AUC_{24} and C_{max} of 90000 ng·hr/mL and 6410 ng/mL, respectively).
- Abrocitinib increased the incidence of skeletal variations at doses ≥30 mg/kg/day, including the incidence of short 13th ribs, thickened ribs (HD only), and cervical arches with reduced ventral processes (HD only).

- Abrocitinib produced a low incidence of dead fetuses and slightly increased late resorptions at the HD.
- The developmental NOAEL was 30 mg/kg/day, corresponding to a GD 17 AUC_{24} and C_{max} of 58300 ng·hr/mL and 4880 ng/mL, respectively). These data support statements made in section 8.1 of labeling.

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

Methods

Dose and frequency of dosing: 0, 10, 30, and 60 mg/kg/day, once daily
Route of administration: Oral gavage
Formulation/Vehicle: (b) (4) in water
Species/Strain: Rat/Sprague Dawley
Number/Group: 22 females
Satellite groups: 3 (control) or 5 (abrocitinib-treated) per group for toxicokinetic assessment
Study design: Females were dosed daily from GD 6 through 17 and euthanized on GD 21. Blood samples were collected on GD 17.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No abrocitinib-related effects.
Clinical Signs	No abrocitinib-related effects.
Body Weights	No abrocitinib-related effects.
Necropsy findings Cesarean Section Data	LD & MD: No abrocitinib-related effects. HD: Low incidence of dead fetuses and slightly increased late resorptions.
Necropsy findings Offspring	MD: Abrocitinib increased the incidence of short 13th rib. HD: Abrocitinib increased the incidence of short 13th rib, thickened ribs, and cervical arches with reduced ventral processes.

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: An Embryo-Fetal Development Study of PF-04965842 by Oral (Gavage) in Rabbits / 14GR183
Key Study Findings

- Abrocitinib did not produce maternal toxicity or adverse developmental effects.

- The maternal and developmental NOAEL was 75 mg/kg/day, corresponding to GD 19 AUC_{24} and C_{max} of 43000 ng·hr/mL and 16800 ng/mL, respectively. These data support statements made in section 8.1 of labeling.

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

Methods
Dose and frequency of dosing: 0, 10, 30, and 75 mg/kg/day, once daily
Route of administration: Oral gavage
Formulation/Vehicle: (b) (4) in water
Species/Strain: Rabbit/New Zealand White
Number/Group: 20 females
Satellite groups: 5/group for toxicokinetic assessment
Study design: Females were dosed daily from GD 7 through 19 and euthanized on GD 21. Blood samples were collected on GD 19.
Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	No abrocitinib-related effects.
Clinical Signs	No abrocitinib-related effects.
Body Weights	No abrocitinib-related effects.
Necropsy findings Cesarean Section Data	No abrocitinib-related effects.
Necropsy findings Offspring	No abrocitinib-related malformations, variations, or adverse findings.

Prenatal and Postnatal Development
Study title/ number: An Oral (Gavage) Study of the Effects of PF-04965842 on Pre- and Postnatal Development, Including Maternal Function, in Sprague Dawley Rats / 18GR074
Key Study Findings

- At the MD and HD, abrocitinib caused adverse dystocia in F_0 dams and reduced F_1 body weights from birth through weaning.
- The HD group was terminated early because of a high rate of total litter loss and markedly decreased postnatal survival.
- No adverse maternal effects were noted at the LD (NOAEL: 10 mg/kg/day).

- No adverse effects on offspring postnatal developmental, neurobehavioral, or reproductive performance were noted at doses up to the MD (NOAEL: 30 mg/kg/day). These data support statements made in section 8.1 of labeling.

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

Methods

Dose and frequency of dosing:	0, 10, 30, and 60 mg/kg/day, once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	F_0: 20 females F_1: 18 to 20
Satellite groups:	None
Study design:	F_0 dams were dosed once daily from gestation day 6 through lactation day 20. On postnatal day 21, F_1 animals were either selected for the next generation (18-20/sex/group) or necropsied. The following parameters were evaluated in the selected F_1 animals: mortality, body weight, clinical observations, food consumption, developmental landmarks (balanopreputial separation and vaginal patency), neurobehavioral evaluations (righting reflex, auditory function, motor activity, and learning and memory), sexual maturation, estrous cycles, reproductive performance, macroscopic observations, and F_2 intrauterine survival.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Generation	Major Findings
F_0 Dams	Dystocia was noted in a single female each at the MD and HD. Total litter loss occurred in 7 HD dams, resulting in termination of the HD group (including 11 additional gravid females).
F_1 Generation	LD: No abrocitinib-related effects. MD: Birth body weights and pre-weaning body weights and body weight gains were slightly lower than controls; body weights were similar to controls by the end of the study.

	HD: Postnatal survival was markedly decreased (91.3%, 11.2%, and 0% on PND 0, PND 0-1, and PND 0-4, respectively). No abrocitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance were noted in surviving (LD and MD) offspring.
F_2 Generation	No abrocitinib-related effects.

Juvenile Animal Studies

Study title/ number: An oral (gavage) juvenile (PND 10 through 63) toxicity study of PF-04965842 in Wistar Han rats with a 2-month recovery / 19GR039

Key Study Findings

- Abrocitinib produced dose-related effects on femur, tibia, and paw development.
- Abrocitinib-related adverse effects (limb malrotation and/or impairment and bone fractures) resulted in premature euthanasia at the MD and HD.
- Dose-related adverse femoral head abnormalities were noted at all dose levels in both sexes and were not reversible.
- A NOAEL could not be established because abrocitinib produced adverse effects on bone development at all dose levels.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 25, and 75 mg/kg/day, once daily

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4) in water

Species/Strain: Rat/Wistar Han

Number/Sex/Group: 10

Satellite groups: 19-21/sex/group for toxicokinetic assessment and 5/sex/group for 2-month recovery

Study design: Juvenile rats were dosed from PND 10 through 63. On PND 64, 9-10 animals/sex/group were assigned to the primary necropsy; the remaining ≤5 animals/sex/group were kept for a 55-day treatment-free period (PND 119) after 54-day treatment. The following additional evaluations were conducted: balanopreputial separation in males, vaginal perforation in females, right femur dimensions, and organ weights of the immune system (spleen and thymus).

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	MD: One male was euthanized prematurely because of abrocitinib-related right hindlimb impairment. HD: Five (1 toxicity and 1 toxicokinetic female; 2 toxicity and 1 toxicokinetic males) were euthanized prematurely because of abrocitinib-related limb impairment. These findings typically corresponded to bone fractures.
Clinical Signs	MD & HD: Impaired use of and/or malrotated limbs were noted (as early as PND 16 in prematurely-euthanized animals and PND 33 in animals surviving until scheduled euthanasia).
Body Weights	MD: Abrocitinib reversibly decreased body weight in MD males, but not females. HD: Abrocitinib decreased body weight in both sexes.
Necropsy findings	At all dose levels, abrocitinib caused dose-related femoral abnormalities, including small or misshapen femoral head. At the MD and HD, abrocitinib decrease femur size. These findings were present in both sexes at all dose levels and not reversible. Abrocitinib caused a reversible dose-related decrease in the primary spongiosa in the metaphysis of the proximal tibia and distal femur. Paw malrotation was present in MD and HD females and HD males at the end of dosing and recovery, with no apparent reversibility. At the HD, paw fractures were noted in both sexes. A single HD female was observed with a fractured tibia.

LD: low dose; MD: mid dose; HD: high dose; PND: postnatal day

5.5.5. Other Toxicology Studies

In vivo phototoxicity:
Study title/ number: A seven-day phototoxicity study to determine the effects of oral (gavage) administration of PF-04965842 on eyes and skin in pigmented rats / 20052793
Abrocitinib (doses: 0, 50, 150, and 300 mg/kg/day) or positive control (50 mg/kg 8-methoxypsoralen) was orally administered to female Long Evans pigmented rats once daily for 7 days, followed by irradiation with 10 J/cm^2 UVA, then 145 mJ/cm^2 UVB. Vehicle and positive control produced expected results. Abrocitinib did not display evidence of phototoxicity potential.

In vitro effects on immune function
Study title/ number: Comparison of PF-04965842 and tofacitinib in in vitro assays of human cellular immune function / 18GR190
Abrocitinib and tofacitinib were evaluated in vitro for their potential to inhibit various elements of immune function, including: NK cells killing of tumor cells; degranulation of activate CD8+ T

cells; intracellular IFN-γ accumulation in activated CD8+ T cells; IFN-γ production following cytomegalovirus or varicella zoster virus anti-specific T cell activation; IP-10 secretion from IFN-α- or IFN-γ-stimulated peripheral blood mononuclear cells; and herpes simplex virus 1 replication in IFN-β-treated human dermal fibroblast cells. In all assays, abrocitinib displayed similar (or less potent) inhibition as tofacitinib.

In vivo impurity qualification:
Study title/ number: 13-week oral gavage impurity qualification study of PF-04965842 in Wistar Han rats / 18GR270
Abrocitinib (doses: 0, 30, and 30 [containing the impurities (b) (4)- (b) (4) at concentrations of (b) (4)%, (b) (4)%, and (b) (4)%, respectively] mg/kg/day) was administered to rats by oral gavage once daily for 13 weeks. Similar non-adverse findings related to the pharmacological effect were noted in neat abrocitinib and impurity-spiked abrocitinib. The NOAEL was 30 mg/kg/day, corresponding to a neat and impurity-spiked AUC_{24} of 54,500 and 51,000 ng·hr/mL, respectively, and C_{max} of 8280 and 7560 ng/mL, respectively.

6 Clinical Pharmacology

6.1.Executive Summary

Abrocitinib (also known as PF-04965802) is a new molecular entity, orally administered inhibitor of the Janus kinase (JAK) 1. Abrocitinib is proposed for the oral treatment of moderate to severe atopic dermatitis (AD) in adults. Proposed dose of abrocitinib is 100 mg or 200 mg once daily with or without food as an immediate-release film-coated tablet.

The Applicant evaluated the safety and efficacy of abrocitinib, in three pivotal Phase 3 trials in which abrocitinib 100 mg or 200 mg, was administered to patients with moderate to severe AD once daily for 12 weeks. The Applicant conducted a Phase 2 dose ranging study to support the dose selection for Phase 3 trials. The Applicant also submitted the results of fifteen Phase 1 trials in healthy subjects and the results of Phase 2 dose-ranging trial in adult subjects with moderate to severe AD to support clinical pharmacology information of abrocitinib.

In addition to abrocitinib, its two major metabolites, M1 (PF-06471658) and M2 (PF-07055087), inhibit cytokines which transduce their signals via JAK1-dependent pathways. The sum of two active metabolites contributes to approximately 37% of overall activity of abrocitinib in healthy subjects. Therefore, combined exposure of abrocitinib and its two active metabolites was utilized in certain drug interaction trials and organ impairment trials.

Key review findings with specific recommendations and comments are summarized in Table 1.

Table 1: Summary of Clinical Pharmacology Review

Review Issues	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Efficacy is established in three pivotal Phase 3 trials (B7451012, B7451013 and B7451029). See Section 8.1 for efficacy trials and their results. The dose-response for Investigator's Global Assessment (IGA) in Phase 2 trial (B7451006) provides supportive evidence of effectiveness.
General dosing instructions	The efficacy data from Phase 3 trials support that the proposed dosing regimen, oral administration of abrocitinib 100 mg or 200 mg once daily (QD). However, the safety data from Phase 3 trials presented that 200 mg QD regimen had more serious safety issues compared to 100 mg QD regimen. Therefore, abrocitinib 100 mg QD is approved for the treatment of moderate-to-severe atopic dermatitis in adults with the option of a 200 mg QD dose for those adults who are not responding to the 100 mg QD and for which they have no other treatment options. See Section 8.2 for safety results and further information.

Dosing in patient subgroups (intrinsic and extrinsic factors)	• Reduce the dose of abrocitinib to 50 mg QD in patients with moderate (eGFR 30 - 59 mL/min) renal impairment. • Avoid use of abrocitinib in patients with severe (eGFR 15-29 mL/min) renal impairment. • Avoid use of abrocitinib in patients with end stage renal disease (eGFR <15 mL/min) including those on renal replacement therapy. • No dose adjustment is required in patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. • Reduce the dose of abrocitinib to 50 mg QD when it is coadministered with strong CYP2C19 inhibitors. • Reduce the dose of abrocitnib to 50 mg QD in known or suspected poor metabolizers of CYP2C19 substrates. • Avoid coadministration of drugs that are moderate to strong inhibitors of both CYP2C19 and CYP2C9. • Avoid coadministration of strong CYP2C19 inducers. • Avoid coadministration of gastric acid reducing agents. • Appropriately monitor or dose titrate P-glycoprotein substrate where small concentration changes may lead to serious or life-threatening toxicities when coadministered with abrocitinib.
Bridge between to-be-marketed and clinical trial formulations	The comparability between the to-be-marketed formulation and the formulation used in Phase 3 trials was demonstrated in study B7451032, Part B.

Abbreviations: eGFR=estimated glomerular filtration rate

Postmarketing Commitment
The Applicant is recommended to conduct the following clinical pharmacology study as a postmarketing commitment (PMC). The PMC study will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
Determination of an appropriate abrocitinib dose for patients with coadministration of gastric acid reducing agents	The solubility of abrocitinib is pH-dependent. The extent of abrocitinib absorption can be significantly changed when it is coadministered with acid reducing agents	Single dose of abrocitinib with and without coadministration of repeat doses of gastric acid reducing agents in healthy subjects.

6.1.1. Recommendations

From a clinical pharmacology standpoint, this NDA is acceptable to support the approval of abrocitinib 100 mg once daily for the treatment of moderate to severe atopic dermatitis in

adults with the option of a 200 mg once daily for subjects who do not respond to the 100 mg after 12 weeks and for who have no other treatment options.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action
Abrocitinib and its two primary metabolites, M1 and M2, selectively inhibit Janus kinase 1 (JAK1).

Pharmacodynamics
Abrocitinib was associated with dose-dependent reduction in pharmacodynamic markers of inflammation, including high sensitivity C-reactive protein (hsCRP), interleukin-31 (IL-31), and thymus- and activation-regulated chemokine (TARC). These changes returned to baseline within 4 weeks of drug discontinuation.

QT Prolongation
At a dose of abrocitinib 600 mg that is 3 times the maximum approved recommended dose, abrocitinib does not prolong the QT interval to any clinically relevant extent.

Pharmacokinetics
Abrocitinib exposure increased dose proportionally across dose range of 3 mg to 200 mg. Following 100 mg and 200 mg once daily oral dosing of abrocitinib in healthy subjects, the geometric mean (coefficient of variation, %CV) of abrocitinib steady state maximum plasma concentration (C_{max}) was 700.0 (31%) and 1199 ng/mL (23%), the average plasma concentration for the dosing interval (C_{avg}) was 82.4 (47%) and 178 ng/mL (34%), and the area under the curve from time zero to time tau (AUC_{tau}) was 1977 (47%) and 4277 ng·hr/mL (34), respectively. The renal clearance was approximately 0.6 L/hr. Steady-state was achieved by 48 hours. The observed accumulation ratio ranged 1.3 to 1.5. The median time for maximum concentration (T_{max}) at steady-state was 0.5 hours (ranged 0.5 to 2.0 hours) and the mean terminal elimination half-life was 3 hours.

Abrocitinib was metabolized by CYP2C19 (53%), CYP2C9 (30%), and CYP3A4 (10%) *in vitro*. The major metabolic pathway was oxidation. Abrocitinib and its two active metabolites, M1 and M2, were 63%, 7%, and 30% of the unbound combined exposure at steady state ($AUC_{24,u,ss}$), respectively (See details in section 16.4). Abrocitinib was the major component of circulating profiled plasma radioactivity, while oxidative metabolites were predominant in pooled urine (study B7451008).

Drug Interaction Studies:
Effect of Other Drugs on Abrocitinib and Its two active Metabolites

- When single dose of abrocitinib 100 mg was coadministered with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor), the combined exposure of abrocitinib and its two active metabolites increased by 91% while the exposure of parent drug increased by 175%. Hence, it is recommended to reduce the dose by half. Subjects who take abrocitinib with a strong CYP2C19 inhibitor concomitantly and do not respond to abrocitinib 50 mg can increase the dose to 100 mg.
- When single dose of abrocitinib 100 mg was coadministered with fluconazole (a strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor), the combined exposure of abrocitinib and its two active metabolites increased by 155% and the exposure of parent drug increased by 383%. Since the exposure of the parent drug alone increased approximately 5-fold, it is recommended not to use drugs that are moderate to strong inhibitrors of both CYP2C19 and CYP2C9 with abrocitinib.
- The coadministration of multiple doses of rifampin (a strong CYP2C19 and CYP3A4, and a moderate CYP2C9 inducer) with single dose of abrocitinib 200 mg reduced the combined exposure of abrocitinib and its two active metabolites by approximately 56%. Hence, the concomitant use of drugs that are strong inducers of CYP2C19 is not recommended.
- When single dose of abrocitinib 200 mg was coadministered with probenecid (an organic anion transporter (OAT) 3 inhibitor), the combined exposure of abrocitinib and its two active metabolites and the exposure of parent drug increased by 66% and 28%, respectively. Hence, no dose adjustment will be recommended.

Effect of Abrocitinib on Other Drugs

- After multiple doses of abrocitinib 200 mg QD, the effect on the PK of oral contraceptives (ethinyl estradiol 30 µg and levonorgestrel 150 µg) was not significant. Hence, there will be no recommendation for any dose modification.
- After the coadministration of midazolam 2 mg with multiple doses of abrocitinib 200 mg QD, the midazolam exposure was similar to that after midazolam administered alone. This result indicates that abrocitinib has limited effect on the induction or inhibition effect on CYP3A4 and CYP3A5. Hence, there will be no recommendation for any dose modification.
- Coadministration with abrocitinib 200 mg QD did not affect the PK of rosuvastatin 10 mg, a substrate for breast cancer resistance protein (BCRP) and OAT3. Hence, there will be no recommendation for any dose modification.
- Coadministration of abrocitinib 200 mg QD with metformin 500 mg did not impact the exposures of metformin, a biomarker for multidrug and toxin compound extrusion protein (MATE)1/2K transporter. Hence, there will be no recommendation for any dose modification.
- Coadministration of a single dose of abrocitinib 200 mg increased the overall exposure of dabigatran (a substrate of P-glycoprotein (P-gp)) 75 mg by 53% relative to dabigatran administered alone. Dose titration and monitoring will be recommended in subjects taking P-gp substrates (for example, digoxin) where small concentration changes may lead to serious or life-threatening toxicities.

Effect of Gastric Acid Reducing Agents on Abrocitinib

- The effect of coadministration of gastric acid reducing agent (ARA) is not known. No clinical drug interaction study with ARA was conducted. Hence, this assessment will be recommended to be conducted as a PMC.

Systemic Safety – Incidence of Thrombocytopenia

Continuous administration of abrocitinib resulted in a dose-related decrease in platelet count. Maximum effects on platelets were observed within 4 weeks followed by gradual restoration despite continued therapy. Confirmed platelet counts of $<50 \times 10^3/mm^3$ were reported in 1 patient (0.2%) exposed to abrocitinib 200 mg QD, and 0 patients treated with abrocitinib 100 mg QD or placebo.

Individuals with a lower baseline platelet count ($170\times10^3/\mu L$) demonstrated a higher probability of thrombocytopenia at the nadir following administration of 100 mg QD and 200 mg QD: Grade 1 - $75\text{-}150\times10^3/\mu L$ platelet counts (80.5% and 76.2%, respectively), Grade 2 - $50\text{-}75\times10^3/\mu L$ platelet counts (9.7% and 16.3%, respectively), Grade 3 or more severe - $<50\times10^3/\mu L$ platelet counts (3% and 1.9%, respectively), compared to all grades thrombocytopenia of < 10% for individuals with a normal baseline platelet count ($270\times10^3/\mu L$).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The dose-response results in the Phase 2 trial and the efficacy results in Phase 3 trials overall support the acceptability of the proposed dosing regimen of abrocitinib 100 mg and 200 mg QD. However, the safety data in Phase 3 trials indicated that abrocitinib 200 mg QD dose presented more serious adverse events than abrocitinib 100 mg QD dose. Therefore, abrocitinib 100 mg QD dose is recommended for approval as it is supported by both efficacy and safety data for the treatment of moderate to severe AD in adults. In addition, the 200 mg QD dose can be used in subjects with inadequate response to the 100 mg QD dose and in patients who have failed other systemic treatments and have tried abrocitinib 100 mg QD. See Section 8 for the design of Phase 3 trials, their efficacy and safety results.

The results of the food effect study support that abrocitinib can be taken with or without food which is consistent with the design of the Phase 3 clinical trials.

6.2.2.2 Therapeutic Individualization

Renal Impairment: Dose reduction to 50 mg once daily is recommended in patients with moderate (estimated glomerular filtration rate (eGFR) 30 - 59 mL/min) renal impairment (RI) based on 2-fold increase in the combined exposure of abrocitinib and its two active metabolites in this population. Patients with moderate RI and do not respond to abrocitinib 50 mg can increase the dose to 100 mg. Avoid use of abrocitinib in patients with severe (eGFR 15 – 29

mL/min) RI. No dose adjustment is recommended in patients with mild (eGFR 60 - 89 mL/min) RI based on the linear regression analysis of the combined exposure of abrocitinib and its two active metabolites versus eGFR. Avoid use of abrocitinib in patients with end stage renal disease (ESRD, eGFR <15 mL/min) including those on renal replacement therapy because the PK and safety of abrocitinib in patients with ESRD has not been studied.

Hepatic Impairment: No dose adjustments are recommended for patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment as there was no clinically meaningful changes in the combined exposure of abrocitinib and its two active metabolites and the safety assessment in these populations compared to subjects with normal hepatic function. The PK and safety of abrocitinib in patients with severe hepatic impairment has not been studied.

Drug Interaction:

- The dose of abrocitinib 50 mg QD is recommended when coadministered with drugs that are strong CYP2C19 inhibitors.
- The coadministration of abrocitinib with drugs that are moderate to strong inhibitors of both CYP2C19 and CYP2C9 is not recommended.
- The coadministration of abrocitinib with strong CYP2C19 inducers is not recommended.
- Appropriate monitoring or dose titration of P-gp substrate is recommended when abrocitinib is coadministered with P-gp substrate (for example, digoxin) where small concentration changes may lead to serious or life-threatening toxicities.
- The coadministration of ARA with abrocitinib is not recommended.

Poor Metabolizers of CYP2C19 Substrates: Dose reduction to 50 mg once daily is recommended in patients who are known or suspected to be poor metabolizers of CYP2C19 based on a 2.3-fold increase in exposure of abrocitinib in CYP2C19 poor metabolizers. Known or suspected CYP2C19 poor metabolizers who do not respond to abrocitinib 50 mg QD can increase the dose to 100 mg QD.

6.2.2.3 Outstanding Issues

There are no outstanding issues other than the requested PMC study that would preclude the approval of abrocitinib from the Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General clinical pharmacology, PK, and PD characteristics of abrocitinib are summarized in Table 2.

Table 2: Summary of Clinical Pharmacology, Pharmacokinetics and Pharmacodynamics of Abrocitinib

Pharmacology	
Mechanism of action	Abrocitinib selectively inhibits Janus kinase 1 (JAK1) by blocking the ATP binding site and its two primary metabolites (M1 and M2) inhibit cytokines which transduce their signals via JAK1-dependent pathways.
Active Moieties	Abrocitinib and its two metabolites, M1 and M2, are pharmacologically active against JAK1. Abrocitinib, M1, and M2 were 63%, 7%, and 30% of the combined exposure ($AUC_{24,u,ss}$) of abrocitinib and its two active metabolites at steady state, respectively. A total pharmacology of abrocitinib and metabolites was utilized in clinical trials to understand the overall pharmacology from both parent and active metabolites. The comprehensive unbound PK metrics ($C_{max,u}$ and AUC_u) were calculated as the sum of the respective unbound PK metric for abrocitinib, M1, and M2, adjusted for relative potencies of the metabolites with respect to the parent. Refer to OCP appendices 16.5 for more details.
Pharmacodynamics	Pharmacodynamic (PD) biomarkers of abrocitinib including IL-31, interferon gamma-induced protein-10 (IP-10) and hsCRP decreased in dose-dependent manner after abrocitinib 100 mg or 200 mg QD (study B7451006). TARC, an atopic dermatitis biomarker, was suppressed at the doses of 100 mg and 200 mg QD. The reduction of biomarkers was observed as early as 2 weeks after the treatment initiation. Most of biomarkers, except IP-10, suppressed during treatment period and went back to the baseline value within 4 weeks after the drug discontinuation. IP-10 returned to the baseline value as early as 6 weeks after the treatment initiation.
QT Prolongation	The effect of abrocitinib 600 mg single dose on the QTc interval was evaluated in 36 healthy subjects. The results indicated that at up to 3 times the maximum approved recommended dose, abrocitinib did not have significant QTc prolongation effect.
General Information	
Bioanalysis	Abrocitinib, M1 and M2 concentrations in human plasma were quantified using high performance LC/MS/MS assays with the sensitivity of 1 ng/mL, 1 ng/mL and 5 ng/mL, respectively. Abrocitinib concentrations in human urine were quantified using validated LC/MS/MS assays with the sensitivity of 10 ng/mL. See section 16.5.5 for details of the method validation.
PK/PD model	*The impact of abrocitinib exposure on platelet time-courses:* A dose-related decrease in platelets followed by a gradual restoration with continuous drug administration was described by a semi-mechanistic PK/PD model. Maximum decreases in platelet counts were

	observed within 4 weeks, and 32% of the maximum drug effect on platelet proliferation diminished after 12 weeks. Intrinsic factors were found to impact baseline platelet counts, which in turn, elicits effect on E_{max} and the nadir. Lower baseline WBC, male sex, older age, higher baseline hematocrit, and disease-type (Psoriasis) were all significant predictors of lower baseline platelet counts. *Exposure-response relationship:* For the typical-AD patient with a baseline platelet count of $270\times10^3/\mu L$, the net percent change from baseline at the nadir was -22.4% for 200 mg QD, and -26.5% for 100 mg QD. The Grade 3 or more severe thrombocytopenia were predicted to be 0% for both 100 mg and 200 mg QD. Individuals with lower baseline platelet counts ($170\times10^3/\mu L$ and $220\times10^3/\mu L$) demonstrated higher net decreases in platelets at the nadir (-37.6% and -29.7%, respectively) following administration of 100 mg dose.
Dose proportionality	In healthy subjects (B7451001), C_{max} and AUCs increased dose proportionally from 3 mg to 200 mg when administered as an oral solution. Plasma accumulation with multiple dosing of abrocitinib QD in healthy subjects ranged 1.3 to 1.5.
ADME	
Absorption	After abrocitinib oral administration, the median time to reach maximum plasma concentration (T_{max}) was 0.5 hour (ranged 0.5 to 2 hours). Absolute bioavailability was estimated 60% and fraction absorbed was 0.9129 (study B7451008).
Food effect	A high-fat, high-calorie (approximately 916 calories containing 55% fat) meal consumption increased the overall systemic exposure of abrocitinib approximately 26% and delayed T_{max} approximately 2 hours compared to the fasting condition.
Distribution	Plasma protein binding of abrocitinib, M1, and M2 were 64%, 37%, and 29%, respectively, *in vitro*. The human blood to plasma concentration ratio was 1.07, 1.13, and 1.27 for abrocitinib, M1, and M2, respectively. After intravenous administration, the volume of distribution of abrocitinib was approximately 100 L.
Elimination	
Metabolism	Abrocitinib is metabolized primarily by CYP2C19 (fraction metabolized [fm] ~0.5), CYP2C9 (fm ~0.3), and CYP3A4 (fm ~0.1). Following IV and oral dose of ^{14}C-abrocitinib 80 µg in healthy subjects (study B7451008), unchanged abrocitinib was the major (26%) circulating component.
Excretion	In the mass balance study (study B7451008), the total radioactivity recovery was 94.5%, of which 85.0% was recovered in urine (16.2% as M1 and <1% as unchanged drug) and 9.5% in feces (1.7% as M1). The

	elimination half-lives of abrocitinib and its two active metabolites ranged from 3 to 5 hours.
Drug-drug interaction	• Coadministration of a strong CYP2C19 inhibitor with a single dose of abrocitinib 100 mg increased the combined exposure of abrocitinib and its two active metabolites by 91%. • Coadministration of a strong CYP2C19 and moderate CYP2C9 inhibitor with a single dose of abrocitinib 100 mg increased the combined exposure of abrocitinib and its two active metabolites and the exposure of abrocitinib by 155% and 383%, respectively. • Coadministration of a strong CYP2C19 inducer with a single abrocitinib 200 mg dose decreased the combined exposure of abrocitinib and its two active metabolites by approximately 56% relative to a single abrocitinib 200 mg dose given alone. • Coadministration of a single dose of abrocitinib 200 mg increased dabigatran exposure by approximately 53% relative to a single dabigatran 75 mg dose given alone.
Pediatric subjects	Pediatric AD patients aged 12-17 years were enrolled in two Phase 3 trials, B7451012 and B7451013. (b) (4) [redacted] Accordingly, the exposure-response relationship for abrocitinib efficacy or safety in pediatric patients has not been evaluated in this application.

Abbreviations: AUC=area under the curve, C_{max}=maximum concentration, T_{max}=time of C_{max}, LC/MS/MS=liquid chromatography with tandem mass spectrometry

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The efficacy of abrocitinib for the treatment of moderate to severe AD was demonstrated in the three Phase 3 trials. See Section 8 of this multidisciplinary review for details of study design and efficacy results of the Phase 3 trials. The efficacy results of abrocitinib on PD biomarkers and dose-response relationships for efficacy described below provide supportive evidence of effectiveness.

Dose-Response for Investigator's Global Assessment:
Abrocitinib treatment improved Investigator's Global Assessment (IGA) compared to the placebo group in the Phase 2 dose-finding study in adult patients with moderate to severe AD. Study B7451006 was a 12 week, randomized, double-blind, placebo-controlled dose ranging study designed to characterize the dose-response of abrocitinib 10, 30, 100, and 200 mg QD dose. Table 3 presents the summary of the efficacy results following multiple doses of abrocitinib. Abrocitinib 100 mg and 200 mg QD dosing regimen showed statistically significant improvement in IGA compared to placebo group which supported the dose selection for Phase 3 trials. Refer to Individual Study Review in OCP appendices 16.5 for more details.

Table 3: Proportion of Subjects Achieving Investigator's Global Assessment (IGA) of Clear or Almost Clear and **≥2** Points Improvement by Abrocitinib from Baseline at Week 12 (Study B7451006)

Treatment (Abrocitinib Dose)	Placebo (n=52)	10 mg (n=46)	30 mg (n=45)	100 mg (n=54)	200 mg (n=48)
Mean (90% CI)	6.3 (-0.2, 12.9)	8.2 (2.2, 14.1)	12.3 (4.9, 19.7)	27.8 (14.8, 40.9)	44.5 (26.7, 62.3)
Difference from Placebo		1.8 (-0.7, 4.4)	6.0 (-1.8, 13.8)	21.5[a] (5.5, 37.6)	38.2[a] (19.7, 56.6)

Source: Study Report B7451006, Table 10
Analysis was done in the full analysis dataset with non-responder imputation
a=statistically significant with *p*-value <0.05
Abbreviation: CI=confidence interval

Pharmacodynamic Effect on Biomarkers:
In Study B7451001, mechanistic biomarkers (hsCRP and IP-10) were measured in healthy participants. The median placebo corrected maximum inhibition was ~86% for hsCRP and ~52% for IP-10 for the 200 mg BID dose. In contrast, the magnitude of inhibition was similar for the 200 mg and 400 mg QD doses for hsCRP (70%-74%) and IP-10 (37%- 40%). The data indicated a dose-related and greater inhibition of the biomarkers following BID versus QD dosing.

The PD results in the Phase 2 study (B7451006) showed abrocitinib dose-dependent reduction in biomarkers of inflammation, including hsCRP, IL-31, and TARC. The reduction in the hsCRP was observed as early as Week 2. The maximum median percent reduction from baseline observed for the placebo, 10, 30, 100 and 200 mg groups was -3.7, -33.7, -27.6, -63.6, and -65.9, respectively. Similarly, there was an apparent dose-dependent reduction in TARC suppression. These changes returned to baseline within 4 weeks of drug discontinuation.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No. The safety data from Phase 3 trials demonstrated that the safety profile of abrocitinib 200 mg QD dosing includes more serious adverse events than that of 100 mg QD dose. For details, refer to Section 8.2 for safety results and analysis.

On the other hand, the efficacy data from Phase 3 trials indicate that both 100 and 200 mg QD, are effective for the treatment of moderate to severe AD in adults. The dose selected for Phase 3 trials are also supported by the dose-response results in Phase 2 dose-finding study (study B7451006) as described above. Based on the totality of the evidence, 100 mg QD dosing regimen is recommended for approval for the treatment of AD in adult patients with the option of 200 mg QD for subjects who failed the 100 mg QD dose and have no other treatment options.

Dose-Response for Safety

PK/PD modeling and simulation also supported the abrocitinib 100mg QD dosing. For both 100 mg and 200 mg QD doses, the probability of Grade 3 and Grade 4 thrombocytopenia was predicted to be 0%. However, for an individual with a baseline of $170\times10^3/\mu L$, the probability of a nadir in Grade 2 or more severe thrombocytopenia ($<75\times10^3/\mu L$) increased from 11.6% with 100 mg QD to 19.3% with 200 mg QD. In addition, an increased exposure in Asian or hepatic impaired patients will likely result in an increased risk of thrombocytopenia. Therefore, 100 mg QD dose is expected to provide a better safety coverage for a broader patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Yes. A dose reduction to 50 mg once daily and avoid use of abrocitinib are recommended in patients with moderate (eGFR 30 - 59 mL/min) and severe (eGFR 15-29 mL/min) RI, respectively, based on the dedicated RI study. No dose adjustment is recommended in patients with mild (eGFR 60 - 89 mL/min) RI based on the results of linear regression analysis.
No dose adjustment is recommended in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment (HI) based on the dedicated HI study. Table 4 presents the summary of the effect of organ impairment on the combined exposure of abrocitinib and its two active metabolites.

Table 4:Effect of Renal and Hepatic Impairment on the Combined Exposure of Abrocitinib and Its Two Active Metabolites

Organ Function	Number of subjects	Ratio (90% CI): Impaired to Normal		
		$C_{max,u}$ (nM)	$AUC_{last,u}$ (nM·hr)	$AUC_{inf,u}$ (nM·hr)
Renal Impairment				
Mild[a]	-	-	-	1.70
Moderate	7	1.34 (1.02, 1.75)	2.13 (1.56, 2.91)	2.10 (1.55, 2.86)
Severe	8	1.29 (0.93, 1.81)	2.95 (2.21, 3.94)	2.91 (2.17, 3.89)
Hepatic Impairment				
Mild	8	0.76 (0.57, 1.00)	1.03 (0.78, 1.37)	0.96 (0.73, 1.27)
Moderate	8	0.84 (0.64, 1.11)	1.23 (0.93, 1.63)	1.15 (0.87, 1.51)

Source: Study Report B7451020, Table 16; Study Report B7451021, Table 17; Section 5.3.3.3 Mild Renal Pred Table, Table 1
a=prediction based on the linear regression of $AUC_{inf,u}$ versus eGFR using data from Study B7451021
Abbreviation: $AUC_{last,u}$=unbound area under the curve from time 0 to time of last observation; $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; $C_{max,u}$=unbound maximum plasma concentration

Effect of Renal Impairment

The impact of various degrees of RI on abrocitinib PK was assessed in a dedicated, open-label, single dose study (study B7451021). Following the administration of a single dose of 200 mg abrocitinib under fasted conditions, the combined exposure ($AUC_{inf,u}$) of abrocitinib and its two active metabolites increased 110% (2.1 fold) and 190% (2.9 fold) in patients with moderate and severe RI, respectively, compared to subjects with normal renal function.

For the dose recommendation in subjects with mild RI, the Applicant conducted linear regression analysis of combined $AUC_{inf,u}$ of abrocitinib and its two active metabolites versus eGFR with data collected in the dedicated RI study (study B7451021). The predicted ratio of combined $AUC_{inf,u}$ of patients with eGFR of 60 mL/min (worst possible eGFR in the mild RI category) to subjects with normal renal function was 1.7 fold. Based on the regression analysis, no dose adjustment is required for patients with mild RI. Refer to Individual Study Review in OCP appendices 16.4.1 for more details.

The Applicant proposed (b) (4) for patients with moderate and severe RI. The proposed dose adjustment for patients with moderate RI is reasonable. However, we did not agree with the Applicant's proposal for patients with severe RI (b) (4) because of risk of serious infections, MACE and malignancy are expected to be higher in subjects with severe renal impairment compared to other stages of renal function and furthermore, there were no subjects with severe renal impairment in Phase 3 trials and hence there is no clinical safety data available in these subjects. Due to this, dosing in subjects with severe renal impairment is not recommended.

In subjects with mild and moderate renal impairment, if an adequate response is not achieved after 12 weeks, abrocitinib dosing can be doubled; i.e. 200 mg in subjects with mild renal impairment and 100 mg in subjects with moderate renal impairment.

Effect of Hepatic Impairment

In a dedicated, open-label, single dose study (Study B7451020), following the administration of a single dose of 200 mg abrocitinib under fasted conditions, the combined exposure of abrocitinib and its two active metabolites in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) HI were similar to that observed in subjects with normal hepatic function. The Applicant proposed no dose adjustment for patients with mild or moderate HI which is reasonable. Refer to Individual Study Review in OCP appendices 16.5.1 for more details.

CYP2C19 Phenotype

The Applicant evaluated the effect of applicant-defined overall CYP2C19 and CYP2C9 phenotypes on the exposure of abrocitinib in a non-compartmental meta-analysis of PK parameters in healthy subjects from nine Phase 1 studies. The Applicant concluded that abrocitinib parent exposures were comparable across overall phenotypes therefore did not propose dose adjustment based on CYPC2C19 or CYP2C9 phenotypes. However, regression analysis of abrocitinib exposure across CYP2C19 phenotypes independent of CYP2C9 phenotypes showed a 126% increase in abrocitinib AUC in CYP2C19 poor metabolizers when

compared to CYP2C19 normal metabolizers. A 50% dose reduction is recommended for known or suspected CYP2C19 poor metabolizers. Refer to Pharmacogenomics Review in OCP appendices 16.5.4 for more details

Other Intrinsic Factors from Population PK Analysis
Age and race also had significant impact on the steady-state exposure. Adolescent subjects demonstrated a 33% decrease in $AUC_{0\text{-}24h}$ compared to weight-matched adult. This cohort is not reviewed for the current application. Asian subjects demonstrated a 51% increase in $AUC_{0\text{-}24h}$ compared to other weight-matched races. With 100 mg QD, the probability of Grade 2 or more severe thrombocytopenia in Asians was 0.5% for Japanese and 0% for non-Japanese Asians at the nadir, suggesting that dose adjustment is not necessary for Asians.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. Dose reduction of abrocitinib to 50 mg once daily is recommended when coadministered with strong CYP2C19 inhibitors with the option of increasing the dose to 100 mg QD in subjects who do not respond to abrocitinib 50 mg QD dose. Coadministration with moderate to strong CYP2C19 and CYP2C9 inhibitors or strong CYP2C19 inducers is not recommended. Appropriate monitoring or dose titration of P-gp substrate is recommended when abrocitinib coadministered with P-gp substrate (for example, digoxin) where small concentration changes may lead to serious or life-threatening toxicities. Coadministration of ARA is not recommended since the effect of ARA on abrocitinib exposure in not known. Abrocitinib tablet can be administered with or without food.

Food-Drug Interaction
In a dedicated food effect study (Study B7451032, Part A), a single 200 mg dose of abrocitinib to-be-marketed (TBM) tablet was administered under fasting and fed conditions. A high-fat, high-calorie (approximately 916 calories containing 55% fat) meal consumption increased abrocitinib C_{max} and $AUC_{0\text{-}inf}$ by 26% and 29%, respectively, as compared to fasting condition. This change was not considered clinically meaningful. Therefore, abrocitinib tablet can be administered with or without food.

Effect of Strong CYP2C19 Inhibitors on Abrocitinib PK:
Coadministration of fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor, 50 mg once daily for 7 days) with a single dose of abrocitinib 100 mg increased the combined $AUC_{inf,u}$ of abrocitinib and its two active metabolites by 91%. Based on this results, abrocitinib dose reduction to 50 mg once daily is recommended when it is coadministered with strong CYP2C19 inhibitors. For subjects that do not adequately respond on the 50 mg QD dosing, then abrocitinib dose can be increased to 100 mg QD during coadministration with strong CYP2C19 inhibitors. Coadministration of fluconazole (a strong CYP2C19, moderate CYP2C9 and CYP3A inhibitor, 400 mg on Day 1 followed by 200 mg once daily for 4 days) with a single dose of abrocitinib 100 mg increased the combined $AUC_{inf,u}$ of abrocitinib and its two active metabolites and the AUC_{inf} of parent drug by 155% and 383%, respectively. Per population PK/PD analysis,

the platelet counts were negatively correlated with the steady-state plasma concentration of abrocitinib. Thus, a 4-times increase of abrocitinib exposure is considered to be a serious safety concern. Coadministration of abrocitinib with moderate to strong CYP2C19 and CYP2C9 inhibitors is not recommended.

Effect of Strong CYP2C19 Inducers on Abrocitinib PK:
Coadministration of rifampin (a strong CYP2C19 and CYP3A4, and a moderate CYP2C9 inducer, 600 mg once daily for 8 days) with a single abrocitinib 200 mg dose decreased the overall combined exposure of abrocitinib and its two active metabolites ($AUC_{inf,u}$) by approximately 56% and decreased the peak exposure ($C_{max,u}$) by approximately 31% relative to a single abrocitinib 200 mg dose given alone. Based on the trial results, coadministration of abrocitinib with strong CYP2C19 inducers is not recommended.

Effect of Abrocitinib on P-glycoprotein Substrate where Small Concentration Changes May Lead to Serious or Life-threatening Toxicities:
Coadministration of a single dose of abrocitinib 200 mg increased total dabigatran (a P-gp substrate) exposure (AUC_{inf}) by approximately 53% relative to a single dabigatran 75 mg dose given alone. Per dabigatran labeling, about 50% increase of exposure is not considered clinically meaningful so that no dose adjustment is required for dabigatran. However, same extent of exposure increase can cause serious adverse reaction in a P-gp substrate where small concentration changes may lead to serious or life-threatening toxicities for example, digoxin. Therefore, appropriate monitoring or dose titration of P-gp substrate is recommended when abrocitinib is coadministered with P-gp substrate where small concentration changes may lead to serious or life-threatening toxicities.

Other In Vivo Study Results:
As a victim, coadministration of probenecid (OAT3 inhibitor) has no clinically meaningful effect on the PK of abrocitinib (Study B7451043). The PK results in this study indicated that probenecid increased the combined exposure of abrocitinib and its two active metabolites ($AUC_{inf,u}$) by 66% (90% CI: 52%, 80%).

Table 5 presents the summary results of abrocitinib effect on the exposure of other drugs.

Table 5: Effect of Abrocitinib on the Exposure of Other Drugs

Drug (Study Number) Analytes (n)	Ratio of Test to Reference (90% CI)		
	C_{max}	AUC_{last}	AUC_{inf}
Oral Contraceptives (B7451016)			
Ethinyl Estradiol (n=17)	1.07 (0.99, 1.16)	1.16 (1.10, 1.23)	1.18 (1.12, 1.26)
Levonorgestrel (n=17)	0.86 (0.76, 0.98)	0.98 (0.87, 1.10)	-[a]
CYP3A4 Substrate (B7451022)			
Midazolam (n=25)	0.94 (0.84, 1.04)	0.92 (0.86, 0.99)	0.92 (0.86, 0.99)
P-gp Substrate (B7451026)			
Dabigatran (n=20)	1.40 (0.92, 1.23)	1.35 (0.90, 2.03)	1.53 (1.09, 2.15)

BCRP and OAT3 Substrate (B7451033)			
Rosuvastatin (n=12)	0.99 (0.86, 1.14)	1.06 (0.95, 1.17)	1.02 (0.93, 1.12)
MATE1/2K Substrate (B7451034)			
Metformin (n=12)	0.88 (0.81, 0.96)	0.94 (0.88, 1.01)	0.93 (0.85, 1.03)

Source: Study Report B7451016 (Table 8 and Table 10), Study Report B7451022 (Table 9), Study Report B7451026 (Table 9), Study Report B7451033 (Table 9), Study Report B7451034 (Table 8)
n=number of subjects; Test=Abrocitinib 200 mg once daily + Other drug; Reference=Other drug alone
a. AUC_{inf} of levonorgestrel was not reported for all subjects because the terminal phase was not well characterized. That is, the percent of AUC_{inf}, obtained by forward extrapolation ($AUC_{extrap\%}$) was greater than 20%.
Abbreviations: CI=confidence interval; AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration; P-gp=P-glycoprotein; BCRP=breast cancer resistance protein; OAT3=organic anion transporter 3, MATE1/2K=multidrug and toxin compound extrusion protein 1/2K

In Vitro Drug-Drug Interactions Results

- CYP enzymes: Abrocitinib, M1 and M2, are not reversible inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Abrocitinib is a time dependent inhibitor (TDI) of CYP2C19, CYP2D6, and CYP3A4/5. M1 and M2 are TDI of CYP3A, CYP2C19, and CYP2D6. Abrocitinib is a weak inducer of CYP3A4, CYP1A2, and CYP2B6. M1 and M2 are weak inducers of CYP1A2 and CYP2B6.
- Uridine diphosphate (UDP)-glucuronosyl transferase (UGT) enzymes: Abrocitinib, M1, and M2 are not inhibitors or inducers of UGT1A1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7.
- Transporter systems: Abrocitinib is an inhibitor of OAT3, OCT1, MATE1/2K, and BCRP but is not an inhibitor of organic anion transporting polypeptide (OATP) 1B1/1B3, bile salt export pump (BSEP), OAT1, or OCT2. M1 and M2 are substrates of OAT3.

Refer to Individual Study Review in OCP appendices 16.5.3 for more details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

A brief description of the pertinent clinical studies under review.

Table 6: Summary Table of Clinical Studies

Phase 2	• B7451005 46 subjects completed with 14 placebo (in Plaque Psoriasis) – terminated early • B7451006 dose ranging 157 completed, 28 placebo
Phase 3	• B7451012: placebo-controlled, 100 mg (156), 200 mg (154) and placebo (77) for 12 weeks and LTE • B7451013: placebo controlled; 100 mg (158), 200 mg (155) and placebo (78) for 12 weeks and LTE • B7451014: randomized withdrawal, placebo controlled; subjects received 12-weeks of 200 mg QD open label, responders were randomized to 200 mg QD, 100 mg QD, or matching placebo up to 52 weeks. 1235 enrolled into OL run-in, 798 randomized (1:1:1) • B7451015: LTE study in subjects previously randomized to 200 mg or 100 mg QD in the qualifying Phase 3 will be allocated to the same dose. 1592 subjects • B7451029: 16-week active controlled; 200 mg or 100 mg abrocitinib, Dupilumab 300mg SQ every other week (load 600 mg at baseline), matching placebo. 200 mg: 226, 100 mg: 238, Dupilumab: 243, Placebo: 131 • B7451036: placebo controlled, abrocitinib co-administered with background medicated topical therapy in adolescent 12 to <18 years old. Planned 225

Source: Reproduced from abrocitinib submission ISS

The applicant reports that COVID 19 did not impact the evaluations and subject's safety or the data provided.

Table 7: Tabular Listing of Clinical Studies Pertinent to Clinical Review

Trial Identity	Trial Design	Regimen/ schedule/ route	No. of patients enrolled	Treatment Duration/ Follow Up	Study Initiation/Completion Date/Status
Phase 3 Controlled Studies to Support Efficacy and Safety					
B7451012	A Phase 3 randomized, DB, PC, parallel group, multicenter study to assess the efficacy of abrocitinib compared with placebo in subjects aged 12 years and older with moderate to severe atopic dermatitis Primary endpoint: proportion of subjects achieving an IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 12. Proportion of subjects achieving an EASI-75 response at Week 12. Key secondary: proportion of subjects achieving at least 4 points improvement from baseline in the severity of PP-NRS at Weeks 2, 4, and 12.	Abrocitinib 100 mg QD; Abrocitinib 200 mg QD; Placebo	Randomized: 387 (2:2:1) 100 mg QD: 156 200 mg QD: 154 Placebo: 77	12 Weeks Eligible subjects completing the study had the option to enter an LTE (B7451015)	07 Dec 2017/26 Mar 2019 Completed
B7451013	A Phase 3 randomized, DB, PC, parallel group, multicenter study to assess the efficacy of abrocitinib compared with placebo in subjects aged 12 years and older with moderate to severe atopic dermatitis Primary endpoint: proportion of subjects achieving an IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 12. Proportion of subjects achieving an EASI-75 response at Week 12. Key secondary: proportion of subjects achieving at least 4 points improvement from baseline in the severity of PP-NRS at Weeks 2, 4, and 12.	Abrocitinib 100 mg QD; Abrocitinib 200 mg QD; Placebo	Randomized: 391 (2:2:1) 100 mg QD: 158 200 mg QD: 155 Placebo: 78	12 Weeks Eligible subjects completing the study had the option to enter an LTE (B7451015)	29 Jun 2018/13 Aug 2019 Completed
B7451014	A Phase 3 randomized withdrawal, DB, PC, multicenter study to evaluate and compare the maintenance of effect of two doses of abrocitinib and placebo in subjects aged 12 and above with moderate to severe atopic dermatitis who respond to an initial open-label run-in treatment of	Open-label: 200 mg QD Randomized: abrocitinib 200 mg QD,	Planned: 600 (controlled phase) (randomized 1:1:1)	12 weeks open-label followed by double-blind, placebo-	ONGOING

	200 mg abrocitinib QD. Primary Endpoint: loss of response requiring rescue treatment will be evaluated and compared among groups during the blinded treatment period. Loss of response is denoted as flare and is defined as loss of at least 50% of the EASI response at Week 12 and an IGA score of 2 or higher.	Abrocitinib 100 mg QD Placebo Open-label Rescue: Abrocitinib 200 mg QD with topical therapy	100 mg QD: 200 200 mg QD: 200 Placebo: 200	controlled 40 weeks up to total of 64 weeks Rescue treatment: 12 weeks	
B7451015	A Phase 3 multicenter, LTE study in subjects at least 12 years of age with moderate to severe atopic dermatitis. To estimate the long-term safety of 100 mg and 200 mg QD abrocitinib with or without topical treatments in adult and adolescent subjects who previously participated in qualifying abrocitinib AD trials. Primary Endpoint: Incidence of treatment emergent adverse events. Incidence of serious adverse events and adverse events leading to discontinuation.	Abrocitinib 200 mg QD or Abrocitinib 200 mg QD	Planned: 3000	The total treatment duration for each subject will vary	ONGOING
B7451029	A Phase 3 randomized, DB, double-dummy, placebo controlled, parallel group, multicenter study investigating the efficacy and safety of abrocitinib and dupilumab in comparison with placebo in adults on background therapy with moderate to severe atopic dermatitis. Primary objective is to compare the efficacy of 100 mg and 200 mg QD of abrocitinib versus placebo in adult subjects on background topical therapy with moderate to severe AD. Primary endpoint is IGA and EASI, secondary endpoint is PP-NRS	Abrocitinib: 200 mg or 100 mg QD Dupilumab: 300 mg SQ every 2 weeks (load of 600 mg at baseline) Matching placebo was administered accordingly	Randomized 837 (2:2:2!) Abrocitinib 200 mg QD: 226 Abrocitinib 100 mg QD: 238 Abrocitinib 100 mg QD: 238 Dupilumab 300 mg Q2W: 242 Placebo: 131	20 weeks 16 weeks randomized, DB, PC, double-dummy followed by a 4 week follow-up period following cessation of treatment	29 Oct 2018/06 Mar 2020 Completed

Phase 2 Studies					
B7451005 -	A Phase 2, multicenter, randomized, DB, PC, 4-week parallel group study with oral abrocitinib in subjects with moderate to severe chronic plaque psoriasis who were candidates for systemic treatment of phototherapy	Abrocitinib 200 mg QD; Abrocitinib 200 mg BID; Abrocitinib 400 mg QD; Placebo	Planned: 196 Actual 59, early terminated	4 weeks	25 Nov 2014/10 Sep 2015
B7451006 -	A Phase 2b, randomized, DB, PC, parallel, multicenter, dose-ranging study to evaluate the efficacy and safety profile of abrocitinib in subjects with moderate to severe atopic dermatitis	Abrocitinib 10 mg QD; Abrocitinib 30 mg QD; Abrocitinib 100 mg QD; Abrocitinib 200 mg QD; Placebo QD	Planned: 250 Actual 269 157 completed 28 placebo 27 10 mg; 27 30 mg; 37 100 mg; 38 200 mg 110 discontinued	12 weeks treatment; 4 weeks follow-up	15 Apr 2016/04 Apr 2017 Completed
Other studies pertinent to the review of efficacy or safety					
B7451036	A Phase 3, randomized, DB, PC, multicenter study investigating the efficacy and safety of abrocitinib co-administered with background medicated topical therapy in adolescent subjects 12 to < 18 years of age with moderate to severe atopic dermatitis. Primary endpoint: Proportion of subjects achieving IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at Week 12. Proportion of subjects achieving EASI-75 at Week 12. Secondary endpoint of PP-NRS	Abrocitinib 100 mg QD Abrocitinib 200 mg QD Placebo	Planned: 225 (randomized 1:1:1) 100 mg QD – 75 200 mg QD – 75 Placebo – 75 Immunogenicity substudy	12 Weeks Subjects completing 12-week treatment will have the option to enter LTE B7451015	Completed and submitted with the 120-day safety update
B7451050	A Phase 3b, randomized, DB, double-dummy, active controlled multicenter study assessing the efficacy and	Abrocitinib: 200 mg QD	Planned: 600 (randomized	26 weeks Eligible	PLANNED

	safety of abrocitinib compared with dupilumab in adult subjects on background topical therapy with moderate to severe atopic dermatitis. Primary endpoint: response based on achieving at least a 4-point improvement in the severity of PP-NRS from baseline at Week 2	Dupilumab: 300 mg SQ QOW (loading 600 mg at baseline) Matching placebo	1:1)	subjects completing the study treatment period will have the option to enter the LTE study B7411015	

Source: Abrocitinib sponsor submission, section 5.2 tabular listing of all clinical studies

7.2.Review Strategy

The monotherapy studies B7451012 (Mono-1) and B7451013 (Mono-2) will represent the main clinical pooling evaluation for safety and efficacy. The secondary pool of placebo-controlled studies (B7451006, Mono-1, Mono-2, and B7451029) will be discussed as supportive safety evaluations and provide some long-term safety events. The safety database will focus on common adverse events and adverse events of special interest.

Compliance with Good Clinical Practices

The applicant reports the studies were conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Council on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), and the Declaration of Helsinki.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

The Applicant conducted three phase 3 trials, B7451012, B7451013 and B7451029. Trials B7451012 and B7451013 were monotherapy trials in adolescents and adults, while B7451029 was a trial with background topical therapy in adults only. For all three trials, the key inclusion criteria for enrollment specified in the protocols are as follows:

- Male or female 12 years of age or older at the time of informed consent and body weight ≥40 kg for the monotherapy trials B7451012 and B7451013. Male or female 18 years or older at the time of informed consent for Trial B7451029
- Diagnosis of chronic atopic dermatitis (AD) for at least 1 year prior to Day 1
- Have moderate to severe AD:
    - Affected body surface area (BSA) of ≥10% at baseline
    - Investigator Global Assessment (IGA) score of ≥3 at baseline; see Table 49 in Appendix 16.3 for details on the IGA scale
    - Eczema Area and Severity Index (EASI) score of ≥16 at baseline; see Figure 11 in Appendix 16.3 for details on the calculation of EASI
    - Pruritus numeric rating scale (NRS) severity score of ≥4 at baseline
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications for at least 4 weeks, or for whom topical treatments are otherwise medically inadvisable, or who have required systemic therapies for control of their disease

<u>Pruritus numeric rating scale (NRS):</u>
The pruritus NRS is a single-item patient-reported outcome (PRO) instrument designed to assess itch intensity at its worst. Subjects were asked to assess their worst itching due to atopic dermatitis over the past 24 hours on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10). Pruritus NRS was assessed using an eDiary, daily during the screening period and from Day 1 to 15. After Day 15, the Pruritus NRS was completed only on trial visit days.

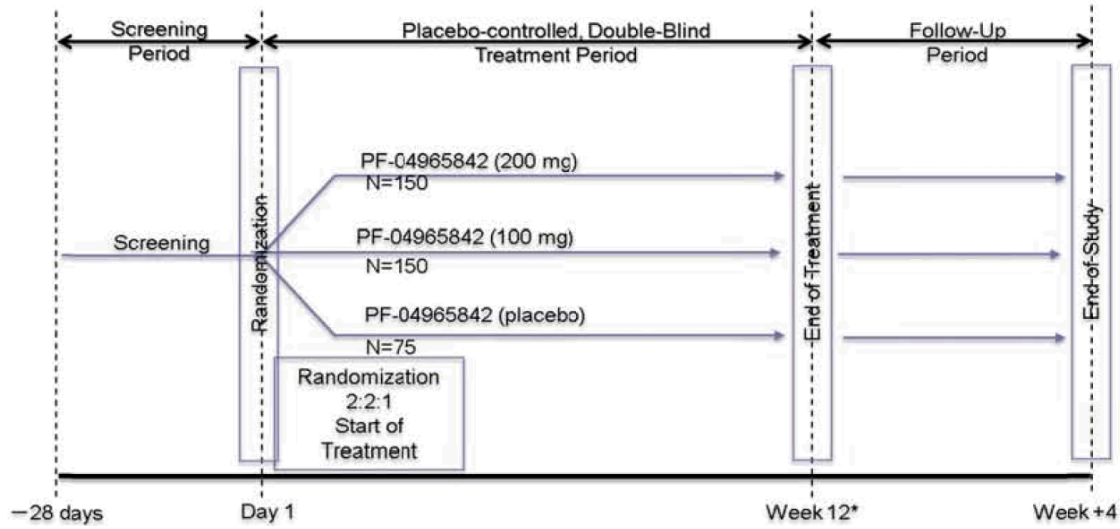
Phase 3 Monotherapy Trials B7451012 (NCT03349060) and B7451013 (NCT03575871):
Trials B7451012 and B7451013 were identically designed, and the trial design schematic is presented in Error! Reference source not found.. Both trials were randomized, multicenter, double-blind, placebo-controlled, parallel group, phase 3 trials to evaluate the efficacy and safety of abrocitinib (PF-04965842) monotherapy in subjects aged 12 years and older with moderate to severe atopic dermatitis (AD).

Trials B7451012 and B7451013 were each designed to enroll and randomize approximately 375 subjects from global investigational sites. Subjects were randomized to one of the following treatment arms in a 2:2:1 ratio: abrocitinib 200 mg daily (QD), abrocitinib 100 mg once daily

(QD) or matching placebo. The protocols specified stratifying randomization by baseline disease severity (moderate [IGA = 3] vs. severe [IGA = 4] AD), and age (<18 and ≥18).

The trials consisted of a screening period (28 days), a 12-week placebo-controlled, double-blind, treatment period and a 4-week follow-up period. The trial design schematic is presented in Error! Reference source not found.. Qualified subjects completing the 12-week treatment period of the monotherapy trials had the option to enter the long-term extension (LTE) trial B7451015. Subjects discontinuing early from treatment, or who were otherwise ineligible for the LTE trial underwent a 4-week follow-up period in the monotherapy trials. Subjects had on-site visits at screening, baseline (Week 0) and Weeks 2, 4, 8, 12 and 16 (follow-up visit). Subjects were also contacted via phone calls at Weeks 1 and 6.

Figure 3: Trial Design Schematic for Trials B7451012 and B7451013



Source: Protocol for Trial B7451012; page 34
*At Week 12, eligible subjects may enter a long-term extension trial all other subjects enter the 4-week follow-up period.

Phase 3 Trial B7451029 (NCT03720470) with Background Topical Therapy:
Trial B7451029 was a multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel group, phase 3 trial to evaluate the efficacy and safety of abrocitinib (PF-04965842) and dupilumab in comparison with placebo in adult subjects on background topical therapy, with moderate to severe AD. The trial design schematic is provided in Figure 4.

Trial B7451029 was designed to enroll and randomize approximately 700 subjects from approximately 270 global sites. Subjects were randomized to one of the following treatment arms in a 4:4:4:1:1 ratio:

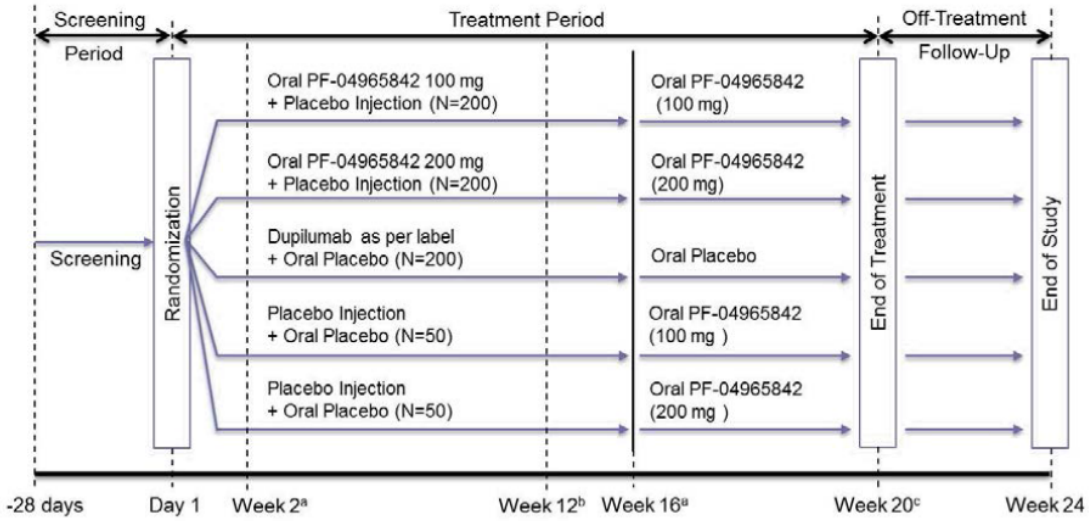
- Abrocitinib 100 mg once daily (QD) + dupilumab-matching placebo every two weeks (Q2W)
- Abrocitinib 200 mg QD + dupilumab-matching placebo Q2W
- Dupilumab 300 mg Q2W (with loading dose of 600 mg at baseline as per label) + Abrocitinib-matching placebo QD
- Abrocitinib-matching placebo QD (100 mg) + dupilumab-matching placebo Q2W
- Abrocitinib-matching placebo QD (200 mg) + dupilumab-matching placebo Q2W

The two placebo sequences were combined for purposes of analyses at all visits up to and including Week 16, which resulted in a 2:2:2:1 randomization ratio. The protocol specified that administering randomization using center-based permuted blocks. According to the protocol (page 59), "randomization will not be stratified by baseline disease severity or age".

The trial consisted of a screening period (28 days), a 20-week treatment period and a 4-week follow-up period. The trial design schematic is presented in Figure 4.The first part of this treatment period consisted of a 16-week randomized, double-blind, placebo-controlled, double-dummy treatment period with subjects receiving both injectable and oral investigational product. The randomization and double-blind was maintained during the final 4 weeks of the treatment period (Weeks 16-20), but subjects received only oral investigational product. At Week 16 in the treatment period, all subjects ceased injectable dupilumab or its matching placebo. This was to facilitate the washout of dupilumab (for a total of 6 weeks; as the final dose of dupilumab or its matching placebo is administered at Week 14) prior to eligible subjects entering the long-term extension trial, in which all subjects receive abrocitinib active treatment. Following Week 16, subjects previously receiving only placebo would receive abrocitinib 100 mg or 200 mg QD as per their randomized allocation. Subjects previously receiving abrocitinib 100 mg or 200 mg QD continued on their respective dose. Subjects previously receiving dupilumab would continue to take oral placebo. According to the clinical study report (CSR), these alterations to treatment were all to be conducted while maintaining the blind when re-issuing oral investigational product to all subjects at the Week 16 time point.

Eligible subjects completing the entire 20-week treatment period of the study had the option to enter a long-term extension (LTE) trial B7451015, in which all subjects received abrocitinib active treatment. Subjects discontinuing early from treatment, or who were otherwise ineligible for the LTE trial, underwent a 4-week follow-up period in Trial B7451029.

Figure 4: Trial Design Schematic for Trial B7451029



Source: Protocol for Trial B7451029; page 49
[a] At Week 2 and Week 16, key secondary endpoints are measured.
[b] At Week 12, primary endpoints are measured.

[c] At Week 20, eligible subjects will enter the B7451015 long-term extension study; ineligible subjects will instead enter the 4-week off-treatment follow-up period in B7451029.
Note: Standardized background topical therapy must be used as per protocol guidelines throughout the study.

The protocol specified that the first injection on Day 1 would be administered by an unblinded administrator/trainer and used to train the subject (or caregiver, if applicable) on correct injection technique. The second injection was planned to be administered by the subject (or caregiver, if applicable) immediately following the first injection, under the observation of the unblinded administrator/trainer. The protocol specified that the unblinded administrator/trainer must not take any action that may potentially reveal treatment assignment to the subject or site staff. Any trial participants other than the unblinded administrator/trainer must not be allowed to know the investigational product assigned to any subject and must not be allowed to see the treatment records.

According to the protocol, subjects dispensed prefilled syringes containing injectable investigational product on Day 1 and Weeks 2, 4, 8, and 12, administered at the site under the observation of the unblinded administer/trainer, and at home by the subject (or caregiver) at Weeks 6, 10, and 14.

For "permitted concomitant medications", the protocol specified the following "Background Topical Therapy":

- Non-medicated topical therapy: emollient without other active ingredients indicated to treat AD or other additives which could affect AD must be applied at least twice daily to all body areas affected with AD, throughout at least the final 7 days prior to Day 1 and throughout the remainder of the study
- Medicated topical therapy: Topical Corticosteroids (TCS) must be applied once daily to areas with active lesions starting on Day 1 and throughout the study, according to the guidance below.
    - Medium potency TCS must be applied to body areas with active lesions that are suitable for the use of medium potency TCS.
    - Low potency TCS must be applied to body areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.), with active lesions instead of medium potency TCS or to body areas where continued treatment with medium potency TCS is considered unsafe.
    - Topical calcineurin inhibitors (e.g., tacrolimus, pimecrolimus) or a PDE4 inhibitor (crisaborole) may be used instead of corticosteroids in body areas of thin skin with active lesions or if continued treatment with TCS of any potency is considered unsafe, and according to locally approved label at the investigator's discretion and considering prior response or intolerance to these medications.

The protocol specified that the background topical therapy must not be applied prior to attending a trial visit, on the day of the trial visit. Background topical therapy instead should be applied after the visit, on trial visit days.

8.1.2. Efficacy Endpoints

For all three phase 3 trials, the protocols specified the following co-primary efficacy endpoints:

- IGA 0/1: Proportion of subjects with IGA score of 0 (clear) or 1 (almost clear) with a reduction of ≥2 points at Week 12
- EASI-75: Proportion of subjects with at least 75% reduction in EASI score from baseline to Week 12

In the advice letter dated 2/15/2018, the Agency noted that while the planned co-primary endpoints based on the IGA and EASI are acceptable, the Agency considers the IGA endpoint to be the main primary endpoint.

Table 8 presents the key secondary efficacy endpoints specified in the protocols/SAPs of the three pivotal trials.

