NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Original BLA
Application Number(s)	BLA 761458/Original 1
Priority or Standard	Standard
Submit Date(s)	December 16, 2024
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PDUFA Goal Date	December 16, 2025
Division/Office	DPACC/OII
Review Completion Date	December 16, 2025
Established/Proper Name	depemokimab-ulaa
(Proposed) Trade Name	EXDENSUR
Pharmacologic Class	Interleukin-5 (IL-5) antagonist
Code name	GSK3511294
Applicant	GlaxoSmithKline
Dosage form	injection
Applicant proposed Dosing Regimen	100 mg once every 6 months by subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	Add-on maintenance treatment of asthma in adult and pediatric patients aged 12 years and older with type 2 inflammation characterized by an eosinophilic phenotype on medium-to-high-dose inhaled corticosteroids (ICS) plus another asthma controller
Applicant Proposed SNOMED CT Indication Disease Term	195967001, Asthma (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older
Recommended SNOMED CT Indication Disease Term	195967001, Asthma (disorder)
Recommended Dosing Regimen	100 mg administered once every 6 months by subcutaneous injection

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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
DRM=Division of Risk Management
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Glossary

ACQ-5	Asthma Control Questionnaire 5-item version
ADA	antidrug antibody
ADSD	Asthma Daily Symptom Diary
AE	adverse event
AESI	adverse event of special interest
AI	autoinjector
ALT	alanine aminotransferase
ANSD	Asthma Nightly Symptom Diary
AUC	area under the plasma concentration-time curve
BA	bioavailability
BD	bronchodilator
BE	bioequivalence
BEC	blood eosinophil count
BLA	biologics license application
BLQ	below level of quantitation
BMI	body mass index
CBE	Changes Being Effected
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRSwNP	chronic rhinosinusitis with nasal polyps
CSR	clinical study report
C_{trough}	trough plasma concentration
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DPMH	Division of Pediatrics and Maternal Health
DPSS	descriptive pregnancy safety study
EBE	empirical Bayes estimate
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ER	exposure-response
FAS	full analysis set
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second

FIH	first-in-human
FVC	forced vital capacity
GCP	good clinical practice
GINA	Global Initiative for Asthma
GMR	geometric mean ratio
HD	high dose
HV	healthy volunteer
IA	interim analysis
ICE	intercurrent event
ICS	inhaled corticosteroid
IDMC	independent data monitoring committee
Ig	immunoglobulin
IIV	interindividual variability
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug application
IPD	important protocol deviation
K_D	dissociation constant
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LD	low dose
LLOQ	lower limit of quantitation
LS	least-squares
mAb	monoclonal antibody
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
NAb	neutralizing antibody
NCA	noncompartmental analyses
OCMQ	Office of New Drugs Custom Medical Queries
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSIS	Office of Study Integrity and Surveillance
PD	pharmacodynamic
PFS	prefilled syringe
PI	prescribing information
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
ppFEV1	percent predicted FEV1
PPND	pre- and postnatal development
PRO	patient-reported outcome
PT	preferred term

Q6M	every 6 months
QTcF	corrected QT interval, Fridericia's equation
RSE	relative standard error
SABA	short-acting beta agonist
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCS	systemic corticosteroids
SD	standard deviation
SDAC	statistical data analysis center
SEE	substantial evidence of effectiveness
SGRQ	St. George's Respiratory Questionnaire
SOC	system organ class
SSD	safety syringe device
TBM	to-be-marketed
TEAE	treatment-emergent adverse event
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Prescribing Information
W&P	Warning and Precaution

Executive Summary

1 Summary of Regulatory Action

The Applicant, GlaxoSmithKline, submitted an original BLA 761458 for depemokimab (tradename: EXDENSUR), a humanized, YTE-modified, monoclonal antibody (immunoglobulin [Ig] G1, kappa) that binds and inhibits interleukin-5 (IL-5), for the proposed indication of "add-on maintenance treatment of adult and adolescent patients 12 years and older with Type 2 inflammation characterized by an eosinophilic phenotype on medium-to high-dose inhaled corticosteroids (ICS) plus another asthma controller" at a proposed dosage of 100 mg subcutaneously once every 6 months. The BLA was reviewed by a multidisciplinary team, all of whom recommend approval of depemokimab for the proposed dosage and indication.

To support the BLA for depemokimab, the Applicant submitted safety and efficacy results from two adequate and well-controlled trials, 206713 (SWIFT-1) and 213744 (SWIFT-2), hereafter referred to as SWIFT-1 and SWIFT-2. SWIFT-1 and SWIFT-2 were replicate, Phase 3, randomized, double-blind, placebo-controlled, trials that enrolled adults and adolescents to evaluate depemokimab 100 mg subcutaneously once every 6 months for 52 weeks. Both trials demonstrated statistically and clinically significant reductions in the primary endpoint of annualized rate of asthma exacerbations. Extrapolation of efficacy from adults with asthma to adolescent patients 12 to 17 years of age with asthma is supported by the similarity in disease pathophysiology, a comparable pharmacokinetic and pharmacodynamic response, and an expected treatment effect consistent with the adult population based on the well-defined drug target (IL-5) and clinical evidence from the use of other approved asthma biologics, including those that target IL-5, in this adolescent subgroup.

The safety database was of adequate size and duration. The safety profile is acceptable for its intended use as an add-on maintenance treatment in patients with severe asthma and elevated peripheral blood eosinophils. The most common adverse reactions were upper respiratory tract infection, allergic rhinitis, influenza, arthralgia, and pharyngitis.

The clinical development program is sufficient to support the recommended dosage of 100 mg subcutaneously once every 6 months for the aforementioned intended population of use. The clinical review team determines that the results of the primary endpoint are robust and clinically meaningful, despite not meeting statistical significance for any secondary endpoints (see Section 8.2.10.1). The well-characterized drug target (IL-5) and established safety profile of other approved biologics with the same mechanism of action for the treatment of asthma provide reassurance with the additional benefit of an extended half-life.

Postmarketing requirement (PMR) studies will be issued for a pediatric trial in patients 6 to 11 years of age with severe asthma characterized by an eosinophilic phenotype, a worldwide descriptive pregnancy safety study (DPSS), and a clinical lactation study (Section 22).

In summary, the recommended regulatory action for this BLA is Approval for the "add-on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older."

2 Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was met with two or more adequate and well-controlled trials.

To support the proposed asthma indication, the Applicant completed two replicate, adequate and well-controlled trials, SWIFT-1 (trial 206713) and SWIFT-2 (trial 213744). The trials included a 52-week, randomized, double-blind, placebo-controlled treatment period with a total of 792 subjects randomized 2:1 to depemokimab or matching placebo (395 participants in SWIFT-1; 397 participants in SWIFT-2). The trials assessed the efficacy and safety of depemokimab 100 mg administered subcutaneously once every 6 months in 762 adults and adolescents ≥12 years of age with asthma and elevated peripheral blood eosinophils. Participants continued their background maintenance therapy of a medium to high dose inhaled corticosteroid plus at least one additional asthma controller with or without oral corticosteroids. The analysis sets excluded participants from sites with potential good clinical practice (GCP) violations and data integrity issues (see Section 12) as well as participants who were randomized in error, but did not receive investigational medicinal product (IMP).

Efficacy results were based on a total 762 subjects in the full analysis set (FAS) analysis sets (382 in SWIFT-1; 380 in SWIFT-2) with a primary efficacy endpoint of annualized rate of clinically significant asthma exacerbations over 52 weeks. Clinically significant asthma exacerbations were defined as the use of systemic corticosteroids and/or hospitalization and/or emergency department visit (see Section 8.2.5). The primary efficacy endpoint is a well-defined, objective, and clinically meaningful outcome measure in asthmatic patients. Key secondary endpoints included a change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score, Asthma Control Questionnaire 5-item version (ACQ-5) score, the Asthma Daily/Nightly Symptom Diary (ADSD/ANSD) weekly mean score, and pre-bronchodilator forced expiratory volume in one second (FEV1) at week 52 as well as the annualized rate of exacerbations requiring hospitalization and/or ED visit over 52 weeks.

Both trials met statistical significance for the primary endpoint. In SWIFT-1, the annualized exacerbation rate ratio of the depemokimab treatment group compared to the placebo treatment group was 0.42 ($p<0.001$, 95% confidence interval [CI] 0.30, 0.6) with a 58% reduction (95% CI 40%, 70%) in the annual rate. In SWIFT-2, the annualized exacerbation rate ratio of the depemokimab treatment group compared to the placebo treatment group was 0.52 ($p<0.001$, 95% CI 0.36, 0.73) with a 48% reduction (95% CI 27%, 64%) in the annual rate. No key secondary endpoints achieved statistical significance based on the hierarchical testing strategy,

yet the statistical robustness and clinical meaningfulness of the primary endpoint is sufficient to demonstrate SEE (See Section 8.2.10).

3 Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma prevalence is approximately 22 million in the U.S. and >300 million worldwide with a mortality rate of 1,000 deaths per day (Brusselle and Koppelman 2022; Centers for Disease Control 2024; Global Initiative for Asthma 2025). • Asthma is a heterogenous, chronic lower airway respiratory disease consisting of airway hyperresponsiveness, inflammation, and bronchodilator associated reversible expiratory airflow. Accordingly, clinical symptoms include cough, wheezing, and shortness of breath among others (Brusselle and Koppelman 2022). • Disease onset can be in childhood or adulthood. Asthma has an initial male predominance followed by a female predominance from adolescence to approximately the 5th decade of life (Dharmage et al. 2019). • Treatment follows a step-wise approach with 10% and 2.5% of adults and children, respectively, categorized as having severe asthma who may benefit from add-on biologic therapies (Brusselle and Koppelman 2022). • The majority of patients with severe asthma have an eosinophilic phenotype characterized by elevated serum eosinophils and/or fractional exhaled nitric oxide, as well as elevated Th2 cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). The local presence of persistent eosinophils is also associated with airway remodeling, chronic obstruction, and exacerbation risk, leading	Asthma is a heterogenous, chronic, lower airway respiratory disease. It is a common condition, though a subpopulation of patients with severe asthma with an eosinophilic phenotype are at risk for exacerbations and chronic obstruction and hence, may require add-on biologic therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to significant morbidity and mortality (Brusselle and Koppelman 2022; Rupani et al. 2024). • Given the well characterized cytokine targets and peripheral eosinophilia as a predictive biomarker for treatment response, targeted therapies for this phenotype are of clinical interest.	
Current Treatment Options	• Asthma treatment follows a step-wise approach (GINA Steps 1-5) with add-on biologic treatments considered at Step 5 (Global Initiative for Asthma 2025). • Currently approved biologics for asthma target IgE (omalizumab once every 2-4 weeks), interleukin-4Rα (dupilumab once every 2-4 weeks), interleukin-5 (mepolizumab once every 4 weeks, reslizumab once every 4 weeks), interleukin-5Rα (benralizumab once every 4-8 weeks), and thymic stromal lymphopoietin (TSLP, tezepelumab once every 4 weeks).	Although there are various approved biologics for severe asthma (including eosinophilic asthma), a therapeutic option with a previously approved target (IL-5) and the benefit of a longer dosing interval (once every 6 months) due to a YTE-modification is desirable.
Benefit	• The efficacy of depemokimab was evaluated in two replicate, 52-week, adequate and well-controlled trials (SWIFT-1 and SWIFT-2) in 762 adults and adolescents aged ≥12 years with severe, uncontrolled, eosinophilic asthma. • Statistical significance was achieved for the primary endpoint, annualized rate of asthma exacerbations over 52 weeks, in both trials (SWIFT-1 rate ratio 0.42, $p<0.001$; SWIFT-2 rate ratio 0.52, $p<0.001$). • No secondary endpoints met statistical significance based on the hierarchical testing strategy; however, the primary endpoint results were robust as well as clinically meaningful and therefore sufficient to demonstrate SEE.	Depemokimab demonstrated SEE on the basis of two adequate and well controlled trials with statistically significant and clinically relevant reductions in the annualized rate of asthma exacerbations over 52 weeks, an established and clinically meaningful outcome for asthma therapeutics.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The most commonly (≥4% incidence) reported on-treatment adverse events (AEs) by preferred term (PT) and occurring more frequently in the depemokimab treatment group than the placebo treatment group were allergic rhinitis, pharyngitis, upper respiratory tract infection, arthralgia, and influenza. Of these, influenza was also seen in the mepolizumab asthma trials. • Additional analysis noted an imbalance in the OCMQ arthritis, but in a subset of participants in which arthritis may be common overall regardless of treatment effect. • In comparison to the Warnings and Precautions (W&P) of mepolizumab, there was no safety signal identified for IgE-mediated hypersensitivity reactions or herpes zoster infection. Nonetheless, a W&P for hypersensitivity reactions in section 5 of the label will be retained as hypersensitivity reactions are expected to occur with injectable monoclonal antibodies. • Further, based on the YTE-modification and prolonged half-life there is potential for higher and prolonged exposure to the fetus and infant when administered in pregnancy. This risk was detailed in the highlights, section 8, and section 17 of labeling.	The safety profile for depemokimab in the proposed asthma indication is reassuring. Potential risks can be mitigated through further labeling and routine pharmacovigilance.

4 Conclusions Regarding Benefit-Risk

The Applicant has demonstrated SEE for depemokimab 100 mg administered subcutaneously once every 6 months for the add-on maintenance treatment of adult and adolescent patients with severe asthma characterized by an eosinophilic phenotype. Review of the safety data did not identify any concerning safety signal that would preclude approval or require narrowing of the indicated target population. Potential risks can be mitigated through labeling and routine pharmacovigilance. Given that depemokimab will be the first, chronically administered biologic with a YTE-modification allowing for a prolonged half-life to an endogenous target, potential risk to the fetus and infant via placental transfer if administered during pregnancy was incorporated into the United States Prescribing Information (USPI) highlights, section 8, and section 17 (see Section 21).

The Pediatric Research Equity Act PMR will be issued to conduct a pharmacokinetic (PK)/PD and safety study in pediatric subjects 6 to 11 years of age with severe asthma characterized by an eosinophilic phenotype. Additionally, based on the prolonged half-life with potential for increased fetal exposure *in utero*, the lack of pregnancy related nonclinical data for depemokimab, and the potential risk of adverse fetal outcomes with anti-IL-5 monoclonal antibodies, a PMR to conduct a worldwide DPSS will also be issued. Further, a PMR for a clinical lactation study will be issued based on its anticipated use in breastfeeding women, its purported potential to be present in human breast milk, and the lack of clinical data for depemokimab use in lactation (see Section 22).

In conclusion, the multidisciplinary review team has determined that the benefit-risk assessment is favorable and supports the approval of depemokimab 100 mg subcutaneously once every 6 months for the add-on maintenance treatment of adult and adolescent patients with severe asthma characterized by an eosinophilic phenotype. Although there are various approved biologics for eosinophilic asthma, including others that target IL-5, the extended half-life of depemokimab offers a favorable alternative for injection-averse patients, reduces the burden of frequent treatment administration, and may promote therapeutic compliance.

Interdisciplinary Assessment

5 Introduction

Asthma is a heterogenous, chronic lower airway respiratory disease affecting approximately 22 million patients in the U.S. and >300 million individuals worldwide with a mortality rate of 1,000 deaths per day (Brusselle and Koppelman 2022; Centers for Disease Control 2024; Global Initiative for Asthma 2025). Asthma is defined by airway hyperresponsiveness, inflammation,

and bronchodilator associated reversible expiratory airflow. Associated symptoms therefore include shortness of breath, cough, and wheezing (Brusselle and Koppelman 2022). Asthma is more common in males then females through the beginning of adolescence, then more common in females from adolescence to approximately the 5th decade of life; asthma onset can occur in either childhood or adulthood (Dharmage et al. 2019). Treatment follows a stepwise approach with approximately 10% and 2.5% of adults and children, respectively, categorized as having severe asthma, often requiring add-on biologic therapies. Of the severe asthma subgroup, more than 50% of patients have an eosinophilic phenotype characterized by elevated serum eosinophils, as well as elevated fractional exhaled nitric oxide and Th2 cytokines, including IL-4, IL-5, and IL-13. The local presence of eosinophils in the airway causes significant morbidity and mortality attributed to its association with an increased exacerbation risk, airway remodeling, and chronic obstruction (Brusselle and Koppelman 2022; Rupani et al. 2024). The majority of currently approved biologics target the eosinophilic phenotype due to its well-characterized cytokine pathways and commercially available predictive biomarkers to identify patients who are likely to respond to therapy, namely peripheral eosinophil counts. Notably, there is no universal threshold for peripheral eosinophils that defines eosinophilic asthma, and eosinophil counts can be variable due to a variety of factors that can depress counts, including use of systemic corticosteroids and infections. For the three approved anti-IL-5/5R biologics, participants were required to have between ≥150 to ≥400 cells/ µL with specific cut-offs varying based on the time of collection.

The treatment of asthma in adults and adolescents ≥12 years-old follows a step-wise approach (Global Initiative for Asthma [GINA] Steps 1-5) in which the dose of ICS is gradually increased with or without the addition of other therapeutics (e.g., long-acting beta agonists [LABAs] or long-acting muscarinic antagonists [LAMAs]). Biologics are considered as add-on therapy at Step 5, of which there are currently six approved treatments shown in Table 1 (Global Initiative for Asthma 2025). Though there are other approved biologics targeting interleukin-5 (IL-5), dosing across all currently approved biologics varies between once every 2 weeks to once every 8 weeks. Thus, depemokimab would be the first approved biologic with a dosing interval of once every 6 months, potentially improving adherence and reducing injection-associated patient burden.

Table 1. Summary of FDA-Approved Biologic Therapies for Asthma

Product Name	Relevant Indication	Initial Year of Approval	Dosing/Administration
Mepolizumab	Add-on maintenance treatment of asthma patients ≥6 years old with severe asthma and with an eosinophilic phenotype	2015	Patients 6-11 years old: 40 mg SC once every 4 weeks Patients ≥12 years old: 100 mg SC once every 4 weeks
Benralizumab	Add-on maintenance treatment of asthma patients ≥6 years old with severe asthma and with an eosinophilic phenotype	2017	Patients 6-11 years old and <35 kg: 10 mg SC every 4 weeks for the first 3 doses followed by once every 8 weeks Patients 6-11 years old and ≥35 kg: 30 mg SC every 4 weeks for the first 3 doses followed by once every 8 weeks Patients ≥12 years old: 30 mg every 4 weeks for the first 3 doses followed by once every 8 weeks
Reslizumab	Add-on maintenance treatment of adults ≥18 years old with severe asthma and with an eosinophilic phenotype	2016	3 mg/kg IV once every 4 weeks
Dupilumab	Add-on maintenance treatment of patients ≥6 years old with moderate to severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma	2017	Patients 6 to 11 years old and 15 to <30 kg: 300 mg SC every 4 weeks Patients 6 to 11 years old and ≥30 kg: 200 mg every other week Patients ≥12 years old: 400 mg SC loading dose followed by 200 mg SC once every 2 weeks or 600 mg SC loading dose followed by 300 mg SC once every 2 weeks. Dosing and dosing regimen may be different for patients with additional co-morbidities.
Omalizumab	Treatment of moderate to severe persistent asthma in patients ≥6 years old with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with an inhaled corticosteroid	2003	75 mg to 375 mg SC once every 2 or 4 weeks based on weight (kg) and serum total IgE level (IU/mL)
Tezepelumab	Add-on maintenance treatment of asthma patients ≥12 years old with severe asthma	2021	210 mg SC once every 4 weeks

Source: clinical reviewer created table based on product labeling for currently approved asthma biologics.
Abbreviations: IgE, immunoglobulin E; IV, intravenous; SC, subcutaneous.

5.1. Review Issue List

5.1.1. Key Efficacy Review Issue

5.1.1.1. Lack of Statistically Significant Secondary Endpoints

5.1.2. Key Safety Review Issues

5.1.2.1. Safety of the YTE Modification in Pregnancy

5.2. Approach to Clinical Review

The efficacy and safety review of depemokimab for the proposed indication of asthma is based on the results of two pivotal Phase 3 trials, SWIFT-1 and SWIFT-2 (see Table 2). The protocols for these two trials are further described in Section 8.2.1with efficacy and safety results in Sections 8.2.9 and 9, respectively. Given the replicate trial design, a single trial description with pooled safety results will be presented. Efficacy results will be presented by individual trial, but displayed side by side.

Safety is further supported by an open-label extension trial, AGILE, and an ongoing non-inferiority trial, NIMBLE, in patients with asthma (Table 2). The efficacy and safety results of AGILE are based on the interim analysis as the trial was ongoing at the time of the BLA submission; however, the Applicant subsequently submitted the final clinical study report (CSR) during the review cycle. The protocols for these additional two trials are further described in Section 18.2 and 18.3. Efficacy results from the AGILE trial are presented in Section 19.8 with safety results in Section 20.2. No efficacy results of the NIMBLE trial will be presented as it is currently ongoing; however, interim safety data from the trial is presented in Section 20.3. The Applicant also conducted two pivotal trials (ANCHOR-1 and ANCHOR-2) for the chronic rhinosinusitis with nasal polyps (CRSwNP) indication for which the general safety of depemokimab can be referenced (b) (4) (b) (4) A detailed clinical pharmacology review is in Section 7.

Table 2. Listing of Clinical Trials Relevant for This BLA

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
206713 (SWIFT-1)	NCT04719832	52-week R, DB, PC, PG, MC	Depemokimab 100 mg or placebo SC every 6 months with SoC	Annualized rate of asthma exacerbations over 52 weeks	52 weeks	Planned: 375 Actual: 395 Number treated: Depemokimab: 259 Placebo: 136	Adults and adolescents with eosinophilic asthma (serum eosinophil count ≥300 cells/µL in past year prior to Visit 1 or ≥150 cells/ µL at Screening)	144 centers 12 countries Czech Republic, France, Germany, Ireland, Italy, Poland, Spain, UK, United States, Canada, China, Russia
213744 (SWIFT-2)	NCT04718103	52-week R, DB, PC, PG, MC	Depemokimab 100 mg or placebo SC every 6 months with SoC	Annualized rate of asthma exacerbations over 52 weeks	52 weeks	Planned: 375 Actual: 397 Number treated: Depemokimab: 251 Placebo: 129	Adults and adolescents with eosinophilic asthma (serum eosinophil count ≥300 cells/ µL in past year prior to Visit 1 or ≥150 cells/ µL at Screening)	187 centers 11 countries Czech Republic, France, Hungary, Italy, Poland, Spain, United States, Australia, Canada, Japan, Taiwan

Trial Identity	NCT No.	Trial Design	Regimen/Schedule/ Route	Primary Study Endpoint	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety								
212895 (AGILE)	NCT05243680	52-week Single-arm, OLE, MC	Depemokimab 100 mg SC every 6 months with SoC	Incidence of AEs/SAEs over 52 weeks Incidence of immunogenicity over 52 weeks	52 weeks	Planned: 637 Actual: 640 as of data cut-off Number treated: Depemokimab: 629	Adults and adolescents with eosinophilic asthma	155 centers 14 countries
206785 (NIMBLE)	NCT04718389	52-week R, DB, DD, PG, MC, NI	Depemokimab 100 mg SC every 6 months with SoC Mepolizumab 100 mg SC every 4 weeks with SoC Benralizumab 30 mg SC every 8 weeks with SoC	Annualized rate of asthma exacerbations over 52 weeks	52 weeks	Planned: 1700 Actual: 1090 as of data cut-off Number treated: Depemokimab: 538 Mepolizumab: 288 Benralizumab: 250	Adults and adolescents with eosinophilic asthma	404 centers 20 countries

Source: clinical reviewer and CDS created from the clinical study reports of trials SWIFT-1, SWIFT-2, AGILE and NIMBLE.
Note: The NIMBLE FAS and safety analysis set excluded 14 participants due to data integrity and GCP violation concerns as well as subjects who were randomized in error and did not receive IMP. The AGILE safety analysis set excluded 11 participants due to data integrity and GCP violation concerns.
Abbreviations: AE, adverse events; BLA, biologics license application; DB, double-blind; DD, double-dummy; MC, multicenter; NCT, national clinical trial; NI, non-inferiority; OLE, open-label extension; PC, placebo-controlled; PG, parallel-group; R, randomized; SAE, serious adverse events; SC, subcutaneous; SoC, standard of care

6 Patient Experience Data

Patient experience data used to assess efficacy of depemokimab are summarized in Table 3.

Table 3. Patient Experience Data Submitted or Considered

☒	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Sections 8.2.5, 8.2.9, and 19
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

7 Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

7.1. Nonclinical Assessment of Potential Effectiveness

The proposed mechanism of action for the drug is that it binds to soluble IL-5 and thus prevents IL-5 from binding to its receptor, IL-5Rα. Inhibition of IL-5 has been shown to reduce eosinophil counts with other approved anti-IL-5 biologics, namely mepolizumab and reslizumab; thus, inhibition of human IL-5 would provide strong evidence of potential effectiveness. GSK3511294 (depemokimab) bound to human IL-5 as evaluated by Biacore with a dissociation constant (K_D) of 23.93. GSK3511294 also bound to human IL-5 with slightly higher affinity than mepolizumab (1.38-fold). A competition assay between mepolizumab and GSK3511294 was used on the Fortebio Octet RED384 biolayer interferometry instrument and indicated that both drugs bound to the same or similar epitope on human IL-5.

GSK3511294 reduced cytokine-induced eosinophil shape change in human whole blood as measured by shift in the forward scatter-Area median fluorescence intensity measured by flow cytometry. GSK3511294 inhibited cynomolgus and human IL-5 induced TF-1 cell proliferation with IC_{50} values of ~0.004 nM. In the 26-week toxicology study with monkeys, treatment groups (10 and 100 mg/kg once every 13 weeks for 2 doses) had reduced absolute eosinophil counts for several weeks. Additionally, prior to dosing, no animals had detectable IL-5. During the treatment period, every treated animal had detectable IL-5 in the plasma throughout the entire treatment period while control animals did not. These findings were considered part of the pharmacodynamic action of the drug.

7.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology information about depemokimab is summarized below in Table 4.

Table 4. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	IL-5 antagonist (monoclonal antibody)
Mechanism of action	Depemokimab is an IL-5 antagonist (IgG1 kappa), which binds to IL-5 with a dissociation constant of 10.5 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the cell surface. Depemokimab-ulaa contains a triple amino acid substitution (YTE) in the Fc region which increases binding to the neonatal Fc receptor and thereby extends the elimination half-life. These modifications allow for dosing Q6M. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Depemokimab-ulaa, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of depemokimab-ulaa action in asthma has not been definitively established.
Active moieties	Depemokimab
QT prolongation	Antibodies have a low likelihood of direct ion channel interaction and therefore are not expected to cause concentration-dependent prolongation of the QTc interval. However, ECG data collected by the Applicant cannot serve as a substitute for a thorough QT study. As depemokimab is a monoclonal antibody, a thorough QT/QTc study is not warranted.
	General Information
Bioanalysis	Plasma concentrations of depemokimab were measured using an ECL immunoassay. Bioanalytical methods were adequately validated.
Healthy subjects versus patients	Steady state geometric mean trough concentrations of depemokimab in healthy subjects are approximately 26% lower relative to patients with severe asthma, although this difference is not considered to be clinically meaningful.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	In patients with severe asthma, the geometric mean (CV%) steady-state trough concentrations of depemokimab ranged from 1.29 (52.5) µg/mL to 1.31 (52.9) µg/mL following administration of 100 mg SC Q6M. No accumulation was observed for the Q6M dosing regimen.
Range of effective dose(s) or exposure	No formal dose-ranging studies were completed. Phase 3 dose selection was based on a modeling and simulation approach using PK/PD data derived from FIH Study 205722 in subjects with mild to moderate asthma, which investigated single SC doses of depemokimab ranging from 2 mg to 300 mg. A single dosage of depemokimab 100 mg SC Q6M was investigated in phase 3 studies, based on dose/ER analyses which predicted comparable PD response (i.e., reduction of blood eosinophil count) to that achieved in the asthma phase 3 program for mepolizumab (another anti-IL-5 monoclonal antibody approved for treatment of asthma). In the phase 3 SWIFT-1/2 trials (severe asthma), depemokimab-treated patients had a statistically significantly reduction in the annualized rate of asthma exacerbations compared to placebo, although no clear exposure-dependency was observed based on ER analyses.

Characteristic	Drug Information
Maximally tolerated dose or exposure	Depemokimab was evaluated at single SC doses up to 300 mg in healthy Chinese adult subjects and in subjects with mild-to-moderate asthma. All pivotal clinical efficacy and safety trials in severe asthma investigated a single depemokimab dosage regimen of 100 mg SC Q6M.
Dose proportionality	Depemokimab exposure increased in an approximately dose-proportional manner following single SC doses ranging from 10 mg to 300 mg (30-fold dose increase), with C_{max} and AUC increasing by approximately 33- and 27-fold, respectively.
Accumulation	No appreciable accumulation was observed in patients with severe asthma following administration of the proposed dosage regimen of depemokimab 100 mg SC Q6M.
Time to achieve steady-state	As no accumulation was observed with Q6M dosing, steady state is estimated to be reached following the first dose of 100 mg SC.
Bridge between to-be-marketed and clinical trial/study formulations	The Applicant is proposing two to-be-marketed presentations, including a safety syringe device (SSD) and autoinjector (AI; or pre-filled pen). Both device presentations contain a 1-mL fill volume of an identical depemokimab 100 mg/mL solution formulation for SC injection. Depemokimab was administered using the proposed SSD device presentation in all pivotal efficacy and safety trials (i.e., SWIFT-1/2), whereas the proposed AI presentation was not used in any phase 3 trials (SWIFT-1/2 or AGILE). The SSD and AI device presentations were bridged in the relative bioavailability Study 214099, in which bioequivalence criteria were met. In FIH study 205722, a (b) (4) mg/mL formulation of depemokimab in a vialed presentation was used. All remaining clinical studies administered a 100 mg/mL formulation using either the SSD or AI devices. Following SC administration of depemokimab 100 mg, plasma concentrations at Week 2 in Study 205722 were comparable with those at Week 2/Week 28 (approximate C_{max} following first and second dose, respectively) in the SWIFT-1/2 trials. However, depemokimab trough concentrations (Week 26) in Study 205722 were approximately 2.5-fold lower compared to those observed in SWIFT-1/2.
	Absorption
Bioavailability	The absolute bioavailability has not been determined as depemokimab PK has only been evaluated in humans following administration via SC injection.
T_{max}	Median T_{max} ranged from approximately 12 to 14 days.
Food effect (fed/fasted) Geometric least square mean and 90% CI	Not applicable
	Distribution
Volume of distribution	Based on popPK analysis, the estimated typical apparent volume of distribution is 6.3 L.
Plasma protein binding	Not applicable
Drug as substrate of transporters	Not applicable

Characteristic	Drug Information
	Elimination
Mass balance results	Not applicable
Clearance	Based on popPK analysis, the estimated typical apparent clearance is 0.092 L/day.
Half-life	The geometric mean (CV%) terminal elimination half-life ranged from 38 (10.7) to 44 (16.2) days.
Metabolic pathway(s)	Depemokimab is a monoclonal antibody which is expected to be metabolized into small peptides and amino acids by catabolic pathways.
Primary excretion pathways (% dose)	Not applicable
	Intrinsic Factors and Specific Populations
Body weight	Based on popPK analyses, body weight was identified as a statistically significant covariate affecting the PK of depemokimab, such that higher systemic exposure is observed in patients with lower body weight. However, body weight-based differences in exposures were not clinically meaningful and no dose adjustments based on body weight are recommended.
Age	Age (12 to 93 years) did not meaningfully influence the PK of depemokimab.
Renal impairment	No dedicated studies have been conducted to assess the impact of renal impairment on the PK of depemokimab. Based on popPK analysis, renal impairment (eGFR ≥ 90 mL/min/1.73 m^2 [normal, N = 398]; eGFR 60 to < 90 mL/min/1.73 m^2 [mild, N = 336]; eGFR 30 to < 60 mL/min/1.73 m^2 [moderate, N = 30], and eGFR ≤ 30 mL/min/1.73 m^2 [severe, N = 2]) did not meaningfully impact the PK of depemokimab.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment on the PK of depemokimab. Based on popPK analysis, bilirubin (1.7 to 42 µmol/L), ALT (5 to 153 IU/L), AST (9 to 115 IU/L), and albumin (41 to 50 g/L; 5^{th} and 95^{th} percentiles, respectively, in the observed dataset) were not identified as statistically significant covariates that impact depemokimab clearance.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Not applicable
Inhibition/induction of transporter systems	Not applicable

Characteristic	Drug Information
	Immunogenicity
Bioanalysis	An acid dissociation homogeneous bridging assay was used to assess depemokimab ADAs with ECL detection. For NAb detection, acid-dissociated NAbs were captured with biotinylated drug, and then bound to an anti-target blocking antibody. This was bound by streptavidin coated MSD plates. With ruthenium-labelled target, the presence or absence of NAbs were detected. A tiered analysis approach was used, which included sequential assays for screening, confirmation, and characterization (titration and NAbs).
Incidence	Among patients with severe asthma in the SWIFT-1/2 and AGILE studies who received at least a single SC dose of depemokimab 100 mg, approximately 10% (66/691) developed treatment-emergent anti-depemokimab ADAs. Among ADA-positive patients, 6% (4/66) tested positive for NAbs.
Clinical impact	There was no apparent impact of immunogenicity on the PK, PD, efficacy, or safety of depemokimab in patients with severe asthma.

Source: m2.7.2, Summary of Clinical Pharmacology; m 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods; m5.3.5.3, Integrated Assessment of Immunogenicity; m5.3.3.5, Population PK Modeling Report (REP-1-PK-GSK-FTE1-DEPE-PMX-1); m5.3, CSRs for Study 205722, 214099, 208021, 206713, 213744, and 212895
Abbreviations: ADA, anti-drug antibody; AI, autoinjector; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CSR, Clinical Study Report CV, coefficient of variation; ECG, electrocardiogram; ECL, electrochemiluminescence; eGFR, estimated glomerular filtration rate; ER, exposure-response; Fc, fragment crystallizable; FIH, first-in-human; IL-5, interleukin 5; IL-5Rα, IL-5 Receptor Alpha; MSD, MesoScale Discovery; NAb, neutralizing antibody; PD, pharmacodynamic; PK, pharmacokinetics; popPK, population PK; Q6M, every 6 months; SC, subcutaneous; SSD, safety syringe device; T_{max}, time to C_{max}.