Table 8: Key Secondary Endpoints

Monotherapy Trials B7451012 and B7451013	Trial B7451029
PP-NRS4: At least 4 points reduction in the severity of pruritus Numeric Rating Scale (NRS) score from baseline to Weeks 2, 4 and 12	PP-NRS4: At least 4 points reduction in the severity of pruritus Numeric Rating Scale (NRS) score from baseline to Week 2
Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12	IGA of clear (0) or almost clear (1) and a reduction from baseline of ≥2 points at Week 16
	Proportion of subjects with at least 75% reduction in EASI score from baseline (EASI-75) to Week 16

Source: Statistical Reviewer's table

Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD)

The PSAAD is an 11-item, patient-reported questionnaire using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Each item was assessed on an 11-point numeric rating scale. The PSAAD was assessed daily. According to the SAPs, the PSAAD total score was calculated as the simple arithmetic mean of items 1-11. For analyses, simple weekly averages of all observed values of the PSAAD score were used.

The protocols also specified 'secondary endpoints', 'other efficacy endpoints' and other endpoints based on Patient Reported Outcomes (PROs); however, such endpoints were not included in the multiplicity testing strategy, and therefore, are not presented in this review.

8.1.3. Statistical Methodologies

Analysis Populations:

The primary analysis population specified in the protocols and Statistical Analysis Plans (SAPs) was the full analysis set (FAS), defined as all randomized subjects receiving at least one dose of study medication. In the SAPs, the Applicant stated that it is expected that the FAS as defined

will be identical to an intent-to-treat analysis set (randomized and dispensed study medication) because the first dose is administered in-clinic.
The protocols/SAPs also specified supportive analyses using the Per Protocol Analysis Set (PPAS), defined a subset of FAS who had no major protocol violations. According to the SAPs, this set included subjects who:

- Were eligible for the study by way of meeting key inclusion criteria and none of the key exclusion criteria.
- Did not permanently discontinue assigned study oral treatment prior to Week 12 (Trial B7451029 only).
- Had valid and non-missing baseline efficacy data (IGA and EASI score).
- Had actual, observed IGA and EASI scores at Week 12.
- Did not take a protocol-prohibited medication for the primary diagnosis prior to completion of the study dosing period (Week 12).
- Did not take a protocol-prohibited concomitant medication prior to Week 12 (only Trial B7451029).
- Took the correct randomized treatment for at least 80% and at most 120% of the assigned amount until completion of the study dosing period (Week 12).
- Adhered to standardized background topical therapy guidelines for ≥80% of days at Week 12 (Trial B7451029 only).
- Had no other major protocol violations as determined by the clinical team prior to database lock.

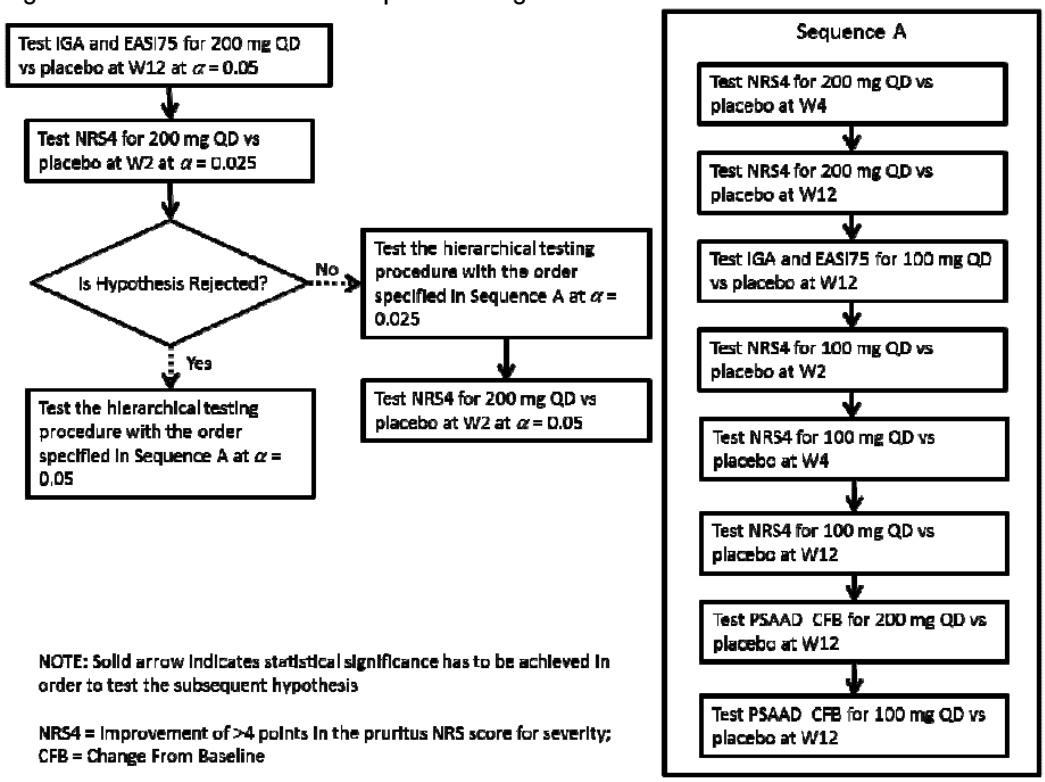
Analysis methods for the primary and key secondary endpoints:
The protocols/SAPs specified analyzing the co-primary endpoints (i.e., IGA 0/1 and EASI-75) and the binary key secondary endpoints using the Cochran-Mantel-Haenszel (CMH) test adjusting for baseline disease severity (all trials) and age (only for monotherapy trials). The SAPs specified summarizing the proportion of responders in the treatment groups by the difference and its 95% confidence interval (CI) obtained by normal approximation. The SAPs specified calculating the difference in proportions within each stratum. The final estimate of the difference in proportions was a weighted average of these stratum-specific estimates using CMH weights.

The protocols and SAPs specified analyzing the change in PSAAD from baseline to Week 12 (endpoint only in monotherapy trials) using a mixed-effect model with repeated measures (MMRM). The SAPs specified including fixed effects of treatment, visit, treatment-by-visit interaction, and randomization stratification factors in the model. The SAPs specified using an unstructured covariance matrix; however, if the model fails to converge, then a compound symmetry covariance matrix was to be used.

Multiplicity Testing Procedure (MTP):
To control the overall Type I error rate at 5%, the SAPs specified a sequential Bonferroni-based iterative multiple testing procedure of the two abrocitinib doses (200 mg QD and 100 mg QD) versus placebo on the primary and key secondary endpoints. The schematic for the multiple testing procedure is provided in

Figure 5 for the monotherapy trials (B7451012 and B7451013) and
Figure 6 for Trial B7451029.

Figure 5: Schematic for Multiple Testing Procedure for Trials B7451012 and B7451013



Source: Protocol for Trial B7451012; page 100

Figure 6: Schematic for Multiple Testing Procedure for Trial B7451029

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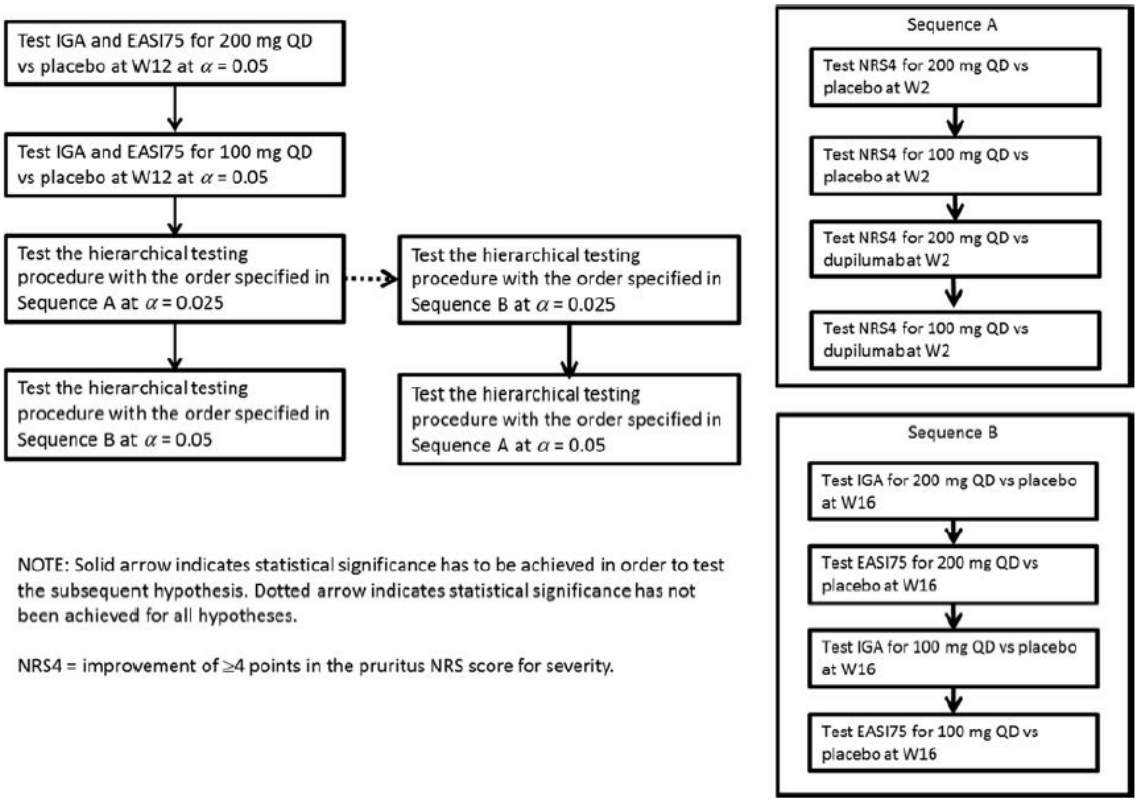


Source: Protocol for Trial B7451029; page 118

Methods for handling the missing data:

The SAPs specified that subjects who permanently discontinue trial for any reason are defined as “non-responders” at all subsequent visits for the analysis of the co-primary endpoints; for other subjects, any observations missing intermittently are considered missing completely at random (MCAR) and remained missing in the analysis.

The SAPs specified a multiple imputation method using a tipping point (TP) approach as a sensitivity analysis to assess the impact of missing data at Week 12 due to subject drop-out for the analysis of the co-primary endpoints. The method is described below:

The observed IGA/EASI-75 responses at Weeks 2, 4, 8, and 12 are used for the imputation model which is a logit Generalized Linear Mixed Model (GLMM) with treatment, visit, treatment-by-visit as fixed factors and a subject-specific, zero-mean, normally-distributed random effect. Estimation of the parameters from this model is performed under the Bayesian framework using Markov Chain Monte Carlo (MCMC) method and the posterior distribution of the model parameters is derived. For each subject, missing responses at Week 12 are imputed using random Bernoulli draws based on the posterior probability of response. For the imputation in each of the active groups, a weighted linear combination of the response probabilities from the active group and the placebo group is considered. Five sets of complete imputed data are created using weight=0, 0.25, 0.5, 0.75 and 1. Values of 0 and 1 for this weight corresponded to analyses under Missing at Random (MAR) and Jump-to-Reference (JTR), respectively. The process is repeated 500 times using seed=332786.

The SAPs for the monotherapy trials (B7451012 and B7451013) stated that "Due to a technical error in the process of transmission and collection of electronic data with the device, the data on the pruritus NRS scale was not collected from several subjects at the scheduled visits of Week 2 (Day 15) and after. This was not restricted to a particular site or country and was not indicative of being related to the missing value of pruritus endpoint or any other endpoints." Therefore, for the analysis of the key secondary endpoint derived from the pruritus NRS, a hybrid approach was specified in the SAPs for the monotherapy trials as described below, while for Trial B7451029, the non-responder imputation was specified for the missing pruritus NRS data.

First, an imputation model based on a GLMM is fit to the observed data with treatment, visit, and treatment-by-visit interaction as fixed factors and a subject specific normally-distributed random effect. Second, any responses which are missing due to the subject discontinuing permanently are defined as "non-response". Third, any other data which remained missing at any intermittent visits are handled using multiple imputation under the MAR assumption. The multiple imputation methodology used here is very similar to the one described in the paragraph above with the weights taken as zero. At any particular visit, if there are 5 or fewer subjects with missing data in each treatment arm after applying the non-responder definition, no imputation is performed, and the data remain missing.

The Agency previously noted (written responses dated 2/24/2019) that it is very difficult to definitively determine the mechanism(s) of missingness in a clinical trial, which may be a combination of different types. The Agency also noted that given the lack of details, it is difficult to provide comments concerning the proposed method to handle missing data for the pruritus endpoint.

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial B7451012 enrolled and randomized a total of 387 subjects from 69 investigational sites. Trial B7451013 enrolled and randomized a total of 391 subjects from 102 investigational sites. All randomized subjects in Trials B7451012 and B7451013 were dosed. Trial B7451029 enrolled and randomized a total of 837 subjects from 194 investigational sites. There was 1 subject in dupilumab arm who was not dosed.

Table 9 presents the disposition of subjects through Week 12 for Trials B7451012 and B7451013, while Table 10 and presents the disposition of subjects through Week 12 for Trial B7451029. In the monotherapy trials (Trials B7451012 and B7451013), the discontinuation rate was higher in the placebo arm compared to the abrocitinib arms. In Trial B7451029 with background therapy, the discontinuation rates were generally similar across the treatment arms.

Table 9: Disposition of Subjects through Week 12 – Trials B7451012 and B7451013

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
	200 mg	100 mg	Placebo	200 mg	100 mg	Placebo
Randomized	154	156	77	155	158	78

Not dosed	0	0	0	0	0	0
FAS	154	156	77	155	158	78
Discontinued	17 (11%)	21 (13%)	16 (21%)	14 (9%)	21 (13%)	26 (33%)
Adverse Event (AE)	9 (6%)	9 (6%)	7 (9%)	5 (3%)	5 (3%)	8 (10%)
Lack of Efficacy	0 (0%)	1 (1%)	2 (3%)	4 (3%)	5 (3%)	7 (9%)
Lost to Follow-up	1 (1%)	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Medication Error without Associated AE	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Protocol Deviation	2 (1%)	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Withdrawal by Parent/Guardian	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawal by Subject	3 (2%)	5 (3%)	4 (5%)	1 (1%)	6 (4%)	9 (11%)
Other	1 (1%)	2 (1%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)
Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSLxpt

Table 10: Disposition of Subjects through Week 12 – Trial B7451029

	Abrocitinib			
	200 mg	**100 mg**	**Dupilumab**	**Placebo**
Randomized	226	238	243	131
Not dosed	0	0	1	0
FAS	226	238	242	131
Discontinued	18 (8%)	21 (9%)	19 (8%)	14 (11%)
Adverse Event (AE)	8 (3%)	5 (2%)	6 (2%)	5 (4%)
Lack of Efficacy	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)
Lost to Follow-up	1 (<1%)	2 (1%)	2 (1%)	1 (1%)
Medication Error without Associated AE	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
Protocol Deviation	1 (<1%)	2 (1%)	1 (<1%)	2 (1.5%)
Withdrawal by Subject	3 (1%)	9 (4%)	6 (2%)	5 (4%)
Pregnancy	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)
Other	2 (1%)	1 (<1%)	2 (1%)	1 (1%)

Source: Statistical Reviewer's Analysis (same as Applicant's analysis); ADSLxpt

Table 11 presents the demographics for the three phase 3 trials. As previously noted, Trial B7451029 enrolled adults only, while approximately 20% and 10% of the enrolled subjects in the monotherapy trial B7451012 and B7451013, respectively, were adolescents (i.e., 12-<18 years of age). The majority of the subjects in all trials were White (approximately 70%) and <65 years of age (more than 90%) and the majority of the investigational sites were in Europe. Demographics were generally balanced across the treatment arms within each trial and across the three trials. A slightly smaller proportion of White subjects with a slightly higher proportion of Asian subjects were enrolled in Trial B7451013 compared to the remaining trials.

Table 12 presents the baseline disease characteristics for all three trials. The baseline disease characteristics were generally balanced across the treatment arms within each trial and across trials. A higher proportion of subjects with moderate disease severity was enrolled in all trials compared with the proportion of subjects with severe disease severity.

Table 11: Demographics - Trials B7451012, B7451013 and B7451029 (FAS[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	Abrocitinib			Abrocitinib			Abrocitinib			
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
Age (years)										
Mean (SD)	33.0 (17.3)	32.6 (15.4)	31.5 (14.4)	33.5 (14.7)	37.4 (15.8)	33.4 (13.8)	38.8 (14.5)	37.3 (14.7)	37.1 (14.6)	37.4 (15.2)
Median	27	30.5	29.0	29.0	35.0	29.0	36	33	34	34
Range	12 – 84	12 – 73	12 - 65	12 – 76	12 – 83	13 – 71	18 – 80	18 – 82	18 – 83	18 – 84
Categories, n (%)										
12-<18	33 (21%)	34 (22%)	17 (22%)	15 (10%)	17 (11%)	8 (10%)	-	-	-	-
18-<65	110 (71%)	118 (76%)	59 (77%)	133 (86%)	130 (82%)	69 (88%)	211 (93%)	224 (94%)	227 (94%)	121 (92%)
≥65	11 (7%)	4 (3%)	1 (1%)	7 (4%)	11 (7%)	1 (1%)	15 (7%)	14 (6%)	15 (6%)	10 (8%)
Sex, n (%)										
Male	81 (53%)	90 (58%)	49 (64%)	88 (57%)	94 (59%)	47 (60%)	104 (46%)	120 (50%)	108 (45%)	77 (59%)
Female	73 (47%)	66 (42%)	28 (36%)	67 (43%)	64 (40%)	31 (40%)	122 (54%)	118 (50%)	134 (55%)	54 (41%)
Race[2], n (%)										
White	104 (67%)	113 (72%)	62 (80%)	91 (59%)	101 (64%)	40 (51%)	161 (71%)	182 (76%)	176 (73%)	87 (66%)
Black or African American	11 (7%)	15 (10%)	6 (8%)	6 (4%)	9 (6%)	6 (8%)	9 (4%)	6 (2%)	14 (6%)	6 (5%)
American Indian or Alaska Native	4 (3%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	2 (1%)	2 (1%)
Asian	26 (17%)	26 (17%)	6 (8%)	54 (35%)	46 (29%)	29 (27%)	1 (<1%)	0 (0%)	0 (0%)	1 (1%)
Multiple	6 (4%)	1 (1%)	1 (1%)	2 (1%)	1 (1%)	1 (1%)	53 (23%)	48 (20%)	46 (19%)	31 (24%)
Missing	2 (1%)	0 (0%)	1 (1%)	2 (1%)	1 (1%)	2 (3%)	1 (<1%)	0 (0%)	2 (1%)	3 (2%)
Region, n (%)										
Us/Canada	68 (44%)	74 (47%)	36 (47%)	29 (19%)	30 (19%)	22 (28%)	56 (25%)	56 (24%)	62 (36%)	34 (26%)
Europe	64 (42%)	59 (38%)	35 (45%)	73 (47%)	69 (44%)	33 (42%)	109 (48%)	125 (52%)	125 (52%)	64 (49%)
Australia	22 (14%)	23 (15%)	6 (8%)	7 (4%)	21 (13%)	4 (5%)	9 (4%)	9 (4%)	11 (5%)	9 (7%)
Asia	0 (0%)	0 (0%)	0 (0%)	46 (30%)	38 (24%)	19 (24%)	41 (18%)	34 (14%)	33 (14%)	17 (13%)
Latin America	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (5%)	14 (6%)	11 (5%)	7 (5%)

Source: Reviewer's Analysis (same as Applicant's analysis); ADSLxpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed

[2] Missing race information for 3 subjects in Trial B7451012 (two in the 200 mg arm and one in the placebo arm) and 5 subjects in Trial B7451013 (two in the 200 mg arm, one in the 100 mg arm and two in placebo arm).

Table 12: Baseline Disease Severity - Trials B7451012, B7451013 and B7451029 (FAS[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	Abrocitinib			Abrocitinib			Abrocitinib			
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
Duration of AD (years)										
Mean (SD)	22.7 (14.5)	24.9 (16.1)	22.5 (14.4)	20.5 (14.8)	21.1 (14.8)	21.7 (14.3)	23.4 (15.6)	22.7 (16.3)	22.8 (14.7)	21.3 (14.4)
Median	18.8	21.3	18.8	18.9	20.2	19.8	23.2	21.5	22.5	21.3
Range	1.0 – 65.5	1.0 – 68.6	1.8 – 65.7	1.2 – 66.9	1.0 – 64.2	1.1 – 62.2	1.0 – 66.3	1.1 – 72.3	1.1 – 65.6	1.2 – 70.8
Prior Use to Systemic Therapy for AD										
Yes	70 (45%)	82 (53%)	41 (53%)	60 (39%)	70 (44%)	32 (41%)	103 (46%)	99 (42%)	112 (46%)	48 (37%)
No	84 (55%)	74 (47%)	36 (47%)	95 (61%)	88 (56%)	46 (59%)	123 (54%)	139 (58%)	130 (54%)	83 (63%)
IGA, n (%)										
3 – Moderate	91 (59%)	92 (59%)	46 (60%)	106 (68%)	107 (68%)	52 (67%)	138 (61%)	153 (64%)	162 (67%)	88 (67%)
4 – Severe	63 (41%)	64 (41%)	31 (40%)	49 (32%)	51 (32%)	26 (33%)	88 (39%)	85 (36%)	80 (33%)	43 (33%)
EASI										
Mean (SD)	30.6 (14.1)	31.3 (13.6)	28.7 (12.5)	29.0 (12.4)	28.4 (11.2)	28.0 (10.2)	32.1 (13.1)	30.3 (13.5)	30.4 (12.0)	31.0 (12.6)
Median	25.2	27.3	22.9	24.9	25.2	25.9	29.75	25.25	26.75	26.0
Range	12 – 69	11.2 – 72	9.8 – 72	10.9 – 69.3	16 – 64.9	12.6 – 57.6	11.3 – 72	13.6 – 72	14.5 – 69.8	5 – 66
Percent BSA										
Mean (SD)	49.9 (24.4)	80.8 (23.4)	47.4 (22.7)	47.7 (22.3)	48.7 (21.4)	48.2 (20.7)	50.8 (23.0)	48.1 (23.1)	46.5 (22.1)	48.9 (24.9)
Median	42	47	43	44	45	45	48.1	44.25	44.45	42.9
Range	10 – 100	12 – 100	11 – 93	11 – 96	10.5 – 100	16 – 100	9.9 – 100	11.1 – 100	10.0 – 99.1	5.9 – 100
Pruritus NRS										
Mean (SD)	7.1 (1.9)	6.9 (1.9)	7.0 (1.8)	7.0 (1.6)	7.1 (1.6)	6.7 (1.9)	7.6 (1.5)	7.1 (1.7)	7.3 (1.6)	7.1 (1.7)
Median	7	7	7	7	7	7	8	7	7	7
Range	0 – 10	2 – 10	2 – 10	2 – 10	2 – 10	2 – 10	4 – 10	2 – 10	3 – 10	2 – 10
>=3	151 (98%)	152 (98%)	76 (99%)	154 (99%)	157 (99%)	76 (97%)	226 (100%)	236 (99%)	241 (100%)	130 (99%)
>=4	147 (95%)	147 (95%)	74 (96%)	153 (99%)	156 (99%)	76 (97%)	226 (100%)	236 (99%)	240 (99%)	130 (99%)

Source: Reviewer's Analysis; ADSLxpt, ADCM.xpt

* Full Analysis Set (FAS) defined as all randomized subjects who were dosed

8.1.5. Results for the Co-Primary Efficacy Endpoints

Table 13 and Table 14 present results for the co-primary endpoints at Week 12 for the monotherapy Trials B7451012 and B7451013, and Trial B7451029, respectively. Missing data are imputed using the non-responder imputation (NRI). It should be noted that such method for handling the missing data is slightly different from the one pre-specified in the protocols/SAPs, where only subjects who permanently discontinued the trial were defined as non-responders at all subsequent visits. Of note, there are a few subjects who did not permanently discontinue the trial and yet had missing outcomes at Week 12, either because they missed the visit or because they were out of the analysis window of time. Such subjects remained missing in Applicant's analysis (results not presented herein), while they were imputed as non-responders in the statistical reviewer's analysis (results in Table 13 and Table 14); conclusions remained the same in the two analyses. The results based on the PPAS (see Table 50 and Table 51 in Appendix 16.3) were similar to those based on the FAS.

Both abrocitinib doses (200 mg and 100 mg) were statistically superior to placebo for the co-primary endpoints at Week 12 in all three trials. A higher treatment effect is observed in the higher dose 200 mg compared to the lower dose of 100 mg in all three trials. In addition, a slightly higher treatment effect is observed for the 200 mg in monotherapy Trial B7451012 compared to monotherapy Trial B7451013 based on the IGA 0/1 response. It should be noted that a slightly higher proportion of subjects with severe IGA at baseline were enrolled in Trial B7451012 compared to Trial B7451013.

Of note, treatment effect was similar between monotherapy trials and the trial with concomitant background therapy for both doses and co-primary endpoints, with the exception of the 100 mg dose, for which treatment effect was slightly lower in the monotherapy trials compared to the combination therapy trial for IGA 0/1 response. We also note that response rates are similar between the 100 mg of abrocitinib and dupilumab for both endpoints in Trial B7451029 with concomitant background therapy.

Table 13: Results for the Co-Primary Endpoints at Week 12 - Trials B7451012 and B7451013 (FAS; NRI[1])

	Trial B7451012			**Trial B7451013**		
	Abrocitinib			**Abrocitinib**		
Co-Primary Endpoint	**200 mg (N=154)**	**100 mg (N=156)**	**Placebo (N=77)**	**200 mg (N=155)**	**100 mg (N=158)**	**Placebo (N=78)**
IGA 0/1	67 (43%)	37 (24%)	6 (8%)	59 (38%)	44 (28%)	7 (9%)
Difference from placebo (95% CI)[2]	36% (26%, 46%)	16% (7%, 25%)	-	29% (19%, 39%)	19% (9%, 29%)	-
P-Value[3]	<0.001	0.031	-	<0.001	<0.001	-
EASI-75	96 (62%)	62 (40%)	9 (12%)	94 (61%)	69 (44%)	8 (10%)
Difference from placebo (95% CI)[2]	51% (40%, 61%)	28% (18%, 39%)	-	50% (40%, 61%)	33% (23%, 44%)	-
P-Value[3]	<0.001	<0.001	-	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method
[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Table 14: Results for the Co-Primary Endpoints at Week 12 – Trial B7451029 (FAS; NRI[1])

Co-Primary Endpoint	Abrocitinib 200 mg (N=226)	Abrocitinib 100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
IGA 0/1	106 (47%)	86 (36%)	88 (36%)	18 (14%)
Difference from placebo (95% CI)[2]	34% (25%, 42%)	23% (15%, 31%)	23% (14%, 31%)	-
P-Value[3]	<0.001	<0.001	-	-
EASI-75	154 (68%)	138 (58%)	140 (58%)	35 (27%)
Difference from placebo (95% CI)[2]	41% (32%, 51%)	32% (22%, 41%)	31% (21%, 41%)	-
P-Value[3]	<0.001	<0.001	-	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method
[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity).

Table 15 and Table 16 present the number of subjects with missing data for the co-primary efficacy endpoints by visit, treatment arm and trial through Week 12. A higher proportion of missing data at Week 12 is observed in the placebo arm of the monotherapy trials B7451012 and B7451013 compared to the concomitant background therapy trial (B7451029).

Table 15: Missing Data for the Co-Primary Endpoints through Week 12 - Trials B7451012 and B7451013 (FAS[1])

	B7451012			B7451013		
	Abrocitinib			Abrocitinib		
Visit	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)
Week 2	1 (1%)	3 (19%)	2 (3%)	4 (3%)	3 (2%)	2 (3%)
Week 4	6 (4%)	8 (5%)	4 (5%)	4 (3%)	9 (6%)	2 (3%)
Week 8	7 (4%)	12 (8%)	6 (8%)	6 (4%)	10 (6%)	12 (15%)
Week 12	11 (7%)	16 (10%)	13 (17%)	9 (6%)	18 (11%)	23 (29%)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed

Table 16: Missing Data for the Co-Primary Endpoints through Week 12 - Trial B7451029 (FAS[1])

	Abrocitinib			
Visit	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
Week 2	5 (2%)	11 (5%)	10 (4%)	4 (3%)
Week 4	7 (3%)	9 (4%)	8 (3%)	4 (3%)
Week 8	5 (2%)	16 (7%)	11 (4%)	5 (4%)
Week 12	16 (7%)	16 (7%)	14 (6%)	13 (10%)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed

The primary method of handling missing data specified in the protocols was non-responder imputation (NRI). The statistical reviewer considered sensitivity analyses using the following methods for the handling of missing data:

- Last Observation Carried Forward (LOCF)

- Observed Cases (OC)
- Multiple Imputation (MI): The MI procedure used the Markov Chain Monte Carlo (MCMC) method stratifying on treatment arm to impute missing scores and generated 100 imputed datasets

Table 17 through

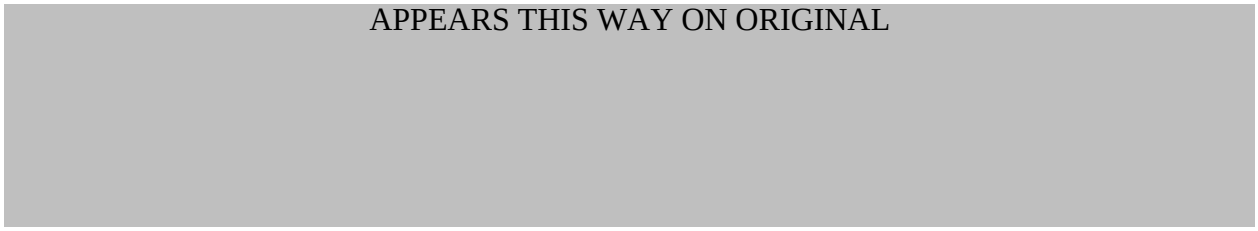


Table 19 present the results for the co-primary efficacy endpoints in all three trials by the various imputation methods. In all three trials, the results for the co-primary endpoints were very similar across the various methods of handling the missing data.

Table 17: Results for Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data - Trial B7451012 (FAS[1])

Co-Primary Endpoint	Abrocitinib 200 mg (N=154)	Abrocitinib 100 mg (N=156)	Placebo (N=77)	200 mg - Placebo (P-Value)[2]	100 mg - Placebo (P-Value)[2]
IGA 0/1					
NRI (Primary)	43%	24%	8%	36% (<0.001)	16% (0.0310)
LOCF	44%	26%	8%	36% (<0.001)	18% (0.0012)
OC	47%	26%	9%	37% (<0.001)	16% (0.0071)
MI	46%	26%	8%	37% (<0.001)	18% (<0.001)
EASI-75					
NRI (Primary)	62%	40%	12%	51% (<0.001)	28% (<0.001)
LOCF	63%	42%	14%	49% (<0.001)	28% (<0.001)
OC	67%	44%	14%	53% (<0.001)	29% (<0.001)
MI	65%	43%	14%	51% (<0.001)	29% (<0.001)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
Abbreviations: NRI=Non Responder Imputation; LOCF= Last Observation Carried Forward; OC=Observed Cases; MI=Multiple Imputation
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed
[2] Difference and P-value were calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity).

Table 18: Results for Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data - Trial B7451013 (FAS[1])

Co-Primary Endpoint	Abrocitinib 200 mg (N=155)	Abrocitinib 100 mg (N=158)	Placebo (N=78)	200 mg - Placebo (P-Value)[2]	100 mg - Placebo (P-Value)[2]
IGA 0/1					
NRI (Primary)	38%	28%	9%	29% (<0.001)	19% (<0.001)
LOCF	38%	29%	11%	26% (<0.001)	17% (0.0026)
OC	40%	31%	13%	28% (<0.001)	19% (0.0075)
MI	39%	31%	14%	25% (<0.001)	17% (0.0036)
EASI-75					
NRI (Primary)	61%	44%	10%	50% (<0.001)	33% (<0.001)
LOCF	61%	47%	13%	48% (<0.001)	34% (<0.001)
OC	65%	49%	14%	50% (<0.001)	35% (<0.001)
MI	63%	47%	15%	47% (<0.001)	32% (<0.001)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
Abbreviations: NRI=Non-Responder Imputation; LOCF= Last Observation Carried Forward; OC=Observed Cases; MI=Multiple Imputation
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed
[2] Difference and P-value were calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity).

Table 19: Results for Co-Primary Efficacy Endpoints at Week 12 with Different Approaches for Handling Missing Data - Trial B7451029 (FAS[1])

Co-Primary Endpoint	Abrocitinib 200 mg (N=226)	Abrocitinib 100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)	200 mg - Placebo (P-Value)[2]	100 mg - Placebo (P-Value)[2]
IGA 0/1						
NRI (Primary)	47%	36%	36%	14%	33% (<0.001)	23% (<0.001)
LOCF	49%	37%	37%	14%	35% (<0.001)	24% (<0.001)
OC	50%	39%	39%	15%	35% (<0.001)	23% (<0.001)
MI	50%	38%	38%	15%	35% (<0.001)	17% (0.0036)
EASI 75						
NRI (Primary)	68%	58%	58%	27%	41% (<0.001)	32% (<0.001)
LOCF	73%	60%	60%	28%	44% (<0.001)	32% (<0.001)
OC	73%	62%	61%	30%	44% (<0.001)	32% (<0.001)
MI	73%	61%	61%	29%	44% (<0.001)	32% (<0.001)

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed
[2] Difference and P-value were calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity).

The Applicant conducted tipping point (TP) analysis as a sensitivity analysis to assess the impact of missing data at Week 12 due to subject drop-out for the analysis for IGA 0/1 and EASI-75 at Week 12. For this TP analysis, missing responses at Week 12 were imputed using multiple imputations using random Bernoulli based on the estimated posterior probability of response using different weight. For the imputation model and estimation method, the reader is referred to Section 8.1.3. For imputing missing responses in each of the active groups, a weighted linear combination of the response probabilities from the active group and the placebo group was considered, using weight=0, 0.25, 0.5, 0.75 and 1. Values of 0 and 1 for this weight corresponded to analyses under Missing at Random (MAR) and Jump-to-Reference (JTR), respectively. For all weights considered for placebo response probability, abrocitinib 100 mg and 200 mg remained significant for IGA 0/1 and EASI-75 responses at Week 12 in all three trials (not presented herein).

The statistical reviewer conducted additional tipping point analyses for IGA 0/1 and EASI-75 at Week 12. For these analyses, subjects with missing data at Week 12 were imputed using multiple imputation using a response rate of 5% to 30%, with increments of 5% in the abrocitinib arms and 5% to 75%, with increments of 5%, in the placebo arm. In Trial B7451012, abrocitinib 100 mg was no longer significant on IGA 0/1 endpoint when the placebo response rate is 30% and abrocitinib response rate is 5% for the missing data; abrocitinib 100 mg did not become insignificant on EASI-75 endpoint in the range explored. In Trial B7451013, abrocitinib 100 mg was no longer significant on IGA 0/1 endpoint when the placebo response rate is 25% and abrocitinib response rate is 5% for the missing data; abrocitinib 200 mg was no longer significant on IGA 0/1 endpoint when the placebo response rate is 55% and abrocitinib response rate is 30% for the missing data. In the same trial (B7451013), abrocitinib 100 mg was no longer significant on EASI-75 endpoint when the placebo response rate is 65% and abrocitinib response rate is 10% for the missing data. For the remaining of the endpoints/treatment arms/trials, abrocitinib remained significant in the worst-case scenario where all subjects with missing data in the placebo arm were imputed as responders and subjects with missing data in the active arm were imputed as non-responders.

8.1.6. Results for the Key Secondary Efficacy Endpoints

The main key secondary endpoint specified in the three trials is the based on the Patient Reported Outcome (PRO) of pruritus numeric rating scale (NRS). The reader is reminded that pruritus NRS was assessed daily from Day 1 to 15, while after Day 15, it was assessed only on trial visits (i.e., at Weeks 4, 8, and 12). Day 15 was considered the target analysis value for Week 2; however, if no observation was available on Day 15, then the observation closest to Day 15 was taken as the analysis value for Week 2 within the window from Day 2 to Day 22. The COA reviewer, Dr. Mira Patel, noted that the single administration of the pruritus NRS at the clinic visits may not provide a complete presentation of the symptom as it may not reflect day-to-day variability in this condition.

The Applicant noted in the CSR for Trial B7451012 that due to a technical error in the process of transmission and collection of electronic data with the device, the data on the pruritus NRS scale was not collected from several subjects at the scheduled visits of Week 2 (Day 15) and after. This issue was noted as beginning of Day 15, when assessment collection changed from daily entries by the subject at home to an entry that was only recorded at the site visit. The Applicant further noted (Response to Information Request dated 11/18/2020) that the primary root cause for this issue was that the vendor's device specifications did not clarify that at the Week 2 visit and beyond, the Pruritus NRS would only appear on the eDiary after a specific sequence of actions were completed. Specifically, the site tablet ePRO assessments were completed by the subject and transmitted, then the PSAAD was completed and transmitted on the eDiary, and then the Pruritus NRS appears on the eDiary device. Since this information was not present in the specifications, it was also omitted from the site training. According to the Applicant, important secondary root causes contributing to the problem of missing data were data transmission issues for some subjects/sites and subjects not bringing eDiaries to on-site visits.

According to the Applicant (Response to Information Request dated 11/18/2020), at the time the missing data issue was discovered for Trial B7451012, Trial B7451013 was assessed, and significant issues were not noted. However, the Applicant noted in the CSR that the pruritus NRS assessment was also not consistently completed at a high level of compliance during the Week 12 and Week 16 visits. According to the Applicant, the reason for this was due to site staff deactivating subjects from the site tablet prior to subjects having the opportunity to complete handheld assessments, including the NRS.

Table 20 and Table 21 present the number of subjects with missing pruritus NRS data by visit, treatment arm and trial from Week 2 through Week 12. A large amount of missing data is observed in Trial B7451012 and at Week 12 in Trial B7451013 as noted by the Applicant.

Table 20: Missing Data for Pruritus NRS by Visit - Trials B7451012 and B7451013 (FAS[1])

	B7451012			B7451013		
	Abrocitinib			Abrocitinib		
Visit	200 mg (N=149)	100 mg (N=147)	Placebo (N=74)	200 mg (N=153)	100 mg (N=156)	Placebo (N=76)
Day 15	60 (41%)	58 (39%)	33 (45%)	22 (14%)	28 (18%)	19 (25%)
Week 2	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Week 4	64 (43%)	58 (39%)	25 (34%)	10 (6%)	24 (15%)	10 (13%)
Week 8	48 (33%)	52 (35%)	32 (43%)	14 (9%)	22 (14%)	20 (26%)
Week 12	39 (26%)	47 (32%)	27 (36%)	31 (20%)	36 (23%)	28 (36%)

Source: Statistical Reviewer's Analysis; ADNR.xpt,
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed
Note: The table excludes subjects with baseline Pruritus NRS score <4.

Table 21: Missing Data for Pruritus NRS by Visit – Trial B7451029 (FAS[1])

	Abrocitinib			
Visit	200 mg (N=226)	100 mg (N=236)	Dupilumab (N=240)	Placebo (N=130)
Day 15	21 (9%)	34 (14%)	34 (14%)	14 (11%)
Week 2	1 (<1%)	2 (1%)	2 (1%)	1 (1%)
Week 4	16 (7%)	22 (9%)	17 (7%)	11 (8%)
Week 8	20 (9%)	27 (11%)	24 (10%)	15 (11%)
Week 12	24 (11%)	29 (12%)	33 (14%)	20 (15%)

Source: Statistical Reviewer's Analysis; ADNR.xpt,
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed
Note: The table excludes subjects with baseline Pruritus NRS score <4.

The results for the key secondary endpoint of at least 4 points reduction from baseline in the pruritus NRS score (PP-NRS4) at Weeks 2, 4 and 12 are presented in Table 22 for the monotherapy trials using the hybrid method described in Section 8.1.3 for the handling of missing data (primary method per SAP). The SAP also specified sensitivity analysis using the non-responder imputation (NRI) method; see results in Table 23. It is noted that the 100 mg dose of abrocitinib is not statistically superior to placebo at Week 4 using the NRI method.

The statistical reviewer also considered additional sensitivity analyses using the following methods for the handling of missing data (see results in Table 24 and Table 25): LOCF, OC and MI. The treatment effect varied across the various methods of handling the missing data for Weeks 4 and 12 in Trial B7451012. The 100 mg dose was not statistically superior to placebo at Week 4 (preceding testing at Week 12 per the MTP) using the NRI and OC methods. Therefore, it is difficult to obtain reliable treatment effect estimates for the PP-NRS4 endpoint due to the large amount of missing data in Trial B7451012. The reader is reminded of the issues regarding the inconsistent assessment of pruritus NRS (initially daily, and later only at trial visits). Results were similar across the various methods of handling the missing data in Trial B7451013.

Table 22: Results for the Key Secondary Efficacy Endpoints - Trials B7451012 and B7451013 (FAS; Hybrid Method[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
PP-NRS4[2]	200 mg (N=147)	100 mg (N=147)	Placebo (N=74)	200 mg (N=153)	100 mg (N=156)	Placebo (N=76)
Week 2	46%	20%	3%	35%	23%	4%
Difference from placebo (95% CI)[3]	43% (34%, 51%)	18% (10%, 26%)	-	31% (22%, 40%)	19% (11%, 27%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	<0.001 (Yes)	<0.001 (Yes)	-
Week 4	59%	32%	17%	52%	33%	4%
Difference from placebo (95% CI)[3]	41% (28%, 54%)	15% (2%, 28%)	-	49% (39%, 58%)	29% (20%, 38%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	0.0251 (Yes)	-	<0.001 (Yes)	<0.001 (Yes)	-
Week 12	57%	38%	15%	55%	45%	12%
Difference from placebo (95% CI)[3]	42% (30%, 54%)	23% (10%, 35%)	-	44% (33%, 55%)	34% (23%, 45%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	<0.001 (Yes)	<0.001 (Yes)	-

Source: Reviewer's Analysis (same as Applicant's Analysis); ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the hybrid method described in Section 8.1.3. Any intermittent missing responses were imputed 500 times. At Week 2, there was no subject with intermittent missing data, so no multiple imputations were performed.

[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

[5] Multiplicity Testing Procedure (MTP): the protocols specified a graphical approach to control the Type I error rate for testing multiple treatment groups and endpoints; see Figure 3

Table 23: Results for the Key Secondary Efficacy Endpoints - Trials B7451012 and B7451013 (FAS; NRI[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
PP-NRS4[2]	200 mg (N=147)	100 mg (N=147)	Placebo (N=74)	200 mg (N=153)	100 mg (N=156)	Placebo (N=76)
Week 2	67 (46%)	30 (20%)	2 (3%)	54 (35%)	36 (23%)	3 (4%)
Difference from placebo (95% CI)[3]	43% (34%, 51%)	18% (10%, 26%)	-	31% (22%, 40%)	19% (11%, 27%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	<0.001 (Yes)	<0.001 (Yes)	-
Week 4	48 (33%)	29 (20%)	10 (13%)	77 (50%)	49 (31%)	3 (4%)
Difference from placebo (95% CI)[3]	19% (8%, 30%)	6% (-4%, 16%)	-	46% (37%, 56%)	27% (19%, 36%)	-
P-Value[4] (Significant per MTP[5])	0.0026 (Yes)	0.2601 (No)	-	<0.001 (Yes)	<0.001 (Yes)	-
Week 12	68 (46%)	41 (28%)	10 (13%)	75 (49%)	62 (40%)	8 (10%)
Difference from placebo (95% CI)[3]	33% (21%, 44%)	14% (4%, 25%)	-	39% (28%, 49%)	29% (19%, 40%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	*	-	<0.001 (Yes)	<0.001 (Yes)	-

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

[5] Multiplicity Testing Procedure (MTP): the protocols specified a graphical approach to control the Type I error rate for testing multiple treatment groups and endpoints; see Figure 3

* Testing stops per MTP.

Table 24: Results for the Key Secondary Efficacy Endpoints for Several Methods of Handling the Missing Data - Trial B7451012 (FAS[1])

PP-NRS4[2]		Abrocitinib 200 mg (N=147)	Abrocitinib 100 mg (N=147)	Placebo (N=74)	200 mg vs. Placebo (P-Value[3])	100 mg vs. Placebo (P-Value[3])
Week 2	Hybrid Method	46%	20%	3%	43% (<0.001)	17% (<0.001)
	NRI	46%	20%	3%	43% (<0.001)	17% (<0.001)
	LOCF	46%	20%	3%	43% (<0.001)	17% (<0.001)
	OC	46%	20%	3%	43% (<0.001)	17% (<0.001)
	MI	46%	21%	3%	43% (<0.001)	18% (<0.001)
Week 4	Hybrid Method	59%	32%	17%	42% (<0.001)	15% (0.0251
	NRI	33%	20%	13%	20% (0.0026)	7% (0.2601)
	LOCF	54%	29%	13%	41% (<0.001)	16% (0.0125)
	OC	58%	33%	20%	38% (<0.001)	13% (0.1213)
	MI	58%	35%	18%	40% (<0.001)	17% (0.0114)
Week 12	Hybrid Method	57%	38%	15%	42% (<0.001)	23% (<0.001)
	NRI	44%	28%	13%	31% (<0.001)	15% (<0.001)
	LOCF	62%	36%	15%	47% (0.0011)	21% (<0.001)
	OC	63%	41%	21%	42% (<.0001)	20% (0.0225)
	MI	60%	37%	9%	51% (<0.001)	28% (0.0023)

Source: Statistical Reviewer's Analysis; ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4.
[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Table 25: Results for the Key Secondary Efficacy Endpoints for Several Methods of Handling the Missing Data - Trial B7451013 (FAS[1])

PP-NRS4[2]		Abrocitinib 200 mg (N=153)	Abrocitinib 100 mg (N=156)	Placebo (N=76)	200 mg vs. Placebo (P-Value[3])	100 mg vs. Placebo (P-Value[3])
Week 2	Hybrid Method	35%	23%	4%	31% (<0.001)	19% (<0.001)
	NRI	35%	23%	4%	31% (<0.001)	19% (<0.001)
	LOCF	35%	23%	4%	31% (<0.001)	19% (<0.001)
	OC	35%	23%	4%	31% (<0.001)	19% (<0.001)
	MI	35%	23%	4%	31% (<0.001)	19% (<0.001)
Week 4	Hybrid Method	52%	33%	4%	48% (<0.001)	29% (<0.001)
	NRI	50%	31%	4%	46% (<0.001)	27% (<0.001)
	LOCF	52%	33%	4%	48% (<0.001)	29% (<0.001)
	OC	54%	37%	4%	50% (<0.001)	33% (<0.001)
	MI	54%	36%	4%	50% (<0.001)	32% (<0.001)
Week 12	Hybrid Method	55%	45%	12%	43% (<0.001)	33% (<0.001)
	NRI	49%	40%	10%	39% (<0.001)	30% (<0.001)
	LOCF	56%	48%	14%	42% (<0.001)	34% (<0.001)
	OC	61%	52%	17%	44% (<0.001)	35% (<0.001)
	MI	59%	49%	18%	41% (<0.001)	31% (<0.001)

Source: Statistical Reviewer's Analysis; ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4.
[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4
[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Table 26 presents results for the key secondary endpoints in Trial B7451029. Regarding the test against dupilumab for the endpoint of PP-NRS4 at Week 2, the Agency previously commented (advice letter dated 10/26/2018) that comparative claims for pruritus vs. dupilumab should assess the NRS change from baseline to Week 16, not Week 2 as proposed in the protocol. We note that response rates are similar between the 100 mg of abrocitinib and dupilumab for all secondary endpoints.

Table 26: Results for the Key Secondary Efficacy Endpoints – Trial B7451029 (FAS; NRI[1])

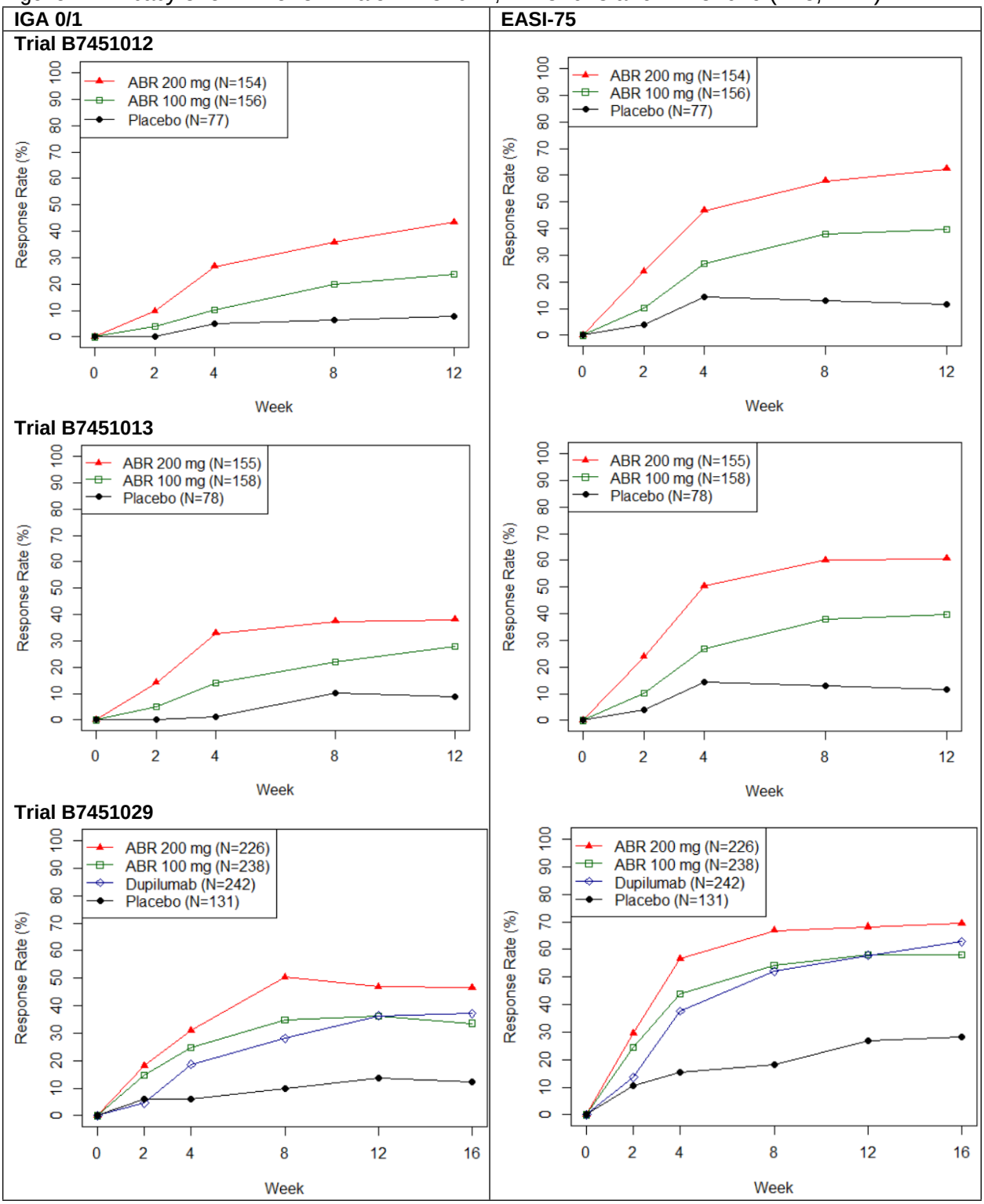
Endpoint	Abrocitinib 200 mg (N=226)	Abrocitinib 100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
PP-NRS4[2] at Week 2	111/226 (49%)	75/236 (32%)	63/240 (26%)	18/130 (14%)
Difference from placebo (95% CI)[3]	35% (26%, 44%)	18% (9%, 26%)	12% (4%, 20%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	-
Difference from Dupilumab (95% CI)[3]	22% (14%, 31%)	5% (-3%, 13%)	-	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	0.1966 (No)	-	-
IGA 0/1 at Week 16	105 (46%)	80 (34%)	90 (37%)	16 (45%)
Difference from placebo (95% CI)[3]	35% (26%, 43%)	22% (14%, 30%)	25% (17%, 33%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	-
EASI 75 at Week 16	157 (69%)	138 (58%)	152 (63%)	37 (28%)
Difference from placebo (95% CI)[3]	41% (31%, 51%)	30% (20%, 40%)	35% (25%, 44%)	-
P-Value[4] (Significant per MTP[5])	<0.001 (Yes)	<0.001 (Yes)	-	-

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt, ADNR.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method
[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4
[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.
[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).
[5] Multiplicity Testing Procedure (MTP): the protocols specified a graphical approach to control the Type I error rate for testing multiple treatment groups and endpoints.
Note: The protocols specified using a graphical approach to control the Type I error rate, see Figure 4
Note: Subject 'B7451029 1224 12249006' in dupilumab arm had no Week 2 visit and was not included in the analysis by the Applicant. The statistical reviewer considered this subject as non-responder in the analysis.

8.1.7. Efficacy Over Time

Figure 7 presents the results of IGA 0/1 and EASI-75 over time for Trials B7451012, B7451013 and B7451029 (up to Week 16).

Figure 7: Efficacy over Time for Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])



Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method
Abbreviations: ABR=abrocitinib.

8.1.8. Patient Reported Outcomes

In addition to PP-NRS4, the protocols for the two monotherapy trials (Trials B7451012 and B7451013) specified the following key secondary efficacy endpoint based on the patient reported outcome (PRO) of Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD).

- Change from baseline in Pruritus and Symptoms Assessment for Atopic Dermatitis (PSAAD) total score at Week 12 [100 mg vs. placebo and 200 mg vs. placebo]

As noted in Section 8.1.2, the PSAAD is an 11-item, patient-reported questionnaire using a 24-hour recall period, designed to assess the severity of key symptoms and signs of atopic dermatitis including itching, pain, dryness, flaking, cracking, bumps, redness, discoloration, bleeding, fluid, and swelling. Each item was assessed on an 11-point numeric rating scale. The PSAAD total score was calculated as the simple arithmetic mean of items 1-11.

Regarding the secondary endpoint of the change from baseline in PSAAD total score, the Agency previously noted (advice letter dated 2/15/2018) that a mere change from baseline might not translate to a clinically relevant difference. Furthermore, the Agency noted that the results from a mixed-effect model with repeated measures (MMRM) approach that incorporates information from each visit might not be clinically meaningful, yet the analysis might yield a statistically significant treatment effect due to the incorporation of all of the data. The results for the absolute change from baseline in PSAAD total score to Week 12 are provided in Table 52 of Appendix 16.3.

The statistical reviewer also explored the proportion of subjects with PSAAD total score of 0 at Week 12. Weekly scores were average values of daily observations over 7 days for this analysis. Only a very small proportion of subjects treated with abrocitinib (1%-6% across the two doses) had PSAAD Total Score of 0 at Week 12 (results are presented in Table 53 of Appendix 16.3).

Of note, itching is one of the 11 items of PSAAD, where subjects responded to the question "how itchy was your skin over the past 24 hours" using a 0 to 10 numeric rating scale from "not itchy" to "extremely itch". The statistical reviewer considered supportive analyses for itching based on a 4-point responder definition for PSAAD itching in subjects with a baseline PSAAD itching score of at least 4. For such analyses, weekly scores were average values of daily observations over 7 days; weekly scores were set to missing if there were less than 4 daily observations in the week.

The Applicant noted in the CSR for Trial B7451012 that the original trial design included daily collection of PSAAD data in selected countries only (US, Canada, and Germany). Later, it was decided to expand PSAAD data collection to all participating countries. Subjects randomized prior to such implementation in their respective country began recording daily assessments at the time of availability. Therefore, there was a population of subjects with Week 12 data but missing assessments at baseline or other earlier time points.

The missing data for PSAAD Itching item at baseline, Weeks 2, 4, 8 and 12 are presented in Table 54 of Appendix 16.3, while the results for the 4-point responder analyses are presented in Table 55 of Appendix 16.3. We note that, in all three trials, the nominal p-values (calculated using the CMH test adjusted for randomization strata) were all <0.025 for the comparison of abrocitinib to placebo, except from the 100 mg in Trial B7451029 at Week 2 (nominal p-value=0.0682). For the comparison of abrocitinib to dupilumab at Week 2, the nominal p-value for the 100 mg dose was >0.05 (p-value=0.1830).

The statistical reviewer also conducted exploratory responder analyses based on the remaining PSAAD items using again a 4-point responder definition; see Table 56 and Table 57 of Appendix 16.3.

8.1.9. Efficacy Results by Prior Use of Systemic Therapy

Table 27 and Table 28 present the results for the co-primary efficacy endpoints at Week 12 by prior use of systemic therapy for AD in all three Phase 3 trials. The treatment effect for abrocitinib 100 mg was lower in subjects with prior use of systemic therapy for AD compared to those without in the monotherapy Trial B7451012, while treatment effect was consistent across these two subgroups for the 200 mg dose in Trial B7451012 and both doses in the monotherapy Trial B7451013. In the concomitant background therapy trial (B7451029), the treatment effect tended to be higher in subjects with prior use of systemic therapy for AD compared to those without.

Table 29 presents the results of the co-primary efficacy endpoints at Week 12 in subjects who had treatment failure or who were intolerant to prior systemic therapy for AD. The treatment effect for both abrocitinib doses in this subpopulation was generally similar to the treatment effect in the overall population (see Table 13 and Table 14).

Table 27: IGA 0/1 Response Rate at Week 12 in Subgroups by Prior Systemic Therapy for AD - Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	ABR 200 mg (N=154)	ABR 100 mg (N=156)	Placebo (N=77)	ABR 200 mg (N=155)	ABR 100 mg (N=158)	Placebo (N=178)	ABR 200 mg (N=226)	ABR 100 mg (N=238)	DUP (N=242)	Placebo (N=131)
Prior Systemic: Yes										
N	70	82	41	60	70	32	103	99	112	48
Estimate, %	41%	15%	5%	33%	26%	6%	52%	37%	37%	10%
Active – Placebo, %	36%	10%	-	27%	19%	-	42%	27%	-	-
95% CI	(23%, 50%)	(<0%, 20%)	-	(12%, 42%)	(6%, 33%)	-	(29%, 55%)	(14%, 40%)	-	-
Prior Systemic: No										
N	84	74	36	95	88	46	123	139	130	83
Estimate, %	45%	34%	11%	41%	30%	11%	42%	35%	36%	16%
Active – Placebo, %	34%	23%	-	30%	19%	-	27%	20%	-	-
95% CI	(19%, 49%)	(8%, 38%)	-	(17%, 44%)	(6%, 32%)	-	(15%, 38%)	(8%, 31%)	-	-

Source: Reviewer's Analysis; ADAD.xpt, ADCM.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

Table 28: EASI-75 Response Rate at Week 12 in Subgroups by Prior Systemic Therapy for AD - Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	ABR 200 mg (N=154)	ABR 100 mg (N=156)	Placebo (N=77)	ABR 200 mg (N=155)	ABR 100 mg (N=158)	Placebo (N=178)	ABR 200 mg (N=226)	ABR 100 mg (N=238)	DUP (N=242)	Placebo (N=131)
Prior Systemic: Yes										
N	70	82	41	60	70	32	103	99	112	48
Estimate, %	61%	30%	12%	60%	36%	6%	73%	61%	61%	12%
Active – Placebo, %	49%	18%	-	54%	29%	-	60%	48%	-	-
95% CI	(34%, 64%)	(4%, 32%)	-	(39%, 69%)	(15%, 44%)	-	(48%, 73%)	(34%, 61%)	-	-
Prior Systemic: No										
N	84	74	36	95	88	46	123	139	130	83
Estimate, %	63%	51%	11%	61%	50%	13%	64%	56%	55%	35%
Active – Placebo, %	52%	39%	-	48%	37%	-	29%	21%	-	-
95% CI	(37%, 66%)	(24%, 54%)	-	(34%, 62%)	(23%, 51%)	-	(16%, 43%)	(8%, 34%)	-	-

Source: Reviewer's Analysis; ADEA.xpt, ADCM.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

Table 29: IGA 0/1 and EASI-75 Response Rates at Week 12 in Subgroup who had Treatment Failure or Intolerance to Prior Systemic Therapy for AD- Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	ABR 200 mg (N=154)	ABR 100 mg (N=156)	Placebo (N=77)	ABR 200 mg (N=155)	ABR 100 mg (N=158)	Placebo (N=178)	ABR 200 mg (N=226)	ABR 100 mg (N=238)	DUP (N=242)	Placebo (N=131)
IGA 0/1 Response										
N	49	54	26	17	36	43	60	63	72	28
Estimate, %	37%	15%	4%	39%	26%	6%	52%	32%	37%	7%
Active – Placebo, %	33%	11%	-	33%	20%	-	44%	25%	-	-
95% CI	(18%, 48%)	(-1%, 23%)	-	(14%, 53%)	(3%, 37%)	-	(28%, 60%)	(10%, 39%)	-	-
EASI-75										
N	49	54	26	17	36	43	60	63	72	28
Estimate, %	59%	33%	12%	64%	37%	6%	69%	58%	61%	14%
Active – Placebo, %	48%	22%	-	58%	31%	-	55%	44%	-	-
95% CI	(29%, 66%)	(4%, 39%)	-	(39%, 77%)	(13%, 50%)	-	(38%, 73%)	(27%, 62%)	-	-

Source: Reviewer's Analysis; ADAD.xpt, ADEA.xpt, ADCM.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

8.1.10. Efficacy Results for Adult Subjects (Monotherapy Trials)

The results of the co-primary and key secondary efficacy endpoints for adult subjects (i.e., ≥18 years of age) in the monotherapy trials are presented in parallel with the results for the overall population in Table 58 through Table 63 of Appendix 16.3. The number of excluded subjects was 84 adolescent subjects in Trial B7451012 (33 subjects in 100 mg, 34 subjects in 200 mg and 17 subjects in placebo) and 40 adolescent subjects in Trial B7451013 (15 subjects in 100 mg, 17 subjects in 200 mg and 8 subjects in placebo). The results for adults only are similar to those in the overall population. It is noted that the proportion of subjects achieving ≥4 points improvement from baseline in pruritus NRS would not reach statistical significance at Weeks 4 and 12 in Trial B7451012 (nominal p-values>0.05).

8.1.11. Additional Analyses for Itching

Assessment of Itching at Week 12:

This section aims to summarize supportive analyses for itching at Week 12 based on Pruritus NRS and PSAAD Itching Item 1.

Table 30 and Table 31 present results for responder analyses based on the pruritus and PSAAD Itching Item 1. The tables also present Peak Pruritus NRS responder results in the clinical trials used to approve dupilumab on 03/28/2017 for the treatment of moderate to severe AD. Response for these endpoints is defined achieving at least a 4-point reduction from baseline to Week 12 among subjects with baseline score of at least 4. It should be noted that peak pruritus NRS in the clinical trials used to approve dupilumab was assessed daily. Results appear similar between analyses on pruritus NRS and PSAAD Itching Item 1 in all three trials, using the non-responder imputation method to handle missing data. Response rates for dupilumab 300 mg Q2W are higher in Trial 1224 (trial used to approve dupilumab) compared to Trial B7451029. The reader is reminded that PP-NRS4 at Week 12 was not included in the MTP for Trial B7451029.

Table 30: Itching Results at Week 12 in Monotherapy Trials for Abrocitinib and Dupilumab (FAS; NRI[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=158)	100 mg (N=158)	Placebo (N=78)
Pruritus NRS (NRI)						
N[2]	147	147	74	153	156	76
Response Rate[3]	46%	28%	13%	49%	40%	10%
Difference from Placebo[4]	33%	14%	-	39%	29%	-
PSAAD Itching Item (NRI)						
N[2]	112	99	56	140	135	62
Response Rate[3]	46%	27%	5%	45%	36%	11%
Difference from Placebo[4]	38%	19%	-	34%	25%	-

	Trial 1334			Trial 1416		
	Dupilumab			Dupilumab		
	300mg QW (N=223)	300mg Q2W (N=224)	Placebo (N=224)	300mg QW (N=239)	300mg Q2W (N=233)	Placebo (N=236)
Peak Pruritus NRS (NRI)						
N[2]	201	213	212	228	225	221
Response Rate[3]	35%	38%	9%	41%	37%	9%
Difference from Placebo[4]	25%	29%	-	32%	28%	-

Source: Statistical Reviewer's Analysis; ADNR.xpt, ADPU.xpt, ADQSNRS.xpt (dupilumab trials)

Abbreviations: NRS = Numerical Rating Scale; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; NRI = Non-responder Imputation

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. Missing data are imputed using NRI

[2] N is the number with a baseline score ≥4

[3] Response rate = Proportion of subjects achieving ≥4 points improvement from baseline among subjects with baseline score of ≥4

[4] The estimate for the difference was adjusted for randomization strata.

Note: For the Trials used to approve dupilumab (Trials 1334 and 1416), the full analysis set is defined as all randomized subjects. Subjects who used rescue medication were considered non-responders.

Note: In the analysis for PSAAD, weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 31: Itching Results at Week 12 in Trials with Concomitant Therapy for Abrocitinib and Dupilumab (FAS; NRI[1])

	Trial B7451029			
	Abrocitinib + TCS		Dupilumab 300mg Q2W +TCS	Placebo + TCS
	200 mg (N=226)	100 mg (N=238)	(N=242)	(N=131)
Pruritus NRS (NRI)				
N[2]	226	236	240	130
Response Rate[3]	61%	44%	51%	27%
Difference from Placebo[4]	33%	17%	24%	-
PSAAD Itching Item (NRI)				
N[2]	211	200	218	111
Response Rate[3]	55%	36%	46%	22%
Difference from Placebo[4]	33%	15%	25%	-

	Trial 1224		
	Dupilumab		Placebo + TCS
	300mg QW + TCS (N=319)	300mg Q2W + TCS (N=106)	(N=315)
Peak Pruritus NRS (NRI)			
N[2]	295	102	299
Response Rate[3]	47%	56%	19%
Difference from Placebo[4]	28%	36%	-

Source: Statistical Reviewer's Analysis; ADNR.xpt, ADPU.xpt, ADQSNRS.xpt (dupilumab trials)
Abbreviations: NRS = Numerical Rating Scale; PSAAD = Pruritus and Symptoms Assessment for Atopic Dermatitis; NRI = Non-responder Imputation
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. Missing data are imputed using NRI
[2] N is the number with a baseline score ≥4
[3] Response rate = Proportion of subjects achieving ≥4 points improvement from baseline among subjects with baseline score of ≥4
[4] The estimate for the difference was adjusted for randomization strata.
Note: For the Trials used to approve dupilumab (Trial 1224), the full analysis set is defined as all randomized subjects. Subjects who used rescue medication were considered non-responders.
Note: In the analysis for PSAAD, weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Pruritus NRS at Week 2:

As noted in Section 8.1.6, the pruritus NRS was assessed daily for the first two weeks in the pivotal trials, while after Day 15, it was assessed only on trial visit (i.e., at Weeks 4, 8, and 12). The reviewer in this section repeats the analysis for the PP-NRS4 endpoint (i.e., the proportion of subjects achieving ≥4 points improvement from baseline pruritus NRS among subjects with baseline score of ≥4) at Week 2 using the weekly average values of daily observations over 7 days for the baseline score and Week 2 score. Results for such analyses are presented in Table 32 and Table 33. Response rates in Table 32 and Table 33 are much lower compared to response rates based on analyses using single timepoint assessment for baseline and Week 2 scores (see PP-NRS4 results at Week 2 in Table 23 and Table 26).