8 Efficacy

8.1. Assessment of Dose and Potential Effectiveness

The proposed dosage of depemokimab is 100 mg subcutaneously (SC) every 6 months (Q6M) as add-on maintenance treatment in adults and adolescents 12 years of age and older with severe asthma with an eosinophilic phenotype. This dose and dosing regimen were investigated in patients with severe asthma in two phase 3 pivotal efficacy and safety trials (206713 [SWIFT-1] and 213744 [SWIFT-2]). Further support for the proposed dosing was provided by population pharmacokinetic (PK)/pharmacodynamic (PD) modeling and exposure-response (ER) analyses based on efficacy data derived from the SWIFT-1/2 trials.

Phase 3 Dose Selection

Phase 3 dose selection was based on a modeling and simulation approach informed by PK/PD data from the first-in-human (FIH) Study 205722 in subjects with mild-to-moderate asthma, in lieu of formal phase 2 dose-ranging studies with clinical efficacy endpoints. The Applicant sought to identify depemokimab doses to match the PD response, in terms of reduction of blood eosinophil count, which was observed from the mepolizumab asthma program.

Specifically, the Applicant targeted depemokimab doses which would meet the following criteria:

- Target > 80% probability of exceeding mepolizumab blood eosinophil count reduction (78% reduction from baseline at 6 months post-dose) from the MUSCA trial, which was a phase 3 study of mepolizumab in subjects with severe asthma
- Target < 10% probability of exceeding mepolizumab blood eosinophil count reduction (84% reduction from baseline at 6 months post-dose) from the MENSA trial, which was a phase 3 study of mepolizumab in subjects with severe asthma

Based on Monte Carlo simulations, depemokimab 100 mg was predicted to have a 75% probability of exceeding MUSCA (78%) blood eosinophil count reduction and 15% probability of exceeding MENSA (84%) blood eosinophil count reduction at 26 + 4 weeks. Notably, this dose-response analysis accounted for an additional 4 weeks to reflect a potential real-world situation in which a patient might experience a delay in dosing. Based on this analysis, the single dosing regimen of depemokimab 100 mg SC Q6M was selected for the asthma phase 3 program. Of note, a non-to-be-marketed (TBM) product (i.e., a vial product with different formulation) was used in Study 205722 compared to other clinical trials. Therefore, the utility of Study 205722 to support phase 3 dose selection is limited.

The Applicant's overall dose selection approach was previously discussed with the Agency during a pre-IND meeting held under IND 146742, during which it was agreed that the Applicant's plan to progress from a single ascending dose study in subjects with mild-to-moderate asthma (Study 205722) to the phase 3 program for severe asthma was acceptable. FDA also stated that the proposed Bayesian modeling and clinical trial simulation approach for supporting phase 3 dose selection was generally reasonable, although the Agency could not specifically endorse the Applicant's proposed dosing given the limited data available at the time (e.g., single-dose, small number of subjects per arm, different patient populations between phase 1 and phase 3 studies). The Agency also recommended that the Applicant consider using absolute blood eosinophil count, which may be a more appropriate and/or conservative target, in addition to relative reduction in eosinophil count for the purpose of phase 3 dose selection. Furthermore, the Agency noted that a new depemokimab formulation and manufacturing process from those used in Study 205722 were planned for the phase 3 program, highlighting that the proposed dose selection approach relied on the assumption that there is no impact of formulation and process change on the bioavailability (BA) and efficacy of depemokimab.

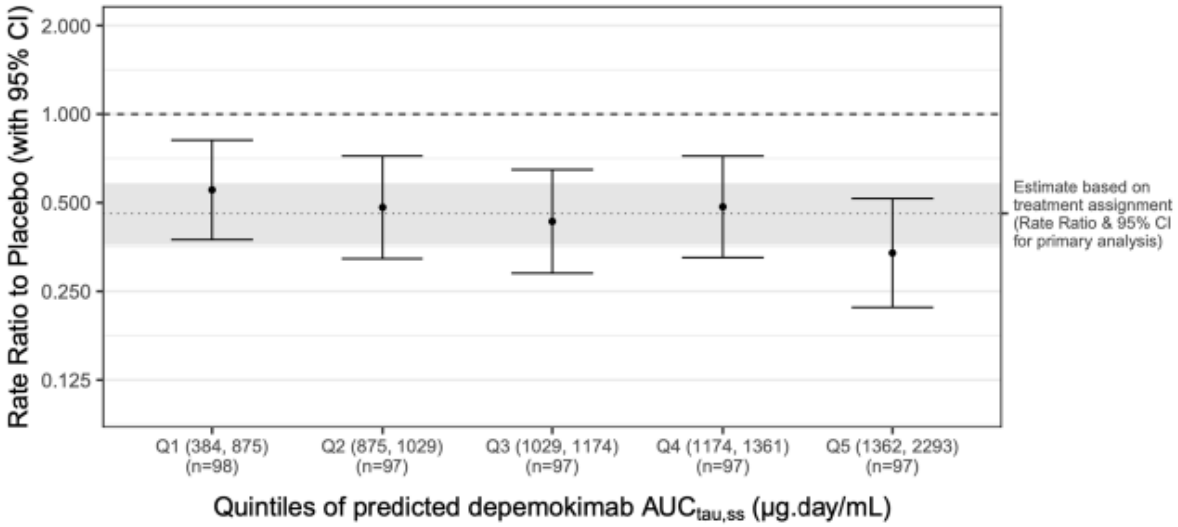
Ultimately, the Agency stated that the decision to select a single nominal dose and dosing regimen to evaluate in phase 3 based on the results of a single-dose FIH study was the Applicant's risk to assume. For additional information regarding the discussions between the Agency and the Applicant regarding phase 3 dose selection for asthma, refer to the Type B pre-IND Meeting Minutes dated February 27, 2020, and held on January 30, 2020 (DARRTS Reference ID: 4567418) (Section 15).

ER Analysis

The Applicant conducted ER analyses to assess the potential impact of depemokimab PK (i.e., predicted [area under the plasma concentration-time curve ($AUC_{tau,ss}$)] and observed [trough plasma concentration ($C_{trough,Week52}$)]) and PD (i.e., blood eosinophil count) metrics on efficacy in patients with severe asthma. In the SWIFT-1/2 trials, the primary efficacy endpoint was the annualized rate (i.e., over 52 weeks) of clinically significant exacerbations.

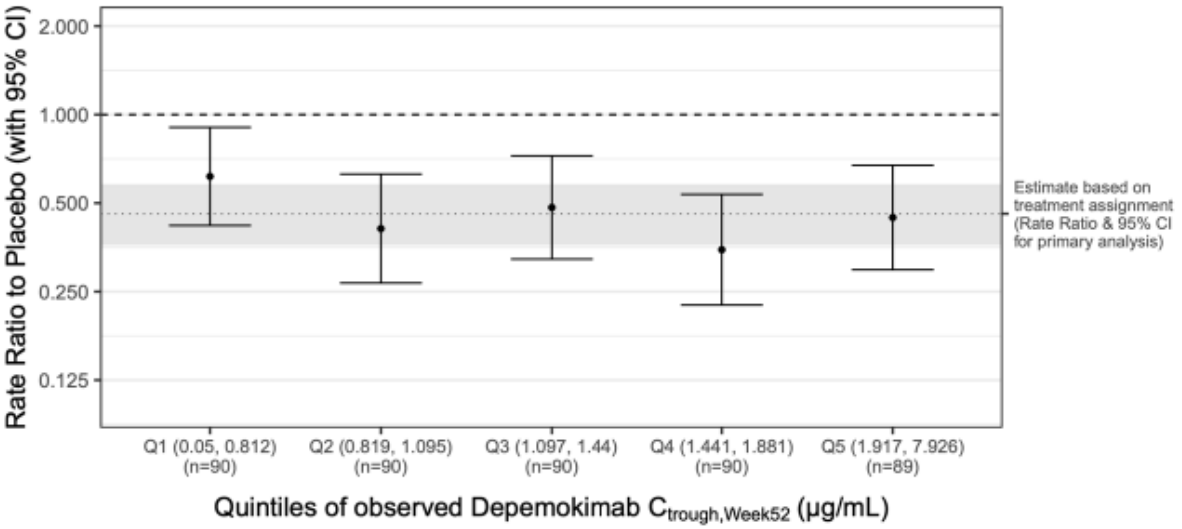
Based on data derived from the pooled SWIFT-1/2 study population, there was a slight overall trend towards greater reduction in placebo-adjusted annualized rate of clinically significant exacerbations with increasing predicted $AUC_{tau,ss}$ (Figure 1). Additionally, it was noted that the point estimate for the highest quintile exceeded the 95% CI of the placebo-adjusted treatment effect in the overall population. No clear ER trend could be identified based on observed $C_{trough,Week52}$, although it was noted that the point estimate for the lowest exposure quintile fell below the 95% CI of the placebo-adjusted treatment effect in the overall population (Figure 2). For both PK metrics, favorable placebo-adjusted treatment effects were observed for depemokimab across all exposure quintiles.

Figure 1. Placebo-Adjusted Annualized Rate of Clinically Significant Exacerbations of Asthma: Quintiles of Predicted $AUC_{tau,ss}$ (SWIFT-1/2 Pooled FAS Population)[a]



Source. Clinical Pharmacology Modeling Report 217780, 219283 (Figure 1, pg. 12)
[a] Analysis based on data from 742 participants from SWIFT-1/2 studies (N = 486/256 depemokimab/placebo)
Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve over the dosing interval at steady state; CI, confidence interval; FAS, full analysis set; N, number of subjects; Q, quintile

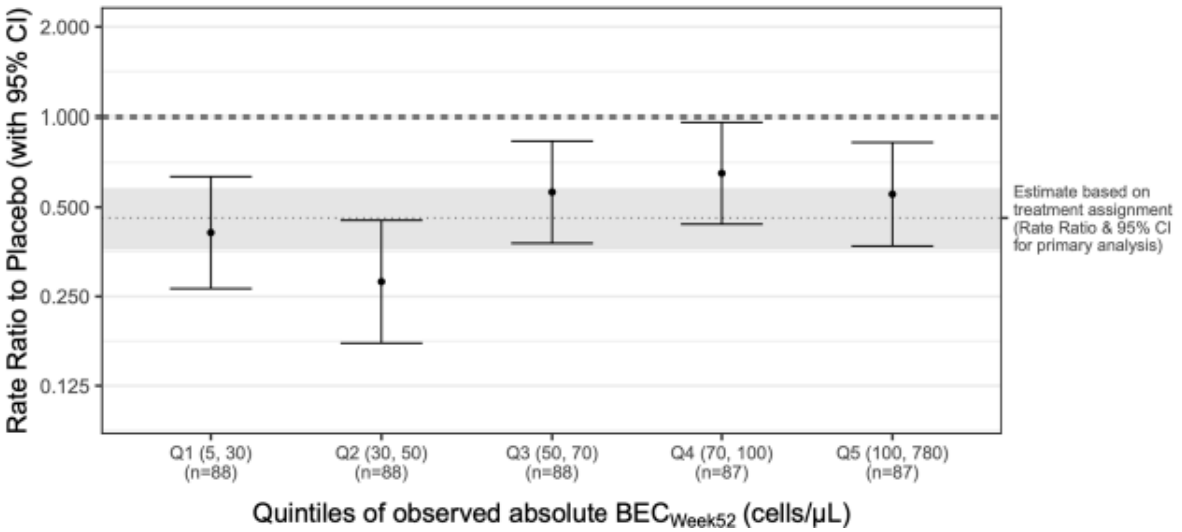
Figure 2. Placebo-Adjusted Annualized Rate of Clinically Significant Exacerbations of Asthma: Quintiles of Observed $C_{trough,Week52}$ (SWIFT-1/2 Pooled FAS Population)[a]



Source. Clinical Pharmacology Modeling Report 217780, 219283 (Figure 29, pg. 31)
[a] Analysis based on data from 705 participants from SWIFT-1/2 studies (N = 449/256 depemokimab/placebo)
Abbreviations: $C_{trough,Week52}$, plasma trough concentration at Week 52; CI, confidence interval; FAS, full analysis set; N, number of subjects

A favorable placebo-adjusted treatment response was observed for depemokimab across all quintiles of blood eosinophil count at Week 52 as a measure of PD response (Figure 3). Of note, the largest treatment effects were observed for the two lowest PD quintiles, whereas lower response was seen for higher absolute blood eosinophil counts in quintiles 3 through 5.

Figure 3. Placebo-Adjusted Annualized Rate of Clinically Significant Exacerbations of Asthma: Quintiles of Observed Blood Eosinophil Count at Week 52 (SWIFT-1/2 Pooled FAS Population)[a]



Source. Clinical Pharmacology Modeling Report 217780, 219283 (Figure 30, pg. 31)
[a] Analysis based on data from 665 participants from SWIFT-1/2 studies (N = 438/227 depemokimab/placebo)
Abbreviations: BEC_{Week52}, blood eosinophil count at Week 52; CI, confidence interval; FAS, full analysis set; N, number of subjects; Q, quintile

Overall, these data are supportive of efficacy for the treatment of severe asthma at the proposed dosage of 100 mg SC Q6M. For additional details on ER analyses, refer to Section 17.4.2.

8.2. Trials 206713 (SWIFT-1) and 213744 (SWIFT-2)

Administrative details for SWIFT-1 and SWIFT-2 are provided in Table 5.

Table 5. Trial Administrative Information (SWIFT-1 and SWIFT-2)

	SWIFT-1	SWIFT-2
Title	A 52-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study of the efficacy and safety of GSK3511294 adjunctive therapy in adult and adolescent participants with severe uncontrolled asthma with an eosinophilic phenotype	
Trial Initiation	March 17, 2021	February 4, 2021
Trial Completion	November 21, 2023	April 11, 2024
Database Lock	December 20, 2023	May 7, 2024
Final CSR	September 2, 2024	September 2, 2024
EudraCT	2020-003632-25	2020-003611-10
IND Number	146742	146742
Countries (% of participants enrolled)	144 centers in 12 countries: Canada (2%), China (13%), Czech Republic (6%), France (<1%), Germany (9%), Ireland (2%), Italy (2%), Poland (16%), Russia (5%), Spain (14%), United Kingdom (3%), and United States (26%)	187 centers in 11 countries: Australia (<1%), Canada (1%), Czech Republic (4%), France (2%), Hungary (3%), Italy (3%), Japan (20%), Poland (11%), Spain (11%), Taiwan (3%), and United States (41%)

Source: Clinical reviewer; SWIFT-1 and SWIFT-2 Final CSRs.
Abbreviations: CSR, clinical study report; EudraCT, European Union drug regulating authorities clinical trials database; IND, investigational new drug.

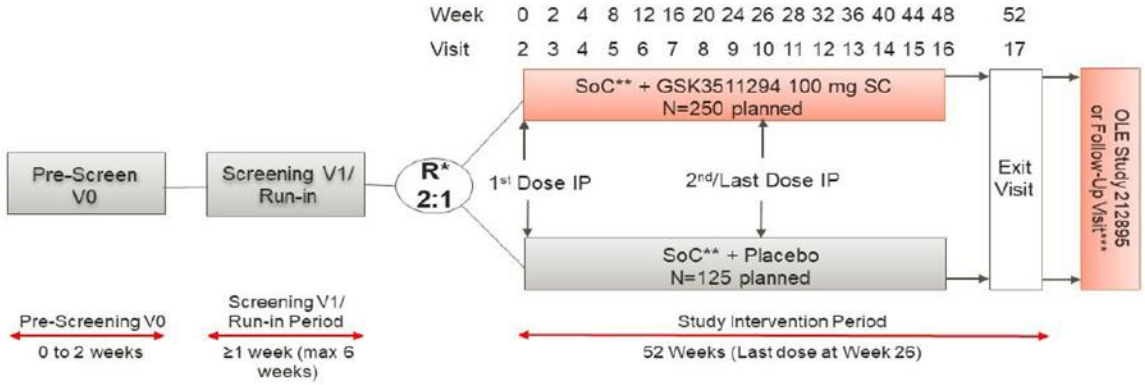
8.2.1. Design and Conduct

SWIFT-1 and SWIFT-2 were replicate, 52-week, global, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trials evaluating depemokimab 100 mg administered SC via prefilled syringe (PFS) device Q6M on top of background asthma maintenance therapy (medium- to high-dose ICS plus at least one additional asthma controller medication with or without maintenance oral corticosteroids) in adults and adolescents aged ≥12 years with severe, uncontrolled, eosinophilic asthma.

The trials consisted of a 2-week Pre-screening Period, an up to 6-week Screening and Run-in Period, a 52-week Treatment Period, and a 4-week Follow-up Period (Figure 4). Participants who experienced a clinically significant asthma exacerbation (defined in Section 8.2.5) during the Run-in Period were treated and remained in this trial phase for up to 6 weeks until reaching their baseline asthma status for at least 7 days. After obtaining informed consent (or assent for minors) during the Pre-screening visit, eligibility (see Section 8.2.2) was determined at the Screening visit. Compliance with study procedures, continued eligibility, and baseline eDiary data were evaluated during the Run-in Period. Once the Run-in Period was complete, participants who met the randomization criteria (see Section 8.2.2) entered the Treatment Period and were randomized 2:1 to receive depemokimab 100 mg or matching placebo, on top

of background asthma maintenance therapy Q6M for 52 weeks. Randomization was stratified by baseline ICS dose (medium or high) with a goal of approximately 50% of participants on medium-dose ICS. Participants who received both doses of study drug (at Weeks 0 and 26) and completed the 52-week Treatment Period, including the Exit Visit, could then roll into an open-label extension (Study 212895; AGILE) or complete a 4-week follow-up visit/call at Week 56.

Figure 4. Trial Design (SWIFT-1 and SWIFT-2)



Source: SWIFT-1 and SWIFT-2 Clinical Study Protocols.
Abbreviations: IP, investigational product; N, planned sample size; OLE, open-label extension; R, randomization; SC, subcutaneously; SoC, standard of care; V, visit.

The schedule of assessments for SWIFT-1 and SWIFT-2 is provided in Table 65. The schedules are identical with the exception of some notes specific to SWIFT-1 clinical sites in China, which were not relevant to SWIFT-2.

8.2.2. Eligibility Criteria

Key eligibility criteria assessed at Screening (Visit 1) are provided below.

Key Inclusion Criteria

- Male or female aged ≥12 years at the time of informed consent (or assent for minors), except at sites in Germany, Russia, and the United Kingdom which only recruited adult participants aged ≥18 years
- Documented physician diagnosis of asthma for ≥2 years consistent with the National Heart, Lung, and Blood Institute (NHLBI) or GINA guidelines
- Have or a high likelihood of having eosinophilic asthma per randomization criteria (see below)
- History of ≥2 asthma exacerbations requiring systemic corticosteroids (SCS) in the 12 months prior to Visit 1 despite treatment with medium- to high-dose ICS (for individuals on maintenance SCS, there should be a >2x greater increase in the dose for exacerbation treatment)
- Chronic airflow obstruction defined by:
  - Pre-bronchodilator (BD) FEV1 <80% of predicted normal at Visit 1 (for ages ≥18 years)
  - Pre-BD FEV1 <90% of predicted normal at Visit 1 or FEV1:FVC ratio <0.8 at Visit 1 (for ages 12-17 years)

- Documented need for chronic treatment with medium- or high-dose ICS in the year prior to Visit 1 with or without maintenance oral SCS
- Current treatment with at least one additional asthma controller, aside from ICS, for at least 3 months prior to Visit 1

Key Exclusion Criteria

- Known, pre-existing, clinically notable lung condition other than asthma
- Other eosinophilic conditions
- Known, pre-existing parasitic infection within 6 months prior to Visit 1
- Current diagnosis of vasculitis
- Prior participation in a trial with mepolizumab, reslizumab, or benralizumab and receipt of study intervention (active drug or placebo) within 1 year prior to Visit 1
- Prior documented failure with an anti-IL-5/5R therapy
- Current or former (quit ≥6 months prior to Visit 1) smoker with a history of ≥10 pack-years

Key Randomization Criteria

The following randomization criteria were assessed after the Screening Visit and Run-in Period to determine eligibility for randomization:

- A peripheral blood eosinophil count ≥300 cells/mcL in the year prior to Visit 1 that is related to asthma or ≥150 cells/mcL at Visit 1 that is related to asthma. If the peripheral blood eosinophil count at Visit 1 did not meet this cutoff, it could be re-measured based on Investigator discretion if assumed to be within the target range in the Run-in Period before Visit 2.
- Airway reversibility or responsiveness by either:
  - Airway reversibility of FEV1 ≥12% and ≥200 mL at Visit 1 or 2, or in the 2 years prior to Visit 1; or
  - Airway hyperresponsiveness (methacholine: PC_{20} <8 mg/mL, histamine: PD_{20} <7.8 µmol, mannitol: decrease in FEV1 per the labeled product instructions) in the 2 years prior to Visit 2
- No changes to the dose or regimen of maintenance ICS and/or additional asthma controller medication during the Run-in Period (except for the treatment of an asthma exacerbation)

The eligibility criteria selected for the study populations in SWIFT-1 and SWIFT-2 were consistent with severe, persistent, eosinophilic asthma based on the need for medium- to high-dose ICS plus at least one additional asthma controller with or without oral corticosteroids, a history of at least two asthma exacerbations requiring systemic corticosteroids in the previous year, and elevated peripheral serum eosinophils historically (≥300 cells/mcL) or at the time of Screening (≥150 cells/mcL). Participants with other eosinophilic or lung conditions were appropriately excluded to select for an asthmatic population rather than diseases with overlapping features (e.g., eosinophilic chronic obstructive pulmonary disease [COPD], eosinophilic granulomatosis with polyangiitis).

The inclusion criteria for SWIFT-1 and SWIFT-2 were generally consistent with pivotal trials in development programs for approved asthma biologics that target IL-5/5R. The required serum eosinophil counts in SWIFT-1 and SWIFT-2 were consistent with the mepolizumab program. Though there is no universally established threshold for defining eosinophilic asthma, requiring a higher cutoff (e.g., ≥300 cells/mcL) at multiple timepoints would ensure that the trial population is more likely to have persistent eosinophilic asthma. The trials did not determine eligibility based on an ACQ score, as was done for benralizumab; however, the required exacerbation history inclusion criterion is sufficient to diagnosis uncontrolled asthma and define the intended use population.

8.2.3. Study Treatments

Investigational Medicinal Product

The IMP consisted of depemokimab and matching placebo supplied as 1 mL (100 mg/mL) sterile liquid formulations in a single-use PFS device. Depemokimab 100 mg and matching placebo were administered SC by the Investigator or designee at the study site at Weeks 0 and 26, and participants were to be monitored for at least two hours after each IMP administration.

Temporary IMP discontinuation was defined as a delayed administration of the second dose. Participants who permanently discontinued IMP were encouraged to remain in the trials and complete all planned visits, including the follow-up and exit visits. The primary reason for IMP discontinuation was recorded in an eCRF.

Participants who withdrew from the trials were recommended to attend an early withdrawal visit 26 weeks after their last dose of IMP and a follow-up visit/call 30 weeks after their last dose of IMP to assess adverse events (AEs)/serious adverse events (SAEs) and pregnancy status.

IMP Discontinuation Criteria

No further doses of IMP were to be administered to participants who met any of the following permanent IMP discontinuation conditions at any time during the 52-week Treatment Period:

- Meets any protocol-defined liver chemistry stopping criteria (see Section 9.5.7)
- Meets any protocol-defined QTc stopping criteria (see Section 9.5.9)
- Pregnancy (positive pregnancy test)
- Severe allergic reaction/anaphylaxis with no clear alternative cause
- Confirmed or suspected vasculitis with no alternative explanation
- Unblinding of randomly assigned IMP

8.2.4. Concomitant and Prohibited Medications

During the trials, participants were required to continue their background asthma maintenance therapy, consisting of a medium- to high-dose ICS plus at least one additional asthma controller medication with or without maintenance oral corticosteroids. A medium- to high-dose ICS was defined as a daily dose of ≥440 mcg of fluticasone propionate HFA daily or equivalent ICS.

Participants who required medium-dose ICS were to also use a LABA. In Japanese subjects aged ≤15 years, medium- to high-dose ICS was defined as ≥200 mcg/day of fluticasone propionate or equivalent ICS based on the Japanese pediatric asthma guidelines. Additional asthma controller medications included a LABA, LAMA, leukotriene receptor antagonist, or theophylline. Rescue therapy with albuterol or salbutamol was permitted throughout the trials; however, a low-dose ICS/formoterol combination was not allowed as rescue. Allergen immunotherapy was allowed if taken routinely in the 6 months prior to Visit 1.

Participants' background asthma maintenance therapy could be modified during the trials if clinically required by the Investigator, who was encouraged to discuss these instances with the medical monitor prior to implementation.

The medications listed in Table 6 were prohibited prior to Screening and throughout the Treatment Period. Bronchial thermoplasty and radiotherapy were not permitted for 1 year prior to Visit 1 or during the trials. CPAP, BiPAP, and oxygen therapy could not be initiated during the Run-in Period, but CPAP and BiPAP were allowed for obstructive sleep apnea if initiated prior to Visit 1. The allowed concomitant and prohibited medications were appropriate for the target asthma population.

Table 6. Prohibited Medications (SWIFT-1 and SWIFT-2)

Prohibited Medication	Time Prior to Screening Visit
Investigational drugs	30 days or 5 half-lives, whichever is longer
Experimental anti-inflammatory drugs (non-biologics)	3 months
Omalizumab	130 days
Dupilumab	130 days
Mepolizumab, reslizumab, benralizumab	12 months
Other monoclonal antibodies	5 half-lives
Immunosuppressive Therapies (not exhaustive)*	
Corticosteroids for conditions other than asthma (intramuscular, long-acting depot, regular systemic (oral or parenteral))	
Methotrexate, cyclosporin, azathioprine	
Oral gold	
Chemotherapy for conditions other than asthma	

Source: Clinical Reviewer; SWIFT-1 and SWIFT-2 Clinical Study Protocols.
* A specified time period prior to the Screening visit was not provided for immunosuppressive therapies in SWIFT-1 and SWIFT-2; however, in the pivotal trials (ANCHOR-1 and ANCHOR-2) for the CRSwNP indication, the time periods were 1 month for chronic corticosteroids, methotrexate, cyclosporin, and azathioprine, 3 months for oral gold, and 12 months for chemotherapy.

8.2.5. Efficacy Variables

Asthma Exacerbations

Asthma exacerbations were collected on the eCRF, per Table 65. A clinically significant asthma exacerbation was defined as a worsening of asthma requiring the use of SCS (intramuscular, IV, or oral) and/or hospitalization and/or ED visit. Courses of IV or oral steroids (e.g., prednisone) were to be for ≥3 days or a single dose of an intramuscular corticosteroid. For participants on maintenance SCS, the dose should be at least double for ≥3 days. Asthma exacerbations separated by <7 days were considered the same exacerbation event. Use of the pre-specified

primary endpoint (see Section 8.2.6) to evaluate efficacy is consistent with other drug development programs for severe asthma and current FDA recommendations.

St. George's Respiratory Questionnaire

The SGRQ was collected with an electronic clinical outcome assessment (eCOA) handheld device, per Table 65, and is a 50-item questionnaire (Figure 48) that was completed to evaluate participants' quality of life, with an Applicant-defined responder threshold of a ≥4-point change from baseline at Week 52. Responses can be dichotomous (yes/no) or based on 3- to 5-point verbal rating scales with total scores ranging from 0 to 100, with a lower score suggestive of better health status. Although included as an efficacy claim for asthma in the mepolizumab label, SGRQ is more often accepted as a patient-reported outcome (PRO) for COPD trials; the clinical review team does not consider the SGRQ to be fit-for-purpose for this context of use in asthma.

ACQ-5

The ACQ-5 was collected with an eCOA handheld device, per Table 65, and is a 5-item questionnaire (Figure 49) to evaluate the frequency and/or severity of asthma symptoms over the prior week. Symptoms are rated on a 7-category verbal rating scale (0 = no impairment or limitation; 6 = total impairment or limitation), with an Applicant-defined responder threshold of a ≥0.5-point change from baseline at Week 52. Total scores can range from 0 to 30, with higher scores suggestive of poorer asthma control. The ACQ-5 has been accepted as a PRO to support labeling claims in asthma.

Spirometry

Spirometry was completed, per Table 65, according to the American Thoracic Society guidelines and included measurements of FEV1, percent predicted FEV1 (ppFEV1), forced vital capacity (FVC), and the FEV1:FVC ratio. FEV1, a secondary endpoint in both trials, assesses the maximum amount of air that a person can exhale within the first second of exhalation and is an accepted surrogate endpoint for obstructive respiratory conditions such as asthma. Spirometry assessments were conducted prior to IMP administration and participants were instructed to withhold administration of short-acting beta agonists (SABAs) for ≥6 hours and LAMAs/LABAs for ≥12 hours prior to the clinic visit. At least 3, but no more than 8, spirometry attempts could be performed. Post-baseline spirometry was recommended to be performed at the same time of day (within ±1 hour) as the baseline (Visit 2) assessment. Spirometry was not performed in participants with confirmed or suspected COVID-19.

Asthma Nightly/Daily Symptom Diary (ANSD/ADSD)

The ANSD and ADSD were completed with an eCOA handheld device, per Table 65. The ANDSD and ADSD, developed by the PRO Consortium's Asthma Working Group, are 6-item questionnaires to evaluate the severity of asthma symptoms, specifically breathing symptoms, chest symptoms, and cough (Figure 50). The ADSD is completed at night to evaluate daytime symptoms, and the ANSD is completed after waking to evaluate symptoms from the previous

night. For both questionnaires, symptoms are rated on an 11-point scale (0 = none; 10 = as bad as you can imagine), with an Applicant-defined meaningful change of ≥1.2 points and ≥1.5 points from baseline at Week 52 for the ANSD and ADSD, respectively.

While ANSD and ADSD endpoints were included in the statistical testing hierarchy for both trials and previously received FDA feedback (see Section 15), the Applicant is not seeking labeling claims for either endpoint; therefore, the results are included for reference only in Section 19.

8.2.6. Efficacy Endpoints

The same efficacy endpoints were pre-specified for SWIFT-1 and SWIFT-2; the primary and secondary endpoints that were pre-specified in the statistical testing hierarchy for each trial are outlined below, followed by other pre-specified endpoints of regulatory interest.

Primary

- Annualized rate of clinically significant asthma exacerbations over 52 weeks

Secondary

- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-BD FEV1 at Week 52
- Change from baseline in ANSD weekly mean score at Week 52
- Change from baseline in ADSD weekly mean score at Week 52
- Annualized rate of asthma exacerbations requiring hospitalization and/or emergency department visit over 52 weeks

Other

- Time to first clinically significant asthma exacerbation over 52 weeks
- ACQ-5 score responder status

8.2.7. Statistical Analysis Plan

The final statistical analysis plans (SAPs) for SWIFT-1 and SWIFT-2 were very similar in nature and contain the information provided below.

Analysis Populations

The Applicant defined the following analysis sets for SWIFT-1 and SWIFT-2:

- Screened Set: All participants who provided informed consent (or assent for minors).
- Enrolled Set: All participants who entered the study (screen failures, and those who were screened and met eligibility criteria but never enrolled, are excluded).
- Randomized Set: All participants who were randomly assigned to study intervention.
- FAS: All randomized participants who received at least one dose of study drug, excluding participants from Site 250190 (for SWIFT-1) or Sites 250085 and 250523 (for SWIFT-2).

Participants will be analyzed according to randomized treatment. This was the main analysis set used for efficacy evaluation.

- Safety Set: All randomized participants who received at least one dose of study drug, excluding participants from Site 250190 (for SWIFT-1) or Sites 250085 and 250523 (for SWIFT-2). Participants will be analyzed according to the intervention they are allocated at randomization, unless a participant receives a different intervention than the randomized intervention at all protocol-defined administrations at which study medication is received, in which case the participant will be analyzed according to the actual intervention received. This was the main analysis set used for safety evaluation.
- FAS-Modified: All participants in the FAS plus the randomized participants at Site 250190 (for SWIFT-1) or Sites 250085 and 250523 (for SWIFT-2) who received at least one dose of study drug.
- Safety-Modified: All participants in the Safety Set plus the randomized participants at Site 250190 (for SWIFT-1) or Sites 250085 and 250523 (for SWIFT-2) who received at least one dose of study drug.

SWIFT-1 enrollees at Site 250190 (located in the US; n = 11) and SWIFT-2 enrollees at Sites 250085 (located in Japan; n = 5) and 250523 (located in Japan; n = 7) were excluded from the main efficacy and safety analyses due to data integrity issues and GCP violations ultimately leading to the three sites being closed (see Section 12). However, due to the small number of participants at these three sites, the overall efficacy results did not substantially differ between the FAS and FAS-Modified populations (see Section 8.2.9.4). Additionally, although not discussed in-depth in Section 9.5, Applicant-provided analyses for the excluded sites did not identify any new safety concerns.

Sample Size Calculation

The sample size considerations and procedures for SWIFT-1 and SWIFT-2 were identical.

The sample size for each trial was determined based on the power to detect a 50% reduction in the primary endpoint (annualized rate of clinically significant asthma exacerbations over 52 weeks) in the depemokimab arm relative to placebo at a two-sided alpha of 5%, assuming a true annualized exacerbation rate of 1.18 in the placebo arm, a dispersion parameter of 0.8 for the pre-specified negative binomial model described below, and that 14% of participant-years data would be missing due to withdrawals. The dispersion parameter and dropout rate were selected based on previous trials (DREAM and MENSA) of mepolizumab (a drug in the same class as depemokimab) that supported its approval for severe eosinophilic asthma. The above assumptions for the placebo exacerbation rate and treatment effect are median values from an elicitation exercise that used expert opinion and historical phase 3 anti-IL-5/5R data (this data was neither referenced nor submitted, but these numerical assumptions are not unreasonable based on the mepolizumab asthma program). Additionally, based on internal calculations, while a negative binomial model was pre-specified for the primary analysis (described below), it appears that the response was assumed to follow a Poisson distribution rather than a negative binomial distribution to simplify the sample size calculation, which is also not unreasonable.