Table 32: Results for Peak Pruritus NRS at Week 2 - Trials B7451012 and B7451013 (FAS; NRI[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
PP-NRS4[2]	200 mg (N=132)	100 mg (N=115)	Placebo (N=63)	200 mg (N=140)	100 mg (N=141)	Placebo (N=62)
Week 2	37 (28%)	13 (11%)	1 (2%)	33 (24%)	16 (11%)	1 (2%)
Difference from placebo (95% CI)[3]	26% (17%, 35%)	10% (2%, 17%)	-	22% (14%, 31%)	10% (3%, 17%)	-
P-Value[4]	<0.001	0.0218	-	<0.001	0.0221	-

Source: Statistical Reviewer's Analysis; ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 33: Results for Peak Pruritus NRS at Week 2 – Trial B7451029 (FAS; NRI[1])

	Abrocitinib			
PP-NRS4[2]	200 mg (N=210)	100 mg (N=202)	Dupilumab (N=223)	Placebo (N=114)
Week 2	64 (30%)	29 (14%)	28 (13%)	9 (8%)
Difference from placebo (95% CI)[3]	22% (14%, 30%)	6% (-1%, 13%)	5% (4%, 20%)	-
P-Value[4]	<0.001	0.0959	-	-
Difference from Dupilumab (95% CI)[3]	17% (10%, 25%)	2% (-5%, 8%)	-	-
P-Value[4]	<0.001	0.5961	-	-

Source: Statistical Reviewer's Analysis; ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in pruritus Numeric Rating Scale (NRS) among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[4] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

8.1.12. Findings in Additional Subgroup Populations

Age, Sex, Race, Weight and Baseline Disease Severity:
The results for IGA 0/1 and EASI-75 at Week 12 by age (<18, 18-64 and ≥65 years), sex, race, weight (<70, 70-100, >100 kg), prior use of systemic immunosuppressants, and baseline IGA score are presented in Table 64 through Table 69 of Appendix 16.3. The sample size in the subgroups of subjects ≥65 years of age and subjects who weighted more than 100 kg was small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

For sex, the treatment effect tended to be higher in females compared to males; however, this was not completely consistent across the abrocitinib doses, endpoints, and trials.

For race, the treatment effect tended to be lower in subjects who identify as White compared to those who identify as non-White for the 100 mg dose of abrocitinib in Trial B7451012 and the 200 mg dose of abrocitinib in Trial B7451029 in both endpoints; however, the treatment effect was similar between White and Non-White subjects for the remaining doses/endpoints/trials.

For weight, the treatment effect was slightly lower in subjects who weighted <70 kg compared to those who weighted 70-100 kg in both abrocitinib doses and endpoints in the monotherapy trials (B7451012 and B7451013); however, the treatment effect was similar between the two subgroups in Trial B7451029.

For baseline IGA score, the treatment effect tended to be higher in the subjects with moderate IGA score at baseline compared to subjects with severe IGA score at baseline in the monotherapy trials (B7451012 and B7451013); however, this was not consistent across the abrocitinib doses and endpoints. The opposite was observed in Trial B7451029, i.e., the treatment effect tended to be higher in the subjects with severe IGA score at baseline compared to subjects with moderate IGA score at baseline.

Country:
Trial B7451012 was conducted in 8 countries (i.e., United States, Canada, Australia, Germany, Poland, Great Britain, Czech Republic, Hungary), Trial B7451013 was conducted in 13 countries (i.e., United States, Canada, Australia, Poland, Germany, Great Britain, Hungary, Bulgaria, Czech Republic, Latvia, Japan, Korea, China) and Trial B7451029 was conducted in 18 countries (i.e., United States, Canada, Australia, Mexico, Chile, Great Britain, Poland, Germany, Bulgaria, Hungary, Czech Republic, Latvia, Slovakia, Spain, Italy, Japan, Korea, Taiwan). Table 70 through Table 72 of Appendix 16.3 present efficacy results for IGA 0/1 and EASI-75 at Week 12 by country for the three trials. The countries in the tables are listed in descending order based on the total number of subjects enrolled. In all three trials, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

8.2. Review of Safety

8.2.1. Review of the Safety Database

A total of 2856 subjects with moderate to severe atopic dermatitis were treated with abrocitinib in clinical studies representing 1614 subject-years of exposure. There were 606 subjects with more than 1 year of exposure to abrocitinib in the total exposure safety pool.

For the integrated review of clinical safety, the primary safety pool reviewed is the placebo-controlled (PC) safety pool which includes subjects in four clinical studies exposing subjects to abrocitinib 100 mg QD, 200 mg QD, DUPIXENT® (as labeled) and placebo (B7451006, B7451012, B7451013, B7451029). A total of 1198 subjects were exposed to abrocitinib with 608 subjects receiving abrocitinib 100 mg once daily and 590 subjects receiving abrocitinib 200 mg once daily for up to 16 weeks. In the Placebo-Controlled safety pool, the median age of subjects was 33.0 years, 124 (8.1%) subjects were adolescents and 94 (6.1%) were older than 65 years of age. Although most subjects were male (53.9%) and White (68.7%), a substantial proportion of subjects were Asian or Black/African American. Approximately 2/3 of the subjects had moderate disease based on IGA; the median EASI was 25.6. More than 1/3 used prior systemic therapy, 45 (2.9%) subjects had prior DUPIXENT® exposure, 61.4% were randomized to monotherapy studies. Demographic and baseline disease characteristics appear balanced across the treatment groups.

Additional analyses will include comparison of safety events between the abrocitinib 100 mg QD dose and the 200 mg QD dose. In particular, that of serious and opportunistic infections, malignancies, retinal detachment, thrombosis, and laboratory abnormalities between the two doses that affects long-term safety.

Overall Exposure

As described above, there were 2856 subjects with atopic dermatitis exposed to abrocitinib, representing 1614 subject-years of exposure (885 exposed to 100 mg QD and 1971 exposed to 200 mg QD). There were 606 subjects exposed for more than 48 weeks (670 subjects with a 12-month visit).

Table 34: Overview of Exposure Duration in the Abrocitinib clinical Development Program

Phase	Study	Abrocitinib 100 mg QD n/PY	Abrocitinib 200 mg QD n/PY	All Abrocitinib n/PY
Phase 2	B7451006	56/ 10.9	55/ 12.0	111/ 23.0
Phase 3	B7451012 + B7451015	195/ 198.4	174/ 193.4	369/ 391.8
	B7451013 + B7451015	206/ 174.4	155/ 133.2	361/ 307.6
	B7451014 + B7451015	NA	1233/ 448.8	1233/ 448.8
	B7451029 + B7451015	428/ 237.1	354/ 205.4	782/ 442.5
Total	**All Exposure Pool**	**885/ 620.8**	**1971/ 992.9**	**2856/ 1614**

Source: Abrocitinib clinical ISS (Table 4)
Abbreviations: NA = not applicable; PY = patient years; QD = once daily.

The placebo-controlled (PC) safety pool includes a total of 1198 subjects (124 [8.1%] adolescents), with 608 exposed to abrocitinib 100 mg QD, 590 exposed to 200 mg QD, and 342 exposed to placebo. Median duration was similar across treatment groups in the placebo-controlled safety pool.

Table 35: Treatment Exposure – Placebo-Controlled Safety Pool

	Placebo (N=342)	Abrocitinib 100 mg QD (N=608)	Abrocitinib 200 mg QD (N=590)	All Abrocitinib (N=1198)
Duration of Treatment (Days)				
n	342	608	590	1198
Median (Q1, Q3)	85.0 (83.0, 112.0)	86.0 (84.0, 112.0)	85.0 (85.0, 112.0)	86.0 (85.0, 112.0)
Mean (Std. Dev.)	83.1 (31.6)	89.2 (25.2)	90.9 (21.9)	90.1 (23.7)
Range	(1-132)	(1-128)	(1-149)	(1-149)
Category n (%)				
< 1 Week	4 (1.2)	8 (1.3)	5 (0.8)	13 (1.1)
≥ 1 Week to < 4 Weeks	30 (8.8)	24 (3.9)	15 (2.5)	39 (3.3)
≥ 1 Weeks to < 8 Weeks	32 (9.4)	21 (3.5)	16 (2.7)	37 (3.1)
≥ 8 Weeks to < 10 Weeks	5 (1.5)	13 (2.1)	9 (1.5)	22 (1.8)
≥ 10 Weeks to < 14 Weeks	151 (44.2)	320 (52.6)	336 (56.9)	656 (54.8)
≥ 14 Weeks	120 (35.1)	222 (36.5)	209 (35.4)	431 (36.0)
Total	342	608	590	1198

Source: Abrocitinib clinical ISS (Table 5)
Includes studies: B7451006, B7451012, B7451013, B7451029

There was a slightly higher mean exposure in the abrocitinib treatment groups compared to the placebo treatment group; more abrocitinib treated subjects completed 10 or more weeks of treatment. More subjects in the abrocitinib treatment groups completed evaluation through Week 12 (Studies B7451006, B7451012, B7451013) or Week 16 (B7451029) in the DUPIXENT® active-comparator to the placebo treatment group.

Table 36: Summary of Discontinuations from Study – Placebo-Controlled Safety Pool

Number (%) of Subjects	Placebo (N=342)	Abrocitinib 100 mg QD (N=608)	Abrocitinib 200 mg QD (N=590)	All Abrocitinib (N=1198)
Discontinued	84 (24.6)	82 (13.5)	66 (11.2)	148 (12.4)
Adverse Event	29 (8.5)	31 (5.1)	30 (5.1)	61 (5.1)
Death	0	1 (0.2)	0	1 (0.1)
Lack of Efficacy	15 (4.4)	8 (1.3)	4 (0.7)	12 (1.0)

Lost to Follow-up	5 (1.5)	5 (0.8)	3 (0.5)	8 (0.7)
Pregnancy	0	0	1 (0.2)	1 (0.1)
Protocol Deviation	9 (2.6)	6 (1.0)	7 (1.2)	13 (1.1)
Withdrawal by Subject or Parent/Guardian	24 (7.0)	23 (3.8)	12 (2.0)	35 (2.9)
Medication Error without associated AE	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
No longer meets eligibility criteria	0	1 (0.2)	1 (0.2)	2 (0.2)
Other	1 (0.3)	6 (1.0)	7 (1.2)	13 (1.1)
Completed the study	141 (41.2)	309 (50.8)	316 (53.6)	625 (52.2)
Completed Evaluations for the Placebo-Controlled Safety Pool	261 (76.3)	533 (87.7)	536 (90.8)	1069 (89.2)

Source: Abrocitinib clinical ISS (Table 6)
Placebo-Controlled safety Pool Includes studies: B7451006, B7451012, B7451013, B7451029

The most frequent reasons for discontinuation in all treatment groups were adverse events and withdrawal by subject; these reasons were numerically higher in the placebo treatment group compared to the abrocitinib treatment groups. Discontinuations from all adverse events was 61 (5.1%).

Adequacy of the safety database:

The applicant's monotherapy (MONO) and placebo-controlled (PC) safety pools had the same 124 adolescents [29 subjects 17 years old (12 200 mg, 9 100 mg, 8 placebo); 25 subjects 16 years old (8 200 mg, 9 100 mg, 8 placebo); 21 subjects 15 years old (8 200 mg, 11 100 mg, 2 placebo); 18 subjects 14 years old (7 200 mg, 8 100 mg, 3 placebo); 18 subjects 13 years old (7 200 mg, 7 100 mg, 4 placebo); 13 subjects 12 years old (7 200 mg, 5 100 mg, 1 placebo)] from 12 years of age to under the age of 18 years. This population made up only 15% of the safety population (the adolescent population was the same for both pools).

Reviewer's comment: In multiple meetings and discussions, the Division had previously recommended at least 750 subjects exposed to the to-be-marketed drug product for at least 1 year and of those 225 (30%) of the safety population be adolescents (12 years to < 18 years of age) for adequate benefit/risk analysis. The provided adolescent safety pool was significantly less than what was recommended. This reviewer cannot make a risk/benefit analysis with 99 subjects < 18 years of age exposed to the two doses of abrocitinib. This issue will be further discussed in the differences between the 100 mg QD dose and the 200 mg QD dose.

8.2.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted from the applicant was supportive of the safety review. There were issues

with the pruritus assessments (PP-NRS) for the Phase 3 clinical trials (b) (4) (b) (4) There was Inconsistent measurements throughout the studies i.e., the Pruritus 11-point NRS was assessed daily during the screening period and from Day 1 to 15 using an eDiary. After Day 15, PP-NRS was assessed only on trial visit days (Weeks 4, 8 and 12). The Week 2 PP-NRS assessment showed the observation collected on Day 15 was considered the target analysis value for Week 2; If no observation was available on Day 15, then the observation closest to Day 15 was taken as the analysis value for Week 2 within the window from Day 2 to Day 22. Finally, monotherapy Trial B7451012, had a large amount of missing data due to technical issues.

In addition to the PP-NRS issues described, the Agency noted for PSAAD total scores (in an advice letter dated 2/15/2018) that a mere change from baseline might not translate to a clinically relevant difference. Furthermore, the Agency noted that the results from a mixed-effect model with repeated measures (MMRM) approach that incorporates information from each visit might not be clinically meaningful, yet the analysis might yield a statistically significant treatment effect due to the incorporation of all the data.

Categorization of Adverse Events

Adverse events were coded using MedDRA version 22.1 (CSR for Phase 3 studies) or 23.0 (SSI). SAEs were defined as described in *ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A*.

Adjudication Process
Each adjudication committee consists of experts in the relevant field, with charters in place to describe the details of event definitions and the committee's purpose.

The applicant used adjudication committees in all Phase 3 studies. These committees were external, blinded to treatment, and independent from Pfizer. The committees were established for review of potential AEs of OIs, malignancies (including a central laboratory pathologist review of biopsies), and CV events.

Opportunistic infections
All infections considered in-scope for committee review were specified in the OI Review Committee Charter and included all serious infections, all AEs with event terms potentially suggestive of OI including viral, bacterial, fungal, mycobacterial, and parasitic infections.

For herpes zoster, cases suspected of affecting more than one dermatome were adjudicated. These cases were classified as OIs if they were adjudicated as disseminated (>6 dermatomes) or multi-dermatomal (involving non-adjacent or more than two adjacent dermatomes). Cases of eczema herpeticum were classified as Special Interest Infections. Herpes zoster cases affecting only one dermatome, or two adjacent dermatomes are excluded from the OI summaries.

Malignancies

All potential malignancy events were adjudicated utilizing medical and histopathology records. In addition, for all available biopsies a Histopathology Review Committee that consisted of a central laboratory pathologist re-reviewed the biopsies to verify the potential malignancy. For non-skin malignancies, if there were different morphologies observed for the same organ but were part of the same disease process, the malignancy event was classified as a single event of interest. For skin malignancies, each disease process from the biopsy information or source document(s) was considered its own event of interest.

MACE
CV events to be adjudicated included death (which was classified as CV and non-CV) and non-fatal CV events (myocardial infarction, coronary revascularization, congestive heart failure, cerebrovascular events, peripheral vascular disease, VTE including PE and DVT, and hospitalization for unstable angina). Events were assessed using commonly accepted definitions of CV outcomes and pre-specified algorithms to arrive at consistent and objective decisions.

Hepatic events
Hepatic events to be adjudicated included potential Hy's Law events, ALT or AST ≥5x ULN, all events meeting hepatic discontinuation criteria per protocol, serious adverse events coding to MedDRA Hepatobiliary SOC, serious and non-serious adverse events coding to MedDRA Liver Infections SMQ, serious and non-serious adverse events coding to MedDRA Infectious biliary disorders SMQ, adverse events coding to MedDRA DILI preferred term, and any death in a patient with ALT or AST ≥3x ULN, bilirubin ≥2x ULN or a report of jaundice.

Routine Clinical Tests
There was evidence of thrombocytopenia, reduction in hemoglobin, changes in lymphocytes, changes in neutrophils, changes in creatinine phosphokinase, changes in hepatic functions, and changes in lipid analysis.

8.2.1. Safety Review Approach

Safety will be comprised by the experience of the Phase 2b dose-ranging (B7451006), two monotherapy studies (B7451012 and B7451013), and the combination study (B7451029). The placebo-controlled pool will include all subjects in placebo-controlled studies exposed dose of 100 mg QD or 200mg QD. In addition, safety will be reviewed looking at an all-exposure pool of all subjects exposed to abrocitinib.

8.2.2. Safety Results

There were 4 deaths in the clinical trials of abrocitinib for atopic dermatitis. The subject reports are described below. None of the death can be correlated completely to a causal relationship by drug.

Deaths

Subject B7451013/ (b) (6) abrocitinib 100 mg QD: This 73-year-old White female subject

from Bulgaria with an SAE of sudden death on Study Day 107, occurring 22 days after discontinuation of study drug. The event was assessed as not related to study drug per the investigator. The subject had a history of aortic sclerosis and calcification as observed in a chest X-ray performed during screening and a history of untreated hypertension. The subject received no concomitant medications. No autopsy was performed, and the sudden death event was adjudicated as a CV death. The event was assessed as not related to study drug per the investigator.

Subject B7451029/ (b) (6) abrocitinib 200 mg QD: This 69-year-old Black or African American female subject from United Kingdom. The subject tested positive for COVID-19 infection on Study Day 84 and was hospitalized. The subject died on Study Day 107. The investigator considered the event to be unrelated to study drug. There is no other information about the clinical course of the event during this reporting period. The investigator considered the event to be unrelated to study drug.

Subject B7451014/ (b) (6) abrocitinib 200 mg QD: This 78-year-old White female subject from Slovakia experienced an SAE of Adenocarcinoma Gastric on Study Day -22, considered medically significant and required hospitalization. Prior to enrollment, the subject experienced pain and discomfort under the ribs. On Study Day 43, the subject had unclear dyspeptic problems and excessive bloating, and additionally she experienced nonserious adverse events of gall bladder disorder and nephrolithiasis. The Investigator considered the non-serious adverse events of gall bladder disorder and nephrolithiasis to be mild in severity. On the same day (Study Day 43), a CT scan showed carcinomatosis with multifocal hepatic metastases. This subject SAE was assessed as not related to treatment as per PI judgment. The action taken in response to the event for the study drug was withdrawn permanently. A follow-up SAE report was received on 09 March 2020 that stated that the subject died approximately 7 months after discontinuation from study participation due to gastric adenocarcinoma (b) (6)

There has been one additional death reported since the initial submission (Subject B7451029/ (b) (6) abrocitinib 200 mg QD): This 42-year-old White male from Poland experienced an SAE of cardiac failure (VT: Cardiac insufficiency) on Day 334. This subject had a history of hypercholesterolemia, hypertension, and anemia. The subject experienced an AE of fever (Day 318 - ongoing), a SARS-COV-2 test was negative. Study drug was interrupted on Day 322. Throat, ear, and skin swabs on Day 323 did not identify a source of infection. The skin swab showed staphylococcus aureus thought to be from colonization. The subject's hemoglobin was 13.7 g/dL. The subject died suddenly during sleep on Day 334. There is limited data available from the event. No autopsy was performed. The records available do not reveal symptoms and signs of heart failure.

Serious Adverse Events

The incidence of SAEs was similar across the placebo and abrocitinib treatment groups in the

Placebo-Controlled safety pool. The most frequent SAEs were in the Infection and Infestation SOC.

Table 37: Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Terms (All Causalities) – Placebo-Controlled Safety Pool

Number (%) of Subjects: by SYSTEM ORGN CLASS and Preferred Term	Placebo (N=342) n (%*)	Abrocitinib 100 mg QD (N=608) n (%*)	Abrocitinib 200 mg QD (N=590) n (%*)	All Abrocitinib (N=1198) n (%*)
Subjects with events	11 (3.2)	19 (3.2)	11 (1.9)	30 (2.5)
Retinal detachment	0	1 (0.2)	0	1 (0.1)
INFECTIONS AND INFESTATIONS	2 (0.7)	7 (1.2)	2 (0.4)	9 (0.8)
Appendicitis	1 (0.3)	1 (0.2)0	0	1 (0.1)
Diarrhea infectious	0	1 (0.2)	0	1 (0.1)
Eczema herpeticum	1 (0.3)	1 (0.2)	0	1 (0.1)
Herpangina	0	1 (0.2)	0	1 (0.1)
Oral herpes	0	1 (0.2)	0	1 (0.1)
Osteomyelitis bacterial	0	1 (0.2)	0	1 (0.1)
Peritonsillitis	0	0	1 (0.2)	1 (0.1)
Pneumonia	0	2 (0.3)	1 (0.2)	3 (0.3)
Staphylococcal infection	0	1 (0.2)	0	1 (0.1)
Staphylococcal skin infection	1 (0.3)	0	0	0
INVESTGATIONS	1 (0.3)	0	0	0
Alanine aminotransferase increased	1 (0.3)	0	0	0
Hepatobiliary Disorders	0	1 (0.2)	0	1 (0.1)
Drug-induced liver injury	0	1 (0.2)	0	1 (0.1)
Immune System Disorder	1 (0.3)	0	1 (0.2)	1 (0.1)
Anaphylactic reaction	1 (0.3)	0	0	0
Anaphylactic shock	0	0	1 (0.2)	1 (0.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.3)	2 (0.4)	3 (0.5)	5 (0.4)
Asthma	0	1 (0.2)	2 (0.3)	3 (0.3)
Dyspnea	1 (0.3)	0	0	0
Interstitial lung disease	0	1 (0.2)	0	1 (0.1)
Pulmonary embolism	0	0	1 (0.2)	1 (0.1)

Source: Applicant Clinical ISS adapted from table FDA.PSP.2.4 (Update 27-NOV-2020)
Includes data up to 28 days after last dose of study. Subjects are only counted once per treatment per event.
* The calculation of proportion was adjusted for study size.

Specific Adverse Events of concerns will be discussed in Section 8.2.3 (Analysis of Submission-Specific Safety Issues). In general, the number of SAEs were low across subgroups. No specific clusters of safety issues were identified. Retinal detachment was seen in patients with concurrent eye issues or significant issues due to rubbing of eye. This specific safety issue will be discussed further in its own section.

Dropouts and/or Discontinuations Due to Adverse Effects

In the Placebo-Controlled safety pool, it appears that the proportion of subjects with AEs leading to discontinuation was similar across the abrocitinib and placebo treatment groups, no dose-relationships were observed. The most frequent AE leading to discontinuation was dermatitis atopic, occurring more frequently in the placebo treatment group (5.6%) than in abrocitinib treated subjects (1.2%). Other frequent AEs leading to discontinuation, occurring more frequently in the abrocitinib treated subjects, were nausea (4 of 1198 subjects: 0.3%) and headache (3 of 1198 subjects: 0.3%).

The AEs leading to discontinuation that occurred in more than 1 subject were abdominal pain, nausea, fatigue, dizziness, headache, dermatitis atopic, and eczema. Although eczema appeared to occur more frequently among abrocitinib treated subjects, atopic dermatitis occurred more frequently among placebo patients. Two (2) subjects reported related non-serious AEs of depression and depression suicidal leading to discontinuation from study.

Across the subgroups, AEs leading to permanent discontinuation from the study were generally similar across the subgroups. The exception was discontinuations occurring more frequently in older subjects (≥65 years) compared to the other age subgroups.

Common Adverse Reactions

Table 38: Adverse Reactions Reported in **≥1%** of TRADENAME Treated-Patients with Moderate to Severe Atopic Dermatitis and at Higher Rate than Placebo for up to 16 Weeks – Placebo-Controlled Safety Pool

	Number (%)[a] of Patients		
	Placebo N=342	Abrocitinib 100 mg N=608	Abrocitinib 200 mg N=590
Nausea	7 (2.1)	37 (6)	86 (14.5)
Vomiting	3 (0.9)	9 (1.5)	19 (3.2)
Fatigue	2 (0.5)	10 (1.6)	8 (1.3)
Gastroenteritis	2 (0.6)	7 (1.1)	8 (1.3)
Herpes simplex[b]	6 (1.8)	20 (3.3)	25 (4.2)
Influenza	0 (0.0)	7 (1.2)	6 (1.1)
Nasopharyngitis	27 (7.9)	75 (12.4)	51 (8.7)
Urinary tract infection	4 (1.2)	10 (1.7)	13 (2.2)
Blood creatinine phosphokinase increased	5 (1.5)	14 (2.3)	17 (2.9)
Dizziness	3 (0.9)	11 (1.8)	17 (2.9)
Headache	12 (3.5)	36 (6)	46 (7.8)
Acne	0 (0.0)	10 (1.6)	28 (4.7)
Impetigo	1 (0.3)	9 (1.5)	3 (0.5)
Oropharyngeal pain	2 (0.6)	8 (1.4)	6 (1.0)
Hypertension	2 (0.7)	7 (1.2)	5 (0.8)
Contact dermatitis	1 (0.3)	6 (1.1)	3 (0.5)
Abdominal pain upper	0	4 (0.6)	11 (1.9)
Abdominal discomfort	1 (0.3)	3 (0.5)	7 (1.2)
Herpes zoster	0	2 (0.3)	7 (1.2)
Thrombocytopenia	0	0	9 (1.5)

[a] Calculations of proportions was adjusted for study size
[b] Herpes simplex includes oral herpes, ophthalmic herpes, herpes dermatitis, genital herpes.
Includes Studies: B7451006, B7451012, B7451013, B7451029
MedDRA V22.1 coding dictionary applied

Common Adverse Reactions are presented the table above for the Placebo-Controlled safety pool. There we no specific cluster of safety issues for abrocitinib adverse reactions. A dose-response relationship was seen for increase in blood creatinine phosphokinase increase and herpes simplex. Thrombocytopenia was higher as a dose-dependent safety issue for the 200 mg QD dose. These safety issues will be discussed in the events of special interest sections of this review. The common adverse reactions table will be provided in the prescribers insert (label).

Treatment Emergent Adverse Events and Adverse Reactions

The treatment emergent adverse events for all causalities in the Placebo-Controlled safety pool was higher in the abrocitinib 200 mg QD than the 100 mg QD.

Table 39: Treatment-Emergent Adverse Events (All Causalities) Excluding Events of Atopic Dermatitis – Placebo-Controlled Safety Pool

Numbers (%) of Subjects	Placebo n (%*)	Abrocitinib 100 mg QD n (%*)	Abrocitinib 200 mg QD n (%*)	All Abrocitinib n (%*)
Subjects evaluable for adverse events	342	608	590	1198
Number of adverse events	323	771	897	1668
Subjects with adverse events	169 (49.3)	365 (60.2)	398 (67.4)	763 (63.8)
Subjects with serious adverse events	8 (2.4)	17 (2.8)	11 (1.9)	28 (2.4)
Subjects with severe adverse events	9 (2.7)	21 (3.6)	16 (2.8)	37 (3.2)
Subjects discontinued from study due to adverse events	13 (3.6)	24 (4.2)	27 (4.7)	51 (4.4)
Subjects discontinued study drug die to AE and continue study	3 (0.9)	6 (1.0)	1 (0.2)	7 (0.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	12 (3.5)	26 (4.2)	26 (4.4)	52 (4.3)

Source: Addendum to placebo-controlled safety pool analysis 27-NOV-2020.
Includes Studies: B7451006, B7451012, B7451013, B7451029. Includes data up to 28 days after last dose of study.
* The calculation of proportion was adjusted for study size.

The total number of subjects that discontinued due to an adverse event was 51 (4.4%). The SOCs with the highest proportion of events in abrocitinib treatment groups and greater frequency than placebo were Infections and infestations, Gastrointestinal disorders, Nervous system disorders, and Investigations.

Laboratory Findings

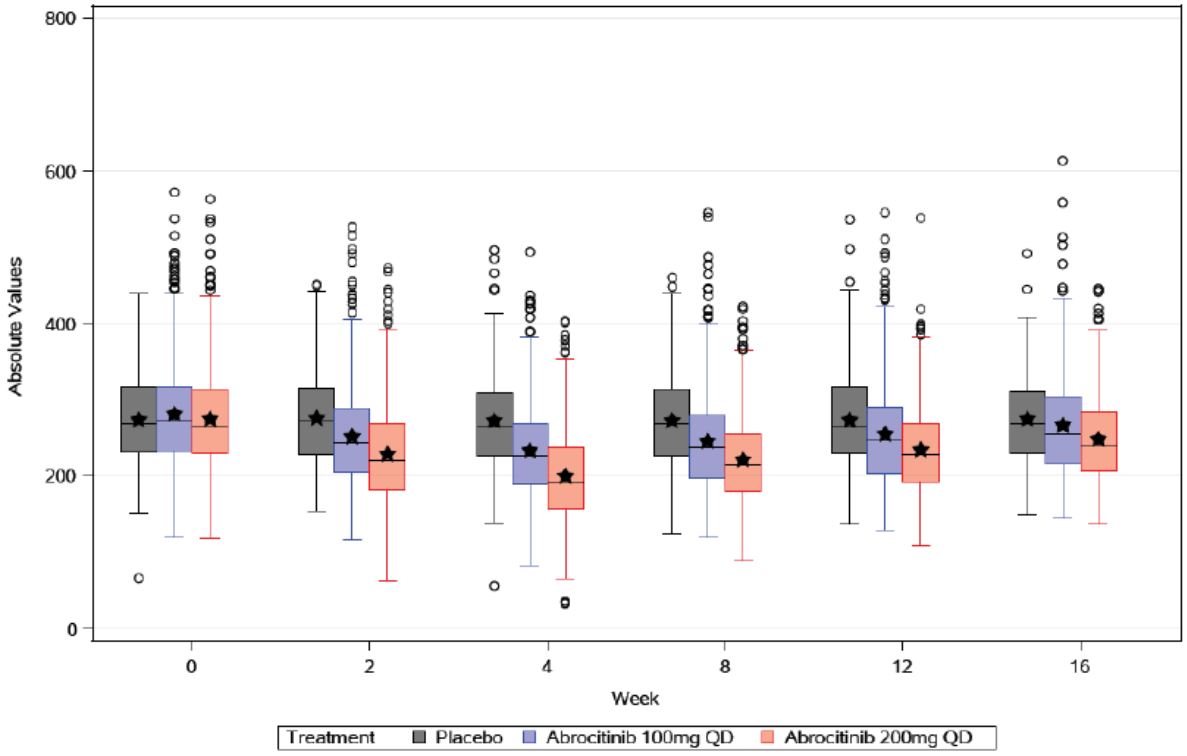
Hematologic Changes
The theoretical changes to red and white cell counts are known with JAK inhibition. In the atopic dermatitis program for abrocitinib, there were no population changes in hemoglobin and/or neutrophil counts that were observed. Specific laboratory findings for hematology that were concerning will be discussed.

Thrombocytopenia
- After initiation of abrocitinib, a dose-related decrease in platelet counts with a nadir in median values at Week 4. 2 subjects met pre-specified discontinuation criteria, both in 200 mg group.
- 4 subjects had lymphopenia; all were older than 65 years old
- CPK elevation, all transient, none led to discontinuation, no rhabdomyolysis

After initiation of abrocitinib, there was a dose-related decrease in platelets with a nadir in median values at Week 4; most values remained above the LLN ($140\times10^3/mm^3$). The median platelet counts in the population increased and reached a plateau at Week 12 that was below

the original baseline. Across all subjects, more than 95% maintained a platelet value > $100\times10^3/mm^3$. In the Placebo-Controlled safety pool, there were 9 subjects (0.3%) with a confirmed value $<75\times10^3/mm^3$, all between Week 2 and 4 of exposure. Among these subjects, 1 had an AE related to bleeding (mild contusion). Among the 9 subjects with low platelet counts, 2 (0.1%) subjects met the pre-specified Phase 3 discontinuation criteria (confirmed <50×103/mm3), both were in the abrocitinib 200 mg QD treatment group. Neither of these subjects had an AE related to bleeding.

Figure 8: Box Plot of Platelet ($10^3/mm^3$) Data by Visit – Placebo-Controlled Safety Pool



Source: abrocitinib clinical ISS Figure 6
Includes studies: B7451006, B7451012, B7451013, B7451029
Included data on study treatment or during lag time (28 days)
Circles represented outlier of individual subject values and stars represented mean.
Box plot provided Median and 25%/75% quartiles with whiskers to the last point within 1.5 times interquartile range.

Although most low platelet values occurred in subjects aged 18 to <65 years, the proportions of subjects ≥65 years with a single and confirmed platelet count $<75\times10^3/mm^3$ were higher than that in the subjects age 18 to <65 years. No adolescent subject had a platelet value $<75\times10^3/mm^3$.

Reviewer's Comment: The abnormal platelet counts experienced by abrocitinib is a known adverse reaction for JAK inhibitors. Thrombocytopenia appears dose-responsive and the higher 200 mg QD clearly shows a reduction of platelet count. Platelets appear to recover with continued treatment and only one subject had platelet counts in the discontinuation range. No subject had a bleeding issue. Thrombocytopenia will be labeled in section 5 and section 6 of the label.

The applicant provided a summary of population pharmacokinetic-pharmacodynamic modeling due to administration of abrocitinib. Lower baseline ABC, male sex, older age, higher baseline hematocrit, and disease-type (PsO) were all significant predictor of lower platelet counts. The probability of Grade 3 or Grade 4 thrombocytopenia is less than 3%.

Lymphocyte Counts

- There was no change over time in absolute lymphocyte counts associated with abrocitinib treatment.
- There were 4 subjects meeting discontinuation criteria for lymphopenia (confirmed < $0.5\times10^3/mm^3$). These subjects were all older than 65 years of age and in 3 of the 4 subjects the confirmed decrease occurred in the first few weeks of therapy.

In the Placebo-Controlled safety pool, approximately 80% subjects in the abrocitinib treated groups maintained an ALC $\geq1\times10^3/mm^3$. A higher percentage of subjects in the abrocitinib 100 mg (18.5%) and abrocitinib 200 mg (20.8%) QD groups had an ALC $<1\times10^3/mm^3$ compared with the placebo group (11.9%). Two (0.4%) subjects, both in the abrocitinib 200 mg QD group, had a confirmed ALC $<0.5\times10^3/mm^3$ meeting protocol-specified discontinuation criteria. These discontinuations occurred at Week 2 and Week 4. Adverse events of lymphopenia were reported in 1 subject (0.2%) in each of the abrocitinib 100 and 200 mg QD groups and in no subjects in the placebo group.

Reviewer's comment: For lymphopenia, a dose-response reduction in lymphocytes was seen with increasing dose. Subjects were discontinued due to reduction in lymphocytes, and all were 65 years of age and older.

Neutrophil Counts

- While there was a dose response with regard to subjects with a neutrophil level $<2.0\times10^3/mm^3$, no subject met the more clinically meaningful threshold for discontinuation (confirmed ANC, $1.0\times10^3/mm^3$).

In the Placebo-Controlled safety pool, the baseline median ANC values were comparable across the placebo ($4.250\times10^3/mm^3$), abrocitinib 100 mg QD ($4.305\times10^3/mm^3$) and abrocitinib 200 mg QD ($4.205\times10^3/mm^3$) groups. There was no meaningful change in measures of central tendency in any group over the 12 to 16-week time period.

Hemoglobin

- Across all exposed subjects, one 66-year-old subject (<0.1%) met the discontinuation criteria of confirmed hemoglobin <8 gm/dL.

In the Placebo-Controlled safety pool, the proportion of the subjects ≥65 years with a confirmed hemoglobin <9 or <8 g/dL (2.3 and 0.8%, respectively) was greater than that in subjects aged 18 to <65 years (<0.1 and 0%, respectively). No adolescent had confirmed values of <8 or <9 g/dL.

Creatine Phosphokinase

- There was no difference in the change over time in either CK or creatinine between the abrocitinib dose groups and the placebo group over 12 weeks.
- There was a dose-related increase in subjects reporting AEs of blood creatine phosphokinase increased.
- There were no events of rhabdomyolysis reported.

In the Placebo-Controlled safety pool, the baseline values for creatine kinase were comparable. There was a dose-related increase in CK beginning at Week 4 and having at plateau at Week 8. The median change at the last observation was increased in the abrocitinib 100 mg QD and 200 mg QD groups (53 U/L and 88 U/L, respectively) relative to the placebo group (-2 U/L). A dose-related increase also occurs in the proportions of subjects crossing a threshold of 2xULN; however, abrocitinib groups did not have a higher proportion of subjects crossing thresholds of 5x and 10x/ULN.

Serum Creatinine

- There was no meaningful change in serum creatinine over time in any treatment group.
- No subject met he protocol pre-specified discontinuation criteria.

Treatment with JAK inhibitors have been known to cause renal impairment and increase in serum creatinine. Abrocitinib did not significantly increase serum creatinine in the atopic dermatitis program. In the Placebo-Controlled safety pool, there was 1 event of increase in serum creatinine in the placebo group. There was 1 event of acute kidney injury in the abrocitinib 100 mg QD group the event was considered not related to the study drug.

Hepatic Laboratory

- In the Placebo-Controlled safety pool, there was no meaningful change over time in measures of central tendency for ALT or AST. There was not an increased proportion of subjects meeting thresholds of interest (i.e., ALT or AST >3x ULN, >5x ULN).
- No identified Hy's Law case.
- There were 2 SAEs of drug-induced liver injury, although both had competing diagnoses. No adjudicated AEs or cases of laboratory elevation were adjudicated as more than possibly a DILI (25-50% probability).

In the Placebo-Controlled safety pool, all ALT and AST values for most subjects in all groups (>80%) were less than ULN. In study B7451012, 1 subject in the 200 mg QD group had a single ALT and AST > 5×ULN which was subsequently confirmed in the long-term extension study (B7451015). In Study B7451029, 1 subject in the placebo group and 1 subject in the abrocitinib 100 mg QD group discontinued due to hepatic enzyme elevation.
Adjudicated Hepatic Cases:
There were 2 AE of Drug-induced Liver injury (DILI).

- Subject B7451029/ (b) (6) abrocitinib 100 mg QD: This 62-year-old White male had an SAE of Drug-induced liver injury (VT: potential DILI), non-serious AEs of Alanine

aminotransferase increased, and Aspartate aminotransferase increased all starting on Day 85 and adjudication criteria of "2 SEQUENTIAL AST OR ALT ≥3X ULN". Drug was interrupted in response to the SAE of DILI and resolved on Day 134. The events of ALT and AST increased were resolving on Day 169. The investigator comment noted that this was an obese male with abnormal baseline and the persistent ALT >3XULN; therefore, DILI was assessed as unlikely; probable NAFLD and in addition the noted low-grade muscle enzyme values abnormality might indicate a myopathy.

- Subject B7451013/ (b) (6) abrocitinib 100 mg QD; This 26-year-old White male experienced an SAE of Drug-induced liver injury (VT: drug induced liver injury) on Day 113 and met protocol defined monitoring criteria of two sequential AST or ALT ≥5 x ULN. The subject had also taken cefalexin for a urinary tract infection for two weeks (initiated just before the increased liver values). In addition, the subject had recently taken recreational cocaine, MDMA (3,4 Methylenedioxymethamphetamine) and alcohol. Study drug was withdrawn in response to the event and the event was resolved on Day 161. This case has not completed the adjudication process.

In total, 24 hepatic cases were adjudicated to determine the likelihood of a DILI case. Most (n = 17) cases were adjudicated as unlikely or unrelated. The other 7 were adjudicated as a possible DILI (probability 25-50%). No cases were adjudicated as a probable, highly likely, or definite DILI case.

Reviewer's comment:
The other adjudicated case reports were reviewed. There were no cases of Hy's Law. These is also an increase hepatic cases with increase dose at 200 mg. A case for approval of only the 100 mg QD dose can be made for the safety of the dose-related laboratory adverse events.

Vital Signs

There was no pattern of concern regarding vital signs. In the Placebo-Controlled safety pool, baseline median SBP was comparable across the placebo (121 mmHg) and the abrocitinib 100 mg and 200 mg QD group (121 and 122 mmHg, respectively). There were no meaningful changes in SBP at Week 12 (B7451006, B7451012, B7451013) or Week 16 (B7451029) in the placebo or abrocitinib groups (range of median change: -1 – 1 mmHg). Baseline median DBP was comparable across the placebo (78 mmHg) and the abrocitinib 100 mg and 200 mg QD group (77 mmHg in both groups). There were no meaningful changes in DBP at Week 12 (B7451006, B7451012, B7451013) or Week 16 (B7451029) in the placebo or abrocitinib groups (range of median change: -2 – 1 mmHg).

Electrocardiograms (ECGs)

In the Phase 3 studies, ECGs were monitored at 2-4-week intervals. In the Placebo-Controlled safety pool, no subjects in any treatment group had a QTcF of > 500 msec. One (1) subject (B7451013/ (b) (6)) in the abrocitinib 200 mg QD group had a change from screening >60 msec, with a screening value of 383 msec that increased to 452 msec (i.e., a change from

screening of 69 msec). The subject's Day 1 QTcF was 452 msec and, as such, the change from baseline was 0.

QT

The applicant conducted a thorough QT study. DDD consulted Agency QTIRT for review of the analysis. It was concluded that "no significant QTc prolongation effect of abrocitinib was detected in the QT Assessment". No QT language will be needed in the label.

Immunogenicity

No clinical studies in immunogenicity were conducted in the atopic dermatitis program.

8.2.3. Analysis of Submission-Specific Safety Issues

Summary of serious risks identified:
Serious adverse events of special interest identified (AESI) in the placebo-controlled safety pool are presented the table below. The exposure-adjusted incidence rates provide context to the placebo exposed and the two doses of abrocitinib exposed.

Table 40: Proportion, Incidence Rates and Risk Difference for Adverse Events of Special Interest (AESI) – Placebo-Controlled Pool (Weeks 0-16)

Placebo-Controlled Pool (N=1198)	Placebo (N=342) Total PY=86.86 n(%[1]) EAIR[1] [PY]	Abrocitinib 100 mg (N=608) Total PY=158.46 n(%[1]) EAIR[1] [PY]	Abrocitinib 200 mg (N=590) Total PY=156.34 n(%[1]) EAIR[1] [PY]
All Infections Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	90 (26.5) 126.75 [72.12]	211 (34.8) 168.81 [127.32] 42.05 (7.03, 77.07)	204 (34.6) 159.47 [126.95] 32.72 (-1.68, 67.12) -9.34 (-41.02, 22.35)
Serious Infections Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	2 (0.7) 2.62 [86.75]	6 (1.0) 3.85 [158.00] 1.22 (-4.03, 6.48)	2 (0.4) 1.32 [156.21] -1.30 (-6.25, 3.64) -2.53 (-6.47, 1.42)
Opportunistic Herpes Zoster Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	0 0.00 [86.86]	0 0.00 [158.46] 0.00 (-3.52, 3.52)	1 (0.2) 0.61 [156.12] 0.61 (-3.09, 4.31) 0.61 (-2.11, 3.33)
Opportunistic Infections (excluding herpes zoster, tuberculosis)	No subjects meet these criteria		
Herpes Zoster (CMQ)	0	3 (0.5)	8 (1.3)

	0.00 [86.86]	1.86 [158.09]	5.11 [155.11]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		1.86 (-2.22, 5.95)	5.11 (0.17, 10.05)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			3.24 (-1.23, 7.72)
Tuberculosis	No subjects meet this criterion		
All Malignancy[a]	0	0	1 (0.2)
	0.0 86.86]	0.00 [158.46]	0.65 [156.19]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		0.00 (-3.52, 3.52)	0.65 (-3.08, 4.39)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			0.65 (-2.11, 3.42)
Malignancies excluding NMSC	No subjects meet these criteria		
NMSC	0	0	1 (0.2)
	0.00 [86.86]	0.00 [158.46]	0.65 [156.19]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		0.00 (-3.52, 3.52)	0.65 (-3.08, 4.39)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			0.65 (-2.11, 3.42)
MACE	0	1 (0.2)	0
	0.00 [86.86]	0.62 [158.46]	0.00 [156.34]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		0.62 (-3.09, 4.32)	0.00 (-3.51, 3.51)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			-0.62 (-3.34, 2.11)
VTE	0	0	1 (0.2)
	0.00 [86.86]	0.00 [158.46]	0.70 [156.26]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		0.00 (-3.52, 3.52)	0.70 (-3.04, 4.45)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			0.70 (-2.08, 3.48)
Retinal Detachment	0	1 (0.2)	0
	0.00 [86.86]	0.62 [158.46]	0.00 [156.34]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		0.62 (-3.09, 4.33)	0.00 (-3.51, 3.51)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			-0.62 (-3.34, 2.11)
Blood creatine phosphokinase increase (> 5x ULN)	6 (1.9) 7.48 [85.94]	11 (1.8) 6.87 [156.89]	19 (3.2) 12.32 [153.47]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		-0.60 (-7.99, 6.78)	4.85 (-3.43, 13.12)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			5.45 (-1.54, 12.44)
Thrombocytopenia (< 75 x10^3/mm^3)	1 (0.2)	0	4 (0.7)
	0.80 [86.77]	0.00 [158.46]	2.55 [155.80]
Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo		-0.80 (-4.26, 3.01)	1.75 (-2.61, 6.10)
Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)			2.55 (-0.90, 6.00)
Herpes Simplex (CMQ)	6 (1.8)	19 (3.1)	25 (4.2)
	7.20 [85.80]	12.07 [155.71]	16.22 [153.23]
Difference of Incidence Rates (95% CI)[2]:		4.87	9.01

Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)		(-3.30, 13.05)	(0.20, 17.83) 4.15 (-4.22, 12.51)
Pulmonary Embolism Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	0 0.00 [86.86]	0 0.00 [158.46] 0.00 (-3.52, 3.52)	1 (0.2) 0.70 [156.26] 0.70 (-3.04, 4.45) 0.70 (-2.08, 3.48)
Deep Vein Thrombosis	No subjects meet this criterion		
Lymphopenia Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	0 0.00 [86.86]	0 0.00 [158.46] 0.00 (-3.52, 3.52)	2 (0.3) 1.24 [156.14] 1.24 (-2.65, 5.13) 1.24 (-1.73, 4.22)
Lipid Elevations (CMQ) Difference of Incidence Rates (95% CI)[2]: Abrocitinib vs Placebo Difference of Incidence Rates (95% CI)[2]: Abrocitinib (200 mg QD vs 100 mg QD)	0 0.00 [86.86]	1 (0.2) 0.62 [158.26] 0.62 (-3.10, 4.34)	3 (0.5) 1.97 [155.79] 1.97 (-2.15, 6.10) 1.35 (-1.93, 4.63)

Source: Addendum to placebo-controlled safety pool analysis 25, 26-MARCH-2021
EAIR = exposure-adjusted incidence rate; diff= difference; CI= confidence interval; VTE= Venous Thromboembolism Events, GI= Gastrointestinal.
Note: Includes data up to the end of risk period (the smaller of [last dose date, death date] for B7451012/13 subjects who enrolled into the LTE study; or the smaller of [last dose date prior to Week 16 dose date/visit date, death date] for B7451029 subjects with available Week 16 dose date/visit date; otherwise, the smaller of [last dose date + 28 days, death date]).
a. Data uses MedDRA SMQ 20000107 (Version 22.1)
[1] Study size adjusted results
[2] A study-size weighted average of difference of incidence rates across studies; the confidence interval for the weighted difference of incidence rates is calculated based on Wald's method

Note the incidence rates and rate differences in the safety events. In particular, the increase in the rates for herpes zoster, infections, and the blood creatinine which are the highest. These adverse events will be summarized in the label. In addition to the described AESI, other risks are summarized:

- Risk of serious and opportunistic infections
  - Pneumonia 3 (0.3%)
  - 1 death in 69-year-old Black female with reported COVID-19 infection on 200 mg – Study 1015 (roll-over from 1029)
    - 69 y Black female from UK with AD (2011) randomized in 1029 with 200 mg QD. Completed blinded treatment and was allocated to 200 mg QD in 1015 LTE on 3-JAN-2020. Investigator was informed by sister that subject died due to COVID19 on 18-APR-2020 (1015 day 107)
  - Herpes zoster 1 (0.1%)
  - Eczema herpeticum 1 (0.1%)
  - Oral herpes 1 (0.1%)
  - Herpes simplex 27 (2.2%)

- Not enough data to make a short term or long-term connection to dose-response causation.

- Retinal Detachment (3 cases), reviewed by Dr Wiley Chambers (Ophthalmology)
  - B7451012 (b) (6)
    - 17-year-old female (Day 64) on 100 mg QD
    - Severe eye rubbing was cause of bilateral retinal detachment
  - B7451014 (b) (6)
    - 19-year-old male (Day 85) on 200 mg QD
    - Previous cataract surgery is a known risk factor for developing a retinal detachment
  - B7451013 (b) (6) (B7451015 (b) (6))
    - 62-year-old female (Day 330) on 100 mg QD
    - The retinal detachment is more likely a result of severe eye rubbing than that of drug treatment.

  Discussion:
  There is not enough data to make a causation both in the short-term or long-term for a dose-response effect. Even though the data is not as meaningful, this reviewer recognizes the high degree of safety issues with retinal detachment. There are other factors that may contribute to have retinal detachment only occurring in atopic dermatitis patients when looks across other JAKs and indications. Based on the events in the atopic dermatitis patients, retinal detachment is clearly a risk and should be labeled.

- Malignancy
  - 1 death in 78-year-old due to gastric adenocarcinoma
  - Across all subjects treated with abrocitinib (2856), there were 7 adjudicated cases of nonmelanoma skin cancer (0.42/100 patient-years [95% CI: 0.17, 0.86]), 3 subjects in the abrocitinib 100 mg QD group and 4 subjects in the abrocitinib 200 mg QD group.
  - There were 4 events of potential malignancy in the clinical database (2 events of prostate cancer and 2 events of ovarian neoplasm).
  - There is limited meaningful data to make a causation for dose effects to malignancies.

- Thrombosis
  - 1 sudden death in 100 mg (appear to be unrelated)—study 1013
  - 3 adjudicated events of PE (0.18/100 PY) all in 200 mg QD
  - 2 adjudicated events of DVT (0.12/100 PY) all in 200 mg QD
  - 2 events of MI in 200 mg (including the sudden death 0.18/100 PY)
    - All events were in subjects >60 with pre-existing CV risk factors

AESI will be discussed in detail in the following sections.

8.2.3.1. Severe Infections/Opportunistic Infections

Severe infections were as defined in Infections and infestation SOC. This includes infections that required parenteral antimicrobial therapy or required hospitalization for treatment or met other criteria that required the infection to be reported as an SAE. All severe infections that met SAE criteria required discontinuation from the study, per protocol.

Pneumonia was the only AE occurring in more than 1 abrocitinib treated subject (2 [0.3%] subjects in the 100 mg group).

Table 41: Incidence of Severe Treatment Emergent Adverse Events for Infection and Infestation – Placebo-Controlled Safety Pool

Number (%) of Subjects: by SYSTEM ORGN CLASS and Preferred Term	Placebo (N=342) n (%*)	Abrocitinib 100 mg QD (N=608) n (%*)	Abrocitinib 200 mg QD (N=590) n (%*)	All Abrocitinib (N=1198) n (%*)
INFECTION AND INFESTATION	5 (1.6)	6 (1.0)	3 (0.5)	9 (0.8)
Appendicitis	1 (0.3)	0	0	0
Cellulitis	1 (0.3)	0	1 (0.2)	1 (0.1)
Eczema herpeticum	1 (0.3)	1 (0.2)	0	1 (0.1)
Eczema infected	2 (0.7)	1 (0.2)	0	1 (0.1)
Herpes zoster	0	1 (0.2)	0	1 (0.1)
Lower respiratory tract infection	0	0	1 (0.2)	1 (0.1)
Mastitis	0	0	1 (0.2)	1 (0.1)
Osteomyelitis bacteria	0	1 (0.2)	0	1 (0.1)
Pneumonia	0	2 (0.3)	0	2 (0.2)
Staphylococcal infection	0	1 (0.2)	0	1 (0.1)
Staphylococcal skin infection	1 (0.3)	0	0	0

Source: Addendum to placebo-controlled safety pool analysis 27-NOV-2020.
Includes Studies: B7451006, B7451012, B7451013, B7451029. Includes data up to 28 days after last dose of study.
* The calculation of proportion was adjusted for study size.

A single death occurred with a COVID-19 infected subjects described in the DEATHS. There was no trend toward more frequent serious infections in subjects with lower confirmed absolute lymphocyte count (ALC) or absolute neutrophil count (ANC). A time to event of serious infection analysis was performed for the All-Exposure Pool.

Herpes Simplex
Patients with atopic dermatitis have an increased risk of herpes simplex infections.[12] Patients

[12] Boguneiwicz M, Leung DY. Recent insights into atopic dermatitis and implications for management of infectious complications. *J Allergy Clin Immunol* 2010; 125(1):4-13.

with atopy have a 2.6-fold higher risk of herpetic ocular disease.[13]
In the Placebo-Controlled safety pool, there was a dose-related increase in the proportion of subjects reporting herpes simplex in the abrocitinib treatment groups compared to the placebo groups. Of the subjects who had an event of herpes simplex, approximately 50% of subjects had an initial event of herpes simplex in the first 3 months of therapy (48.2% in abrocitinib 100 mg QD group and 57.8% in abrocitinib 200 mg QD group). The median time to resolution was 9 days. Ophthalmic herpes simplex was reported in low proportion (< 1%) of subjects.

Eczema Herpeticum
In the Placebo-Controlled safety pool, subjects reported events of Eczema herpeticum or Kaposi's varicelliform eruption only in the placebo and abrocitinib 100 mg QD group (≤1%). No events were reported in the abrocitinib 200 mg QD group. There was 1 (0.3%) subject in the placebo group and 1 (0.2%) subject in the 100 mg QD group with an event that was severe in intensity.

Reviewer's comment: A clear dose-related increase in opportunistic infection of herpes is experienced on abrocitinib. This is supported by the mechanism of action for JAK inhibitors and the reduction in immune function. What was not seen in the clinical studies were other possible opportunistic infections such as CMV, zoster, and EBV reactivation or infection. Future long-term clinical studies will be needed to evaluate other serious and opportunistic infections while on JAK inhibitors.

8.2.3.2. Retinal Detachment

The Division (DDD) requested Dr. Wiley Chambers (Ophthalmology) to review the cases of retinal detachment and render comments to the relationship of drug to adverse event. This is the summary of the consult review.

Subject ID: B7451012 (b) (6): PF-04965842 Protocol B7451012
This subject was enrolled in a Phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects with moderate to severe atopic dermatitis (B7451012). A serious adverse event of retinal detachment on (b) (5), (b) (6) (Study Day 64) that ended on (b) (6) (Study Day 106) leading to permanent discontinuation from study treatment.

Demographics

[13] Borkar DS, Gonzales JA, Tham VM, et al. Association between atopy and herpetic eye disease: results from the pacific ocular inflammation study. *JAMA Ophthalmol* 2014; 132(3):326-31.

Randomization Date	Age at Study Start	Sex	Race	Country	Weight	Height
(b) (6)	17 years	Female	White	United States	60.5 kilograms	156 centimeters

MedDRA Preferred Term	Start Date	End Date
Atrial septal defect	(b) (6)	Ongoing
Dermatitis atopic		Ongoing
Drug hypersensitivity		Ongoing
Asthma		Ongoing
Conjunctivitis allergic		Ongoing
Food allergy		Ongoing
Milk allergy		Ongoing
Seasonal allergy		Ongoing
Attention deficit/hyperactivity disorder		Ongoing
Menstruation irregular		Ongoing
Impetigo		(b) (6)

Study Treatment

Treatment	Dose	Route	Start Day	End Day
PF-04965842	100 mg QD	Oral	(b) (6) (Study Day	(b) (6) (Study Day

Serious Adverse Event
The subject experienced a serious adverse event of retinal detachment on (b) (6) (Study Day 64).

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MedDRA Preferred Term: Retinal detachment	Investigator Term: Bilateral retinal detachment
Seriousness: Yes	Case Number: 2018289842
Start Day: Study Day 64	End Day: Study Day 106
Toxicity Grade/Severity: Severe	Most Recent Dose administered on: (b) (6) (b) (6) Study Day 63)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	Led to Permanent Discontinuation from Study Treatment (Yes/No): Yes
Date of Discontinuation from Study: (b) (6) (Study Day 79)	Date of Death: Not applicable
Concomitant Treatment or Additional Treatment Given (Yes/No): Yes	Adjudication Event ID: Not applicable

Narrative Summary
This was a 17-year-old White female subject in the United States with a history of atopic dermatitis (since (b) (6)). The subject received PF-04965842 100 mg from (b) (6) (Study Day 1) to (b) (6) (Study Day 63).

Past medical history included impetigo (from (b) (6) to (b) (6)). Current medical history included atrial septal defect (since (b) (6)); drug hypersensitivity: Rocephin (since (b) (6)); asthma (since (b) (6)); conjunctivitis allergic, food allergy and seasonal allergy (since (b) (6)); attention deficit/hyperactivity disorder (since (b) (6)); and irregular menstruation (since (b) (6)). Prior medications taken for atopic dermatitis included topical triamcinolone (from (b) (6) to (b) (6)), topical crisaborole (from (b) (6) to (b) (6)

(b) (6)), and oral prednisolone (from (b) (6) to (b) (6)). Concomitant medications included oral methylphenidate hydrochloride (since (b) (6)) for attention deficit hyperactivity disorder, oral cetirizine (since (b) (6)) for seasonal allergic rhinitis, salbutamol sulfate (respiratory inhalation, since (b) (6)) for mild intermittent asthma, ophthalmic olopatadine hydrochloride (since (b) (6)) for seasonal allergic rhinitis, salbutamol (respiratory inhalation, since (b) (6)) for mild intermittent asthma, oral montelukast and nasal mometasone furoate (since (b) (6)) for seasonal allergic rhinitis, and oral drospirenone/ethinylestradiol (since (b) (6)) for birth control.

On an unknown date, the subject had initial symptoms of loss of vision (right eye more than left), flashes, floaters (right eye), and blurry milk vision. On (b) (6) (Study Day 63), the subject had ophthalmological examination which revealed bilateral cataract, bilateral amblyopia, left eye hypermetropia, left hyperopic astigmatism with no improvement. The subject was referred to pediatric ophthalmologist on (b) (6) (Study Day 64). On the same day (Study Day 64), the ophthalmological examination noted bilateral vitreous degeneration, bilateral retinal detachments (retinal detachment with proliferative vitreoretinopathy of left eye and retinal detachment with single break of right eye), and intertemporal retinal dialysis with localized subretinal fluid/proliferative vitreoretinopathy. A serious adverse event of retinal detachment was reported on (b) (6) (Study Day 64). The Investigator considered the event of retinal detachment to be severe and medically significant. The study drug was permanently discontinued in response to the event of retinal detachment with the last dose taken on (b) (6) (b) (6) (Study Day 63). The subject underwent cryotherapy and scleral buckle procedure for the left eye on (b) (6) (Study Day 67). On the same day (Study Day 67), the subject was diagnosed with bilateral cataracts. The Investigator considered the event of cataract to be moderate in severity.

Additionally, on (b) (6) (Study Day 53), the subject experienced an adverse event of left eyebrow folliculitis. The Investigator considered the event of folliculitis to be moderate in severity. No treatment was reported for the event. The event of left eyebrow folliculitis resolved on (b) (6) (Study Day 69). The subject was discontinued from the study on (b) (6) (b) (6) (Study Day 79), as she no longer wanted to participate in the trial.

The subject underwent left eye cataract surgery on (b) (6) (Study Day 80), and cryotherapy and scleral buckle procedure for the right eye on (b) (6) (Study Day 106). She was administered with dexamethasone/neomycin/polymyxin B and atropine sulfate 1% drops for the right eye (unknown dates). The events of bilateral cataract and retinal detachment were considered resolved on (b) (6) (Study Day 106).

In the opinion of the Investigator, the event of retinal detachment was not related to the study drug, concomitant medications, or a clinical trial procedure; but was due to “other - ocular trauma secondary to pruritus.” The study Sponsor concurred with the Investigator and did not attribute the event to the study drug, concomitant medications, or a clinical trial procedure. This narrative reflects information available to the Sponsor as of 30 Apr 2019.

Concomitant medications reported within 14 days before the onset of the event and through the end of study

Treatment	Start Day	End Day
Ritalin	Study Day -3635	Ongoing
Ritalin la	Study Day -3635	Ongoing
Cetirizine	Study Day -2905	Ongoing
Proair – albuterol	Study Day -2691	Ongoing
Proventil	Study Day -1595	Ongoing
Pataday eyedrops	Study Day -1595	Ongoing
Montelukast	Study Day -1536	Ongoing
Nasonex	Study Day -1536	Ongoing
Yasmin	Study Day -27	Ongoing

Concomitant non-drug treatment/surgeries were reported within 14 days before the onset of the event and through the end of study

Treatment	**Start Day**	**End Day**
Cryotherapy left eye	Study Day 67	Study Day 67
Scleral buckle procedure left	Study Day 67	Study Day 67

Other Non-Serious Adverse Events

MedDRA Preferred Term/Investigator	**Toxicity Grade or**	**Start Day**	**End Day**
Folliculitis/Left eyebrow folliculitis	Moderate	Study Day	Study Day
Cataract/Bilateral cataract	Moderate	Study Day	Study Day

Reviewer's Comments: *Temporal retinal dialysis associated with eye rubbing in an individual with facial atopic dermatitis and severe allergic conjunctivitis. It is more likely that severe eye rubbing was the cause of the bilateral retinal detachments than the drug product.*

Subject ID: B7451014 (b) (6)

Subject originally enrolled in B7451014 study and treated received open-label treatment with PF-04965842 200 mg once daily (QD) for 92 days. The subject was subsequently enrolled in B7451015, a Phase 3 multi-center, long-term extension study investigating the efficacy and safety of PF-04965842 for severe atopic dermatitis. This narrative summarizes all relevant subject participation available through to the 22 Apr 2020 database snapshot.

Demographics:

Randomization Date	Age at B7451014 Study Start	Age at B7451015 Study Start	Sex	Race	Country	Weight	Height
(b) (6)	19 years	19 years	Male	White	Poland	66 kilograms	185 centimeters

Relevant Medical History:

MedDRA Preferred Term	Start Date	End Date
Dermatitis atopic#	(b) (6)	Not Available
Conjunctivitis allergic		Ongoing
Rhinitis allergic		Ongoing

Cataract	(b) (6)	(b) (6)

This is a primary diagnosis event. If there is no End Date, "Not Available" will be displayed.

Medications Used Prior to the B7451014 Study for Atopic Dermatitis:

Treatment	Start Day	End Day
Latopic	B7451014 Study Day -1124	Ongoing
Methylprednisolone acetonate	B7451014 Study Day -100	B7451014 Study Day -55

Study Treatments

Study	Assigned Treatment	Start Dose Frequency Route of Administration	Start Date	End Date
B7451014	PF-04965842 (Open-Label)	200 mg QD Oral	(b) (6) (B7451014 Study Day 1)	(b) (6) (B7451014 Study Day 92)
B7451015	PF-04965842	200 mg QD Oral	(b) (6) (B7451015 Study Day 1)	Ongoing

Serious Adverse Event:
The subject also experienced serious dermatitis atopic on (b) (6) (B7451015 Study Day 169).

MedDRA Preferred Term: Dermatitis atopic	Investigator Term: Acceleration of atopic dermatitis
Seriousness: Yes	Case Number: 2019453088
Start Day: B7451015 Study Day 169	End Day: B7451015 Study Day 171
Toxicity Grade/Severity: Severe	Most Recent Dosing Date Prior to the Onset of the AE: (b) (6) (B7451015 Study Day 169)
	Outcome: Recovered/Resolved
Led to Permanent Discontinuation from Study (Yes/No): No	Led to Permanent Discontinuation from Study Treatment (Yes/No): No

Narrative Summary:
This subject was a 19-year-old White male in Poland who had a history of atopic dermatitis (since (b) (6)). The subject entered Study B7451014 and received treatment with open-label PF-04965842 200 mg QD from (b) (6) to (b) (6) (B7451014 Study Day 1 to 92). While participating in B7451014 Study, the subject experienced a serious adverse event of retinal detachment. On (b) (6) (B7451014 Study Day 85), the subject was diagnosed with a serious adverse event of retinal detachment of the left eye, resulting in hospitalization on the same day. The Investigator considered the event to be severe in severity. The subject received levofloxacin (Oftaquix) and dexamethasone sodium phosphate (Dexafree) from (b) (6) to (b) (6) (B7451014 Study Day 87 to 92) for retinal detachment. The study drug was temporarily interrupted in response to the event of retinal detachment with the most recent dose administered on (b) (6) (B7451014 Study Day 85). On (b) (6) (B7451014 Study Day 86), the subject underwent ophthalmic surgery. On (b) (6) (B7451014 Study Day 87), the study drug was resumed, and the event of retinal detachment resolved on the same day. The subject was discharged from the hospital on an unknown date. In the opinion of the Investigator, the event of retinal detachment was considered unrelated to the study drug, concomitant medications, or a clinical trial procedure; however, this serious adverse event was probably related to cataract surgery on (b) (6) The study Sponsor concurred with the Investigator's causality assessment. On (b) (6) (B7451014 Study Day 92), the subject

completed treatment in the open- label run-in period in the B7451014 Study. On (b) (6) (B7451015 Study Day 1), the subject was allocated to PF-04965842 200 mg QD and started receiving treatment in this B7451015 Extension Study. This narrative reflects information available to the Sponsor as of 18 May 2020.

Concomitant medications reported within 14 days before the onset of the event and through the end of the study.

Treatment	Start Day	End Day
Latopic	B7451015 Study Day -1216	Ongoing
Alphagan (brimonidine tartrate)	B7451015 Study Day 1	Ongoing
Aspargin magnesium hydroaspartate/potassium hydroaspartate	B7451015 Study Day 1	Ongoing
Cosopt	B7451015 Study Day 1	Ongoing
Diuramid	B7451015 Study Day 1	Ongoing
Xalatan (latanoprost)	B7451015 Study Day 21	Ongoing
Amertil	B7451015 Study Day 28	Ongoing
Clemastin	B7451015 Study Day 28	Ongoing
Elocom	B7451015 Study Day 28	Ongoing

The subject also experienced the following non-serious adverse event during the course of the study.

MedDRA Preferred Term/Investigator Term	Toxicity Grade or Severity	Start Day	End Day
Skin bacterial infection/Bacterial superinfection of skin lesions	Mild	B7451014 Study Day 13	B7451014 Study Day 23
Intraocular pressure increased/High eye pressure	Mild	B7451015 Study Day 55	Ongoing

Supplemental Information provided on January 11, 2021

There were cataracts in both eyes and surgery was done for both eyes in (b) (6) The retinal detachment was not of rhegmatogenous origin.

Reviewer's Comments: *Previous cataract surgery is a known risk factor for developing a retinal detachment.*

Subject ID: B7451013 (b) (6)
B7451015 (b) (6)

This subject was a 62-year-old White female in Poland who had a history of atopic dermatitis (since (b) (6)). The subject was randomized in Study B7451013 and received treatment with PF-04965842 100 mg QD, from (b) (6) (B7451013 Study Day 1) to (b) (6) (B7451013 Study Day 88). The subject completed treatment in the B7451013 Study and was allocated to PF-04965842 100 mg QD in a blinded manner and started receiving treatment in this B7451015 Extension Study on (b) (6) (B7451015 Study Day 1). Past and current medical history included atopic dermatitis.

On (b) (6) (B7451015 Study Day 242, Exposure Day 330 relative to start of B7451013), the subject experienced a non-serious event of retinal detachment. The Investigator considered the

event to be moderate in severity. No treatment was reported for the event of retinal detachment and no action was taken with the study drug in response to the event. The event was considered resolved on the same day on (b) (6) (B7451015 Study Day 242).

Reviewer's Comments: *As noted below, the subject was treated for a rhegmatogenous retinal detachment.*

Six weeks before the reported retinal detachment, the patient underwent a cataract surgery of the right and left eye by phacoemulsification on (b) (6) performed in the Czech Republic and reimbursed by the Polish National Health Fund. The cataract diagnosis took place approximately 3 weeks before the operation. On (b) (6) due to retinal detachment, the patient underwent cryotherapy treatment of the retinal detachment (procedure performed in Poland). The investigator indicated this should be AE grade 2, right and left cataracts starting on (b) (6) (The patient did not report any complaints indicating cataracts) and ending (b) (6) The investigator considers this not related to IP and not related to audit procedures B7451015.

The subject's baseline Day 1 IGA score was 3, EASI sub-score for head/neck was 3, SCORAD Area of Involvement for Head/Neck was 3. and PP-NRS was 6. On (b) (6) (B7451015 Study Day 252, Exposure Day 340) was 0, EASI sub-score for head/neck was 0, and PP-NRS was 0.