Based on the above assumptions, a total sample size of 375 participants (randomized 2:1 to depemokimab [n = 250] or placebo [n = 125]) would provide 99% power to detect a 50% reduction in the primary endpoint. This sample size would also provide 96% power to detect a 7-point reduction in the secondary SGRQ endpoint and 83% power to detect a 0.35-point reduction in the secondary ACQ-5 endpoint under different assumptions based on previous mepolizumab asthma trials (DREAM, MENSA, and MUSCA).

About 540 eligible participants were planned to be screened to ensure that 375 participants would be randomized in each trial. Ultimately, 622 participants were screened for SWIFT-1 (with 382 participants in the FAS who were randomized to depemokimab [n = 250] or placebo [n = 132]), and 663 participants were screened for SWIFT-2 (with 380 participants in the FAS who were randomized to depemokimab [n = 252] or placebo [n = 128]).

Estimands

The same main estimands were pre-specified for the above primary, secondary, and other endpoints in SWIFT-1 and SWIFT-2. All treatment, population, and intercurrent event (ICE) attributes were identical and are summarized below.

Treatments

- Depemokimab 100 mg administered SC via PFS device Q6M on top of background asthma maintenance therapy
- Matching placebo on top of background asthma maintenance therapy

Background asthma maintenance therapy included medium- to high-dose ICS plus at least one additional asthma controller medication with or without maintenance oral corticosteroids and could be modified during the trials if clinically required by the Investigator.

Population

- Adults and adolescents (aged 12+ years) with severe, uncontrolled, eosinophilic asthma on medium- to high-dose ICS plus at least one additional asthma controller medication with or without maintenance oral corticosteroids

Intercurrent Events

- Treatment discontinuation due to reasons unrelated to the COVID-19 pandemic (addressed using a treatment policy strategy)
- Treatment discontinuation due to reasons related to the COVID-19 pandemic (addressed using a hypothetical strategy)
- Change in asthma maintenance therapy (addressed using a treatment policy strategy)
- Use of concomitant/prohibited medications (addressed using a treatment policy strategy)

All primary, secondary, and other endpoints and associated summary measures for the main estimands are outlined in Section 8.2.6 and below.

Type I Error Control

Testing Hierarchy

The same multiplicity adjustment plan to control the overall type I error rate was pre-specified for SWIFT-1 and SWIFT-2.

A fixed-sequence hierarchical testing procedure was carried out using the closed-testing principle, where statistical inference for an endpoint was dependent on achieving statistical significance for the previous endpoint in the hierarchy. The following endpoints were formally tested in the order shown below at a two-sided alpha of 5%:

- Annualized rate of clinically significant asthma exacerbations over 52 weeks (primary)
- Change from baseline in SGRQ total score at Week 52
- Change from baseline in ACQ-5 score at Week 52
- Change from baseline in pre-BD FEV1 at Week 52
- Change from baseline in ANSD weekly mean score at Week 52
- Change from baseline in ADSD weekly mean score at Week 52
- Annualized rate of asthma exacerbations requiring hospitalization and/or emergency department visit over 52 weeks

Interim Analysis

The final SAPs for SWIFT-1 and SWIFT-2 pre-specified an unblinded, binding interim analysis (IA) for futility conducted by an independent statistical data analysis center (SDAC) in conjunction with an independent data monitoring committee (IDMC) to maintain study integrity (the unblinded outputs from the IA were sent from the SDAC to the IDMC, and then a recommendation was communicated from the SDAC to the IDMC and then to GlaxoSmithKline following agreement from the IDMC).

The futility analysis evaluated efficacy based on the primary endpoint (annualized rate of clinically significant asthma exacerbations over 52 weeks) using interim data from SWIFT-1 and SWIFT-2 when about 675 participants were randomized across both trials (90% of the total planned number of randomized participants across both trials); at this time, it was estimated that about 200 participants would complete the trials and 500 participants would receive both doses. Further details regarding the IA procedure and stopping criteria are provided in Section 19.

Ultimately, the IA did not demonstrate futility; therefore, both trials continued to the final analysis (described below). Additionally, since this was a futility analysis without the possibility of early stopping for efficacy/success, the overall alpha was controlled at the pre-specified 5% significance level.

Final Analysis

The final analysis was conducted for each trial separately after all participants had the opportunity to complete 52 weeks of follow-up. The endpoints listed in the hierarchy above

were tested inferentially at a pre-specified, two-sided alpha of 5% until statistical significance was not achieved. All endpoints not listed in the hierarchy above were evaluated without multiplicity control. Analyses of the endpoints above in populations other than the FAS were also conducted without multiplicity control.

Statistical Methods

All statistical approaches described below were pre-specified for both SWIFT-1 and SWIFT-2.

Primary Endpoint

The primary endpoint was the annualized rate of clinically significant asthma exacerbations over 52 weeks, analyzed using a generalized linear model assuming a negative binomial distribution with the following terms: treatment arm, exacerbation history (2, 3, or ≥4 in the past year), baseline ICS dose (medium or high), geographical region (Europe, US, or rest of the world), baseline pre-BD ppFEV1, and an offset for total years in the trial. The model fit was examined using Q-Q plots of the standardized residuals with simulation-generated tolerance boundaries for interpretation purposes. The model-estimated rates for each treatment arm and the corresponding rate ratio and percent reduction in the rate for the depemokimab arm relative to placebo were reported with associated 95% CIs and p-values. For participants who discontinued IMP due to reasons related to COVID-19 (only one case in SWIFT-1), observed data after this ICE were excluded from the analysis and assumed to be missing at random (MAR). Data following withdrawals were also assumed to be MAR.

A tipping point sensitivity analysis was conducted to assess the robustness of the primary endpoint results when departing from the MAR assumption, where participants who withdrew from the trial had missing data imputed based on a range of values for the annualized rate of clinically significant asthma exacerbations after withdrawal.

Pre-specified subgroup analyses were also conducted for the primary endpoint by the following measures at baseline: peripheral blood eosinophil count (<0.15 or ≥0.15 GI/L; <0.3 or ≥0.3 GI/L), ICS dose (medium or high), and ACQ-5 score (<1.5 or ≥1.5). At our request, post-hoc subgroup analyses were submitted for the primary endpoint by age (12-17 years, 18-64 years, or ≥65 years), sex (female or male), race (Asian, Black or African American, or White), ethnicity (Hispanic or Latino, or not Hispanic or Latino), and geographical region (Europe, US, and rest of the world).

Additionally, the primary analysis was performed in the FAS-Modified population to determine whether the inclusion of participants enrolled at the three above sites with data integrity concerns and GCP violations substantially impacted the results.

Secondary Endpoints

Changes from baseline in SGRQ total score, ACQ-5 score, and pre-BD FEV1 at Week 52 were analyzed using a mixed model for repeated measures (MMRM) with the following terms: treatment arm, baseline ICS dose (medium or high), asthma exacerbation history (2, 3, or ≥4 in the past year), geographical region (Europe, US, and rest of the world), visit, the respective

baseline value, and interactions for baseline value and visit and for treatment arm and visit. All models were fit with an unstructured variance-covariance matrix, with the Kenward-Roger method used to approximate the denominator degrees of freedom. Distributional assumptions underlying the MMRMs were examined using normal probability plots of residuals and plots of residuals versus fitted values to evaluate the normality and constant variance assumptions. Least-squares (LS) means and mean changes from baseline for each treatment arm were reported with associated standard errors (SEs) and 95% CIs. The estimated treatment differences and associated SEs, 95% CIs, and p-values were also reported. For participants who discontinued IMP due to reasons related to COVID-19 (only one case in SWIFT-1), observed data after this ICE were excluded from the analysis and assumed to be MAR. Data following withdrawals were also assumed to be MAR.

Of note, based on internal calculations, it appears that all the above MMRMs used proportional weighting when computing the LS means; a specific weighting approach was not pre-specified in the final SAPs for SWIFT-1 and SWIFT-2, but proportional weighting is generally reasonable.

Although ANSD and ADSD endpoints were included in the pre-specified statistical testing hierarchy for both trials, the Applicant did not propose any labeling claims for either endpoint. As such, these instruments and endpoints were not reviewed to determine if they are fit-for-purpose. However, the descriptions of the pre-specified analyses and Applicant-submitted results for the changes from baseline in ANSD and ADSD weekly mean scores at Week 52 are provided in Section 19.6 for reference.

The annualized rate of asthma exacerbations requiring hospitalization and/or emergency department visit over 52 weeks was analyzed using the same approaches described above for the primary endpoint. However, this analysis was only conducted if ≥20 such exacerbations occurred during the trial.

Other Endpoints

See Section 19.

8.2.8. Protocol Amendments

The original protocols for SWIFT-1 and SWIFT-2 (both dated October 1, 2020) each had two amendments. The key modifications made in the first amendments (both dated August 17, 2021) included changes to analysis populations and clinical elements, namely extending the time period during which airway reversibility or airway hyperresponsiveness needed to be documented prior to Visit 2 and clarification that a low-dose ICS/formoterol combination was prohibited as rescue medication during the trials. The key modifications made in the second amendments (dated April 8, 2022, for SWIFT-1 and April 5, 2022, for SWIFT-2) included changes to randomization stratification and analysis populations, allowance of repeat peripheral blood eosinophil count and spirometry measurements during the Run-in Period to meet inclusion criteria, and the addition of an IA for futility. These protocol modifications were reasonable and did not impact the interpretability of the trial results.

8.2.9. Results of Efficacy Analyses

8.2.9.1. Participant Disposition

The dispositions of participants in SWIFT-1 and SWIFT-2 are summarized in Table 7.

For SWIFT-1, a total of 622 individuals were screened; of them, 464 were enrolled and 395 were randomized 2:1 to depemokimab or placebo. Of the 395 randomized participants, 382 were included in the FAS (11 participants randomized at Site 250190 were excluded from the FAS due to data integrity concerns and GCP violations [see Section 12], and 2 participants were randomized in error but did not receive any IMP and were also excluded from the FAS). Of the 382 participants in the FAS, 250 and 132 were randomized to depemokimab and placebo, respectively. The study and treatment discontinuation rates and reasons did not considerably differ by study or treatment arm. The most common reasons for treatment discontinuation were non-fatal AEs and lack of efficacy, and the most common reasons for study discontinuation were lack of efficacy and self-withdrawal.

For SWIFT-2, a total of 663 individuals were screened; of them, 456 were enrolled and 397 were randomized 2:1 to depemokimab or placebo. Of the 397 randomized participants, 380 were included in the FAS (12 participants randomized at Sites 250085 and 250523 were excluded from the FAS due to data integrity concerns and GCP violations [see Section 12], and 5 participants were randomized in error but did not receive any IMP and were also excluded from the FAS). Of the 380 participants in the FAS, 252 and 128 were randomized to depemokimab and placebo, respectively. The study and treatment discontinuation rates and reasons did not considerably differ by study or treatment arm. The most common reasons for treatment discontinuation were lack of efficacy and self-withdrawal, and the most common reasons for study discontinuation were lack of efficacy, loss to follow-up, and self-withdrawal.

There was 1 participant in SWIFT-1 randomized to depemokimab who withdrew from the trial due to physician decision (continued trial participation was not in the participant's best interest given chronic mental health issues). In the SWIFT-2 depemokimab arm, 2 participants withdrew from the trial due to physician decision (no improvement in participant's health; participant traveling for an indefinite period of time). Additionally, 1 depemokimab participant in SWIFT-2 withdrew from the trial due to an SAE of bilateral ovarian cancer and peritoneal metastases.

Table 7. Participant Disposition (SWIFT-1 and SWIFT-2)

	SWIFT-1			SWIFT-2		
Disposition	**Depemokimab**	**Placebo**	**Overall**	**Depemokimab**	**Placebo**	**Overall**
Randomized, n	259	136	395	263	134	397
Analysis population, n						
FAS-Modified[1]	257	136	393	259	133	392
Safety-Modified[1]	257	136	393	258	134	392
FAS	250	132	382	252	128	380
Safety	250	132	382	251	129	380
Treatment status, n (%)						
Completed treatment	236 (94)	126 (95)	362 (95)	239 (95)	125 (98)	364 (96)
Discontinued treatment	14 (6)	6 (5)	20 (5)	13 (5)	3 (2)	16 (4)
Discontinued treatment and study simultaneously	9 (4)	6 (5)	15 (4)	12 (5)	3 (2)	15 (4)
Discontinued treatment but continued in study	5 (2)	0 (0)	5 (1)	1 (<1)	0 (0)	1 (<1)
Completed study with off-treatment assessments	5 (2)	0 (0)	5 (1)	1 (<1)	0 (0)	1 (<1)
Did not complete study	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Reason for treatment discontinuation, n (%)						
Adverse event	3 (1)	2 (2)	5 (1)	1 (<1)	0 (0)	1 (<1)
Lack of efficacy	4 (2)	2 (2)	6 (2)	3 (1)	0 (0)	3 (1)
Lost to follow-up	2 (1)	0 (0)	2 (1)	0 (0)	1 (1)	1 (<1)
Met liver chemistry stopping criteria	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)
Pregnancy	1 (<1)	0 (0)	1 (<1)	0 (0)	1 (1)	1 (<1)
Self-withdrawal	1 (<1)	2 (2)	3 (1)	8 (3)	1 (1)	9 (2)
Sponsor terminated study treatment	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Study status, n (%)						
Completed	237 (95)	122 (92)	359 (94)	233 (92)	117 (91)	350 (92)
Withdrawn	13 (5)	10 (8)	23 (6)	19 (8)	11 (9)	30 (8)
Completed treatment	4 (2)	4 (3)	8 (2)	7 (3)	8 (6)	15 (4)

	SWIFT-1			SWIFT-2		
Disposition	**Depemokimab**	**Placebo**	**Overall**	**Depemokimab**	**Placebo**	**Overall**
Reason for study withdrawal, n (%)						
Adverse event	0 (0)	2 (2)	2 (1)	1 (<1)	1 (1)	2 (1)
Lack of efficacy	4 (2)	2 (2)	6 (2)	4 (2)	1 (1)	5 (1)
Lost to follow-up	2 (1)	0 (0)	2 (1)	2 (1)	2 (2)	4 (1)
Physician decision	1 (<1)	0 (0)	1 (<1)	2 (1)	0 (0)	2 (1)
Pregnancy	1 (<1)	1 (1)	2 (1)	0 (0)	1 (1)	1 (<1)
Self-withdrawal	5 (2)	5 (4)	10 (3)	10 (4)	6 (5)	16 (4)

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
[1] Includes participants from sites with concern for data integrity issues and GCP violations.
Notes: All percentages are based on the Full Analysis Set. Self-withdrawal related to treatment discontinuation and/or study withdrawal in the SWIFT-1 depemokimab treatment group were due to subject relocation, subject out of the country, “patient wants to start dupilumab”, “subject doesn’t want to continue taking blood samples”, and subject moving out. Self-withdrawal related to treatment discontinuation and/or study withdrawal in the SWIFT-2 depemokimab treatment group were due to subject decision/intention, “due to mental health issues and stress”, “too far to travel”, “difficult to visit the hospital for AE treatment”, “subject would like to participate in another study where you get the study drug every 2-4 weeks”, “unable to keep visit schedule due to having to take care of an elderly parent”, “due to hospitalization and further other treatment”, withdrawing consent, and “subject has to travel for an indefinite period of time”. Of these, the reason “due to hospitalization and further other treatment” could be re-categorized as an AE though this does not alter the safety evaluation. Based on the post-hoc important protocol deviations reported in the SWIFT-1 Clinical Study Report Errata, two additional SWIFT-1 participants discontinued the study, one due to pregnancy (placebo arm) and the other due to an unspecified adverse event (depemokimab arm), though both were listed as protocol deviations for not performing two required visits.
Abbreviations: FAS, full analysis set; n, number of participants in the respective group

8.2.9.2. Protocol Deviations

The important protocol deviations (IPDs) that occurred in SWIFT-1 and SWIFT-2 that were reported in the CSRs are summarized in Table 68, and additional IPDs that were reported after the CSRs were finalized are provided in Section 12. None were likely to have had a major impact on the quality or conclusions of the trials.

8.2.9.3. Baseline Demographics and Clinical Characteristics

Participant demographics at baseline are presented in Table 8 and were mostly balanced by treatment arm and across the trials, though there was a higher proportion of SWIFT-2 participants aged ≥65 years in the depemokimab arm compared to placebo.

SWIFT-1/SWIFT-2 enrolled mostly women (58%/63%) and included 8/22 adolescents (aged 12 to 17 years), 276/262 adults (aged 18 to 64 years), and 98/96 geriatrics (aged ≥65 years), with an average age of 54/53 years. Most participants were White (83%/73%) and neither Hispanic nor Latino (94%/83%), with 15%/20% of participants being Asian and 2%/7% of participants being Black or African American. Most participants (87%/64%) were located at ex-US sites; however, results from these ex-US populations remain relevant to US patients based on consistency in international guidelines (in particular, the GINA guidelines (2025) for recommending the addition of biologics in refractory asthma cases). Although there were limited adolescents enrolled in the trials, this was comparable to the mepolizumab asthma program. Overall, the demographic breakdown of the trial populations was generally representative of the intended use population.

Table 8. Baseline Demographics (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1			SWIFT-2		
Demographic	**Depemokimab N=250**	**Placebo N=132**	**Overall N=382**	**Depemokimab N=252**	**Placebo N=128**	**Overall N=380**
Sex, n (%)						
Female	144 (58)	79 (60)	223 (58)	160 (63)	81 (63)	241 (63)
Male	106 (42)	53 (40)	159 (42)	92 (37)	47 (37)	139 (37)
Age (years)						
Mean (SD)	54.1 (13.8)	53.6 (14.9)	53.9 (14.2)	53.6 (16.0)	51.2 (16.6)	52.8 (16.2)
Median (min, max)	56 (14, 79)	56 (15, 78)	56 (14, 79)	57 (12, 82)	53 (12, 81)	56 (12, 82)
Age group (years), n (%)						
12-17	3 (1)	5 (4)	8 (2)	12 (5)	10 (8)	22 (6)
18-64	185 (74)	91 (69)	276 (72)	169 (67)	93 (73)	262 (69)
≥65	62 (25)	36 (27)	98 (26)	71 (28)	25 (20)	96 (25)
Ethnicity, n (%)						
Hispanic or Latino	12 (5)	11 (8)	23 (6)	45 (18)	20 (16)	65 (17)
Not Hispanic or Latino	238 (95)	121 (92)	359 (94)	207 (82)	108 (84)	315 (83)
Race, n (%)						
Asian	38 (15)	20 (15)	58 (15)	52 (21)	23 (18)	75 (20)
Black or African American	5 (2)	3 (2)	8 (2)	17 (7)	11 (9)	28 (7)
White	207 (83)	109 (83)	316 (83)	181 (72)	91 (73)	272 (73)
Unknown	0 (0)	0 (0)	0 (0)	2 (1)	3 (2)	5 (1)
Geographical region, n (%)						
Europe	158 (63)	85 (64)	243 (64)	108 (43)	57 (45)	165 (43)
United States	33 (13)	18 (14)	51 (13)	90 (36)	46 (36)	136 (36)
Rest of the world	59 (24)	29 (22)	88 (23)	54 (21)	25 (20)	79 (21)
BMI (kg/m^2)						
Mean (SD)	27.8 (5.6)	28.5 (6.5)	28.0 (5.9)	28.7 (6.1)	28.7 (6.7)	28.7 (6.3)
Median (min, max)	27 (15, 53)	27 (19, 53)	27 (15, 53)	28 (14, 49)	28 (16, 57)	28 (14, 57)

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
Abbreviations: BMI, body mass index; max, maximum; min, minimum; N, number of participants in the full analysis set; n, number of participants in the respective group; SD, standard deviation.

Participant clinical characteristics at baseline are presented in Table 9 and were mostly balanced by treatment arm and across the trials.

Among participants in SWIFT-1/SWIFT-2, the average duration of asthma was 22/25 years, 53%/59% of participants were on high-dose ICS at baseline, 51%/43% of participants had a peripheral blood eosinophil count ≥150/mcL at Screening, and 49%/57% of participants had a peripheral blood eosinophil count ≥300/mcL in the year before Screening. Only a small portion of SWIFT-1/SWIFT-2 participants (5%/5%) were taking maintenance oral corticosteroids at baseline (mostly a prednisone equivalent of <7.5 mg/day), and the majority of participants were never smokers (75%/77%). All SWIFT-1 and SWIFT-2 participants (except for one participant in SWIFT-1) had ≥2 asthma exacerbations requiring oral/systemic corticosteroids in the prior year, and most SWIFT-1/SWIFT-2 participants (94%/91%) did not have any asthma exacerbations requiring hospitalization in the prior year. For both trials, the average FEV1 and ppFEV1 at baseline was 1.8 L and 62%, respectively, and the average FEV1 reversibility at baseline was 17%/18% in SWIFT-1/SWIFT-2. Regarding concomitant conditions, 9%/10% of participants had nasal polyposis, 20%/26% had gastroesophageal reflux disease, 4%/4% had aspirin allergy symptoms, and 3%/3% had non-steroidal anti-inflammatory drug allergy symptoms in SWIFT-1/SWIFT-2. For asthma medications at Screening, 25%/33% were taking ICS+LABA+LAMA therapy in SWIFT-1/SWIFT-2.

There were no notable imbalances consistently observed across SWIFT-1 and SWIFT-2 that were determined to be clinically relevant. Although an asthma duration ≥25 years was more common in the depemokimab arm compared to placebo in both trials, the mean and median asthma durations, as well as other baseline disease characteristics, were similar within and across the trials.

Table 9. Baseline Clinical Characteristics (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1			SWIFT-2		
Clinical Characteristic	**Depemokimab N=250**	**Placebo N=132**	**Overall N=382**	**Depemokimab N=252**	**Placebo N=128**	**Overall N=380**
Duration of asthma (years), n (%)						
1 to <5	18 (7)	15 (11)	33 (9)	23 (9)	13 (10)	36 (9)
5 to <10	40 (16)	21 (16)	61 (16)	35 (14)	17 (13)	52 (14)
10 to <15	43 (17)	29 (22)	72 (19)	42 (17)	22 (17)	64 (17)
15 to <20	28 (11)	16 (12)	44 (12)	20 (8)	13 (10)	33 (9)
20 to <25	31 (12)	13 (10)	44 (12)	24 (10)	14 (11)	38 (10)
≥25	90 (36)	38 (29)	128 (34)	108 (43)	49 (38)	157 (41)
Mean (SD)	22.5 (16.1)	20.0 (16.3)	21.6 (16.2)	25.6 (18.7)	24.1 (17.9)	25.1 (18.5)
Median (min, max)	18 (2, 75)	15 (2, 71)	17 (2, 75)	21 (2, 73)	19 (2, 78)	20 (2, 78)
Baseline ICS dose level, n (%)						
Medium	118 (47)	61 (46)	179 (47)	94 (37)	60 (47)	154 (41)
High	132 (53)	71 (54)	203 (53)	158 (63)	68 (53)	226 (59)
Baseline ICS/LABA/LAMA use, n (%)	63 (25)	32 (24)	95 (25)	83 (33)	44 (34)	127 (33)
Baseline peripheral blood eosinophil count related to asthma (cells/µL)						
Median (min, max)	310 (20, 2360)	315 (20, 1490)	310 (20, 2360)	345 (10, 1810)	320 (30, 4440)	340 (10, 4440)
≥150/µL at screening, n (%)	123 (49)	71 (54)	194 (51)	101 (40)	62 (48)	163 (43)
≥300/µL in the 12 months prior to screening, n (%)	127 (51)	61 (46)	188 (49)	151 (60)	66 (52)	217 (57)
Intubated in relation to asthma prior to the trial, n (%)	9 (4)	2 (2)	11 (3)	6 (2)	5 (4)	11 (3)
Maintenance OCS at baseline (prednisone equivalent)						
n (%)	8 (3)	13 (10)	21 (5)	13 (5)	6 (5)	19 (5)
<7.5 mg/day	5 (2)	8 (6)	13 (3)	9 (4)	3 (2)	12 (3)
7.5 to <15 mg/day	3 (1)	2 (2)	5 (1)	4 (2)	3 (2)	7 (2)
15 to <30 mg/day	0 (0)	3 (2)	3 (1)	0 (0)	0 (0)	0 (0)
Baseline total IgE (U/mL)						
n (%)	250 (100)	130 (98)	380 (99)	246 (98)	128 (100)	374 (98)
Geometric mean (GSD)	144 (1.5)	180 (1.5)	155 (1.5)	158 (1.5)	189 (1.4)	168 (1.4)
Median (min, max)	181 (2, 12143)	191 (2, 5266)	185 (2, 12143)	167 (5, 16199)	200 (2, 2702)	180 (2, 16199)
Smoking history, n (%)						
Current	1 (<1)	0 (0)	1 (<1)	0 (0)	2 (2)	2 (1)
Former	67 (27)	26 (20)	93 (24)	53 (21)	31 (24)	84 (22)
Never	182 (73)	106 (80)	288 (75)	199 (79)	95 (74)	294 (77)

	SWIFT-1			SWIFT-2		
Clinical Characteristic	**Depemokimab N=250**	**Placebo N=132**	**Overall N=382**	**Depemokimab N=252**	**Placebo N=128**	**Overall N=380**
Asthma exacerbations requiring oral/systemic corticosteroids in the past year, n (%)						
0	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	210 (84)	118 (89)	328 (86)	188 (75)	90 (70)	278 (73)
3	32 (13)	9 (7)	41 (11)	36 (14)	17 (13)	53 (14)
4	2 (<1)	3 (2)	5 (1)	14 (6)	7 (5)	21 (6)
>4	5 (2)	2 (2)	7 (2)	14 (6)	14 (11)	28 (7)
Asthma exacerbations requiring hospitalization in the past year, n (%)						
0	233 (93)	125 (95)	358 (94)	233 (92)	111 (87)	344 (91)
1	13 (5)	4 (3)	17 (4)	6 (2)	12 (9)	18 (5)
2	4 (2)	3 (2)	7 (2)	10 (4)	2 (2)	12 (3)
3	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	2 (<1)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
>4	0 (0)	0 (0)	0 (0)	1 (<1)	3 (2)	4 (1)
Baseline pre-BD FEV1 (L)						
Mean (SD)	1.9 (0.7)	1.8 (0.7)	1.8 (0.7)	1.8 (0.7)	1.8 (0.7)	1.8 (0.7)
Median (min, max)	1.9 (0.5, 4.1)	1.8 (0.4, 3.8)	1.8 (0.4, 4.1)	1.7 (0.6, 3.8)	1.7 (0.7, 4.5)	1.7 (0.6, 4.5)
Baseline pre-BD ppFEV1 (%)						
Mean (SD)	62.3 (14.5)	60.8 (16.6)	61.8 (15.2)	62.5 (16)	60.9 (15.7)	62 (15.9)
Median (min, max)	63.1 (23.9, 98.8)	61.3 (19.2, 114.3)	62.3 (19.2, 114.3)	62.7 (25.7, 110.3)	60.7 (27, 96.4)	62.5 (25.7, 110.3)
Baseline FEV1 reversibility (%)						
Mean (SD)	16.5 (15.3)	17.9 (15.3)	17 (15.3)	17.6 (17.5)	19.4 (17.3)	18.2 (17.4)
Median (min, max)	14.6 (-16.5, 94.8)	16.3 (-10.1, 89.8)	14.9 (-16.5, 94.8)	13.4 (-23.1, 127.4)	15.6 (-5, 101.7)	14.2 (-23.1, 127.4)
Comorbid conditions, n (%)						
Nasal polyposis	25 (10)	10 (8)	35 (9)	24 (10)	13 (10)	37 (10)
GERD	44 (18)	32 (24)	76 (20)	69 (27)	31 (24)	100 (26)
Aspirin allergy symptoms	13 (5)	2 (2)	15 (4)	10 (4)	5 (4)	15 (4)
NSAID allergy symptoms	8 (3)	2 (2)	10 (3)	8 (3)	4 (3)	12 (3)

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports; Integrated Summary of Efficacy, Table 1.64
Abbreviations: BD, bronchodilator; FEV1, forced expiratory volume in one second; GERD, gastroesophageal reflux disease; GSD, geometric standard deviation; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; max, maximum; min, minimum; N, number of participants in the full analysis set; n, number of participants in the respective group; NSAID, non-steroidal anti-inflammatory drug; OCS, oral corticosteroid; ppFEV1, percent predicted forced expiratory volume in one second; SD, standard deviation; U, units.

8.2.9.4. Primary Efficacy Endpoint

The ICEs defined for all SWIFT-1 and SWIFT-2 estimands were treatment discontinuation due to reasons related or unrelated to the COVID-19 pandemic, change in asthma maintenance therapy, and use of concomitant/prohibited medications. For the primary and all secondary analyses below, all ICEs were handled using a treatment policy strategy, except for treatment discontinuation due to reasons related to the COVID-19 pandemic (only one case in SWIFT-1), which used a hypothetical strategy. The frequency of each ICE that occurred throughout the trials in the FAS were appreciably balanced by treatment arm and across the trials. The most common ICE in SWIFT-1 and SWIFT-2 was treatment discontinuation unrelated to COVID-19 (5% of the FAS) and use of concomitant/prohibited medications (6% of the FAS), respectively. Overall, the frequency of ICEs, including treatment discontinuation, were low and generally consistent within and across the trials. See Section 19.3 for further information.

The primary endpoint in SWIFT-1 and SWIFT-2 was the annualized rate of clinically significant asthma exacerbations over 52 weeks. The pre-specified analysis was a negative binomial model (described in Section 8.2.7), conducted in the FAS. In both SWIFT-1 and SWIFT-2, treatment with depemokimab resulted in a statistically significant reduction in the annualized rate of exacerbations compared to placebo, with rate ratios of 0.42 (95% CI: 0.3, 0.6) and 0.52 (95% CI: 0.36, 0.73), respectively (Table 10). Additionally, in both trials, the proportion of participants with ≥1 clinically significant asthma exacerbations in the depemokimab arm was numerically less than the placebo arm.

Table 10. Primary Endpoint Results: Annualized Rate of Clinically Significant Asthma Exacerbations Over 52 Weeks (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=128**
Number of evaluable participants[a], n (%)	249 (>99)	132 (100)	252 (100)	128 (100)
Participants with ≥1 clinically significant asthma exacerbation, n (%)	79 (32)	61 (46)	81 (32)	64 (50)
Annualized asthma exacerbation rate	0.46	1.1	0.54	1.05
95% CI	0.35, 0.58	0.81, 1.38	0.41, 0.67	0.76, 1.33
Rate ratio[b]	0.42		0.52	
95% CI	0.3, 0.6		0.36, 0.73	
P-value	< 0.001		< 0.001	
Percent reduction[c]	58%		48%	
95% CI	40%, 70%		27%, 64%	

Source: Statistical analyst; SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] One SWIFT-1 participant on depemokimab was excluded from analysis due to missing covariate data at Week 52 (this participant did not have any clinically significant asthma exacerbations).
[b] Calculated as: rate in depemokimab arm / rate in placebo arm.
[c] Calculated as: (1 – rate ratio) * 100%.
Note: All results were obtained from a negative binomial model with an offset term for years in study and fixed effects for treatment arm, asthma exacerbation history, baseline ICS dose, geographical region, and baseline pre-bronchodilator ppFEV1.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; N, number of participants in the Full Analysis Set; n, number of evaluable participants; ppFEV1, percent predicted forced expiratory volume in 1 second.

Furthermore, the primary endpoint results for SWIFT-1 and SWIFT-2 were consistent between the FAS (SWIFT-1: rate ratio = 0.42, 95% CI = 0.3, 0.6; SWIFT-2: rate ratio = 0.52, 95% CI = 0.36, 0.73) and FAS-Modified (SWIFT-1: rate ratio = 0.42, 95% CI = 0.29, 0.59; SWIFT-2: rate ratio = 0.52, 95% CI = 0.37, 0.74) populations. Additionally, for SWIFT-2, the primary endpoint results were also consistent between the FAS (rate ratio = 0.52, 95% CI = 0.36, 0.73) and the FAS excluding all 12 participants enrolled at Site 251152 (rate ratio = 0.51, 95% CI = 0.36, 0.72) due to the 7 participants on depemokimab having no detectable study drug concentration (except at Visit 8) and no pharmacodynamic effect on serum eosinophils at any study timepoint.

In both trials, robustness of the main analyses above to departures from the MAR assumption was supported by tipping point analyses, where participants who withdrew from the trial had missing data imputed based on a range of values for the annualized rate of clinically significant asthma exacerbations after withdrawal. The imputed values investigated were based on increases or decreases relative to the estimated rates obtained within each treatment arm under the MAR assumption (0.0625 to 64 times the observed rates in each treatment arm), which included scenarios where participants in the depemokimab arm had worse outcomes after withdrawing from the trial than participants on placebo. For SWIFT-1 and SWIFT-2, when participants with an unobserved period in the depemokimab arm had an exacerbation rate imputed that was >16 or >4 times, respectively, the average depemokimab rate (clinically implausible scenarios) and participants with an unobserved period in the placebo arm had an exacerbation rate imputed that was equal to the observed exacerbation rate in the placebo arm, statistical significance was maintained (see Section 19). Therefore, for both trials, the results from the primary analysis were robust to plausible assumptions about the outcomes for participants with missing data during the 52-week Treatment Period.

For SWIFT-1 and SWIFT-2, subgroup analyses were also conducted for the primary endpoint by age, sex, race, ethnicity, geographical region, and baseline ICS dose, peripheral blood eosinophil count, and ACQ-5 score. For both trials, the subgroup analysis results were generally consistent with the overall (FAS) population (see Section 19.5). Some 95% CIs included the null value of 1, but no subgroups were powered, and all treatment effects (rate ratios) numerically favored depemokimab (except for the subgroup of Black or African American participants in SWIFT-2, but conclusions based on this analysis are very limited due to the small sample size). In both trials, subgroup analyses could not be conducted for some age (adolescents) and race (Asian and Black or African American) groups due to small sample sizes leading to model convergence issues, but no concerns were identified when examining the exacerbation data descriptively. Additionally, only 30 adolescents (aged 12 to 17 years) were enrolled across the trials (15 received depemokimab), and the Applicant noted annualized clinically significant asthma exacerbation rates of 0.55 and 0.96 in the pooled depemokimab and placebo arms, respectively, with a rate ratio of 0.57 (95% CI = 0.15, 2.13). Although point estimates for the primary endpoint in the adolescent subgroup favored depemokimab and are consistent with the overall results, efficacy and safety in adolescents is primarily based on extrapolation of data from adults given the small number of adolescent subjects evaluated in SWIFT-1 and SWIFT-2. Extrapolation from adults to adolescents is justified by the similarity in disease pathophysiology

and a comparable PK/PD response, and thus an expected treatment effect in adolescents that is consistent with the adult population (see Section 1 and Section 10.1.2).

8.2.9.5. Secondary Efficacy Endpoints

Change From Baseline in SGRQ Total Score at Week 52

Details of the SGRQ are provided in Section 8.2.5. For both trials, the pre-specified analysis was an MMRM (described in Section 8.2.7), conducted in the FAS. In SWIFT-1 and SWIFT-2, treatment with depemokimab resulted in a slight numerical improvement in the absolute change from baseline in SGRQ total score at Week 52 compared to placebo, with LS mean differences of -3.4 (95% CI: -7.1, 0.4) and -2.3 (95% CI: -5.8, 1.2), respectively (Table 11). However, these results were not statistically significant. While the results favored depemokimab numerically, the magnitude of the observed treatment effects is notably small when assessed in the context of the 0 to 100 scale for the SGRQ total score. (b) (4)

(b) (4)

Table 11. Secondary Endpoint Results: Change From Baseline in SGRQ Total Score at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=126**
Number of evaluable participants[a], n (%)	240 (96)	128 (97)	246 (98)	124 (98)
LS mean (SE)	-13.05 (1.11)	-9.69 (1.54)	-14.82 (1.04)	-12.52 (1.45)
95% CI	-15.23, -10.87	-12.72, -6.67	-16.86, -12.78	-15.37, -9.66
Difference[b]	-3.36		-2.31	
95% CI	-7.08, 0.36		-5.81, 1.2	
P-value	0.078		0.198	

Source: Statistical analyst; SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] 14 SWIFT-1 participants (10 on depemokimab and 4 on placebo) and 8 SWIFT-2 participants (6 on depemokimab and 2 on placebo) were excluded from analysis due to missing SGRQ data at baseline and Week 52.
[b] Calculated as: LS mean in depemokimab arm – LS mean in placebo arm.
Note: All results were obtained from an MMRM with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, baseline value, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; LS, least squares; MMRM, mixed model for repeated measures; N, number of participants in the full analysis set; n, number of evaluable participants; SE, standard error; SGRQ, St. George's Respiratory Questionnaire.

Since the change from baseline in SGRQ total score at Week 52 was not statistically significant, according to the pre-specified testing hierarchy for SWIFT-1 and SWIFT-2 (described in Section 8.2.7), all subsequent secondary endpoints were not tested inferentially and were deemed not statistically significant. However, for the completion of presentation, results for the remaining secondary endpoints are provided below, and results for other efficacy endpoints of regulatory interest are provided in Section 19.

Change From Baseline in ACQ-5 Score at Week 52

Details of the ACQ-5 are provided in Section 8.2.5. For both trials, the pre-specified analysis was an MMRM (described in Section 8.2.7), conducted in the FAS. In SWIFT-1 and SWIFT-2, treatment with depemokimab did not result in a considerable improvement (i.e., improved

asthma control) in the absolute change from baseline in ACQ-5 score at Week 52 compared to placebo, with LS mean differences of -0.04 (95% CI: -0.26, 0.17) and -0.11 (95% CI: -0.33, 0.11), respectively (Table 12). These results were numerically small and not clinically meaningful.

Table 12. Secondary Endpoint Results: Change From Baseline in ACQ-5 Score at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=127**
Number of evaluable participants[a], n (%)	241 (96)	129 (98)	246 (98)	124 (98)
LS mean (SE)	-0.81 (0.07)	-0.77 (0.09)	-0.81 (0.06)	-0.70 (0.09)
95% CI	-0.94, -0.68	-0.94, -0.59	-0.93, -0.68	-0.87, -0.52
Difference[b]	-0.04		-0.11	
95% CI	-0.26, 0.17		-0.33, 0.11	
P-value	0.686		0.326	

Source: Statistical analyst; SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] 12 SWIFT-1 participants (9 on depemokimab and 3 on placebo) and 9 SWIFT-2 participants (6 on depemokimab and 3 on placebo) were excluded from analysis due to missing ACQ-5 data at baseline and Week 52.
[b] Calculated as: LS mean in depemokimab arm – LS mean in placebo arm.
Note: All results were obtained from an MMRM with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, baseline value, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: ACQ-5, Asthma Control Questionnaire (5-item version); CI, confidence interval; ICS, inhaled corticosteroid; LS, least square; MMRM, mixed model for repeated measures; N, number of participants in the full analysis set; n, number of evaluable participants; SE, standard error.

The Applicant designated a change from baseline at Week 52 of ≥0.5 points as a clinically meaningful improvement, a responder threshold that FDA has previously accepted. Therefore, although not a multiplicity-adjusted endpoint, the ACQ-5 responder analysis results based on a ≥0.5-point change from baseline at Week 52 will be included descriptively in the depemokimab label (Table 73).

Change From Baseline in Pre-BD FEV1 at Week 52

For both trials, the pre-specified analysis was an MMRM (described in Section 8.2.7), conducted in the FAS. In SWIFT-1 and SWIFT-2, treatment with depemokimab did not result in a considerable improvement in the absolute change from baseline in pre-BD FEV1 at Week 52 compared to placebo, with LS mean differences of -1 mL (95% CI: -89, 88) and 56 mL (95% CI: -43, 154), respectively (Table 13).

Table 13. Secondary Endpoint Results: Change From Baseline in Pre-BD FEV1 (L) at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=128**
Number of evaluable participants[a], n (%)	236 (94)	126 (95)	239 (95)	119 (93)
LS mean (SE)	0.160 (0.026)	0.160 (0.036)	0.240 (0.029)	0.184 (0.041)
95% CI	0.108, 0.211	0.089, 0.232	0.183, 0.296	0.104, 0.264
Difference[b]	-0.001		0.056	
95% CI	-0.089, 0.088		-0.043, 0.154	
P-value	0.99		0.267	

Source: Statistical analyst; SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] 20 SWIFT-1 participants (14 on depemokimab and 6 on placebo) and 22 SWIFT-2 participants (13 on depemokimab and 9 on placebo) were excluded from analysis due to missing pre-BD FEV1 data at baseline and Week 52.
[b] Calculated as: LS mean in depemokimab arm – LS mean in placebo arm.
Note: All results were obtained from an MMRM with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, baseline value, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: BD, bronchodilator; CI, confidence interval; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroid; L, liters; MMRM, mixed model for repeated measures; N, number of participants in the full analysis set; n, number of evaluable participants; SE, standard error.

Change From Baseline in ANSD and ADSD Weekly Mean Scores at Week 52

The ANSD and ADSD endpoints (described in Section 8.2.5) were included in the statistical testing hierarchy for SWIFT-1 and SWIFT-2. However, the Applicant is not seeking labeling claims for these endpoints; the results for these endpoints are provided in Section 19.6 for reference.

Annualized Rate of Asthma Exacerbations Requiring Hospitalization and/or ED Visit Over 52 Weeks

For both trials, the pre-specified analysis was a negative binomial model (described in Section 8.2.7), conducted in the FAS. This analysis was not performed for SWIFT-1 due to the occurrence of <20 asthma exacerbation events requiring hospitalization and/or emergency department visit, but numerically fewer such exacerbations occurred in the depemokimab arm (5 total among 3 participants) compared to placebo (13 total among 11 participants). In SWIFT-2, treatment with depemokimab resulted in a numerical reduction in the annualized rate of asthma exacerbations requiring hospitalization and/or emergency department visit compared to placebo, with a rate ratio of 0.43 (95% CI: 0.16, 1.12), as shown in Table 14. Additionally, for both trials, the proportion of participants with ≥1 asthma exacerbations requiring hospitalization and/or emergency department visit in the depemokimab arm was numerically less than the placebo arm.

Table 14. Secondary Endpoint Results: Annualized Rate of Asthma Exacerbations Requiring Hospitalization and/or ED Visit Over 52 Weeks (Full Analysis Set, SWIFT-2)

	SWIFT-2	
Analysis Statistic	**Depemokimab N=252**	**Placebo N=128**
Participants with ≥1 asthma exacerbations requiring hospitalization and/or ED visit, n (%)	10 (4)	13 (10)
Annualized rate of asthma exacerbations requiring hospitalization and/or ED visit	0.05	0.11
95% CI	0.01, 0.08	0.03, 0.18
Rate ratio[a]	0.43	
95% CI	0.16, 1.12	
P-value	0.078	
Percent reduction[b]	57%	
95% CI	-12%, 84%	

Source: Statistical analyst; SWIFT-2 Clinical Study Report.
[a] Calculated as: rate in depemokimab arm / rate in placebo arm.
[b] Calculated as: (1 – rate ratio) * 100%.
Notes: All results were obtained from a negative binomial model with an offset term for years in study and fixed effects for treatment arm, asthma exacerbation history, baseline ICS dose, geographical region, and baseline pre-bronchodilator ppFEV1. SWIFT-1 results are omitted from this table due to not meeting the pre-specified minimum number of 20 events and model convergence issues.
Abbreviations: CI, confidence interval; ED, emergency department; ICS, inhaled corticosteroid; N, number of participants in the full analysis set; n, number of participants in the respective group; ppFEV1, percent predicted forced expiratory volume in 1 second; SE, standard error.

8.2.10. Key Efficacy Review Issues

8.2.10.1. Demonstration of Substantial Evidence of Effectiveness

Issue

Has the Applicant adequately demonstrated SEE for the proposed asthma indication?

Background

The Applicant achieved statistical significance for the primary endpoint of annualized rate of clinically significant asthma exacerbations over 52 weeks for SWIFT-1 and SWIFT-2; however, no multiplicity-adjusted secondary endpoints were met based on the pre-specified hierarchical testing strategies.

Assessment

As shown in Section 8.2.9.5, none of the multiplicity-adjusted secondary endpoints demonstrated statistically significant treatment effects. These endpoints included:

- Absolute changes from baseline in patient-reported outcomes (SGRQ, ACQ-5, ADSD, and ANSD) at Week 52
- Effects on lung function (pre-BD FEV1) at Week 52
- Asthma exacerbations requiring hospitalization and/or emergency department visit over 52 weeks

However, several considerations support the interpretation of these results:

- The SGRQ is not considered fit-for-purpose for asthma clinical trials, despite its inclusion as an efficacy claim in the mepolizumab label
- The ACQ-5 is typically assessed using a responder analysis (an improvement of ≥0.5 points) rather than change from baseline in the total score, based on precedence in other development programs for asthma biologics
- The ANSD and ADSD have not been determined to be fit-for-purpose for regulatory decision-making (b) (4) in this context of use in asthma
- The lack of effect on lung function via pre-BD FEV1 is consistent with the results from the mepolizumab asthma clinical trials
- The subset of asthma exacerbations requiring hospitalization or emergency department visit numerically favored the depemokimab arm, consistent with the primary endpoint results

The Applicant achieved statistical significance for the primary endpoint in both SWIFT-1 and SWIFT-2. In SWIFT-1, the annualized exacerbation rate ratio for the depemokimab arm relative to placebo was 0.42 (95% CI = 0.30, 0.6; $p < 0.001$), with a 58% reduction (95% CI = 40%, 70%) in the annualized exacerbation rate relative to placebo. Similarly, in SWIFT-2, the annualized exacerbation rate ratio for the depemokimab arm relative to placebo was 0.52 (95% CI = 0.36, 0.73; $p < 0.001$), with a 48% reduction (95% CI = 27%, 64%) in the annualized exacerbation rate relative to placebo. These results were statistically robust, clinically persuasive, and of comparable magnitude to other asthma biologics.

Based on the totality of the primary and secondary endpoint results, determination of whether SEE could be met solely from the primary endpoint was assessed. For asthma drug development programs, a reduction in the rate of exacerbations is considered a convincing, clinically meaningful outcome on its own, and in the setting of a robust treatment effect, does not require additional support from other efficacy measures. Furthermore, for the reasons stated above, the absence of statistically significant secondary endpoints in these trials does not raise questions regarding the efficacy of depemokimab.

Conclusion

The primary endpoint results are sufficiently robust, clinically meaningful, comparable to other asthma biologics, and well-validated to independently establish SEE regardless of the secondary endpoint results.

9 Safety

9.1. Potential Risks or Safety Concerns Based on Nonclinical Data, Drug Class, or Other Drug-Specific Factors

Nonclinical Data

The totality of nonclinical studies conducted support the approval and marketing of depemokimab. Nonclinical safety was primarily evaluated in a 26-week toxicology study conducted in cynomolgus monkeys. A human tissue cross reactivity study was also conducted. Notable nonclinical studies are summarized below.

General Toxicology

In the 26-week toxicology study conducted in monkeys, doses of 10 (low dose [LD]) and 100 (high dose [HD]) mg/kg were administered to adult male and female monkeys (4/sex/group) once every 13 weeks for a total of 2 doses. Study assessments included MCP-1 and IL-5 analysis in blood. There were no treatment-related findings on histopathology. The only treatment-related findings in this study were non-adverse and related to the expected pharmacology of the drug (reduced eosinophils for several weeks and increased IL-5 in plasma after dosing). The patients in clinical trials were recommended to be monitored for alterations in eosinophil counts. The modifications to the antibody relative to mepolizumab, including YTE modification, did not appear to change the toxicity profile of the drug since all toxicity was related to IL-5 inhibition.

Reproductive and Developmental Toxicology

After reviewing the nonclinical data, it was decided that conducting an enhanced pre- and postnatal development (PPND) study in monkeys would not be necessary as the study only provides hazard identification. The effects of IL-5 inhibition have been studied with approved drugs such as mepolizumab as well as peer-reviewed literature with IL-5 deficient mice. Since the general toxicology studies demonstrated the toxicity profile for depemokimab was similar to mepolizumab, an additional monkey study to evaluate potential reproductive effects would be of limited value. Reproductive toxicity data can be taken from the mepolizumab program.

In the fertility and early embryonic development study, mepolizumab at IV doses up to 100 mg/kg q4 weeks or a SC dose of 10 mg/kg q4 weeks had no effects on male or female fertility. In an embryo-fetal development mouse study, CD-1 mice received SB264091, a rat anti-human IL-5 surrogate monoclonal antibody (lgG2b), which cross reacts with human and murine IL-5. SB264091 was not teratogenic in CD-1 mice that received a dose of 50 mg/kg/week. In a PPND monkey study, 12 pregnant female cynomolgus monkeys/group received mepolizumab at intravenous doses of 0, 10, or 100 mg/kg once per month on gestation days 20, 50, 80, 110, and 140. The development of offspring was followed for 9 months after birth. There was no evidence of treatment-related maternal toxicity or effects on pregnancy outcome or natural

delivery nor of the offspring. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

Carcinogenicity

After reviewing the nonclinical data, it was decided that conducting a carcinogenicity study in monkeys for depemokimab would not be necessary. Carcinogenicity information can be taken from the mepolizumab program. The mepolizumab label states "Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown."

Drug Class

Depemokimab is a humanized, YTE-modified, monoclonal antibody (IgG1, kappa) that binds and inhibits IL-5, a cytokine involved in the growth, survival, differentiation, activation, and recruitment of eosinophils. There are two other approved biologic inhibitors of IL-5, mepolizumab and reslizumab, and one approved interleukin-5 receptor alpha-directed cytolytic monoclonal antibody, benralizumab. These inhibitors have been evaluated and approved for the indications of severe eosinophilic asthma, chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis, and hypereosinophilic syndrome. A class effect due to inhibition of IL-5/5R, and thereby eosinophils, are parasitic/helminth infections, a risk which is included in the Warnings and Precautions section of all approved anti-IL-5/5R biologic labels. Other Warnings and Precautions for anti-IL-5/5R therapies are hypersensitivity reactions (mepolizumab and benralizumab), herpes zoster infections (mepolizumab), and malignancy (reslizumab). Reslizumab also has a boxed warning for anaphylaxis based on an incidence of 0.3% in asthma patients in placebo-controlled trials.

9.2. FDA Approach to the Safety Review

The clinical data scientist performed an independent safety analysis using R Studio version 4.1.0. The primary safety analyses are based on the safety population, which included all subjects who received at least one dose of study drug and excluded subjects from sites 250190, 250085, and 250523 due to potential data integrity issues and GCP violations (Section 12). Subjects were analyzed based on their randomized intervention, unless it was different from their actual treatment received in which case the latter was used. The sample size of the safety analysis set (N=382) was identical to the full analysis set (FAS) in the SWIFT-1 trial. In the SWIFT-2 trial, one participant randomized to depemokimab received a dose of placebo in error and did not receive a second dose of study drug. This subject was assigned to the depemokimab randomized treatment group in the FAS, but in the placebo actual treatment group in the safety analysis set (N=380, Table 7). Given the replicate study design, pooling of safety data across trials SWIFT-1 and SWIFT-2 was considered appropriate. The pooled safety population serves as the primary source of data for the safety assessment to support the use of depemokimab in

asthma patients. The prespecified safety analysis plan was reviewed during development under the IND and was appropriate.

9.3. Safety Parameters

Safety assessments included the collection of AEs/SAEs, concomitant medications, vital signs (temperature, blood pressure, and heart rate), 12-lead electrocardiograms (ECGs), physical examinations, laboratory tests (clinical and liver chemistry, hematology, urinalysis, and pregnancy testing), and spirometry. Clinical tests were conducted per Table 65. Any abnormal results, including a worsening from baseline, were reported as AEs if determined to be clinically significant by the Investigator.

For asthma-specific safety evaluation, participants recorded morning peak expiratory flow prior to rescue medication use (best of 3 measurements), frequency of rescue medication use, asthma symptom score over the prior 24 hours, and frequency of nighttime awakenings due to asthma symptoms requiring rescue medication use in an eDiary starting at Visit 1. The daily asthma symptom score was on a 5-point scale (0 = no symptoms during the prior 24 hours; 1 = symptoms for one short period during the prior 24 hours; 2 = symptoms for two or more short periods during the prior 24 hours; 3= symptoms for most of the prior 24 hours which did not affect normal daily activities; 4 = symptoms for most of the prior 24 hours which did affect normal daily activities; 5 = severe symptoms inhibiting ability to go to work/school or perform normal daily activities). The daily asthma symptom score is Applicant-derived and is not a validated PRO measure.

The eDiary was programmed with the following alerts to indicate a worsening asthma status:

- Decrease in morning peak expiratory flow ≥30% on at least 2 of 3 consecutive days compared with baseline (last 7 days of the Run-in Period)
- A ≥50% increase in rescue medication use on at least 2 of 3 consecutive days compared to the average rescue medication use in the prior week
- Nighttime awakening due to asthma symptoms requiring rescue medication use for at least 2 of 3 consecutive nights
- An asthma symptom score of 5 for at least 2 of 3 consecutive days

If any of the above criteria were met, the participant was recommended to contact the Investigator, and the study site was notified to follow up with the participant. Although related to asthma exacerbations, worsening of asthma symptoms / deterioration in asthma status was used by investigators to assess subject safety; these measures were not part of the efficacy assessment.

9.4. Adequacy of Clinical Safety Database

The safety database is of sufficient size and duration to evaluate depemokimab at the proposed dosage of 100 mg SC Q6M for the treatment of adults and adolescents with severe asthma. Data integrity issues were noted at some sites in SWIFT-1 and SWIFT-2 (see Section 12);

however, data from participants enrolled at these sites were not included in the safety dataset and did not impact the overall safety and efficacy conclusions from the trials.

In the asthma clinical development program, the Applicant's definition of AEs and SAEs were consistent with the requirements in the 21 Code of Federal Regulations 312.32. All AEs were collected from the start of study intervention (Visit 2) until the Exit Visit or follow-up visit/call (Week 56) for subjects who entered into the open-label extension trial (AGILE) and those who did not, respectively. SAEs related to trial participation or IMP were collected from the time of subject consent. Asthma exacerbations were not recorded as AEs unless meeting criteria for a SAE.

On-treatment adverse events (subsequently referred to as AEs) were defined as any untoward medical occurrence, sign/symptom, or new or worsening disease temporally associated with, but not necessarily related, to study drug. See Figure 46 for the complete definition of an AE. The Applicant coded AEs from SWIFT-1 and SWIFT-2 using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. The Applicant's mapping of verbatim terms to MedDRA preferred terms was reviewed and found to be appropriate. On-treatment AEs were categorized as those that occurred after the first dose, but before or equal to the last dose of IMP plus 182 days. Pre-treatment AEs were those that occurred prior to the first dose of IMP, and post-treatment AEs occurred after the on-treatment period (i.e., >182 days after last dose of IMP). Assessment of intensity was categorized as mild, moderate, or severe (see Figure 47). Safety analyses in this review are based on the on-treatment AEs.

The primary safety database for the proposed depemokimab dosage of 100 mg SC Q6 months in the proposed asthma indication consists of the 762 subjects treated in the replicate, 52-week, randomized, double-blind and placebo-controlled treatment periods in trials SWIFT-1 and SWIFT-2 (Section 8.2). Additional supportive safety data are provided from an interim analysis of the 52-week, open-label extension AGILE trial, an interim analysis of the active comparator NIMBLE trial, and the ANCHOR-1 and ANCHOR-2 controlled trials in adults with CRSwNP. See Sections 18.2, 18.3, 20.2, and 20.3 for further details of the AGILE and NIMBLE trials and results. (b) (4)

The extent of exposure in SWIFT-1 and SWIFT-2 is shown in Table 15. A total of 475 (95%) subjects in the depemokimab treatment groups received both doses of IMP, which based on the long half-life of depemokimab equates to one year of exposure. Overall, the extent and duration of depemokimab exposure in SWIFT-1 and SWIFT-2 meet the International Council for Harmonization guidelines (March 1995) for the safety evaluation of chronic use drugs (i.e., 300-600 patients exposed to IMP for 6 months, 100 patients exposed to IMP for 1 year, and 1500 patients exposed to IMP across asthma and CRSwNP indications).

Table 15. Duration of Exposure, Pooled Safety Population, SWIFT-1 and SWIFT-2

Parameter	Depemokimab N=501	Placebo N=261
Duration of treatment, weeks		
Mean (SD)	51 (5.9)	51.2 (5.4)
Median (Q1, Q3)	52 (51.9, 52.6)	52 (51.9, 52.3)
Min, max	26, 59	26, 59.1
Total exposure (person years)	490	256
Patients treated, by duration, n (%)		
<26 weeks	0	0
≥26 to <39 weeks	26 (5.2)	11 (4.2)
≥39 to <52 weeks	132 (26.3)	67 (25.7)
≥52 to <65 weeks	343 (68.5)	183 (70.1)

Source: adex.xpt and adsl.xpt; Software: R
Duration is 52 weeks.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

9.5. Safety Results

9.5.1. Overview of On-Treatment AEs

Table 16 summarizes the on-treatment AEs and SAEs in pooled SWIFT-1 and SWIFT-2 trials. There were numerically more SAEs in the placebo group (35, 13.4%) than the depemokimab group (33, 6.6%) with no fatal SAEs. AEs leading to permanent discontinuation of study drug were comparable among treatment groups with a single depemokimab subject requiring interruption of study drug. The majority of AEs were mild to moderate in severity. There was a single placebo participant in SWIFT-1 with a life-threatening AE of rib fracture due to a motor vehicle accident. Additionally, there were four depemokimab participants in SWIFT-2 who experienced life-threatening AEs of COVID-19, bilateral ovarian cancer and peritoneal metastases, first-time episode of epileptic seizure, and ingestion of psychiatric medication. One placebo participant in SWIFT-2 had a life-threatening AE of sepsis without acute organ dysfunction due to urinary tract infection associated pyelonephritis.

Table 16. Overview of On-Treatment Adverse Events, Pooled Safety Population, SWIFT-1 and SWIFT-2

Event Category	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
SAE	33 (6.6)	35 (13.4)	-6.8 (-11.9, -2.4)*
SAEs with fatal outcome	0	0	0.0 (-1.5, 0.8)
AE leading to permanent discontinuation of study drug	5 (1.0)	2 (0.8)	0.2 (-1.8, 1.7)
AE leading to dose modification of study drug	1 (0.2)	0	0.2 (-1.3, 1.1)
AE leading to interruption of study drug	1 (0.2)	0	0.2 (-1.3, 1.1)
AE leading to reduction of study drug	0	0	0.0 (-1.5, 0.8)
AE leading to dose delay of study drug	0	0	0.0 (-1.5, 0.8)
Any AE	362 (72.3)	198 (75.9)	-3.6 (-9.9, 3.1)
Severe and worse	19 (3.8)	22 (8.4)	-4.6 (-8.9, -1.2) *
Moderate	207 (41.3)	106 (40.6)	0.7 (-6.7, 8.0)
Mild	136 (27.1)	70 (26.8)	0.3 (-6.5, 6.8)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Severity as assessed by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Note: one placebo participant in SWIFT-2 was withdrawn from study due to an AE (acute depression) but was not listed as discontinuing treatment. This subject is not included within the permanent discontinuation of study drug category.
Note: the clinical data scientist re-categorized 3 AEs (COVID-19, bilateral ovarian cancer, peritoneal metastases) from 2 depemokimab participants as severe and worse as they were also considered life-threatening SAEs by the Applicant. These AEs were originally categorized as mild and moderate severity, respectively, by the Applicant.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event

9.5.2. Serious Adverse Events

Deaths

There were no deaths in SWIFT-1 or SWIFT-2. To date, there have been no reported deaths during the on-treatment period in depemokimab participants across the entire depemokimab phase 3 clinical development program.

Non-Fatal SAEs

Pooled, non-fatal, on-treatment SAEs occurring in at least 1 depemokimab subject and more common than placebo were evaluated and are summarized in Table 17. Preferred terms (PTs) occurring in both the depemokimab and placebo treatment arms were COVID-19, pneumonia, intervertebral disc protrusion, headache and asthma.

The most common system organ classes (SOCs) in the depemokimab and placebo groups were respiratory, thoracic and mediastinal disorders (1.8% and 4.6%, respectively), infection and infestations (0.8% and 3.1%, respectively), and musculoskeletal and connective tissue disorders (1.2% and 1.1%, respectively). The SOCs hepatobiliary disorders and associated laboratory investigations were observed exclusively in the depemokimab group, though each accompanying PT was a single occurrence and both SOCs were observed in a mutually exclusive manner across the two trials; hepatobiliary disorders was reported only in SWIFT-1, while investigations was only reported in SWIFT-2. Common SAEs by PT were pneumonia and asthma,

though both occurred with higher frequency in the placebo group. No additional findings were illustrated when reviewing SAEs by SOC and Office of New Drugs Custom Medical Queries (OCMQ) (Table 75). By OCMQ, bronchospasm (4.2%) had the highest incidence overall, though predominantly in the placebo group. No concerning safety signals were identified in the review of SAEs, as most were single events and none appear related to depemokimab.

Table 17. Serious Adverse Events More Common Than Placebo by System Organ Class and Preferred Term, Pooled Safety Population, SWIFT-1 and SWIFT-2

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Any SAE	33 (6.6)	35 (13.4)	-6.8 (-11.9, -2.4)*
Cardiac disorders (SOC)	2 (0.4)	2 (0.8)	-0.4 (-2.4, 0.8)
Angina unstable	1 (0.2)	0	0.2 (-1.3, 1.1)
Atrial fibrillation	1 (0.2)	0	0.2 (-1.3, 1.1)
Eye disorders (SOC)	1 (0.2)	0	0.2 (-1.3, 1.1)
Rhegmatogenous retinal detachment	1 (0.2)	0	0.2 (-1.3, 1.1)
Gastrointestinal disorders (SOC)	3 (0.6)	2 (0.8)	-0.2 (-2.2, 1.1)
Large intestine polyp	2 (0.4)	0	0.4 (-1.1, 1.4)
Abdominal pain	1 (0.2)	0	0.2 (-1.3, 1.1)
General disorders and administration site conditions (SOC)	1 (0.2)	2 (0.8)	-0.6 (-2.6, 0.5)
Chest pain	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatobiliary disorders (SOC)	3 (0.6)	0	0.6 (-0.9, 1.7)
Cholecystitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Cholecystitis acute	1 (0.2)	0	0.2 (-1.3, 1.1)
Cholelithiasis	1 (0.2)	0	0.2 (-1.3, 1.1)
Jaundice cholestatic	1 (0.2)	0	0.2 (-1.3, 1.1)
Infections and infestations (SOC)	4 (0.8)	8 (3.1)	-2.3 (-5.2, -0.4) *
Bronchiolitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatitis A	1 (0.2)	0	0.2 (-1.3, 1.1)
Injury, poisoning and procedural complications (SOC)	1 (0.2)	2 (0.8)	-0.6 (-2.6, 0.5)
Accidental exposure to product	1 (0.2)	0	0.2 (-1.3, 1.1)
Investigations (SOC)	1 (0.2)	0	0.2 (-1.3, 1.1)
Alanine aminotransferase abnormal	1 (0.2)	0	0.2 (-1.3, 1.1)
Blood bilirubin abnormal	1 (0.2)	0	0.2 (-1.3, 1.1)
Metabolism and nutrition disorders (SOC)	1 (0.2)	0	0.2 (-1.3, 1.1)
Hypoglycaemia	1 (0.2)	0	0.2 (-1.3, 1.1)
Musculoskeletal and connective tissue disorders (SOC)	6 (1.2)	3 (1.1)	0.0 (-2.2, 1.7)
Foot deformity	1 (0.2)	0	0.2 (-1.3, 1.1)
Osteoarthritis	1 (0.2)	0	0.2 (-1.3, 1.1)
Osteochondritis	1 (0.2)	0	0.2 (-1.3, 1.1)
Rotator cuff syndrome	1 (0.2)	0	0.2 (-1.3, 1.1)
Tenosynovitis stenosans	1 (0.2)	0	0.2 (-1.3, 1.1)

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	5 (1.0)	2 (0.8)	0.2 (-1.8, 1.7)
Adenocarcinoma of colon	1 (0.2)	0	0.2 (-1.3, 1.1)
Basal cell carcinoma	1 (0.2)	0	0.2 (-1.3, 1.1)
Metastases to peritoneum	1 (0.2)	0	0.2 (-1.3, 1.1)
Ovarian cancer	1 (0.2)	0	0.2 (-1.3, 1.1)
Small intestine adenocarcinoma	1 (0.2)	0	0.2 (-1.3, 1.1)
Uterine leiomyoma	1 (0.2)	0	0.2 (-1.3, 1.1)
Nervous system disorders (SOC)	3 (0.6)	2 (0.8)	-0.2 (-2.2, 1.1)
Cerebral infarction	1 (0.2)	0	0.2 (-1.3, 1.1)
Epilepsy	1 (0.2)	0	0.2 (-1.3, 1.1)
Seizure	1 (0.2)	0	0.2 (-1.3, 1.1)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Note: review of the clinical narrative for one depemokimab participant in SWIFT-2 who experienced an SAE of asthma reported eyelid swelling in addition to respiratory symptoms. Eyelid swelling is not typical for asthma; however, an alternate etiology could not be determined.
Note: there was one post-treatment SAE of asthma exacerbation in a depemokimab participant in SWIFT-2.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

9.5.3. Adverse Events Leading to Treatment Discontinuation, Interruption, or Study Withdrawal

The incidence of adverse events leading to treatment discontinuation, treatment interruption, or study withdrawal was overall low and comparable among depemokimab and placebo groups (Table 16). Table 18 presents subject level data for treatment discontinuations/interruptions due to on-treatment AEs in the depemokimab arm. Overall, there was no definitive pattern in the adverse events by SOC and PT leading to treatment discontinuation, treatment interruption, or study withdrawal in either treatment group.

Table 18. Depemokimab Subjects With Adverse Events Leading to Treatment Discontinuation, Treatment Interruption, or Study Withdrawal by System Organ Class and Preferred Term, Safety Population, Pooled Trials SWIFT-1 and SWIFT-2

Study	Age/Sex/Race	Preferred Term	AE Severity	Action Taken	Treatment Related
SWIFT-1	57/F/White	Acute sinusitis	Moderate	Drug interrupted	N
SWIFT-1	50/F/White	Alanine aminotransferase increased	Moderate	Drug withdrawn	N
SWIFT-1	55/M/White	Grief reaction	Mild	Drug withdrawn	N
SWIFT-1	73/M/Asian	Myasthenia gravis	Moderate	Drug withdrawn	N
SWIFT-2	67/F/White	Alanine aminotransferase abnormal	Severe	Drug withdrawn	N
		Alanine aminotransferase increased	Severe	Drug withdrawn	N
		Blood bilirubin abnormal	Severe	Drug withdrawn	N
SWIFT-2	72/F/White	Metastases to peritoneum	Life-Threatening	Drug withdrawn	N
		Ovarian cancer	Life-Threatening	Drug withdrawn	N

Source: adae.xpt; Software: R
Duration is 52 weeks.
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Severity as rated by investigator. Severity increased to “Life-threatening” in cases where AESLIFE (life-threatening flag) is Y.
Treatment-related as determined by investigator.
Note: The SWIFT-2 depemokimab participant who experienced AEs of ovarian cancer and metastases to the peritoneum also withdrew from the study.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PT, preferred term; Q1, first quartile; Q3, third quartile; SAE, serious adverse event; SD, standard deviation.

9.5.4. Severe Adverse Events

Table 19 presents severe adverse events more common than placebo by SOC and PT. See Figure 47 for definitions of adverse event severity.

The overall incidence of severe AEs was higher in the placebo treatment group with asthma as the most common PT overall. Most severe AEs occurred as single events, thus there was no definitive pattern among severe AEs in the depemokimab group. Additional analysis by SOC, OCMQ (narrow), and PT did not demonstrate any patterns in the depemokimab group (Table 76).