Reviewer's Comments: *Cryotherapy is used to treat retinal detachments which have breaks in the retina (rhegmatogenous), often in the anterior portion of the retina. These types of breaks in patients with atopic dermatitis of the face are often due to severe eye rubbing.*

Randomization Date	Age at B7451013 Study Start	Age at B7451015	Sex	Race	Country	Weight	Height
(b) (6)	61 Years	62 Years	Female	Whit	POL	71	160 cm

Details of the adverse event are listed below: APPEARS THIS WAY ON ORIGINAL

MedDRA Preferred Term: Retinal detachment	Investigator Term: PARTIAL RETINAL DETACHMENT
Seriousness: N	Case Number: Not Available
Start Date (Day): (b) (6) (B7451015 Study Day 242)	End Date (Day): (b) (6) (B7451015 Study Day 242)
Toxicity Grade / Severity: MODERATE	Most Recent Dosing Date Prior to the Onset of the AE: (b) (6) (B7451015 Study Day 242)
	Outcome: RECOVERED/RESOLVED
Led to Permanent Discontinuation from Study (Yes/No): No	Led to Permanent Discontinuation from Study Treatment (Yes/No): No
Date of Discontinuation from Study: NA	Date of Death: NA
Concomitant Treatment or Additional Treatment Given (Yes/No): N	Adjudication Event ID: NA

Reviewer's Comments: *The retinal detachment is more likely a result of severe eye rubbing that drug treatment.*

Summary Conclusions:
Three cases of retinal detachment have been reported. For two of the reports, it is more likely that severe eye rubbing was the cause of the retinal detachments than the drug product. For the third case, it is likely that the patient's previous cataract surgery was a major factor in the development of the retinal detachment. At this time, it is unlikely that the drug product is a significant cause of retinal detachments.

Reviewer's comment: Based on the seriousness of this adverse event and in review of other JAK inhibitors, this reviewer recommends the addition of retinal detachment relevant sections of the label for abrocitinib. Although the relationship to drug is not clear and retinal detachment was not seen in RA treated patients with other JAK inhibitors, this reviewer believes that the population of atopic dermatitis is particularly at risk for retinal detachment. In addition, any changes in vision should prompt the physician to make a determination based on the patient's risks for eye issues and judgement should be used to start or stop abrocitinib. Specific labeling additions will be addressed with the team during labeling meetings.

8.2.3.3. Malignancy

Malignancy events were adjudicated by an external blinded adjudication committee consisting of experts in their field. In addition, a Histopathology Review Committee that consisted of a central laboratory pathologist review of biopsies also assisted in evaluation of potential malignancies. All malignancies included NMSC (non-melanoma skin cancer) and NMSCs and excluded subjects from B7451014.

- Across all subjects treated with abrocitinib (All Exposure Pool, excluding trial 1014), there were 6 adjudicated cases of all malignancies. In the abrocitinib 100 mg group there were 4 (0.4%) [0.61/100 PY] and in the abrocitinib 200 mg group there were 2 (0.3%) [0.35/100 PY].

- A subject with melanoma skin cancer in the abrocitinib 10 mg group of the Phase 2 study (B7451006). Investigator considered it to be unrelated, observed as skin cleared.

- A subject in the abrocitinib 200 mg QD group in Study B7451014 with gastric adenocarcinoma which was diagnosed on Study Day 43. However, as symptoms began prior to randomization, the start date was changed by the investigator to Day -22 as symptoms began prior to randomization. This subject died 9 months after stopping treatment.

- A subject with an adverse event of breast cancer in the dupilumab arm in Study B7451029.

There were 4 events of Non-melanoma skin cancer (NMSC) confirmed by adjudication. These

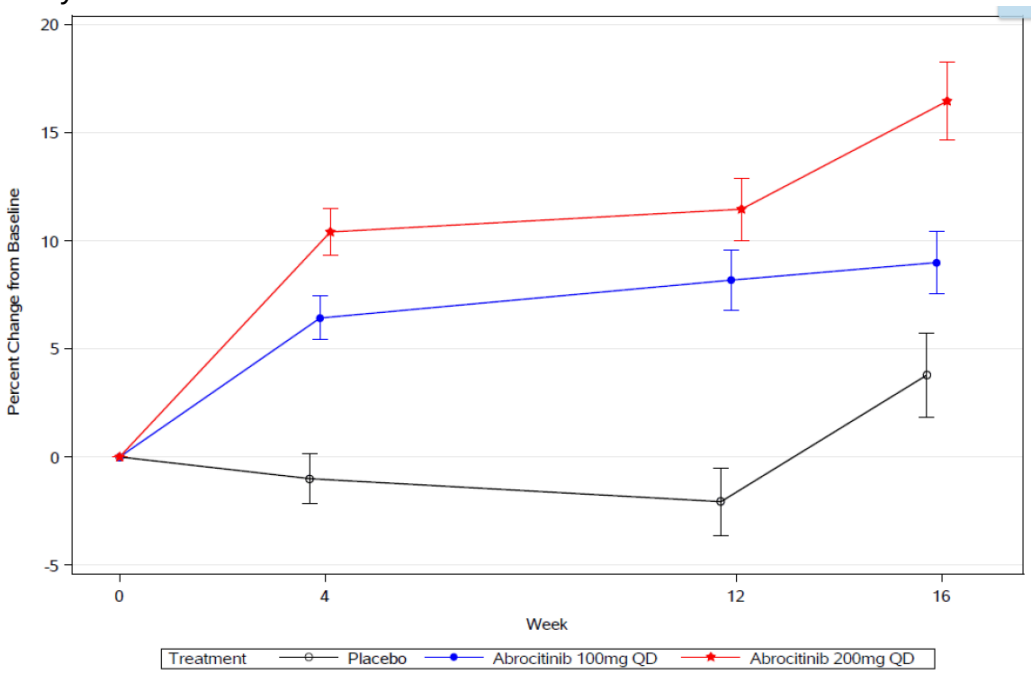
events included 2 events of basal cell carcinoma and 1 event of cutaneous T-cell lymphoma in the abrocitinib 100 mg QD group. There were 4 adjudicated events of squamous cell carcinoma in the abrocitinib 200 mg QD group, one with a preferred term of actinic keratosis.
Given the early time frame for which NMSC occurred, it is likely that the NMSC was present prior to enrollment in the trial.

Reviewer's comment: It is difficult to make a causal connection of cancer to the drug product currently. A long-term study is encouraged to evaluate the immunogenicity of abrocitinib and cancer events. In addition, the tofacitinib safety labeling update will include language for all JAK inhibitors.

8.2.3.4. Thrombosis/MACE

The analysis of thrombosis and Major Adverse Cardiac Events (MACE) was adjudicated by the external blinded committee. In the Placebo-Controlled safety pool, total cholesterol changes over time were consistent with that of LDL-c; there was no meaningful change in triglycerides relative to placebo. The LDL-c was a dose-related percent increase relative to placebo at Week 4, which remained through the final visit in the treatment period (Week 12 for Studies B7451006, B7451012, B7451013, and Week 16 for B7451029).

Figure 9: Mean (+/- SE) Percent Change from Baseline in LDL-c by Visit – Placebo-Controlled Safety Pool



Source: Abrocitinib ISS submission (Figure 17)
Includes Studies: B7451006, B7451012, B7451013, B7451029
Includes data on study treatment or during lag time (28 days)

The median change from baseline to last observation was higher in the abrocitinib 100 mg QD

and 200 mg QD group (5 and 7 mg/dL, respectively) relative to placebo (-2 mg/dL). Changes in total cholesterol were similar to those of LDL-c. The LDL/HDL ration were comparable (placebo: 1.904, abrocitinib 100 mg QD: 1.923, abrocitinib 200 mg QD: 1.843). There was a dose-related percent change decrease in LDL/HDL ratio at Week 4 and no meaningful difference in the ratio at Week 12/Week 16 relative to placebo.

Reviewer's comment: The changes in LDL/HDL/cholesterol/triglycerides for abrocitinib is not consistent with increase in risk for major cardiovascular disease. The relationship for lipid changes to JAK inhibitors is not clear.[14] [15] Although no distinct connection can be made, the continuation of tofacitinib long-term clinical trials identified MACE and malignancy that may need further evaluation in post-marketing.

Summary of Cardiovascular Safety

In the evaluation of the All-Exposure Cumulative Pool excluding Study B7451014 (cutoff date 24 July 2020), there was one subject with a MACE in the abrocitinib 100 mg QD group (0.12/100 PY) and 2 subjects in the 200 mg QD group (0.28/100 PY).

Table 42: Abrocitinib Summary of Clinical Safety (Atopic Dermatitis) Proportion and Incidence Rates for Adjudicated MACE, Non-MACE, and Non-Fatal VTE (CMQ) – All Exposure Cumulative Pool (Excluding Subjects from Study B7451014)

EVENTS	Abrocitinib 100 mg QD (N=885) Total PY[1]=789.11 n(%[2]) EAIR[3] [PY[4]]	Abrocitinib 200 mg QD (N=738) Total PY[1]=687.12 n(%[2]) EAIR[3] [PY[4]]
Adjudicated Major Adverse Cardiovascular Events (MACE)	1 (0.1) 0.12 [789.11]	2 (0.3) 0.28 [686.97]
Venous Thromboembolism (VTE)	0 0.00 [789.11]	5 (0.7) 0.70 [686.66]

Source: Abrocitinib information response 25,26-March-2021, Table 11
Includes Studies: B7451012, B7451013, B7451029, B7451015PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
[1] Total patient years: sum of risk periods for all subjects in each treatment group.
[2] Study-size adjusted proportion.
[3] Exposure-adjusted incidence rate: study-size adjusted number of subjects with events per 100 patient years.
[4] Patient-Year: Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.

[14] Charles-Schoeman C, Gonzalez-Gay MA, Kaplan I, et al. Effects tofactinib and other DMARDs on lipid profiles in rheumatoid arthritis: implications for the rheumatologist. *Semin Arthritis Rheum* 2016; 46(1): 71-80.
[15] Charles-Schoeman C, DeMasi R, Valdez H, et al. Risk factors for major adverse cardiovascular events in Phase III and long-term extension studies of tofacitinib in patients with rheumatoid arthritis: a randomized controlled trial. *Arthritis Rheumatol* 2020; 72(1): 31-40.

There were 2 SAEs that suggested a MACE event, 2 events of myocardial infarction and 1 event of sudden death (did not report as MACE). Conclusions regarding the cases were reviewed. The events did not cluster in the studies, all occurring 3-6 months after initiation of abrocitinib.

- Subject B7451013/ (b) (6) abrocitinib 100 mg QD: This 73-year-old White female subject in Bulgaria reported an SAE of sudden death on Study Day 107, occurring 22 days after discontinuation of study drug. This event was adjudicated as a Cardiac death. The event was assessed as not related to study drug per the investigator. The subject had a history of aortic sclerosis and calcification as observed in a chest X-ray performed during screening and a history of untreated hypertension. The subject received no concomitant medications. No autopsy was performed. The event was assessed as not related to study drug per the investigator

- Subject B7451012/ (b) (6) abrocitinib 200 mg QD: This 60-year-old White, male subject with a BMI of 32 kg/m^2 in the United States reported a medical history of impaired glucose tolerance. He experienced an SAE of myocardial infarction on Day 104 of exposure to abrocitinib. The subject lost consciousness at home and was taken by ambulance to hospital. He was admitted with a diagnosis of myocardial infarction and a stent was placed. The subject recovered from the event of myocardial infarction on Day 106 and was discontinued from the study due to use of clopidogrel. In the opinion of the Investigator, the event of myocardial infarction was considered to be unrelated to the study drug. The event was confirmed during adjudication.

- Subject B7451014/ (b) (6) abrocitinib 200 mg QD: This 63-year-old White male in the United States reported a medical history of HTN, COPD, and hypercholesterolemia. The subject experienced an SAE of myocardial infarction on Day 159 of exposure to abrocitinib. The subject presented to the emergency room with chest pain and was diagnosed with an ST elevation myocardial infarction. The subject was admitted to the hospital and had heart catheterization with placement of 3 stents. The subject discontinued the study due to the event which was considered resolved on Day 159. In the opinion of the Investigator, the event of myocardial infarction was considered to be unrelated to the study drug. The event was confirmed during adjudication.

Adjudicated Non-MACE cardiovascular events

There were 2 subjects with adverse events, 1 with an event of seizure and 1 with an event vertigo, that were adjudicated as having met criteria for as a TIA.

- Subject B7451012/ (b) (6) abrocitinib 100 mg QD: This 55-year-old White female subject experienced an SAE of seizure (probable seizure) on Study Day 14. The subject had a medical history which included seizure disorder, history of meningitis (b) (6) and pulmonary hypertension. The subject experienced left sided intermittent weakness along with facial weakness and was admitted to the hospital and had tests including an

electroencephalogram which was within normal limits. An NMI brain and ultrasound were within normal limits and negative for significant abnormalities. The subject recovered from the event on Day 16. No action was taken regarding study drug and there was no recurrence of a similar event.

- Subject B7451029/ (b) (6) abrocitinib 100 mg QD: This 75-year-old White male subject in the Czech Republic experienced an SAE of vertigo (vertigo) on Study Day 85. The subject had a medical history including hypertension, hypercholesterolemia, and atrial fibrillation. The subject was hospitalized in the neurology department with dizziness and diplopia. He was released with diagnosis: vertigo, diplopia, and walking obstruction. Possible cause of vertigo could be short-term vertebrobasilar insufficiency. The subject recovered from the event on Day 88. There was a concurrent AE of mild vision blurred (Day 85-146). No action was taken regarding study drug and the subject had no other AEs.

Pulmonary embolism

There were 3 (0.4%) AEs of pulmonary embolism in the All-Exposure Pool excluding Study B7451014 (cutoff date 22 April 2020), all in the abrocitinib 200 mg QD group (0.50/100 PY). One event occurred in Phase 2, prior to external adjudication, but is included in the IR.

Deep venous thrombosis

There were 1 (0.1%) adverse events that were adjudicated as meeting the criteria for DVT in the All-Exposure Pool excluding Study B7451014 and only in the abrocitinib 200 mg QD group (0.19/100 PY). A description of all possible cases is provided below.

- Subject B7451006/ (b) (6) abrocitinib 200 mg QD: This 55-year-old White male subject had a medical history of back pain, vertigo, asthma, environmental allergies. He experienced an SAE of pulmonary embolism (VT: pulmonary embolism) on Day 80. The subject presented to ER with right sided pleuritic chest pain. Work up including CXR, CT and blood tests indicated several small blood clots on the right lung. No DVT was evident on ultrasound. He was treated with rivaroxaban. He was released from the ER on the same day and the event was recovered on Day 155. Drug was withdrawn in response to the event.

- Subject B7451012/ (b) (6) abrocitinib 200 mg QD: This 68-year-old White female had a medical history of uterine prolapse, menopause, hypertension, blood cholesterol increased and AV block first degree. The subject experienced an SAE of pulmonary embolism (bilateral pulmonary emboli) on Day 98 of exposure to abrocitinib. The subject went to her doctor who did a CXR. They called her back and sent her to ER, she was admitted overnight. She had CTA and CXR indicating bilateral pulmonary emboli. She was placed on a 6-month course of apixaban which required discontinuation from study. The subject recovered from the event on Day 102.

- Subject B7451012/ (b) (6) abrocitinib 200 mg QD: This 16-year-old Black or African American male subject experienced an SAE of pulmonary embolism (VT: pulmonary embolism) on Study Day 565. Subject had no prior history of deep vein thrombosis (DVT) and pulmonary embolism. Subject reported other concurrent SAEs of pneumothorax (right hydropneumothorax) on Study Day 574 and acute kidney injury (acute kidney failure) on Study Day 578; both concurrent SAEs were considered by the investigator as not related to the study drug. The study drug was permanently withdrawn, and the outcome of the event acute pulmonary embolism was recovered with sequalae on Study Day 574. The investigator reported that the event acute pulmonary embolism was related to the study drug.

- Subject B7451013/ (b) (6) abrocitinib 200 mg QD: This 44-year-old White female experienced an SAE of thrombosis (VT: calf thrombosis) on Day 232, which was an important medical event. The subject's last dose of study drug was Day 224 prior to arthroscopic surgery on Day 227. The subject received bemiparin sodium as prophylaxis for thrombosis. The subject developed calf pain on Day 232, was seen in the ER and an ultrasound showed thrombosis of fibular veins and muscle branches. The subject was withdrawn from study drug in response to the event. She recovered from the event on Day 276. In the opinion of the Investigator, the event of calf thrombosis was considered to be unrelated to the study drug, concomitant medications, or a clinical trial procedure. The event was reported as related to arthroscopic surgery.

- Subject B7451014/ (b) (6) abrocitinib 200 mg QD: This 50-year-old Asian female subject with a medical history of hypertension experienced a non-serious moderate event of thrombophlebitis superficial (VT: small thrombus formation, left great saphenous vein and left superficial femoral vein) on Day 48 and was ongoing at the time of last available report. No change was made to the study drug in response to the event. The subject had one other AE of moderate edema peripheral from Day 9 to Day 85.

Reviewer's comment: Although a clear connection cannot be made to venous thrombosis, abrocitinib at the 200 mg QD dose was the causal dose in all the adverse events of pulmonary embolism and deep venous thrombosis. The higher dose profile of abrocitinib at 200 mg QD presents a higher risk to patients with atopic dermatitis.

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability
No COA review was conducted for the safety or tolerability of abrocitinib. See review of secondary and PRO endpoints for COA evaluations.

8.2.4. Safety Analyses by Demographic Subgroups

During the review cycle, new safety information was released from the Tofacitinib (XELJANZ) PMR/PMC safety study A3921133. This study, in rheumatoid arthritis (RA) patients, identified increase risks for MACE and malignancy in the RA population. For purposes of identifying risk

factors associated with excess events, a univariate Cox proportional hazard analyses was performed, and the A3921133 patients were divided in two groups: those who have never smoked AND are younger than 65 and those who ever smoked OR are 65 or older. The incidence rates of MACE and malignancies among tofacitinib treated patients are comparable to the rates among TNF treated patients in the group of never smokers who were younger than 65; essentially all of the excess risk was associated with those over 65 or current or past smokers.

Similarly, in the AD abrocitinib development program, increased age ≥65 years old has consistently been shown to be associated with an increased incidence of some adverse events of interest such as MACE, malignancies, and herpes zoster.

In addition, concern may exist for the life-long potential use of agents such as abrocitinib in a young and relatively healthy population. It is noteworthy that the median drug survival for effective systemic drugs in inflammatory skin diseases like psoriasis has been widely reported to be 47 months, mostly limited by loss of efficacy and discontinuations due to adverse events (Gniadecki et al, 2015)[16]. It is unknown, but likely, that the survival of recently approved more effective drugs will be longer, but these data are not yet available. Data on dupilumab drug survival is emerging and although survival appears to exceed 26 months, it is important to note that no alternative to dupilumab therapy is currently available, and many patients in that report remained on dupilumab despite uncontrolled disease (Dal Bello et al, 2020)[17].

In the subgroup analyses, we evaluated safety responses based on prior AD treatment with systemic drugs to further identify a population of patients where benefit of therapy with abrocitinib may outweigh the risks associated with JAK inhibition.

Prior Systemic Treatment Safety Analysis
Systemic treatment used prior to abrocitinib trials was evaluated for subgroup analysis. The most frequently reported prior systemic therapy was systemic corticosteroids, followed by cyclosporine. Biologic agents (including dupilumab) and immunosuppressants other than systemic corticosteroids and cyclosporine were reported in a minority of subjects.

[16] Gniadecki R, Bang B, Bryld LE, et al. Comparison of long-term drug survival and safety of biologic agents in patients with psoriasis vulgaris. *Br J Dermatol*. 2015 Jan;172(1):244-52.
[17] Dal Bello G, Maurelli M, Schena D, et al. Drug survival of dupilumab compared to cyclosporin in moderate-to-severe atopic dermatitis patients. *Dermatol Ther*. 2020 Nov;33(6): e13979.

Table 43: Proportion of Subjects with Prior Systemic Treatment for Atopic Dermatitis – Combination Therapy Trial and Monotherapy Pool

	Trial B7451029			Monotherapy Pool		
	Placebo (N=131) n (%)	Abrocitinib 100 mg QD (N=238) n (%)	Abrocitinib 200 mg QD (N=226) n (%)	Placebo (N=210) n (%)	Abrocitinib 100 mg QD (N=369) n (%)	Abrocitinib 200 mg QD (N=363) n (%)
Systemic treatment	48 (36.6)	99 (41.6)	103 (45.6)	96 (45.7)	172 (46.6)	158 (43.5)
Non-biologic agents	43 (32.8)	96 (40.3)	96 (42.5)	82 (39.0)	142 (38.5)	135 (37.2)
Corticosteroids	32 (24.4)	76 (31.9)	81 (35.8)	60 (28.6)	111 (30.1)	107 (29.5)
Cyclosporine	13 (9.9)	29 (12.2)	28 (12.4)	24 (11.4)	47 (12.7)	43 (11.8)
Other non-biologic	9 (6.9)	13 (5.5)	10 (4.4)	22 (10.5)	40 (10.8)	29 (8.0)
Biologic agents	5 (3.8)	3 (1.3)	7 (3.1)	14 (6.7)	30 (8.1)	23 (6.3)
Dupilumab	0	0	0	11 (5.2)	20 (5.4)	14 (3.9)
Other biologic	5 (3.8)	3 (1.3)	7 (3.1)	3 (1.4)	11 (3.0)	11 (3.0)

Source: Applicant response to FDA IR 31-MARCH-2021; Table 1: page 4
Monotherapy pool includes B7451006, B7451012, B7451013
'other non-biologic' included any systemic non-biologic immunomodulatory drugs used to treat AD, excluding corticosteroids and cyclosporine.
'other biologic' included any systemic biologic drugs used to treat AD, excluding dupilumab

The efficacy of the responder/non-responder subgroup analyses is provided in the efficacy sections of this review.

Clearly, the numbers in the subgroup analyses are small when subdivided. The TEAE for responder/non-responder analyses in the All-Exposure Pool is presented.

Table 44: Abrocitinib Summary of Clinical Safety TEAE for Non-Responder and Responders to Dupilumab – All Exposure Pool Subanalyses

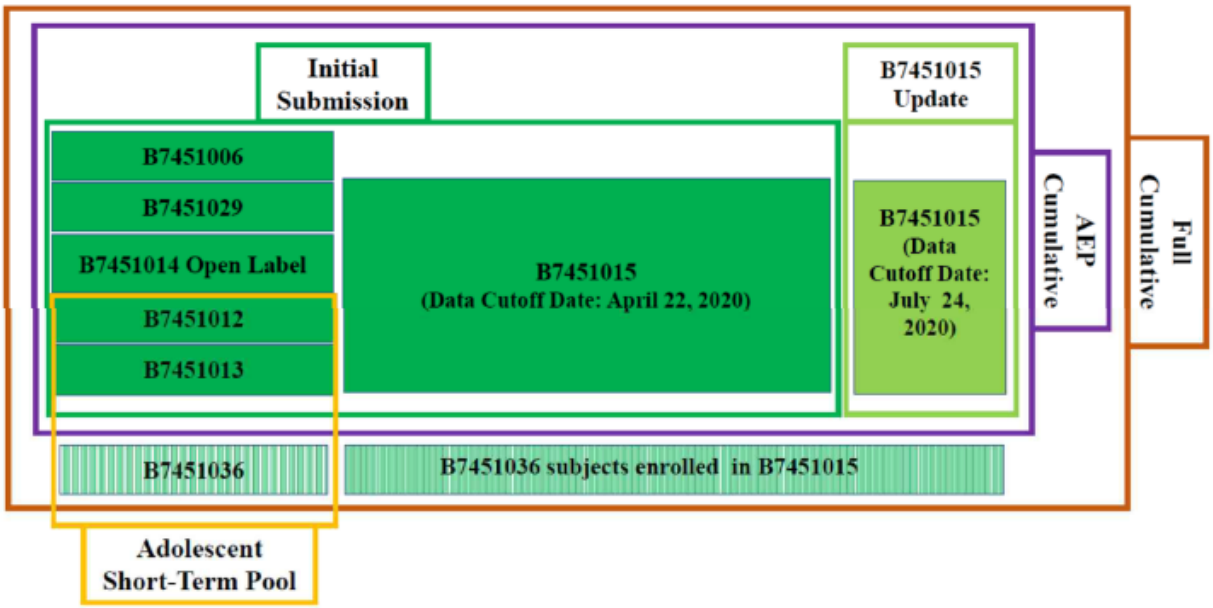
	Abrocitinib 100 mg		Abrocitinib 200 mg		All Abrocitinib	
Dupilumab Responder	NO	YES	NO	YES	NO	YES
N	75	52	39	30	114	82
AEs	34 (45.3)	25 (48.1)	21 (53.8)	15 (50.0)	55 (48.2)	40 (48.8)
SAEs	3 (4.0)	1 (1.9)	1 (2.6)	0	4 (3.5)	1 (1.2)
Severe AEs	2 (2.7)	2 (3.8)	1 (2.6)	1 (3.3)	3 (2.6)	3 (3.7)
Discontinued due to AE	1 (1.3)	0	0	1 (3.3)	1 (0.9)	1 (1.2)

Source: Pfizer response to Agency request for information 3-November, 2020.
Includes studies: B7451006, B7451012, B7451013, B7451029, B7451014, B7451015

The safety analyses provided has no placebo arm comparison. Subjects were switch from dupilumab to abrocitinib 100 mg QD or 200 mg QD in randomized fashion. No specific increase in adverse events were observed between the 100 mg QD and the 200 mg QD dosing.

Analysis of the Full Cumulative Exposure Safety Pool

Figure 10: Graphic Representation of the 120-Day Safety Update



The figure above represents the totality of the data provided in the application for abrocitinib for the treatment of atopic dermatitis. The applicant submitted Study B7451036 (TEEN) to the 120-day safety update. The Full Cumulative pool contains the safety from the TEEN study. The efficacy was not pooled in our review. The applicant requested that the Agency holds off on the review of that data (b) (4)

In the review of the All-Exposure Cumulative Pool, Study B7451014 was excluded from the safety pool analysis.

Some trends were evaluated for the Full Cumulative Safety Pool:

- Herpes zoster showed a dose-response in both the moderate and severe group, given the risk in the whole population.
- All VTE events occurred in 200 mg treated patients.
- The incidence of SAEs is higher in patients in the ≥ 65 years age subgroup (13.1%).
- Of the 4 deaths, all but 1 were in patients aged 65 years and older.
- The rate of herpes zoster was higher in patients aged 65 years and older.
- Most subjects with low platelets (< 75 $10^3/mm^3$) and all patients with low lymphocytes (< 0.5) were patients 65 years and older.

8.2.5. Long-Term Safety

Evaluation of long-term safety for the adverse events of special interest (AESI) examined the All-Exposure Cumulative pool (cutoff date 24 July 2020) with Study B7451014 omitted from the analysis.

Table 45: Proportion and Incidence Rates for AESI – All Exposure Cumulative Pool (Excluding B7451014)

System Organ Class and Preferred Term	Abrocitinib 100 mg QD (N=885) Total PY[1]=789.11 n (%[2]) EAIR[3] [PY[4]]	Abrocitinib 200 mg QD (N=738) Total PY[1]=687.12 n (%[2]) EAIR[3] [PY[4]]
All Infections	427 (48.3) 91.83 [469.92]	394 (53.3) 103.21 [378.07]
Serious Infections	18 (2.0) 2.30 [784.40]	16 (2.2) 2.34 [683.55]
Opportunistic Herpes Zoster *	4 (0.4) 0.51 [786.78]	10 (1.4) 1.50 [682.60]
Opportunistic Infections (excluding HZ and TB)	No subjects meet these criteria	
Herpes Zoster (CMQ)	16 (1.8) 2.02 [777.93]	35 (4.7) 5.23 [667.18]
Tuberculosis	No subjects meet this criterion	
All Malignancies	4 (0.4) 0.50 [786.50]	2 (0.3) 0.28 [685.68]
Malignancies excluding NMSC *	1 (0.1) 0.13 [789.04]	1 (0.1) 0.14 [685.98]
NMSC	3 (0.3) 0.37 [786.57]	1 (0.1) 0.15 [686.81]
MACE	1 (0.1) 0.12 [789.11]	2 (0.3) 0.28 [686.97]
VTE	0 0.00 [789.11]	5 (0.7) 0.70 [686.66]
Gastrointestinal Perforation	2 (0.2) 0.24 [788.87]	0 0.00 [687.12]
Retinal Detachment	2 (0.2) 0.25 [788.41]	0 0.00 [687.12]
Laboratory		
Blood CPK increase > 5x ULN	43 (5.0) 5.89 [753.04]	57 (7.7) 8.77 [649.44]
Thrombocytopenia (<75x10^3/ mm^3)	0 0.00 [789.11]	6 (0.8) 0.87 [681.94]

Source: Information request response table 11: 25, 26 MAR-2021 from Pfizer
Includes Studies: B7451012, B7451013, B7451029, B7451015
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date

B7451015]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. Incidence Rates: Number of subjects with events per 100 patient-years.
[1] Total patient years: sum of risk periods for all subjects in each treatment group.
[2] Study-size adjusted proportion.
[3] Exposure-adjusted incidence rate: study-size adjusted number of subjects with events per 100 patient years.
[4] Patient-Year: Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
*For AEP, including treatment-emergent adverse events reported for the initial submission and adjudicated for the safety update.

Note that herpes infections appear to have a dose-related increase and that venous thromboembolism was reported only in the abrocitinib 200 mg QD dose. We can parse out the events of VTE to pulmonary embolism and deep vein thrombosis in the all exposure cumulative pool.

Table 46: Proportion and Incidence Rates for Additional AESI – All Exposure Cumulative Pool (Excluding B7451014)

System Organ Class and Preferred Term	Abrocitinib 100 mg QD (N=885) Total PY[1]=789.11 n (%[2]) EAIR[3] [PY[4]]	Abrocitinib 200 mg QD (N=738) Total PY[1]=687.12 n (%[2]) EAIR[3] [PY[4]]
Herpes Simplex (CMQ)	56 (6.3) 7 41 [752 66]	64 (8.7) 9 93 [647 62]
Pulmonary Embolism	0 0.00 [789.11]	3 (0.4) 0.4 [686.83]
Deep Vein Thrombosis	0 0.00 [789.11]	2 (0.3) 0.29 [686.95]
Lymphopenia	1 (0.1) 0.13 [788.85]	5 (0.7) 0.71 [684.57]
Lipid Elevations (CMQ)	6 (0.7) 0.77 [785.95]	11 (1.5) 1.64 [682.00]

Source: Information request response table 4: 21 JUN-2021 from Pfizer
Includes Studies: B7451012, B7451013, B7451029, B7451015
Includes data up to the end of risk period (the smallest of [last dose date + 28 days], [death date] and [data cut date B7451015]).
PY (Patient-Year): Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.
n: Number of subjects with the event. Incidence Rates: Number of subjects with events per 100 patient-years.
[1] Total patient years: sum of risk periods for all subjects in each treatment group.
[2] Study-size adjusted proportion.
[3] Exposure-adjusted incidence rate: study-size adjusted number of subjects with events per 100 patient years.
[4] Patient-Year: Total follow up time calculated up to the day of the first event for subjects with events, and up to the end of risk period for subjects without events.

The adverse events profile in the short-term and long-term will be expressed in the physicians labeling to help evaluate benefit and risk. The higher dose of 200 mg QD does put the atopic dermatitis patient at a higher risk for rare events such as DVT and pulmonary embolic events.

Reviewer's comment: The Full Cumulative Exposure Pool considered in the section supports the current reviewer recommendation for approval (adults at 100 mg QD). There was no notable increase in the IR for SAEs; however, events were added to the Infections and Infestations SOC. In addition, the cardiovascular adverse events added one additional MACE due to cardiac failure and VTEs in the updated pool, all occurred in subjects on 200 mg QD. This reviewer is concerned that although abrocitinib 200 mg QD achieved greater efficacy than 100 mg QD, the minor efficacy achievement is limited by the adverse events for the MACE, VTE, and herpes infections. A long-term safety profile to establish the differences in the 100 mg QD and 200 mg QD the malignancies and thrombosis, would be meaningful in determining the higher dose of abrocitinib for treatment of atopic dermatitis.

8.2.6. Specific Safety Studies/Clinical Trials

All safety studies are incorporated into the clinical review.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No clinical studies were completed specifically for human carcinogenicity or tumor development.

Human Reproduction and Pregnancy

Abrocitinib did not cause fetal malformations in rats or rabbits. In the EFD study in rats, the developmental NOAEL was established at exposures of 2.4x the unbound human AUC at the clinical dose of 200 mg. In a rat PPND study, no effects on parturition and postnatal development were noted at NOAEL exposures of 2.4x the unbound human AUC.

There were 7 cases of maternal exposure in the Full Cumulative Pool for atopic dermatitis studies. One event was reported during the update period (Subject B7451029/ (b) (6)). The outcomes of these events are listed below:

- Subject B7451029/ (b) (6) abrocitinib 100 mg QD: outcome unknown
- Subject B7451029/ (b) (6) abrocitinib 100 mg QD: outcome unknown
- Subject B7451029/ (b) (6) abrocitinib 100 mg QD: outcome unknown
- Subject B7451012/ (b) (6) abrocitinib 200 mg QD: outcome unknown
- Subject B7451012/ (b) (6) abrocitinib 200 mg QD: miscarriage
- Subject B7451029/ (b) (6) abrocitinib 200 mg QD: outcome unknown
- Subject B7451014/ (b) (6) abrocitinib 200 mg QD: miscarriage

There were 4 cases of partner exposure in the Full Cumulative Pool with the following outcomes:

- Subject B7451006/ (b) (6) abrocitinib 100 mg QD: male study subject, live full-term

birth
- Subject B7451012/ (b) (6) abrocitinib 100 mg QD: male study subject, pregnancy outcome unknown
- Subject B7451013/ (b) (6) abrocitinib 100 mg QD: male study subject, pregnancy outcome unknown
- Subject B7451014/ (b) (6) abrocitinib 200 mg QD: male study subject, outcome unknown

There's no data on the presence of abrocitinib in human milk, the effects on the breast-fed infant, or the effects on milk production. Abrocitinib was secreted in milk of lactating rats. A risk to newborns/infants cannot be excluded and abrocitinib should not be used during breast-feeding. The Division is considering a Pregnancy Registry and a Lactation study for PMR.

Pediatrics and Assessment of Effects on Growth

(b) (4) A microscopic finding of bone dystrophy was noted in rapidly growing rats (in short-term toxicology studies ≤1 month). The NOEL exposure margin was at least 6x the unbound human AUC at the clinical dose of 200 mg QD for this microscopic bone finding in rats. There were no bone effects in chronic rat or any of the monkey toxicity studies.

In adolescent subjects who entered the long-term safety study (B7451015), height measurements in the LTE were obtained every 12 weeks and examined. Adolescent subjects enrolling in the LTE study (B7451015) were asked to provide 3 historical height values after the age of 5 years, separated by at least 6 months.

The Standard Deviation Scores (SDS) standardized to the US population by age and gender was calculated at each time point where height measurement is available. As such the findings are normalized across age and gender. At Month 6 and Month 12, the SDS changes ranged from -0.9 to 1.3 with median of 0, suggesting no meaningful change in the subjects' growth curves.

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Table 47: Summary of Standard Deviation Scores (SDS) for Height Measurement and Its Change from Baseline Overtime for Adolescent Subjects – All Exposure Pool

		Abrocitinib 100mg QD (N=885)		Abrocitinib 200mg QD (N=1971)		All Abrocitinib (N=2856)	
		Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline
	Summary Statistics						
Baseline [1]	n	64		298		362	
	Mean (SD)	-0.2 (1.0)		-0.2 (1.1)		-0.2 (1.0)	
	Median (Q1, Q3)	0 (-1, 0)		0 (-1, 1)		0 (-1, 1)	
	Range (Min, Max)	(-4.2, 2.0)		(-3.4, 3.7)		(-4.2, 3.7)	
Day 180 (+/- 30 days) [2]	n	50	50	98	98	148	148
	Mean (SD)	-0.1 (0.9)	-0.0 (0.3)	-0.0 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)
	Range (Min, Max)	(-2.1, 2.4)	(-0.7, 1.1)	(-3.2, 2.8)	(-0.9, 1.3)	(-3.2, 2.8)	(-0.9, 1.3)
Day 360 (+/- 30 days) [2]	n	28	28	66	66	94	94
	Mean (SD)	-0.1 (0.9)	-0.0 (0.4)	-0.1 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)
	Range (Min, Max)	(-1.9, 1.5)	(-0.8, 1.2)	(-3.4, 1.7)	(-0.6, 1.1)	(-3.4, 1.7)	(-0.8, 1.2)
Day 540 (+/- 30 days) [2]	n	6	6	9	9	15	15
	Mean (SD)	0.4 (1.1)	0.3 (0.5)	-0.1 (1.1)	-0.1 (0.5)	0.1 (1.1)	0.0 (0.5)
	Median (Q1, Q3)	1 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)
	Range (Min, Max)	(-1.4, 1.5)	(-0.5, 1.2)	(-2.9, 1.0)	(-0.8, 0.7)	(-2.9, 1.5)	(-0.8, 1.2)
Day 720 (+/- 30 days) [2]	n	1	1	2	2	3	3
	Mean (SD)	-0.5 (NA)	0.2 (NA)	-1.0 (0.2)	-0.5 (0.2)	-0.8 (0.3)	-0.2 (0.4)
	Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	-1 (-1, -1)	0 (-1, 0)	-1 (-1, 0)	0 (-1, 0)
	Range (Min, Max)	(-0.5, -0.5)	(0.2, 0.2)	(-1.1, -0.8)	(-0.6, -0.3)	(-1.1, -0.5)	(-0.6, 0.2)

Source: Abrocitinib ISS, Table 51.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029

In the clinical studies, there were 2 adolescents with a fracture in the All-Exposure Pool. Both subjects were on the abrocitinib 200 mg QD dose. Neither of the adverse events were deemed as related to the study drug.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is abuse potential for abrocitinib. There is no withdrawal or rebound safety issues.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

This product is not marketed in the United States or other countries.

Expectations on Safety in the Postmarket Setting

Recent long-term clinical studies for tofacitinib identified adverse events of malignancy and MACE.

8.2.9. Integrated Assessment of Safety

Pfizer Inc. has submitted a 505 (b)(1) application for abrocitinib (CIBINQO), a Janus kinase (JAK) inhibitor proposed [redacted] (b) (4) Abrocitinib is an oral tablet (50 mg, 100 mg, 200 mg) that works by inhibiting JAK by blocking the ATP binding sit, inhibiting cytokine induced STAT phosphorylation mediated by receptors utilizing JAK in response to inflammatory and proliferative signals in atopic dermatitis.

To establish the safety of abrocitinib, this clinical review evaluated the 12-week monotherapy safety pool (MONO-1 and MONO-2), which contained a total of 778 subjects: 314 subjects in the 100 mg QD group and 309 subjects in the 200 mg QD group (155 subjects in the Placebo group). Median age was 30-year-old; 15.9% were adolescents under the age of 18 years old. Most frequent reported adverse reactions were nausea, headaches, vomiting, dizziness, herpes simplex, abdominal pain, and increase in blood creatinine phosphokinase.

A second Placebo-Controlled safety pool identified 1540 subjects (8.1% adolescents) in the placebo-controlled studies (MONO-1, MONO-2, B7451006 and B7451029) with abrocitinib doses of 100 mg QD and 200 mg QD and placebo (608 subjects exposed to abrocitinib 100 mg QD, 590 subjects exposed to 200 mg QD, and 342 subjects exposed to placebo). Significant safety events include serious infections (opportunistic infections, multidermatomal cutaneous herpes zoster infections, and serious herpetic infections), possible lymphoma and other malignancies, venous thromboembolic events (VTE) including MACE, pulmonary embolism (PE) and deep vein thrombosis (DVT), and retinal detachment was also suspect in subjects exposed to abrocitinib. In addition, during the clinical trials subjects had dose-dependent increase in blood lipid parameters, reduction in absolute neutrophil counts, and thrombocytopenia (low platelet counts) that had a nadir at 4-weeks during treatment with abrocitinib.

Additional safety data obtained with the post-marketing evaluation of tofacitinib (XELJANZ) for the possibility of increased signals in MACE and malignancy changes the benefit/risk calculus for all JAK inhibitors.

The applicant's monotherapy and Placebo-Controlled safety pools had the same 124 adolescents [29 subjects 17 years old (12 200 mg, 9 100 mg, 8 placebo); 25 subjects 16 years old (8 200 mg, 9 100 mg, 8 placebo); 21 subjects 15 years old (8 200 mg, 11 100 mg, 2 placebo); 18 subjects 14 years old (7 200 mg, 8 100 mg, 3 placebo); 18 subjects 13 years old (7 200 mg, 7 100 mg, 4 placebo); 13 subjects 12 years old (7 200 mg, 5 100 mg, 1 placebo)] from 12 years of age to under the age of 18 years. The Division had previously recommended at least 30% or 225 patients of the safety population be adolescents for adequate benefit/risk analysis. (b) (4)

8.3. Summary and Conclusions

8.3.1. Statistical Issues

To establish the efficacy of abrocitinib for the treatment of AD, the Applicant submitted data from three adequate and well controlled clinical trials. Trials B7451012 and B7451013 evaluated abrocitinib as monotherapy in adolescents and adults. Trial B7451029 evaluated abrocitinib in combination with background topical therapy in adults only. The trials included subjects who had moderate to severe AD, with IGA score ≥ 3 (moderate), EASI score ≥16, and ≥10% of BSA involvement. The co-primary endpoints, assessed at Week 12, were the proportion of subjects with an IGA score of 0 ("clear") or 1 ("almost clear") and at least a 2-point improvement from baseline, and the proportion of subjects achieving improvement of at least 75% in the EASI score (EASI-75). Both abrocitinib doses (200 mg and 100 mg) were statistically superior to placebo for the co-primary endpoints in all three trials, with higher treatment effect in the 200 mg dose compared to 100 mg. The amount of missing data for the co-primary was relatively small (< 12%) at Week 12 (i.e., the primary efficacy timepoint). A higher proportion of missing data was observed in the placebo arm compare to the active arms in the monotherapy trials (Trials B7451012 and B7451013). The statistical reviewer conducted additional sensitivity analyses using 1) the last observation carried forward (LOCF), 2) observed cases and 3) multiple imputation (MI). In all three trials, the results for the co-primary endpoints were very similar across the various methods of handling the missing data.

For the key secondary endpoint of PP-NRS4 (i.e., at least 4-point reduction in pruritus NRS) at Week 12 in the monotherapy trials, pruritus was assessed daily for the first two weeks and then at the study visits (i.e., Weeks 4, 8, and 12). Furthermore, a large amount of missing Pruritus NRS data was observed in the monotherapy trials (see Table 20 and Table 21). The treatment effect for PP-NRS4 varied across the various methods of handling the missing data for Weeks 4 and 12 in Trial B7451012. The result for the 100 mg dose was not statistically superior to placebo at Week 4 (preceding testing at Week 12 per the MTP) using the NRI and OC methods. Therefore, due to the single administration of the PP-NRS at the clinic visit, as well as, the large

amount of missing data in Trial B7451012, it is difficult to obtain reliable treatment effect estimates for the PP-NRS4 endpoint. Results for PP-NRS4 were similar across the various methods of handling the missing data in Trial B7451013 for all timepoints. The statistical reviewer conducted supportive analyses for itching at Week 12 in the monotherapy trials using the PSAAD Itching item (see discussion in Section 8.1.11). Results from the supportive analyses indicated improvement in itch at Week 12 in the two monotherapy trials. It should be noted that the PP-NRS4 at Week 12 endpoint was not included in the MTP for the combination therapy trial.

Regarding improvement in AD signs and symptoms as measured by the PSAAD total score, the Agency previously noted (advice letter dated 2/15/2018) that a mere change from baseline might not translate to a clinically relevant difference. The statistical reviewer also explored the proportion of subjects with PSAAD total score of 0 at Week 12. Only a very small proportion of subjects treated with abrocitinib (1%-6% across the two doses) had PSAAD Total Score of 0 at Week 12.

8.3.2. Conclusions and Recommendations

Pfizer has provided evidence of safety and efficacy for the use of abrocitinib in adult subjects (18 years and older) with moderate-to-severe atopic dermatitis who have failed or are intolerant to systemic treatment. In the opinion of this reviewer, (b) (4) In addition, the 200 mg QD dose has some observed safety issues that is not present in the 100 mg QD group. This includes serious infections, opportunistic infections, malignancies, retinal detachment, thromboembolism, MACE, and laboratory abnormalities (i.e., thrombocytopenia, lipid abnormalities). Given the 3rd line therapy indication this Reviewer is recommending for the 100 mg QD dose, the 200 mg QD dose should be approved for treatment failure of the 100 mg QD dose for those patients that have no other option and understand the increased risks the higher dose presents.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee was not convened for this product.

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10 Pediatrics

Phase 3 pivotal clinical trials included subject 12 years of age and over with a minimum body with of ≥ 40 kg with moderate-to-severe atopic dermatitis. A deferral of clinical studies is proposed in the age range (b) (4) to <12 years old. Development will be staged (b) (4) for the deferred studies.

Bone Changes in Clinical Trials

(b) (4) A microscopic finding of bone dystrophy was noted in rapidly growing rats (in short-term toxicology studies ≤1 month). The NOEL exposure margin was at least 6x the unbound human AUC at the clinical dose of 200 mg QD for this microscopic bone finding in rats. There were no bone effects in chronic rat or any of the monkey toxicity studies.

In adolescent subjects who entered the long-term safety study (B7451015), height measurements in the LTE were obtained every 12 weeks and examined. Adolescent subjects enrolling in the LTE study (B7451015) were asked to provide 3 historical height values after the age of 5 years, separated by at least 6 months.

The Standard Deviation Scores (SDS) standardized to the US population by age and gender was calculated at each time point where height measurement is available. As such the findings are normalized across age and gender. At Month 6 and Month 12, the SDS changes ranged from -0.9 to 1.3 with median of 0, suggesting no meaningful change in the subjects' growth curves.

Table 48: Summary of Standard Deviation Scores (SDS) for Height Measurement and Its Change from Baseline Overtime for Adolescent Subjects – All Exposure Pool

		Abrocitinib 100mg QD (N=885)		Abrocitinib 200mg QD (N=1971)		All Abrocitinib (N=2856)	
		Result	Change from Baseline	Result	Change from Baseline	Result	Change from Baseline
	Summary Statistics						
Baseline [1]	n	64		298		362	
	Mean (SD)	-0.2 (1.0)		-0.2 (1.1)		-0.2 (1.0)	
	Median (Q1, Q3)	0 (-1, 0)		0 (-1, 1)		0 (-1, 1)	
	Range (Min, Max)	(-4.2, 2.0)		(-3.4, 3.7)		(-4.2, 3.7)	
Day 180 (+/- 30 days) [2]	n	50	50	98	98	148	148
	Mean (SD)	-0.1 (0.9)	-0.0 (0.3)	-0.0 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)
	Range (Min, Max)	(-2.1, 2.4)	(-0.7, 1.1)	(-3.2, 2.8)	(-0.9, 1.3)	(-3.2, 2.8)	(-0.9, 1.3)
Day 360 (+/- 30 days) [2]	n	28	28	66	66	94	94
	Mean (SD)	-0.1 (0.9)	-0.0 (0.4)	-0.1 (1.0)	-0.0 (0.3)	-0.1 (1.0)	-0.0 (0.3)
	Median (Q1, Q3)	0 (-1, 0)	0 (0, 0)	0 (-1, 1)	0 (0, 0)	0 (-1, 1)	0 (0, 0)
	Range (Min, Max)	(-1.9, 1.5)	(-0.8, 1.2)	(-3.4, 1.7)	(-0.6, 1.1)	(-3.4, 1.7)	(-0.8, 1.2)
Day 540 (+/- 30 days) [2]	n	6	6	9	9	15	15
	Mean (SD)	0.4 (1.1)	0.3 (0.5)	-0.1 (1.1)	-0.1 (0.5)	0.1 (1.1)	0.0 (0.5)
	Median (Q1, Q3)	1 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0 (0, 0)
	Range (Min, Max)	(-1.4, 1.5)	(-0.5, 1.2)	(-2.9, 1.0)	(-0.8, 0.7)	(-2.9, 1.5)	(-0.8, 1.2)
Day 720 (+/- 30 days) [2]	n	1	1	2	2	3	3
	Mean (SD)	-0.5 (NA)	0.2 (NA)	-1.0 (0.2)	-0.5 (0.2)	-0.8 (0.3)	-0.2 (0.4)
	Median (Q1, Q3)	0 (0, 0)	0 (0, 0)	-1 (-1, -1)	0 (-1, 0)	-1 (-1, 0)	0 (-1, 0)
	Range (Min, Max)	(-0.5, -0.5)	(0.2, 0.2)	(-1.1, -0.8)	(-0.6, -0.3)	(-1.1, -0.5)	(-0.6, 0.2)

Source: Abrocitinib ISS, Table 51.
Includes Studies: B7451006, B7451012, B7451013, B7451014, B7451015, B7451029

In the clinical studies, there were 2 adolescents with a fracture in the All Exposure Pool. Both subjects were on the abrocitinib 200 mg QD dose. Neither of the adverse events were deemed as related to the study drug.

11 Labeling Recommendations

(b) (4)

28 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

12 Risk Evaluation and Mitigation Strategies (REMS)

REMS is not proposed for this application. Labeling and pharmacovigilance activities should adequately convey the risks of this product, particularly as informed by other JAK product applications.

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13 Postmarketing Requirements and Commitment

Clinical

4217-1 [redacted] clinical trial B7451036 (TEEN) data in adolescents [redacted] Draft Protocol Submission: NA
Final Protocol Submission: complete
Study/Trial Completion: complete
Final Report Submission: 05/2022

4217-2 Conduct a clinical trial in subjects 2 to 12 years of age with moderate-to-severe atopic dermatitis
Draft Protocol Submission,: 05/2025
Final Protocol Submission: 09/2025
Study/Trial Completion: 06/2030
Final Report Submission: 12/2030

4217-3 Conduct a **prospective observational study** (analyses conducted in patient cohorts enrolled prospectively and followed actively in accordance with a written protocol) to assess the long-term safety of abrocitinib treatment in U.S. adult patients with moderate-to-severe atopic dermatitis. Fully ascertain and centrally verify serious adverse events, Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), malignancies (including lymphoma, lung cancer, and other malignancies), serious infections, opportunistic infections (including herpes zoster), retinal detachment, thrombosis (including deep venous thrombosis, pulmonary embolism and arterial thrombosis), hepatoxicity (including drug induced liver injury) , and possibly other adverse events of special interest. For each adverse-event outcome separately, compare incidence in abrocitinib-treated patients against reference rates internally derived from analyses conducted in patients treated with dupilumab or other chronic systemic treatments for moderate-to-severe atopic dermatitis. Regardless of treatment discontinuation or switch to a different treatment for atopic dermatitis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events of special interest in representative U.S. patients who start treatment with abrocitinib for atopic dermatitis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with abrocitinib. Enroll patients over a 4-year period and follow each patient for at least 8 years from time of enrollment.

Draft Protocol Submission,: 074/2022
Final Protocol Submission: 04/2023
Study/Trial Completion: 10/2033
Interim /Other : 12/2028 (Submission of interim study report)
Final Report Submission: 10/2034

Pregnancy related PMR's

4217-4 Conduct or participate in a relevant Pregnancy Exposure Registry, a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to abrocitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. For more information, see the May 2019 FDA draft Guidance for Industry Postapproval Pregnancy Safety Studies.

For more information, see the May 2019 FDA draft Guidance for Industry "Post approval Pregnancy Safety Studies".
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safetystudies-guidance-industry
Draft Protocol Submission: 07/2022
Final Protocol Submission: 12 /2022
Study/Trial Completion: 12 /2027
Interim /Other[18]: 12 /2025
Final Report Submission: 12 /2028

4217-5 Conduct an additional pregnancy study that uses a different design from the Pregnancy Exposure Registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to abrocitinib during pregnancy compared to an unexposed control population.

[18] Interim or "other" milestones may include interim report submission or subject accrual milestones. Justification for these milestones should be described in Section D.3.

For more information, see the May 2019 FDA draft Guidance for Industry "Post approval Pregnancy Safety Studies".

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safetystudies-guidance-industry

Draft Protocol Submission,: 07 /2022
Final Protocol Submission: 12 /2022
Study/Trial Completion: 12 /2027
Final Report Submission: 06 /2028

Clinical Pharmacology

4217-6 Conduct a drug-drug interaction trial in healthy subjects using clinical dose of oral abrocitinib and a gastric acid reducing agents (e.g., esomeprazole).

The Sponsor has conducted a clinical DDI Study B7451061 with famotidine, an H2-receptor antagonist that increases gastric pH, to evaluate the effect of famotidine on the pharmacokinetics and bioavailability of abrocitinib and its metabolites. Famotidine was selected because it has been shown to reliably increase gastric pH after single doses and does not have any effects on the principal enzymes (CYP219 and CYP2C9) or transporters (OAT3) involved in the disposition of abrocitinib and its metabolites. This allows conclusive interpretation of study results, knowing that in contrast with some proton-pump inhibitors (e.g., omeprazole), famotidine's effect on PK of abrocitinib as observed in study B7451061 can be attributed to its pH-raising effects in maintaining gastric pH >4, which would have lasted up to 12 hours .

Draft Protocol Submission,: NA
Final Protocol Submission: complete
Study/Trial Completion: complete
Final Report Submission: 04 /2022

14 Division Director (Clinical) Comments

Pfizer submitted a 505(b)1 application for abrocitinib (CIBINQO), an oral JAKi, for the treatment of moderate-to-severe atopic dermatitis [redacted] (b) (4) In support of the efficacy of abrocitinib, the applicant conducted two 12-week, phase 3, multicenter, placebo-controlled clinical trials evaluating abrocitinib 100 mg QD and abrocitinib 200 mg QD versus placebo. A 12-week, phase 3, multicenter clinical trial comparing abrocitinib to placebo in which all subjects used topical corticosteroids was also conducted. The efficacy of abrocitinib was convincingly demonstrated in all three trials. In the two monotherapy trials, the clinical trials compared co-primary endpoints for abrocitinib to placebo. The IGA responder proportion of clear or almost clear with abrocitinib 100 mg QD was 27% and with 200 mg QD was 41%, compared to 8% with placebo. The EASI-75 responder proportion with abrocitinib 100 mg QD was 42% and with 200 mg QD was 62%, compared to 12% with placebo. In the trial in which all subjects were also treated with topical corticosteroids, the IGA responder proportion of clear or almost clear with abrocitinib 100 mg QD was 36% and with 200 mg QD was 47%, compared to 14% with placebo. The EASI-75 responder proportion with abrocitinib 100 mg QD was 58% and with 200 mg QD was 68%, compared to 27% with placebo. Significantly more subjects receiving abrocitinib as compared to placebo achieved a 4-point reduction on the pruritis 11-point numeric rating scale.

The safety database appeared to be adequate to assess risk/benefit in the adult patient population. A total of 2856 subjects with atopic dermatitis were exposed to abrocitinib for any duration in the development program, representing 1614 subject-years of exposure (885 exposed to 100 mg QD and 1971 exposed to 200 mg QD). There were 606 subjects exposed to either dose of abrocitinib for at least 48 weeks. The most frequently reported adverse reactions were nausea, headaches, vomiting, dizziness, herpes simplex, abdominal pain, and increase in blood creatinine phosphokinase. Adverse events of special interest observed during clinical trials included serious infections (opportunistic infections, multidermatomal cutaneous herpes zoster infections, and serious herpetic infections), possible lymphoma and other malignancies, venous thromboembolic events (VTE) including pulmonary embolism (PE) and deep vein thrombosis (DVT), and retinal detachment. Thrombocytopenia and lymphopenia were observed in trial subjects and reached a nadir at Week 4. No clinical adverse events appeared to be related to these lab abnormalities.

In addition to safety data collected in the clinic development program, analysis of recently submitted data from a trial in subjects with rheumatoid arthritis (RA) who received tofacitinib (PMR Study A3921133), another member of the class of JAKis, prompted the Division of Rheumatology and Transplant Medicine (DRTM) to re-evaluate the benefit-risk and indications for tofacitinib and other JAKi for the treatment of inflammatory conditions. The results indicated a dose-dependent increased risk of Major Adverse Cardiac Events (MACE) with the use of tofacitinib compared to TNF blockers. Currently, there is insufficient information to link a specific mechanism of action or target selectivity to an adverse event. In the absence of data to exclude these findings as a class effect, the FDA required the implementation of a safety

labeling change (SLC) to all JAKis, including abrocitinib, to communicate these potential adverse events to prescribers. To further evaluate these risks in patients with atopic dermatitis, a postmarketing requirement is being issued to require the sponsor to conduct a prospective observational study to assess the long-term safety of abrocitinib in U.S. adult patients with moderate-to-severe AD.

In summary, the abrocitinib package insert will include a boxed warning for risk of serious or opportunistic infections, higher all-cause mortality, lymphoma and other malignancies, MACE events, and thrombotic events. The safety and proposed risk management approach for abrocitinib is similar to other agents within the JAK inhibitor class approved for inflammatory conditions. We expect healthcare providers to be appropriately informed about the risks through labeling.

In consideration of the serious risks associated with JAKi including abrocitinib, DDD recommends approval with an indication limited to treatment of AD with abrocitinib in adults with refractory, moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics (e.g., oral or biologic), or when use of those therapies is inadvisable. The 200 mg dose will be limited to patients who have an inadequate response to the 100 mg dose. (b) (4)

15 Office Director Comments

I concur with the recommendation from the Division of Dermatology and Dentistry to approve NDA 213871 for abrocitinib for the treatment of adult patients with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, biologics or when use of those therapies is inadvisable. Abrocitinib, a new molecular entity, is a selective inhibitor of JAK1 signaling and is administered orally.

The efficacy of once daily 100 mg and 200 mg abrocitinib as monotherapy in adults was demonstrated in two placebo-controlled trials; responses to both doses were statistically superior relative to placebo as assessed by the co-primary endpoints of IGA (clear or almost clear on a 5-point scale and at least a 2 point reduction from baseline) and EASI-75 (at least a 75% improvement over baseline). A higher proportion of patients on either abrocitinib dose achieved improvement in pruritis relative to placebo-treated patients (b) (4) A third placebo-controlled trial in adults that included background therapy with topical corticosteroids showed similar findings as the monotherapy trials.

During the course of this NDA review, new safety information became available from a recently completed long-term safety postmarketing trial of tofacitinib, another JAK inhibitor. In this trial, rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor who were treated with tofacitinib were found to have higher rates of all-cause mortality, including sudden cardiovascular death, major adverse cardiovascular events, malignancies, including lymphoma and lung cancer, and thrombosis, relative to patients treated with a TNF blocker. Review of this information resulted in a review clock extension and ultimately a missed PDUFA goal so that the implications of these serious risks on the labeling of the JAK inhibitor product class for inflammatory conditions could be fully considered. A re-evaluation of the benefits vs. risks of abrocitinib was deemed necessary in a more refractory patient population. Subgroup analyses showed that abrocitinib efficacy was maintained in patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, biologics or when use of those therapies is inadvisable. I concur with the review team's recommendation that this be the indicated population for abrocitinib.

Abrocitinib labeling will contain safety warnings that reflect the risks identified in the tofacitinib trial and that were approved for other JAK inhibitors for inflammatory conditions on December 2, 2021. In addition, labeling will describe the risk of serious infections that have occurred in patients receiving other JAK inhibitors. In clinical trials of abrocitinib for atopic dermatitis, the most frequent serious infections were herpes simplex, herpes zoster, and pneumonia. A 4-year prospective observational study will be required to assess potential serious risks associated with use of the product including major adverse cardiovascular events, malignancy, thrombosis, serious infections and retinal detachment.

Additionally, abrocitinib labeling will recommend the lower 100 mg dose as the once daily starting dose, with the option to increase to 200 mg once daily if an adequate response is not achieved with the lower dose after 12 weeks; dosing should be discontinued if an inadequate response is seen after the dosage increase to 200 mg once daily. A dose of 50 mg once daily is recommended for patients with moderate (b) (4) renal impairment, (b) (4) for patients who are CYP2C19 poor metabolizers, and for patients taking dual strong inhibitors of CYP2C19 and moderate inhibitors of CYP2C9, or strong inhibitors of CYP2C19 alone.

16 Appendices

16.1. References

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16.2. Financial Disclosure

Financial Disclosure

Financial certification, using Form FDA 3434, showed none of the financial interest or arrangements described in 21 CFR Part 54 exists, is provided for 2.332 of the 2,353 clinical investigators who participated in the covered studies listed by the applicant. Pfizer has identified 0 clinical investigators who were full-time or part-time employees of the sponsor of the covered studies.

Reviewer's comment: Financial certifications and due diligence for certain investigators were evaluated by this reviewer. No issues were found.

Covered Clinical Study (B7451005, B7451006, B7451012, B7451013, B7451014, B7451015, B7451020, B7451021, B7451029): Nine (9) Covered Clinical Studies

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2,353		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 20		
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: 0 Significant payments of other sorts: 20 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
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) 20		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. Clinical/Biostatistics

Scales Used to Evaluate Efficacy

Table 49: Investigator's Global Assessment (IGA) Scale

Score	Category	Description*
0	Clear	Atopic dermatitis is cleared, except for any residual discoloration (post-inflammatory hyperpigmentation and/or hypopigmentation).
1	Almost Clear	Overall, the atopic dermatitis is not entirely cleared and remaining lesions are light pink (not including post inflammatory hyperpigmentation) and/or; have barely palpable hard thickened skin and/or papules and/or; have barely perceptible lichenification; excoriation and oozing/crusting are absent.
2	Mild	Overall, the atopic dermatitis consists of lesions that are light red; with slight, but definite hard thickened skin and/or papules; with slight, but definite linear or picked scratch marks or penetrating surface injury; with slight, but definite thickened skin, fine skin markings, and lichenoid scale; oozing/crusting is absent.
3	Moderate	Overall, the atopic dermatitis consists of lesions that are red; with easily palpable moderate hard thickened skin and/or papules; with moderate linear or picked scratch marks or penetrating surface injury; with moderate thickened skin, coarse skin markings, and coarse lichenoid scale; with slight oozing/crusting.
4	Severe	Overall, the atopic dermatitis consists of lesions that are deep, dark red; with severe hard thickened skin and/or papules; with severe linear or picked scratch marks or penetrating surface injury; with severe thickened skin with very coarse skin markings and lichenoid scale; with moderate to severe oozing/crusting.

Source: Protocol for Trial B7451012; page 79

* The IGA will exclude scalp, palms, and soles from the assessment/scoring.

Figure 11: Eczema Area and Severity Index (EASI)

The EASI quantifies the severity of a subject's atopic dermatitis based on both severity of lesion clinical signs and the percent of BSA affected. EASI is a composite scoring by the atopic dermatitis clinical evaluator of the degree of erythema, induration/papulation, excoriation, and lichenification (each scored separately) for each of four body regions, with adjustment for the percent of BSA involved for each body region and for the proportion of the body region to the whole body.

Lesion Severity by Clinical Signs: The basic characteristics of atopic dermatitis lesions-erythema, induration/papulation, excoriation, and lichenification-provide a means for assessing the severity of lesions. Assessment of these four main clinical signs is performed separately for four body regions: head and neck, upper limbs, trunk (including axillae and groin) and lower limbs (including buttocks). Average erythema, induration/papulation, excoriation, and lichenification are scored for each body region according to a 4 point scale: 0 = absent; 1 = mild; 2 = moderate; 3 = severe.

Percent BSA with Atopic Dermatitis: The number of handprints of skin afflicted with atopic dermatitis in a body region can be used to determine the extent (%) to which a body region is involved with atopic dermatitis:

Body Region	Total Number of Handprints in Body Region*	Surface Area of Body Region Equivalent of One Handprint*
Head and Neck	10	10%
Upper Limbs	20	5%
Trunk (including axillae and groin/genitals)	30	3.33%
Lower Limbs (including buttocks)	40	2.5%

Handprint refers to the hand size of each individual subject.

* The number of handprints will be for the entire body region; these values will not be adjusted for exclusion of scalp, palms, and soles from the BSA assessment.

The extent (%) to which each of the four body regions is involved with atopic dermatitis is categorized to a numerical Area Score using a non-linear scaling method according to the following BSA scoring criteria:

0 = no involvement
1 = >0 - <10% involvment
2 = 10 - <30% involvement
3 = 30 - <50% involvement
4 = 50 - <70% involvement
5 = 70 - <90% involvement
6 = 90 - <30% involvement

The EASI formula is: EASI = 0.1Ah(Eh+Ih+Exh+Lh) + 0.2Au(Eu+Iu+ExU+Lu) + 0.3At(Et+It+Ext+Lt) + 0.4Al(El+Il+ExI+Ll)

where A = Area Score; E = erythema; I = induration/papulation; Ex = excoriation; L = lichenification; h = head and neck; u = upper limbs; t = trunk; l = lower limbs

Source: Protocol for Trial B7451012; pages 80-82

Sensitivity Analyses for the Co-Primary Efficacy Endpoints

Table 50: Results for the Co-Primary Endpoints at Week 12 - Trials B7451012 and B7451013 (PPAS; NRI[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
Co-Primary Endpoint	**200 mg (N=132)**	**100 mg (N=132)**	**Placebo (N=57)**	**200 mg (N=130)**	**100 mg (N=128)**	**Placebo (N=52)**
IGA 0/1	61 (46%)	34 (26%)	3 (5%)	50 (38%)	39 (30%)	6 (11%)
Difference from placebo	40%	20%	-	27%	19%	-
(95% CI)[2]	(29%, 50%)	(10%, 30%)		(14%, 39%)	(6.8%, 31%)	
P-Value[3]	<0.001	0.0015	-	<0.001	0.0078	-
EASI 75	89 (67%)	59 (45%)	5 (9%)	81 (62%)	63 (49%)	7 (13%)
Difference from placebo	56%	35%	-	49%	36%	-
(95% CI)[2]	(48%, 70%)	(24%, 46%)		(36%, 61%)	(23%, 48%)	
P-Value[3]	<0.001	<0.001	-	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt

[1] Per Protocol Analysis Set (PPAS) as defined in Section 8.1.3; Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Table 51: Results for the Co-Primary Endpoints at Week 12 – Trial B7451029 (PPAS; NRI[1])

	Abrocitinib			
Co -Primary Endpoint	**200 mg (N=161)**	**100 mg (N=174)**	**Dupilumab (N=172)**	**Placebo (N=93)**
IGA 0/1	77 (48%)	68 (39%)	65 (38%)	14 (15%)
Difference from placebo	33%	24%	-	-
(95% CI)[2]	(23%, 43%)	(14%, 34%)		
P-Value[3]	<0.001	<0.001	-	-
EASI 75	115 (71%)	106 (61%)	105 (61%)	26 (28%)
Difference from placebo	44%	33%	-	-
(95% CI)[2]	(33%, 55%)	(22%, 44%)		
P-Value[3]	<0.001	<0.001	-	-

Source: Statistical Reviewer's Analysis (slightly different from Applicant's Analysis); ADAD.xpt, ADEA.xpt

[1] Per Protocol Analysis Set (PPAS) as defined in Section 8.1.3; Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

[3] P-value was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Analyses for PSAAD

Table 52: Absolute Change from Baseline to Week 12 in PSAAD Total Score - Trials B7451012 and B7451013 (FAS[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)
Baseline PSAAD total score						
N[2]	119	111	58	148	143	66
Mean (SD)	5.6 (2.1)	5.1 (2.4)	5.5 (2.0)	5.1 (2.0)	5.4 (2.1)	5.1 (2.1)
Median	5.4	5.2	5.2	5.2	5.4	5.0
Range	0.2 – 9.9	0.4 – 10	1.7 – 10	0.7 – 9.5	0.8 – 9.9	1.7 – 9.4
Change from baseline in PSAAD total score to Week 12						
Applicant's Analysis						
N[3]	119	111	58	148	143	66
LS Mean (repeated measures)[4]	-3.4	-2.3	-1.0	-3.0	-2.5	-0.7
Difference from Placebo (95% CI)[4]	-2.4 (-3.1, -1.7)	-1.3 (-2.1, -0.6)	-	-2.3 (-2.9, -1.6)	-1.8 (-2.4, -1.2)	-
P-Value[4]	<0.001	0.001	-	<0.001	<0.001	-
Reviewer's Analysis						
N[5]	119	111	58	148	143	66
Mean	-3.3	-2.2	-0.9	-2.9	-2.5	-0.6
LS Mean[6]	-3.1	-2.3	-0.9	-2.8	-2.2	-0.5
Difference from Placebo (95% CI)[6]	-2.3 (-2.9, -1.7)	-1.4 (-2.1, -0.8)	-	-2.3 (-2.9, -1.8)	-1.7 (-2.3, -1.2)	-
P-Value[6]	<0.001	<0.001	-	<0.001	<0.001	-

Source: Statistical Reviewer's Analysis; ADPU.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed.
[2] Subjects with baseline PSSD total score
[3] Subjects with baseline PSSD total score; missing data were omitted (i.e., observed data)
[4] Least square (LS) means, difference (95% CI) and p-value are based on Mixed Model Repeated Measure (MMRM) with fixed factors of treatment, week, treatment by week interaction and randomization strata, baseline value as a covariate and an unstructured covariance matrix.
[5] Subjects with baseline PSSD total score; missing data was imputed using the last observation carried forward (LOCF).
[6] Least square (LS) means, difference (95% CI) and p-value are based on ANCOVA with factors of treatment group and randomization stratum, and baseline value as a covariate.
Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 53: Proportion of Subjects with PSAAD Total Score of 0 at Week 12 – Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	Trial B7451012			Trial B7451013			Trial B7451029			
	Abrocitinib			Abrocitinib			Abrocitinib			
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	200 mg (N=158)	Placebo (N=78)	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
N[1]	119	111	58	148	143	66	217	213	227	123
n (%)	4 (3%)	1 (1%)	0 (0%)	9 (6%)	4 (3%)	0 (0%)	8 (4%)	1 (<1%)	4 (2%)	0 (0%)

Source: Statistical Reviewer's Analysis; ADPU.xpt
[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number of subjects with a baseline PSAAD total score > 0. Missing data are imputed using the non-responder imputation (NRI) method.
Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 54: Missing PSAAD Itching Item Data from Baseline through Week 12 – Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	B7451012			B7451013			B7451029			
	Abrocitinib			Abrocitinib			Abrocitinib			
Visit	200 mg (N=156)	100 mg (N=154)	Placebo (N=77)	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
Baseline	37 (24%)	46 (29%)	19 (25%)	7 (4%)	15 (9%)	12 (15%)	9 (4%)	25 (10%)	15 (6%)	8 (6%)
Week 2	20 (13%)	18 (11%)	14 (18%)	10 (6%)	8 (5%)	8 (10%)	14 (6%)	26 (11%)	16 (7%)	9 (7%)
Week 4	20 (13%)	26 (17%)	12 (16%)	8 (5%)	10 (6%)	11 (14%)	11 (5%)	23 (10%)	19 (8%)	7 (5%)
Week 8	28 (18%)	33 (21%)	21 (27%)	19 (12%)	25 (16%)	26 (33%)	19 (8%)	33 (14%)	29 (12%)	17 (13%)
Week 12	38 (25%)	45 (29%)	25 (32%)	33 (21%)	32 (20%)	32 (41%)	27 (12%)	41 (17%)	36 (15%)	22 (17%)

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed

Note: Missing data include also missing weekly data due to having less than 4 daily observations in the week.