Table 19. Severe Adverse Events More Common Than Placebo by System Organ Class and Preferred Term, Pooled Safety Population, SWIFT-1 and SWIFT-2

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference (%) (95% CI)
Any severe AE	19 (3.8)	22 (8.4)	-4.6 (-8.9, -1.2)*
Eye disorders (SOC)	1 (0.2)	0	0.2 (-1.3, 1.1)
Rhegmatogenous retinal detachment	1 (0.2)	0	0.2 (-1.3, 1.1)
Gastrointestinal disorders (SOC)	1 (0.2)	1 (0.4)	-0.2 (-2.0, 0.8)
Abdominal pain	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatobiliary disorders (SOC)	2 (0.4)	0	0.4 (-1.1, 1.4)
Cholecystitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Cholecystitis acute	1 (0.2)	0	0.2 (-1.3, 1.1)
Infections and infestations (SOC)	5 (1.0)	6 (2.3)	-1.3 (-4.0, 0.5)
Bronchiolitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Injury, poisoning and procedural complications (SOC)	2 (0.4)	2 (0.8)	-0.4 (-2.4, 0.8)
Accidental exposure to product	1 (0.2)	0	0.2 (-1.3, 1.1)
Investigations (SOC)	1 (0.2)	0	0.2 (-1.3, 1.1)
Alanine aminotransferase abnormal	1 (0.2)	0	0.2 (-1.3, 1.1)
Alanine aminotransferase increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Aspartate aminotransferase increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Blood bilirubin abnormal	1 (0.2)	0	0.2 (-1.3, 1.1)
Blood bilirubin increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Gamma-glutamyltransferase increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Musculoskeletal and connective tissue disorders (SOC)	3 (0.6)	2 (0.8)	-0.2 (-2.2, 1.1)
Myalgia	1 (0.2)	0	0.2 (-1.3, 1.1)
Rotator cuff syndrome	1 (0.2)	0	0.2 (-1.3, 1.1)
Tenosynovitis stenosans	1 (0.2)	0	0.2 (-1.3, 1.1)

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference (%) (95% CI)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2 (0.4)	0	0.4 (-1.1, 1.4)
Metastases to peritoneum	1 (0.2)	0	0.2 (-1.3, 1.1)
Ovarian cancer	1 (0.2)	0	0.2 (-1.3, 1.1)
Small intestine adenocarcinoma	1 (0.2)	0	0.2 (-1.3, 1.1)
Nervous system disorders (SOC)	2 (0.4)	1 (0.4)	0.0 (-1.8, 1.1)
Epilepsy	1 (0.2)	0	0.2 (-1.3, 1.1)
Headache	1 (0.2)	0	0.2 (-1.3, 1.1)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Includes AE records assessed by investigator as "Severe" and also includes 3 records that are not labelled "Severe" but are labelled life-threatening.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Note: the clinical data scientist re-categorized 3 AEs (COVID-19, bilateral ovarian cancer, peritoneal metastases) from 2 depemokimab participants as severe and worse as they were also considered life-threatening SAEs by the Applicant. These AEs were originally categorized as mild and moderate severity, respectively, by the Applicant.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

9.5.5. Common On-Treatment Adverse Events

Table 20 summarizes the on-treatment AEs that occurred in at least 4% of subjects and were more common than placebo. Common AEs included allergic rhinitis, pharyngitis, upper respiratory tract infection, arthralgia, and influenza. Of these, allergic rhinitis, pharyngitis, and upper respiratory tract infection had a more notable difference in frequency whereas other aforementioned AEs were slightly more common in the depemokimab group. In SWIFT-1, influenza was observed more frequently in the depemokimab group, though this difference was attenuated in the pooled analysis. Moreover, the difference in allergic rhinitis among groups was more pronounced in SWIFT-2. Further, the predominance of upper respiratory tract infection in depemokimab participants was more notable in SWIFT-2 and the PT of arthralgia was only present in SWIFT-2. In comparison with mepolizumab, only the PT of influenza was shared between the depemokimab and mepolizumab asthma trials.

No additional AEs of interest were captured based on review of adverse events by SOC and PT occurring in at least 1% of depemokimab subjects and more common than placebo (Table 77). Evaluation by SOC, OCMQ (narrow), and PT identified a notable risk difference in the OCMQ arthritis though not meeting the 4% incidence threshold (Table 78). Additional in-depth analysis of this OCMQ (Table 79) revealed a range of PTs with different underlying etiologies (e.g., gout, osteoarthritis, rheumatoid arthritis), none of which occurred with frequency >1%, and most events occurred in participants ≥48 years-old, an age range during which arthritis may be more common overall in the general population. Arthritis is also not expected clinically based on depemokimab's mechanism of action and was not observed at an incidence of ≥3% and more common than placebo in the mepolizumab pivotal asthma trials. Based on this rationale, arthritis was not included as an adverse reaction in the Prescribing Information (PI) for depemokimab.

Table 20. Common Adverse Events Occurring at ≥4% Frequency and Greater Than Placebo, Safety Population, Pooled Trials SWIFT-1 and SWIFT-2

Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Any AE	362 (72.3)	198 (75.9)	-3.6 (-9.9, 3.1)
Upper respiratory tract infection	46 (9.2)	20 (7.7)	1.5 (-2.9, 5.4)
Rhinitis allergic	29 (5.8)	7 (2.7)	3.1 (-0.1, 5.9)
Influenza	24 (4.8)	11 (4.2)	0.6 (-2.9, 3.5)
Arthralgia	19 (3.8)	8 (3.1)	0.7 (-2.4, 3.3)
Pharyngitis	18 (3.6)	3 (1.1)	2.4 (-0.0, 4.7)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Coded as MedDRA preferred terms.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

9.5.6. Laboratory Findings

Laboratory evaluation consisted of clinical chemistry, hematology, and urinalysis parameters per the schedule of assessments (Table 65). Outlier analysis of chemistry laboratory studies in the pooled safety population did not identify any clinically notable findings. There was one depemokimab participant with a medical history of diabetes who had an SAE of hypoglycemia. Consistent with the mechanism of action, serum eosinophil levels were reduced in subjects in the depemokimab group compared to the placebo group starting at Week 2 (first measured timepoint). Accordingly, a greater incidence of low total leukocytes was observed in the depemokimab arm. Further, there were no clinically significant urinalysis findings for the depemokimab treatment group compared to the placebo treatment group.

Of note, based on the pharmacodynamic effect of depemokimab on serum eosinophil count, the site staff and Applicant were blinded to the absolute and differential value for eosinophil, lymphocyte, basophil, neutrophil, and monocyte levels post-randomization for each subject. However, total white blood cell counts were not blinded. While recognition of a lower total leukocyte in the depemokimab treatment group may have led to the potential for unblinding, the clinical reviewer attributes this risk to be low. For SWIFT-1, the Applicant also notes that due to the late provision of updated requisition forms from Amendment 1, clinical chemistry studies were not completed for 120 participants at Visit 16.

In addition, in the SWIFT-2 clinical study report errata, the Applicant notes that the total leukocyte counts were processed by the laboratory, but not reported to the investigators or Applicant, included in the central laboratory dataset, or statistical analysis for SWIFT-2. This occurred in 5 samples across 3 placebo and 1 depemokimab treated participants in Japan and the United States. The total leukocyte counts were within normal limits and therefore do not impact the laboratory associated safety results.

9.5.7. Assessment of Drug-Induced Liver Injury

Liver Chemistry

Liver chemistry stopping criteria were consistent with the FDA Guidance for Industry *Drug-Induced Liver Injury – Premarketing Clinical Evaluation* (July 2009). Cases meeting liver chemistry stopping criteria were reported within 24 hours and were also reviewed by the Applicant's Hepatic Safety Panel. Possible Hy's law cases were reported as an SAE. Resumption or rechallenge with IMP after liver chemistry stopping criteria were met was prohibited.

In SWIFT-1 and SWIFT-2 trials, the incidences of elevated liver biochemistry laboratory values were generally comparable between the depemokimab treatment group and placebo treatment group (Table 21). The single depemokimab subject with alanine aminotransferase (ALT) >10 x upper limit of normal (ULN) was diagnosed with hepatitis E based on serology. There was a marginally elevated incidence of Temple's corollary in depemokimab participants, but no potential cases of Hy's law (Table 22). Of note, the imbalance in Temple's corollary was not present in the Applicant's CRSwNP trials, ANCHOR-1/2 (b) (4) .

Regarding liver monitoring and liver stopping criteria across both trials, six depemokimab subjects required increased liver monitoring and 5 depemokimab subjects reached liver stopping criteria. In SWIFT-1, the Applicant reports that one of the aforementioned depemokimab subjects who met liver monitoring criteria (ALT ≥3) at Week 52 was not recorded in the eCRF. Review of case narratives of depemokimab subjects meeting liver stopping criteria in SWIFT-1 and SWIFT-2 trials demonstrated possible alternative etiologies for liver abnormalities and an inability to adhere to liver monitoring in one SWIFT-1 participant.

In review of liver stopping events and AEs leading to treatment discontinuation, treatment interruption, or study withdrawal, 2 depemokimab subjects in SWIFT-1 who met liver stopping criteria are not accounted for in Table 18 likely due to meeting criteria based on local, rather than central, laboratory results. In SWIFT-2, one depemokimab participant who was diagnosed with Hepatitis E is not reflected in Table 18, but met liver stopping criteria after receiving the second depemokimab dose.

Overall, no potential drug-induced liver injury safety signal was identified as elevated levels of liver biochemistry values were similar between treatment arms, the imbalance in incidence of Temple's corollary seen in asthma participants was not identified for the CRSwNP indication, there were no potential cases of Hy's law, and other possible etiologies or causes for meeting liver stopping criteria were identified.

Table 21. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Upper Limit of Normal, Pooled Safety Population, SWIFT-1 and SWIFT-2

Laboratory Parameter	Depemokimab N=501 n/N_w (%)	Placebo N=261 n/N_w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	11/501 (2.2)	4/258 (1.6)	0.6 (-1.9, 2.6)
Level 2 (>2X ULN)	3/501 (0.6)	0/258 (0)	0.6 (-0.9, 1.7)
Level 3 (>3X ULN)	0/501 (0)	0/258 (0)	0.0 (-1.5, 0.8)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	9/500 (1.8)	1/258 (0.4)	1.4 (-0.5, 3.1)
Level 2 (>5X ULN)	2/500 (0.4)	1/258 (0.4)	0.0 (-1.8, 1.1)
Level 3 (>10X ULN)	1/500 (0.2)	0/258 (0)	0.2 (-1.3, 1.1)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	5/500 (1.0)	0/258 (0)	1.0 (-0.5, 2.3)
Level 2 (>5X ULN)	2/500 (0.4)	0/258 (0)	0.4 (-1.1, 1.4)
Level 3 (>10X ULN)	0/500 (0)	0/258 (0)	0.0 (-1.5, 0.8)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	6/501 (1.2)	4/258 (1.6)	-0.4 (-2.8, 1.3)
Level 2 (>2X ULN)	1/501 (0.2)	2/258 (0.8)	-0.6 (-2.6, 0.5)
Level 3 (>3X ULN)	1/501 (0.2)	0/258 (0)	0.2 (-1.3, 1.1)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot…"
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Note: Subject counts are cumulative for each abnormality threshold.
Note: One depemokimab subjects in SWIFT-1 met liver stopping criteria based on local laboratory results and is therefore not included in the table (ALT 2095 IU/L [reference range 8-53 IU/L] and total bilirubin 211 µmol/L [reference range 5-24 pmol/L]). The case narrative revealed a diagnosis of Hepatitis A and adjudicated as unrelated to study drug by the Applicant's Hepatic Safety Panel. An additional depemokimab subject in SWIFT-1 also met liver stopping criteria based on local laboratory results (ALT 532.4 IU/L [reference range 0-35 IU/L] and total bilirubin 140.6 µmol/L [reference range 0-21 pmol/L]). The case narrative revealed a diagnosis of bile duct stones and adjudicated as unrelated to study drug by the Applicant's Hepatic Safety Panel. Further, there was one depemokimab subject in SWIFT-2 who met liver stopping criteria based on local laboratory results (ALT 835 U/L [reference range 10-41 U/L] and total bilirubin 3.1 mg/dL [reference range 0.2-1.2 mg/dL]). The case narrative revealed a diagnosis of autoimmune hepatitis post-study and adjudicated as unlikely to study drug by the Applicant's Hepatic Safety Panel.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 22. Potential Hepatocellular DILI Screen, Pooled Safety Population, SWIFT-1 and SWIFT-2

Quadrant	Depemokimab N=501 n/N_w (%)	Placebo N=261 n/N_w (%)
Potential Hy's Law (right upper)	0/500 (0)	0/258 (0)
Cholestasis (left upper)	1/500 (0.2)	2/258 (0.8)
Temple's corollary (right lower)	11/500 (2.2)	1/258 (0.4)
Total	12/500 (2.4)	3/258 (1.2)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.
The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

9.5.8. Vital Signs

No clinically significant changes in vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) were observed for SWIFT-1 and SWIFT-2 based on time-trend analysis, box plots, and outlier analysis. In general, no treatment effect on vital signs was observed.

ECGs

ECGs were obtained according to the timepoints in Table 65. The 12-lead ECG machine read values were used at Weeks 0 and Week 26 whereas the 12-lead ECG central over-read were used at all other timepoints. In SWIFT-1, there was a single depemokimab participant with an SAE event of atrial fibrillation which was recovered/resolved and in SWIFT-2, there was an additional depemokimab subject who experienced an epileptic seizure, though of non-cardiac origin based on a normal ECG. Overall, no AE-related treatment effects on ECG were noted in depemokimab participants. See Section 9.5.9 for evaluation of QTc.

9.5.9. Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) that were prospectively captured in the trials included allergic (Type 1 hypersensitivity) reactions including anaphylaxis or other systemic reactions, Type III hypersensitivity reactions (immune complex disease/vasculitis), local injection site reactions, and QTc prolongation. Given the Warnings and Precautions for herpes zoster infection in the mepolizumab label, herpes infection and herpes zoster were evaluated as an additional AESI for this review. Hypersensitivity reactions are discussed separately under Section 9.6 Key Safety Review issues below.

QTc Prolongation

The QT interval for each subject was corrected using Fridericia's formula (QTcF). At Screening Visit 1, subjects with QTcF ≥450 msec or QTcF ≥480 msec with bundle branch block in the 12-lead ECG central over-read were excluded. Stopping criteria included QTcF >500 msec or uncorrected QT >600 msec, and a change from baseline of QTcF > 60 msec. In subjects with underlying bundle branch block and baseline QTcF <450 msec or 450-480 msec, discontinuation was advised if QTcF was >500 msec and ≥530 msec, respectively.

No safety signal was observed for QTc prolongation. The majority of subjects had a decrease, no change, or increase of ≤450 msec and increase from baseline of ≤30 msec in QTcF (Table 80, Table 81). A single depemokimab subject in SWIFT-1 (Screening QTcF 449 msec, Visit 1 QTcF 459 msec) had an increase in QTcF to 513 msec at Week 28. However, the subject had a left bundle branch block due to a cardiac pacemaker and therefore did not meet QTcF stopping criteria.

Herpes Infection

Review of all adverse event participant listings for SWIFT-1/2 identified a single depemokimab participant in SWIFT-1 and no depemokimab subjects in SWIFT-2 with the PT 'herpes zoster'. In

comparison, there were 2 placebo subjects with the PT of 'herpes zoster infection neurological' and 'herpes zoster' in SWIFT-1 and one placebo participant in SWIFT-2 with the PT 'herpes zoster'. The overall incidence of 'herpes zoster' was 0.2% (1) and 0.8% (2) in the depemokimab and placebo treatment arms, respectively (data not shown).

There was an additional depemokimab participant in SWIFT-1 with two instances of the PT 'post-herpetic neuralgia' and one depemokimab participant in SWIFT-2 with the PT 'herpes virus infection', which are not included within the PT of 'herpes zoster', but do not alter the safety conclusion.

Based on this assessment, there was no apparent increased risk for herpes infection or herpes zoster in depemokimab-treated subjects in the asthma development program.

9.5.10. Subgroup Analyses

Additional analyses in the pooled safety population were conducted by age, sex, region, race, and ethnicity to assess for potential safety imbalances. AEs among Asian subjects were more common in the depemokimab treatment group than the placebo treatment group, which may be due to the higher depemokimab exposure levels seen in Asian subjects (see Section 10.1.3). Although there was a higher risk difference for AEs among adolescents who received depemokimab compared to those who received placebo, this was due to the lower incidence of AEs in the placebo-treated subjects as the actual frequency of any AE was similar across all depemokimab-treated subjects regardless of age (Table 23).

Table 23. Overview of Adverse Events by Demographic Subgroup, Safety Population, Pooled Trials SWIFT-1 and SWIFT-2

Characteristic	Depemokimab N=501 n/N_S (%)	Placebo N=261 n/N_S (%)	Risk Difference % (95% CI)
Sex			
Female	228/303 (75.2)	124/161 (77.0)	-1.8 (-9.6, 6.7)
Male	134/198 (67.7)	74/100 (74.0)	-6.3 (-16.7, 4.9)
Age group, years			
12 to 17	11/15 (73.3)	9/15 (60.0)	13.3 (-20.7, 44.7)
18 to 64	254/353 (72.0)	145/185 (78.4)	-6.4 (-13.7, 1.4)
≥65	97/133 (72.9)	44/61 (72.1)	0.8 (-12.0, 15.0)
Age group ≥75, years			
≥75	14/22 (63.6)	9/11 (81.8)	-18.2 (-45.0, 17.0)
Race			
American Indian or Alaska Native	1/2 (50.0)	1/1 (100)	-50.0 (-93.1, 64.2)
Asian	84/90 (93.3)	38/43 (88.4)	5.0 (-4.8, 18.5)
Black or African American	12/22 (54.5)	10/14 (71.4)	-16.9 (-45.1, 16.4)
White	265/387 (68.5)	148/201 (73.6)	-5.2 (-12.6, 2.7)
Multiple	0/0 (NA)	1/2 (50.0)	NA

Characteristic	Depemokimab N=501 n/N_s (%)	Placebo N=261 n/N_s (%)	Risk Difference % (95% CI)
Ethnicity			
Hispanic or Latino	28/57 (49.1)	19/31 (61.3)	-12.2 (-32.4, 9.7)
Not Hispanic or Latino	334/444 (75.2)	179/230 (77.8)	-2.6 (-9.1, 4.3)
Is in United States			
United States	75/123 (61.0)	46/64 (71.9)	-10.9 (-24.2, 3.7)
Non-United States	287/378 (75.9)	152/197 (77.2)	-1.2 (-8.3, 6.3)

Source: adae.xpt; Software: R
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

9.6. Key Safety Review Issues

9.6.1. Safety of YTE Modification in Pregnancy

Issue

Depemokimab is a novel, chronically administered YTE-modified IgG1 monoclonal antibody targeting IL-5 with a prolonged half-life (administration once every 6 months). Though the IL-5 target is not unique, the effects of the YTE modification in pregnancy and on the developing fetus are unknown.

Background

Asthma is a chronic lower airway respiratory disease with severe asthma affecting approximately 10% and 2.5% of adults and children, respectively, and often requiring add-on biologic therapies (Brusselle and Koppelman 2022). Currently approved asthma biologics for patients ≥12 years-old are administered once every 2 weeks to once every 8 weeks. However, introduction of a YTE modification (M252Y/S254T/T256E) can improve half-life and prolong dosing intervals through its binding to the neonatal Fc receptor (FcRn). FcRn is mainly located on vascular endothelial cells and allows for the maternal transfer of IgG to the developing fetus.

There are two currently approved biologics with a YTE modification, clesrovimab and nirsevimab. Both are respiratory syncytial virus F protein-directed fusion inhibitors for the prevention of respiratory syncytial virus. Clesrovimab is approved for neonates and infants, while nirsevimab may be given in pediatric patients up to 24 months of age. In comparison to depemokimab, both bind to an exogenous target, and neither are chronically administered nor for use in pregnancy.

Assessment

Depemokimab is a humanized, monoclonal antibody (IgG1, kappa) that binds and inhibits interleukin-5 (IL-5), an integral cytokine involved in the growth, survival, differentiation, activation, and recruitment of eosinophils. It also contains a triple amino acid change (YTE modification) in the Fc region allowing for increased affinity for the FcRn, thereby prolonging its half-life.

The review team considered potential risks of the YTE modification and interaction with the FcRn in pregnancy related to neonatal placental transfer. The Division of Pediatrics and Maternal Health (DPMH) was consulted during the review of the BLA application.

In their consultation, the DPMH review team notes there are no nonclinical data related to pregnancy for depemokimab; however, nonclinical data for mepolizumab may be used given its similarity in mechanism of action. There were no overt nonclinical safety signals based on a mepolizumab enhanced PPND monkey study and there is no known reproductive risk associated with IL-5 inhibition as demonstrated by IL-5 deficient mice (see Section 16). Moreover, to determine the effect of the YTE-modification on fetal exposure, the Applicant developed an *in silico* placental transfer model in which the Applicant demonstrated that following the same single dose (10 mg/kg), the AUC and C_{max} of depemokimab in the fetus are about 40% and 130% higher, respectively, than that of mepolizumab[1]. In addition, the simulated depemokimab C_{max} value in the fetus is about 18% higher than that of the mother. The Applicant claims that the magnitude of increased fetal exposures with depemokimab were covered by PK and safety data from the mepolizumab enhanced PPND study. Review of pregnancies during depemokimab's entire clinical development program and literature reported pregnancies for other anti-IL-5 therapies(Jang et al. 2025) may suggest an association between anti-IL-5 monoclonal antibodies and spontaneous abortion. However, as noted by DPMH, limited information was provided in the depemokimab pregnancy case narratives and scientific observational studies regarding other risk factors for spontaneous abortion (e.g., asthma severity), hence 'the association between anti-IL-5 [monoclonal antibodies (mAbs)] and [spontaneous abortions (SABs)] is not clear'.

Based on the uncertainties and available data, the review team included labeling language to inform prescribers about the potential for higher and prolonged exposure to the fetus and infant via placental transfer if used during pregnancy in the highlights, section 8 and section 17 of the USPI (see Section 21) and a PMR for a DPSS to determine the effect of the YTE modification on placental transfer, fetal developmental, and adverse pregnancy outcomes (Section 22). Additional PMRs recommended by DPMH are also in Section 22.

Conclusion

The potential risks of the YTE modification of a chronically administered biologic in pregnancy and fetal and infant development is unknown, but can be mitigated with the aforementioned labeling changes and a postmarketing requirement.

[1] \\CDSESUB1\EVSPROD\bla761458\0047\m1\us\111-information-amendments\response-ir-17oct2025.pdf

9.6.2. Systemic and Hypersensitivity Reactions

Issue

(b) (4)

Background

The Applicant prospectively captured allergic (Type I hypersensitivity) reactions including anaphylaxis or 'other systemic reactions' as an AESI. Allergic/systemic reactions, Type III hypersensitivity reactions, and local injection site reactions considered related to or temporarily associated with IMP were documented on dedicated eCRFs. The protocol-defined criteria for these reactions were as follows:

Anaphylaxis

Anaphylaxis criteria was defined by the 2006 Joint National Institute of Allergy and Infectious Disease/ Food Allergy and Anaphylaxis Network Second Symposium on Anaphylaxis (Sampson et al. 2006); Table 24).

Table 24. Anaphylaxis Diagnostic Criteria

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:
1. Acute onset (minutes to several hours) of an illness with involvement of the skin, mucosal tissue, or both and at least one of the following a. Respiratory compromise (e.g., dyspnea, stridor, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., syncope, incontinence)
2. Two or more of the following that occur rapidly (minutes to several hours) after exposure to a likely allergen a. Skin-mucosal tissue involvement b. Respiratory compromise c. Reduced blood pressure or associated symptoms d. Persistent gastrointestinal symptoms
3. Reduced blood pressure after exposure to a known allergen (minutes to several hours) a. Infants and children: low systolic blood pressure (age specific) or >30% decrease in systolic blood pressure b. Adults: systolic blood pressure < 90 mm Hg or > 30% decrease from the individual's baseline

Source: Adapted from Sampson et al. (2006).

Type III Hypersensitivity Reactions

Symptoms of potential Type III hypersensitivity reactions included, but were not limited to, persistent rash, persistent fever, persistent fatigue, persistent muscle and joint pain, peripheral neuropathy, and laboratory abnormalities. Persistent symptoms were defined as those occurring for ≥2 days. As noted in Section 8.2.2, vasculitis was an exclusion criterion in the pivotal trials.

Other Systemic Reactions

The Applicant did not define criteria for 'other systemic reactions'. Rather, events that were considered systemic reactions were determined to be either allergic or 'other systemic reactions' and evaluated on whether or not they met anaphylaxis criteria.

Injection Site Reactions

The PTs that contributed to this AESI were 'injection site reaction', 'erythema', 'injection site pain', and 'pruritus'.

Assessment

As shown in Table 25, there were no cases of anaphylaxis or type III hypersensitivity reaction (immune complex disease/vasculitis) in SWIFT-1 and SWIFT-2 trials. There was a single SAE of anaphylaxis to loxoprofen sodium hydrate in the placebo treatment group; however, this was not categorized as an AESI. Incidence of general hypersensitivity reaction by OCMQ (narrow) was balanced between treatment arms (1.2% in depemokimab participants, 0.8% in placebo participants), but more common in the depemokimab cohort by narrow standardized MedDRA query (12% in depemokimab subjects and 7.3% in placebo subjects) likely attributable to the imbalance in allergic rhinitis. Although there was a slight numerical difference in 'other systemic reactions' between treatment groups, review of the case narratives for depemokimab participants noted that the events were non-specific (e.g., PTs headache, rash), immediate or delayed, mild-moderate severity, and primarily recovered/resolved, therefore, the small difference does not appear to be clinically relevant or reflective of a difference in what would be considered actual 'systemic reactions' from a clinical perspective.

The incidence of injection site reactions (e.g., erythema, edema, itching) were also comparable between groups, of mild severity, immediate or delayed, and all recovered/resolved. Although injection site reactions were uncommon, it is an expected adverse drug reaction that is informative to prescribers and therefore included within section 6 of the USPI.

Table 25. Subjects With Adverse Events of Special Interest, Safety Population, Pooled Trials SWIFT-1 and SWIFT-2

AESI Category	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Depemokimab vs Placebo Risk Difference (%) (95% CI)
Allergic Reactions not including Other Systemic Reactions or Anaphylaxis	0	0	0.0 (-1.5, 0.8)
Other Systemic Reactions	8 (1.6)	2 (0.8)	0.8 (-1.3, 2.5)
Systemic Reactions Meeting Anaphylaxis Criteria	0	0	0.0 (-1.5, 0.8)
Type III Hypersensitivity/Vasculitis	0	0	0.0 (-1.5, 0.8)
Injection Site Reactions	7 (1.4)	2 (0.8)	0.6 (-1.5, 2.2)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Adverse Events of Special Interest under each category as reported by the investigator.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Conclusion

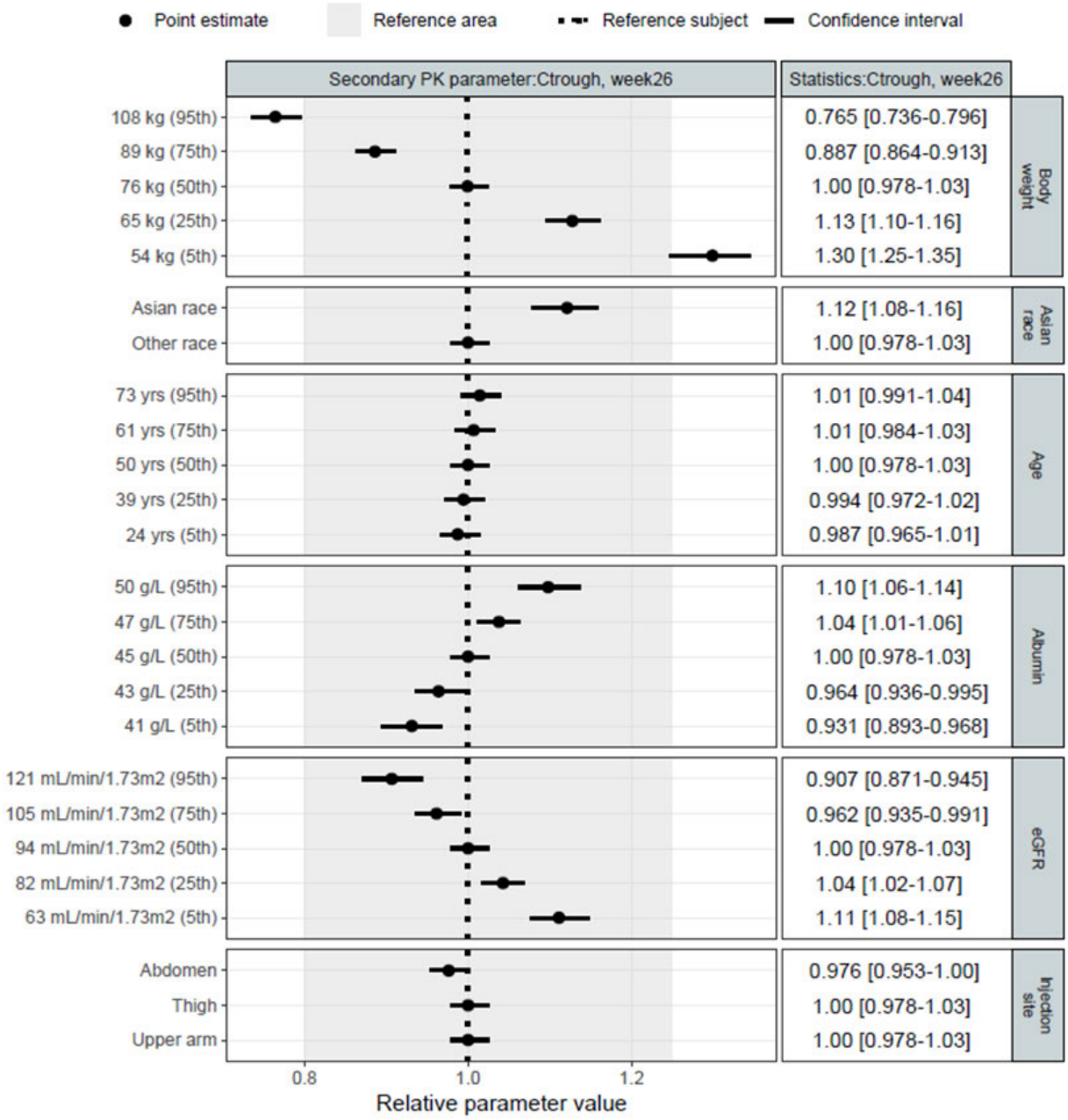
There was no safety signal for AESIs observed in depemokimab participants. Despite the lack of IgE-mediated/immediate hypersensitivity reactions, including anaphylaxis, among depemokimab participants in the SWIFT-1/2 trials, the potential for hypersensitivity reaction to occur was included within section 5 for class labeling purposes. Similarly, although the incidence of injection site reactions was low and nearly comparable among treatment arms, the risk was included within section 6 of the PI. (b) (4)

(b) (4)

10 Therapeutic Individualization

Based on both observed data and population PK analyses, intrinsic/extrinsic factors including age (≥ 12 years), race/ethnicity, and site of injection (upper arm, abdomen, or thigh), were not found to meaningfully influence the PK of depemokimab (Figure 5). Higher body weight subjects were found to have a lower depemokimab systemic exposure relative to those with lower body weight, although this PK difference did not appear to confer a clinically significant impact on efficacy. No dosage adjustments are recommended based on any intrinsic or extrinsic factors. For additional details regarding the Applicant's population PK model, refer to Section 17.4.1.

Figure 5. Univariate Forest Plot Illustrating Covariate Effects on Depemokimab Steady-State $C_{trough,W26}$ Compared to a Reference Subject[a,b]



Source: Adapted from Population PK Report REP-1-PK-GSK-FTE1-DEPE-PMX-1 (Figure 15, pg. 67)
[a] Closed dots represent the median of the predicted relative change from the reference subject. The 90% CIs associated with the medians are visualized by the error bars. The specific values of the medians and 90% CIs are shown in the Statistics box on the right-hand side of the parameter; these values are calculated based on 250 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided below the plot) are shown by the dotted vertical line; the shaded area indicates the 80-125% margins relative to the reference subject and are based on the standard bioequivalence limits.
[b] Reference subject defined as a 76 kg, 50 years, non-Asian asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 94 mL/min/1.73m2, receiving a dose of depemokimab 100 mg into the upper arm
Abbreviations: $C_{trough,W26}$, plasma trough concentration at W26; CI, confidence interval; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; W26, Week 26

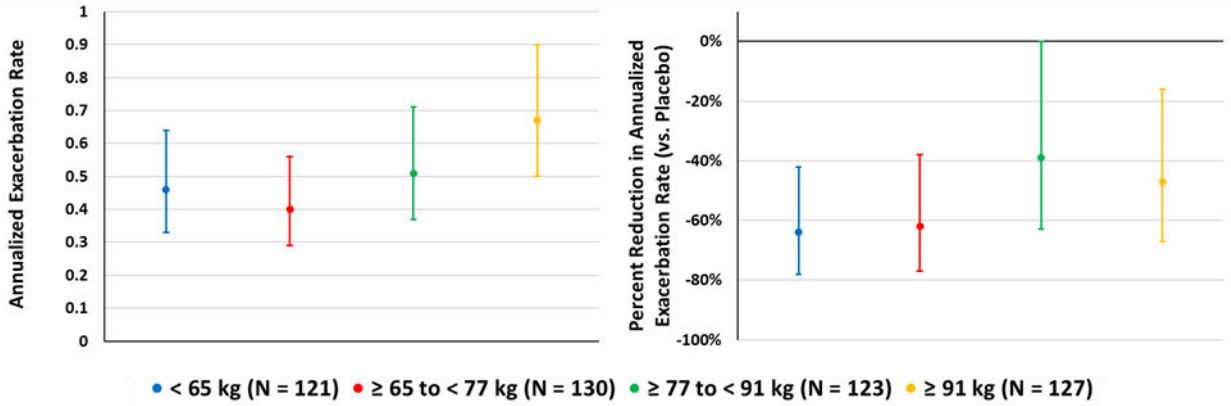
10.1. Intrinsic Factors

10.1.1. Body Weight

In the Applicant's population PK analysis, body weight was identified as a statistically significant covariate impacting both the clearance and volume of distribution (V_d) of depemokimab. In general, a higher depemokimab exposure was observed in subjects with lower body weight. Based on population PK analysis, the median steady-state $C_{trough,W26}$ in a subject weighing 54 kg and 108 kg (5^{th} and 95^{th} percentiles, respectively, in the observed dataset) is predicted to be approximately 30% higher and 24% lower, respectively, relative to the reference steady-state $C_{trough,W26}$ of a typical patient weighing 76 kg (Figure 5).

To assess the potential impact of body weight on efficacy in patients with asthma, efficacy data obtained from the pivotal SWIFT-1/2 trials were analyzed as a function of body weight. In both studies, a single dosage regimen of depemokimab 100 mg SC Q6M was investigated over a 52-week double-blind treatment period. The primary efficacy endpoint was the annualized rate (i.e., over 52 weeks) of clinically significant exacerbations. As demonstrated below in Figure 6, there was a slight trend of a higher annualized clinically significant exacerbation rate with increasing body weight group from quartiles 2 through 4, with the lowest treatment effect observed for the highest body weight quartile. However, after adjusting for placebo, clinically significant exacerbation rate was favorable for depemokimab across all body weight groups, suggesting that the observed difference in systemic exposure based on body weight did not result in a clinically meaningful reduction in treatment effect.

Figure 6. Annualized Clinically Significant Exacerbation Rate (Left)[a] and Percent Reduction Relative to Placebo (Right)[b] for Depemokimab-Treated Subjects, Stratified by Baseline Body Weight (SWIFT-1/2 Pooled Population)



Source. Generated by reviewer based on ISE - Asthma (Table 2.11, pg. 663-666)
[a] Solid circles represent the annualized clinically significant exacerbation rate in depemokimab-treated subjects; Vertical bars represent the 95% CI
[b] Solid circles represent the percent reduction in annualized clinically significant exacerbation rate in depemokimab-treated subjects compared to placebo; Vertical bars represent the 95% CI
Abbreviations: CI, confidence interval; ISE, integrated summary of efficacy; N, number of subjects

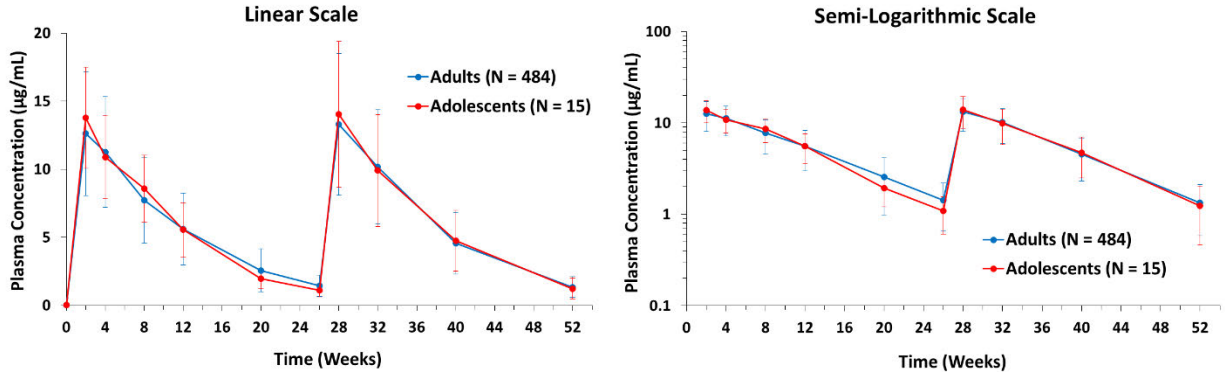
10.1.2. Age

Overall, no dosage adjustments are recommended based on age.

The proposed population for depemokimab includes adolescent subjects with severe asthma with an eosinophilic phenotype aged 12 years and older. Adolescents with asthma were enrolled in the 52-week pivotal efficacy and safety clinical studies SWIFT-1 (N = 8) and SWIFT-2 (N = 22), as well as the OLE study AGILE (N = 22 rollover subjects from SWIFT-1/2). Depemokimab PK and PD (i.e., blood eosinophil count) were assessed in both SWIFT-1/2 studies, although only PD was evaluated in AGILE. In total, PK data are available for 15 depemokimab-treated adolescents from the pooled SWIFT-1/2 population. PD data are available for 30 adolescents from the SWIFT-1/2 trials (N = 15 depemokimab and N = 15 placebo) as well as 22 adolescents from AGILE (including N = 11 previous depemokimab and N = 11 previous placebo rollover subjects from SWIFT-1/2 studies).

As discussed above in Section 10.1.1, a higher depemokimab exposure was generally associated with lower body weight. Across both SWIFT-1/2 trials, a slightly lower median (range) body weight was observed among depemokimab-treated adolescents (72.3 [39.7, 141.0] kg) compared to adults (77.0 [34.6, 161.0] kg). Overall, depemokimab PK profile is similar between adolescents and adults throughout the 52-week treatment period (Figure 7).

Figure 7. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile Following 100 mg SC Q6M Dosing: Adults Versus Adolescents (SWIFT-1/2 Pooled PK Population)



Source: Reviewer's analysis based on adpc.xpt for Studies 206713 and 213744
Abbreviations: PK, pharmacokinetic; Q6M, every 6 months; N, number of subjects; SC, subcutaneous; SD, standard deviation

Using the final population PK model, the Applicant derived key secondary steady-state PK parameters for the SWIFT-1/2 patient population according to age group (Table 26). Notably, absorption rate was found to be significantly associated with age, such that a slower rate of absorption was exhibited for older patients. This is reflected by the predicted earlier time to maximum plasma concentration (T_{max}) in adolescents compared with those ≥ 18 years of age. There was also a slight trend of reduced predicted C_{trough} with lower age, with a ~16% and 25% lower C_{trough} predicted for adolescents relative to adults aged 18 to 64 and elderly subjects ≥ 65 years of age, respectively. However, in general, model-predicted depemokimab exposure (C_{trough}, AUC_{tau}, and maximum plasma concentration [C_{max}]) in adolescents is comparable to and within the range of that in adults.

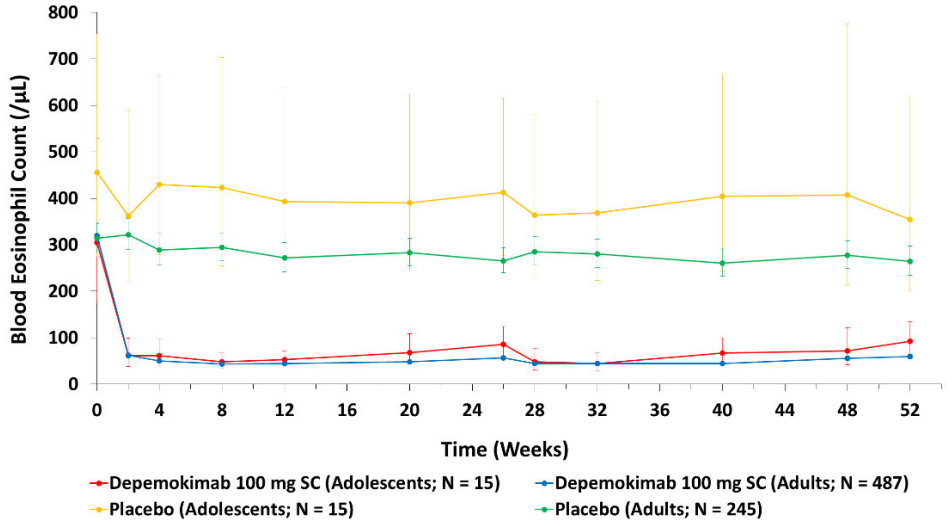
Table 26. Population PK Model-Derived Key Steady-State Secondary PK Parameters for Depemokimab According to Age (SWIFT-1/2 Pooled PK Population)

PK Parameter[a]	12-17 Years (N=15)	18-64 Years (N=352)	≥65 Years (N=127)	Overall (N=494)
$AUC_{tau,ss}$ (µg*day/mL)	1051 (31.18)	1068 (28.34)	1121 (25.46)	1081 (27.75)
$C_{av,ss}$ (µg/mL)	5.77 (31.18)	5.87 (28.34)	6.16 (25.46)	5.94 (27.75)
$C_{max,26-52}$ (µg/mL)	14.58 (30.44)	13.60 (28.49)	13.59 (25.14)	13.63 (27.69)
$T_{max,26-52}$ (day)	10.83 (8.75)	13.17 (16.47)	15.22 (15.83)	13.59 (17.80)
$C_{trough,W52}$ (µg/mL)	1.08 (39.32)	1.28 (39.02)	1.45 (34.12)	1.32 (38.37)
$t_{1/2}$ (day)	44.73 (8.578)	48.23 (9.802)	49.91 (8.432)	48.55 (9.645)

Source. Adapted from Summary of Clinical Pharmacology (Table 7, pg. 31)
[a] PK parameters reported as geometric mean (CV%)
Abbreviations: $AUC_{tau,ss}$, area under the plasma concentration-time curve from 0 to the end of the dosing interval at steady state; $C_{av,ss}$, average plasma concentration at steady state; $C_{max,26-52}$, maximum plasma concentration from W26 to W52; CV, Coefficient of Variation; PK, pharmacokinetic; N, number of subjects; $T_{max,26-52}$, time to C_{max} from W26 to W52; $C_{trough,W52}$, plasma trough concentration at W52; $t_{1/2}$, terminal elimination half-life; W26, Week 26; W52, Week 52

The geometric mean (95% CI) blood eosinophil count over time for adolescents and adults enrolled in the SWIFT-1/2 studies is shown below in Figure 8. Overall, the post-dose blood eosinophil count-time profiles were comparable between depemokimab-treated adults and adolescents, with overlapping 95% CIs at all timepoints, supporting a similar PD response between the two age groups. Similar findings were observed in the OLE study AGILE, which further supports comparable long-term PD response in adults and adolescents.

Figure 8. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Treatment Group: Adults Versus Adolescents (SWIFT-1/2 Pooled FAS Population)



Source: Reviewer's analysis based on adpd.xpt for Studies 206713 and 213744
Abbreviations: CI, confidence interval; FAS, full analysis set; N, number of subjects; SC, subcutaneous

For additional details on depemokimab PK/PD in adults and adolescents in SWIFT-1/2 and AGILE, refer to Sections 17.5.4 and 17.5.5, respectively. For additional details regarding the Applicant's population PK model, refer to Section 17.4.1.

10.1.3. Race/Ethnicity

Overall, no dosage adjustments are recommended based on race or ethnicity.

Based on a cross-study PK comparison, Study 208021 showed that depemokimab clearance in Chinese adults was approximately 22% lower when compared to the typical value, as reflected by the increased AUC, C_{max}, and terminal half-life observed for these subjects compared to other phase 1 studies (Table 27). Notably, this finding could not be fully explained by the influence of other covariates known to affect depemokimab PK, including body weight and plasma albumin levels. Therefore, additional exploration of the potential PK differences according to race between Asian and non-Asian subjects was conducted.

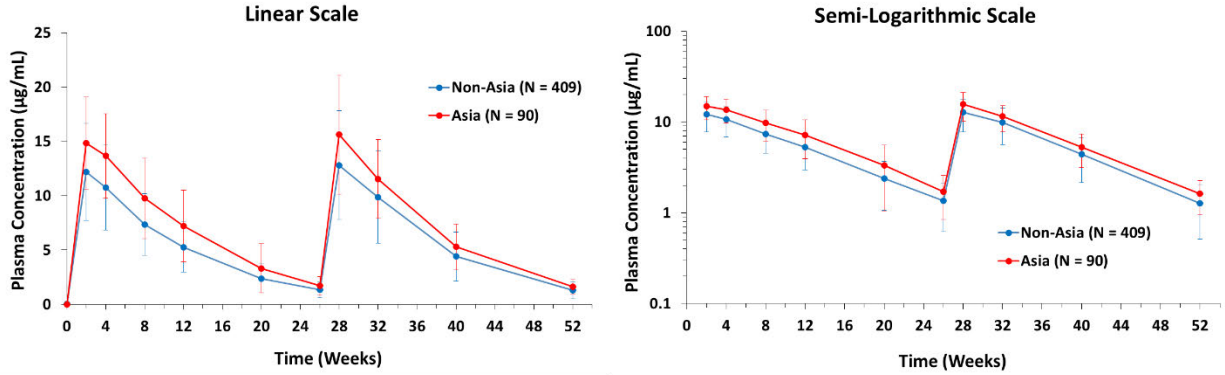
Table 27. Comparison of Depemokimab PK Parameters Between Study 208021 (Healthy Chinese Subjects) and Other Phase 1 Studies Following a Single SC Dose of 100 mg

PK Parameter[a,b]	Study 208021 (N=10)[c]	Study 205722 (N=9)[d]	Study 214099 (N=70)[e,f]
AUC_{inf} (day*µg/mL)	1685.9 (12.6)	846.7 (7.3)	1061.0 (26.9)
AUC_{last} (day*µg/mL)	1473.0 (12.6)	830.2 (7.4)	999.4 (26.1)
C_{max} (µg/mL)	16.82 (18.2)	12.25 (15.9)	14.68 (24.2)
CL/F (L/day)	0.0593 (12.6)	0.1181 (7.3)	0.0942 (26.9)
$t_{1/2}$ (day)	58.8 (8.1)	38.9 (11.7)	41.4 (24.5)
T_{max} (day)	14.0 (4.0, 28.0)	14.0 (4.0, 16.0)	13.0 (4.0, 28.9)
Vz/F (L)	5.0 (13.9)	6.6 (12.1)	5.6 (25.0)

Source. Reviewer's analysis based on adpp.xpt for Studies 208021, 205722, and 214099
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] PK parameters shown only for subjects who received a single dose of depemokimab 100 mg SC
[c] Study 208021 enrolled healthy adult Chinese subjects
[d] Study 205722 enrolled subjects with mild to moderate asthma with an eosinophilic phenotype (all subjects in 100-mg cohort were of white race)
[e] Study 214099 enrolled healthy adult subjects (SSD arm included N = 3 Asian subjects; all other subjects were non-Asian)
[f] PK parameters reported for the SSD arm, as the SSD device was used to administer depemokimab in Chinese PK study 208021
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC from 0 to last timepoint sampled; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; min, minimum; max, maximum; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution during the terminal phase.

Across the phase 3 program for the severe asthma, Asian, Black, and White race categories represented approximately 18%, 4%, and 77%, respectively, of the pooled SWIFT-1/2 PK population. The arithmetic mean (standard deviation [SD]) depemokimab plasma concentration-time profiles according to race for Asian versus non-Asian subjects in the pooled SWIFT-1/2 population are shown in Figure 9, which shows a slightly higher exposure at all timepoints in Asians compared to non-Asians.

Figure 9. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile Following 100 mg SC Q6M Dosing: Asian Versus Non-Asian Race (SWIFT-1/2 Pooled PK Population)[a]



Source. Reviewer's analysis based on adpc.xpt for Studies 206713 and 213744
[a] Asian race category includes subjects from China, Japan, Taiwan, and US
Abbreviations: N, number of subjects; PK, pharmacokinetic; Q6M, every 6 months; SC, subcutaneous; SD, standard deviation

As discussed above in Section 10.1.1, a higher depemokimab exposure was associated with lower body weight. In the pooled SWIFT-1/2 population, the mean (SD) body weight among depemokimab-treated Asian subjects was 63.7 (13.6) kg compared with 82.5 (19.1) kg in non-Asians. The higher exposure observed in Asian subjects in the pivotal SWIFT-1/2 trials is likely attributed primarily to the lower baseline body weight among individuals of Asian descent compared with non-Asians, though other unknown contributing factors cannot be excluded.

The Applicant also used the final population PK model to derive secondary PK parameters as a function of race based on the integrated PK populations from the phase 3 programs for severe asthma and CRSwNP, in which all subjects received the (b) (4) dosage of depemokimab 100 mg SC Q6M (Table 28). Based on this population PK analysis, the predicted geometric mean AUC_{tau}, C_{max}, and C_{trough} are approximately 14%, 11%, and 24% higher, respectively, for Asian subjects compared to the overall population, which is within the observed variability. Overall, the differences in depemokimab PK according to race are not expected to be clinically meaningful.

For additional details regarding the Applicant's population PK model, refer to Section 17.4.1. For additional details on depemokimab PK/PD across the clinical pharmacology program, refer to Section 17.5.

Table 28. Population PK Model-Derived Key Steady-State Secondary PK Parameters According to Race[a]

	Race Category					
PK Parameter[b]	Asian[c] (N=154)	Black (N=26)	White (N=578)	Asian-China (N=72)	Asian-Japan (N=70)	Overall (N=766)
$AUC_{tau,ss}$ (µg*day/mL)	1181 (27.64)	952.0 (31.72)	1001 (26.71)	1085 (25.15)	1280 (28.70)	1033 (28.06)
$C_{max,26-52}$ (µg/mL)	14.65 (27.79)	12.08 (31.37)	12.91 (26.99)	12.99 (24.18)	16.43 (27.19)	13.20 (27.90)
$C_{av,ss}$ (µg/mL)	6.489 (27.64)	5.231 (31.72)	5.502 (26.71)	5.959 (25.15)	7.033 (28.70)	5.674 (28.06)
$C_{trough,W52}$ (µg/mL)	1.497 (38.49)	1.138 (44.77)	1.150 (37.34)	1.452 (38.20)	1.540 (40.14)	1.211 (39.73)
$t_{1/2}$ (day)	49.80 (10.17)	48.02 (10.33)	46.96 (9.569)	51.26 (10.55)	48.49 (9.230)	47.54 (10.01)

Source. Adapted from Summary of Clinical Pharmacology (Table 9, pg. 47)
[a] All subjects received depemokimab 100 mg SC Q6M administered via SSD device presentation
[b] PK parameters reported as geometric mean (CV%)
[c] Asian race category includes subjects from China, Japan, Taiwan, and US; Additionally, race categories with low enrollment (N<10) are not presented (i.e., American Indian, Alaska Native, and Other). Therefore, the overall population is not a sum of all categories
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC from 0 to last timepoint sampled; $C_{av,ss}$, average plasma concentration at steady state; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; min, minimum; max, maximum; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution during the terminal phase.

10.1.4. Renal or Hepatic Impairment

No dedicated studies have been conducted to evaluate the impact of renal impairment or hepatic impairment on the PK of depemokimab, although these covariates were assessed using a population PK approach. Based on population PK analysis, renal impairment category (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m^2 [normal, N = 398]; eGFR ≥ 60 to < 90 mL/min/1.73 m^2 [mild, N = 336]; eGFR ≥ 30 to < 60 mL/min/1.73 m^2 [moderate, N = 30], and eGFR ≤ 30 mL/min/1.73 m^2 [severe, N = 2]) did not meaningfully impact the PK of depemokimab. Additionally, there was no association between depemokimab clearance and common biomarkers of liver function or damage, such as total bilirubin (1.7 – 42 µmol/L), ALT (5 – 153 IU/L), and aspartate aminotransferase (9 – 115 IU/L), in patients with asthma, although most values were within the normal range. There was a slight, albeit not clinically meaningful, association between serum albumin (41 to 50 g/L; 5th and 95th percentiles, respectively, in the observed dataset) and depemokimab systemic exposure.

For additional details regarding the Applicant's population PK model, refer to Section 17.4.1.

10.2. Extrinsic Factors

10.2.1. Site of Injection

Depemokimab may be administered via SC injection in either the upper arm, abdomen, or thigh.

The PK of depemokimab following single SC administration in the upper arm, abdomen, and thigh using both the proposed safety syringe device (SSD) and autoinjector (AI) device

presentations was evaluated in healthy subjects as part of the relative BA Study 214099. Comparable depemokimab exposure was observed for both device presentations, regardless of the site of injection. Refer to Section 17.5.2 for additional details pertaining to Study 214099.

10.2.2. Drug-Drug Interactions

Dedicated drug-drug interaction studies with depemokimab have not been conducted. Since depemokimab is a mAb and is eliminated by non-specific clearance pathways, direct drug-drug interactions via inhibition or induction of cytochrome P450 enzymes or transporters are not expected. Additionally, given that depemokimab is administered via SC injection, no food effect studies have been conducted and no impact of food on PK is expected.

10.3. Plans for Pediatric Drug Development

The Applicant has an agreed upon pediatric study plan entailing the inclusion of adolescents 12 to 17 years of age in the adult pivotal asthma trials (SWIFT-1 and SWIFT-2), a deferral of pediatric studies in patients 6 to 11 years of age, and a waiver in pediatric patients <6 years of age because studies would be highly impracticable or impossible in this age cohort.

(b) (4)

The Pediatric Research Equity Act PMR to be issued at the time of approval is detailed in Section 22.

10.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Pregnancy

Pregnancy information in female subjects was obtained from the start of study drug until 30 weeks following the last dose of study drug. There were two pregnancies in SWIFT-1, each occurring in one subject from the depemokimab and placebo treatment groups, respectively. Both pregnancies resulted in a live birth with no apparent congenital anomalies. In SWIFT-2, there was a single pregnancy in the placebo treatment group that resulted in a live birth with no apparent congenital anomalies. Review of case narratives by the clinical reviewer did not identify any major post-delivery neonatal complications, though assessment was limited based on details provided by the Applicant.

As described in Section 9.6.1, DPMH was consulted by the review team to provide recommendations regarding the safety of the YTE modification in the developing fetus and

infant when used in pregnancy. Based on review of nonclinical data from the similar anti-IL-5 biologic, mepolizumab, review of pregnancy cases during the depemokimab clinical development program, and a literature review, the safety of the YTE modification remained uncertain. To inform prescribers about the potential for higher and prolonged exposure to the fetus and infant via placental transfer if used during pregnancy, the review team included labeling language in the highlights, section 8 and section 17 of the USPI (Section 21) and the DPMH review team recommended a PMR for a DPSS (Section 22) (DARRTS Reference ID: 5633246, dated 7/29/2025).

Lactation

Based on the presence of maternal IgG in human breastmilk and depemokimab's drug class as an IgG1 kappa monoclonal antibody, potential transfer to a nursing infant is a consideration. There are no nonclinical or clinical data for the use of depemokimab during lactation and breastfeeding women were excluded from the SWIFT-1 and SWIFT-2 trials. In general, the DPMH review team asserts that the transfer of depemokimab to human milk and absorption by the breastfed infant is minimal based on nonclinical data of similar anti-IL-5 biologic levels in the breastmilk, its large molecular weight, and poor oral absorption. Nonetheless, based on the lack of data and its potential use in lactating women, the DPMH review team recommended a PMR for a clinical lactation study (milk only) to evaluate the depemokimab concentration in human breastmilk and associated effects on the breastfed infant (Section 22). See Section 21 for labeling related to risk of use in lactation.

Females/Males of Reproductive Potential

In the SWIFT-1 and SWIFT-2 trials, women of childbearing potential were required to use a highly effective method of contraception from at least 14 days prior to the first dose of study drug until at least 30 weeks after the last dose of study drug. Women of non-childbearing potential could be enrolled. The Applicant did not require male contraception based on depemokimab's purported limited potential to interact with genetic material or be present in the semen. Based on review of nonclinical data, drug-drug interaction studies, and a literature review, the DPMH review team concluded that depemokimab should not adversely affect fertility, impair the effectiveness of hormonal contraceptives, and is not genotoxic or carcinogenic. Accordingly, DPMH recommended omitting subsection 8.3 of the PI (see Section 21).

11 Product Quality

Approval With a Postmarketing Commitment

The Office of Pharmaceutical Quality (OPQ) review team has assessed BLA 761458 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this BLA from a quality perspective. The CMC

postmarketing commitment (PMC) and (any other postapproval quality agreements) between OPQ and the Applicant are listed in Section 22.

11.1. Device or Combination Product Considerations

The Center for Devices and Radiological Health has determined that the device constituent of the combination product is approvable for the proposed indication.

12 Human Subjects Protections/Good Clinical Practice Site Inspections/Financial Disclosure Review

Human Subject Protections

The Applicant states that the study protocols (including all amendments), informed consent form, and other relevant study documents were reviewed and approved by an Institutional Review Board and Institutional Ethics Committee prior to initiating the studies, and that the studies were conducted in accordance with the Declaration of Helsinki, US 21 CFR 312.120, and other national and local laws and regulations.

However, in SWIFT-1, Site 250190 was closed due to data integrity concerns and GCP violations and included 11 participants, all of whom were withdrawn from the study. These participants were excluded from the FAS and Safety Set. The Applicant excluded this participant data from the main safety and efficacy analyses, but provided supplementary efficacy analyses and safety results (a listing of AEs) that included these participants.

The Applicant was also informed by (b) (4) of GCP violations by (b) (4) a site management organization (SMO), involved with outside Sponsors. The SWIFT-2 sites associated with (b) (4) were Sites 250085 and 250523, which included a total of 12 participants. Site 250085 was closed prior to knowledge of the (b) (4) GCP violations, and 2 participants at this site were transferred to Site 250638, where their remaining assessments were completed. All participants at Site 250523 were considered lost to follow-up. As done for SWIFT-1, the Applicant excluded participant data from these sites from the main safety and efficacy analyses but provided supplementary efficacy analyses and safety results (a listing of AEs) that included these participants.

Additionally, 7 participants on depemokimab in SWIFT-2 who were enrolled at Site 251152 were determined to have no detectable study drug concentration (except at Visit 8, week 20) and no pharmacodynamic effect on serum eosinophils at any study timepoint; therefore, the Applicant conducted a post-hoc sensitivity analysis of the primary endpoint that excluded all participants at this site due to data integrity concerns and GCP violations to assess the potential impact on the results.

Further, in the NIMBLE clinical study report the Applicant notes that there was a GCP non-compliance issue for a SWIFT-2 site identified after database lock and unblinding. Data from

this site was included in all planned primary analyses based on when the data integrity issue was identified. Data from this site (1 participant randomized at site 250439) was therefore also included for the NIMBLE IA.

Clinical Study Report Errata

The Applicant notes a clinical study report errata (dated November 21, 2024 and November 25, 2024) in SWIFT-1 and SWIFT-2, respectively, related to a programming error affecting the post-hoc subgroup analysis of exacerbations by 13 week intervals. The errata were determined to be minor and the corrected data output was provided.

Further, the Applicant reported 8 and 14 IPDs in SWIFT-1 and SWIFT-2, respectively, following finalization of the clinical study report. Review of the additional IPDs in SWIFT-1 noted one depemokimab participant who discontinued study due to an unspecified adverse event and did not complete two required consecutive visits. In SWIFT-2, 2 depemokimab and 1 placebo participant used a prohibited concomitant medication, though the Applicant notes that there was no effect on the primary and secondary endpoints based on use of a treatment policy strategy for these intercurrent events. There was also one depemokimab subject who reached liver monitoring criteria (ALT >3 x ULN, 153 IU/L) that was not performed. The elevated ALT was noted on Day 1 with all subsequent ALT measurements <153 IU/L (range 38-112 IU/L).

Clinical Site Inspections

Four clinical sites in Spain and Poland across SWIFT-1 (sites 251016 and 250201) and SWIFT-2 (sites 259373 and 259220) were inspected due to high enrollment. At all sites, there were no discrepancies for the primary efficacy endpoint data in the paper source documents and the Applicant's data listings and no unreported adverse events. Based on the inspection results, the Office of Scientific Investigations concluded that the trials were conducted appropriately and the primary efficacy endpoint data were adequately reliable to support review for the asthma indication. Please refer to the Clinical Inspection Summary from the Office of Scientific Investigations, dated November 12, 2025 for the full evaluation (DARRTS Reference ID: 5694116).

Financial Disclosures

The Applicant disclosed financial interests/arrangements with clinical investigators consistent with the guidance for industry *Financial Disclosure by Clinical Investigators* (February 2013), and 21 CFR Part 54.4 (see Section 23). The investigator financial disclosures do not affect the data integrity nor the interpretability of the primary efficacy endpoint. Therefore, the results of the pivotal trials, and thus approvability of depemokimab, should not be impacted by the financial interests.

13 Advisory Committee Summary

This BLA application was not taken to an FDA advisory committee because there were no significant or unexpected safety or efficacy issues, and no controversial findings that would benefit from further discussion and recommendations from an advisory committee. Please refer to the Advisory Committee Decision Aid (DARRTS Reference ID: 5627668, dated July 25, 2025).

14 Associate Director for Therapeutic Review Comments

I concur with the Review Team's analyses, conclusions, and recommendation of **Approval** of this BLA.

Use in Special Populations - Pregnancy

Depemokimab is a novel YTE-modified IgG1 monoclonal antibody targeting IL-5 that is administered every 6 months due to its prolonged half-life (terminal half-life 48 days). The prolonged half-life results from the YTE modification in the Fc region that enhances binding to FcRn on endothelial cells. There are currently two approved biologics with YTE modifications, clesrovimab and nirsevimab, both for prevention of respiratory syncytial virus infections; clesrovimab has a terminal half-life of 71 days and nirsevimab has a terminal half-life of 44 days. Unlike depemokimab, both products target an exogenous protein (respiratory syncytial virus F protein), are not administered chronically, and are indicated for use in neonates and children up to 24 months.

The approval of depemokimab is the first approval of a YTE-modified therapeutic antibody intended for chronic use and recognizing an endogenous antigen. While the enhanced binding to the FcRn is beneficial in extending the half-life of depemokimab, it also facilitates maternal-fetal IgG transfer, especially in the third trimester, raising concerns about increased fetal exposure during pregnancy and prolonged exposure in infants exposed in utero. Based on data provided by the Applicant, but not confirmed by the Office of Clinical Pharmacology, in silico modeling demonstrates that depemokimab produces approximately 40% higher AUC and 130% higher C_{max} in the fetus compared to mepolizumab, with fetal C_{max} being 18% higher than maternal levels. While nonclinical data from similar IL-5 inhibitors, most notably mepolizumab, show no overt safety signals, depemokimab-specific pregnancy studies are lacking. Given these uncertainties, the Division of Pediatrics and Maternal Health recommended a postmarketing requirement for a descriptive pregnancy safety study to better characterize the effects of YTE modification on placental transfer and pregnancy outcomes.

Labeling

During the review and labeling discussions, I strongly favored inclusion of a Warning and Precaution (W&P) in Section 5 of the label to highlight the reasonable likelihood of increased fetal exposure, as well as prolonged exposure to depemokimab in infants exposed in utero and

the uncertain effects on the newborn. While nonclinical findings for mepolizumab are reassuring, given the availability of alternative biologics for use during pregnancy, including mepolizumab, and the absence of benefit to the newborn, I believe that the benefit-risk assessment for the mother and newborn is not favorable in many cases. While I do not advocate for a limitation of use in pregnancy, I do believe that a W&P is supported based on a potential risk, given uncertainty, and implications for prescribing decisions, specifically to adequately inform shared decision-making between providers and patients. I also proposed inclusion of language in the W&P to advise providers of infants with in utero exposure of the need for close observation given the likelihood of prolonged exposure to a biologic.

Based on discussions with the review team, office signatory, and DPMH, a W&P was not included. However, Section 8.1 (Pregnancy) of the label includes a description of potential increased and prolonged levels of depemokimab in infants with in utero exposure:

> Transport of endogenous IgG antibodies and monoclonal antibodies, such as depemokimab-ulaa, across the placenta increases as pregnancy progresses and peaks during the third trimester. The impact of the YTE modification on placental transfer is uncertain *[see Clinical Pharmacology (12.1)]*; however, the presence of the YTE modification may lead to prolonged and increased exposure of the infant exposed *in utero*, and the potential of clinical impact is unknown and should be considered. No treatment-related effects on embryofetal or postnatal development have been shown in animal studies targeting IL-5 signaling pathways *(see Data)*.

This information is further emphasized by inclusion of Use in Specific Populations in the HIGHLIGHTS OF PRESCRIBING INFORMATION:

> Pregnancy: EXDENSUR can cross the placenta during pregnancy and the presence of the YTE modification may prolong and increase exposure to the infant exposed in utero. The impact of EXDENSUR transmission to the fetus should be considered. (8.1)

In addition, Section 17 (PATIENT COUNSELING INFORMATION) includes language to advise patients of the uncertainty of clinical impact of exposure on infants and to inform providers of infants with in utero exposure to depemokimab to promote close observation for adverse events that may be related to the biologic:

> Advise patients that the potential clinical impact of prolonged and increased EXDENSUR exposure in infants that were exposed *in utero* is unknown. Inform providers of infants exposed to EXDENSUR *in utero* of the potential for the infant to be exposed to elevated levels of EXDENSUR for a prolonged period *[see Use in Specific Populations (8.1)]*.

Although not my preferred labeling approach, I believe that the final label is acceptable for this product to convey uncertainty of risk, to inform shared decision-making, and to adequately inform providers for infants with in utero exposure.

Postmarketing Requirement

In addition to the labeling recommendation, I proposed inclusion of a PMR to obtain limited longitudinal depemokimab blood levels from infants exposed to depemokimab in utero to complement findings from the descriptive pregnancy safety study. Given the uncertainty of extent of exposure to YTE-modified therapeutics in affected infants, such data would be beneficial to inform safety and for future regulatory decisions related to depemokimab and other YTE-modified products, particularly for products recognizing targets with higher risk.

Based on discussions with the review team, office signatory , and DPMH, a PMR to obtain depemokimab levels in infants exposed in utero was not included with approval of this YTE-modified biologic.

Appendix of Additional Analyses and Information

15 Summary of U.S. Regulatory Activity and Marketing History

Depemokimab has been developed under IND 146742 and has no approved indications. The Applicant submitted an original BLA in December 2024 for the indications of asthma and CRSwNP, which are currently under review. The Applicant is also evaluating depemokimab for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA), hypereosinophilic syndrome, as well as COPD (b) (4) (b) (4) In addition to the U.S., depemokimab has been accepted for review of its asthma and CRSwNP indications by the European Medicines Agency, China National Medical Products Administration, Japanese Ministry of Health, Labour, and Welfare, and (b) (4) other countries.

The applicable regulatory history for the asthma indication is provided in Table 29.