Table 55: Responder Analysis for PSAAD Itching Item at Week 12 – Trials B7451012, B7451013 and B7451029 (FAS; NRI[1])

	Trial B7451012			Trial B7451013						
	Abrocitinib			Abrocitinib			Abrocitinib			
PSAAD Itching	200 mg (N=112)	100 mg (N=99)	Placebo (N=56)	200 mg (N=140)	200 mg (N=135)	Placebo (N=62)	200 mg (N=211)	100 mg (N=200)	Dupilumab (N=218)	Placebo (N=111)
Week 2										
≥4-point reduction[2]	36 (32%)	11 (11%)	1 (1%)	34 (24%)	19 (14%)	2 (3%)	69 (33%)	31 (15%)	24 (11%)	9 (8%)
Difference from Placebo[3]	30%	10%	-	21%	11%	-	24%	7%	-	-
Difference from Dupilumab[3]	-	-	-	-	-	-	21%	4%	-	-
Week 4										
≥4-point reduction[2]	58 (52%)	23 (23%)	3 (5%)	65 (46%)	34 (25%)	3 (5%)	104 (49%)	64 (32%)	66 (30%)	17 (15%)
Difference from Placebo[3]	46%	18%	-	42%	20%	-	34%	17%	-	-
Week 12										
≥4-point reduction[2]	52 (46%)	27 (27%)	5 (9%)	63 (45%)	49 (36%)	7 (11%)	116 (55%)	73 (36%)	101 (46%)	24 (22%)
Difference from Placebo[3]	38%	19%	-	34%	25%	-	33%	15%	-	-

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline among subjects with baseline score of ≥4

[3] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category.

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 56: Responder Analysis for PSAAD Items 2-10 at Week 12 – Trials B7451012 and B7451013 (FAS; NRI[1])

	Trial B7451012			Trial B7451013		
	Abrocitinib			Abrocitinib		
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=155)	200 mg (N=158)	Placebo (N=78)
How Painful						
N[1]	90	78	50	104	109	44
≥4-point reduction	52%	37%	12%	41%	35%	9%
Difference from Placebo[2]	40%	26%		32%	24%	-
How Dry						
N[1]	104	90	54	128	124	51
≥4-point reduction	46%	24%	13%	46%	41%	6%
Difference from Placebo[2]	34%	12%	-	40%	35%	-
How Flaky						
N[1]	84	74	53	114	110	46
≥4-point reduction	50%	31%	11%	48%	44%	9%
Difference from Placebo[2]	40%	20%	-	49%	34%	-
How Cracked						
N[1]	79	60	40	92	90	39
≥4-point reduction	53%	30%	12%	46%	42%	3%
Difference from Placebo[2]	40%	18%	-	43%	39%	-
How Bumpy						
N[1]	89	71	42	95	103	44
≥4-point reduction	49%	22%	17%	39%	31%	5%
Difference from Placebo[2]	38%	7%	-	35%	26%	-
How Red						
N[1]	101	80	47	113	115	49
≥4-point reduction	44%	17%	11%	41%	36%	4%
Difference from Placebo[2]	34%	7%	-	37%	31%	-
How Discolored						
N[1]	81	67	43	100	98	42
≥4-point reduction	51%	25%	16%	32%	33%	2%
Difference from Placebo[2]	38%	8%	-	30%	29%	-
How much Bleed						
N[1]	65	52	31	72	77	25
≥4-point reduction	54%	36%	16%	39%	40%	0%
Difference from Placebo[2]	41%	21%	-	40%	38%	-
How much Seep/Ooze						
N[1]	58	48	27	63	73	25
≥4-point reduction	48%	35%	26%	40%	40%	4%
Difference from Placebo[2]	23%	10%	-	37%	34%	-
How Swollen						
N[1]	77	60	36	87	92	36
≥4-point reduction	57%	30%	17%	36%	33%	6%
Difference from Placebo[2]	44%	14%	-	30%	26%	-

Source: Statistical Reviewer's Analysis; ADPU.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Table 57: Responder Analysis for PSAAD Items at Week 12 – Trial B7451029 (FAS; NRI[1])

	Abrocitinib			
	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
How Painful				
N[1]	169	151	170	81
≥4-point reduction	64%	44%	53%	25%
Difference from Placebo[2]	39%	20%	-	-
How Dry				
N[1]	196	183	197	101
≥4-point reduction	53%	38%	44%	15%
Difference from Placebo[2]	38%	23%	-	-
How Flaky				
N[1]	173	161	172	87
≥4-point reduction	57%	39%	45%	17%
Difference from Placebo[2]	39%	22%	-	-
How Cracked				
N[1]	153	132	149	76
≥4-point reduction	50%	33%	46%	22%
Difference from Placebo[2]	26%%	11%	-	-
How Bumpy				
N[1]	158	146	159	82
≥4-point reduction	51%	36%	43%	22%
Difference from Placebo[2]	29%	14%	-	-
How Red				
N[1]	182	174	195	94
≥4-point reduction	55%	32%	39%	15%
Difference from Placebo[2]	37%	17%	-	-
How Discolored				
N[1]	158	154	152	84
≥4-point reduction	48%	37%	10%	11%
Difference from Placebo[2]	37%	26%	-	-
How much Bleed				
N[1]	107	87	104	51
≥4-point reduction	60%	45%	61%	20%
Difference from Placebo[2]	39%	25%	-	-
How much Seep/Ooze				
N[1]	107	92	101	54
≥4-point reduction	62%	43%	69%	37%
Difference from Placebo[2]	23%	7%	-	-
How Swollen				
N[1]	147	133	146	76
≥4-point reduction	58%	38%	49%	17%
Difference from Placebo[2]	39%	20%	-	-

Source: Statistical Reviewer's Analysis

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Note: Weekly scores were average values of daily observations over 7 days for this analysis; weekly scores were set to missing if less than 4 daily observations in the week.

Results for Adults Only (Monotherapy Trials)

Table 58: Results for the Co-Primary Endpoints at Week 12 in Adult Subjects - Trial B7451012 (FAS; NRI[1])

	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
Co-Primary Endpoint	**200 mg (N=154)**	**100 mg (N=156)**	**Placebo (N=77)**	**200 mg (N=121)**	**100 mg (N=122)**	**Placebo (N=60)**
IGA 0/1	67 (43%)	37 (24%)	6 (8%)	58 (48%)	28 (23%)	4 (7%)
Difference from placebo (95% CI)[2]	36% (26%, 45%)	16% (7%, 25%)		41% (30%, 52%)	16% (6%, 26%)	-
EASI 75	96 (62%)	62 (40%)	9 (12%)	78 (64%)	47 (38%)	7 (12%)
Difference from placebo (95% CI)[2]	51% (40%, 61%)	28% (18%, 39%)	-	53% (41%, 64%)	27% (15%, 39%)	-

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

Table 59: Results for the Co-Primary Endpoints at Week 12 in Adult Subjects – Trial B7451013 (FAS; NRI[1])

	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
Co-Primary Endpoint	**200 mg (N=155)**	**100 mg (N=158)**	**Placebo (N=78)**	**200 mg (N=140)**	**100 mg (N=141)**	**Placebo (N=70)**
IGA 0/1	59 (38%)	44 (28%)	7 (9%)	53 (38%)	42 (30%)	7 (10%)
Difference from placebo (95% CI)[2]	29% (19%, 39%)	19% (9%, 28%)	-	28% (17%, 38%)	20% (9%, 30%)	-
EASI 75	94 (61%)	69 (44%)	8 (10%)	85 (61%)	62 (44%)	8 (11%)
Difference from placebo (95% CI)[2]	50% (40%, 61%)	33% (23%, 44%)	-	49% (38%, 60%)	32% (21%, 44%)	-

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

Table 60: Results for the Key Secondary Efficacy Endpoints in Adult Subjects – Trial B7451012 (FAS; NRI[1])

	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
PP-NRS4[2]	**200 mg (N=147)**	**100 mg (N=147)**	**Placebo (N=74)**	**200 mg (N=118)**	**100 mg (N=116)**	**Placebo (N=58)**
Week 2	67 (46%)	30 (20%)	2 (3%)	61 (52%)	23 (20%)	1 (2%)
Difference from placebo (95% CI)[3]	42% (34%, 51%)	18% (10%, 26%)	-	50% (40%, 60%)	18% (10%, 27%)	-
Week 4	48 (33%)	29 (20%)	10 (13%)	42 (36%)	22 (19%)	10 (17%)
Difference from placebo (95% CI)[1]	19% (8%, 30%)	6% (-4%, 16%)	-	18% (5%, 31%)	2% (-10%, 14%)	-
Week 12	68 (46%)	41 (28%)	10 (13%)	57 (48%)	32 (28%)	9 (15%)
Difference from placebo (95% CI)[1]	33% (21%, 44%)	14% (4%, 25%)	-	33% (20%, 46%)	12% (-<1%, 25%)	-

Source: Statistical Reviewer's Analysis

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in Numeric Rating Scale (NRS) for severity of pruritus among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

Table 61: Results for the Key Secondary Efficacy Endpoints in Adult Subjects – Trial B7451013 (FAS; NRI[1])

	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
PP-NRS4[2]	**200 mg (N=153)**	**100 mg (N=156)**	**Placebo (N=76)**	**200 mg (N=138)**	**100 mg (N=139)**	**Placebo (N=68)**
Week 2	54 (35%)	36 (23%)	3 (4%)	49 (35%)	34 (24%)	3 (4%)
Difference from placebo (95% CI)[3]	31% (22%, 40%)	19% (11%, 27%)	-	31% (22%, 40%)	20% (11%, 29%)	-
Week 4	77 (50%)	49 (31%)	3 (4%)	39 (50%)	46 (33%)	3 (4%)
Difference from placebo (95% CI)[3]	46% (37%, 56%)	27% (19%, 36%)	-	46% (36%, 55%)	29% (19%, 38%)	-
Week 12	75 (49%)	62 (40%)	8 (10%)	64 (46%)	59 (42%)	7 (10%)
Difference from placebo (95% CI)[3]	39% (28%, 49%)	29% (19%, 40%)	-	36% (25%, 47%)	32% (21%, 43%)	-

Source: Statistical Reviewer's Analysis

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

[2] Proportion of subjects achieving ≥4 points improvement from baseline in Numeric Rating Scale (NRS) for severity of pruritus among subjects with baseline score of ≥4

[3] The estimate and confidence interval (CI) for the difference were calculated based on the weighted average of difference for each randomization stratum using the normal approximation of binomial proportions.

Table 62: Responder Analysis for PSAAD Itching Item at Week 12 in Adult Subjects – Trial B7451012 (FAS; NRI[1])

	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
PSAAD Itch	**200 mg (N=112)**	**100 mg (N=99)**	**Placebo (N=56)**	**200 mg (N=93)**	**100 mg (N=79)**	**Placebo (N=47)**
Week 2						
≥4-point reduction	36 (32%)	1 (1%)	1 (2%)	1 (2%)	9 (11%)	2 (4%)
Difference from Placebo[2]	30%	-	-	-	10%	-
Week 4						
≥4-point reduction	58 (52%)	3 (5%)	3 (6%)	3 (6%)	20 (25%)	3 (6%)
Difference from Placebo[2]	46%	-	-	-	19%	-
Week 12						
≥4-point reduction	52 (46%)	5 (9%)	5 (11%)	5 (11%)	23 (29%)	7 (13%)
Difference from Placebo[2]	38%	-	-	-	19%	-

Source: Statistical Reviewer's Analysis; ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Table 63: Responder Analysis for PSAAD Itching Item at Week 12 in Adult Subjects – Trial B7451013 (FAS; NRI[1])

PSAAD Itch	Overall			Adults Only		
	Abrocitinib			Abrocitinib		
	200 mg (N=140)	200 mg (N=135)	Placebo (N=62)	200 mg (N=127)	200 mg (N=122)	Placebo (N=54)
Week 2						
≥4-point reduction	34 (24%)	19 (14%)	2 (3%)	29 (23%)	18 (15%)	2 (4%)
Difference from Placebo[2]	21%	11%	-	19%	11%	-
Week 4						
≥4-point reduction	65 (46%)	34 (25%)	3 (5%)	59 (46%)	32 (26%)	3 (6%)
Difference from Placebo[2]	42%	20%	-	41%	21%	-
Week 12						
≥4-point reduction	63 (45%)	49 (36%)	7 (11%)	56 (44%)	45 (37%)	7 (13%)
Difference from Placebo[2]	34%	25%	-	31%	24%	-

Source: Statistical Reviewer's Analysis; ADNR.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed. N is the number with a baseline score ≥4. Missing data are imputed using the non-responder imputation (NRI) method

[2] The estimate for the difference was calculated using the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline disease severity and age category).

Findings in Special/Subgroup Populations

Table 64: IGA 0/1 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451012 (FAS; NRI[1])

	Abrocitinib				
Subgroups (n[ABR200], n[ABR100], n[P])	**200 mg (N=154)**	**100 mg (N=156)**	**Placebo (N=77)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)					
<18 (33, 34, 17)	27%	26%	12%	15% (-6%, 37%)	15% (-7%, 36%)
18-64 (110, 118, 59)	46%	20%	7%	40% (29%, 51%)	14% (4%, 23%)
≥65 (11, 4, 1)	64%	100%	0%	64% (35%, 92%)	-
Sex					
Male (81, 90, 49)	36%	20%	12%	24% (10%, 37%)	8% (-5%, 20%)
Female (73, 66, 28)	52%	33%	0%	52% (41%, 63%)	29% (18%, 40%)
Race					
White (104, 113, 62)	45%	17%	10%	35% (23%, 48%)	7% (-3%, 17%)
Non-White (50, 43, 15)	40%	42%	0%	40% (26%, 54%)	42% (27%, 57%)
Weight					
<70 Kg (62, 56, 32)	37%	14%	9%	27% (12%, 43%)	5%(-9%, 18%)
70 – 100 Kg (77, 79, 33)	45%	29%	3%	42% (30%, 55%)	26% (14%, 38%)
>100 Kg (15, 21, 12)	30%	29%	17%	43% (11%, 76%)	12% (-17%, 40%)
Baseline IGA					
Moderate (91, 92, 46)	53%	26%	11%	42% (28%, 56%)	15% (2%, 28%)
Severe (63, 64, 31)	30%	20%	3%	27% (14%, 40%)	17% (5%, 29%)
Overall	**43%**	**24%**	**8%**	**36% (26%, 46%)**	**16% (7%, 25%)**

Source: Reviewer's Analysis (same as Applicant's analysis); ADAD.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

Table 65: EASI-75 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451012 (FAS; NRI[1])

	Abrocitinib				
Subgroups (n[ABR200], n[ABR100], n[P])	**200 mg (N=154)**	**100 mg (N=156)**	**Placebo (N=77)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)					
<18 (33, 34, 17)	54%	44%	12%	43% (20%, 66%)	32% (10%, 55%)
18-64 (110, 118, 59)	64%	36%	12%	52% (40%, 64%)	25% (13%, 37%)
≥65 (11, 4, 1)	73%	100%	0%	73% (46%, 99%)	-
Sex					
Male (81, 90, 49)	57%	33%	41%	42% (28%, 57%)	19% (5%, 33%)
Female (73, 66, 28)	68%	48%	7%	61% (47%, 76%)	41% (26%, 57%)
Race					
White (104, 113, 62)	63%	33%	13%	51% (38%, 63%)	20% (8%, 32%)
Non-White (50, 43, 15)	60%	58%	7%	53% (35%, 72%)	51% (32%, 71%)
Weight					
<70 Kg (62, 56, 32)	56%	30%	9%	47% (31%, 63%)	21% (5%, 37%)
70 – 100 Kg (77, 79, 33)	65%	43%	9%	56% (41%, 70%)	34% (19%, 49%)
>100 Kg (15, 21, 12)	73%	52%	25%	48% (15%, 81%)	27% (-5%, 60%)
Baseline IGA					
Moderate (91, 92, 46)	65%	47%	11%	54% (41%, 67%)	36% (22%, 49%)
Severe (63, 64, 31)	58%	30%	13%	46% (29%, 63%)	17% (<1%, 33%)
Overall	**62%**	**40%**	**12%**	**51% (40%, 61%)**	**28% (17%, 39%)**

Source: Reviewer's Analysis (same as applicant's analysis); ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; missing data imputed using non-responder imputation (NRI)

Table 66: IGA 0/1 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451013 (FAS; NRI[1])

Subgroups (n[ABR200], n[ABR100], n[P])	Abrocitinib 200 mg (N=155)	Abrocitinib 100 mg (N=158)	Placebo (N=78)	200 mg – Placebo (95% CI)	100 mg – Placebo (95% CI)
Age (years)					
<18 (15, 17, 8)	40%	12%	0%	40% (15%, 65%)	12% (-3%, 27%)
18-64 (133, 130, 69)	38%	29%	10%	27% (17%, 38%)	18% (8%, 29%)
≥65 (11, 7, 1)	43%	48%	0%	43% (6%, 79%)	45% (16%, 75%)
Sex					
Male (88, 94, 47)	28%	29%	8%	20% (7%, 32%)	20% (8%, 32%)
Female (67, 64, 31)	51%	27%	10%	41% (25%, 57%)	17% (2%, 32%)
Race					
White (91, 101, 40)	38%	30%	10%	28% (15%, 42%)	20% (7%, 33%)
Non-White (64, 57, 38)	37%	25%	8%	30% (15%, 44%)	17% (3%, 31%)
Weight					
<70 Kg (69, 68, 38)	38%	26%	10%	27% (12%, 42%)	16% (2%, 30%)
70 – 100 Kg (76, 76, 36)	41%	32%	6%	35% (22%, 49%)	26% (13%, 39%)
>100 Kg (10, 14, 4)	20%	14%	25%	-<1% (-5%, 4%)	-11% (-57%, 35%)
Baseline IGA					
Moderate (106, 107, 52)	42%	30%	11%	31% (18%, 44%)	18% (6%, 31%)
Severe (49, 51, 26)	29%	23%	4%	25% (10%, 39%)	20% (6%, 33%)
Overall	**38%**	**28%**	**9%**	**30% (19%, 39%)**	**19% (9%, 28%)**

Source: Reviewer's Analysis (same as applicant's analysis); ADAD.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; missing data imputed using non-responder imputation (NRI)

Table 67: EASI-75 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451013 (FAS; NRI[1])

Subgroups (n[ABR200], n[ABR100], n[P])	Abrocitinib 200 mg (N=155)	Abrocitinib 100 mg (N=158)	Placebo (N=78)	200 mg – Placebo (95% CI)	100 mg – Placebo (95% CI)
Age (years)					
<18 (15, 17, 8)	60%	41%	0%	60% (35%, 85%)	41% (18%, 66%)
18-64 (133, 130, 69)	59%	42%	12%	48% (36%, 59%)	31% (19%, 42%)
≥65 (11, 7, 1)	86%	64%	0%	86% (60%, 100%)	64% (35%, 92%)
Sex					
Male (88, 94, 47)	51%	46%	11%	40% (27%, 54%)	35% (22%, 48%)
Female (67, 64, 31)	73%	41%	10%	63% (49%, 78%)	31% (15%, 47%)
Race					
White (91, 101, 40)	60%	45%	10%	50% (37%, 64%)	35% (22%, 49%)
Non-White (64, 57, 38)	61%	40%	10%	50% (35%, 66%)	30% (14%, 46%)
Weight					
<70 Kg (69, 68, 38)	61%	44%	13%	48% (32%, 63%)	31% (15%, 47%)
70 – 100 Kg (76, 76, 36)	63%	45%	6%	58% 944%, 71%)	39% (26%, 53%)
>100 Kg (10, 14, 4)	40%	36%	25%	15% (-37%, 67%)	11% (-39%, 60%)
Baseline IGA					
Moderate (106, 107, 52)	65%	47%	11%	54% (41%, 66%)	35% (22%, 48%)
Severe (49, 51, 26)	51%	37%	8%	43% (26%, 61%)	30% (13%, 46%)
Overall	**61%**	**44%**	**10%**	**50% (40%, 61%)**	**33% (23%, 44%)**

Source: Reviewer's Analysis (same as applicant's analysis); ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data are imputed using the non-responder imputation (NRI) method

Table 68: IGA 0/1 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451029 (FAS; NRI[1])

	Abrocitinib					
Subgroups (n[ABR200], n[ABR100], n[DUP], n[P])	**200 mg (N=226)**	**100 mg (N=238)**	**Dupilumab (N=242)**	**Placebo (N=131)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)						
18-64 (211, 224, 227, 21)	48%	36%	37%	15%	33% (24%, 42%)	21% (12%, 30%)
≥65 (15, 14, 15, 10)	33%	43%	20%	0%	33% (9%, 57%)	43% (17%, 69%)
Sex						
Male (104, 120, 108, 77)	46%	32%	32%	10%	36% (24%, 47%)	21% (10%, 32%)
Female (122. 118. 134. 54)	47%	41%	39%	18%	29% (15%, 43%)	22% (8%, 36%)
Race						
White (161, 182, 176, 87)	47%	37%	40%	17%	29% (18%, 40%)	20% (9%, 31%)
Non-White (68, 56, 66, 44)	48%	32%	35%	7%	41% (27%, 55%)	25% (11%, 40%)
Weight						
<70 Kg (98, 94, 99, 48)	49%	36%	39%	15%	34% (20%, 48%)	22% (8%, 35%)
70 – 100 Kg (109, 126, 116, 70)	47%	36%	34%	14%	32% (20%, 45%)	22% (10%, 34%)
>100 Kg (19, 18, 27, 13)	37%	33%	33%	8%	29% (3%, 55%)	26% (<0%, 52%)
Baseline IGA						
Moderate (138, 153, 162, 88)	46%	43%	42%	19%	27% (15%, 39%)	23% (12%, 34%)
Severe (88, 85, 80, 43)	48%	25%	25%	2%	45% (34%, 57%)	22% (12%, 33%)
Overall	**47%**	**36%**	**36%**	**14%**	**33% (42%)**	**22% (14%, 31%)**

Source: Reviewer's Analysis (same as applicant's analysis); ADAD.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

Table 69: EASI-75 Response at Week 12 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy for AD – Trial B7451029 (FAS; NRI[1])

	Abrocitinib					
Subgroups (n[ABR200], n[ABR100], n[DUP], n[P])	**200 mg (N=226)**	**100 mg (N=238)**	**Dupilumab (N=242)**	**Placebo (N=131)**	**200 mg – Placebo (95% CI)**	**100 mg – Placebo (95% CI)**
Age (years)						
18-64 (211, 224, 227, 21)	69%	57%	58%	26%	43% (33%, 53%)	31% (30%, 41%)
≥65 (15, 14, 15, 10)	53%	71%	53%	30%	23% (-15%, 61%)	41% (4%, 78%)
Sex						
Male (104, 120, 108, 77)	65%	56%	56%	22%	43% (30%, 56%)	34% (21%, 47%)
Female (122. 118. 134. 54)	70%	60%	59%	33%	37% (22%, 52%)	27% (11%, 42%)
Race						
White (161, 182, 176, 87)	66%	57%	57%	34%	32% (20%, 44%)	23% (10%, 35%)
Non-White (68, 56, 66, 44)	72%	61%	61%	11%	61% (47%, 75%)	49% (33%, 65%)
Weight						
<70 Kg (98, 94, 99, 48)	68%	55%	63%	29%	39% (23%, 55%)	26% (10%, 42%)
70 – 100 Kg (109, 126, 116, 70)	68%	59%	57%	27%	41% (27%, 54%)	32% (19%, 46%)
>100 Kg (19, 18, 27, 13)	68%	61%	44%	15%	53% (24%, 82%)	46% (16%, 76%)
Baseline IGA						
Moderate (138, 153, 162, 88)	63%	60%	59%	34%	29% (16%, 42%)	26% (13%, 39%)
Severe (88, 85, 80, 43)	76%	54%	55%	12%	64% (51%, 78%)	42% (28%, 57%)
Overall	**68%**	**58%**	**58%**	**27%**	**41% (32%, 51%)**	**31% (21%, 41%)**

Source: Reviewer's Analysis (same as applicant's analysis); ADEA.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing

Table 70: IGA 0/1 and EASI-75 Response at Week 12 by Country – Trial B7451012 (FAS; NRI[1])

Country (n[ABR200], n[ABR100], n[P])	IGA 0/1			EASI-75		
	Abrocitinib			Abrocitinib		
	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)	200 mg (N=154)	100 mg (N=156)	Placebo (N=77)
United States (41, 51, 22)	51%	27%	9%	68%	47%	14%
Canada (27, 23, 14)	52%	26%	7%	67%	43%	7%
Germany (26, 27, 11)	42%	15%	0%	45%	48%	33%
Australia (22, 23, 6)	32%	39%	17%	65%	30%	0%
Poland (24, 13, 12)	42%	0%	8%	58%	23%	17%
Czech Republic (6, 6, 7)	17%	17%	0%	50%	17%	0%
Great Britain (5, 7, 2)	40%	43%	0%	100%	57%	50%
Hungary (3, 6, 3)	33%	0%	33%	33%	17%	0%
Overall	43%	24%	8%	62%	40%	12%

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADAE.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

Table 71: IGA 0/1 and EASI-75 Response at Week 12 by Country – Trial B7451013 (FAS; NRI[1])

Country (n[ABR200], n[ABR100], n[P])	IGA 0/1			EASI-75		
	Abrocitinib			Abrocitinib		
	200 mg (N=155)	100 mg (N=158)	Placebo (N=78)	200 mg (N=154)	100 mg (N=156)	Placebo (N=78)
United States (25, 21, 2)	44%	29%	0%	64%	48%	0%
Poland (24, 17, 11)	46%	41%	0%	63%	53%	0%
Japan (22, 15, 7)	9%	13%	14%	45%	27%	0%
Germany (12, 16, 11)	42%	13%	18%	75%	19%	9%
Korea (14, 13, 8)	21%	23%	0%	50%	38%	0%
Australia (7, 21, 4)	43%	29%	25%	43%	43%	25%
China (10, 10, 4)	90%	40%	25%	100%	50%	50%
Canada (4, 9, 10)	100%	22%	0%	100%	67%	10%
Great Britain (10, 9, 4)	10%	33%	0%	3%	44%	0%
Bulgaria (12, 8, 2)	42%	38%	100%	58%	38%	100%
Czech Republic (8, 4, 2)	50%	25%	0%	75%	50%	0%
Hungary (5, 7, 1)	20%	29%	0%	40%	57%	0%
Latvia (2, 8, 2)	0%	38%	0%	100%	63%	50%
Overall	38%	28%	9%	61%	44%	10%

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADAE.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

Table 72: IGA 0/1 and EASI 75 Response Rates at Week 12 by Country – Trial B7451029 (FAS; NRI[1])

Country (n[ABR200], n[ABR100], n [Dup], n[P])	IGA 0/1				EASI-75			
	Abrocitinib				Abrocitinib			
	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)	200 mg (N=226)	100 mg (N=238)	Dupilumab (N=242)	Placebo (N=131)
Poland (47, 57, 50, 28)	51%	35%	40%	11%	79%	53%	66%	36%
United States (47, 47, 52, 26)	21%	32%	23%	15%	45%	49%	42%	31%
Japan (25, 19, 21, 11)	48%	42%	48%	18%	68%	63%	67%	27%
Great Britain (118, 20, 20, 9)	61%	35%	35%	0%	83%	70%	60%	22%
Germany (13, 17, 15, 10)	62%	35%	60%	30%	77%	65%	60%	50%
Czech Republic (15, 14, 16, 10)	73%	50%	38%	10%	87%	57%	50%	10%
Australia (9, 9, 11, 9)	44%	56%	9%	0%	56%	89%	36%	11%
Canada (9, 9, 10, 8)	44%	22%	50%	0%	78%	56%	90%	0%
Korea (11, 9, 8, 5)	45%	33%	13%	0%	82%	78%	38%	0%
Chile (8, 9, 8, 5)	63%	78%	75%	60%	75%	78%	100%	60%
Bulgaria (5, 5, 4, 2)	20%	0%	0%	0%	40%	40%	25%	0%
Taiwan (5, 6, 4, 1)	60%	17%	25%	0%	80%	50%	75%	0%
Hungary (2, 3, 7, 3)	50%	0%	71%	33%	50%	33%	71%	33%
Slovakia (4, 2, 7, 2)	25%	0%	29%	0%	25%	50%	29%	0%
Mexico (3, 5, 3, 2)	67%	40%	67%	50%	67%	40%	100%	50%
Latvia (2, 4, 3, 0)	100%	25%	0%	0%	100%	50%	67%	0%
Spain (1, 2, 3, 0)	100%	50%	33%	0%	100%	50%	67%	0%
Italy (2, 1, 0, 0)	50%	100%	0%	0%	50%	100%	0%	0%
Overall	47%	36%	36%	14%	68%	58%	58%	27%

Source: Statistical Reviewer's Analysis; ADAD.xpt, ADAE.xpt

[1] Full Analysis Set (FAS) defined as all randomized subjects who were dosed; Missing data imputed using non-responder imputation (NRI)

16.4. Nonclinical Pharmacology/Toxicology

16.4.1. Calculations for multiples of exposures

At the maximum recommended human dose (200 mg QD) in adult subjects, the unbound steady state AUC_{inf} and C_{max} were 1550 ng·hr/mL and 434 ng/mL, respectively (trial #B7451001). The following table summarizes the multiples of exposure based on AUC comparisons between the MRHD and AUC values from nonclinical studies referenced in the label.

Study	Dose (mg/kg /day)	Dose Note[a]	AUC (ng·hr/mL)		Multiples of exposure[c]
			Total	Unbound[b]	
Rat embryofetal development	30	NOAEL (development)	58300	22300	14
	60	LOAEL (development)	90000	34500	22
Rabbit embryofetal development	75	NOAEL	43000	8210	5
Rat prenatal and postnatal development[d]	10	NOAEL (F_0)	12900	4940	3
	30	LOAEL (F_0) / NOAEL (F_1 development)	58300	22300	14
	60	LOAEL (F_1)	90000	34500	22
Rat juvenile animal study	5	LOAEL	4270	1640	1.1
	25	MD	38600	14800	10
	75	HD	147000	56300	36
Rat Carcinogenicity	3	NOAEL (female)	3150	1210	0.8
	10	LOAEL (female)	15200	5820	4
	30	NOAEL (male)	76000	29100	19
Rat fertility and early embryonic development	70	Male NOAEL	142000[e]	54400	35
	70	LOAEL (female fertility)	157000[f]	60100	39
	45	LOAEL (development)	91200[g]	34900	23
Rat female fertility with recovery	10	NOAEL	11000	4210	3
	70	LOAEL	157000	60100	39

[a]LOAEL (lowest-observed-adverse-effect-level), NOAEL (no-observed-adverse-effect-level), MD (mid dose), HD (high dose)

[b]Calculated by multiplying rat AUC and rabbit AUC by 0.383 and 0.191, respectively
[c]Calculated by dividing the nonclinical AUC_{free} by the AUC_{free} at the MRHD (1550 ng·hr/mL)
[d]Using AUC values from the rat EFD study
[e]Using the Day 182 AUC_{24} for the 70 mg/kg/day dose level in the 6-month rat repeat dose toxicity study, which had a similar C_{max} (12700 ng/mL) to this study
[f]Using the AUC_{24} for the 70 mg/kg/day dose level in the female rat fertility study with recovery
[g]Using the Day 182 combined sex AUC_{24} for the 45 mg/kg/day dose level in the 6-month rat repeat dose toxicity study, which had the same C_{max} (12100 ng/mL) as this study

16.4.2. Nonclinical labeling

Recommended changes to nonclinical information in sections 8.1, 12.1, and 13.1 of the applicant's proposed labeling are provided below. (b) (4) Reviewer-recommended deletions and additions are indicated by ~~struck through~~ and <u>underlined</u> text, respectively.

(b) (4)

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

The revised nonclinical sections are presented as clean-copy text below:

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE
CIBINQO is a Janus kinase (JAK) inhibitor indicated for …

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available data from pregnancies reported in clinical trials with CIBINQO are not sufficient to establish a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of abrocitinib to pregnant rats and rabbits during organogenesis at exposure 14 or 5 times the maximum recommended human dose (MRHD) based on AUC comparison, respectively, resulted in maternal dystocia and skeletal variations in rats and no adverse effects in rabbits *(see Data)*.

Data
Animal Data
In an embryofetal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, or 60 mg/kg/day during the period of organogenesis. No fetal malformations were observed. Abrocitinib increased the incidence of skeletal variations of short 13th ribs at 30 mg/kg/day (14 times the MRHD based on AUC comparison). Increased embryofetal lethality and additional skeletal variations (cervical arches with reduced ventral processes, thickened ribs, and unossified metatarsals) were noted at 60 mg/kg/day (22 times the MRHD based on AUC comparison).

In an embryofetal development study, abrocitinib was administered orally to pregnant rabbits at doses of 10, 30, or 75 mg/kg/day during the period of organogenesis. No abrocitinib-related maternal or developmental toxicity was noted at doses up to 75 mg/kg/day (5 times the MRHD based on AUC comparison).

In a prenatal and postnatal development study, abrocitinib was administered orally to pregnant rats at doses of 10, 30, and 60 mg/kg/day beginning on gestation day 6 and continuing through lactation day 20. Dystocia with prolonged parturition and reduced offspring body weights were noted at 30 mg/kg/day (14 times the MRHD based on AUC comparison). Postnatal survival was markedly decreased at 60 mg/kg/day (22 times the MRHD based on AUC comparison). No

maternal toxicity was observed at 10 mg/kg/day (3 times the MRHD based on AUC comparison). No abrocitinib-related effects on postnatal developmental, neurobehavioral, or reproductive performance of offspring was noted at doses up to 30 mg/kg/day (14 times the MRHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of abrocitinib in human milk, the effects on the breast-fed infant, or the effects on milk production. Abrocitinib was secreted in milk of lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, malignancy, and thrombosis, advise women not to breastfeed during treatment with CIBINQO and for one day after the last dose (approximately 5-6 elimination half-lives).

Data

Animal Data

Lactating female rats were orally administered a single dose of 10 mg/kg abrocitinib on lactation day 12. Abrocitinib AUC was approximately 5 times greater in milk than in plasma.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the findings in rats, oral administration of CIBINQO may impair female fertility. Impaired fertility in female rats was reversible 1 month after cessation of abrocitinib oral administration *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Juvenile Animal Toxicity Data

In a juvenile animal toxicity study, abrocitinib was administered orally to juvenile rats at doses of 5, 25, and 75 mg/kg/day beginning on postnatal day 10 (approximately equivalent to a human infant) and continuing through postnatal day 63 (approximately equivalent to an adolescent). Abrocitinib caused a reversible, dose-related decrease in the primary spongiosa in the metaphysis of the proximal tibia and distal femur. Abrocitinib produced adverse effects on bone development at all dose levels. Abrocitinib caused irreversible dose-related small or misshapen femoral heads at doses ≥5 mg/kg/day (1.1 times the MRHD based on AUC comparison). Abrocitinib also irreversibly decreased femur size and caused paw malrotation and limb impairment at doses ≥25 mg/kg/day (10 times the MRHD based on AUC comparison). At 75 mg/kg/day (36 times the MRHD based on AUC comparison), paw fractures generally corresponded to limb impairment, a fractured tibia was noted in a single female, and effects noted at lower doses were increased in frequency and severity. Irreversible bone findings have not been observed in older animals.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
CIBINQO is a Janus kinase (JAK) inhibitor.

Abrocitinib reversibly inhibits JAK1 by blocking the adenosine triphosphate (ATP) binding site. In a cell-free isolated enzyme assay, abrocitinib was selective for JAK1 over JAK2 (28-fold), JAK3 (>340-fold), and tyrosine kinase (TYK) 2 (43-fold), as well as the broader kinome. The relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known. Both the parent compound and the active metabolites inhibit JAK1 activity in vitro with similar levels of selectivity.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 2-year oral carcinogenicity study in rats, abrocitinib increased the incidence of benign thymomas in female rats at doses of 10 and 30 mg/kg/day (4 and 19 times the MRHD, respectively, based on AUC comparison). Abrocitinib was not carcinogenic in female rats at 3 mg/kg/day (0.8 times the MRHD based on AUC comparison) or male rats at doses up to 30 mg/kg/day (19 times the MRHD based on AUC comparison). Abrocitinib was not carcinogenic in Tg.rasH2 mice at oral doses up to 60 mg/kg/day in males and 75 mg/kg/day in females.

Abrocitinib was not mutagenic in the bacterial mutagenicity assay (Ames assay). Although abrocitinib was aneugenic in the in vitro TK6 micronucleus assay, abrocitinib was not aneugenic or clastogenic in an in vivo rat bone marrow micronucleus assay.

Abrocitinib did not impair male fertility at doses up to 70 mg/kg/day (35 times the MRHD based on AUC comparison) or female fertility at 10 mg/kg/day (3 times the MRHD based on AUC comparison). Abrocitinib impaired female fertility (reducing fertility index, corpora lutea, and implantation sites) at 70 mg/kg/day (39 times the MRHD based on AUC comparison). Impaired fertility in female rats reversed 1 month after cessation of abrocitinib administration.

16.4.3. Review of Carcinogenicity Studies Conducted with Abrocitinib

Study Title: 104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with PF-04965842 in Rats

APPEARS THIS WAY ON ORIGINAL

Study no.:	17MA056
Study report location:	SDN 1
Study initiation date:	October 9, 2017
Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Drug, lot #, and % purity:	Abrocitinib (PF-04965842), lot #GR11722, 99.0% purity
Prior Exec CAC Dose Concurrence:	Yes
Basis for Dose Selection:	Maximum tolerated dose based on immunosuppression, skin sores and/or scabs, and abnormal urinary crystals in the 6-month oral repeat dose toxicity study in rats

Reviewer Carcinogenicity Conclusion: Positive
ECAC Carcinogenicity Conclusion: Positive

Tumor Findings:
Abrocitinib increased the incidence of benign thymomas in females at 10 and 30 mg/kg/day. No abrocitinib-related tumors were observed in females given 3 mg/kg/day or in males.

Methods

Doses:	0, 3, 10, and 30 mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	60 (plus 5/sex/group for toxicokinetic assessment)
Dose volume:	10 mL/kg
Formulation/Vehicle:	(b) (4) in water
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR HAN
Age:	6 to 7 weeks at dosing initiation
Comment on Study Design and Conduct:	No noteworthy deviations.
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments were made. No groups were terminated early. An advice letter was sent to the sponsor on September 10, 2019 conveying early termination criteria for this study, including the recommendation to terminate all groups of a sex if a control group of that sex reaches 20 animals.

Dosing Solution Analysis: Samples from Weeks 1, 12, 26, 36, 48, 60, 72, 84, 96, and 104 were analyzed. Dosing solutions were homogenous and within 15% of nominal concentrations. The current formulation was previously determined to be stable at room temperature for up to 18 days. Abrocitinib was not detected in control formulations.

Key Study Findings

- Abrocitinib significantly increased the incidence of benign thymoma of the thymus in female rats at the MD and HD, without a dose relationship.
- Abrocitinib increased the incidence of thymic mass or large thymus in MD and HD females, corresponding to the tumor findings.
- Abrocitinib increased mortality and decreased body weight in HD males, but not at lower doses or in females.
- Abrocitinib increased the incidence of skin scabs and/or scabs in MD and HD males and of skin sores in HD females.

Observations and Results

Mortality

Animals were checked twice daily for health/mortality. Per the statistical reviewer, abrocitinib significantly increased mortality compared to vehicle controls in HD males; abrocitinib did not significant increase mortality in females.

Clinical Signs

Beginning on Day 1 of dosing, cageside observations were conducted once daily. A detailed physical examination, including mass observations on each grossly visible or palpable mass, was conducted once weekly. Abrocitinib markedly increased the incidence of malocclusion and discolored (white) teeth at the HD; no microscopic correlates were noted to explain tooth discoloration. Skin scabs were of higher incidence in HD males (but not females) and skin sores were of higher incidence at the HD in both sexes. No other abrocitinib-related findings were noted.

Body Weights

Body weights were recorded once weekly during Weeks 1 to 26 (excluding Week 15), then once every 4 weeks thereafter and during Week 105. Abrocitinib decreased body weight in HD males, beginning during Week 66 and continuing through the end of the study. No other abrocitinib-related effects were noted.

Feed Consumption

Food consumption per cage was recorded once weekly during Weeks 1 to 13, then once every 4 weeks thereafter and during Week 104. Consumption was calculated as g/animal/day. No abrocitinib-related effects were noted.

Gross Pathology

Necropsies were performed after Week 104, following an overnight fast. Abrocitinib increased the incidence of large thymus or thymic mass in MD and HD females, generally corresponding to microscopic findings of benign thymomas.

Histopathology

Peer Review Conducted: Yes, by an independent pathologist
Historical Control Provided for Tumor Incidence: Yes

Neoplastic

No abrocitinib-related tumor findings were noted in male rats. Although the trend for benign thymoma in female rats did not meet the statistical criteria for common tumors (p<0.005), there was a clear, statistically significant increase in the incidence of thymomas in MD and HD females that exceeded historical controls. Consequently, this finding was considered abrocitinib-related and is summarized in the following table.

Sex	Organ Name	Tumor Name	0 mg/kg/day *p*: Trend	3 mg/kg/day *p*: Vehicle vs. LD	10 mg/kg/day *p*: Vehicle vs. MD	30 mg/kg/day *p*: Vehicle vs. HD
Female	Thymus	Thymoma	2/57 (43) 0.0148	10/56 (45) 0.0163	20/60 (53) <0.001	15/57 (47) <0.001
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed						

Non Neoplastic

No non-neoplastic abrocitinib-related microscopic findings were noted. All microscopic findings lacked a dose relationship and/or were of similar incidence and severity to controls.

Toxicokinetics

Blood samples were collected via cardiac puncture from TK animals on Day 178 at 1, 4, 7, and 24 hours post-dose; a sample was not collected from controls at 24 hours post-dose. Exposure did not differ markedly between sexes and increased approximately dose-proportionally for C_{max}, but more than dose-proportionally for AUC_{24}. Abrocitinib was not detected in samples collected from controls. Combined female and male toxicokinetic parameters for abrocitinib are summarized in the following table.

Abrocitinib toxicokinetic parameters in rats on Day 178 in a 2-year carcinogenicity study

Dose (mg/kg/day)	**3**	**10**	**30**
AUC_{24} (ng·hr/mL)	3150 ± 1050	15200 ± 3010	76000 ± 20000
AUC_{24}/Dose [(ng·hr/mL) / (mg/kg/day)]	1050 ± 350	1520 ± 301	2530 ± 666

C_{max} (ng/mL)	930 ± 250	3530 ± 644	10700 ± 2080
t_{max} (hr)	1.0	1.0	1.0

Study Title: 6-Month Oral Gavage Carcinogenicity Study of PF-04965842 in rasH2 (tg/wt) Mice

Study no.: 18GR243
Study report location: SDN 1
Study initiation date: January 9, 2019
Conducting laboratory and location: (b) (4)
GLP compliance: Yes
Drug, lot #, and % purity: Abrocitinib (PF-04965842), lot #GR10502, 97.8% purity

Prior Exec CAC Dose Concurrence: Yes
Basis for Dose Selection: Maximum tolerated dose based on body weight gain decrements or loss and treatment-related effects in kidney (chronic obstructive nephropathy) in 1-month oral repeat dose toxicity studies in mice

Reviewer Carcinogenicity Conclusion: Negative
ECAC Carcinogenicity Conclusion: Negative

Tumor Findings:
No abrocitinib-related tumors were observed in either sex.

APPEARS THIS WAY ON ORIGINAL

Methods

Doses:	Females: 0, 10, 25, or 75 mg/kg/day Males: 0, 10, 20, or 60 mg/kg/day
Frequency of dosing:	Once daily
Number/Sex/Group:	25 (plus 15/sex positive control group given a single 75 mg/kg intraperitoneal dose of N-methyl-N-nitrosourea on Day 1; plus 12/sex vehicle controls and 15/sex abrocitinib-treated groups for toxicokinetic assessment)
Dose volume:	10 mL/kg
Formulation/Vehicle:	(b) (4) in water
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CB6F1-TgN (RasH2)
Age:	8 to 9 weeks at dosing initiation
Comment on Study Design and Conduct:	No noteworthy deviations.
Dosing Comments (Dose Adjustments or Early Termination):	No dose adjustments were made. No groups were terminated early. On March 14, 2019, the sponsor requested to reduce the HD female dose from 75 mg/kg/day to 50 mg/kg/day based on decreased body weight gain. An advice letter was sent to the sponsor on March 27, 2019 rejecting the proposal to reduce the HD female dose because the decrease in body weight gain was transient and the four HD females affected had recovered by Day 43.
Dosing Solution Analysis:	Samples from Weeks 1, 6, 12, 18, and 26 were analyzed. The MD dosing solution from Week 12, and backup samples, were out of specifications (79% of theoretical concentration). All other samples of dosing solutions (or backups) were homogenous and within 15% of nominal concentrations. The current formulation was previously determined to be stable at room temperature for up to 18 days. Abrocitinib was not detected in control formulations.

Key Study Findings

- No abrocitinib-related tumors were noted in either sex.
- Abrocitinib increased mortality in HD females, but not at lower doses or in males. No abrocitinib-related clinical observations or adverse body weight effects were noted.

- Abrocitinib-related microscopic findings were limited to the thymus (decreased lymphoid cellularity and epithelial hyperplasia in MD and HD females) and kidney (obstructive nephropathy and pelvic dilatation at the HD).

Observations and Results

Mortality

Animals were checked twice daily for health/mortality. Per the statistical reviewer, mortality was significantly higher in positive control groups and in HD females; no significant effects were noted on mortality in males or in LD or MD females.

Clinical Signs

Beginning on Day 1 of dosing, cageside observations were conducted once daily. A detailed physical examination, including mass observations on each grossly visible or palpable mass, was conducted once weekly. No abrocitinib-related effects were noted.

Body Weights

Body weights were recorded once prior to dosing initiation, once weekly during dosing, and on Day 182. No adverse abrocitinib-related effects were noted.

Feed Consumption

Food consumption per cage was recorded once weekly beginning on Day 1 and calculated as g/animal/day. No abrocitinib-related effects were noted.

Gross Pathology

Necropsies were performed on Day 183 and following unscheduled euthanasia or death. Abrocitinib-related macroscopic kidney findings were noted in 20 HD females and 14 HD males; findings generally correlated with microscopic kidney findings, noted below. No other abrocitinib-related effects were noted.

Histopathology

Peer Review Conducted: Yes, by a Pfizer pathologist
Historical Control Provided for Tumor Incidence: Yes

Neoplastic

No abrocitinib-related neoplastic findings were noted. Positive controls displayed significantly increased incidence of malignant lymphoma (12 females; 13 males); squamous cell papilloma in the skin/subcutis (2 females; 8 males); and squamous cell papilloma (5 females; 7 males) and squamous cell carcinoma in nonglandular stomach (2 females; 4 males).

Non Neoplastic

Abrocitinib non-neoplastic microscopic findings were limited to the kidney and thymus. Minimal to severe obstructive nephropathy and mild to marked pelvic dilatation was noted in both sexes and limited to the HD, except for a single LD male with mild pelvis dilatation. Decreased lymphoid cellularity in the thymus was noted at the MD and HD in both sexes, with a

higher incidence in females. Epithelial hyperplasia was increased in MD and HD females without dose relationship and was attributed to a combination of aging, sex, and the pharmacology of abrocitinib; this appears reasonable.

Toxicokinetics
Blood samples were collected via cardiac puncture from TK animals on Day 29 at 0.5, 1, 2, 7, and 24 hours post-dose; a sample was not collected from controls at 24 hours post-dose. Abrocitinib was not detected in samples collected from controls. Female and male toxicokinetic parameters for abrocitinib are summarized in the following table.

Abrocitinib toxicokinetic parameters in mice on Day 29 in a 6-month carcinogenicity study

	Female			Male		
Dose (mg/kg/day)	**10**	**25**	**75**	**10**	**20**	**60**
AUC_{24} (ng·hr/mL)	91	274	3200	111	244	1350
AUC_{24}/Dose [(ng·hr/mL) / (mg/kg/day)]	9	11	43	11	12	23
C_{max} (ng/mL)	60	262	1290	96	284	980
t_{max} (hr)	0.5	0.5	0.5	0.5	0.5	0.5

16.5. OCP Appendices

16.5.1. Clinical Pharmacology Studies

The abrocitinib atopic dermatitis (AD) clinical development program included 20 clinical trials and 4 population modeling analysis in support of the proposed indication.

All studies were conducted using the formulation used in Phase 3 trials except three studies: B7451001, B7451004 and B7451008. The sponsor made some changes in the to-be-marketed (TBM) formulation compared to the formulation used in the Phase 3 trials. The Applicant demonstrated the comparability between the TBM formulation and the formulation used in Phase 3 trials in the Study B7451032. The Applicant has not demonstrated the comparability between the TBM formulation and the formulations used in Studies B7451001, B7451004 and

B7451008. Since the labeling information relying on the results from aforementioned three studies are not formulation specific (e.g., PK linearity and ADME properties), there is no need to bridge the TBM formulation to the formulation used in Studies B7451001, B7451004 and B7451008.

In the assessment of pharmacological activity, not only abrocitinib but its two major metabolites (M1 and M2) were considered since all of them exhibited Janus kinase (JAK) inhibitory activity against the signaling of multiple cytokines implicated in the pathogenesis of AD and maintained selectivity for JAK1 signaling. Therefore, a total activity index was being utilized in human to understand the contribution of both parent and active metabolites to activity. In drug-drug interaction trials and dedicated organ impairment trials, the unbound plasma PK metrics (i.e., $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) for abrocitinib and active metabolites were calculated for each participant as the sum of the respective unbound PK metrics for abrocitinib, M1, and M2, adjusted for relative potencies of the metabolites using following equation.

$$AUC_{24,u}AM = AUC_{24,u}P + AUC_{24,u}M1 \bullet \left(\frac{IC_{50,u}P}{IC_{50,u}M1}\right) + AUC_{24,u}M2 \bullet \left(\frac{IC_{50,u}P}{IC_{50,u}M2}\right)$$

where $AUC_{24,u}$AM is the combined unbound exposure of abrocitinib and its two active metabolites at steady state; $AUC_{24,u}$P, $AUC_{24,u}$M1, and $AUC_{24,u}$M2 are the steady state unbound exposures of abrocitinib, M1, and M2, respectively; $IC_{50,u}$P / $IC_{50,u}$M1 and $IC_{50,u}$P / $IC_{50,u}$M2 are the relative potencies of abrocitinib to metabolite M1 and M2 respectively.

Unbound potencies for interferon alpha (IFNα) (i.e., $IC_{50,u}$P, $IC_{50,u}$M1, and $IC_{50,u}$M2) were adjusted by their respective free fraction in plasma and the blood to plasma concentration ratio values. IFNα was chosen as a representative cytokine that incorporated in JAK1 signaling. The relative inhibition potencies of abrocitinib, M1, and M2 for different cytokines are similar to IFNα. Therefore, other cytokines could have equally been used to calculate the total pharmacological activity from parent drug and its two active metabolites; however, IFNα is considered to be the most sensitive. For details, refer to the Applicant's response to IR #2 received 1/14/2021.

For the safety evaluation, abrocitinib exposure was the main consideration because the exposure-response relationship for safety was established using the exposure of parent drug in Phase 3 trials. Hence, sensitivity analysis was conducted using the exposure of the parent only for the organ impairment and DDI studies, in addition to using the combined unbound concentrations of the parent and active metabolites. According to the population PK/PD analysis, the platelet counts on day 29 was negatively correlated with the steady-state plasma concentration (C_{ss}) of parent drug.

Following is an overview of the clinical program:

- Fifteen Phase 1 trials in healthy subjects
  PK/PD/Bioavailability
  - Study B7451001: A single ascending dose and multiple ascending dose pharmacokinetic (PK) study in healthy Japanese and Western subjects

- Study B7451004: Pilot relative bioavailability and food effect study
- Study B7451008: Mass-balance study
- Study B7451032: Pivotal food effect and bioequivalence study

Effect of intrinsic factors

- Study B7451020: Dedicated hepatic impairment study
- Study B7451021: Dedicated renal impairment study

Effect of extrinsic factors (abrocitinib as a victim):

- Study B7451017: Drug-drug interaction (DDI) with fluvoxamine (a strong CYP2C19 and moderate CYP3A inhibitor) or fluconazole (a strong cYP 2C19 and a moderate CYP2C9 and CYP 3A inhibitor)
- Study B7451019: DDI with rifampin (a strong CYP inducer)
- Study B7451043: DDI with probenecid (an OAT3 inhibitor)

Effect of extrinsic factors (abrocitinib as a perpeturator)

- Study B7451016: DDI with oral contraceptives
- Study B7451022: DDI with midazolam (CYP3A4/5 substrate)
- Study B7451026: DDI with dabigatran (P-gp substrate)
- Study B7451033: DDI with rosuvastatin (BCRP and OAT3 substrate)
- Study B7451034: DDI with metformin (MATE1/2K substrate)

Cardiovascular safety

- Study B7451027: A repeat-dose QT/QTc study

- Two Phase 2 trials:
  - Study B7451005: Efficacy and safety trial in patients with moderate to severe psoriasis – This study will not be discussed in this section because it is conducted in patients with psoriasis. We defer the safety findings in Study B7451005 to Clinical and Biostatistical Sections.
  - Study B7451006: Dose ranging study in patients with moderate to severe AD
- Three Phase 3 efficacy and safety trials in patients with moderate to severe AD: Population modeling analysis includes efficacy and safety data from Phase 3 trials. For other details, defer to Clinical and Biostatistical Sections
  - Study B7451012: in AD patients older than 12 years
  - Study B7451013: in AD patients older than 12 years
  - Study B7451029: in adult AD patients

16.5.1.1 Study B7451001: A Single- and Multiple-Ascending Dose Study in Healthy Subjects

A total of 79 subjects (70 Western and 9 Japanese subjects) were randomized and received study treatments. Plasma and urine samples were collected and analyzed for abrocitinib concentrations using a validated, sensitive and specific liquid chromatography tandem mass spectrometric method (LC-MS/MS).

Reviewer comments: The applicant has used the term "Western" to indicate non-Asian subjects.

Single Ascending Dose (SAD)

In the SAD period of the study, Western subjects received single doses of 3, 10, 30, 100, 200, 400 or 800 mg of abrocitinib or placebo in a dose escalation format (Cohort 1-7). Japanese subjects received a single dose of 800 mg abrocitinib or placebo (Cohort 8).

Plasma abrocitinib C_{max} appeared to increase proportionally across dose range 3 mg to 800 mg, while increases in area under the concentration-time profile from time zero to infinity (AUC_{inf}) were greater than proportional at doses of 400 and 800 mg. Table 73 summarizes the abrocitinib PK parameter following single oral doses in the Study B7451001.

Table 73. Summary of Plasma Abrocitinib PK Parameters Following Single Oral Doses in the Study B7451001.

	Parameter Summary Statistics[a] for PF-04965842 by Cohort and Dose						
Parameter, units	**3 mg Cohort 1 N=6**	**10 mg Cohort 2 N=6**	**30 mg Cohort 3 N=6**	**100 mg Cohort 4 N=7**	**200 mg Cohort 5 N=6**	**400 mg Cohort 6 N=6**	**800 mg Cohorts 7+8 N=16**
n^1, n^2	6, 5	6, 5	6, 6	7, 5	6, 6	6, 6	15, 14
AUC_{last}, ng•hr/mL	36.84 (84)	135.1 (40)	386.6 (44)	1226 (60)	2878 (29)	10150 (28)	22090 (49)
AUC_{inf}, ng•hr/mL	48.83 (64)	142.8 (44)	392.3 (43)	1465 (41)	2886 (29)	10180 (28)	23740 (40)
C_{max}, ng/mL	17.05 (27)	46.97 (21)	142.5 (50)	459.7 (53)	1072 (35)	2291 (42)	3712 (41)
T_{max}, hr	0.634 (0.517-1.27)	0.750 (0.500-1.00)	0.792 (0.500-1.08)	0.550 (0.500-1.03)	0.767 (0.500-1.17)	1.50 (0.517-4.03)	3.92 (1.00-4.30)
$t_{½}$, hr	2.086 ±0.868	1.938 ±0.545	2.530 ±1.321	3.588 ±2.077	3.888 ±2.197	3.552 ±1.114	4.884 ±2.056
CL/F, L/hr	61.44 (65)	70.02 (44)	76.41 (43)	68.34 (41)	69.31 (29)	39.32 (28)	33.69 (41)
V_z/F, L	172.5 (26)	190.1 (18)	256.2 (63)	318.5 (66)	343.0 (46)	193.3 (39)	220.7 (66)

Source: Table 14.4.3.1.1.1
Parameters are defined in Table 6.
Data for Subject 10011055 in Cohort 7 (800 mg) were excluded due to vomiting.
Abbreviations: %CV = percent coefficient of variation; N = number of subjects in the treatment group; n^1 = number of subjects contributing to the mean; n^2 = number of subjects where $t_{½}$, AUC_{inf}, CL/F and V_z/F were determined; SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean±SD for $t_{½}$.
Source: Study Report B7451001, Table 17

While C_{max} was similar in Western and Japanese subjects, geometric mean AUC_{inf} was 26% higher in Western subjects than that observed in Japanese subjects at the same 800 mg dose (Cohort 7,

Table 74).

Table 74. Summary of Plasma Abrocitinib PK Parameters in Western and Japanese Subjects Following a Single 800 mg Oral Dose in Study B7451001

	Parameter Summary Statistics[a] by Cohort	
	Western Subjects Cohort 7	Japanese Subjects Cohort 8
Parameter, units	N=6	N=10
n^1, n^2	5, 5	10, 9
AUC_{last}, ng.hr/mL	27480 (35)	19810 (53)
AUC_{inf}, ng.hr/mL	27540 (35)	21860 (43)
C_{max}, ng/mL	3819 (26)	3660 (48)
T_{max}, hr	4.03 (2.00-4.30)	2.02 (1.00-4.00)
$t_{½}$, hr	5.266 ±2.917	4.672 ±1.573
CL/F, L/hr	29.00(35)	36.61 (43)
V_z/F, L	197.1 (77)	235.0 (64)

Source: Table 14.4.3.1.1.2
Parameters are defined in Table 6.
Data for Subject 10011055 in Cohort 7 (800 mg) were excluded due to vomiting.
Abbreviations: %CV = percent coefficient of variation; N = number of subjects in the treatment group; n^1 = number of subjects contributing to the mean; n^2 = number of subjects where $t_{½}$, AUC_{inf}, CL/F and V_z/F were determined; SD = standard deviation.
a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean±SD for $t_{½}$.
Source: Study Report B7451001, Table 18

Multiple Ascending Dose (MAD)

In the MAD period, the Western subjects received doses of 30, 100 or 200 mg once daily (QD) and 100 or 200 mg twice daily (BID) for 10 consecutive days. An additional cohort of Western subjects (Cohort 9) received 400 mg abrocitinib or placebo QD for 10 days. Steady state had been reached by Day 4 for QD dosing. Plasma abrocitinib accumulation with multiple dosing ranged from 1.3 to 1.5 for QD dosing. Urinary recovery of abrocitinib was low, with <4% of the dose recovered unchanged in urine across all doses and regimens in all cohorts. PK parameters are summarized in Table 75 for each dose level.

Table 75. Summary of Plasma Abrocitinib PK Parameters Following Multiple Oral Doses in the Study B7451001.

	Parameter Summary Statistics[a] for PF-04965842 by Cohort and Dose					
Parameter, units	30 mg QD Cohort 3 N=6	100 mg QD Cohort 4 N=5	200 mg QD Cohort 5 N=6	100 mg BID Cohort 6 N=6	200 mg BID Cohorts 7+8 N=14	400 mg QD Cohort 9 N=8
n^1, n^2	5, 5	5, 5	6, 6	6, 6	11, 11	6, 6
AUC_{tau}, ng•hr/mL	500.3 (38)	1977 (47)	4277 (34)	3107 (31)	10720 (36)	18230 (24)
C_{max}, ng/mL	161.3 (50)	700.0 (31)	1199 (23)	773.0 (36)	2467 (22)	3334 (17)
T_{max}, hr	0.550 (0.500-1.03)	0.550 (0.500-2.02)	1.05 (1.02-1.05)	0.759 (0.500-1.02)	0.500 (0.500-1.07)	0.767 (0.500-2.05)
C_{av}, ng/mL	20.85 (38)	82.36 (47)	178.1 (34)	259.0 (31)	893.1 (36)	758.3 (24)
C_{min}, ng/mL	NP[b]	NP[b]	2.506 (86)	40.05 (62)	175.6 (89)	30.36 (159)
PTF	NP[b]	NP[b]	6.712 (15)	2.816 (15)	2.512 (34)	4.322 (34)
$t_{½}$, hr	2.758 ±1.112	2.994 ±0.761	3.060 ±0.239	5.027±2.343	4.336 ±1.418	4.845 ±1.856
CL/F, L/hr	59.93 (38)	50.56 (47)	46.76 (34)	32.16 (31)	18.65 (36)	21.99 (24)
V_z/F, L	223.0 (43)	212.9 (43)	206.0 (29)	212.3 (65)	111.6 (35)	145.4 (34)
Ae_{tau}, mg	0.3088 (75)	1.167 (99)	2.845 (48)	NC[c]	6.599 (47)	10.54 (37)
Ae_{tau}%	1.030 (74)	1.167 (99)	1.420 (49)	NC[c]	3.298 (47)	2.635 (37)
CLr, L/hr	0.6177 (33)	0.5900 (41)	0.6651 (20)	NC[c]	0.6153 (27)	0.5793 (23)

Source: Table 14.4.3.1.2.1 and Table 14.4.3.1.3.1
Data for Subject 10011070 (400 mg QD, Cohort 9) were excluded due to vomiting.
Parameters are defined in Table 6.
Abbreviations: %CV = percent coefficient of variation; BID = twice daily; N = number of subjects in the treatment group (start of multiple dosing on Day 1); n^1 = number of subjects contributing to the mean (completed multiple dosing through Day 10); n^2 = number of subjects where $t_{½}$ and V_z/F were determined; NC = not calculated; NP = not presented; PTF = peak-trough fluctuation; SD = standard deviation.

a. Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean±SD for $t_{½}$.
b. NP: Summary statistics are not presented where the data include 0 values for C_{min} (geometric mean for C_{min} was biased, and PTF could not be determined for subjects where C_{min}=0).
c. NC: Protocol deviation in urine collection for Cohort 6.

Source: Study Report B7451001, Table 19;
Cohort 7 (200 mg abrocitinib in Western subjects, n=5) and Cohort 8 (200 mg abrocitinib in Japanese subjects, n=9) were combined for presentation.

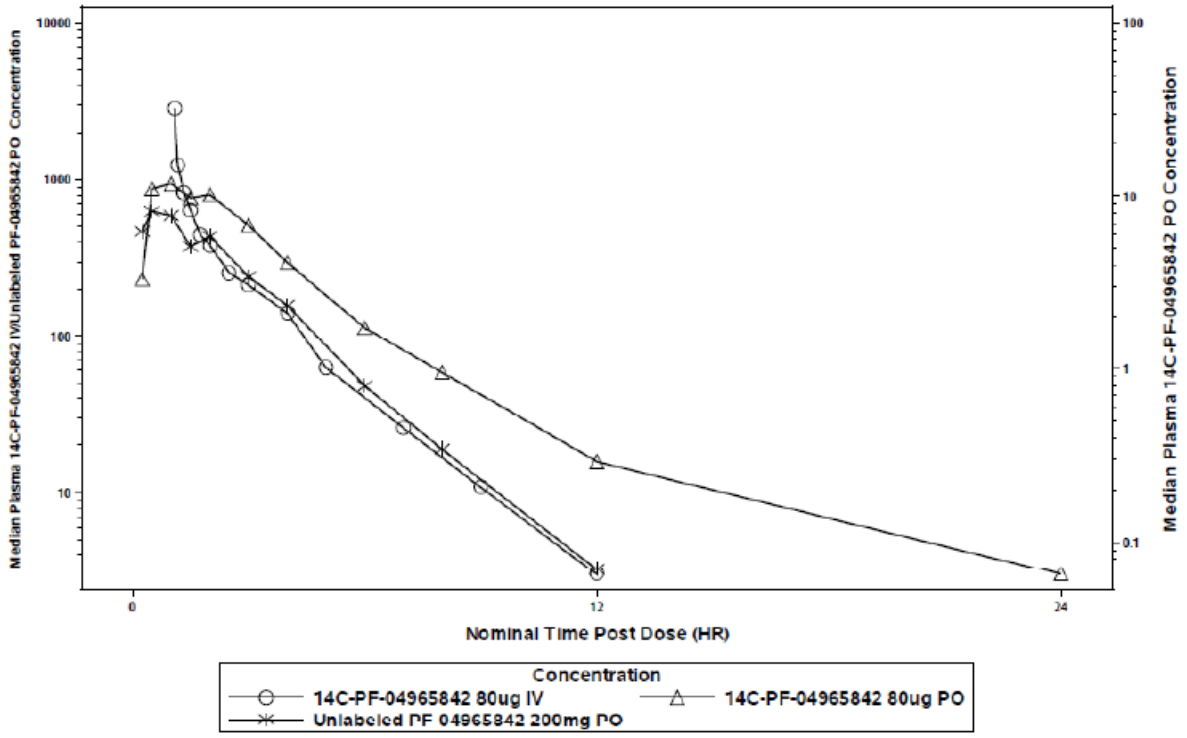
16.5.1.2 Study B7451008: Mass Balance Study to Characterize the Absorption, Distribution, Metabolism and Elimination of Abrocitinib

Following oral administration of a single unlabeled abrocitinib 200 mg, and oral (PO) and intravenous (IV) infusion of radiolabeled ^{14}C-abrocitinib 80 µg to 6 healthy male subjects, the median plasma concentration-time profiles are presented in Figure 12.