Table 29. Relevant Regulatory History

Date	Summary of Key Points
November 18, 2019 **Pre-IND submission**	Acknowledgement of PIND submission
January 22, 2020 **Type B TCON**	CMC only meeting responses
January 30, 2020 **Type B WRO**	The Agency recommended two, replicate, 12-month studies for demonstration of substantial evidence of effectiveness. Depemokimab nonclinical studies as described in the meeting package may be sufficient to support Phase 2/3 clinical trials. A monkey juvenile toxicity is not needed to support dosing of adolescent subjects. The Applicant should submit their formal justification for not conducting an ePPND study with depemokimab with a decision determined by the Agency after the IND is opened. The Agency concurred with the plan to progress from the Phase 1 study (205722) to the Phase 3 clinical development program, while noting that depemokimab may have an alternate immunogenicity and risk profile compared to other anti-IL-5 biologics. The Bayesian modeling and clinical trial simulations completed by the Applicant for dose selection appeared reasonable, noting limitations such as that the PD data was from a mild-to-moderate asthma population rather than a severe asthma population and the PK/PD data from the Phase 1 first-in-human study was limited due the small sample size. The clinical development program should determine whether efficacy is maintained throughout the entire dose interval since the PD effects begin to rise around 24 weeks and/or consider a more frequent dosing interval (e.g., once every 4 months). Agency comments provided for the NIMBLE trial (e.g., definition of response to anti-IL-5 therapy as an inclusion criterion). The statistical plans for SWIFT-1 and NIMBLE appeared reasonable.

Date	Summary of Key Points
February 18, 2021 Opening IND study may proceed	Reiterated prior comments that based on the potential for depemokimab to have a unique immunogenicity and risk profile related to its prolonged half-life, the Division is unable to agree to the selected dose given the limited data available from the first-in-human, single-dose study. Case report forms should capture distinct criteria related to an asthma exacerbation event. Secondary efficacy endpoints in the hierarchical testing strategy should be arranged based on clinical relevance. The utility of the (b) (4) in the SWIFT-1 and SWIFT-2 trials is unclear and unlikely to support labeling claims. Recommended additional 12-lead ECG collection based on the 4-week toxicity study in monkeys. Recommended data analysis according to the intervention as-randomized, (b) (4) An ePPND study in monkeys is not necessary.
May 14, 2021 Agreed iPSP	Partial waiver for patients 0 to < 6 years of age Deferral in patients 6 to < 12 years of age Inclusion of adolescents 12 to 17 years of age within the adult clinical development program and submitted at the time of the BLA file
September 20, 2021 Type C WRO	Written responses related to the drug substance, drug product, and device.
August 16, 2023 Type C WRO	CMC only meeting written responses.
December 11, 2023 preBLA VCON	The SWIFT-1 and SWIFT-2 trials were consistent with a severe asthma population, and as such the indication statement should reflect the study population. The (b) (4) is not fit-for-purpose to support regulatory decision making or labeling claims. The clinical pharmacology proposal is reasonable. The Division generally agreed with the Applicant's QT assessment strategy. Agreed with the proposed safety interim analysis and blinding strategy for the NIMBLE trial (206785). Proposed safety database is reasonable. The extrapolation strategy for adolescents with asthma to assess benefit-risk in this cohort is reasonable. (b) (4) Agreed with the exclusion of all data from a (b) (4) SMO with potential GCP violations from the primary analyses. Recommended submission of narratives and eCRFs for all SAEs, AESIs, AEs leading to treatment discontinuation and pregnancy cases. The Agency initially recommended collection of all laboratory data (central and local); however, given that the Applicants development program was focused on central labs, incorporation of local laboratory data at the current stage of their Phase 3 trial could affect the reliability of their results. Local lab data is provided in the SAE narratives. Based on the rationale, the Agency agreed with a primary focus on central lab data.

Date	Summary of Key Points
April 11, 2024 Type C WRO	Agreed that the ANSD and ADSD appeared to be acceptable for use as secondary endpoints in the SWIFT-1 and SWIFT-2 trials
February 26, 2025 Type C WRO	Comments on the pediatric asthma protocol in patients 6 to 11 years of age.

Source: Correspondences in DARRTS under IND 146742 and BLA 761458.
Abbreviations: ADSD, asthma daily symptom diary; AE, adverse event; AESI, adverse event of special interest; ANSD, asthma nightly symptom diary; BLA, biologics license application; CMC, chemistry, manufacturing, and controls; ECG, electrocardiogram; eCRF; electronic case report form; ePPND, enhanced pre-and postnatal development study; GCP, good clinical practices; IND, investigational new drug; iPSP, initial pediatric study plan; PD, pharmacodynamic; PIND, pre-investigational new drug; PK, pharmacokinetic; PRO, patient-reported outcome; (b) (4) SAE: serious adverse event; SMO, site management organization; (b) (4) TCON, teleconference; WRO, written responses only

16 Nonclinical Pharmacology/Toxicology

16.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Most of the nonclinical pharmacology studies were originally reviewed under the IND, with the exception of one pharmacology study submitted to the BLA. Summaries are provided here.

Pharmacology

Interleukin-5 (IL-5) is known to be a specific activator of eosinophils and eosinophil differentiation (Angulo et al. 2019). Inhibition of IL-5 has been shown to reduce eosinophil counts with other drugs such as mepolizumab. GSK3511294 only has 7 amino acid differences from mepolizumab; however, the drug has 4 amino acid changes in the heavy change variable region to increase affinity to IL-5 and has a longer half-life due to enhanced FcRn binding, which could result in placental transfer.

GSK3511294 had similar affinity for cynomolgus IL-5 compared to human as evaluated by biacore (K_D of 23.93 and 39.13 pM for monkeys and human, respectively) and bound to both human and monkey IL-5 with slightly higher affinity than mepolizumab (2.31 and 1.38-fold for monkey and human IL-5, respectively). A competition assay between mepolizumab and GSK3511294 was used on the Fortebio Octet RED384 biolayer interferometry instrument and indicated that both drugs bound to the same or similar epitope on human IL-5.

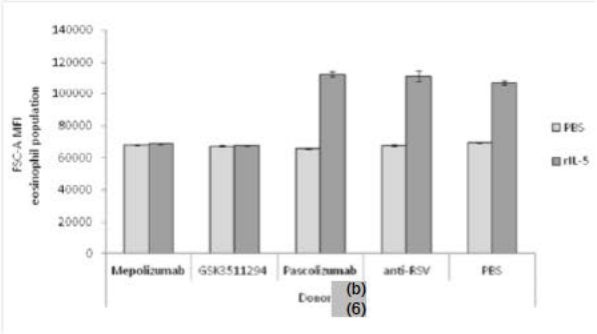
Table 30. Binding of GSK3511294 and Mepolizumab to Human and Cynomolgus Monkey IL-5 by Biacore

Capture	Analyte	Temp(°C)	ka (1/Ms)	Kd (1/s)	K_D (M)	K_D (pM)
(b) (4)	cIL-5	37	1.58E+06	3.79E-05	2.39E-11	23.93
	hIL-5	37	1.24E+06	4.85E-05	3.91E-11	39.13
SB240563	cIL-5	37	7.78E+05	4.31E-05	5.54E-11	55.4
SB240563	hIL-5	37	7.34E+05	3.98E-05	5.42E-11	54.21

Source: Excerpted from Sponsor submission

GSK3511294 reduced cytokine-induced eosinophil shape change in human whole blood as measured by shift in the forward scatter-Area median fluorescence intensity measured by flow cytometry.

Figure 10. Effect of GSK3511294 on IL-5 Induced Eosinophil Shape Change in Human Whole Blood

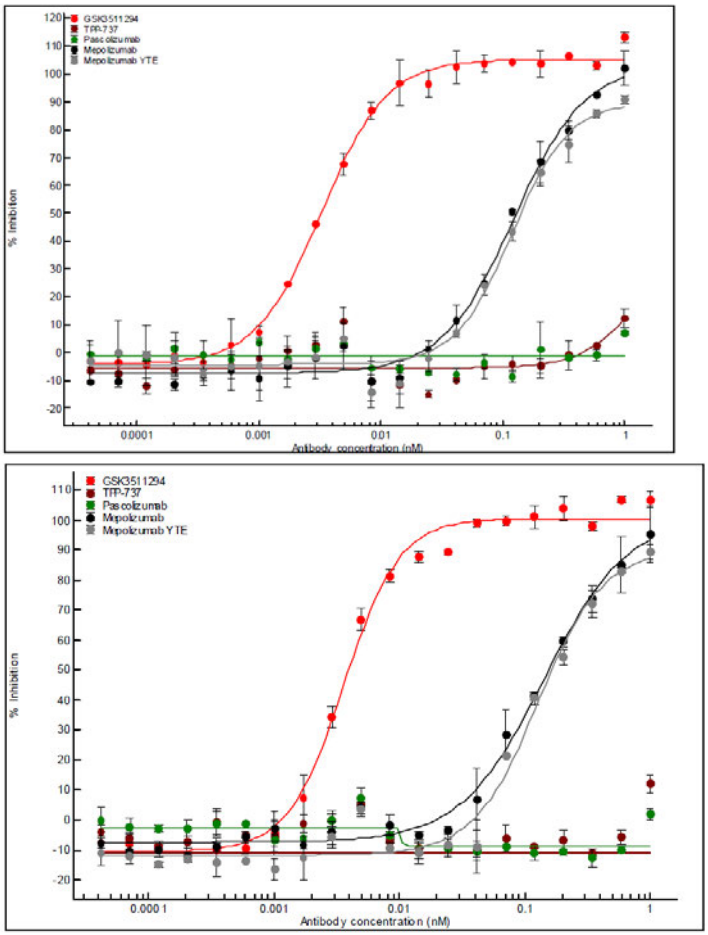


(Data shown is representative of 6 donors, N36771-21)

Source: Excerpted from Sponsor submission
Abbreviations: anti-RSV, antibodies against respiratory syncytial virus; FSC-A, forward scattered area; MFI, mean fluorescence intensity; PBS, phosphate-buffered saline; rIL-5, recombinant interleukin-5

GSK3511294 inhibited cynomolgus and human IL-5 induced TF-1 cell proliferation with IC_{50} values of ~0.004 nM.

Figure 11. Inhibition of Human (Top) and Cynomolgus (Bottom) IL-5 Induced TF-1 Cell Proliferation



Source: Excerpted from Sponsor submission
Abbreviations: IL-5, interleukin-5

GSK3511294 bound to Fcγ receptors (Fcγ RI, FcγRIIa (H131 and R131), FcγRIIb, and FcγRIIIa (V158 and F158)) with similar affinity to wildtype control (K_D values were within 2-fold). GSK3511294 also bound to complement component C1q with lower affinity than YTE and wildtype antibodies.

Table 31. Binding Affinities of GSK3511294 to Recombinant Soluble Human Fcγ Receptors Compared to GSK2800528 (YTE Antibody), Wildtype Control, and Fc Disabled Control

Sample	Batch	KD (nM)					
		FcγRI	FcγRIIa (H131)	FcγRIIa (R131)	FcγRIIb	FcγRIIIa (V158)	FcγRIIIa (F158)
GSK3511294	GRITS54630	39.8	907	948	776	261	843
GSK2800528	DP267083 lot 22370377	34.5	674	773	825	269	935
Fix Fc+ (hIgG1 wildtype control)	GRITS27588	33.8	512	593	1080	175	614
Fix Fc – (hIgG1 Fc disabled control)	GRITS26815	NB	NB	NB	NB	NB	NB

NB= No Binding

Source: Excerpted from Sponsor submission

Table 32. Binding Affinities of GSK3511294 to Recombinant Human Complement Component C1q Receptors Compared to GSK2800528 (YTE Antibody), Wildtype Control, and Fc Disabled Control

Antibodies	Batch	KD (nM)
GSK3511294	GRITS54630	750.0
GSK2800528	DP267083, lot 122370377	184.0
Fix Fc + (IgG1 wildtype isotype control)	GRITS27588	465.0
Fix Fc – (IgG1 Fc disabled isotype control)	GRITS26815	NB

NB = no binding

Source: Excerpted from Sponsor submission

The YTE mutation is designed to increase binding to FcRn under acidic conditions thereby protecting the antibody from lysosomal degradation but disassociates at physiological pH to release the antibody into the blood, thereby increasing the half-life of the drug. GSK3511294 bound to human FcRn with high affinity at pH 6 (K_D 157nM) but low affinity at pH 7.4 (K_D 16160 nM) consistent with successful YTE substitution.

Table 33. Binding Affinity to Recombinant Human FcRn in Acidic and Physiological pH Conditions

	Human FcRn Affinity (nM)	
	pH 6.0	pH 7.4
Mepolizumab	2082	N/A
GSK3511294	157	16160

Source: Excerpted from Sponsor submission

Pharmacokinetics

Pharmacokinetic studies in monkeys administered GSK3511294 via the intravenous (0.5-1 mg/kg) or subcutaneous route (1 mg/kg) observed half-life values ranging from 22.3-24.5 days, greater-than dose-proportional increases in AUC values, slow subcutaneous absorption (T_{max} ~7 days), and relatively high subcutaneous bioavailability (>97%). The volume of distribution was generally consistent with the blood volume (70 mL/kg) throughout all the PK studies indicating little distribution into tissues.

In an *in vitro* serum stability study, drug stability in serum was generally comparable between human and monkey serum. Drug recovery remained above 70% for 6 weeks.

Table 34. PK Parameters for GSK3511294 in Monkeys

Group	Animal	AUC_{0-t} (hr*µg/mL)	AUCINf (hr*µg/mL)	Cmax (µg/mL)	Tmax (hr)	Half-life (hr)	CL_F (mL/hr/kg)	Vz_F (mL/kg)
Group 1 GSK3511294 1 mg/kg SC	101	9320	10700	12.3	168	552	0.0937	74.6
	102	10900	12700	13.5	96.0	591	0.0785	66.9
	152	7580	8330	11.9	168	464	0.120	80.5
	Mean	**9270**	**10600**	**12.5**	**168***	**536**	**0.0974**	**74.0**

Group	Animal	AUC_{0-t} (hr*µg/mL)	AUCINf (hr*µg/mL)	Cmax (µg/mL)	Tmax (hr)	Half-life (hr)	MRT (hr)	CL (mL/hr/kg)	Vss (mL/kg)
Group 3 GSK3511294 0.05 mg/kg IV	301	493	542	1.30	0.25	598	672	0.0923	80.1
	302	394	467	1.20	3.00	501	447	0.107	74.8
	351	427	556	1.23	0.25	649	484	0.0899	81.1
	352	515	573	1.41	0.25	614	630	0.0873	75.1
	Mean	**457**	**534**	**1.29**	**0.25***	**590**	**558**	**0.0942**	**77.8**
Group 4 GSK3511294 1 mg/kg IV	401	9930	9950	24.1	0.25	543	735	0.100	75.1
	402	9400	9430	22.6	0.25	616	748	0.106	81.3
	451	9840	9870	23	0.25	558	745	0.101	77.0
	452	9020	9070	24	0.25	603	749	0.110	85.3
	Mean	**9550**	**9580**	**23.4**	**0.25**	**580**	**744**	**0.105**	**79.7**

* Median value reported

Source: Excerpted from Sponsor submission
Abbreviations: AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC0-t, AUC from 0 to last timepoint sampled; CL_F, apparent clearance; C_{max}, maximum plasma concentration; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; T_{max}, time to C_{max}; Vss, volume of distribution at steady state; Vz/F, apparent volume of distribution during the terminal phase.

Table 35. Mean Drug Concentrations and % Recovery for GSK3511295 in Human and Monkey Serum for up to 6 Weeks as Measured by MSD IL-5 Capture Immunoassay

Sample	Mean Concentration (µg/mL)	% of T0
Human T0	128.6	100.0
Human T1	124.8	97.0
Human T2	119.8	93.1
Human T4	106.9	83.1
Human T6	94.0	73.1
Cynomolgus monkey T0	123.7	100.0
Cynomolgus monkey T1	118.3	95.6
Cynomolgus monkey T2	116.2	93.9
Cynomolgus monkey T4	107.4	86.8
Cynomolgus monkey T6	95.4	77.1

Source: Excerpted from Sponsor submission
Abbreviations: IL-5, interleukin-5; MSD, MesoScale Discovery

Toxicology

In a 26-week toxicology study, sexually mature adult monkeys (4/sex/group) received GSK3511294 via subcutaneous injection at doses of 10 (LD) and 100 (HD) mg/kg every 13 weeks (2 doses total in the study). The study included a vehicle-control containing excipients used in the clinical formulation. An additional 2/sex/group were included for a 30-week recovery period from the control and LD groups. Study assessments included MCP-1 and IL-5 analysis in blood.

Treatment groups in both sexes were noted to have reduced absolute eosinophil counts for several weeks. Reduction in eosinophil counts was part of the pharmacodynamic action of the drug and was considered monitorable. During pretreatment, no animals had detectable IL-5. During the treatment period, every treated animal had detectable IL-5 in the plasma throughout the entire treatment period while control animals did not. This finding was part of the pharmacodynamic action of the drug. There were no treatment-related findings on histopathology. There were no notable sex differences in the toxicokinetic parameters. Exposure was generally dose-proportional on both an AUC and C_{max} basis. T_{max} ranged from 72-120 hours (3-5 days). Half-life was not reported, but the drug was still detectable 84 days after administration. There was a slight increase in drug exposure (1.1 to 1.3-fold for LD and HD, respectively) on Week 14 compared to Week 1. The presence of antidrug antibodies (ADAs) did

not appear to reduce drug exposure in the animals. Drug exposure was maintained throughout the 26-week treatment period.

The no-observed-adverse-effect level was the HD of 100 mg/kg administered every 13 weeks due to a lack of adverse findings.

A study used immunohistochemistry to assess potential cross reactivity of GSK3511294 with a panel of human tissues from 3 donors for each tissue. No specific staining was observed in any of the tissues examined.

During a type B pre-IND meeting held January 20, 2020, it was communicated that the need for an enhanced PPND study from the Sponsor would be decided after opening the IND and after evaluation of the nonclinical data. GSK3511294 only has 7 amino acid differences from mepolizumab; however, the drug has 4 amino acid changes in the heavy change variable region to increase affinity to IL-5 and has a longer half-life due to enhanced FcRn binding, which could result in placental transfer. Findings in 26-week toxicology studies with mepolizumab and GSK3511294 were comparable. Considering there is no known reproductive risk associated with IL-5 inhibition, which has been evaluated in multiple approved products and in IL-5 deficient mice in peer-reviewed literature, and no novel toxicity was observed for GSK3511294 indicating the risk would be very likely similar to mepolizumab, it was decided that an enhanced PPND study would not be necessary for this product.

ADCC/CDC was not requested with the initial IND because the target of the drug is IL-5 which is a soluble protein not expressed by cells. The mechanism of action of depemokimab is to inhibit the binding of IL-5 to its target IL-5Rα, so the risk of ADCC/CDC from depemokimab binding is fairly low.

16.2. Individual Reviews of Studies Submitted With the New Drug Application

New studies to the BLA included a pharmacology study and extractables and leachables studies.

The binding of depemokimab to mouse, rat, rabbit and dog recombinant IL-5 was assessed using surface plasmon resonance on a Biacore™ T200 instrument. Depemokimab (1µM) did not bind to mouse, rat, rabbit, and dog recombinant IL-5. All positive controls (i.e. reslizumab, AF1964, and TRFK5) bound to their respective IL-5 proteins except for TRFK5 which did not bind to rabbit IL-5. This antibody is an anti-mouse/human IL-5 antibody and the Sponsor noted that it was not listed as rabbit cross-reactive. Reslizumab was also tested as a positive control for rabbit IL-5 binding, but also did not bind.

The safety evaluation consisted of extractable and leachable studies for depemokimab. The drug product is stored in a clear glass PFS housed in either an AI or SSD before subcutaneous administration. The Sponsor considered the container closure system to be consisted of the syringe stopper, needle shield, and glass syringe with stainless-steel needle, although the needle shield does not come into direct contact with the product. The glass syringe with

stainless-steel needle does not contribute organic leachables into the drug product. However, the syringe stopper has the potential to contribute organic leachables.

Extractable studies were conducted with the syringe stopper and needle shield as well as some manufacturing products that could potentially provide leachables. The Sponsor tested the drug product for leachables following inverted storage for 6 months at 40°C (accelerated degradation) or up to 12 months at 25°C with 24 and 36 time points being planned for September 2025 and 2026.

The extractables and leachables for the depemokimab drug product did not appear to pose any safety concerns.

17 Clinical Pharmacology

17.1. In Vivo Studies

The Applicant has provided pertinent clinical pharmacology data from a total of six clinical studies conducted in healthy subjects and patients with asthma (Table 36). In addition, the Applicant conducted population PK/PD and ER analyses to support the proposed dosage of 100 mg SC every 6 months. The objectives of the population PK/PD modeling were (1) to characterize the PK and PD (i.e., blood eosinophil count) following depemokimab treatment, and (2) to evaluate the impact of covariates on depemokimab PK and PD. ER analyses were conducted based on the pooled SWIFT-1/2 population for the primary efficacy endpoint, which was the annualized rate (i.e., over 52 weeks) of clinically significant asthma exacerbations. For additional details on population PK/PD and ER analyses, refer to Section 17.4. Summaries of clinical pharmacology data derived from each study are provided in Section 17.5.

Table 36. Summary of Clinical Pharmacology Studies Supporting BLA 761458

Study	Description	Population (N)	Dose(s) and Route[a,b]	Treatment Duration
205722	Phase 1, FIH, randomized, PC, DB, SAD	Adults with mild to moderate asthma (48)	2, 10, 30, 100, and 300 mg SC once	Single-dose
208021	Phase 1, OL, SAD	Healthy Chinese adults (20)	100 or 300 mg SC once	Single-dose
214099	Phase 1, OL, parallel, relative BA	Healthy adults (140)	100 mg SC once (AI or SSD)	Single-dose
206713 (SWIFT-1)	Phase 3, randomized, DB, PC (pivotal efficacy and safety)	Adults/adolescents with severe asthma (382)	100 mg SC Q6M (two doses)	52 weeks
213744 (SWIFT-2)	Phase 3, randomized, DB, PC (pivotal efficacy and safety)	Adults/adolescents with severe asthma (380)	100 mg SC Q6M (two doses)	52 weeks
212895 (AGILE)	Phase 3, single-arm, OLE, long-term safety and efficacy	Rollover subjects from SWIFT-1/SWIFT-2 (629)	100 mg SC Q6M (two doses)	52 weeks[c]

Source. Compiled by reviewer
[a] Depemokimab was administered using only the SSD device presentation in all clinical trials except for Studies 205722 (non-TBM vialed presentation used) and 214099 (both SSD and AI presentations used for bridging)
[b] Only depemokimab dosage regimens are shown; Studies 205722, 206713, and 213744 also included placebo arms
[c] Study 212895 (AGILE) is ongoing as of the date of this BLA submission
Abbreviations: AI, autoinjector; BA, bioavailability; BLA, Biologics License Application; DB, double-blind; FIH, first-in-human; N, number of subjects; OL, open-label; OLE, open-label extension; PC, placebo-controlled; Q6M, every 6 months; SAD, single-ascending dose; SC, subcutaneous; SSD, safety syringe device; TBM, to-be-marketed

17.1.1. Bridging the To-Be-Marketed AI and SSD Presentations

Two device presentations are proposed to be marketed, including an SSD/PFS and an AI. Both presentations contain a 1-mL fill volume of an identical 100 mg/mL depemokimab solution formulation for SC injection. The SSD device presentation was used in both pivotal efficacy and safety trials (SWIFT-1/SWIFT-2), the OLE trial AGILE, and phase 1 studies 208021 and 214099, whereas the AI device presentation was only used in Study 214099.

Study 214099 was a relative BA study designed to compare depemokimab PK following SC administration of a single 100 mg dose using either the SSD or AI device presentation for the purposes of establishing a clinical bridge. The statistical analysis of relative BA between device presentations based on the primary PK parameters C_{max}, AUC_{inf}, and AUC_{last} is depicted below in Table 37.

This reviewer's statistical analysis was conducted using a univariate analysis of variance model to determine the geometric mean ratios (GMRs) and associated 90% CIs of C_{max}, AUC_{inf}, and AUC_{last}. The GMRs and 90% CIs for C_{max}, AUC_{inf}, and AUC_{last} when comparing the AI (test) to the SSD (reference) were 101.8 (95.3, 108.8), 101.3 (93.7, 109.4), and 101.4 (94.1, 109.3), respectively. This analysis corroborates the Applicant's conclusions that bioequivalence (BE) criteria were met between the SSD and AI. Refer to Section 17.5.2 for additional details pertaining to Study 214099.

Table 37. Statistical Analysis of Relative BA for Primary Depemokimab PK Parameters for SSD vs. AI Presentation Following Single 100 mg SC Dose (PK Population; Study 214099)

	Depemokimab SSD (N=70)		Depemokimab AI (N=70)		Test vs. Reference (AI / SSD)	
Parameter	**Geo LSMean (SE)**	**N**	**Geo LSMean (SE)**	**N**	**GMR**	**90% CI of GMR**
C_{max} (µg/mL)	14.68 (0.028)	70	14.94 (0.029)[a]	68	101.8	(95.3, 108.8)
AUC_{inf} (day*µg/mL)	1058.2 (0.033)	70	1071.5 (0.033)[a,b]	67	101.3	(93.7, 109.4)
AUC_{last} (day*µg/mL)	995.3 (0.032)	70	1009.5 (0.032)[a,b]	67	101.4	(94.1, 109.3)

Source. Reviewer's analysis based on adpc.xpt for Study 214099
[a] Excluded two subjects (b) (6) due to an event (pregnancy and severe pelvic inflammation) for which significant impact on the PK could not be excluded
[b] Excluded one subject (b) (6) due to early withdrawal after the W12 visit
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to Infinity; AUC_{last}, AUC from 0 to last timepoint sampled; BA, bioavailability; CI, confidence interval; C_{max}, maximum plasma concentration; Geo, Geometric; GMR, geometric mean ratio; LSMean, Least-Squares Mean; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SE, standard error; SSD, safety syringe device; W12, Week 12

Cross-Study PK Analysis: Vialed Presentation Versus To-Be-Marketed Presentations

In FIH Study 205722, the Applicant administered a different, non-TBM formulation and presentation of depemokimab ((b) (4) mg/mL; 1-mL vial presentation). In addition to a (b) (4) depemokimab strength, the vialed formulation also contains (b) (4) (not present in the TBM formulation) as well as (b) (4) concentrations of (b) (4) histidine and (b) (4) arginine compared with the TBM products. All subsequent studies were conducted with the TBM formulation using the SSD and/or AI presentations. The Applicant did not submit any clinical or nonclinical data to compare depemokimab exposure following administration of the vialed presentation with the TBM products. However, given that the PK data derived from Study 205722 formed the basis of the Applicant's phase 3 dose selection approach, a cross-study PK analysis was conducted to compare depemokimab PK following SC administration with each presentation throughout the clinical program (Table 38).

Following a SC dose of 100 mg, the Week 2 geometric mean depemokimab plasma concentration (corresponding to the approximate C_{max}) was comparable between Study 205722 and the phase 3 SWIFT-1/2 studies, ranging from approximately 10 to 12 µg/mL. However, at Week 26 (C_{trough}), depemokimab geometric mean plasma concentration was approximately 50 to 60% lower in Study 205722 compared to the SWIFT-1/2 studies and relative BA Study 214099 (both the SSD and AI cohorts). Furthermore, observed depemokimab clearance was approximately 16% higher in Study 205722 compared to the typical value, the root cause of which was not clearly discernable. Notably, although cross-validated, Study 205722 used a different bioanalytical assay (Method GSK3511294HUPLVALA) from all subsequent clinical studies to measure depemokimab plasma concentrations. The lower lower limit of quantitation (LLOQ) value adopted by Method GSK3511294HUPLVALA may also partially contribute to the differences in observed systemic exposure despite administration of equivalent depemokimab dosages. Overall, there remains uncertainty regarding whether the vialed presentation/formulation used in Study 205722 yields similar depemokimab exposure to the TBM products.

Table 38. Summary of Depemokimab Plasma Concentration at Week 2 and Week 26 (C_{trough}) Following SC Administration in Healthy Subjects and Subjects With Asthma

Clinical Study	Population	Drug Product	Dose (mg)	N[a]	Body Weight (kg)[b]	W2 Conc. (µg/mL)[c]	W26 Conc. (µg/mL)[c]
205722	Asthma	1-mL Vial	100	9	76.6 (7.7)	11.74 (13.87)	0.49 (16.76)
			300	6	87.3 (8.2)	27.27 (18.15)	1.32 (18.93)
208021[d]	Healthy Adults	SSD	100	10	64.9 (8.1)	16.34 (15.73)	2.46 (18.35)
			300	10	62.6 (6.4)	53.14 (16.62)	7.22 (16.63)
214099	Healthy Adults	SSD	100	70	71.9 (11.3)	13.86 (29.97)	0.96 (49.82)
		AI	100	70	73.2 (10.9)	14.26 (23.36)	0.96 (53.69)
206713 (SWIFT-1)	Asthma	SSD	100	250	78.7 (18.0)	11.85 (34.55)	1.29 (52.53)
213744 (SWIFT-2)	Asthma	SSD	100	249	79.8 (21.1)	12.38 (39.47)	1.31 (52.92)

Source: Reviewer's analysis based on CSRs and adpc.xpt for Studies 205722, 208021, 214099, 206713, and 213744
[a] Number of subjects included in the PK population
[b] Body weight reported as arithmetic mean (SD)
[c] Depemokimab plasma concentrations reported as geometric mean (CV%)
[d] Enrolled healthy Chinese adult subjects. Note that mean body weight was lower for subjects in 208021 relative to that for subjects in other studies.
Abbreviations: AI, autoinjector; CSR, clinical study report; C_{trough}, trough plasma concentration at Week 26; Conc., concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation; SSD, safety syringe device; W2, Week 2; W26, Week 26.

17.2. Bioanalytical Method Validation and Performance

Overall, bioanalytical methods used to quantitate depemokimab concentrations in clinical study samples were determined to be acceptable in accordance with Guidance for Industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022).

PK Assessment

A total of three bioanalytical methods were utilized by the Applicant to measure plasma concentrations of depemokimab across five clinical studies. All three methods were sandwich format capture and detection electrochemiluminescence immunoassays. Method GSK3511294HUPLVALA was developed and validated internally by the Applicant as a fit-for-purpose assay which supported FIH Study 205722. All subsequent clinical studies were supported by two bioanalytical methods which were developed and validated by (b) (4) (b) (4) Method BTM-3365 ((b) (4)) and Method (b) (4) -2293 ((b) (4) (b) (4)). Method BTM-3365 was used for the quantitation of rest-of-the-world study samples (excluding mainland China), while Method (b) (4) -2293 was utilized for the quantitation of samples collected from all participants in mainland China.

Method validation reports for each assay, as well as in-study bioanalysis results for each clinical study, were reviewed and found to be acceptable. Additionally, two cross-validation procedures were completed between (1) Methods GSK3511294HUPLVALA and BTM-3365, using spiked quality control samples and (2) Methods BTM-3365 and (b) (4) -2293, using quality control samples and pooled incurred samples from Study 206713 (SWIFT-1). Both cross-validations met acceptance criteria. A brief summary of method validation parameters for each assay is provided below in Table 39. Additionally, a summary of method performance during each clinical study is summarized below in Table 40.

PD Assessment

Across all clinical studies, blood eosinophil counts were measured as part of the standard hematology and differential assessment via central laboratory (b) (4) The site staff and central study team were both blinded to each participant's blood eosinophil count (as well as overall hematology differential [absolute and % values of eosinophils, lymphocytes, basophils, neutrophils, and monocytes]) from all post-randomization blood tests.

Table 39. Summary of Method Validation Parameters for Bioanalytical Assays Used To Measure Plasma Concentrations of Depemokimab

	Bioanalytical Method ID		
Method Parameter	**GSK3511294HUPLVALA**	**BTM-3365**	(b) (4)**-2293**
Analytical Site	Stevenage, UK (GlaxoSmithKline R&D)	(b) (4)	(b) (4)
Clinical Studies Supported	205722	214099, 206713, 213744	208021, 206713
Bioanalytical Methodology	Sandwich format using capture and detection methodology with MSD-based ECL immunoassay platform		
Matrix	Human Plasma K_2EDTA	Human Plasma K_2EDTA	Human Plasma K_2EDTA
Assay Range (LLOQ to ULOQ)	50 to 10,000 ng/mL	100 to 5,000 ng/mL	100 to 5,000 ng/mL
Regression Model	5-parameter logistic algorithm with $1/X^2$ weighing factor	4-parameter logistic (Marquardt) regression with $1/Y^2$ weighing factor	4-parameter logistic (Marquardt) regression with $1/Y^2$ weighing factor
MRD	100-fold	200-fold	200-fold
Calibration Concentrations	30 (anchor), 50, 100, 300, 500, 1000, 3000, 5000, 10,000, and 30,000 (anchor) ng/mL	100, 250, 500, 1000, 2500, 4500, and 5000 ng/mL	100, 250, 500, 1000, 2500, 4500, and 5000 ng/mL
Calibration Curve/Linearity During A&P Runs	No. Calibrators: 8 Cumulative Accuracy (%RE): -1.5% to 1.4% Cumulative Precision (%CV): ≤ 10.0%	No. Calibrators: 7 Cumulative Accuracy (%RE): -0.8 to 3.2% Cumulative Precision (%CV): ≤ 7.3%	No. Calibrators: 7 Cumulative Accuracy (%RE): -3.6 to 3.6% Cumulative Precision (%CV): ≤ 6.8%
QC Levels	50 (LLOQ), 150 (LQC), 1,000 (MQC), 8,000 (HQC), and 10,000 (ULOQ) ng/mL	100 (LLOQ), 300 (LQC), 800 (MQC), 4,000 (HQC), and 5,000 (ULOQ) ng/mL	100 (LLOQ), 300 (LQC), 800 (MQC), 4,000 (HQC), and 5,000 (ULOQ) ng/mL
QC Performance During A&P Runs	Cumulative Accuracy (%RE): -7.3% to 3.5% Cumulative Precision (%CV): ≤ 7.5% Percentage Total Error (%TE): ≤ 11.2%	Cumulative Accuracy (%RE): -8.6 to -3.6% Cumulative Precision (%CV): ≤ 10.4% Percentage Total Error (%TE): ≤ 19.0%	Cumulative Accuracy (%RE): -3.0 to 11.7% Cumulative Precision (%CV): ≤ 11.1% Percentage Total Error (%TE): ≤ 18.6%
Selectivity and Matrix Effect	Established in healthy human plasma	Established in human plasma of healthy subjects and severe asthma with eosinophilic phenotype	
Interference and Specificity	Not performed	**ADA:** Tolerance of 30,000 ng/mL at LQC/HQC **IL-5:** Tolerance of 50,000 pg/mL at HQC and 5 pg/mL at LQC	**ADA:** Tolerance of 100 ng/mL at LQC/HQC **IL-5:** Tolerance of 5,000 pg/mL at LQC/HQC
Hemolysis Effect	Not performed	Not observed	Not observed
Lipemic Effect	Not performed	Not observed	Not observed
Dilution Linearity	Not performed	Acceptable up to 50,000-fold	Acceptable up to 2,000-fold
Hook Effect	Not performed	Not observed up to 10,000,000 ng/mL	Not observed up to 490,000 ng/mL
Parallelism	Demonstrated up to 10-fold dilution	Demonstrated up to 20-fold dilution	Demonstrated up to 200-fold dilution

	Bioanalytical Method ID		
Method Parameter	**GSK3511294HUPLVALA**	**BTM-3365**	**(b) (4)-2293**
Established Stability	**Bench-Top:** 24 h at RT **LTS:** 313 days at -80°C **Freeze/Thaw:** 5 cycles from -80°C to RT	**Bench-Top:** 24 h at RT **LTS:** 379 days at -20°C, 907 days at -70°C **Freeze/Thaw:** 6 cycles from -20°C/-70°C to RT	**Bench-Top:** 74 h at RT **LTS:** 712 days at -20°C/-70°C **Freeze/Thaw:** 5 cycles from -20°C/-80°C to RT

Source. Compiled by reviewer based on Bioanalytical Reports 2017N340919_01, 2022N520511_00, 2022N520511_01, 2024N548011_00, 2024N560124_00, 2022N519225_00, and 2024N549671_00
Abbreviations: A&P, accuracy and precision; ADA, anti-drug antibody; CV, coefficient of variation; ECL, electrochemiluminescence; HQC, high quality control; IL-5, interleukin 5; LLOQ, lower limit of quantitation; LQC, low quality control; LTS, long-term stability; MQC, medium quality control; MRD, minimum required dilutions; MSD, MesoScale Discovery; QC, quality control; RE, relative error; RT, room temperature; TE, total error; ULOQ, upper limit of quantitation.