The total recovery of orally administered radioactive (80 µg [500 nCi] ^{14}C-abrocitinib) dose over a period of 240 hours postdose was 94.5%, with 85.0% in the urine and 9.5% in the feces. The total recovery of the IV administered radioactive (80 µg [500 nCi] ^{14}C- abrocitinib) dose in urine over a period of 144 hours postdose was 93.8%. Abrocitinib was absorbed rapidly following oral administration with a median time to reach maximum plasma concentration (T_{max}) of 0.5 hour (ranges 0.5 to 2 hours). Absolute bioavailability (F) was estimated 60% (Table 76). Fraction absorbed was 0.9129 (Table 77).

The species of parent drug and metabolites were assessed in pooled urine and feces samples. Abrocitinib was the major component of circulating profiled plasma radioactivity, while oxidative metabolites M1 and M2 (both are sulfonamide propanes), M4 (pyrrolo-pyrimidine core), and M6 (sulfonamide propane and pyrrolo-pyrimidine core) were predominant in pooled urine. Figure 13 presents the proposed biotransformation pathways of abrocitinib in human plasma and excreta.

Figure 12. Median Plasma Concentration-Time Following Administration of Unlabeled Abrocitinib 200 mg per oral (PO) + ^{14}C-Abrocitinib 80 µg PO (Period A) and Unlabeled Abrocitinib 200 mg PO + ^{14}C-Abrocitinib 80 µg intravenous (IV) (Period B)



Source: Study Report B7451008, Figure 3

Table 76. Statistical Analysis for Absolute Oral Bioavailability (F)

Parameter, units	Adjusted (Least-Squares) Geometric Means		F: Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Unlabeled PF-04965842 (200 mg PO) (Test)	^{14}C-PF-04965842 (80 µg IV) (Reference)		
AUC_{last}(dn), ng•hr/mL/mg	9.247	15.48	59.75	(45.82, 77.90)
AUC_{inf}(dn), ng•hr/mL/mg	9.297	15.55	59.77	(45.94, 77.78)

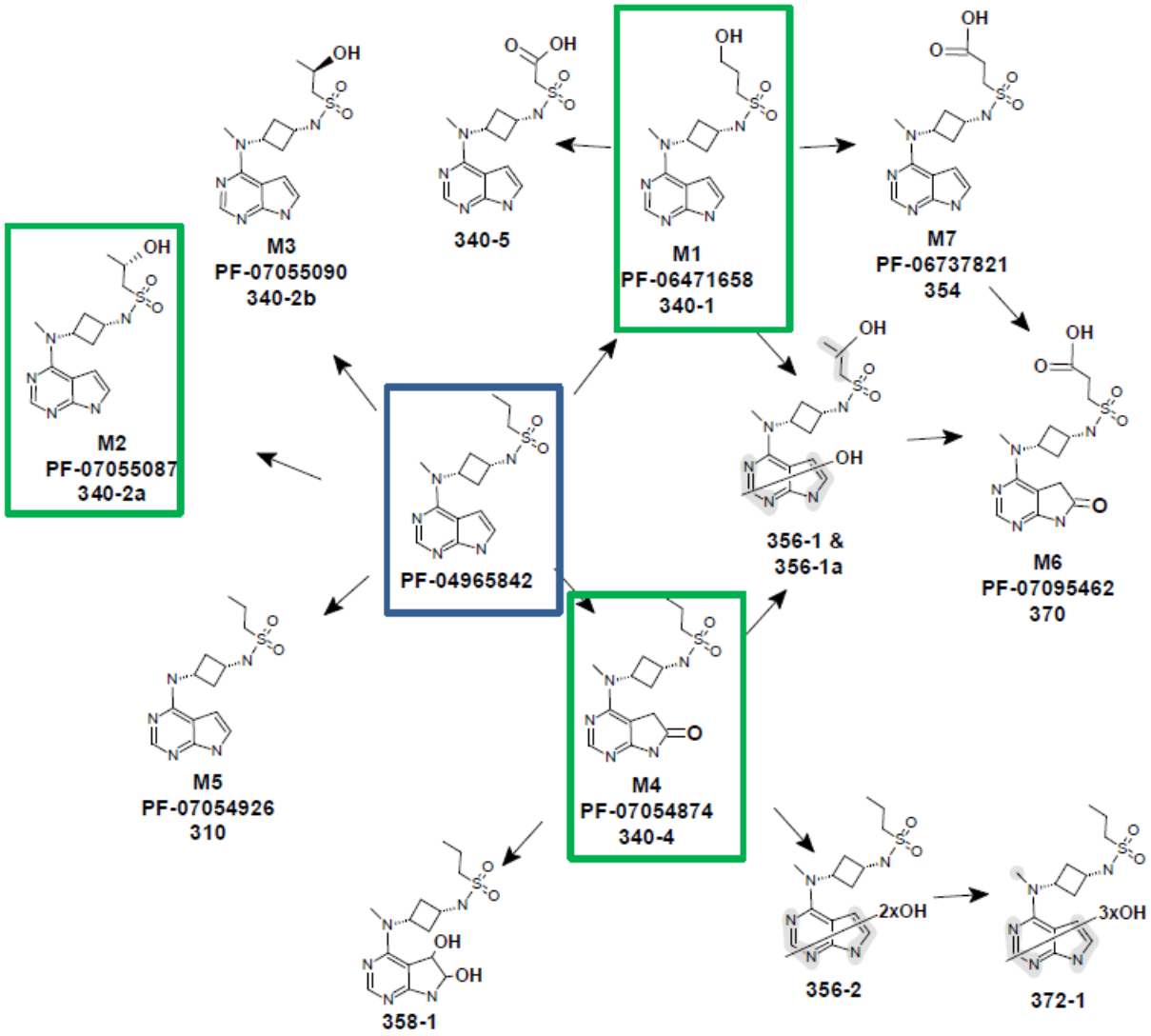
Source: Study Report B7451008, Table 14
Abbreviation: PO=per oral; IV=intravenous; F=absolute bioavailability as percentage; AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity

Table 77. Geometric Mean Ratio for Fraction Absorbed (F_a)

Parameter	Geometric Means		F_a: Ratio[b]
	^{14}C-PF-04965842 80 µg PO (Test)	^{14}C-PF-04965842 80 µg IV[a] (Reference)	Test (PO)/Reference (IV)
%^{14}C_Total	85.14	93.26	91.29

Source: Study Report B7451008, Table 16
Abbreviation: PO=per oral; IV=intravenous; F_a=fraction absorbed as percentage

Figure 13. Proposed Biotransformation Pathways of PF-04965842 in Human Plasma and Excreta



Source: Study Report B7451008, Figure 6

16.5.1.3 Study B7451032: Food Effect and Pivotal Bioeqivalence Study

Study B7451032 consisted of two parts: Part A to evaluate the effect of food consumption on the relative bioavailability of to-be-marketed (TBD) formulation and Part B to establish bioequivalence (BE) of TBM formulation and Phase 3 formulation. The description of investigational products in Study B7451032 is presented in Table 78.

Table 78. Investigational Product Description

Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency
PF-04965842 100 mg Round (b) (4) Film Coated Tablet (Phase 3 Formulation)	(b) (4)	18-002731	100 mg
PF-04965842 To-be-marketed 200 mg Tablet	19-(b) (4)-00015	19-000690	200 mg

Source: Study Report B7451032, Table 4

Food Effect on To-be-marketed Formulation (Part A)

Sixteen healthy subjects were enrolled and randomized to Part A to estimate the food effect on the abrocitinib PK of TBM formulation after a single 200 mg oral dose. Participants consumed a standard high-fat, high-calorie (approximately 890 calories containing 57% fat) breakfast after an overnight fast of at least 10 hours. Table 79 presents descriptive summary of plasma aborocitinib PK parameters in Study B7451032. Food consumption increased AUC_{inf} and C_{max} compared to fasting condition by 26% and 29%, respectively. T_{max} was prolonged approximately 2 hours after taking high-fat, high-calorie meal. It was concluded that the drug can be administered without regards to meals.

Pivotal Bioequivalence Study of To-be-marketed Formulation and the Formulation Used in the Phase 3 Trials (Part B)

A total of 30 subjects were enrolled in Part B to establish BE of TBM tablet and Phase 3 tablet. Given that the observed within-individual standard deviaion (SD) of C_{max} was >0.294 (i.e., percent coefficient of variation (%CV) was >30%) from Part A, a Reference-Scaled Average BE approach was adopted for Part B with a fully replicate four-way crossover design. In Part B, each randomized treatment sequence consisted of 4 treatment periods as presented in Table 80. Subjects were randomly assigned to one of the two sequences when they met the enrollment criteria.

Reviewer's comments:

The extent of variation (%CV) of C_{max} was similar in other clinical trials: 56% (n=8) in B7451021 (dedicated renal impairment study), 44% (n=8) in B7452010 (dedicated hepatic impairment study), 50% (n=12) in B7451017 (DDI study with strong CYP2C19 inhibitors), and 72% in B7451019 (DDI study with a strong CYP inducer). Thus, fully replicated study design and reference-scaled average BE approach for Part B were appropriate.

Median plasma abrocitinib concentration-time profiles for Part B are presented in

Figure 14 following single oral doses of abrocitinib (1x200 mg TBM tablet (test) and 2x100 mg Phase 3 tablet (reference)) under fasted conditions. BE criteria were met for the TBM formulation relative to the Phase 3 formulation in Part B. Table 81 presents statistical analysis results of Part B in the Study B7451032.

Table 79. Descriptive Summary of Plasma Abrocitinib Pharmacokinetic Parameters in the Study B7451032

Parameter (Units)[a]	Part A (Food Effect Study)		Part B (Pivotal BE Study)	
	TBM Tablet 200 mg (Fast)	TBM Tablet 200 mg (Fed)	Phase 3 Tablet 2 x 100 mg (Fast)	TBM Tablet 200 mg (Fast)
Number of subjects	15	15	30	30
AUC_{inf} (ng·hr/mL)	3492 (61)	4398 (55)	3820 (51)	3753 (55)
AUC_{last} (ng·hr/mL)	3456 (62)	4382 (55)	3622 (56)	3719 (55)
C_{max} (ng/mL)	802.5 (75)	1034 (39)	929.6 (56)	951.9 (60)
T_{max} (hr)	1.00 (0.5-6.0)	3.0 (1.0-6.0)	1.0 (0.5-4.0)	1.0 (0.5-4.0)
$t_{1/2}$ (hr)	3.9 ± 3.3	3.0 ± 0.9	5.7 ± 4.2	4.7 ± 3.6

Source: Study Report B7451032, Table 14 and Table 15

Abbreviations: TBM=to-be-marketed; AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration; T_{max}=time for C_{max}; $t_{1/2}$=terminal half-life

a. Geometric mean (geometric %coefficient of variation) for all except median (range) for T_{max} and arithmetic mean ± standard deviation for $t_{1/2}$

Table 80. Randomized Treatment Sequences of Part B

Sequence	Period 1	Period 2	Period 3	Period 4
1 (n=15)	Comm-Fast[a]	P3-Fast	Comm-Fast	P3-Fast
2 (n=15)	P3-Fast[b]	Comm-Fast	P3-Fast	Comm-Fast

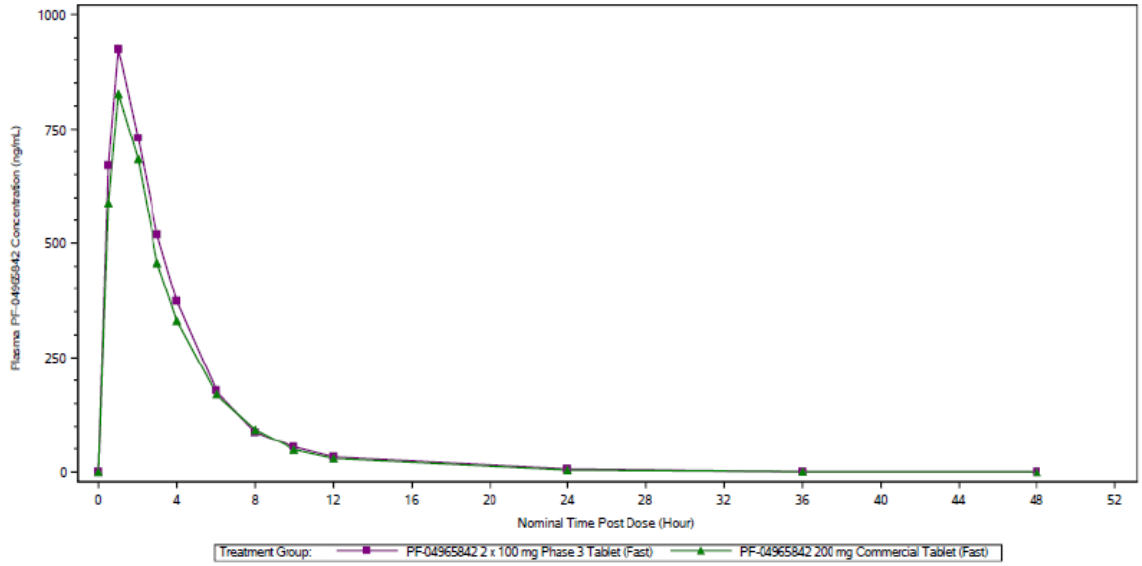
Source: Appendix 16.1.1

a. Comm-Fast: 200 mg PF-04965842 commercial tablet formulation under fasted conditions.

b. P3-Fast: 200 mg (2×100 mg) PF-04965842 Phase 3 tablet formulation under fasted conditions.

Source: Study Report B7451032, Table 3

Figure 14. Median Plasma Abrocitinib Concentration-Time Profiles Following To-be-marketed Tablet and Phase 3 Tablet in Part B, Study B7451032



Source: Study Report B7451032, Figure 2

Table 81. Summary of Statistical Analysis for Bioequivalence Following Single Dose of To-be-marketed Tablet 200 mg (Test, T) and Phase 3 Tablet 2x100 mg (Reference, R)

Parameter	Geometric Mean	T/R Ratio (%)	Number of Subjects	90% Confidence Interval (%)	95% Upper Limit of Critical Bound Limit	s_{WR}[a]	Method Used	BE Outcome
AUC_{last} (ng·hr/mL)	T: 3598 R: 3570	100.8	30	94.5 - 104.2	N/A	0.1544	Unscaled	Pass
AUC_{inf} (ng·hr/mL)	T: 3632 R: 3638	99.8	30	95.7 - 104.8	N/A	0.0192	Unscaled	Pass
C_{max} (ng/mL)	T: 928 R: 920	100.9	30	NA	-0.053	0.3212	Scaled	Pass

Source: Reviewer's analysis using PK data of Study B7451032
Abbreviations: AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration; BE=bioequivalence
a. If $s_{WR} \geq 0.294$ where s_{WR} is the within-subject standard deviation of the reference product, then reference scaled average BE approach is applied

16.5.1.4 Study B7451020: Dedicated Hepatic Impairment Study

Study B7451020 was an open-label, single-dose study to compare the PK, safey, and tolerability of aborocitinib in adult subjects with mild or moderate hepatic impairment (HI) relative to subjects with normal hepatic function. The Child-Pugh classification score was utilized to assess entry criteria and to assign participants into the appropriate hepatic impairment group. Twenty-four (24) subjects were enrolled into the study, with 8 subjects in normal hepatic function, mild (Child-Pugh A) HI, and moderate (Child-Pugh B) HI, respectively.

Following single 200 mg oral dose of abrocitinib, mild and moderate HI had minimal effect on the combined exposure of abrocitinib and its two active metabolites: $AUC_{inf,u}$ increased less than 15%. The exposure of abrocitinib increased less than 54%. Table 82 statistical summary of combined exposure of abrocitinib and its two active metabolites and the exposure of abrocitinib in the Study B7451020.

Table 82. Statistical Summary of Combined Exposure of Abrocitinib and Its Two Active Metabolites and the Exposure of Abrocitinib in the Study B7451020

	Combined Exposure		Exposure of Abrocitinib	
	$AUC_{inf,u}$ (nM·hr)	$C_{max,u}$ (nM)	AUC_{inf} (ng.hr/mL)	C_{max} (ng/mL)
Mild HI (n=8) *vs* normal (n=8)	95.7 (72.7, 126.1)	75.9 (57.4, 100.5)	133.3 (86.2, 206.3)	94.4 (63.0, 141.6)
Moderate HI (n=8) *vs* normal (n=8)	114.8 (87.2, 151.2)	84.1 (63.6, 111.3)	154.0 (99.5, 238.3)	105.5 (70.4, 158.2)

Source: Study Report B7451020, Table 11 and Table 16
Abbreviations: $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; $C_{max,u}$=unbound maximum plasma concentration; HI=hepatic impairment

16.5.1.5 Study B7451021: Dedicated Renal Impairment Study

Study B7451021 was an open-label, single-dose study to compare the PK, safey, and tolerability of aborocitinib in adult subjects with mild or moderate renal impairment (RI) relative to subjects with normal renal function. Twenty-three (23) subjects were enrolled into the study: 8 subjects with normal renal function, 7 subjects with moderate RI, and 8 subjects with severe RI. After statistical evaluation of results from severe RI, study in moderate RI was to be conducted if the combined exposure of abrocitinib and its two active metabolites unadjusted mean $AUC_{last,u}$ ratio for the severe RI group compared to the normal group as control is ≥2.8.
The combined $AUC_{inf,u}$ of abrocitinib and its two active metabolites increased by 110% and 191% in subjects with moderate RI and severe RI, respectively. The increase of abrocitinib exposure was less than 83% in subjects with moderate or severe RI. Table 83 presents statistical summary of combined exposure of abrocitinib and its two active metabolites and the exposure of abrocitinib in the Study B7451021.

Table 83. Statistical Summary of Combined Exposure of Abrocitinib and Its Two Active Metabolites and the Exposure of Abrocitinib in the Study B7451021

	Combined Exposure		Exposure of Abrocitinib	
	$AUC_{inf,u}$ (nM·hr)	$C_{max,u}$ (nM)	AUC_{inf} (ng.hr/mL)	C_{max} (ng/mL)
Moderate RI (n=7) *vs* normal (n=8)	210.2 (154.6, 285.8)	133.9 (102.5, 174.9)	182.9 (117.1, 285.7)	138.5 (93.7, 204.6)
Severe RI (n=8) *vs* normal (n=8)	290.7 (217.4, 388.7)	129.5 (92.9, 180.6)	121.3 (68.3, 215.4)	99.1 (57.3, 171.4)

Source: Study Report B7451021, Table 9 and Table 17
Abbreviations: $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; $C_{max,u}$=unbound maximum plasma concentration; RI=renal impairment

For the dose recommendation in subjects with mild RI, the Applicant conducted linear regression analysis of eGFR versus combined $AUC_{inf,u}$ of abrocitinib and its two active metabolites with data collected in the dedicated RI study. There was a linear relationship between logarithm value of $AUC_{inf,u}$ and eGFR as presented Figure 15 (adjusted R^2= 0.755). The predicted ratio of $AUC_{inf,u}$ between patients with eGFR of 60 mL/min (lowest eGFR of mild RI category) and subjects with normal renal function was 1.7 (

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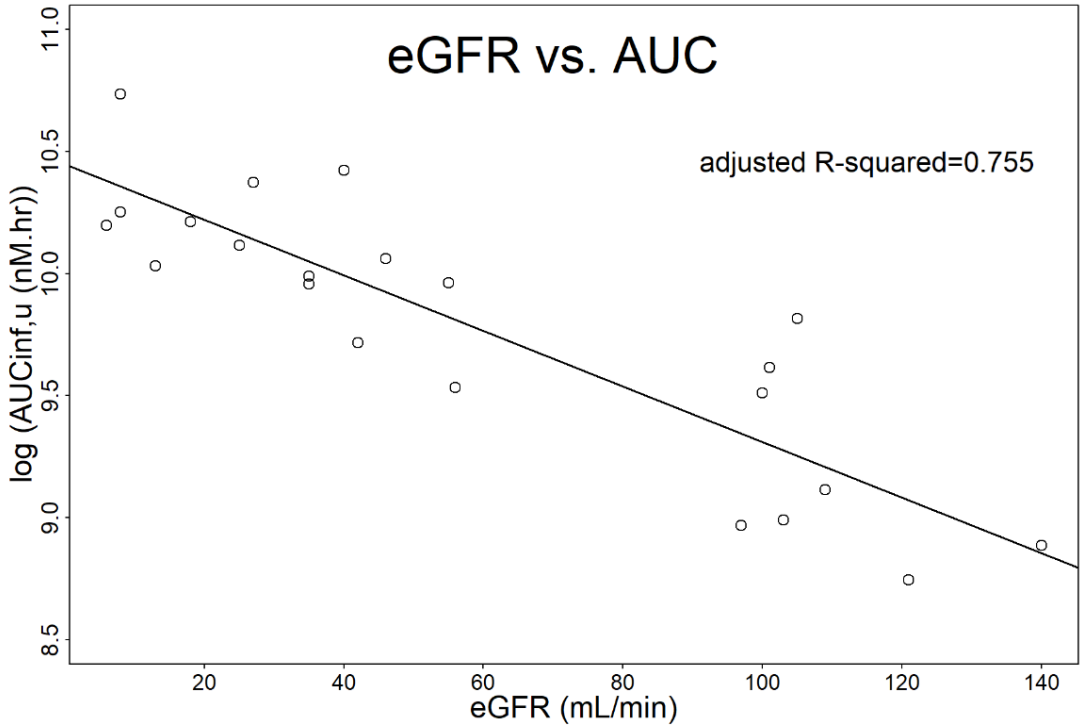
Table 84). Reviewer's independent analysis agreed with the Applicant's results. In addition, the prediction of $AUC_{inf,u}$ of aborocitinib and its two active metabolites in subjects with mild RI (eGFR 60 - 89 mL/min) is intrapolation between moderate RI and normal renal function. Intrapolation is more reliable than extrapolation because it predicts where the extreme conditions are already known (i.e. $AUC_{inf,u}$ of moderate RI and normal renal function are available). Based on the regression results, no dose adjustment is required for patients with mild RI.

Figure 15. Estimated Glomerular Filtration Rate (eGFR) versus the Combined Exposure of Abrocitinib and Its Two Active Metabolites



Source: Reviewer's analysis using data from Study B7451021
Abbreviation: $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; eGFR=estimated glomerular filtration rate

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Table 84. Predicted Combined Exposure of Abrocitinib and Its Two Active Metabolites ($AUC_{inf,u}$) Ratio for Subjects with Mild Renal Impairment and Normal Renal Function Based on Linear Regression Analysis of $AUC_{inf,u}$ vs. Estimated Glomerular Filtration Rate (eGFR), Protocol B7451021

Analyte	Linear Regression Parameter Values for AUC_{inf} vs. eGFR			Predicted AUC_{inf} (ng.hr/mL) for Mild Renal Impairment		Predicted AUC_{inf} Ratio[b] (Mild Renal Impairment vs. Normal Renal Function[c])	
	Slope	Intercept	Adjusted Coefficient of Determination	eGFR=60 mL/min	eGFR=75 mL/min	eGFR=60 mL/min	eGFR=75 mL/min
PF-04965842	-0.00407	8.98	0.0514[d]	-	-	-	-
M1	-0.00935	7.81	0.4476	1406.70	1222.62	161.20	140.10
M2	-0.0169	9.18	0.8809	3519.24	2731.21	238.48	185.08
M4	-0.0168	9.70	0.8361	5955.08	4628.55	243.07	188.93
Active Moiety[a]	-0.0111	10.4	0.8041	16881.95	14292.64	169.59	143.57

Source: Study B7451021 Tables 14.4.3.3.1.1, 14.4.3.3.2.1, 14.4.3.3.3.1, 14.4.3.3.4.1, 14.4.3.3.5.1, 14.4.3.4.1, 14.4.3.4.2, 14.4.3.4.3, 14.4.3.4.4, and 14.4.3.4.5.

a. $AUC_{inf,u}$ (nM.hr) instead of AUC_{inf} (ng.hr/mL) is presented for Active moiety.
b. The ratios are expressed as percentages.
c. Normal Renal Function: adjusted geometric means from ANOVA model were used in ratio calculation.
d. Low coefficient of determination, therefore, AUC_{inf} values were not predicted for PF-04965842.

16.5.1.6 Study B7451017: Drug-Drug Interaction Study with Fluvoxamine or Fluconazole (Strong CYP2C19 Inhibitors)

In vitro metabolism studies have shown that abrocitinib is a substrate of CYP2C19 (fraction metabolized [fm] ~0.5), CYP2C9 (fm ~0.3), and CYP3A4 (fm ~0.1). Therefore, a drug-drug interaction study evaluating the effect of CYP2C19 and/or CYP2C9 inhibitors is warranted. Fluvoxamine has been selected as a strong inhibitor of CYP2C19 and a moderate inhibitor of CYP3A (Cohort 1) and fluconazole as a strong inhibitor of CYP2C19 and moderate inhibitor of CYP2C9 and CYP3A (Cohort 2). A total of 24 subjects were randomized to study treatment, 12 subjects for each cohort. The results of Study B7451017 indicated that coadministration of fluvoxamine or fluconazole with abrocitinib increased the plasma exposure of abrocitinib and its two active metabolites when compared to abrocitinib administered alone.

Cohort 1 was designed to evaluate the effect of repeat-dose of fluvoxamine (50 mg once daily for 7 days) on abrocitinib PK following a single 100 mg oral dose. Cohort 2 was designed to evaluate the effect of repeat-dose of fluconazole (400 mg loading dose on Day 1 followed by 200 mg once daily for 4 days) on abrocitinib PK following a single 100 mg oral dose. Results of the statistical analysis of Cohoart 1 and Cohort 2 are summarized in Table 85.

Table 85. Descriptive and Statistical Summary of Combined Exposure of Abrocitinib and Its Two Active Metabolites and the Exposure of Abrocitinib, Study B7451017

		Combined Exposure		Abrocitinib Exposure	
		$AUC_{inf,u}$ (nM·hr)	$C_{max,u}$ (nM)	AUC_{inf} (ng.hr/mL)	C_{max} (ng/mL)
Cohort 1 (n=12)	Abrocitinib	3527	807	1578	420.2
	Fluvoxamine + abrocitinib	6746	1074	4343	775
	Ratio (%)	191 (174, 210)	133 (100, 178)	275 (239, 317)	184 (133, 255)
Cohort 2 (n=12)	Abrocitinib	3359	960.3	1549	518.8
	Fluconazole + abrocitinib	8561	1186	7482	998.5
	Ratio (%)	255 (242, 269)	123 (108, 142)	483 (384, 607)	192 (154, 239)

Source: Study Report B7451017, Table 10 and Table 12; Study Report B7451017-metabolite-moiety-tables-2, Table 14.4.5.6.1 and Table 14.4.5.6.2

Abbreviations: AUC_{inf}= area under the curve from time zero to infinity; $AUC_{inf,u}$=unbound AUC_{inf}; C_{max}= maximum plasma concentration; $C_{max,u}$=unbound C_{max}

16.5.1.7 Study B7451019: Drug-Drug Interaction Study with Rifampin (a Strong CYP2C19 and CYP3A4 and a Moderate CYP2C9 Inducer)

Study B7451019 was designed to evaluate the effect of repeat-dose rifampin (600 mg once daily for 8 days) on abrocitinib PK following a single 200 mg oral dose. Rifampicin has been selected as an inducer because of its substantial inductive effects on CYP2C19, CYP2C9, CYP3A4, and CYP2B6. Results of the statistical comparisons of the combined exposure of abrocitinib and its two active metabolites with and without coadministration of rifampin are summarized inTable 86. Coadministration of multiple rifampin 600 mg decreased the combined overall exposure of abrocitinib and its two active metabolites ($AUC_{inf,u}$) by approximately 56% and decreased the combined peak exposure of abrocitinib and its two active metabolites ($C_{max,u}$) by approximately 31% relative to a single abrocitinib 200 mg dose given alone.

Table 86. Descriptive and Statistical Summary of Combined Exposure of Abrocitinib and Its Two Active Metabolites in the Study B7451019

		Adjusted Geometric Means					
Parameter (Units)	Comparison (Test vs. Reference)	Test	N[1]	Reference	N[2]	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratios[a]
$AUC_{inf,u}$ (nM.hr)	Rifampicin 600 mg QD+PF-04965842 200 mg SD vs.PF-04965842 200 mg SD	3374	12	7694	9	43.86	(40.94, 46.98)
$AUC_{last,u}$ (nM.hr)	Rifampicin 600 mg QD+PF-04965842 200 mg SD vs.PF-04965842 200 mg SD	3291	12	7311	12	45.01	(39.85, 50.85)
$C_{max,u}$ (nM)	Rifampicin 600 mg QD+PF-04965842 200 mg SD vs.PF-04965842 200 mg SD	1117	12	1621	12	68.91	(50.28, 94.46)

Source: Study Report B7451019-metabolite-moiety-tables-2, Table 14.4.5.7.1

Abbreviations: $AUC_{last,u}$=unbound area under the curve from time 0 to time of last observation; $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; $C_{max,u}$=unbound maximum plasma concentration

16.5.1.8 Study B7451043: Drug-Drug Interaction Study with Probenecid (an OAT3 Inhibitor)

The results of transporter profiling in vitro studies with active metabolites (M1 and M2) of abrocitinib suggested that both metabolites were identified as substrates for organic anion transporter 3 (OAT3). Therefore, a DDI study was warranted to evaluate the effect of potent OAT3 inhibitor on PK of these metabolites. Probenecid was selected as an inhibitor because of its substantial inhibition effect on OAT3. Enrolled subjects (n=12) received single dose of abrocitinib 200 mg with and without multiple doses of probenecid 1000 mg BID. The PK results in this study indicated that probenecid increased the combined overall exposure ($AUC_{inf,u}$) of abrocitinib and its two active metabolites by 66% as presented in Table 87. The overall exposure (AUC_{inf}) of abrocitinib increased less than 30% (data not shown).

Table 87. Descriptive and Statistical Summary of Combined Exposure Metrics of Abrocitinib and Its Two Active Metabolites in the Study B7451043

	Adjusted Geometric Means			
Parameter, unit	**Probenecid 1000 mg BID + PF-04965842 200 mg SD Test**	**PF-04965842 200 mg SD Reference**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio[a]**
$AUC_{inf,u}$, nM.hr	11390	6881	165.54	(152.00, 180.29)
$AUC_{last,u}$, nM.hr	11120	6739	164.98	(153.95, 176.81)
$C_{max,u}$, nM	1835	1410	130.13	(104.10, 162.65)

Source: Table 14.4.5.5.5
a. The ratios (and 90% CIs) were expressed as percentages.

Source: Study Report B7451043, Table 18

Abbreviations: $AUC_{last,u}$=unbound area under the curve from time 0 to time of last observation; $AUC_{inf,u}$=unbound area under the curve from time zero to infinity; $C_{max,u}$=unbound maximum plasma concentration

16.5.1.9 Study B7451016: Drug-Drug Interaction Study with Oral Contraceptive

Study B7451016 was a Phase 1, randomized, 2-way crossover, open-label study to estimate the effect of multiple-dose abrocitinib 200 mg QD on single-dose oral contraceptive (OC, ethinyl estradiol (EE) 30 µg and levonorgestrel (LN) 150 µg) PK in healthy female subjects. A total of 17 subjects were randomized to the study treatment and 16 completed. AUC_{inf} of LN was not reported for all subjects due to lack of a well-characterized terminal phase i.e., the percent of the AUC_{inf}, obtained by forward extrapolation (AUC_{extrap}%) was greater than 20%. The PK results present that the 90% CI for the ratio of test to reference adjusted geometric means of AUC (primary PK endpoint) included the unity that implied the limited abrocitinib effect on the PK of OC (

Table 88).

Table 88. Descriptive and Statistical Summary of Plasma Oral Contraceptive (Ethinyl Estradiol (EE) and Levonorgestrel (LN)) in the Study B7451016

Analytes	PK Metric (Units)	Adjusted Geometric Means		Ratio[a] (%) (Test/Reference)	90% CI (%) for Ratio[a]
		Test	Reference		
EE	AUC_{inf} (pg.hr/mL)	803.3	676.3	118.8	112.0, 126.0
	AUC_{last} (pg.hr/mL)	710.8	610.4	116.4	110.4, 122.9
	C_{max} (pg/mL)	70.94	66.19	107.2	99.2, 115.8
LN	AUC_{last} (pg.hr/mL)	32760	33580	97.6	86.6, 110.0
	C_{max} (pg/mL)	2879	3347	86.0	75.7, 97.7

Source: Study Report B7451016, Table 8 and Table 10
Test=Abrocitinib 200 mg once daily + Oral Contraceptive; Reference=Oral Contraceptive
a.The ratios (and 90% confidence intervals) were expressed as percentages
Abbreviations: CI=confidence interval; AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration

16.5.1.10 Study B7451022: Drug-Drug Interaction Study with Midazolam (a CYP3A4/5 Substrate)

Study B7451022 was designed to assess the effect of abrocitinib on the in vivo PK of a sensitive CYP3A4/5 substrate. Midazolam was selected as a probe for evaluating drug interation via CYP3A4/5 because it undergoes extensive metabolism by CYP3A4 and CYP3A5.

A total of 25 subjects were randomized to treatment and 24 subjects completed the Study B7451022. The ratio of the adjusted geometric means of midazolam AUC_{inf} (primary PK endpoint) on Day 7 were similar to those values on Day 2 following administration of midazolam 2 mg with abrocitinib 200 mg, relative to midazolam 2 mg administered alone. The result suggests a limited induction effect of abrocitinib on CYP3A4/5. On Day 2, the ratio of the adjusted geometric means of midazolam AUC_{inf} following administration of midazolam with abrocitinib, relative to midazolam administered alone was 84% (Table 89). This result implies the limited inhibition effect of abrocitinib on CYP3A4 and CYP3A5.

Table 89. Descriptive and Statistical Summary of Plasma Midazolam in the Study B7451022

	PK Metric (Units)	Adjusted Geometric Means		Ratio[a] (%) (Test/Reference)	90% CI (%) for Ratio[a]
		Test	Reference		
Day 2	AUC_{inf} (ng.hr/mL)	28.2	33.4	84.3	78.9, 90.0
	AUC_{last} (ng.hr/mL)	27.4	32.5	84.2	78.8, 90.0
	C_{max} (ng/mL)	9.4	10.9	86.3	77.3, 96.4
Day 7	AUC_{inf} (ng.hr/mL)	30.9	33.4	92.3	86.5, 98.5
	AUC_{last} (ng.hr/mL)	30.0	32.5	92.3	86.4, 98.7
	C_{max} (pg/mL)	10.2	10.9	93.5	83.8, 104.5

Source: Study Report B7451022, Table 9
Test=Abrocitinib 200 mg once daily + Midazolam 2 mg; Reference=Midazolam 2 mg alone
a.The ratios (and 90% confidence intervals) were expressed as percentages

Abbreviations: CI=confidence interval; AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration

16.5.1.11 Study B7451026: Drug-Drug Interaction Study with Dabigatran (a P-glycoprotein Substrate)

A preclinical in vitro inhibition study showed that the theoretical gut concentration was 25-fold higher than the estimated 50% inhibitory concentration (IC_{50}) value suggesting that abrocitinib has a potential to inhibit P-glycoprotein (P-gp) in vivo. Therefore, a clinical interaction study with a sensitive P-gp substrate is needed to assess the effect of abrocitinib on the exposure of a P-gp substrate. Dabigatran was selected as a probe drug since it is a sensitive P-gp substrate. A total of 20 subjects were randomized to treatment and all of them completed the Study B7451026. Coadministration of a single dose of abrocitinib 200 mg increased total dabigatran exposure (AUC_{inf}) by approximately 53% and increased the peak exposure (C_{max}) by approximately 40% relative to a single dabigatran 75 mg dose given alone as presented in Table 90.

Table 90. Descriptive and Statistical Summary of Plasma Total Dabigatran PK Metrics in the Study B7451026

	Adjusted Geometric Means			
Parameter, unit	**Dabigatran 75 mg + PF-04965842 200 mg Test**	**Dabigatran 75 mg Reference**	**Ratio (Test/Reference) of Adjusted Means[a]**	**90% CI for Ratio[a]**
AUC_{inf}, ng.hr/mL	451.1	295.1	152.86	(108.79, 214.80)
AUC_{last}, ng.hr/mL	362.4	269.1	134.64	(89.52, 202.50)
C_{max}, ng/mL	42.25	30.15	140.10	(92.20, 212.90)

Source: Table 14.4.3.3
a. The ratios (and 90% CIs) were expressed as percentages.

Source: Study Report B7451026, Table 9

Abbreviations: AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration

16.5.1.12 Study B7451033: Drug-Drug Interaction Study with Rosuvastatin (a BCRP/OAT3 Substrate)

Based on the in vitro data, abrocitinib is a potential inhibitor for both breast cancer resistance protein (BCRP) and organic anion transporter 3 (OAT3). Study B7451033 was designed to estimate the effect of abrocitinib 200 mg on the PK of rosuvastatin 10 mg. Rosuvastatin was selected because it is a substrate for BCRP and OAT3. A total of 12 healthy subjects were randomized to treatments and all of them completed the Study B7451033.

The the ratios of the adjusted geometric means for rosuvastatin AUC_{inf} and CL_r (primary PK endpoints) were close to the unity and their 90% CIs were within 80-125% suggesting that there was limited abrocitinib effect on the PK of rosuvastatin through BCRP and OAT3 (

Table 91).

Table 91. Descriptive and Statistical Summary of Rosuvastatin PK Parameters in the Study B7451033

	PK Parameter (Units)	Adjusted Geometric Means		Ratio[a] (%) (Test/Reference)	90% CI (%) for Ratio[a]
		Test	Reference		
Plasma	AUC_{inf} (ng.hr/mL)	56.44	55.4	101.9	92.9, 111.9
	AUC_{last} (ng.hr/mL)	54.9	51.9	105.7	95.3, 117.2
	C_{max} (ng/mL)	5.3	5.4	98.8	85.5, 114.1
Urine	CL_r (L/hr)	13.33	14.6	91.3	82.7, 100.8

Source: Study Report B7451033, Table 9 and Table 10
Test=Abrocitinib 200 mg once daily + Rosuvastatin 10 mg; Reference=Rosuvastatin 10 mgalone
a.The ratios (and 90% confidence intervals) were expressed as percentages
Abbreviations: AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration; CL_r=renal clearance

16.5.1.13 Study B7451034: Drug-Drug Interaction Study with Metformin (a MATE1/2K Substrate)

In vitro inhibition studies showed abrocitinib have the potential to inhibit multidrug and toxic compound extrusion transporter 1 (MATE1) and MATE2K, therefore a clinical interaction study with a sensitive MATE1 and MATE2K substrate (e.g., metformin) was needed to assess the effect of abrocitinib on the activity of these transporters. Twelve (12) subjects were randomized and all of them completed the Study B7451034. Coadministration of abrocitinib 200 mg with metformin 500 mg did not impact the CL_r (primary PK endpoint) of metformin (Table 92). In addition, the exposure of metformin (secondary PK endpoints) was similar when coadministered with and without abrocitinib. Hence, abrocitinib does not appear to inhibit renal clearance mediated by MATE1 and MATE2K.

Table 92. Descriptive and Statistical Summary of Metformin PK Parameters in the Study B7451033

	PK Parameter (Units)	Adjusted Geometric Means		Ratio[a] (%) (Test/Reference)	90% CI (%) for Ratio[a]
		Test	Reference		
Plasma	AUC_{inf} (ng.hr/mL)	4906	5247	93.5	85.2, 102.7
	AUC_{last} (ng.hr/mL)	4849	5145	94.3	88.2, 100.7
	C_{max} (ng/mL)	634.7	720.7	88.1	81.0, 95.8
Urine	CL_r (L/hr)	32.8	33.3	98.5	82.1, 118.2

Source: Study Report B7451034, Table 8 and Table 10
Test=Abrocitinib 200 mg once daily + Metformin 500 mg; Reference=Metformin 500 mg alone
a.The ratios (and 90% confidence intervals) were expressed as percentages
Abbreviations: AUC_{last}=area under the curve from time 0 to time of last observation; AUC_{inf}=area under the curve from time zero to infinity; C_{max}=maximum plasma concentration; CL_r=renal clearance

16.5.1.14 Study B7451027: Thorough-QT Study in Healthy Subjects

Study B7451027 was a Phase 1, randomized, 3-treatment, 3-period, placebo- and positive-controlled crossover study investigating the effect of abrocitinib single dose (600 mg) on QTc interval in healthy subjects. The 600 mg dose covers the highest clinical exposure scenario that is the exposure increased 2.5 times in the case of CYP2C19 inhibition. Moxifloxacin (positive treatment) administration was unblinded and the 3 treatment periods were separated by a washout period of at least 5 days. Thirty-six eligible subjects received abrocitinib tablet 600 mg, matching placebo, and moxifloxacin 400 mg.

The assay sensitivity was established using oral moxifloxacin. Per the Applicant, the peak concentration (C_{max}=1890 ng/mL) observed with highest dose studied (i.e., 600 mg single dose) is expected to offer only ~1.7-fold margin over the therapeutic exposures (C_{max}=1123 ng/mL based on the Population-PK analysis) associated with the maximum proposed dose (abrocitinib 200 mg) at the steady-state in target population. Since only 100 mg dose of abrocitinib is recommended for approval the safety margin of C_{max} in Study B7451027 would be larger than the suggested 1.7 fold.

Pharmacokinetics
The PK metrics of abrocitinib are summarized in Table 93.

Table 93. Descriptive Summary of Plasma Abrocitinib PK Metrics in the Study B7451027

PK Parameter (Units)	Summary Statistics[a]
The number of participants	36
AUC_{24} (ng·hr/mL)	12863 (66)
C_{max} (ng/mL)	2156 (47)
T_{max} (hr)	3.0 (0.55 – 6.0)

Source: Reviewer's analysis using PK data of Study B7451027
a. Arithmetic mean (%CV) for AUC_{24} and C_{max}; median (range) for T_{max}.
Abbreviations: AUC_{24}=area under the curve from time 0 to 24 hours; C_{max}=maximum plasma concentration; T_{max}=time for C_{max}

Pharmacodynamics
No significant QTc prolongation effect of abrocitinib was detected in this QT assessment. (for details see QT Study Consultation Review in the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) dated December 22, 2020).

16.5.1.15 Study B7451006: A Phase 2 Dose-Ranging Study in Patients with Moderate to Severe Atopic Dermatitis

Study B7451006 was a Phase 2b, randomized, double-blind, parallel group study designed to evaluate the efficacy of 4 QD dose levels (10, 30, 100, and 200 mg) of abrocitinib relative to placebo in adult subjects with moderate to severe AD, using the Investigator's Global Assessment (IGA) at week 12. The treatment period was 12 week long followed by a follow up period of 4 weeks. A total of 267 subjects with moderate to severe AD were randomized and treated: placebo (n=56), abrocitinib 10 mg (n=49), abrocitinib 30 mg (n=51), abrocitinib 100 mg (n=56), and abrocitinib 200 mg (n=55). Blood samples for PK analysis were collected at the

following time points: 2 hours pre-dose on Days 43 and 85; pre-dose on Days 15, 29, 43, 57 and 85; 0.5 hours post-dose on Day 43; 1, 2 and 4 hours post-dose on Day 85.

The IGA response results are summarized in Table 94. Both 100 mg and 200 mg treatment groups were statistically significantly different from pacebo group. A dose-dependent response relationship was observed as illusted in Figure 16Figure 16.

Observed plasma concentration of abrocitinib in AD patients was similar to the one observed in healthy subjects. After 200 mg QD multiple doses, the median concentration in AD patients (at Day 85, 1 hour post-dose) was 1095 ng/mL where the median C_{max} in healthy subjects was 1160 ng/mL (B7451001). Median plasma concentration of abrocitinib versus time is plotted in Figure 17.

Table 94. Proportion of Subjects Achieving IGA Response of Clear or Almost Clear and **≥2** Points Improvement from Baseline at Week 12 - Emax (FAS, NRI)

	Observed Response		Summary of Emax Model Estimate					
			Estimate			Difference from Placebo		
Treatment	N	n (%)	Response (SE)	95% CI	p-value	Estimate (SE)	95% CI	p-value
Placebo	52	3 (5.8)	6.3 (2.55)	(-0.2, 12.9)	0.0555			
PF-04965842 10 mg	46	5 (10.9)	8.2 (2.32)	(2.2, 14.1)	0.0168	1.8 (0.99)	(-0.7, 4.4)	0.1210
PF-04965842 30 mg	45	4 (8.9)	12.3 (2.88)	(4.9, 19.7)	0.0079	6.0 (3.05)	(-1.8, 13.8)	0.1065
PF-04965842 100 mg	54	16 (29.6)	27.8 (5.07)	(14.8, 40.9)	0.0027	21.5 (6.25)	(5.5, 37.6)	0.0184
PF-04965842 200 mg	48	21 (43.8)	44.5 (6.92)	(26.7, 62.3)	0.0013	38.2 (7.18)	(19.7, 56.6)	0.0032

Source: Table 14.2.1.1.1
Baseline was defined as last measurement prior to first dosing.
For discontinued subjects, any missing value for all subsequent visits until Week 12 was imputed using NRI approach.
Emax model: Log(pi/(1-pi)) = E0 + Emax × dose / (ED50 + dose). P-value was 2-sided.
Response (SE) and its 95% CI are presented as percent. Difference (SE) and its 95% CI are presented as percent.
Abbreviations: CI = confidence interval; Emax = the difference between maximum achievable response (at infinite dose) and baseline; FAS = full analysis set; IGA = Investigator's Global Assessment; N = number of evaluable subjects; n = number of subjects in the category; NRI = non-responder imputation; SE = standard error.
Source: Study Report B7451006, Table 10

Figure 16. Emax Fitted Curve with 95% CI - Proportion of Subjects Achieving IGA Response of Clear or Almost Clear and **≥2** Points Improvement from Baseline at Week 12 (FAS, NRI)

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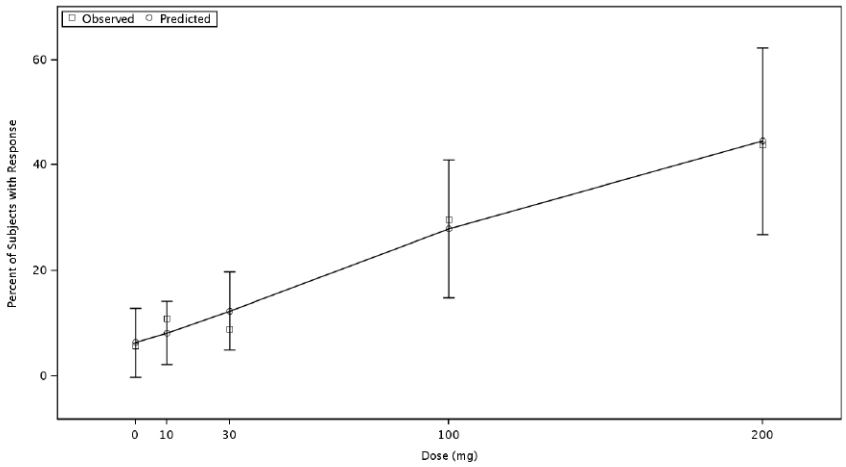
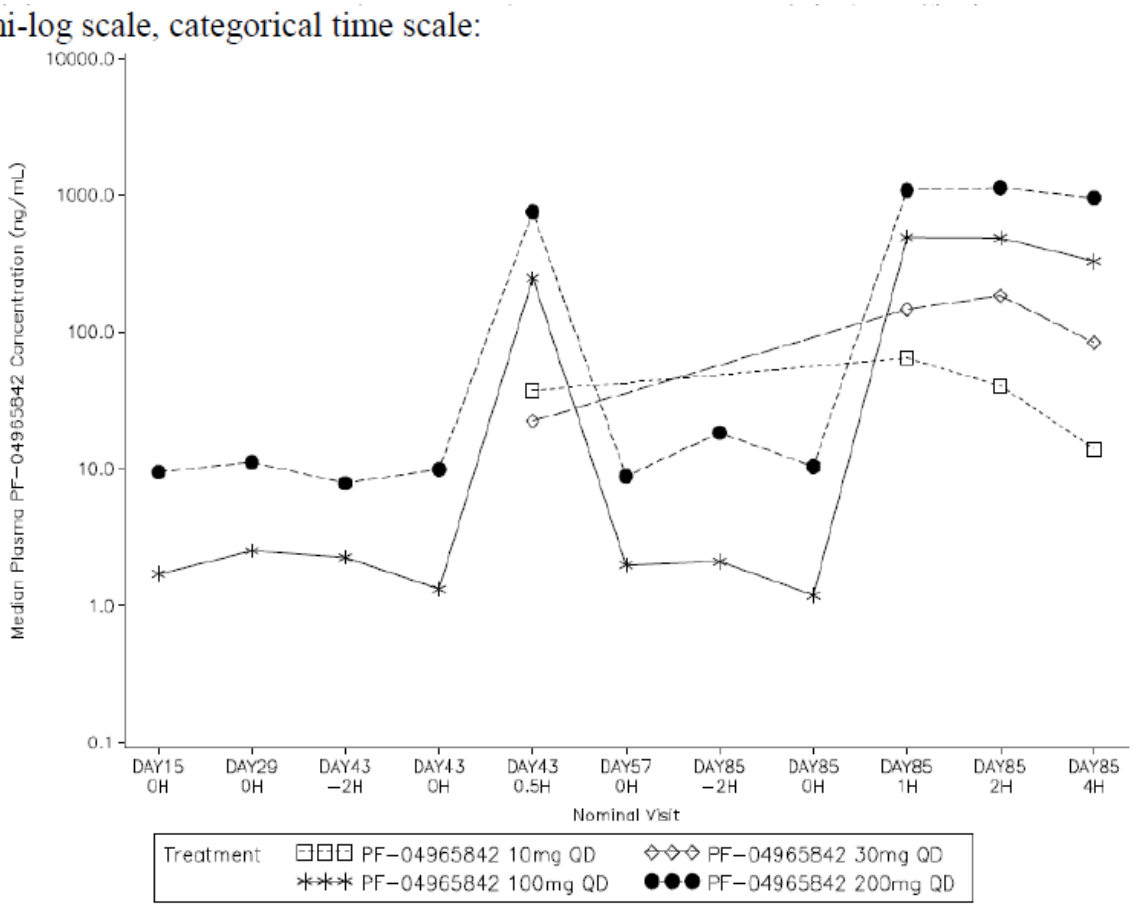


Source: Figure 14.2.1.1.2
Baseline was defined as last measurement prior to first dosing.
For discontinued subjects, any missing value for all subsequent visits until Week 12 was imputed using NRI approach. Bars indicated 95% CI.
Abbreviations: CI = confidence interval; Emax = the difference between maximum achievable response (at infinite dose) and baseline; FAS = full analysis set; IGA = Investigator's Global Assessment; NRI = non-responder imputation.

Source: Study Report B7451006, Figure 2

Figure 17. Median Plasma Abrocitinib Concentration-Time Plot



Source: Study Report B7451006, Figure 17
The lower limit of quantification was 1.00 ng/mL.
Summary statistics were calculated by setting concentration values below the lower limit of quantification to 0. Unplanned readings were excluded from the presentation.

Abbreviations: H=hour; QD=once daily.

PD biomarkers of abrocitinib including interferon gamma-induced protein-10 (IP-10) and high-sensitivity C-reactive protein (hsCRP) and AD biomarkers, interleukin 31 (IL-31) and thymus- and activation-regulated chemokine (TARC) were measured at baseline, during the study period (Weeks 2, 4, 6, 8, and 12), and at the end of follow-up period (Week 16) or at the early termination. IL-31, IP-10 and hsCRP decreased in dose-dependent manner after abtocitinib 100 mg or 200 mg QD. TARC was also suppressed at the doses of 100 mg and 200 mg QD. They reached nadir at Week 2 and recovered a baseline value within 4 weeks after drug discontinuation (

Figure 18). However, IP-10 levels returned to the baseline value as early as 6 weeks after the treatment initiation.

Figure 18. Biomarkers Change from Baseline

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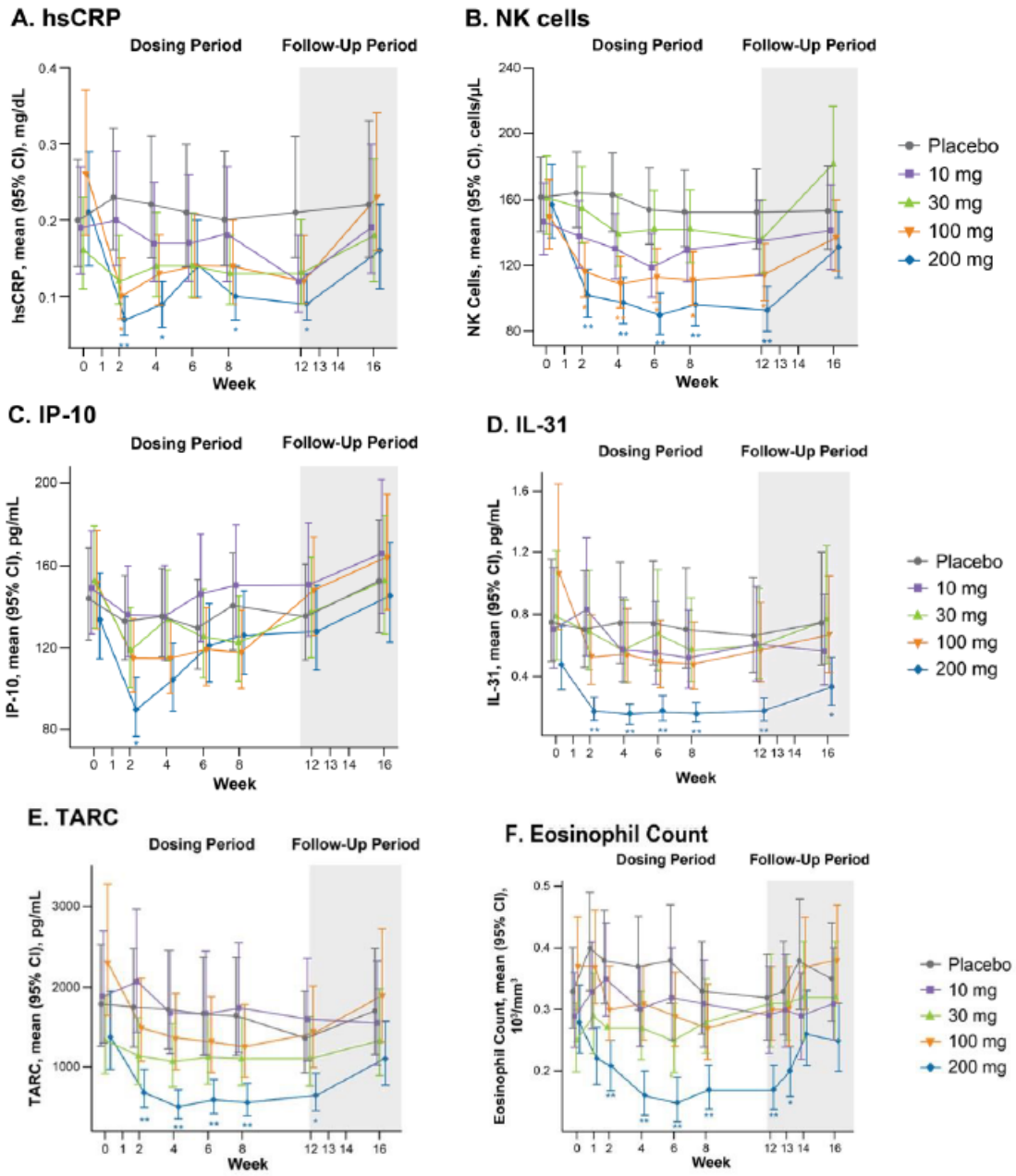

Source: Exploratory Biomaerker Report B7451006, Figure 2
Abbreviations: hsCRP=high-sensitivity C-reactive protein, NK=natural killer, IP-10=interferon-γ–induced protein-10, IL-31=interleukin-31, TARC=thymus- and activation-regulated chemokine
*P < 0.05, **P < 0.001 versus placebo.

16.5.2. Population PK and PK/PD Studies

16.5.2.1 Population PK Analysis

16.5.2.1.1 Review Summary

The applicant's population PK analysis is acceptable for characterization of PK of abrocitinib. Both goodness-of-fit plots and prediction corrected visual predictive checks indicate that the final population PK model is adequate in characterizing the PK profile of abrocitinib in healthy adults, psoriasis patients, and moderate to severe AD patients. The inter-individual variability (IIV) for CL (57.7%), and Vc (41.4%) were moderate. IIV for Vp and Q were fixed to 0%.

Intrinsic (sex, age, race, body weight, patient status, hepatic function) and extrinsic (DDI, fed status) factors were identified as covariates on F, Ak1 (amount absorbed by first-order processes), CL, and Vc. Renal excretion is a major route for abrocitinib elimination, but creatinine clearance (CCL) was not evaluated as a covariate because most subjects had normal renal function. Body weight was the covariate on clearance (CL, Q) and volume (Vc, Vp), with estimated allometric exponents of 0.453 and 0.52 respectively. The estimated PK parameters and Eta and epsilon shrinkages are reasonable (<30%) for EBE estimation used in PK/PD analyses.

The sponsor's population PK analysis was verified by the reviewer, with no significant discordance identified. The developed model is therefore acceptable to be used for estimating individual-level PK and exposure simulation for the subsequent PK/PD analyses.

16.5.2.1.2 Objectives

The primary objective of this analysis was to:

- To examine if the final population PK model reasonably describe the observations.

16.5.2.1.3 Population PK Model

16.5.2.1.3.1 Data

Analyses were based on PK data from 11 Phase 1~3 studies. The study design, study population, dose, and timing of blood samples varied among the studies as presented in Table 95.
The final NONMEM data file for analysis contained 7795 PK observations from 995 subjects. Table 96 provides summary statistics of the baseline patient characteristics in the analysis dataset.

Table 95. Summary of Studies with PK Sampling Included in Population PK Analysis

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Plasma Sampling[a]
B7451001	1	A phase 1, within cohort, randomized, double blind, third-party open, placebo-controlled, single- and multiple dose escalation, parallel group study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of PF-04965842 in healthy Western and Japanese subjects	HV	79	SAD: Western subjects received single doses of 3, 10, 30, 100, 200, 400, or 800 mg[b] PF-04965842 or placebo. Japanese subjects received a single dose of 800 mg PF-04965842 or placebo. MAD: Western subjects received 30, 100, 200, or 400 mg QD or 100 or 200 mg BID for 10 days. Japanese subjects received 200 mg BID for 10 days. Fasted	0 (pre-dose), 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48 hours on Day 1 and Day 10 post-dose(s)
B7451004	1	A phase 1, open label, single-dose 3-way crossover study to evaluate the bioavailability of a solid dose formulation of PF-04965842 relative to a suspension formulation under fasting conditions and the effect of of food on the bioavailability of the solid dosage formulation of PF-04965842 in healthy subjects	HV	12	4 x 100 mg PF-04965842 tablet[c] under fasted conditions, 400 mg PF-04965842 oral suspension[b] under fasted conditions, and 4 x 100 mg PF-04965842 tablet[c] under fed conditions, each as a single-dose	0 (pre-dose), 0.5, 1, 2, 4, 5, 8, 12, 16, 24, 36, and 48 hours post-doses
B7451005	2	A phase 2 randomized, double-blind, placebo-controlled study to evaluate safety and efficacy of PF-04965842 in subjects with moderate to severe psoriasis	PsO	59	200 mg BID, 400 mg QD, or 200 mg QD[c] of PF-04965842 or matching placebo for 4 weeks. Fasted	0 (pre-dose) on Day 1, 7 and 21. -2 (pre-dose), 0 (pre-dose), and 0.5 hours post-dose on Day 14. -2 (pre-dose), 0 (pre-dose), 1, 2, and 4 hours post-dose on Day 28
B7451006	2b	A phase 2b randomized, double-blind, placebo-controlled, parallel, multi-center, dose-ranging study to evaluate the efficacy and safety profile of PF-04965842 in subjects with moderate to severe atopic dermatitis	AD	267	10, 30, 100, 200 mg QD[d] of PF-04965842 or matching placebo for 12 weeks. Fasted	Pre-dose on Day 15 (Week 2), Day 29 (Week 4) and Day 57 (Week 8). -2 (pre-dose), 0 (pre-dose), and 0.5 hours post-dose on Day 43 (Week 6). -2 hours (pre-dose), 0 (pre-dose), 1, 2 and 4 hours post-dose on Day 85 (Week 12)
B7451012	3	A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older, with moderate to severe atopic dermatitis	AD	387	100 or 200 mg QD[e] of PF-04965842 or matching placebo for 12 weeks. Fasted	0 (pre-dose) and 0.5 hours post-dose on Day 29 (Week 4). 0.5 and 4 hours post-dose on Day 85 (Week 12)
B7451013	3	A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older, with moderate to severe atopic dermatitis	AD	391	100 or 200 mg QD[e] of PF-04965842 or matching placebo for 12 weeks. Fasted	-2 (pre-dose) hours on Day 57 (Week 8). 1 and 2 hours post-dose on Day 85 (Week 12)

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Plasma Sampling[a]
B7451017	1	A phase 1, open-label, randomized, fixed-sequence, parallel-cohort study to estimate the effect of fluvoxamine or fluconazole on the pharmacokinetics, safety and tolerability of a single-dose of PF-04965842 in healthy subjects	HV	24	Fluvoxamine: Single-dose 100 mg[e] PF-04965842 (Period 1), and then 9 days of continuous fluvoxamine 50 mg QD dosing with a single-dose of 100 mg[e] PF-04965842 on Day 8 (Period 2). Fluconazole: Single-dose 100 mg[e] PF-04965842 (Period 1), and then 7 days of continuous fluconazole dosing (400 mg on Day 1 and then 200 mg QD on Days 2 to 7) with a single-dose of 100 mg[e] PF-04965842 on Day 5 (Period 2). Fasted	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours (and 72 hours for the fluconazole cohort) post-PF-04965842 dose in Period 1 and Period 2
B7451019	1	A phase 1, open-label, fixed-sequence study to estimate the effect of repeat-dose rifampin on the pharmacokinetics of PF-04965842 in healthy subjects	HV	12	Single-dose 200 mg[e] PF-04965842 (Period 1), and then 8 days of continuous rifampin 600 mg QD dosing with a single-dose of 200 mg[e] PF-04965842 on Day 8 (Period 2). Fasted	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, and 48 hours post-PF-04965842 dose in Period 1 and Period 2
B7451020	1	A phase 1, non-randomized, open-label, single-dose study to compare the pharmacokinetics, safety and tolerability of PF-04965842 in adult subjects with mild and moderate hepatic impairment relative to subjects with normal hepatic function	HV, MiHI and MoHI	24	Single-dose of 200 mg[e] PF-04965842. Fasted	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 24, 36, and 72 hours post-dose
B7451027	1	A phase 1, randomized, placebo- and positive-controlled crossover study to determine the effect of single-dose PF-04965842 on QT_c interval in healthy volunteers	HV	36	600 mg[e] PF-04965842, placebo, and 400 mg moxifloxacin, each as a single-dose. Fasted	0 (pre-dose), 0.25, 0.5, 1, 2, 3, 6, 12, and 24 hours post-PF-04965842 dose
B7451043	1	A phase 1, open-label, fixed-sequence study to assess single-dose and multiple dose pharmacokinetics of PF-04965842 and its metabolites, and the effect of repeat-dose probenecid on the single-dose pharmacokinetics of PF-04965842 and its metabolites in healthy participants	HV	12	Single-dose of 200 mg[e] PF-04965842 (Period 1), then 200 mg QD[e] PF-04965842 for 4 days (Period 2), and then single-dose of 200 mg[e] PF-04965842 on Day 2 in the presence of probenecid (Period 3)	0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours post-PF-04965842 dose on Period 1 Day 1, Period 2 Day 4, and Period 3 Day 2

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Table 96. Summary of Baseline Patient Characteristics in the PK Dataset by Patient Type

Characteristics	level	HV	PsO	AD	MiHI	MoHI	Total
N		165	45	769	8	8	995
RACE, n (%)	Unknown	0	0	5 (0.7)	0	0	5 (0.5)
	White	99 (60.0)	32 (71.1)	521 (67.8)	4 (50.0)	7 (87.5)	663 (66.6)
	Black	37 (22.4)	7 (15.6)	61 (7.9)	4 (50.0)	0	109 (11.0)
	Asian	12 (7.3)	4 (8.9)	162 (21.1)	0	0	178 (17.9)
	Other	17 (10.3)	2 (4.4)	20 (2.6)	0	1 (12.5)	40 (4.0)
SEX, n (%)	Male	147 (89.1)	29 (64.4)	419 (54.5)	5 (62.5)	5 (62.5)	605 (60.8)
	Female	18 (10.9)	16 (35.6)	350 (45.5)	3 (37.5)	3 (37.5)	390 (39.2)
AGE GROUP, n	Adolescent	0	0	90 (11.7)	0	0	90 (9.0)
(%)	Adult	165 (100.0)	45 (100.0)	679 (88.3)	8 (100.0)	8 (100.0)	905 (91.0)
Age (Yrs), Mean (Sd)		37.6 (11.0)	45.7 (11.9)	35.5 (16.3)	57.9 (4.19)	58.6 (8.21)	36.7 (15.7)
Weight (Kg), Mean (Sd)		79.4 (11.1)	90 (20.2)	76.9 (20)	96.8 (16.4)	87.5 (22.4)	78.1 (19.1)

Characteristics level	HV	PsO	AD	MiHI	MoHI	Total
BMI (kg/m^2), Mean (Sd)	25.7 (3.09)	30.4 (5.19)	26.6 (6.02)	32 (5.27)	29.6 (5.31)	26.7 (5.68)
CCL (mL/min), Mean (Sd)	120 (23.1)	137 (49.4)	131 (42.9)	127 (32.4)	133 (50.7)	130 (40.7)
Bilirubin (mg/dL), Mean (Sd)	0.6 (0.249)	0.436 (0.205)	0.485 (0.254)	0.55 (0.321)	1.31 (0.702)	0.509 (0.271)

Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-962\pmar-eqdd-b745d-962.pdf (Table 4 and Table 6)

16.5.2.1.3.2 Final Population PK Model

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.3 using sequential SAEM and IMP. Concentration collected before the first dose as well as post-dose observations that were below the limit of quantification (BLQ, 20% of all PK samples) were included in the PK analysis using M3 method.

The plasma concentrations of abrocitinib were described by a two-compartment disposition model with parallel first-order and zero-order absorptions and linear elimination. The model was parameterized in absorption constant (ka), zero-order absorption rate (k0), amount absorbed by first-order processes (Ak1), clearance (CL), central compartment volume (Vc), inter-compartment clearance (Q), and peripheral volume (Vp). Intrinsic (sex, age, race, body weight, patient status, hepatic function) and extrinsic (DDI, fed status) factors were identified as covariates on F, Ak1, CL, and Vc.

The final population PK parameters are presented in

Table 97. Fixed and random effect parameters were all estimated with good precision (|%RSE| < 30%, value derived from lst file). The magnitude of the IIV was moderate for CL/F (57.7 %CV) and Vc/F (41.4 %CV). IIV for Vp and Q were fixed to 0%. Residual variability was moderate for most studies, but high for Study B7451043 (94.4 %CV, value derived from final model). Eta and epsilon shrinkages were reasonable (<30%) for EBE estimation.

Model evaluations were based on successful model convergence, accuracy of parameter estimation (RSE/95% confidence interval, and bootstrap,

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Table 97), goodness-of-fit plots (Figure 19), and prediction-corrected visual predictive check (

Figure 20). The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

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Table 97. Parameters Estimates of the Final Population PK Model

Parameter	Value	95% CI	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Objective Function Value	65016.7				
Condition Number	10				
Population Parameter					
Clearance (CL; L/hr)	22	20.2, 23.8	21.7	17.9, 27.1	
Volume of the central compartment (V_c; L)	87.8	81.1, 94.5	86.3	73.7, 102	
Inter-compartmental clearance (Q; L/hr)	1.16	0.994, 1.33	1.13	0.718, 1.67	
Volume of the peripheral compartment (V_p; L)	8.25	7.6, 8.9	8.11	5.41, 11.5	
Zero-order absorption rate (k_0; mg/hr)	75.3	71.2, 79.4	73.1	55.1, 93.9	
Amount absorbed by first-order processes (Ak_1; mg)	121	109, 133	122	102, 146	
First-order absorption rate constant (k_a; hr^{-1})	4.01	3.48, 4.54	3.99	3.02, 5.41	
Proportional residual error (*RUVPRO*; SD)	0.437	0.429, 0.445	0.431	0.406, 0.46	
Additive residual error (*RUVADD*; SD)	0.509	0.48, 0.538	0.506	0.416, 0.599	
Effect of moderate variability studies on *RUVPRO*	0.495	0.434, 0.556	0.514	0.382, 0.636	
Effect of high variability studies on *RUVPRO*	1.16	1.05, 1.27	1.19	0.921, 1.54	
Effect of tablet formulations on *ALAG1*	0.183	0.167, 0.199	0.184	0.141, 0.212	
Effect of rifampin on CL	0.264	0.169, 0.359	0.24	-0.0167, 1.19	
Effect of rifampin on F	-2.08	-1.96, -2.2	-2.12	-2.48, -1.6	
Effect of fluconazole on CL	-0.541	-0.513, -0.569	-0.533	-0.61, -0.403	
Effect of fluvoxamine on CL	-0.234	-0.194, -0.274	-0.227	-0.336, -0.0594	
Effect of fluconazole or fluvoxamine on F	1.31	1.01, 1.61	1.3	0.795, 2.13	
Effect of high-fat meal on Ak_1	-1	Fixed	-1	Fixed	
Effect of Phase 2 10 and 50 mg tablets on F	-1.02	-0.744, -1.3	-1.07	-1.49, -0.627	
Effect of Phase 3 100 mg tablet on F	-0.766	-0.653, -0.879	-0.811	-1.12, -0.446	
Effect of suspension on Ak_1	1.17	0.858, 1.48	1.23	0.773, 2.34	
Effect of Phase 2 10 and 50 mg tablets on Ak_1	-0.68	-0.584, -0.776	-0.685	-0.787, -0.233	
Effect of multiple-dosing on F	0.241	0.131, 0.351	0.253	-0.0216, 0.698	
Maximum change in CL with respect to time (TAFO; %)	-0.186	-0.167, -0.205	-0.192	-0.485, -0.106	
Rate of change in CL with respect to time (half-life; hr)	21.6	14.5, 28.7	23.1	8.31, 1189	
Effect of effective daily dose on CL	-0.169	-0.136, -0.202	-0.166	-0.227, -0.108	
Effect of Asian/Other subjects on F	0.815	0.692, 0.938	0.737	0.337, 1.92	
Combined effect of PsO and AD patients on F	0.489	0.256, 0.722	0.512	0.0678, 0.852	
Combined effect of mild and moderate hepatic impairment on F	1.3	0.783, 1.82	1.36	0.489, 2.3	
Effect of weight on CL and Q (referenced to 70 kg)	0.453	0.278, 0.628	0.472	0.238, 0.702	
Effect of weight on V_c and V_p (referenced to 70 kg)	0.52	0.379, 0.661	0.524	0.341, 0.705	
Effect of adolescent subjects on F	-0.589	-0.306, -0.872	-0.591	-0.916, -0.307	
Effect of 800 mg dose on F	-0.778	-0.666, -0.89	-0.776	-1.39, -0.508	
Effect of female subjects on F	0.353	0.24, 0.466	0.348	0.103, 0.666	
Inter-Individual Variability					
ω_{CL} (% CV)	57.7	51.8, 63.6	58	54, 63.2	9.71
ω_{V_c} (% CV)	41.4	34.8, 48	41.5	37.4, 46.3	27.3
Correlation					
ρ_{CL-V_c}	0.326	0.22, 0.432	0.337	0.211, 0.454	
Random Unexplained Variability					
ε_{res}	1	Fixed	1	Fixed	13.8

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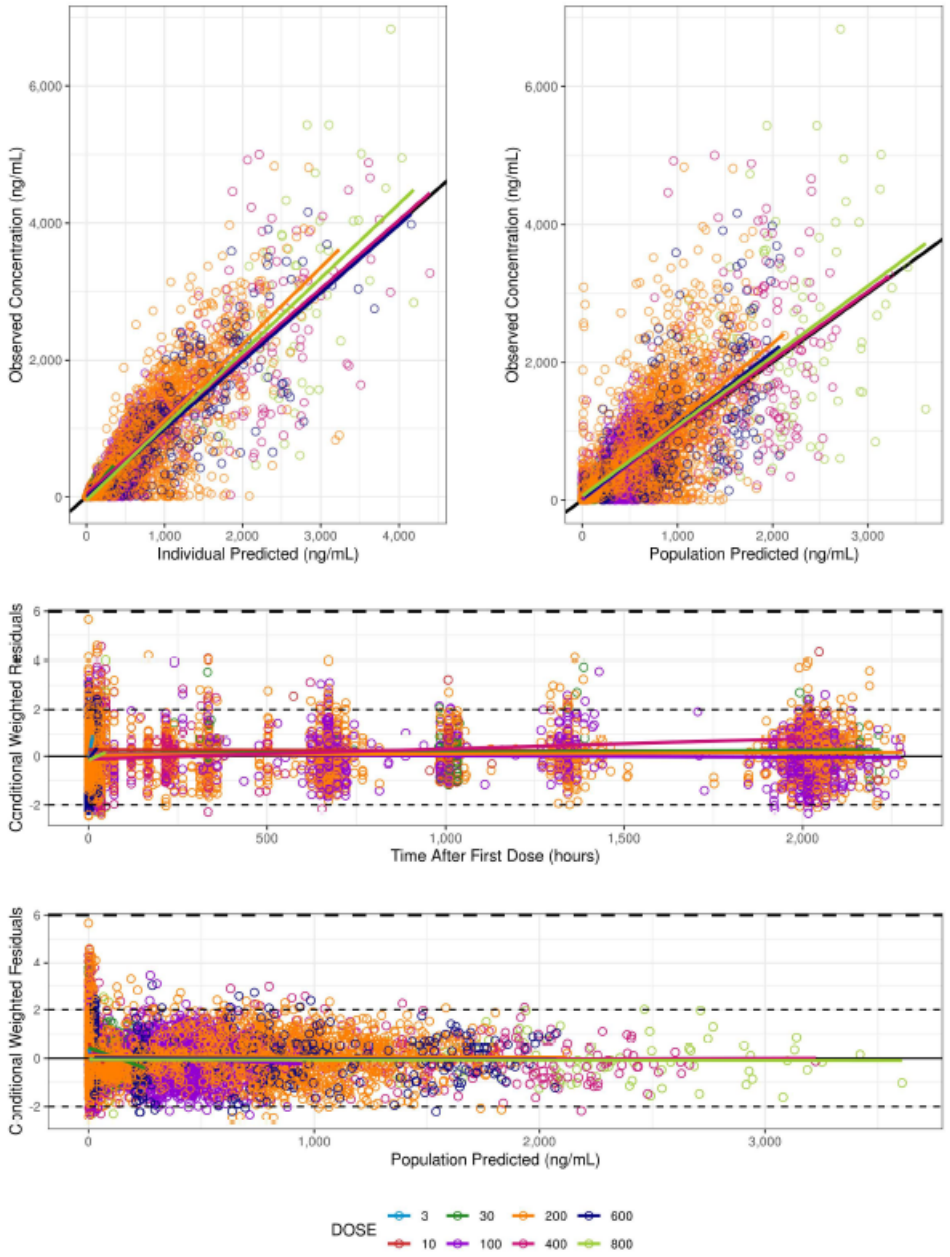
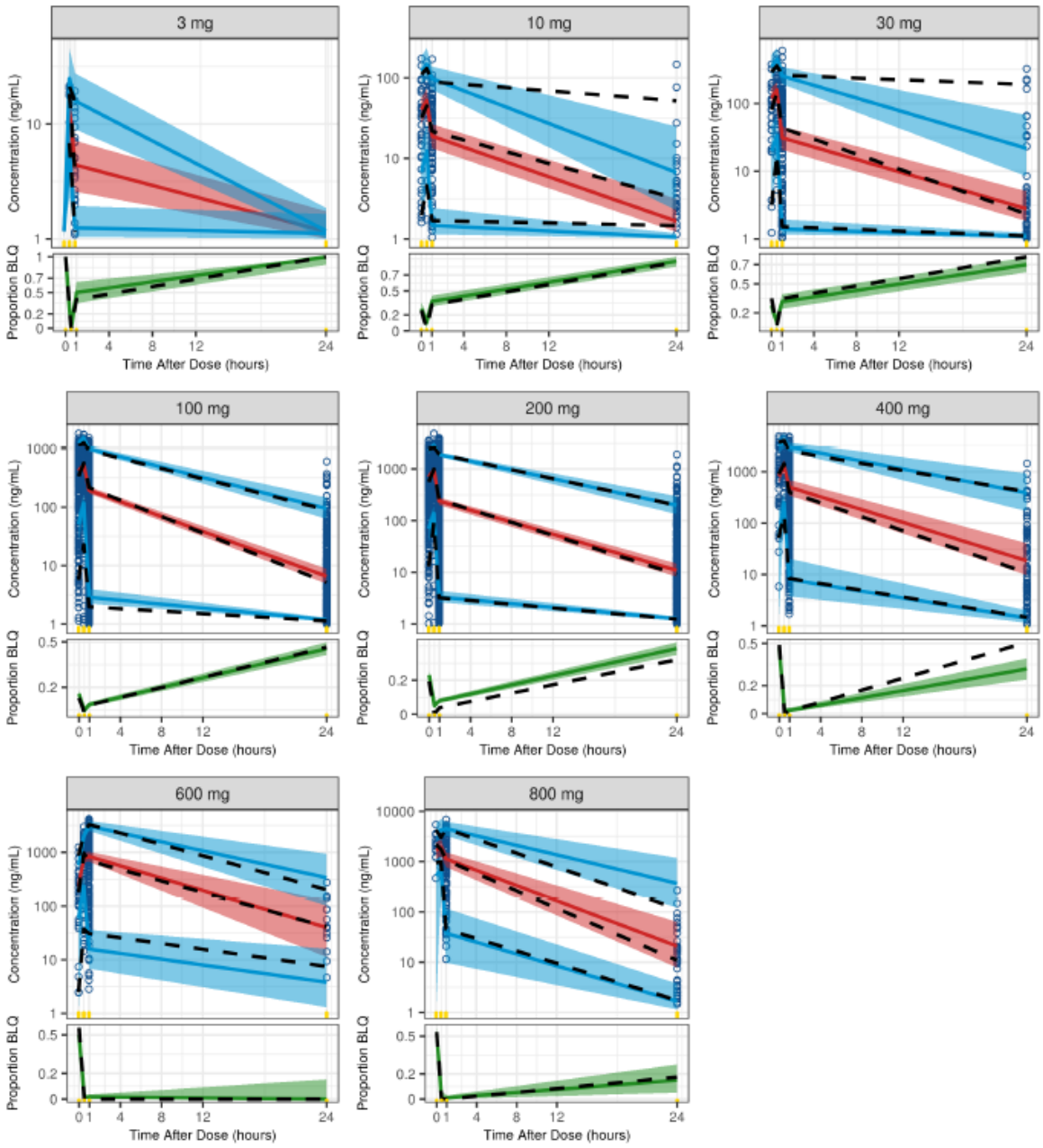
Figure 19. Goodness-of-fit Plots for the Final Population PK Model



Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-962\pmar-eqdd-b745d-962.pdf (Figure A5.3)

Figure 20. Visual Predictive Check Stratified by Dose for Final Population PK Model



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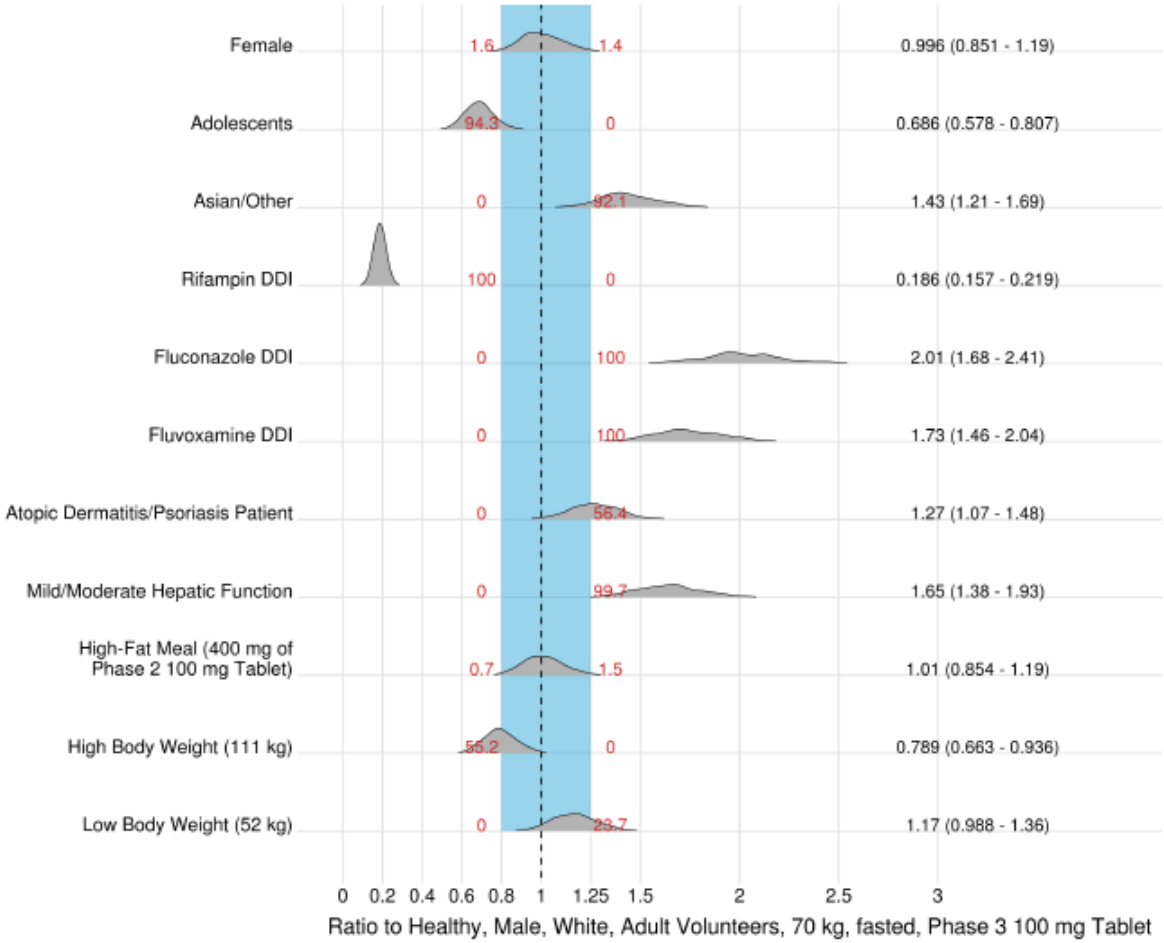
16.5.2.1.3.3 Covariates Effects on Steady-state Exposure

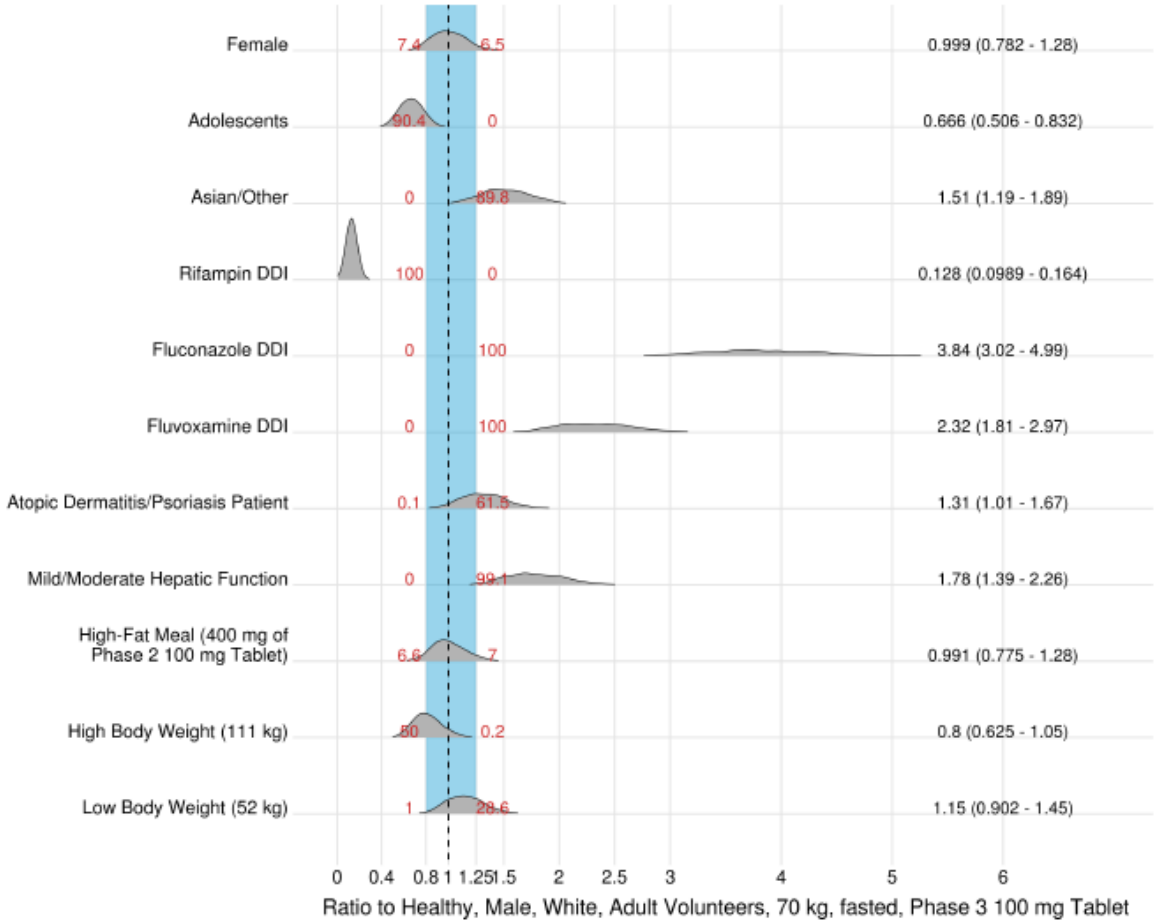
Among the identified covariates, adolescents and rifampin co-administration resulted in a lower exposure, while Asian/Other race, co-administration with fluconazole and fluvoxamine, patient population (PsO/AD), and hepatic impairment resulted in a higher exposure, relative to the reference (Figure 21 and Figure 22).

Figure 21. Ratios of Steady-State Cmax Following 200 mg QD for Given Covariates



Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-962\pmar-eqdd-b745d-962.pdf (Figure 3)

Figure 22. Ratios of Steady-State AUC_{0-24h} Following 200 mg QD for Given Covariates



Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-962\pmar-eqdd-b745d-962.pdf (Figure 4)

16.5.2.2 Clinical PK/PD Analysis

16.5.2.2.1 Review Summary

The applicant's PK/PD analysis is acceptable for characterizing the PD profile of platelet counts for thrombocytopenia risk, and EASI/IGA scores for treatment response in AD patients over 12 weeks of treatment.

For platelet model, the drug-induced platelet reduction was characterized by a tachyphylactic Emax function for a declining drug effect over time on platelet proliferation. IIV (17.5 %CV) was only evaluated on baseline platelet counts, and intrinsic factors (sex, age, baseline WBC, baseline hematocrit, and disease type) were identified as significant covariates.

For treatment response, two endpoints (EASI, IGA) were modeled separately. The magnitude of drug effect was characterized by "stimulation on K_{off}" of an indirect response model for changes in EASI scores, and as a covariate of a logistic regression for IGA response. IIV was only evaluated for a single parameter in each model: baseline EASI score in EASI model and intercept

in IGA model. Most factors identified as covariates would not result in a reduction in treatment response. Adolescents were predicted to have 8% less EASI75 response rate than the reference, and patients with baseline IGA of 4 were predicted to be about 50% less likely to have an IGA response than the reference.

The sponsor's analyses were verified by the reviewer, with no significant discordance identified. The developed model was used for simulation to provide support for the proposed dose with respect to safety and efficacy.

16.5.2.2.2 Objectives

The primary objectives of the analyses were to:

- To examine if the final platelet model reasonably described the time-course of drug-induced platelet reduction;
- To determine if the simulation with platelet model adequately addressed the safety concerns in at-risk patient population;
- To examine if the final EASI model reasonably described the time-course of disease score.
- To examine if the final IGA model adequately captured the IGA response over time.

16.5.2.2.3 PK/PD model for Safety

16.5.2.2.3.1 Data

Analyses were based on platelet data from 2 Phase 2 studies and (B7451005, B7451006) and 3 Phase 3 studies (B7451912, B7451013, B7451014). Summary of study design, study population, dose, and timing of blood samples are provided in

Table 98.

The final NONMEM data file for analysis contained 12189 PD observations from 2333 subjects. Table 99 provides summary statistics of the baseline demographic covariates in the analysis dataset.

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Table 98. Summary of Studies Included in PK/PD Modeling for Safety

Protocol	Phase	Protocol Design	Population	n	Dose Administration	Platelet Count Sampling
B7451005	2	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Safety and Efficacy of PF-04965842 in Subjects with Moderate to Severe Psoriasis	PsO	59	200 mg BID, 400 mg QD, or 200 mg QD of PF-04965842 or matching placebo for 4 weeks.	Screening, Week 0, 1, 2, 3, and 4, and follow-up at Week 8.
B7451006	2b	A Phase 2b Randomized, Double-Blind, Placebo-Controlled, Parallel, Multi-Center, Dose-Ranging Study to Evaluate the Efficacy and Safety Profile of PF-04965842 in Subjects with Moderate to Severe Atopic Dermatitis	AD	269	10, 30, 100, 200 mg QD of PF-04965842 or matching placebo for 12 weeks.	Screening, Week 0, 1, 2, 4, 6, 8, and 12, and follow-up at Week 13, 14, and 16.
B7451012	3	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy and Safety of PF-04965842 Monotherapy in Subjects Aged 12 Years and Older, with Moderate to Severe Atopic Dermatitis	AD	387	100 or 200 mg QD of PF-04965842 or matching placebo for 12 weeks.	Screening, Week 0, 2, 4, 8, and 12, and follow-up at Week 16.
B7451013	3	A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Study to Evaluate the Efficacy and Safety of PF-04965842 Monotherapy in Subjects Aged 12 Years and Older, with Moderate to Severe Atopic Dermatitis	AD	391	100 or 200 mg QD of PF-04965842 or matching placebo for 12 weeks.	Screening, Week 0, 2, 4, 8, and 12, and follow-up at Week 16.
B7451014	3	A Phase 3 Randomized Withdrawal, Double-Blind, Placebo-Controlled, Multi-Center Study Investigating the Efficacy and Safety of PF-04965842 in Subjects Aged 12 years and Over, with Moderate to Severe Atopic Dermatitis with the Option of Rescue Treatment in Flaring Subjects	AD	1236	200 mg QD of PF-04965842 for 12 weeks, then randomized to 100 or 200 mg QD of PF-04965842 or matching placebo for 40 weeks.	Screening, Week 0, 2, 4, 8, and 12.

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Table 99. Summary of Baseline Patient Characteristics in the Dataset by Study

Characteristics	level	B7451005	B7451006	B7451012	B7451013	B7451014	Total
N		59	263	387	391	1233	2333
Dosing Regimen,	Placebo	14 (23.7)	55 (20.9)	77 (19.9)	78 (19.9)	0	224 (9.6)
n (%)	10 mg QD	0	49 (18.6)	0	0	0	49 (2.1)
	30 mg QD	0	50 (19.0)	0	0	0	50 (2.1)
	100 mg QD	0	55 (20.9)	156 (40.3)	158 (40.4)	0	369 (15.8)
	200 mg QD	15 (25.4)	54 (20.5)	154 (39.8)	155 (39.6)	1233 (100)	1611 (69.1)
	200 mg BID	14 (23.7)	0	0	0	0	14 (0.6)
	400 mg QD	16 (27.1)	0	0	0	0	16 (0.7)
RACE, n (%)	Unknown	0	0	3 (0.8)	5 (1.3)	6 (0.5)	14 (0.6)
	White	42 (71.2)	190 (72.2)	279 (72.1)	232 (59.3)	931 (75.5)	1674 (71.8)
	Black	10 (16.9)	39 (14.8)	32 (8.2)	21 (5.4)	75 (6.1)	177 (7.6)
	Asian	5 (8.5)	27 (10.3)	58 (15.0)	129 (33.0)	196 (15.9)	415 (17.8)
	Other	2 (3.4)	7 (2.7)	15 (3.9)	4 (1.0)	25 (2.0)	53 (2.3)
SEX, n (%)	Male	40 (67.8)	123 (46.8)	220 (56.8)	229 (58.6)	684 (55.5)	1296 (55.6)
	Female	19 (32.2)	140 (53.2)	167 (43.2)	162 (41.4)	549 (44.5)	1037 (44.4)
AGE GROUP, n	Adolescent	0	0	84 (21.7)	32 (8.2)	224 (18.2)	340 (14.6)
(%)	Adult	59 (100.0)	263 (100.0)	303 (78.3)	359 (91.8)	1009 (81.8)	1993 (85.4)
Age (Yrs), Mean (Sd)		45.7 (11.5)	40.6 (16.0)	32.5 (16.0)	35.1 (15.1)	31.6 (14.9)	33.7 (15.5)
Weight (Kg), Mean (Sd)		90.2 (19.8)	79.2 (21.0)	77.3 (20.3)	74.0 (17.6)	73.6 (19.7)	75.4 (19.9)
Hematocrit (%), Mean (Sd)		44.0 (3.47)	42.8 (3.52)	42.6 (3.66)	42.9 (3.97)	43.3 (3.98)	43.1 (3.87)
Neutrophils (%), Mean (Sd)		63.7 (8.09)	63.6 (8.91)	61.4 (8.31)	61.6 (8.21)	61.3 (9.14)	61.7 (8.84)
WBC (·1000µL), Mean (Sd)		6.84 (2.00)	7.03 (2.04)	7.38 (2.09)	6.89 (1.92)	7.32 (2.20)	7.22 (2.12)
Platelets (·1000µL), Mean (Sd)		241 (51.5)	277 (64.4)	288 (69.9)	267 (63.2)	288 (70.6)	282 (68.9)

Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-963\pmar-eqdd-b745d-963.pdf (Table 5 and Table 6)

16.5.2.2.3.2 Final Platelet Model

The population PK/PD analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.3 using FOCE-I.

The drug-induced platelet reduction with a nadir occurring at Week 4 was described by a tachyphylactic Emax function on platelet proliferation which underwent 3 transit compartments with a mean transit time of 7.21 days until maturation. The drug effect on platelet proliferation was parameterized in E_{max}, EC_{50}, abrocitinib concentration (*CP*), and tachyphylaxis (*KTCPX*) as described in the equation below:

$$E^{Drug} = \frac{E^{max} * CP}{EC^{50} + CP} * exp(-KTCPX * t)$$

The effect of baseline platelet counts ($CIRC_0$) on E_{max} was represented by a power model referenced to the population-typical estimate for baseline platelet counts (ϑ_{CIRC0}) with a parameter quantifying the effect of $CIRC_0$ on E_{max} ($\vartheta_{CIRC0Emax}$) as described in equation below:

$$E^{max} = \theta^{Emax} * \left(\frac{CIRC^0}{\theta^{CIRC0}}\right)^{\theta^{CIRC0Emax}}$$

Intrinsic factors (sex, age, baseline hematocrit, and baseline WBC) were identified as covariates on $CIRC_0$, which in turn elicits effect on E_{max} and the nadir.
The final population parameters are presented in Table 100. Fixed and random effect parameters were all estimated with good precision (|%RSE| < 30%, value derived from lst file). The magnitude of the IIV was low for $CIRC_0$ (17.5 %CV). Residual variability was small (proportional error CV: 12%, additive error SD: 16.4). Eta and epsilon shrinkages were small (<10%).

Model evaluations were based on accuracy of parameter estimation (RSE/95% confidence interval, and bootstrap, Table 100), goodness-of-fit plots (

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Figure 23), and visual predictive check (

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Figure 24). The model described the observed data well and the model predictions were generally within the 90% prediction intervals. No apparent bias was observed in the overall model fit for the data.

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Table 100. Parameters Estimates of the Final Platelet Model

Parameter	Value	95% CI	Bootstrap Median	Bootstrap 95% CI	SHR (%)
Objective Function Value	103325.1				
Condition Number	12.5				
Population Parameter					
Baseline platelet count ($CIRC_0$; ·1000/μL)	270	(267, 273)	270	(267, 274)	
Feedback exponent (GAM, γ)	0.232	(0.214, 0.250)	0.231	(0.186, 0.276)	
Mean transit time (MTT; days)	7.21	(6.95, 7.47)	7.21	(6.74, 7.65)	
Maximum drug effect on platelet proliferation (E_{max})	0.109	(0.102, 0.116)	0.109	(0.0889, 0.134)	
Concentration at 50% of maximum drug effect (EC_{50}; ng/mL)	55.3	(42.8, 67.8)	55.6	(30.4, 112)	
Half-life of tachyphlaxis (k_{TCPX}; days)	151	(130, 172)	149	(113, 202)	
Effect of $CIRC_0$ on E_{max}	-1.11	(-1.21, -1.01)	-1.11	(-1.36, -0.869)	
Proportional residual error ($RUV\,PRO$; SD)	0.120	(0.117, 0.123)	0.119	(0.109, 0.129)	
Additive residual error ($RUVADD$; SD)	16.4	(15.3, 17.5)	16.2	(12.4, 20.1)	
Effect of baseline WBC on $CIRC_0$ (referenced to 6.9·1000/μL)	0.199	(0.173, 0.225)	0.200	(0.171, 0.227)	
Effect of female sex on $CIRC_0$	0.0584	(0.0395, 0.0773)	0.0580	(0.0387, 0.0794)	
Effect of age on $CIRC_0$ (referenced to 30 years)	-0.0695	(-0.0854, -0.0536)	-0.0695	(-0.0846, -0.0538)	
Effect of baseline hematocrit on $CIRC_0$ (referenced to 43%)	-0.203	(-0.301, -0.105)	-0.201	(-0.307, -0.101)	
Effect of PsO patients on $CIRC_0$	-0.118	(-0.159, -0.0768)	-0.118	(-0.161, -0.0712)	
Inter-Individual Variability					
ω_{CIRC_0} (% CV)	17.5	(16.3, 18.7)	17.5	(16.7, 18.2)	4.66
Random Unexplained Variability					
ε_{res}	1.00	Fixed	1.00	Fixed	8.55

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Figure 23. Goodness-of-fit Plots for the Final Platelet Model

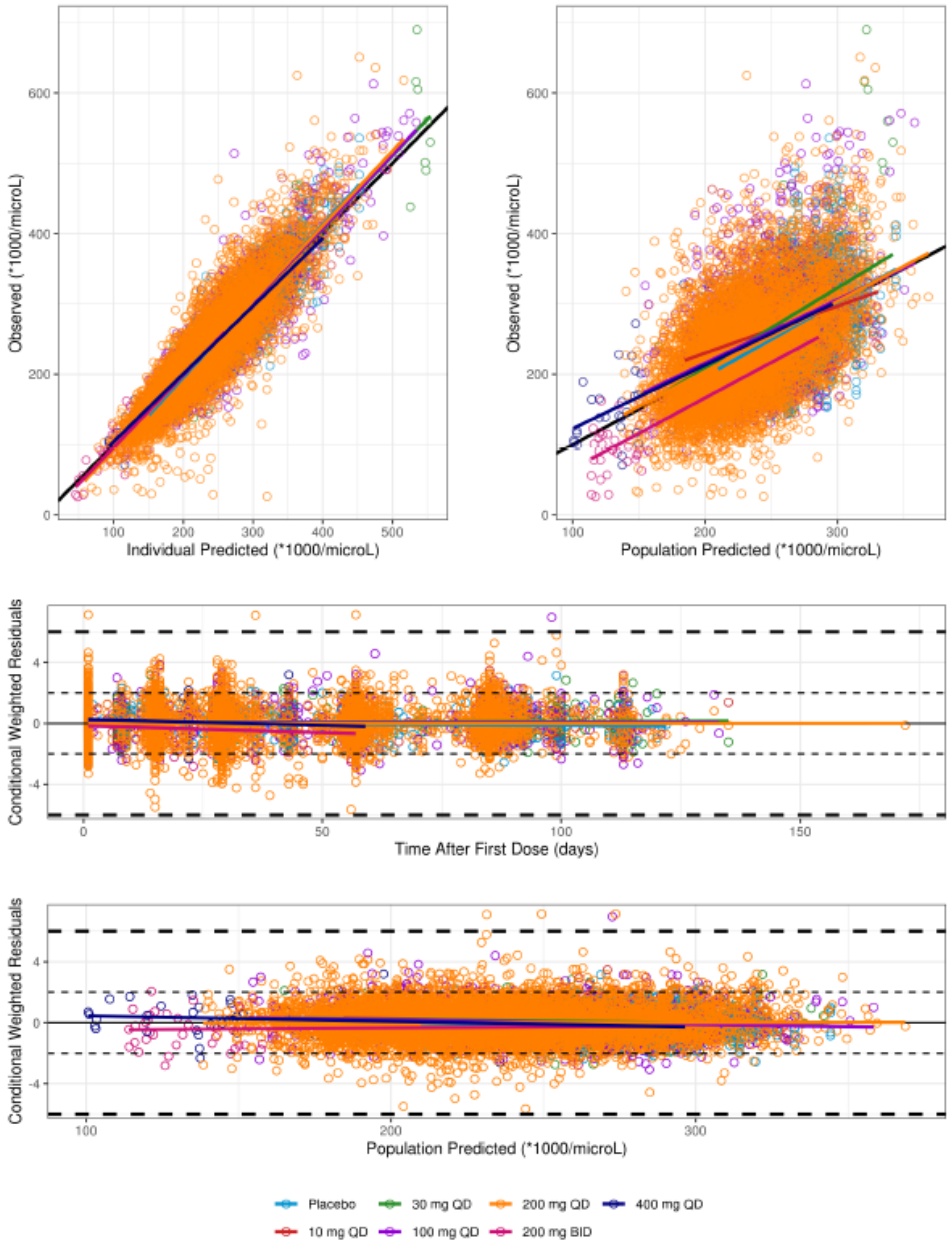

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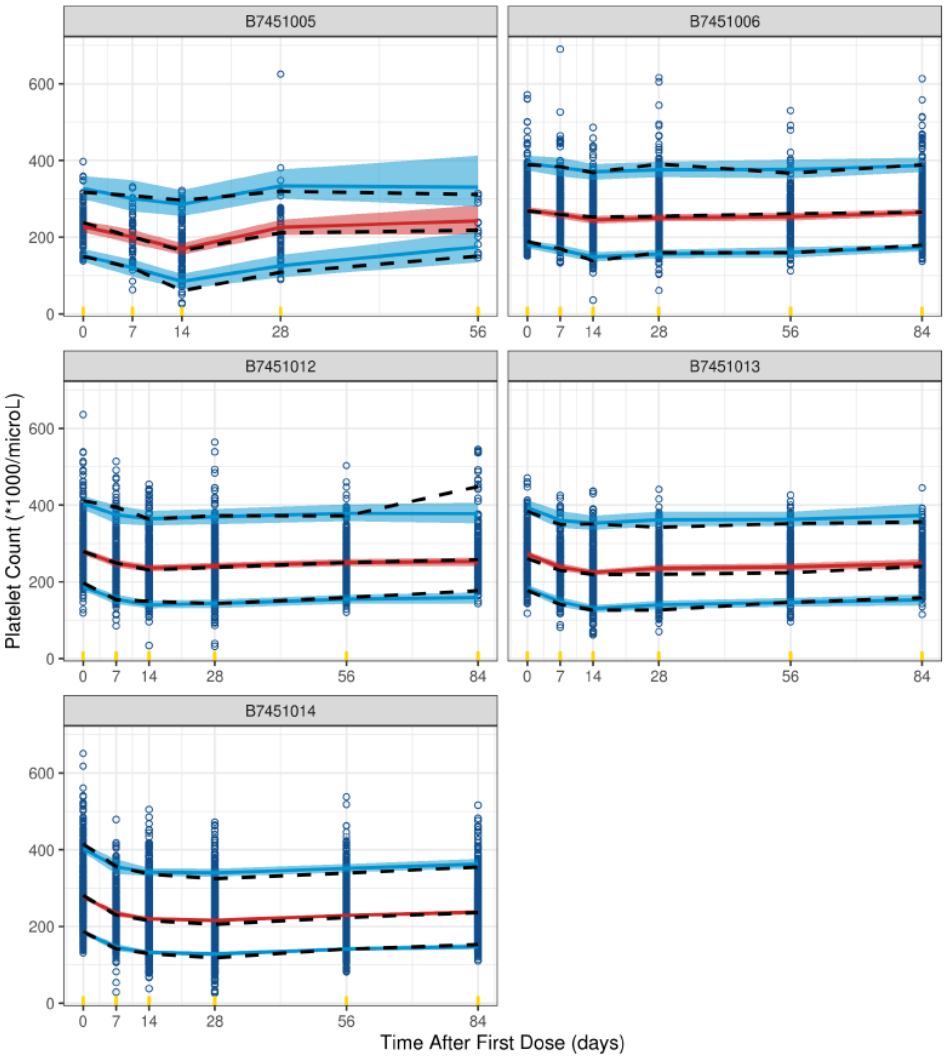
Figure 24. Visual Predictive Check Stratified by Study for Final Platelet Model



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16.5.2.2.3.3 Evaluation of Thrombocytopenia Using Platelet Model

The final PK/PD model was used to simulate platelet counts to evaluate thrombocytopenia, with the primary focus on the probability of Grade 3 or more severe thrombocytopenia **(<50·1000/µL)** for platelet count scenarios of 170, 220, and **270·1000/µL** at baseline (Figure 25 and

Table 101). Sponsor summarized the percentage of thrombocytopedia for each grade based on the predicted platelet counts at the nadir and concluded that the probability of observing

Grade 3 or more severe thrombocytopenia was low (<3%) for all baseline platelet count scenarios.

There are some limitations noted in the analysis. Baseline platelet count of 170·1000/µL is approximately 2.5th percentile of the baseline platelet counts in the study population, hence very few patients had baseline platelet counts below 170·1000/µL. This is because the patients with baseline platelet counts under 150·1000/µL were not eligible for the treatment. However, in the simulation for a baseline platelet count of 170·1000/µL (Figure 25, left panel), there was a significant proportion of platelet counts under 150·1000/µL at baseline. Therefore, the summary statistics for the probability of Grade 3 or more severe thrombocytopenia is not appropriate for evaluating the risk of thrombocytopenia on a population scale for baseline platelet count scenarios other than the study population.

Rather, the central tendency of predicted platelet counts, which is the median values indicated by blue lines in Figure 25, may be more appropriate to evaluate the platelet counts at the nadir than the probability of Grade 3 or more severe thrombocytopenia that was generated based on the distribution of the residual error. The median values were above the 100·1000/µL for all three baseline platelet scenarios. The probability of Grade 3 or more severe thrombocytopenia with a baseline platelet count of 270·1000/µL was predicted to be 0%, which is consistent with the observed event rate. Together, Grade 3 and more severe thrombocytopenia is not anticipated with 100 QD dose.

Sponsor also carried out simulations to evaluate thrombocytopenia risk for Asians with an increased exposure and found <1% of Grade 3 or more severe thrombocytopenia. However, moderate hepatic impairment which is expected to increase abrocitinib exposure by 65% was not evaluated. Therefore, reviewer carried out independent analysis to further investigate the exposure related risk for thrombocytopenia.

Figure 25. Simulated Platelet Counts for Baseline Values Administered 100 mg QD

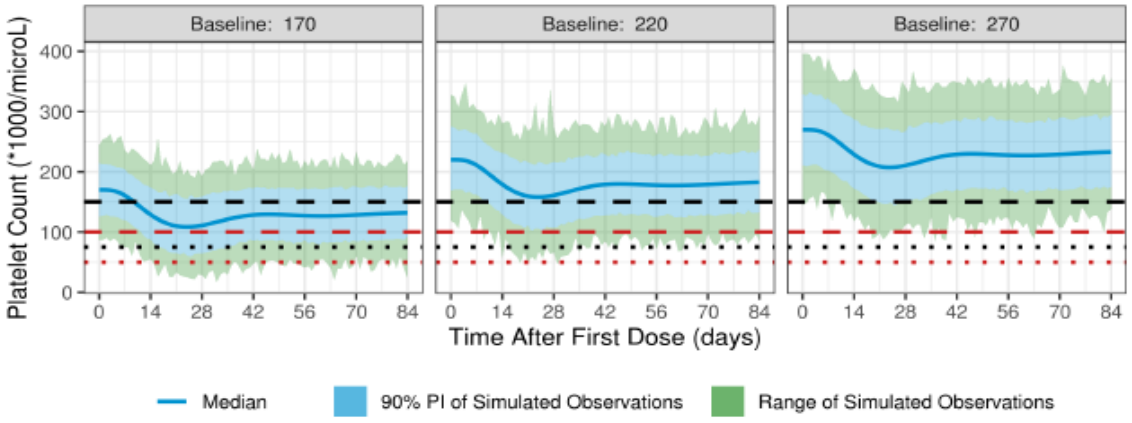

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Table 101. Probability of Thrombocytopenia Grades at the Nadir for Baseline Values Administered 100 mg QD

Summary	Baseline: 170·1000/μL	Baseline: 220·1000/μL	Baseline: 270·1000/μL
Nadir			
Change from Baseline (·1000/μL)[a]	-63.9 (-109.4, -12.0)	-65.4 (-117.5, -8.9)	-66.0 (-124.3, -2.1)
Change from Baseline (%)[a]	-37.6 (-64.3, -7.1)	-29.7 (-53.4, -4.1)	-24.4 (-46.0, -0.8)
Grade 1 Thrombocytopenia (%)	80.5	42.8	7
Grade 2 Thrombocytopenia (%)	9.7	0.7	0
Grade 3 Thrombocytopenia (%)	1.9	0	0
Grade 4 Thrombocytopenia (%)	0	0	0
< 100·1000/μL (%)	40.9	4	0.2

Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-963\pmar-eqdd-b745d-963.pdf (Table 12)

16.5.2.2.3.4 Independent E-R Analysis Assessing Thrombocytopenia Risk with Increased Exposure

To circumvent the limitations in sponsor's simulation and further test exposure related thrombocytopenia risk, reviewer carried out exposure-response analysis to characterize platelet at the nadir (~Week 4) with exposures and other risk factors.

Platelet measures were extracted from lb data from the sdtm dataset of the five studies indicated in

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Table 98. Abrocitinib exposures were generated using the post-hoc parameters from the population PK model, and steady-state exposures were used for analysis. After removing records without baseline/Week4 platelet counts or exposure, the final data for analysis contained 1037 platelet observations. Graphical exploration suggested a linear relationship between exposure and platelet counts at the nadir and platelets reduction from baseline (

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Figure 26).
A multivariate linear regression was performed using R (version 4.0.2). Covariates evaluated included baseline platelet counts, age, sex, Asian race, and body weight. The final model was established with stepwise AIC to select for significant covariates ($p < 0.05$) (Table 102).

Exposure was positively correlated with platelet count at nadir. Similar to sponsor's platelet model, a lower baseline platelet count predicted a lower nadir. In addition, older age also contributed to a lower nadir.

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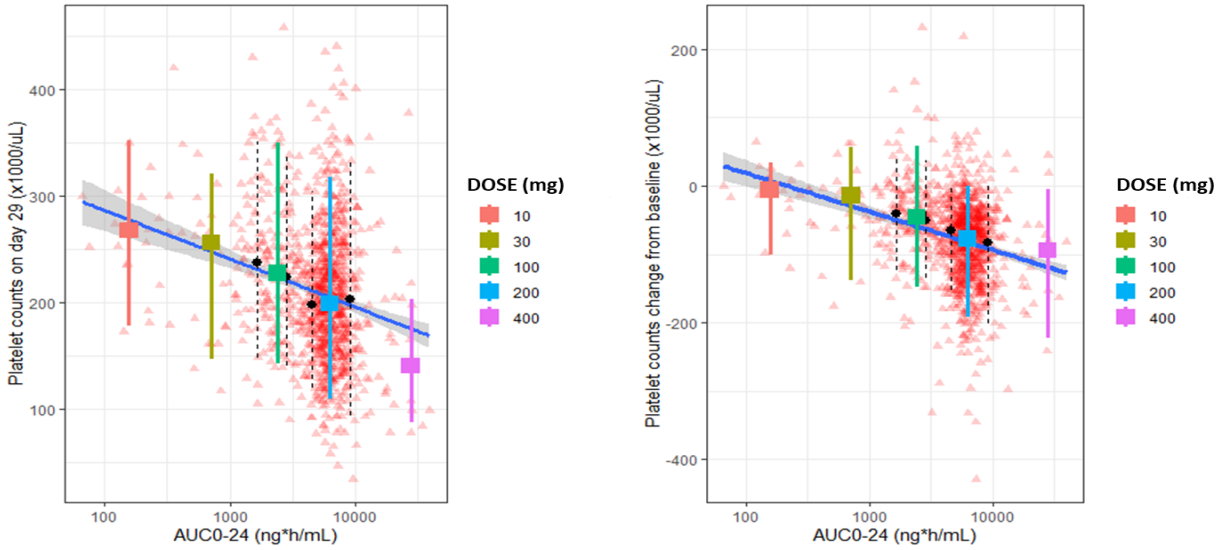
Figure 26. Relationship of Platelets Counts at Nadir and Platelet Reduction from Baseline



Source: Reviewer's analysis. Dashed vertical lines indicate 4 quartiles of $AUC_{0\text{-}24h}$ in the pivotal study B7451012 and B7451013. Regression line was based on all available data from five studies.

Table 102. Coefficients of the Final E-R Model

Parameter	Estimate	SE	P-value
Intercept	285	19.2	< 2e-16 ***
Log10($AUC_{0\text{-}24h}$)	-56.1	4.81	< 2e-16 ***
Baseline Platelets	0.512	0.0221	< 2e-16 ***
Age	-0.437	0.103	2.64e-05 ***

Source: Reviewer's analysis.

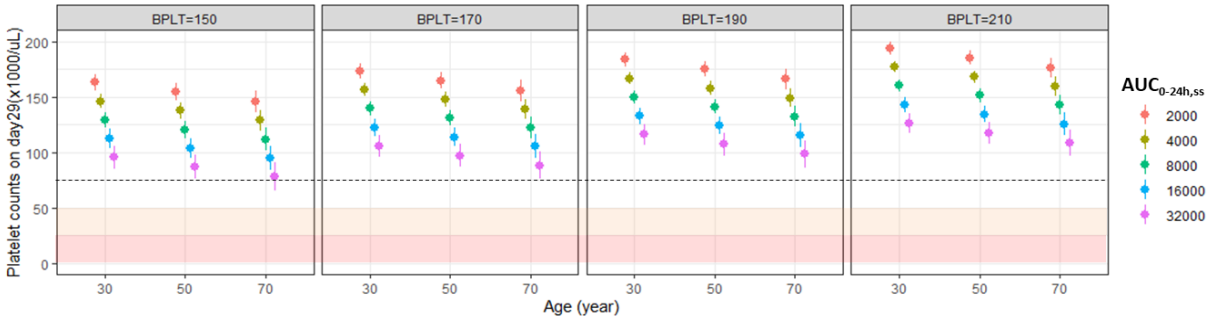
The final E-R model was used to predict the platelet counts at the nadir for scenarios of interaction amongst baseline platelet (150, 170, 190, 210·1000/μL), age (30, 50, 70 yr), and exposure (2000, 4000, 8000, 16000, 32000 ng*h/mL). The exposure for 100 mg QD ranges from 353 to 14900 ng*h/mL with a median, 75th, and 95th percentiles of 2430, 7346, and 10286 ng*h/mL, respectively. Therefore, the investigated exposure range covered 2 folds of the maximal exposure, 3 folds of the 95th percentile exposure, and 11 folds of the median exposure for 100 mg QD dose in the study population. The highest exposure scenario provides a sufficient margin in consideration of patients with increased exposure such as hepatic impairment, Asian race, co-medications, etc.

As shown in Figure 27, platelet count at the nadir for a 70-year old patient (at-risk cohort) with a baseline platelet count of 150·1000/uL (the minimal value allowed for treatment) who achieves 32000 ng*h/mL $AUC_{0\text{-}24h}$ at steady-state is predicted to be above Grade 2 thrombocytopenia (<75·1000/μL; black dashed). Therefore, the Grade 3 or more severe thrombocytopenia is not anticipated with 100 QD dose.

The exposure for 200mg QD ranges from 1840 to 395000 ng*h/mL with a median of 6360 ng*h/mL. The older patients with low baseline platelet counts were likely to have an increased

risk for Grade 2 thrombocytopenia when exposure is increased as a result of hepatic impairment or co-medications, etc.

Figure 27. Predicted Platelets Counts at Nadir for Various Scenarios of Baseline Platelet Counts, Age, and Exposure.



Source: Reviewer's analysis.

Reviewer's comments: The applicant's final platelet model adequately describes the observed data and is acceptable to be used for exploratory analysis for thrombocytopenia risk. Reviewer agreed with sponsor's conclusion but noted some limitations in the analysis and carried out independent analysis to further verify the conclusion. Reviewer's results support 100 mg and 200 mg QD dose of abrocitinib for an adequate safety margin of exposure over the platelet count of Grade 3 thrombocytopenia. Periodic monitoring of platelet after dose escalation to 200 mg may be considered for at-risk patients (age 65 years and older with baseline platelet <210·1000/µL) to avoid Grade 3 or more severe thrombocytopenia.

16.5.2.2.4 PK/PD model for Efficacy

16.5.2.2.4.1 Data

The co-primary endpoints of efficacy were assessed by EASI and IGA scores. EASI characterizes the eczema area and severity by a composite score ranging from 0 to 72, and IGA is a discrete measure of disease severity with 5-point scale.

Analyses were based on efficacy data of patients with moderate to severe AD from 1 Phase 2 study (B7451006) and 3 Phase 3 studies (B7451912, B7451013, B7451014). Summary of study design, study population, dose, and timing of efficacy assessment are provided in

Table 103.

The final NONMEM data file for analysis contained 11951 PD observations for EASI model, and 11864 PD observations for IGA model from 2273 subjects. Table 104 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 103. Summary of Studies Included in PK/PD Modeling for Efficacy

Protocol	Protocol Design	Population	n	Dose Administration	Efficacy Assessments
B7451006	A phase 2b randomized, double-blind, placebo-controlled, parallel, multi-center, dose-ranging study to evaluate the efficacy and safety profile of Abrocitinib (PF-04965842) in subjects	Patients ages 18-75 with moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥12 at the baseline visit).	267	10, 30, 100, 200 mg QD[a] of Abrocitinib (PF-04965842) or matching placebo for 12 weeks.	Weeks 0 (Day 1), 1 (Day 8), 2, 4, 6, 8, 12, 13, 14, and 16
B7451012	A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of Abrocitinib (PF-04965842) monotherapy	Patients aged 12 years and older with moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, and Pruritus NRS ≥4 at the baseline visit).	387	100 or 200 mg QD[b] of Abrocitinib (PF-04965842) or matching placebo for 12 weeks	Weeks 0 (Day 1), 2 (Day 15), 4, 8, 12 (EOT), and 16 (Follow-up)
B7451013	A phase 3 randomized, double-blind, placebo-controlled, parallel group, multi-center study to evaluate the efficacy and safety of Abrocitinib (PF-04965842) monotherapy	Patients aged 12 years and older with moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, and Pruritus NRS ≥4 at the baseline visit).	391	100 or 200 mg QD[b] of Abrocitinib (PF-04965842) or matching placebo for 12 weeks	Weeks 0 (Day 1), 2 (Day 15), 4, 8, 12 (EOT), and 16 (Follow-up)
B7451014	A phase 3 withdrawal, double-blind, placebo-controlled, multi-center study investigating the efficacy and safety of Abrocitinib (PF-04965842) with the option of rescue treatment	Patients aged 12 years and older with moderate to severe AD (affected BSA ≥10%, IGA ≥3, EASI ≥16, and Pruritus NRS ≥4 at the baseline visit).	1235	200 mg QD[b] open-label 12-week run-in period of Abrocitinib (PF-04965842) or matching placebo for a 40 week maintenance period.	Weeks 0 (Day 1), 2 (Day 15), 4, 8, 12 (EOT), and 16 (Follow-up)

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Table 104. Summary of Baseline Patient Characteristics in the Dataset by Dose

Characteristics	level	0 mg QD	10 mg QD	30 mg QD	100 mg QD	200 mg QD	Total
N		208	48	50	365	1568	2239
RACE, n (%)	Unknown	3 (1%)	0	0	1 (0%)	10 (1%)	14 (1%)
	White	139 (67%)	37 (77%)	38 (76%)	250 (68%)	1143 (73%)	1607 (72%)
	Black	22 (11%)	5 (10%)	4 (8%)	31 (8%)	103 (7%)	165 (7%)
	Asian	39 (19%)	5 (10%)	5 (10%)	79 (22%)	276 (18%)	404 (18%)
	Other	5 (2%)	1 (2%)	3 (6%)	4 (1%)	36 (2%)	49 (2%)
SEX, n (%)	Male	115 (55%)	20 (42%)	22 (44%)	212 (58%)	867 (55%)	1236 (55%)
	Female	93 (45%)	28 (58%)	28 (56%)	153 (42%)	701 (45%)	1003 (45%)
AGE GROUP, n	Adolescent	23 (11%)	0	0	45 (12%)	265 (17%)	333 (15%)
(%)	Adult	185 (89%)	48 (100%)	50 (100%)	320 (88%)	1303 (83%)	1906 (85%)
IGA,	0	0	0	0	0	0	0
n (%)	1	0	0	0	0	0	0
	2	0	0	0	0	1 (0%)	1 (0%)
	3	131 (63%)	27 (56%)	28 (56%)	226 (62%)	945 (60%)	1357 (61%)
	4	77 (37%)	21 (44%)	22 (44%)	139 (38%)	622 (40%)	881 (39%)
EASI, Mean (Sd)		27.6 (11.8)	28.1 (13.2)	22.1 (10.7)	29.4 (12.5)	30.6 (12.7)	29.9 (12.6)
Age (Yrs), Mean (Sd)		35.0 (14.9)	43.8 (15.7)	36.9 (15.3)	35.9 (15.8)	32.2 (15.3)	33.4 (15.5)
Weight (Kg), Mean (Sd)		75.0 (17.9)	79.1 (24.6)	76.1 (18.1)	77.4 (20.2)	74.3 (19.8)	75.0 (19.8)
BSA (m^2), Mean (Sd)		1.86 (0.23)	1.87 (0.28)	1.84 (0.23)	1.88 (0.26)	1.84 (0.25)	1.85 (0.25)
Affected BSA (%), Mean (Sd)		45.8 (22.1)	44.4 (22.9)	34.1 (20.8)	48.6 (22.6)	48.0 (22.2)	47.5 (22.3)

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16.5.2.2.4.2 Final EASI Model

The population PK/PD analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.3 using LAPLACE.

The time-course of EASI scores was characterized by a longitudinal dose-response model. The effect of the drug in reducing EASI (*R*) was described by a linear combination of an E_{max} function and an open label effect (P_{max}) that stimulates K_{out} in an indirect response model:

$$\frac{dR}{dt} = K^{in} - \left(1 + \frac{E^{max} * C^{avg}}{EC^{50} + C^{avg}} + P^{max}\right) * K^{out} * R$$

Beta regression was used to account for the bounded nature of the EASI scores. Therefore, the score was converted to percentile scaled by the upper boundary. Zero-inflation at the zero boundary was used due to a large percentage of EASI scores equal to 0 with treatment. The combined likelihood for EASI score of zero or non-zero is described in the equation below:

$$y \sim zi_0(y, \alpha, \phi, \mu) = \begin{cases} \alpha & \text{if y=0} \\ (1-\alpha) \cdot f(y, \mu, \phi) & \text{otherwise} \end{cases}$$

Where α is modeled using a logit function with intercept ζ_1 (fixed to 0) and slope ζ_2, and $f(y,\mu,\phi)$ is the probability density function of a beta distribution with mean (μ) and precision (ϕ):

$$h_2\left(\frac{\alpha}{1-\alpha}\right) = \zeta_1 + \zeta_2 \cdot (\mu - \theta_{CP})$$

$$f(y, \mu, \phi) = \frac{\Gamma(\phi)}{\Gamma(\phi\mu)\Gamma(\phi(1-\mu))} y^{\phi\mu-1}(1-y)^{\phi(1-\mu)-1}$$

Weight, sex, and baseline EASI were identified as covariates. Baseline EASI was added to the precision parameter and thus would not influence the central tendency of EASI. Lower body weights were associated with a higher EC_{50}, and female was associated with a higher E_{max}. Since females tend to weigh less than males, the increase in E_{max} is tempered by an increase in EC_{50}. The final population parameters are presented in Table 105. Most fixed and random effect parameters were estimated with good precision (|%RSE| < 30%) except ϑ_{CP} (%RSE: 62.9%) and effect of weight >72.58 kg (%RSE: -67.57%) or ≤72.58 kg (%RSE: -47.50%) on EC_{50}. The magnitude of the IIV was moderate for baseline EASI (SD: 0.434). Eta shrinkage was reasonable (<30%). Bootstrap 95% CI of effect of weight ≤72.58 kg on EC_{50} crossed 0 but was retained in the final model because weight was parameterized using a hockey-stick function. A reparameterization of weight using power function can avoid this issue and improve parameter precision as well as reduce model condition number. The reparameterization minimally impacts parameter estimates thus the sponsor's final model is acceptable.

Model evaluations were based on accuracy of parameter estimation (RSE, and bootstrap, Table 105), goodness-of-fit plots (Figure 28), and visual predictive check (Figure 29). The model described the observed data reasonably well and the model predictions were generally within the 90% prediction intervals. In the VPC plots of 100 mg QD and 200 mg QD dose, a tachyphylactic drug effect was observed from Week 8 for patients with a high baseline EASI (95th percentile of EASI score). This effect was absent in open-label treatment (as seen in 200 mg QD-OL panel) of a much larger sample size. Therefore, the tachyphylaxis is likely an artifact of the data. The overall model fit is reasonable for time-course of EASI scores.

Table 105. Parameters Estimates of the Final EASI Model

Parameter	Estimate	SE	RSE (%)	Shrinkage (%)	Bootstrap 95% CI
$\theta_{TV,Baseline}$	24.51	0.1767	0.72	-	(24.19, 24.79)
$\theta_{TV,Emax}$	5.40	0.9681	17.9	-	(4.06, 7.70)
$\theta_{TV,EC_{50}}$(ng/mL)	312.19	92.882	29.8	-	(180.79, 548.77)
$k_{out}\,(d^{-1})$	0.0162	0.0008040	5.0	-	(0.0151, 0.0174)
θ_{Pmax}	0.353	0.08334	23.6	-	(0.201, 0.506)
θ_{CP_0}	0.0198	0.01244	62.9	-	(0.00930, 0.0294)
$\theta_{TV,\phi}$	13.07	0.5226	4.0	-	(12.19, 13.95)
Zeta1	0	(fix)	-	-	-
Zeta2	39.14	5.158	13.2	-	(32.78, 49.24)
θ_{OPLB}	0.484	0.08027	16.6	-	(0.330, 0.654)
$\theta_{BASE.BEASI}$	0.0377	0.001397	3.7	-	(0.0365, 0.0391)
$\theta_{EC50.BWT1}$	-0.01630	0.007741	-47.50	-	(-0.0332, -0.003027)
$\theta_{EC50.BWT2}$	-0.00356	0.002405	-67.57	-	(-0.00680, 0.00169)
$\theta_{Emax.SEX}$	0.200	0.05877	29.5	-	(0.0738, 0.316)
$\theta_{\phi,BEASI1}$	-0.0751	0.01483	-19.74	-	(-0.0982, -0.0565)
$\theta_{\phi,BEASI2}$	-0.01848	0.0006890	-3.73	-	(-0.01964, -0.01702)
$\eta_{Baseline}$	0.188	0.01290	6.9	23.2	(0.163, 0.213)
OFV	-20386.818	-	0	-	-

Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-969\pmar-eqdd-b745d-969.pdf (Table 21)

Figure 28. Goodness-of-fit Plots for the Final EASI Model

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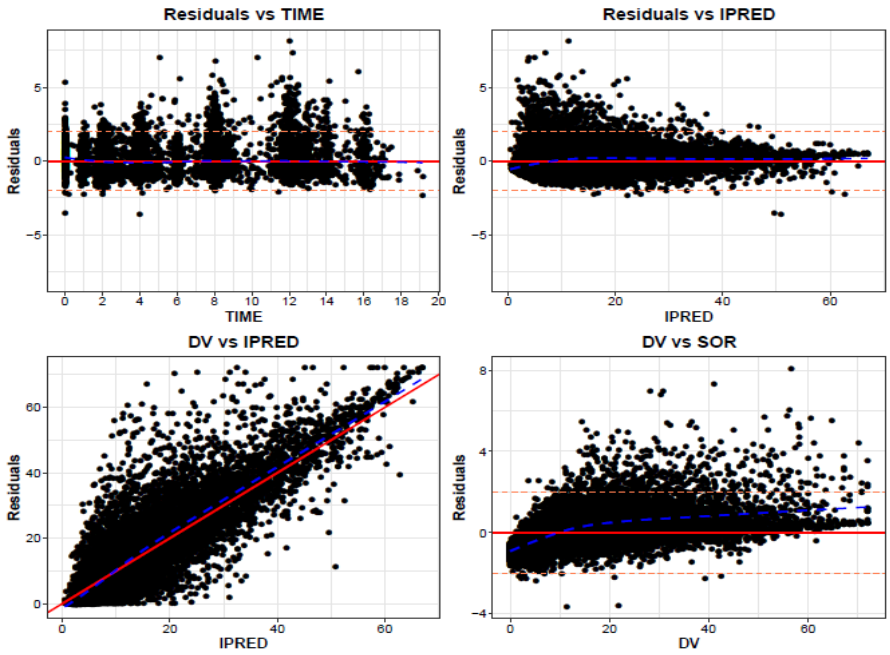
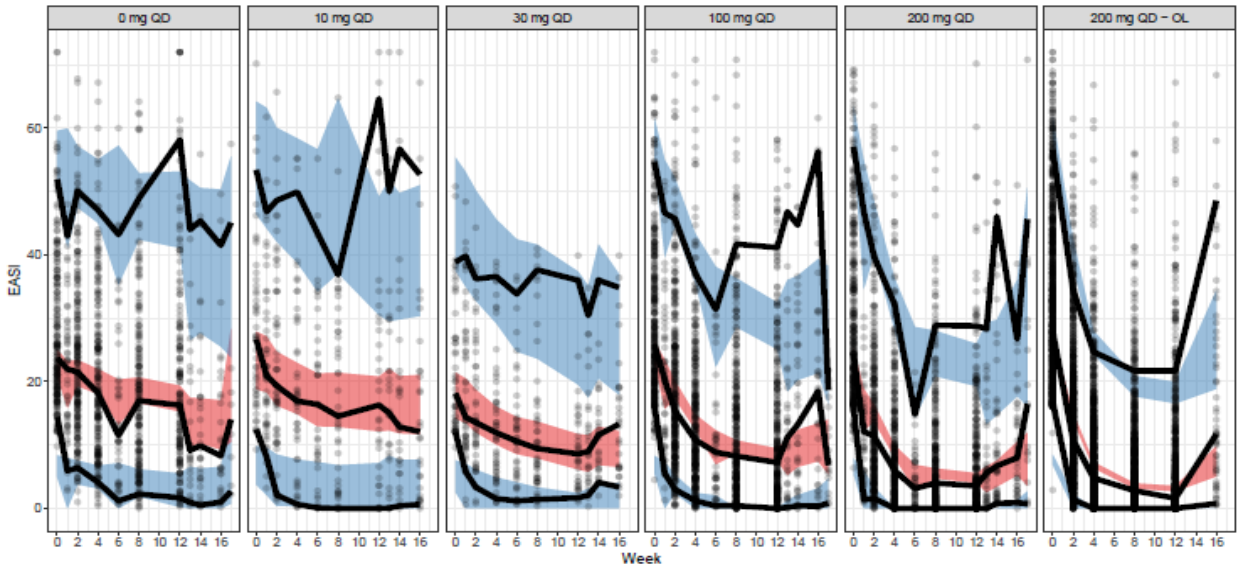


Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-969\pmar-eqdd-b745d-969.pdf (Figure A5.13)

Figure 29. Visual predictive check stratified by study for final EASI model



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16.5.2.2.4.3 Final IGA Model

The population PK/PD analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.3 using LAPLACE.

A longitudinal logistic regression model was developed to characterize the time-course of the probability of achieving an IGA response. The probability of responding is parameterized in a time-dependent placebo effect (θ_{pbo}) and drug effect (θ_{drug}) as described below:

$$\log\left(\frac{p}{1-p}\right) = \theta_{int} + \eta_{1i} + (\theta_{pbo} + \theta_{drug}) \cdot (1 - \exp(-k_{\text{drug}} \cdot t))$$

Where the drug effect was modeled as an Emax function and placebo effect included an open-label effect (θ_{OL}):

$$\theta_{\text{drug}} = \theta_{\text{Emax}} * C_{avg} / (\theta_{\text{EC}_{50}} + C_{avg})$$
$$\theta_{pbo} = \theta_{pbo} \cdot (1 + \theta_{OL})$$

Age, sex, and Asian race, and baseline IGA score were identified as covariates. Younger age and Asian race were associated with a lower E_{max}, females were associated with a larger k_{drug} (a quicker time-dependent increase in drug effect), and baseline IGA score of 4 was associated with a smaller placebo effect.

The final population parameters are presented in Table 106. Most fixed and random effect parameters were estimated with good precision (|%RSE| < 30%) except sex effect on k_{drug} (%RSE: 36.9%) and Asian race on E_{max} (%RSE: -35.56%). The magnitude of the IIV was high for baseline EASI (SD: 2.49). Eta shrinkage was reasonable (<30%).

Model evaluations were based on accuracy of parameter estimation (RSE and bootstrap, Table 106) and individual predicted probabilities (Figure 30). Overall, the predicted probability of achieving the IGA response is well described. A strong exposure-response relationship was observed (

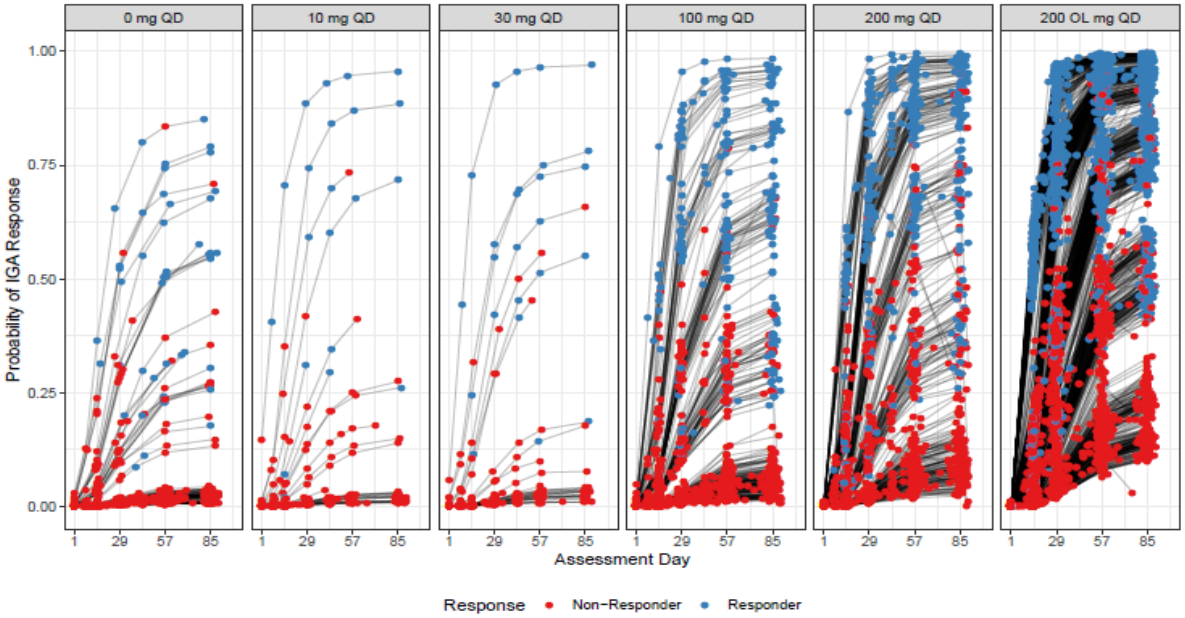
Figure 31).

Table 106. Parameters Estimates of the Final IGA Model

Parameter	Estimate	SE	RSE (%)	Shrinkage (%)	Bootstrap 95% CI
$\theta_{Intercept}$	-8.948	0.3918	-4.38	-	(-9.858, -8.200)
$\theta_{\text{TV,Emax}}$	7.57	1.314	17.4	-	(5.44, 11.05)
$\theta_{\text{TV,Pmax}}$	5.87	0.3862	6.6	-	(5.08, 6.72)
$\theta_{TV,k_{drug}}(d^{-1})$	0.0551	0.003478	6.3	-	(0.0481, 0.0615)
$\theta_{EC_{50}}$ (ng/mL)	403.43	117.187	29.0	-	(224.91, 757.55)
OL_{Pmax}	0.351	0.04288	12.2	-	(0.263, 0.450)
$\theta_{Pmax.BIGA}$	-0.2245	0.02207	-9.83	-	(-0.2712, -0.1824)
$\theta_{Age.Emax}$	0.00720	0.002136	29.7	-	(0.00309, 0.0119)
$\theta_{Sex.k_{drug}}$	0.187	0.06886	36.9	-	(0.0590, 0.330)
$\theta_{Asian.Emax}$	-0.1919	0.06825	-35.56	-	(-0.320, -0.0464)
η_{int}	6.21	0.5294	8.5	29.1	(5.27, 7.43)
η_{Pmax}	0	(fix)	-	-	-
η_{Drug}	0	(fix)	-	-	-
OFV	8017.95	-	0	-	-

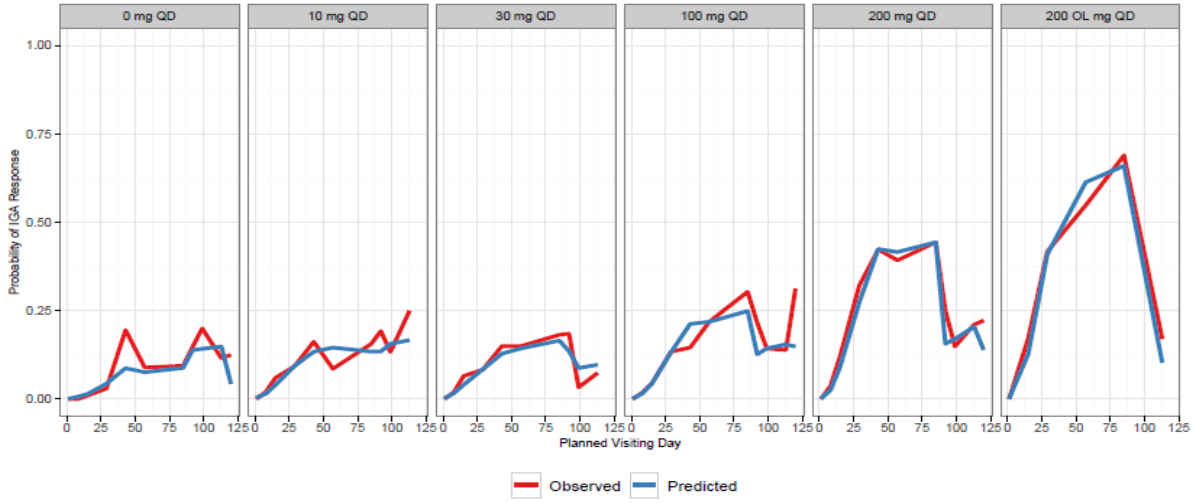
Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-969\pmar-eqdd-b745d-969.pdf (Table 15)

Figure 30. Individual Predicted Probabilities of Responding Over Time for the Final IGA Model



Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-969\pmar-eqdd-b745d-969.pdf (Figure 4)

Figure 31. Predicted Probabilities of Responding Over Time by Dose Group for the Final IGA Model



Source: \\CDSESUB1\evsprod\nda213871\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-eqdd-b745d-969\pmar-eqdd-b745d-969.pdf (Figure 5)

16.5.2.2.4.4 Evaluation of Efficacy in Subgroups Using EASI and IGA Models

Simulation was performed for subgroups of patients to evaluate the effect of sex, Asian race, adolescents, and body weight on efficacy endpoints. The simulations used a 30-year old, White, male, adult with baseline EASI score of 26 as the reference. The weight of the reference patient was 80 kg and 70 kg for EASI and IGA simulation, respectively.

The typical EASI75 response (75% reduction in EASI from baseline) was 38.6% and 55.9% with 100 mg QD and 200 mg QD abrocitinib in the reference patient, respectively. Subgroups were predicted to have either similar or higher EASI75 response rate as the reference except adolescents that had ~8% less patients achieving EASI75 response. This is related to a lower exposure in adolescents.

The typical probability of IGA response (at least 2 points and the score being (0) clear or (1) almost clear) was 31.4% and 46.8% with 100 mg QD and 200 mg QD abrocitinib in the reference patient, respectively. The predicted probability of an IGA response in subgroups was similar to or higher than the reference except patients with baseline IGA of 4. These patients were about 50% less likely to have an IGA response than the reference patient; the probability of IGA response was 16.9% compared to 15.3% with placebo.

Reviewer's comments: The applicant's final PK/PD models for efficacy adequately describe the observed data and are acceptable to be used for evaluating responses in subgroups of patients. The simulation supported a dose-response relationship for efficacy endpoints. Approximately 50% reduction in IGA response is expected for patients with IGA score of 4 at baseline who may have marginal benefits with 100 mg QD dose.

16.5.3. In Vitro Studies Using Human Biomaterials

16.5.3.1 Absorption

Abrocitinib was identified to be a substrate for both P-gp and BCRP in vitro (PF-04965842_07Jun17_125532 and 16PFIZP3R1S2). However, the Applicant did not conducted a clinical trial with P-gp/BCRP inhibitors based on the high oral absorption of abrocitinib (approximately 91%) in clinical Study B7451008 indicated that the influence of these intestinal efflux transporters on absorption would be minimal.

16.5.3.2 Distribution

The unbound fraction (f_u) of abrocitinib, M1, and M2 are 0.36, 0.63, and 0.71, respectively (ADME-2012-001-0021, YDP/067/273, and YDP/067/275). The partitioning of 1 μM of abrocitinib, M1, and M2 between red blood cells and plasma was investigated in human whole blood, with respective B/P ratios of 1.07, 1.13, and 1.27 (Studies YDP/067/154, YDP/067/272, and YDP/067/271). There was no preferential partitioning of abrocitinib and its major metabolites into blood cells.

16.5.3.3 Metabolism

Plasma metabolite profiling from the single dose [^{14}C]-abrocitinib human mass balance study (PF-04965842_01Nov17_093820) indicated abrocitinib as the most abundant circulating species (26%), with 3 mono-hydroxylated metabolites with abundance >10%: M1 (3-hydroxypropyl, 11%), M2 (2-hydroxypropyl, 12%), and M4 (pyrrolidinone pyrimidine, 14%) (Table 107). Although M4 is a major metabolite, it is not pharmacologically active. Hence, it is not included in further discussion.

Table 107. Pharmacokinetics: Metabolism *in vivo*, Human

Metabolite Label	Metabolites Derived from [^{14}C] Abrocitinib (Mean)		
	Plasma (% of Total Radioactivity) (0-12 hour post-dose)[a]	Urine (% of Dose) (0-12 hour post-dose)[b,c]	Feces (% of Dose) (0-192 hour post-dose)[b,c]
Abrocitinib	25.8	0.6	0.3
M1 (PF-06471658)	11.3	16.2	1.7
M2 (PF-07055087)	12.4	13.5	0.5
M4 (PF-07054874)	13.8	15.4	0.3

Source: Module 2.6.5 Pharmacokinetics Tabulated Summary, Table 2.6.5.9D
a. Represents ≥90% plasma total radioactivity Area Under-the-Curve (AUC)
b. Represents ≥90% of radioactivity excreted in matrix
c. Abrocitinib and reported metabolites account for 86.7% of the oral dose recovered in the excreta of humans

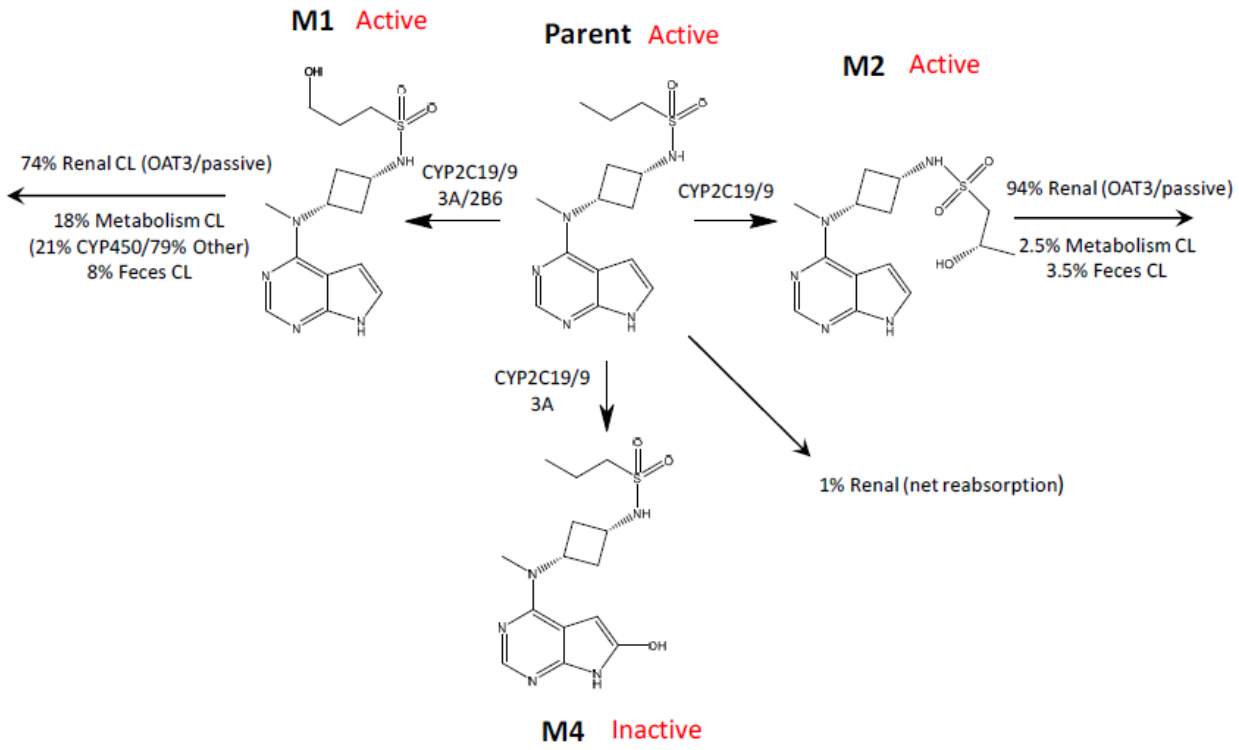
In vitro human CYP phenotyping studies (PF-04965842_28Nov12_140212 and PF-04965842_20Oct17_054208) indicated that CYP2C19 (fm ~0.5), CYP2C9 (fm ~0.3), CYP3A4 (fm ~0.1), and CYP2B6 (fm ~0.1) were involved in the metabolism of abrocitinib (Table 108). In vitro human CYP phenotyping studies with M1 and M2 (PF-04965842_16Oct19_025347 and PF-04965842_29Jan20_025345) indicated downstream metabolism via CYP- and non-CYP-mediated pathyways. The clearance pathways of abrocitinib and its metabolites are presented in Figure 32.

Table 108. Pharmacokinetics: Metabolism in Vitro, CYP Enzyme Phenotyping

Matrix	CYP Enzyme[a]	Chemical Inhibitor	Inhibitor Concentration (μM)	% Inhibition of Formation Rate (Scaled)				f_m[b]
				M1	M2/M3	M4	m/z 149	
HLM	1A2	Furafylline	10	--	--	--	--	--
	2B6	2-phenyl-2-(1-piperdinyl)propane	5	16	--	--	--	0.066
	2C8	Gemfibrozil glucuronide	100	--	--	--	--	--
	2C9	Tienilic acid	15	24	45	25	--	0.30
	2C19	Esomeprazole	5	52	55	57	--	0.53
	2D6	Quinidine	10	--	--	--	--	--
	3A4/5	Troleandomycin	25	8.0	--	18	100	0.11

-- = No contribution; CYP = Cytochrome P450 isoform; f_m = Fraction metabolized; HLM = Human liver microsomes; LC-MS/MS = Liquid chromatography-tandem mass spectrometry; M = Metabolite; m/z = Mass to charge ratio.
a. Although not achieving statistical significance, minor contributions by the remaining CYP isoforms for M1 (1A2, 2C8, 2D6), M2/M3 (1A2, 2B6, 2C8, 2D6, 3A), M4 (1A2, 2B6, 2C8, 2D6), and 149 (1A2, 2B6, 2C8, 2C9, 2C19, 2D6) were observed.
b. f_m assigned based on combined M1, M2/M3, M4 and m/z 149 metabolite formation rates.
Source: Table 2.6.5.10B in Module 2.6.5 Pharmacokinetics Tabulated Summary

Figure 32. Clearance Mechanisms of Abrocitinib and its Major Metabolites M1 and M2.



Source: Figure 2.6.4-3 in Module 2.6.4 Pharmacokinetics Written Summary

16.5.3.4 Pharmacokinetic Drug Interactions

CYP450-Mediated Interactions

Abrocitinib demonstrated no reversible inhibition of the major CYP isoforms however, it was a weak time dependent inhibition (TDI) of CYP3A, CYP2C19, and CYP2D6 (Table 109). Abrocitinib was a weak inducer of CYP3A4, CYP1A2 and CYP2B6.

Active metabolites, M1 and M2, demonstrated no reversible inhibition of the major CYP isoforms but they were weak TDI of CYP3A and CYP2C19 (Table 110). M1 and M2 were weak inducers of CYP1A2 and CYP2B6.

Table 109. Inhibition of CYP Enzymes by Abrocitinib

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CYP	Enzyme Reaction	Direct (reversible) Inhibition Zero-Minute Preincubation			TDI 30-Minute Preincubation without NADPH			MDI 30-Minute Preincubation with NADPH			Potential for TDI[a] (NADPH-independent inhibition)	Potential for MDI[a] (Time- and NADPH-dependent inhibition)
		IC_{50} (μM)[b]	Inhibition at 100 μM (%)[c]	r^2	IC_{50} (μM)[b]	Inhibition at 100 μM (%)[c]	r^2	IC_{50} (μM)[b]	Inhibition at 100 μM (%)[c]	r^2		
1A2	Phenacetin *O*-dealkylation	>100	8.6	NC	>100	13	NC	>100	26	0.668	No	No
2B6	Bupropion hydroxylation	>100	21	0.857	>100	22	0.787	>100	22	0.777	No	No
2C8	Paclitaxel 6α-hydroxylation	>100	13	NC	>100	10	NC	>100	35	0.957	No	23%[d]
2C9	Diclofenac 4′-hydroxylation	>100	18	NC	>100	14	NC	>100	26	0.972	No	No
2C19	*S*-Mephenytoin 4′-hydroxylation	>100	34	0.995	>100	40	0.963	42	68	0.991	No	34%[d]
2D6	Dextromethorphan *O*-demethylation	>100	31	0.994	>100	35	0.988	92	51	0.991	No	20%[d]
3A4/5	Testosterone 6β-hydroxylation	>100	24	0.671	>100	9.3	NC	81	56	0.993	No	32%[d]
3A4/5	Midazolam 1′-hydroxylation	>100	18	NC	>100	19	NC	75	55	0.991	No	37%[d]
3A4/5	Nifedipine oxidation	>100	47	0.926	>100	43	0.927	40	70	0.997	No	23%[d]

CYP = Cytochrome P450; IC_{50} = 50% inhibitory concentration; LC-MS/MS = Liquid chromatography-tandem mass spectrometry; MDI = Metabolism-dependent inhibition; NADPH = Reduced form of nicotinamide adenine dinucleotide phosphate; NC = Not calculated; r^2 = Regression coefficient; TDI = Time-dependent inhibition.

a. Potential for time-dependent and metabolism-dependent inhibition was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC_{50} plots. In the cases in which a number is listed, this number represents the change in percent difference of inhibition after preincubation of 100 μM abrocitinib with NADPH-fortified human liver microsomes.

b. Average data (i.e., percent of control activity) obtained from duplicate samples for each test article at 7 concentrations were used to calculate IC_{50} values.

c. Inhibition at 100 μM (%) is calculated with the following formula for the highest concentration of test article evaluated (results are rounded to 2 significant figures): Inhibition at 100 μM (%) = 100% − Percent solvent control.

d. This number represents the difference in percent of control activity after preincubation of 100 μM abrocitinib with NADPH-fortified human liver microsomes for 30 min.

Source: Table 2.6.5.12A in Module 2.6.5 Pharmacokinetics Tabulated Summary

Table 110. Time-dependent Inhibition (TDI) of CYP Enzymes by M1 and M2

CYP	Probe Substrate (Concentration)	k_{inact} / K_I ± SE **(mL/μmol/min)**	R2
M1			
3A4/5	Midazolam (23 μM)	0.0229 ± 0.0028	1.02
3A4/5	Testosterone (386 μM)	0.0222 ± 0.0011	1.02
3A4/5[a]	Testosterone (-NADPH)	0.00364 ± 0.0015	1.00
M2			
2C19[b]	S-Mephenytoin (393 μM)	NC	NC
3A4/5	Midazolam (23 μM)	0.0170 ± 0.0009	1.01
3A4/5	Testosterone (386 μM)	0.0251 ± 0.0021	1.02

Source: Module 2.6.5 Pharmacokinetics Tabulated Summary, Table 2.6.5.12F and Table 2.6.5.12G

Abbreviations: k_{inact}=maximal rate of enzyme inactivation; K_I=apparent inactivation constant at half-maximal rate of inactivation; k_{inact}/K_I=measure of inactivator efficiency (composite slope); NC=not calculated; R2=predicted ratio of the victim drug area under the curve in the presence and absence of an inhibitor; SE=standard error

a. Using testosterone as the probe substrates, the data indicated M1 is a TDI in the absence of NADPH at concentrations ≥53.3 μM

b. M2 is TDI positive but the inactivation is too weak to estimate K_I, k_{inact}, and composite slope

Uridine Diphospho-Glucuronosyltransferase (UGT) and sulfotransferase (SULT)-Mediated Interactions

Abrocitinib and its two active metabolites, M1 and M2, did not inhibit any of the uridine diphospho-glucuronosyltransferase (UGT) enzymes studied (UGT1A1, 1A4, 1A6, 1A9, and 2B7) with IC_{50} values >100 μM.

Abrocitinib did not inhibit any of the sulfotransferase (SULT) enzymes studied (1E1, 1A1, and 2A1) with IC_{50} values >100 μM.

Transporter-Mediated Interactions

Abrocitinib neither was a substrate for organic anion transporting polypeptide (OATP) 1B1 or OATP1B3 nor did it inhibit these transporters. Abrocitinib was a substrate of multi-drug resistance (MDR)1/P-gp and breast cancer resistance protein (BCRP). Abrocitinib did not inhibit organic anion transporter (OAT) 1, organic cation transporter (OCT) 2, and bile salt export pump (BSEP), but inhibited OAT3 (IC_{50}, 26 µM), P-gp (IC_{50}, 100 µM), BCRP (IC_{50}, 9.8 µM), OCT1 (IC_{50}, 44 µM), multidrug and toxin compound extrusion protein (MATE) 1 (IC_{50}, 5.5 µM), and MATE2K (IC_{50}, 10.7 µM).

M1 and M2 were substrates of OAT3 but not of OAT1, OCT2, MATE1, and MATE2K.
M1 and M2 did not inhibit P-gp, OCT2, and OAT1; M2 did not inhibit OATP1B1 and OATP1B3.
M1 and M2 inhibited BCRP, MATE1, MATE2K, and OAT3 (IC_{50}, 45-121 µM).
Table 111 presents the summary of transporter inhibition.

Table 111. Transporter Inhibition of Abrocitinib and Its Active Metabolites, M1 and M2

Transporter	Test System	Test Article Concentrations Tested	Probe Substrate (Concentration)	IC_{50}[b] (µM)	K_i[c] (µM)	% Inhibition at Highest Concentration Tested
Abrocitinib						
MDR1/P-gp	MDCKII-MDR1	0.6 to 400 µM	Digoxin (10 µM)	100.3	100.3	86
BCRP	HEK293-BCRP vesicles	0.1 to 300 µM	Rosuvastatin (0.2 µM)	9.8	9.8	97
OATP1B1	HEK293-OATP1B1	0.1 to 300 µM	Rosuvastatin (5 µM)	>300	>300	52
OATP1B3	HEK293-OATP1B3	0.1 to 300 µM	Rosuvastatin (5 µM)	>300	>300	0
OCT1	HEK293-OCT1	0.1 to 300 µM	[^{14}C]Metformin (20 µM)	44.2	44.2	92
BSEP	BSEP-HEK293	0.82 to 200 µM	[^{3}H]Taurocholate (0.2 µM)	>200	>200	22
BSEP	BSEP-Hi5	0.82 to 200 µM	[^{3}H]Taurocholate (2 µM)	>200	>200	42
OAT1	HEK293-OAT1	0.073 to 300 µM	[^{3}H]PAH (2.0 µM)	>300	>150	25
OAT3	HEK293-OAT3	0.073 to 300 µM	[^{3}H]E3S (0.2 µM)	26.0	26.0	86
OCT2	HEK293-OCT2	0.073 to 300 µM	[^{14}C]Metformin (10 µM)	>300	>300	30
MATE1	HEK293-MATE1	0.073 to 300 µM	[^{14}C]Metformin (10 µM)	5.5	5.5	92
MATE2K	HEK293-MATE2K	0.07 to 300 µM	[^{14}C]Metformin (10 µM)	10.7	10.7	87
M1						
MDR1/P-gp	MDCKII-MDR1	0.018 to 300 µM	[^{3}H]Digoxin (10 µM)	>300	>300	1
BCRP	HEK293-BCRP vesicles	0.018 to 300 µM	Rosuvastatin (0.2 µM)	44.9	44.9	85
OATP1B1	HEK293-OATP1B1	0.018 to 300 µM	Rosuvastatin (0.5 µM)	208.9	208.9	61
OATP1B3	HEK293-OATP1B3	0.018 to 300 µM	Rosuvastatin (0.5 µM)	279.5	279.5	50
OCT1	HEK293-OCT1	0.018 to 300 µM	[^{14}C]Metformin (20 µM)	223.2	223.2	65
OAT1	HEK293-OAT1	0.14 to 300 µM	[^{3}H]PAH (0.5 µM)	>300	>300	0
OAT3	HEK293-OAT3	0.14 to 300 µM	[^{3}H]E3S (0.2 µM)	56.2	56.2	83
OCT2	HEK293-OCT2	0.14 to 300 µM	[^{14}C]Metformin (10 µM)	>300	>300	0
MATE1	HEK293-MATE1	0.14 to 300 µM	[^{14}C]Metformin (10 µM)	55.1	55.1	79
MATE2K	HEK293-MATE2K	0.14 to 300 µM	[^{14}C]Metformin (25 µM)	121.2	121.2	79
M2						
MDR1/P-gp	MDCKII-MDR1	0.018 to 300 µM	[^{3}H]Digoxin (10 µM)	>300	>300	0
BCRP	HEK293-BCRP vesicles	0.018 to 300 µM	Rosuvastatin (0.2 µM)	79.0	79.0	87
OATP1B1	HEK293-OATP1B1	0.018 to 300 µM	Rosuvastatin (0.5 µM)	>300	>300	42
OATP1B3	HEK293-OATP1B3	0.018 to 300 µM	Rosuvastatin (0.5 µM)	>300	>300	27
OCT1	HEK293-OCT1	0.018 to 300 µM	[^{14}C]Metformin (20 µM)	149.4	149.4	72
OAT1	HEK293-OAT1	0.14 to 300 µM	[^{3}H]PAH (0.5 µM)	>300	>300	31
OAT3	HEK293-OAT3	0.14 to 300 µM	[^{3}H]E3S (0.2 µM)	44.6	44.6	87
OCT2	HEK293-OCT2	0.14 to 300 µM	[^{14}C]Metformin (10 µM)	>300	>300	0
MATE1	HEK293-MATE1	0.14 to 300 µM	[^{14}C]Metformin (10 µM)	54.4	54.4	71
MATE2K	HEK293-MATE2K	0.14 to 300 µM	[^{14}C]Metformin (25 µM)	121.4	121.4	66

BCRP = Breast cancer resistance protein; BSEP = Bile salt export pump; DDI = Drug-drug interactions; E3S = Estrone-3-sulfate; EMA = European medicines agency; FDA = Food and drug administration; HEK293 = Human embryonic kidney cells; Hi5 = *Trichoplusia ni* ovarian cells; K_i = Concentration at 50% maximum inhibition (unbound inhibition constant); K_m = Concentration at 50% maximum velocity/rate; OAT = Organic anion transporter; OATP = Organic anion-transporting polypeptide; OCT = Organic cation transporter; IC_{50} = 50% inhibitory concentration; MATE = Multidrug and toxin extrusion protein; MDCKII = Madin Darby canine kidney type II cells; MDR = Multidrug resistance protein; PAH = P-aminohippuric acid; P-gp = P-glycoprotein.
a. An assessment of risk for in vivo DDI between abrocitinib, M1, M2, and M4 and coadministered substrates of these transporters, based on the 2020 FDA and 2012 EMA guidances, are provided in Tabulated Summaries 2.6.5.15A to 2.6.5.15E.
b. Data are a mean of ≥ triplicate measurements for all transporters.
c. For most transporters, the K_i was estimated to be equal to the IC_{50} because the substrate concentrations used were below the in-house or reported K_m values. For the OAT1 transporter in the abrocitinib study (PF-04965842_03Jun17_024506), the K_i is estimated to be ½ of the IC_{50} because the substrate concentrations used in these assays are near the reported K_m values (in-house K_m data).

Source: Table 2.6.5.12T in Module 2.6.5 Pharmacokinetics Tabulated Summary

16.5.4. Pharmacogenomics

The Applicant conducted a non-compartmental meta-analysis of PK parameters in healthy subjects from nine Phase 1 studies (B7451001, B7451004, B7451017, B7451019, B7451020, B7451021, B7451027, B7451032, and B7451043) and evaluated the effect of CYP2C19 and CYP2C9 genotypes on the AUC and C_{max} of abrocitinib parent and AUC of the active moiety in these subjects. The Applicant genotyped CYP2C19 (*1 *2, *3, *4, and *17 alleles) and CYP2C9 (*1, *2, and *3 alleles). CYP2C19 and CYP2C9 genotypes were used to determine phenotype classifications as shown in Table 112.

Table 112. CYP2C19 and 2C9 Genotype Phenotype Classification

CYP2C19 Genotype	CYP2C19 Predicted Metabolizer Status	CYP2C9 Genotype	CYP2C9 Predicted Metabolizer Status
*17/*17	UM		
*1/*17	RM		
*1/*1	EM	*1/*1	EM
*1 or *17/*(2,3,4)	IM	*1/*(2,3) or *2/*2	IM
(2,3,4)/(2,3,4)	PM	*2/*3 or *3/*3	PM

EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer; RM=rapid metabolizer; UM=ultra-rapid metabolizer.

Source: Table 4 Non-Compartmental Analysis of Abrocitinib Pharmacokinetics in Healthy Volunteers

The applicant further derived phenotype categorizations based on a combination of the genotype-inferred CYP2C19 and CYP2C9 phenotypes to create “overall” phenotype categories based on expected elevated, mixed, or reduced enzymatic activity relative to the subjects with *1/*1 genotype for both CYP2C19 and CYP2C9. The resulting overall phenotype categories are as shown in

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Table 113.

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Table 113. CYP2C19 and CYP2C9 Phenotype Categorizations

Overall Phenotype	Phenotype Combinations	CYP2C19 Genotype	CYP2C19 Phenotype	CYP2C9 Genotype	CYP2C9 Phenotype
Wild-Type	EM/EM	*1/*1	EM	*1/*1	EM
Elevated	RM/EM	*1/*17	RM	*1/*1	EM
Elevated	UM/EM	*17/*17	UM	*1/*1	EM
Mixed	RM/IM	*1/*17	RM	*1/*2	IM
Mixed	RM/IM	*1/*17	RM	*1/*3	IM
Reduced	EM/IM	*1/*1	EM	*1/*2	IM
Reduced	IM/EM	*2/*17	IM	*1/*1	EM
Reduced	EM/IM	*1/*1	EM	*1/*3	IM
Reduced	EM/PM	*1/*1	EM	*2/*2	PM
Reduced	EM/PM	*1/*1	EM	*2/*3	PM
Reduced	EM/PM	*1/*1	EM	*3/*3	PM
Reduced	IM/EM	*1/*2	IM	*1/*1	EM
Reduced	IM/IM	*1/*2	IM	*1/*2	IM
Reduced	IM/IM	*1/*2	IM	*1/*3	IM
Reduced	PM/EM	*2/*2	PM	*1/*1	EM
Reduced	PM/EM	*2/*3	PM	*1/*1	EM

EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer; RM=rapid metabolizer; UL=ultra-rapid metabolizer.

Source: Table 5 Non-Compartmental Analysis of Abrocitinib Pharmacokinetics in Healthy Volunteers

The frequency of derived overall phenotypes and CYP2C19 and CYP2C9 genotypes across studies in the meta-analysis is summarized below (Table 114).

Table 114. Overall Phenotype and CYP2C19 and CYP2C9 Genotypes by Study

Group	B7451001	B7451004	B7451017	B7451019	B7451020	B7451021	B7451027	B7451032	B7451043	Total
Phenotype; N(%)										
Elevated	14 (23)	0	4 (17)	2 (17)	2 (25)	1 (12)	8 (22)	13 (28)	4 (33)	48 (22)
Mixed	1 (2)	0	2 (8)	0	2 (25)	0	3 (8)	2 (4)	0	10 (5)
Reduced	21 (35)	0	14 (58)	8 (67)	3 (38)	6 (75)	15 (42)	16 (35)	4 (33)	87 (40)
Wild-Type	17 (28)	0	4 (17)	2 (17)	1 (12)	1 (12)	10 (28)	15 (33)	4 (33)	54 (25)
Missing	7 (12)	12 (100)	0	0	0	0	0	0	0	19 (9)
CYP2C19 Genotype; N(%)										
*1/*1	20 (33)	0	9 (38)	7 (58)	3 (38)	2 (25)	17 (47)	22 (48)	5 (42)	85 (39)
*1/*17	14 (23)	0	4 (17)	2 (17)	4 (50)	1 (12)	9 (25)	11 (24)	4 (33)	49 (22)
*1/*2	15 (25)	0	8 (33)	1 (8)	0	3 (38)	7 (19)	5 (11)	2 (17)	41 (19)
*17/*17	1 (2)	0	2 (8)	0	0	0	2 (6)	4 (9)	0	9 (4)
*2/*17	1 (2)	0	1 (4)	1 (8)	1 (12)	2 (25)	1 (3)	3 (7)	1 (8)	11 (5)
*2/*2	1 (2)	0	0	1 (8)	0	0	0	1 (2)	0	3 (1)
*2/*3	1 (2)	0	0	0	0	0	0	0	0	1 (0)
Missing	7 (12)	12 (100)	0	0	0	0	0	0	0	19 (9)
CYP2C9 Genotype; N(%)										
*1/*1	45 (75)	0	16 (67)	7 (58)	4 (50)	7 (88)	24 (67)	37 (80)	10 (83)	150 (69)
*1/*2	5 (8)	0	4 (17)	4 (33)	3 (38)	0	9 (25)	6 (13)	2 (17)	33 (15)
*1/*3	3 (5)	0	3 (12)	1 (8)	0	1 (12)	2 (6)	2 (4)	0	12 (6)
*2/*2	0	0	1 (4)	0	0	0	0	0	0	1 (0)
*2/*3	0	0	0	0	1 (12)	0	0	1 (2)	0	2 (1)
*3/*3	0	0	0	0	0	0	1 (3)	0	0	1 (0)
Missing	7 (12)	12 (100)	0	0	0	0	0	0	0	19 (9)

Source: Table A10.2 Non-Compartmental Analysis of Abrocitinib Pharmacokinetics in Healthy Volunteers, no pharmacogenomic samples were collected in Study B7451004

The frequency of the derived overall phenotype and constituent genotype combinations is summarized below (Table 115).

Table 115. Frequency of Overall Phenotype by Study

Group	B7451001	B7451004	B7451017	B7451019	B7451020	B7451021	B7451027	B7451032	B7451043	Total
Wild-Type; N(%)										
2C19*1/*1 : 2C9*1/*1	17 (28)	0	4 (17)	2 (17)	1 (12)	1 (12)	10 (28)	15 (33)	4 (33)	54 (25)
Reduced; N(%)										
2C19*1/*1 : 2C9*1/*2	2 (3)	0	2 (8)	4 (33)	1 (12)	0	6 (17)	4 (9)	1 (8)	20 (9)
2C19*1/*1 : 2C9*1/*3	1 (2)	0	2 (8)	1 (8)	0	1 (12)	0	2 (4)	0	7 (3)
2C19*1/*1 : 2C9*2/*2	0	0	1 (4)	0	0	0	0	0	0	1 (0)
2C19*1/*1 : 2C9*2/*3	0	0	0	0	1 (12)	0	0	1 (2)	0	2 (1)
2C19*1/*1 : 2C9*3/*3	0	0	0	0	0	0	1 (3)	0	0	1 (0)
2C19*1/*2 : 2C9*1/*1	11 (18)	0	7 (29)	1 (8)	0	3 (38)	5 (14)	5 (11)	1 (8)	33 (15)
2C19*1/*2 : 2C9*1/*2	2 (3)	0	0	0	0	0	2 (6)	0	1 (8)	5 (2)
2C19*1/*2 : 2C9*1/*3	2 (3)	0	1 (4)	0	0	0	0	0	0	3 (1)
2C19*2/*17 : 2C9*1/*1	1 (2)	0	1 (4)	1 (8)	1 (12)	2 (25)	1 (3)	3 (7)	1 (8)	11 (5)
2C19*2/*2 : 2C9*1/*1	1 (2)	0	0	1 (8)	0	0	0	1 (2)	0	3 (1)
2C19*2/*3 : 2C9*1/*1	1 (2)	0	0	0	0	0	0	0	0	1 (0)
Mixed; N(%)										
2C19*1/*17 : 2C9*1/*2	1 (2)	0	2 (8)	0	2 (25)	0	1 (3)	2 (4)	0	8 (4)
2C19*1/*17 : 2C9*1/*3	0	0	0	0	0	0	2 (6)	0	0	2 (1)
Elevated; N(%)										
2C19*1/*17 : 2C9*1/*1	13 (22)	0	2 (8)	2 (17)	2 (25)	1 (12)	6 (17)	9 (20)	4 (33)	39 (18)
2C19*17/*17 : 2C9*1/*1	1 (2)	0	2 (8)	0	0	0	2 (6)	4 (9)	0	9 (4)
Missing	7 (12)	12 (100)	0	0	0	0	0	0	0	19 (9)

Source: Table 12 Non-Compartmental Analysis of Abrocitinib Pharmacokinetics in Healthy Volunteers

The applicant estimated the effect of the overall phenotype on PK using the wild-type phenotype as reference. The applicant's analysis indicated a statistically-significant decrease in AUC and C_{max} (19.5% and 23.4%, respectively) in the elevated phenotype, a statistically-significant increase in AUC (25.6%) with no increase in C_{max} in the reduced phenotype. No statistically-significant differences were observed in the mixed phenotype. In addition, the analysis showed the 90% confidence interval for the active moiety AUC ratios across phenotypes contained 0 signifying no evidence of phenotype-mediated differences in AUC. The Applicant concluded that abrocitinib parent exposures were comparable across overall phenotypes.

The applicant noted [redacted] (b) (4)

[redacted] (b) (4)

Are the CYP2C19 and CYP2C9 phenotypes inferred from genotypes appropriate?
The Applicant has evaluated the common alleles in CYP2C19 and CYP2C9 that have established functional impact on each enzyme. The CYP2C19 and CYP2C9 genotype-inferred assignments of

phenotype is consistent with standard assignments of ultrarapid, rapid, extensive (now normal [PMID: 27441996]), intermediate and poor metabolizer phenotypes based on the functional status of CYP2C19 *1, *2, *3, *4, and *17 and CYP2C9 *1, *2, and *3 alleles. However, in the combined classification of CYP2C19/CYP2C9 phenotypes, the Applicant deviates from the genotype-inferred phenotype assignment of a CYP2C9 *2/*2 as an intermediate metabolizer and assigns CYP2C9*2/*2 as a poor metabolizer when combined with CYP2C19 phenotypes in the overall phenotype categories. This inconsistency impacted (n=1) subject (Table 116).

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The impact of CYP2C19 and CYP2C9 phenotypes independently, the impact of the combined CY2C19/CYP2C9 phenotype, and the impact of the overall categorization on abrocitinib AUC in single dose studies are summarized in Table 116.

Table 116. Dose-Normalized AUC in Single Dose Studies by CYP2C19 and CYP2C9 Independently, Combined, and Overall Phenotypes

CYP2C19 Phenotype (N=250)	Geometric Mean AUC [95% CI]	Fold Change	CYP2C19/CYP2C9 Phenotype (N=250)	Geometric Mean AUC [95% CI]	Fold Change	Overall Phenotype (N=250)	Geometric Mean AUC [95% CI]	Fold Change
EM (113)	18.28 [16.89; 19.79]	-	EM/EM (76)	16.88 [15.36; 18.55]	-	Wild Type (76)	16.88 [15.36; 18.55]	-
IM (52)	23.9 [21.33; 26.79]	1.31	EM/IM* (33)	20.72 [18.17; 23.62]	1.23	Mixed (11)	25.03 [17.27; 36.29]	1.48
PM (6)	41.23 [32.34; 52.57]	2.26	EM/PM (4)	29.81 [11.91; 74.58]	1.77	Reduced (95)	23.76 [21.80; 25.90]	1.41
RM (63)	15.77 [13.79; 18.03]	0.86	IM/EM (48)	24.13 [21.35; 27.28]	1.43	Elevated (68)	13.92 [12.28; 15.79]	0.82
UM (16)	12.76 [9.03; 18.03]	0.70	IM/IM (4)	21.3 [15.82; 28.68]	1.26			
CYP2C9 Phenotype			PM/EM (6)	41.23 [32.34; 52.57]	2.44			
EM (198)	17.7 [16.47; 19.03]		RM/EM (52)	14.3 [12.52; 16.34]	0.85			
IM (48)	21.69 19.26; 24.41]	1.23	RM/IM (11)	25.03 [17.27; 36.29]	1.48			
PM (4)	29.81 11.91; 74.58]	1.68	UM/EM (16)	12.76 [9.03; 18.03]	0.76			

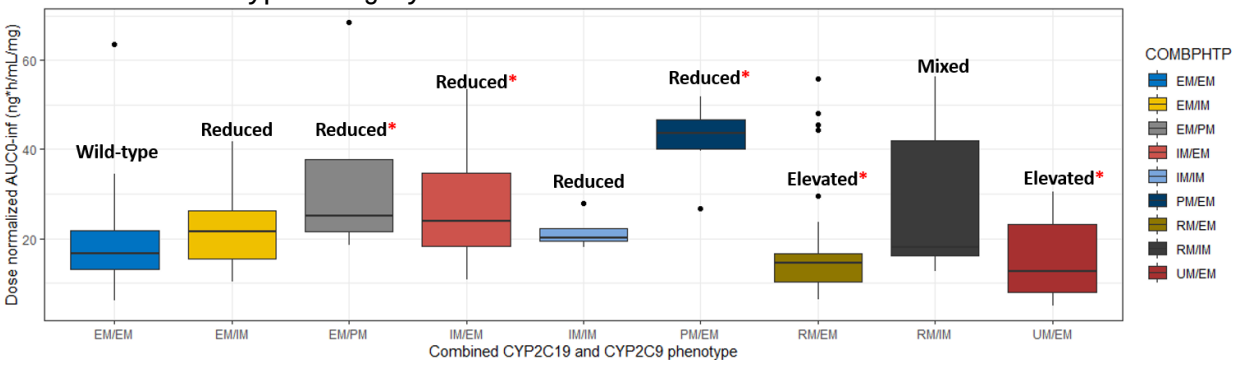
Regression analysis from NCA data (ncamf.xpt) of 648 records. 331 records were excluded for PK of other moieties, absence of metabolizer phenotype or AUC. Additional 15 records were excluded due to an effect in exposure identified in Phase 2 tablet. From the remaining 316 records, doses higher than 200mg or given BID were excluded due to non-linear dose proportionality. Ultimately, 250 records (single dose) in healthy subjects treated with abrocitinib alone were included and used in summary statistics.* Subject misclassified as EM/PM by Applicant was recategorized and included as EM/IM.

The evaluation of CYP2C19 phenotypes independently in single dose studies indicated that CYP2C19 IM and PM phenotypes had a 31% and 126% increase in AUC respectively while CYP2C19 RM and UM phenotypes showed a 14% and 30% reduction in exposure respectively when compared to the EM phenotype. CYP2C9 IM and PM phenotypes showed a 23% and 68% increase in exposure respectively when compared to the CYP2C9 EM phenotype.

Of the CYP2C19/2C9 combined the phenotypes, UM/EM and RM/EM phenotypes were associated with a 24% and 15% decrease in AUC compared to EM/EM phenotype. The PM/EM combination (n=6) showed a 144% increase in exposure when compared to the EM/EM combination. In comparison, the EM/PM combination (with a similarly small sample size n=4) increased by 77%, reflecting the predominance of the contribution of CYP2C19 to the metabolism of abrocitinib. Similarly, abrocitinib AUC increased by 48% in IM/EM compared to EM/EM however, the increase in AUC was 23% in EM/IM phenotypes suggesting the decreased CYP2C19 enzyme activity in the IM/EM combination made more impact on the exposure than the decreased CYP2C9 activity in the EM/IM phenotype combination.

In the overall phenotype categories as proposed by the applicant, the mixed and reduced overall phenotypes showed a 48% and 41% increase in exposure respectively while elevated overall phenotype showed a 18% reduction in exposure when compared to wild type. The variability observed between the combined phenotypes that constitute the reduced overall phenotype (Figure 33) indicates that the overall categorization diminishes the impact of the CYP2C19 PM phenotype when combined with other phenotypes.

Figure 33. Dose-Normalized AUC in Single Dose Studies by Combined CYP2C19 and CYP2C9 and Overall Phenotype Category



	EM/EM (N=76)	EM/IM (N=33)	EM/PM (N=4)	IM/EM (N=48)	IM/IM (N=4)	PM/EM (N=6)	RM/EM (N=52)	RM/IM (N=11)	UM/EM (N=16)	Overall (N=250)
AUC.DOSE										
Mean (SD)	18.4 (8.51)	22.1 (8.29)	34.3 (23.0)	26.3 (10.8)	21.6 (4.31)	42.1 (8.64)	16.3 (10.4)	28.7 (15.6)	15.3 (8.77)	21.1 (11.3)
Median [Min, Max]	16.7 [6.06, 63.5]	21.6 [10.3, 41.7]	25.1 [18.6, 68.4]	24.0 [10.7, 53.6]	20.2 [18.1, 27.9]	43.7 [26.8, 51.8]	14.5 [6.42, 55.8]	18.0 [12.7, 56.2]	12.6 [4.81, 30.6]	18.1 [4.81, 68.4]
SEX										
Male	71 (93.4%)	33 (100%)	4 (100%)	37 (77.1%)	3 (75.0%)	6 (100%)	39 (75.0%)	9 (81.8%)	16 (100%)	218 (87.2%)
Female	5 (6.6%)	0 (0%)	0 (0%)	11 (22.9%)	1 (25.0%)	0 (0%)	13 (25.0%)	2 (18.2%)	0 (0%)	32 (12.8%)
RACE.N										
White/Black	69 (90.8%)	29 (87.9%)	4 (100%)	45 (93.8%)	2 (50.0%)	5 (83.3%)	47 (90.4%)	11 (100%)	16 (100%)	228 (91.2%)
Asian/Other	3 (3.9%)	4 (12.1%)	0 (0%)	2 (4.2%)	2 (50.0%)	1 (16.7%)	5 (9.6%)	0 (0%)	0 (0%)	17 (6.8%)
Unknown	4 (5.3%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (2.0%)
FASTED										
Fast	71 (93.4%)	31 (93.9%)	3 (75.0%)	45 (93.8%)	4 (100%)	6 (100%)	51 (98.1%)	10 (90.9%)	14 (87.5%)	235 (94.0%)
Fed	5 (6.6%)	2 (6.1%)	1 (25.0%)	3 (6.2%)	0 (0%)	0 (0%)	1 (1.9%)	1 (9.1%)	2 (12.5%)	15 (6.0%)
AGE										
Mean (SD)	36.7 (11.6)	38.7 (9.41)	54.3 (6.50)	37.5 (12.5)	35.8 (8.54)	41.2 (6.01)	34.6 (9.25)	44.2 (10.3)	40.2 (10.6)	37.6 (11.0)
Median [Min, Max]	36.0 [19.0, 65.0]	39.0 [23.0, 54.0]	51.0 [51.0, 64.0]	33.0 [22.0, 68.0]	33.0 [29.0, 48.0]	45.0 [32.0, 45.0]	33.0 [22.0, 62.0]	49.0 [32.0, 56.0]	43.5 [22.0, 53.0]	36.0 [19.0, 68.0]
BWT										
Mean (SD)	81.8 (9.25)	77.0 (10.8)	93.0 (5.90)	78.2 (14.2)	79.0 (10.2)	80.4 (7.91)	79.3 (16.8)	79.3 (8.48)	64.6 (10.0)	78.8 (12.9)
Median [Min, Max]	83.5 [60.8, 98.7]	77.0 [57.0, 101]	95.9 [84.1, 95.9]	77.3 [59.5, 118]	75.6 [71.2, 93.5]	82.5 [64.7, 87.4]	74.9 [55.5, 108]	78.7 [62.3, 87.9]	60.0 [55.7, 87.9]	79.3 [55.5, 118]

* indicates statistical significance; sex, fed, age, weight, race had significant impact on AUC which might not be balanced among different metabolizer phenotypes. Increased AUC was associated with female sex, increased age, fed state and race Asian/Other > White/Black > unknown. Increased BW was associated with decreased AUC

In multiple dose studies, no subjects with CYP2C19 PM phenotype were in the analysis and the impact either independently or in combination with CYP2C9 phenotypes could not be evaluated (Table 117).The EM/IM phenotype in multiple dose studies demonstrated a 66% decrease in AUC when compared to the EM/EM phenotype. The sample size (n=1) limits the interpretation of this finding, which is in contrast to the EM/IM phenotype in single dose studies that showed a 23% increase in AUC.

Table 117. Dose-Normalized AUC in Single Dose Studies by CYP2C19 and CYP2C9 Independent, Combined, and Overall Phenotypes

CP2C19 Phenotype (N=28)	Geometric Mean AUC [95% CI]	Fold Change	CYP2C19/CYP2C9 Phenotype (N=28)	Geometric Mean AUC [95% CI]	Fold Change	Overall Phenotype (N=28)	Geometric Mean AUC [95% CI]	Fold Change
EM (10)	18.28 [13.21;25.28]	-	EM/EM (9)	20.36 [15.97;25.96]	-	Wild Type (11)	20.36 [15.97;25.96]	-
IM (7)	25.79 [17.64;37.72]	1.41	EM/IM (1)	6.91 [NA;NA]	0.34	Reduced (8)	21.88 [13.23;36.17]	1.07
RM (11)	21.17 [15.56;28.83]	1.16	IM/EM (5)	26.96 [14.66;49.59]	1.32	Elevated (9)	21.17 [15.54;28.83]	1.04
CP2C9 Phenotype (N=28)			IM/IM (2)	23.08 [7.46;71.42]	1.13			
EM (25)	21.91 [18.45;26.01]	-	RM/EM (11)	21.17 [15.54;28.83]	1.04			
IM (3)	15.44 [2.70;88.26]	0.70						

Regression analysis from NCA data (ncamf.xpt) of 648 records. 331 records were excluded for PK of other moieties, absence of metabolizer phenotype or AUC. Additional 15 records were excluded due to an effect in exposure identified in Phase 2 tablet. From the remaining 316 records, doses higher than 200mg or given BID were excluded due to non-linear dose proportionality. Ultimately 28 records (multiple doses) in healthy subjects treated with abrocitinib alone were included and used in summary statistics.

Other possible combinations not reflected in the pool of analyzed subjects include the scenarios of PM/IM and PM/PM combination. The mean increase observed in the EM/PM phenotypes, though 77% higher than the reference phenotype, is characterized by high variability in a small sample size therefore undermining a compelling rationale for CYP2C9 PM phenotype-directed

dosing recommendation. It is expected that the dose recommendation for CYP2C19 PM phenotypes mitigates exposure differences in PM/PM phenotypes. In a September 17, 2021 response to an information request to detail the adverse event profile of CYP2C19 poor metabolizers in the abrocitinib development program, the applicant noted CYP2C19 genotyping information was not available from Phase 2 and Phase 3 studies. A large variability in exposure was observed in AD patients (1840 to 39500 ng*h/mL for 200 mg QD) and based on the PK/PD analysis, significant thrombocytopenia with serious clinical concerns is not expected for patients with baseline platelet counts >=210·000/µL at the dose of 200 mg. (See Section 16.5.2 for details). In the context of increasing the recommended abrocitinib dose in non-responders, dose increase to 100 mg may be permitted in patients known to be CYP2C19 poor metabolizers who do not respond to the initial recommended 50 mg dose.

16.5.5. Summary of Bioanalytical Method Validation and Performance

Abrocitinib and Its Active Metabolites (M1 and M2) Concentrations in Plasma and Urine

Plasma and urine concentrations of abrocitinib and its active metabolites i.e., M1 and M2, were measured using validated bioanalytical methods with HPLC-MS/MS. The performance and validation parameters of the analytical methods are summarized in Table 118.

Table 118. Summary of the Performance and Validation Parameters of the Bioanalytical Method to Measure Abrocitinib, M1, and M2 in Human K_2EDTA Plasma or in Human Urine

Abrocitinib (PF-04965842) in Plasma			
Bioanalytical method review summary	Method validation was adequate		
Report title	The Validation of an HPLC-MS/MS Assay Method for the Determination of PF-04965842 in Human K_2EDTA Plasma		
Method ID	B7459003		
Matrix	Human plasma		
Anticoagulant	K_2EDTA		
Extraction method	Liquid-liquid Extraction		
Detection method	HPLC-MS/MS		
Sample aliquot volume	75 µL		
Regression, weighting	Quadratic, $1/x^2$		
Calibration Range	1.00 (LLOQ) to 2000 (ULOQ) ng/mL		
Calibration standard concentrations	1.00, 2.00, 10.0, 50.0, 200, 800, 1200, 1800 and 2000 ng/mL		
Assay performance			Acceptability
	Precision (%CV)	Accuracy (%RE)	
Intra-assay validation	< 7.8%	-8.1% - 3.1%	Yes
Inter-assay validation	< 7.3%	-8.2% - 0.6%	Yes
Dilution factors	1/10, 1/50		Yes
Mean analyte recovery	90.4%		Yes

Mean internal standard recovery	86.8%		Yes
Selectivity			
Matrix effects in normal matrices	10 out of 10 Human Plasma Lots Passed		Yes
Matrix effects in hemolyzed matrices	2 out of 2 Human hemolyzed Plasma Lots Passed		Yes
Matrix effects in hyperlipidemic matrices	2 out of 2 Human hyperlipidemic Plasma Lots Passed		Yes
Analyte carryover	< 14.1%		Yes
Internal standard carryover	< 0.2%		Yes
Stability			
Ambient Temperature Matrix Stability	52 Hours at Ambient Temperature (25±5°C)		
Refrigerated Storage Matrix Stability	51.5 Hours at 2-8°C		
Frozen Storage Matrix Stability	744 Days at -20±5 °C and -70±10 °C		
Freeze/Thaw Matrix Stability	5 Freeze-thaw Cycles at -20±5 °C and -70±10 °C		
M1 (PF-06471658) in Plasma			
Bioanalytical method review summary	Method validation was adequate		
Report title	The Validation of an HPLC/MS/MS Method for the Determination of PF-04965842, PF-06471658, and PF-07054874 in Human K_2EDTA Plasma		
Method ID	B7459012		
Matrix	Human plasma		
Anticoagulant	K_2EDTA		
Sample volume required for analysis	100 µL		
Sample preparation	Protein precipitation		
Method type	HPLC-MS/MS		
Regression, weighting	linear, $1/x^2$		
Calibration range	1.00 (LLOQ) to 1000 (ULOQ) ng/mL		
Calibration standard concentrations	1.00, 2.00, 5.00, 20.0, 100, 400, 800, and 1000 ng/mL		
Assay performance			Acceptability
	Precision (%CV)	Accuracy (%RE)	
Intra-assay validation	< 5.9%	-3.6% - 7.0%	Yes
Inter-assay validation	< 5.5%	0.0% - 4.0%	Yes
Dilution factor	1/10		Yes
Mean analyte recovery	48.3%		Yes
Mean internal standard recovery	46.9%		Yes

Selectivity			
Matrix effects in normal matrices	10 out of 10 Human Plasma Lots Passed		Yes
Matrix effects in hemolyzed matrices	2 out of 2 Human hemolyzed Plasma Lots Passed		Yes
Matrix effects in hyperlipidemic matrices	2 out of 2 Human hyperlipidemic Plasma Lots Passed		Yes
Stability			
Processed Extract Stability	147 Hours at 5°C		
Frozen Storage Matrix Stability	349 Days at -20°C and -80°C		
Freeze/Thaw Matrix Stability	5 Freeze-thaw Cycles -20°C and -80°C		
M2 (PF-07055087) in Plasma			
Bioanalytical method review summary	Method validation was adequate		
Report title	The Validation of a HPLC/MS/MS Method for the Determination of PF-07055087 in K_2EDTA Human Plasma		
Method ID	B7459013		
Matrix	Human plasma		
Anticoagulant	K_2EDTA		
Sample volume required for analysis	100 µL		
Sample preparation	Protein precipitation		
Method type	HPLC-MS/MS		
Regression, weighting	linear, $1/x^2$		
Calibration range	5.00 (LLOQ) to 5000 (ULOQ) ng/mL		
Calibration standard concentrations	5.00, 10.0, 25.0, 100, 400, 2000, 4000, and 5000 ng/mL		
Assay performance			Acceptability
	Precision (%CV)	Accuracy (%RE)	
Intra-assay validation	< 7.3%	-6.8% - 13.4%	Yes
Inter-assay validation	< 2.3%	-1.3% - 2.0%	Yes
Dilution factor	1/10		Yes
Mean analyte recovery	114%		Yes
Mean internal standard recovery	113%		Yes
Selectivity			
Matrix effects in normal matrices	10 out of 10 Human Plasma Lots Passed		Yes
Matrix effects in hemolyzed matrices	2 out of 2 Human hemolyzed Plasma Lots Passed		Yes
Matrix effects in hyperlipidemic matrices	2 out of 2 Human hyperlipidemic Plasma Lots Passed		Yes

Analyte carryover	No Carryover	Yes
Internal standard carryover	No Carryover	Yes
Stability		
Processed Extract Stability	147 Hours at 5°C	
Bench Top Stability	24 Hours at 15°C to 30°C; 24 Hours at 2°C to 8°C	
Frozen Storage Matrix Stability	349 Days at -20°C and -80°C	
Freeze/Thaw Matrix Stability	5 Freeze-thaw Cycles at -20°C and -80°C	

Abrocitinib (PF-04965842) in Urine	
Bioanalytical method review summary	Method validation was adequate
Report title	Validation of an LC/MS/MS assay for the quantitation of PF-04965842 in human urine
Method ID	B7459002
Matrix	Human urine
Sample volume required for analysis	25 µL
Extraction procedure	Liquid-liquid extraction (LLE)
Method type	LC-MS/MS
Regression, weighting	Quadratic, $1/x^2$
Calibration range	10.0 (LLOQ) to 10,000 (ULOQ) ng/mL
Capability of Dilution (concentration tested; dilution factor)	50,000 ng; 100x
Selectivity (number of lots tested / passed)	10/10
Matrix Effects Assessment (number of lots tested / passed)	10/10
Recovery	69-76%
Run Size Evaluation	192 consecutive injections
Long-Term Storage Stability at -20°C	37 days
Bench Top Stability	313 hours
Freeze-Thaw Stability	6 cycles
Processed Sample Stability	6 days

Method performance in study B7451032		
Analyte(s)	Abrocitinib	Acceptability
Assay run perfermance	53 out of 60 runs met the acceptance criteria	Yes
Mean inter-assay performance	Precision (%CV): ≤4.2%; Accuracy (%RE): -1.8% to -0.3%	Yes
ISR assessment	96.9%	Yes

Maximum days from collection to analysis		64 Days			Yes
Maximum number of freeze/thaw cycles		3 Freeze/Thaw Cycles			Yes
Method performance in study B7451020					
Analyte(s)		Abrocitinib	M1	M2	Acceptability
Assay run performance: # of runs that met the acceptance criteria		9 out of 10 runs	9 out of 10 runs	7 out of 8 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤10.9%	≤5.7%	≤6.3%	Yes
	Accuracy (%RE)	9.6% to 0.0%	-2.9% to 3.0%	-2.4% to 3.6%	Yes
ISR assessment		91.7%	93.2%	100%	Yes
Maximum days from collection to analysis		187 Days	172 Days	204 Days	Yes
Maximum number of freeze/thaw cycles		5 Cycles	5 Cycles	5 Cycles	Yes
Method performance in study B7451021					
Analyte(s)		Abrocitinib	M1	M2	Acceptability
Assay run performance: # of runs that met the acceptance criteria		9 out of 9 runs	9 out of 10 runs	9 out of 12 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤5.8%	≤7.2%	≤6.9%	Yes
	Accuracy (%RE)	2.3% to 0.6%	-0.4% to 6.8%	-0.7% to -7.7%	Yes
ISR assessment		100%	96.3%	87.0%	Yes
Maximum days from collection to analysis		214 Days	214 Days	211 Days	Yes
Maximum number of freeze/thaw cycles		4 Cycles	2 Cycles	4 Cycles	Yes
Method performance in study B7451017					
Analyte(s)		Abrocitinib	M1	M2	Acceptability
Assay run performance: # of runs that met the acceptance criteria		15 out of 18 runs	13 out of 13 runs	14 out of 15 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤5.0%	≤13.3%	≤5.0%	Yes
	Accuracy (%RE)	-3.3% to 1.0%	-0.9% to 6.4%	-4.3% to -2.5%	Yes
ISR assessment		99.0%	85.0%	98.3%	Yes
Maximum days from collection to analysis		55 Days	343 Days	343 Days	Yes
Maximum number of freeze/thaw cycles		3 Cycles	5 Cycles	5 Cycles	Yes

Method performance in study B7451019					
Analyte(s)		Abrocitinib	M1	M2	Acceptability
Assay run performance: # of runs that met the acceptance criteria		7 out of 9 runs	7 out of 7 runs	7 out of 7 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤2.8%	≤10.6%	≤3.8%	Yes
	Accuracy (%RE)	-4.0% to 0.0%	3.8% to 6.3%	-1.3% to 0.0%	
ISR assessment		85.0%	92.9%	100%	Yes
Maximum days from collection to analysis		54 Days	322 Days	322 Days	Yes
Maximum number of freeze/thaw cycles		3 Cycles	5 Cycles	5 Cycles	Yes
Method performance in study B7451043					
Analyte(s)		Abrocitinib	M1	M2	Acceptability
Assay run performance: # of runs that met the acceptance criteria		14 out of 16 runs	13 out of 14 runs	13 out of 13 runs	Yes
Mean inter-assay performance	Precision (%CV)	≤5.0%	≤8.0%	≤6.1%	Yes
	Accuracy (%RE)	-1.3% to 0.0%	-5.9% to 7.2%	-2.9% to 1.3%	
ISR assessment		98.1%	98.1%	98.1%	Yes
Maximum days from collection to analysis		29 Days	29 Days	29 Days	Yes
Maximum number of freeze/thaw cycles		3 Cycles	3 Cycles	3 Cycles	Yes
Method performance in study B7451027					
Analyte(s)		Abrocitinib			Acceptability
Assay run perfermance		8 out of 11 runs met the acceptance criteria			Yes
Mean inter-assay performance		Precision (%CV): ≤7.2%; Accuracy (%RE): -2.3% to -2.0%			Yes
ISR assessment		97.5%			Yes
Maximum days from collection to analysis		46 Days			Yes
Maximum number of freeze/thaw cycles		4 Freeze/Thaw Cycles			Yes
Method performance in study B7451006					
Analyte(s)		Abrocitinib			Acceptability
Assay run perfermance		46 out of 49 runs met the acceptance criteria			Yes
Mean inter-assay performance		Precision (%CV): ≤4.4%; Accuracy (%RE): -3.3% to 2.4%			Yes
ISR assessment		93.1%			Yes

Maximum days from collection to analysis	342 Days	Yes
Maximum number of freeze/thaw cycles	4 Freeze/Thaw Cycles	Yes

Source: Validation Report of Method B7459002; Validation Report of Method B7459003; Validation Report of Method B7459012; Validation Report of Method B7459013; Bioanalytical Report of B7451006; Bioanalytical Report of B7451017; Bioanalytical Report of B7451019; Bioanalytical Report of B7451020; Bioanalytical Report of B7451021; Bioanalytical Report of B7451027; Bioanalytical Report of B7451032; Bioanalytical Report of B7451043;
Abbreviations: CV=coefficient of variation; RE=relative error

Ethinyl Estradiol and Levonorgestrel Plasma Concentrations (Study B7451016)

Plasma samples obtained in Study B7451016 were analyzed for ethinyl estradiol (EE) and levonorgestrel (LN) concentrations by (b) (4) using HPLC-MS/MS. The validated ranges of quantitation were 1 to 400 pg/mL for EE and 10 (LLOQ) to 10,000 pg/mL for LN. Method validations were adequate to support the study B7451016 (Pfizer method validation report: B7459009 for EE; B7459008 for LN). All samples were analyzed within 427 days and 673 days of collection for EE and LN, respectively, following storage at -20°C within established long-term stability.

Midazolam Plasma Concentrations (B7451022)

Plasma samples obtained in Study B7451022 were analyzed for midazolam concentrations by (b) (4) using LC-MS/MS. The validated ranges of quantitation were 0.05 (LLOQ) to 50 ng/mL for midazolam. Method validation was adequate to support the study B7451022 (Pfizer method validation report: B7459006). All samples were analyzed within 45 days of collection following storage at -20°C within established long-term stability.

Dabigatran Plasma Concentrations (B7451026)

Plasma samples obtained in Study B7451026 were analyzed for dabigatran concentrations by (b) (4) using HPLC-MS/MS. The validated ranges of quantitation were 1.0 (LLOQ) to 800 ng/mL for dabigatran. Method validation was adequate to support the study B7451026 (Pfizer method validation report: B7459007). All samples were analyzed within 95 days of collection following storage at -20°C within established long-term stability.

Rosuvastatin Plasma and Urine Concentrations (B7451033)

Plasma samples obtained in Study B7451033 were analyzed for rosuvastatin concentrations by (b) (4) using UPLC-MS/MS. The validated ranges of quantitation were 5 (LLOQ) to 2000 ng/mL for rosuvastatin. Method validation was adequate to support the study B7451033 (Pfizer method validation report: B7459010). All samples were analyzed within 45 days of collection following storage at -80°C within established long-term stability.

Urine samples obtained in Study B7451033 were analyzed for rosuvastatin concentrations by [redacted] using HPLC-MS/MS. The validated ranges of quantitation were 5 (LLOQ) to 2000 ng/mL for rosuvastatin. Method validation was adequate to support the study B7451033 (Pfizer method validation report: B7459011). All samples were analyzed within 45 days of collection following storage at -80°C within established long-term stability.

Metformin Plasma Concentrations (B7451034)

Plasma samples obtained in Study B7451034 were analyzed for metformin and N1-Methylnicotinamide (NMN) concentrations by [redacted] using LC-MS/MS. The validated ranges of quantitation were 2 (LLOQ) to 2000 ng/mL for metformine and 1 (LLOQ) to 1000 ng/mL for NMN. Method validation was adequate to support the study B7451034 (Pfizer method validation report: C2549003). All samples were analyzed within 26 days and 28 days of collection following storage at -20°C and -70°C for metformin and NMN, respectively, within established long-term stability.

Urine samples obtained in Study B7451034 were analyzed for metformin and NMN concentrations by [redacted] using LC-MS/MS. The validated ranges of quantitation were 0.5 (LLOQ) to 200 µg/mL for metformin and 0.1 (LLOQ) to 100 µg/mL for NMN. Method validation was adequate to support the study B7451034 (Pfizer method validation report: C2549005). All samples were analyzed within 22 days and 28 days of collection following storage at -20°C and -70°C for metformin and NMN, respectively, within established long-term stability

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