Table 40. Summary of Bioanalytical Method Performance for Measurement of Depemokimab Plasma Concentrations Across Clinical Studies

	Study ID					
Parameter	**Study 205722**	**Study 208021**	**Study 206713**		**Study 214099**	**Study 213744**
Bioanalytical method ID	GSK3511294HUPLVALA	(b) (4)-2293	(b) (4)-2293	BTM-3365	BTM-3365	BTM-3365
Assay passing rate	72% (18/25)	86% (12/14)	(100% (13/13)	50/62 (81%)	41/42 (98%)	85% (67/79)
Standard curve performance	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
Cumulative bias range (%RE)	-2.2 to 1.7%	-2.0 to 5.0%	-2.4 to 4.0%	-1.8 to 3.4%	-4.7 to 10.3%	-1.9 to 3.3%
Cumulative precision (%CV)	≤ 7.8%	≤ 4.4%	≤ 5.2%	≤ 0.1%	≤ 5.2%	≤ 8.9%
QC performance	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
Cumulative bias range (%RE)	-0.6 to 0.9%	1.9% to 6.7%	-3.1% to -0.1%	-2.1 to 6.0%	0.9 to 3.2%	0.2 to 4.8%
Cumulative precision (%CV)	≤ 8.9%	≤ 5.5%	≤ 5.2%	≤ 0.1%	≤ 0.1%	≤ 9.1%
Percentage total error (%TE)	≤ 9.8%	≤ 10.6%	≤ 8.1%	≤ 6.1%	≤ 3.3%	≤ 14.0%
Method reproducibility	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable
ISR occurrence rate	10.7% (57/531)	11.6% (32/277)	16.8% (65/388)	9.4% (221/2346)	7.8% (153/1952)	7.4% (206/2771)
ISR passing rate	92.9% (53/57)	100% (32/32)	98.5% (64/65)	94.1% (208/221)	96.1% (147/153)	86.9% (179/206)
Sample Analysis/Stability	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

Source. Compiled by reviewer based on Bioanalytical Reports 2024N548310_01, 2024N549274_00, 2024N555453_00, 2020N430678_00, 2023N527272_00, and 2024N547467_00
Abbreviations: CV, coefficient of variation; ISR, incurred sample reanalysis; QC, quality control; RE, relative error; TE, total error.

17.2.1. OSIS Bioanalytical Site Inspection

Given that relative BA Study 214099 provided pivotal data to support the use of the proposed AI device presentation, a request for an inspection of the clinical and analytical sites for Study 214099 was submitted to the Office of Study Integrity and Surveillance (OSIS).

No on-site inspection was scheduled for the analytical site (b) (4) (b) (4) as an inspection was recently conducted under a separate regulatory submission, at which time OSIS concluded that data from the reviewed studies were reliable.

There were three clinical sites which enrolled subjects in Study 214099. Of these, OSIS arranged a clinical site inspection for the site which enrolled the largest number of subjects (Austin, TX), which comprised over half of the total subjects included in the trial:

1. **PPD Development L.P. (Austin, TX):** Although OSIS had recently completed an inspection for this clinical site under a separate regulatory submission, a clinical site inspection was still conducted. Of note, at the conclusion of the previous inspection, it was reported that Form FDA 483 was not issued, although no action was indicated and OSIS determined that the study results were reliable. Following the current inspection, it was noted again that Form FDA 483 was not issued at the inspection close-out. Additionally, there was a discussion item for an unreported AE of a toothache (subject (b) (6) which was documented in the source records, but not transcribed into the EDC and ultimately not reported as part of the submission. The clinical site stated that this AE was left open due to this subject being lost to follow up, after which is was mistakenly omitted when entering data into the EDC of the submission. OSIS recommended that the review division consider the AE and associated medication in their review of subject (b) (6)
2. **PPD Development L.P. (Orlando, FL):** Although OSIS has no inspection history for this site, OSIS has planned an inspection for another clinical site listed on the consult (i.e., Austin, TX), which enrolled a large number of subjects for the study.
3. **PPD Development L.P. (Las Vegas, NV):** OSIS declined to conduct an on-site inspection, as an inspection was recently conducted under a separate regulatory submission, during which OSIS concluded that data from the reviewed studies were reliable.

Of note, the only concomitant medication reported for Subject (b) (6) was acetaminophen, presumably as an analgesic to treat the pain relief associated with the toothache AE. No other potential explanations for this AE could be identified, although this finding is considered unlikely to impact the resulting PK data or the overall assessment. Overall, the data reported from Study 214099 are considered reliable to support BE between the SSD and AI device presentations.

Refer to Bioequivalence Establishment Inspection Report Review Memorandums dated February 26, 2025 (DARRTS Reference ID: 5538317), March 20, 2025 (DARRTS Reference ID: 5553588), and August 21, 2025 (DARRTS Reference ID: 5647008).

17.3. Immunogenicity Assessment – Impact on PK/PD, Efficacy, and Safety

ADA Incidence

A summary of immunogenicity results from all clinical studies conducted in healthy subjects and patients with asthma is provided below in Table 41. Considering that the open-label extension (OLE) Study AGILE included rollover subjects from the SWIFT-1 and SWIFT-2 studies, comprising 210 and 419 participants who were previously randomized to placebo and depemokimab, respectively, a total of 712 patients with severe asthma received at least a single dose of depemokimab, of which 691 provided at least one post-baseline immunogenicity sample. Of these subjects, less than 1% (N = 1) had a positive ADA result at baseline and approximately 10% (N = 66) developed post-baseline anti-depemokimab ADAs.

Table 41. Summary of Immunogenicity Results Across Depemokimab Clinical Program

Study Population Study ID	Dosing (Weeks)	N[a]	ADA Incidence		NAb Incidence	
			Baseline +	Post-Baseline+	Baseline +	Post-Baseline+
Mild-to-moderate asthma with eosinophilic phenotype						
205722[b]	0	36	0	9	N/A	N/A
Healthy subjects						
208021	0	20	0	0	0	0
214099	0	140	1	2	1	1
Severe asthma with eosinophilic phenotype						
206713 (SWIFT-1)	0, 26	249	1	31	0	0
213744 (SWIFT-2)	0, 26	250	0	13	0	2
212895 (AGILE)	0, 26	588[c]	12[d]	43	0	3
Total	-	691[e]	1[f]	66[g]	0	4[h]

Source. Adapted from ISI (Table 4, pg. 18)
[a] Population includes only depemokimab-treated subjects who provided at least one post-baseline immunogenicity sample
[b] Immunogenicity samples were not analyzed for NAbs in Study 205722
[c] Population includes rollover subjects from SWIFT-1 and SWIFT-2 studies who previously received depemokimab (N = 396) and placebo (N = 192)
[d] Baseline immunogenicity results for AGILE were determined by the results obtained at Week 52 from SWIFT-1 and SWIFT-2; Note that the baseline immunogenicity status for all previous placebo subjects was ADA-negative for AGILE, as post-baseline samples for placebo subjects were not analyzed for immunogenicity in SWIFT-1 and SWIFT-2.
[e] Population includes depemokimab-treated subjects from SWIFT-1 (N = 249) and SWIFT-2 (N = 250), as well as previous placebo rollover subjects from AGILE (N = 192)
[f] Total only includes the single baseline-positive subject from SWIFT-1, as all baseline ADA-positive subjects in AGILE were treatment-emergent responses from the parent SWIFT-1 and SWIFT-2 studies
[g] Note that 21/43 post-baseline ADA-positive subjects in AGILE were also ADA-positive in either SWIFT-1 or SWIFT-2. Therefore, these subjects were excluded from the total post-baseline ADA-positive count for AGILE in order to avoid double-counting.
[h] One subject who was NAb-positive was enrolled in both SWIFT-2 and AGILE – this subject is only counted once in the calculation of total post-baseline NAb+ incidence
Abbreviations: ADA, anti-drug antibody; ISI, integrated summary of immunogenicity; N, number of subjects; Nab, neutralizing antibody; N/A, not applicable;

Across all studies, there were 6 subjects who tested positive for neutralizing antibodies (NAbs), including 2 healthy subjects from Study 214099 and 4 patients with severe asthma from SWIFT-2/AGILE. Notably, one of the healthy subjects from Study 214099 had a positive NAb response at baseline as well as all post-baseline timepoints. Given that no treatment-boosted titer response was observed, this response was considered unrelated to depemokimab treatment. Additionally, one patient with severe asthma tested positive for NAbs in both SWIFT-2 (Week

52) and AGILE (Week 78), with a negative ADA sample recorded between these timepoints at Week 64.

A summary of ADA incidence according to intrinsic factors, including age, sex, race, and region is provided below in Table 42, based on pooled data derived from the severe asthma and CRSwNP phase 3 programs.

Table 42. Summary of ADA Incidence According to Intrinsic Factors[a]

Category		Week 52	Week 104	Anytime Post-Baseline
All		4% (32/805)	4% (9/214)	9% (87/963)
Age	12-17	0% (0/16)	0% (0/4)	4% (1/23)
	18-64	4% (26/580)	5% (8/146)	11% (74/704)
	≥ 65	3% (6/208)	2% (1/64)	5% (12/235)
Sex	Female	3% (14/414)	3% (4/132)	8% (39/504)
	Male	5% (18/390)	6% (5/82)	10% (48/458)
Race	Native	0% (0/3)	0% (0/1)	0% (0/4)
	Asian	14% (21/153)	25% (6/24)	25% (47/187)
	Black	8% (2/26)	0% (0/7)	9% (3/33)
	White	1% (8/617)	2% (3/182)	5% (36/733)
Region 1	Europe	2% (7/435)	2% (3/135)	6% (31/515)
	U.S.	< 1% (1/146)	0% (0/52)	3% (5/183)
	RoW	11% (24/223)	22% (6/27)	19% (51/264)
Region 2	Asian	14% (21/150)	25% (6/24)	26% (47/183)
	Non-Asian	2% (11/654)	2% (3/190)	5% (40/774)

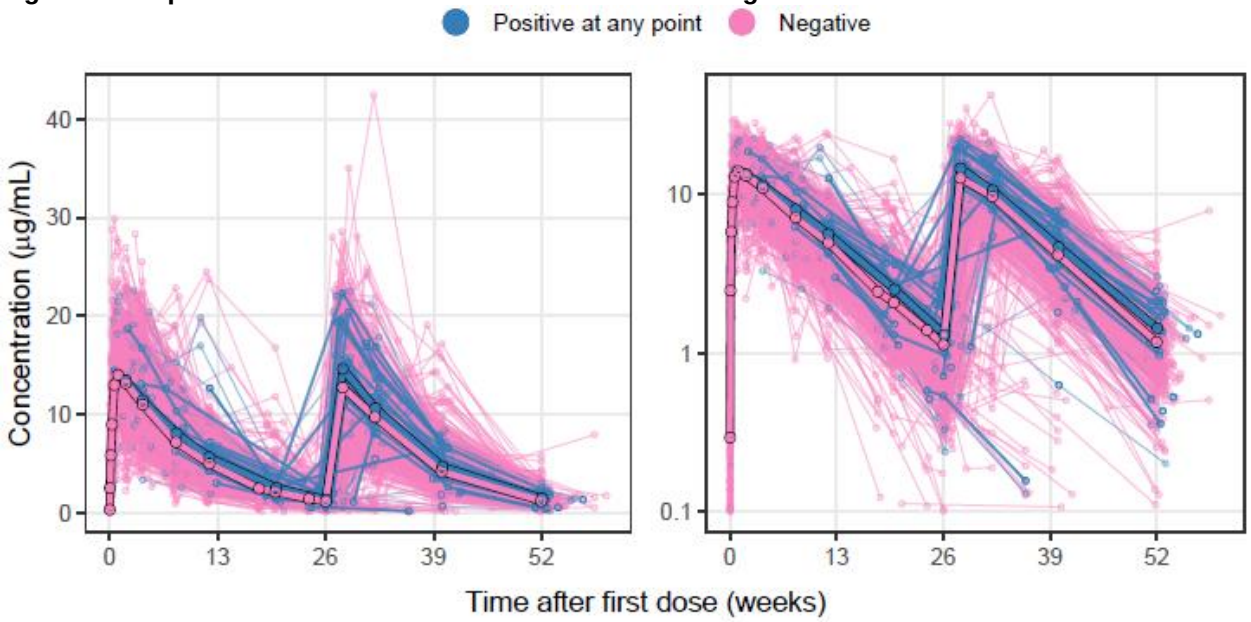
Source. Adapted from ISI (Table 12, pg. 30)
[a] Includes pooled immunogenicity data derived from phase 3 programs for severe asthma and CRSwNP
Abbreviations: ADA, Anti-Drug Antibody; CRSwNP, chronic rhinosinusitis with nasal polyps; ISI, integrated summary of immunogenicity; RoW, rest of world;

There appeared to be a similar incidence of post-baseline ADA development between males (10%; 48/458) and females (8%; 39/504). Regarding age, only 4% (N = 1/23) of depemokimab-treated adolescents had a post-baseline ADA-positive response, while 11% (74/704) and 5% (12/235) of adults aged 18 to 64 and elderly subjects ≥ 65 years of age, respectively, developed post-baseline ADAs. Additionally, a higher ADA incidence was noted for Asian race (25%, 47/187) and Asian region (26%, 47/183) relative to non-Asians, which the Applicant partially attributes to differences in assay performance between samples assayed in China versus the rest of the world. This is supported by the fact that most titers were low and near the sensitivity limit of the bioanalytical method used.

ADA Impact on Depemokimab PK

Individual observed depemokimab concentration-time profiles according to ADA status (at any timepoint) for all subjects who received the (b) (4) dosage of 100 mg SC across the severe asthma and CRSwNP programs are shown below in linear and semi-logarithmic scales in Figure 12. Depemokimab exposure in ADA-positive subjects was comparable to and within the range of that observed in ADA-negative subjects.

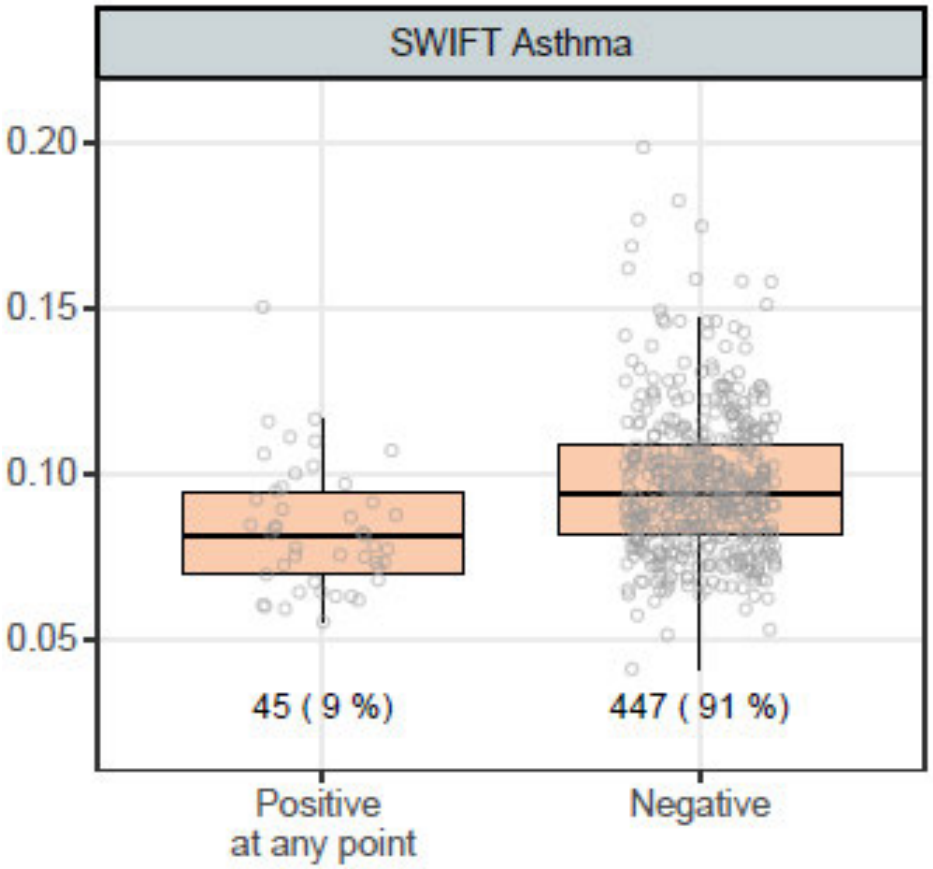
Figure 12. Depemokimab Plasma Concentrations According to ADA Status[a,b]



Source. Population PK Report REP-1-PK-GSK-FTE1-DEPE-PMX-1 (Figure A2-13, pg. 179)
[a] Note that the thicker blue and pink lines represent the median depemokimab concentration-time profiles for ADA-positive and ADA-negative subjects, respectively
[b] Analysis includes PK data derived for all subjects who received at least a single dose of depemokimab 100 mg SC across the severe asthma and CRSwNP development programs
Abbreviations: ADA, anti-drug antibody; CRSwNP, chronic rhinosinusitis with nasal polyps; ISI, integrated summary of immunogenicity; PK, pharmacokinetic; SC, subcutaneous

The Applicant also evaluated depemokimab clearance according to ADA status based on the pooled SWIFT-1/2 PK population (Figure 13). Median clearance was comparable between ADA-positive and ADA-negative subjects. Overall, there was no apparent impact of ADAs on the PK of depemokimab.

Figure 13. Depemokimab Apparent Clearance (CL/F) According to ADA Status (Pooled SWIFT-1/2 Population)

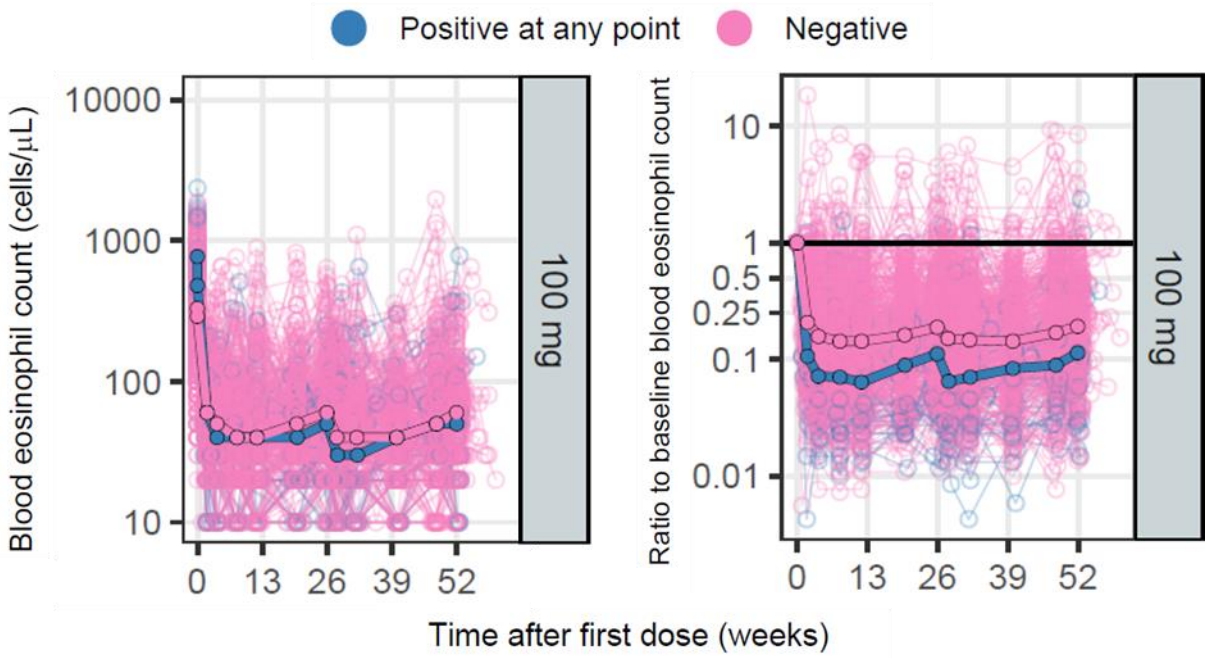


Source: Adapted from Population PK Report REP-1-PK-GSK-FTE1-DEPE-PMX-1 (Figure A3-34, pg. 233)
Abbreviations: ADA, anti-drug antibody; CL/F, apparent clearance; PK, pharmacokinetic

ADA Impact on Depemokimab PD

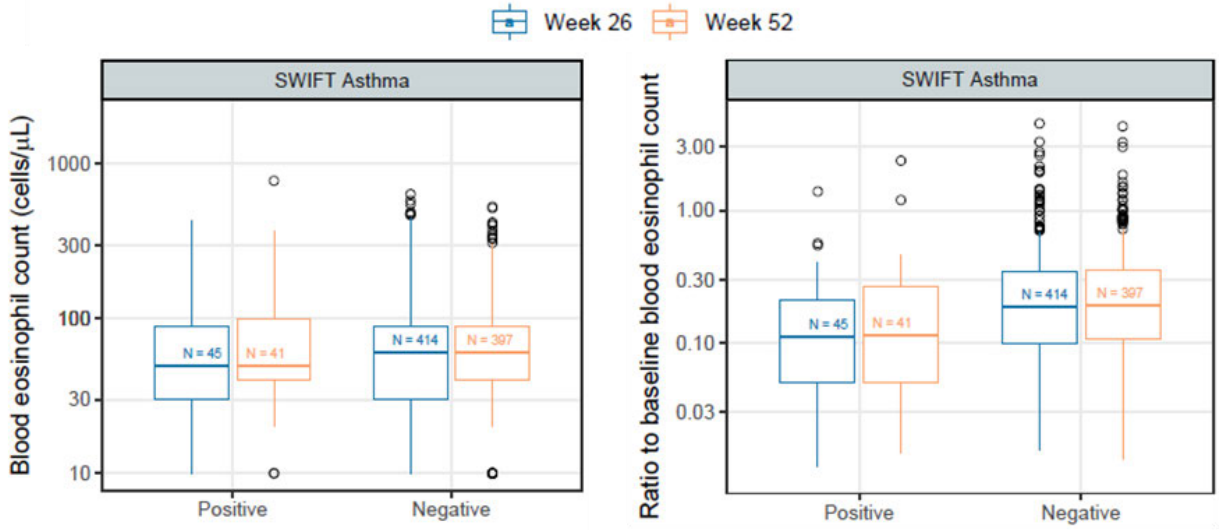
The individual observed absolute and ratio-to-baseline eosinophil count-time profiles according to ADA status (at any timepoint) for all subjects from the pooled SWIFT-1/2 PK population are depicted below on a semi-logarithmic scale in Figure 14. Additionally, the distributions of observed absolute and ratio-to-baseline blood eosinophil count at Weeks 26 and 52 in the pooled SWIFT-1/2 study population are displayed below in Figure 15. The individual blood eosinophil count-time profiles for ADA-positive subjects were comparable to and within the range of those observed in ADA-negative subjects and overall, blood eosinophil count reduction results did not appear to be impacted by ADA status.

Figure 14. Individual Observed Absolute (Left Panel) and Ratio to Baseline (Right Panel) Blood Eosinophil Count-Time Profile by ADA Status (Pooled SWIFT-1/2 Population)[a]



Source: Population PK/PD Report REP-2-PKPD-GSK-FTE1-DEPE-PMX-1 (Figure A2-26, pg. 166; Figure A2-27, pg. 167)
[a] Note that the thicker blue and pink lines represent the median eosinophil count-time profiles for ADA-positive and ADA-negative subjects, respectively
Abbreviations: ADA, anti-drug antibody; PD, pharmacodynamic; PK, pharmacokinetic

Figure 15. Distribution of Observed Absolute (Left Panel) and Ratio to Baseline (Right Panel) Blood Eosinophil Count at Weeks 26 and 52 by ADA Status (Pooled SWIFT-1/2 Population)



Source: Adapted from Population PK/PD Report REP-2-PKPD-GSK-FTE1-DEPE-PMX-1 (Figure A2-29, pg. 169)
Abbreviations: ADA, anti-drug antibody; N, number of subjects; PD, pharmacodynamic; PK, pharmacokinetic

ADA Impact on Efficacy

The primary efficacy endpoint in the SWIFT-1/2 trials was the annualized rate (i.e., over 52 weeks) of clinically significant exacerbations. A summary of the efficacy data in the SWIFT-1/2 population according to ADA status is shown below in Table 43. The annualized rate (95% CI) of

clinically significant exacerbations in ADA-positive subjects was comparable to that observed in ADA-negative subjects, indicating no apparent impact of ADAs on the efficacy of depemokimab.

Table 43. Summary of Annualized Rate of Clinically Significant Exacerbations by ADA Status in Subjects With Severe Asthma With Eosinophilic Phenotype (Pooled SWIFT-1/2 Population)

Primary Efficacy Endpoint	ADA Status	N	Primary Estimand Value
Annualized rate of clinically significant exacerbations[a,b]	ADA-positive	44	0.40 (0.22, 0.70)
	ADA-negative	455	0.52 (0.43, 0.61)

Source. Applicant's response to Agency request for information, dated April 15, 2025 (Table 3, pg. 4); Corroborated by reviewer's analysis based on adis.xpt and adexaca.xpt for Studies 206713/213744
[a] Analysis performed using a generalized linear model assuming a negative binomial distribution and covariates of baseline ICS dose (medium or high), exacerbation history (2, 3, 4+), geographical region, baseline pre-bronchodilator percent predicted FEV1, study (206713 or 213744) and ADA status (ADA+ or ADA-)
[b] Values reported as annualized rate (95% CI)
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; N, number of subjects

ADA Impact on Safety

A summary of the frequency of on-treatment AEs in depemokimab-treated subjects according to ADA status based on safety data derived from patients with severe asthma (SWIFT-1/2 + AGILE studies) is provided below in Table 44. Incidence of treatment-emergent adverse events (TEAEs) were generally higher for ADA-positive compared to ADA-negative subjects. The most common AEs were upper respiratory infections (including COVID-19 and influenza), nasopharyngitis, sinusitis, and rhinitis, which occurred with similar frequency regardless of ADA/NAb status. Regarding TEAEs of interest related to immunogenicity, there were no hypersensitivity reactions (HSRs) reported among those with positive ADA responses, whereas HSRs were reported for 2% (13/604) of ADA-negative subjects. Injection site reactions were reported in a single ADA-positive subject and approximately 1% (N = 8/691) of ADA-negative subjects. It is unclear if the higher incidence of general TEAEs in ADA-positive subjects is biased by the small sample size of ADA-positive subjects as compared to the overall population investigated in phase 3 trials.

Table 44. Summary of Incidence of TEAEs by ADA Status in Subjects With Severe Asthma With Eosinophilic Phenotype

	ADA Status		
Study ID	ADA-Positive	ADA-Negative	Overall
SWIFT-1/SWIFT-2 (pooled)	89% (39/44)	71% (323/455)	73% (362/499)
AGILE	86% (37/43)	63% (346/545)	65% (383/588)

Source. Generated by reviewer based on safety data obtained from ISI (pg. 30-32)
Abbreviations: ADA, anti-drug antibody; ISI, integrated summary of immunogenicity; TEAE, treatment-emergent adverse event

17.4. Pharmacometrics Review

17.4.1. Population PK Analysis

17.4.1.1. Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of describing the PK/PD of depemokimab and providing exposure metrics for ER analyses. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 45.

Table 45. Specific Comments on Applicant's Final Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Racial Groups, Age and [redacted]: There was no clinically relevant effect of age, race, or [redacted] on depemokimab-xxxx pharmacokinetics.	The statement is acceptable. [redacted] is not a significant covariate in the final model. The effect of age and race on exposure is not clinically relevant (Figure 18).
		Asthma (section 8.4) The pharmacokinetics of depemokimab-xxxx in pediatric patients aged 12 to 17 years were consistent with adults based on population pharmacokinetic analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same EXDENSUR treatment.	The statement is acceptable (Figure 19, Figure 23).
		Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no clinically relevant effect on depemokimab-xxxx apparent clearance.	The statement is acceptable. Baseline hepatic function biomarkers (ALT, AST, and bilirubin) are not significant covariates in the final model.
		Based on population pharmacokinetic analyses, no dose adjustment is required in patients with an eGFR <60 mL/min/1.73 m2. Data are limited in patients with an eGFR <60 mL/min/1.73 m2.	The individual post-hoc estimates of PK parameters from final PK model were comparable across renal impairment groups, however the number of subjects with eGFR <30 mL/min/1.73 m^2 (n=2) is too limited to draw a conclusion on the impact of severe renal impairment on PK (Table 53).
		Depemokimab-xxxx pharmacokinetics were consistent in patients with asthma or CRSwNP with average concentration during a dosing interval at steady state of 5.9 mcg/mL and 5.2 mcg/mL, respectively after SC administration of 100 mg of EXDENSUR every 6 months.	The statement is acceptable (Table 52).

Utility of the Final Model		Reviewer's Comments
Derive exposure metrics for Exposure-response analyses	$AUC_{tau,ss}$, $C_{trough,Week52}$, BEC_{Week52}, ratio to baseline BEC_{Week52}	Acceptable

Source: Module 5.3.3.5, Population Pharmacokinetic Analysis Report; Module 5.3.3.5, Population Pharmacokinetic and Pharmacodynamic Analysis Report
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; $AUC_{tau,ss}$, area under the curve over one dosing interval at steady state; BEC_{Week52}, baseline eosinophil count at week 52; CRSwNP, chronic rhinosinusitis with nasal polyps; $C_{trough,Week52}$, trough concentration at Week 52; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic; SC, subcutaneous

17.4.1.2. Introduction

The primary objectives of Applicant's analysis were to:

- Characterize the PK of depemokimab, including associated interindividual variability (IIV) and residual unexplained variability in healthy volunteers (HVs), patients with asthma and CRSwNP.
- Evaluate the impact of identified covariates on depemokimab PK parameters.
- Derive individual PK parameters and PK exposure metrics that will subsequently be used a) to present summary metrics of PK exposure, across subgroups, and b) as input in exposure-response analyses.
- Describe the relationship between the pharmacokinetic(s) of depemokimab and blood eosinophil count, including associated IIV and residual unexplained variability, and including the placebo response in patients with asthma and CRSwNP.
- Evaluate the impact of identified covariates on depemokimab PK/PD parameters.

17.4.1.3. Model Development

17.4.1.3.1. Data

PK Data

The PK analyses for depemokimab were based on PK data from 1 Phase 1 study in adult asthma patients (205722), 2 Phase 1 studies in healthy subjects (208021 and 214099), and 4 Phase 3 studies in adult and adolescent asthma subjects (206713, 213744, 217095 and 218079). Brief descriptions of the studies included are presented in Table 46.

The overall percent of below level of quantification (BLQ) samples was 1.8%. Excluding BLQ samples is reasonable. The final NONMEM data file for depemokimab model development contained 9383 PK observations from 961 subjects. Table 47 provides summary statistics of the baseline demographic covariates in the PK analysis dataset.

PD Data

The PK/PD analyses for depemokimab were based on PK/PD data from 1 Phase 1 study in adult asthma patients (205722) and 4 Phase 3 studies in adult and adolescent asthma subjects (206713, 213744, 217095 and 218079). Brief descriptions of the studies included are presented in Table 46.

The final NONMEM data file for depemokimab PK/PD model development contained 14273 blood eosinophil count observations from 1324 subjects. Of these, a total of 5580 blood eosinophil count observations from 523 subjects were from subjects who received placebo. There were <1% blood eosinophil count observations, which were retained in the data with the values set to half of lower limit of detection. It seems to be reasonable to not testing alternative modeling approaches for handling BLQ data. Table 48 provides summary statistics of the baseline demographic covariates in the PK/PD analysis dataset.

Table 46. Summary of Studies With PK/PD Sampling Included in Population PK/PD Analysis

Studies	Phase	Population	Treatments	Route	Device	Assessment design
205722[1]	1	Adult mild to moderate asthma patients with BEC ≥200 cells/μL at screening	Depemokimab 2, 10, 30, 100, 300 mg or placebo in a single dose	subcu-taneous (SC)	Syringe + vial	**PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168, 182, 224, 252 and 280 days post-dose[a] **BEC:** screening[b], pre-dose and 1, 2, 3, 4, 7, 14, 28, 56, 84, 126, 168, 182, 224, 252 and 280 days post-dose[a] **QTcF:** screening[b], pre-dose, 2, and 8 hours post-dose and 1, 2, 3, 4, 7, 14, 28, 56, 84, 126, 168, 182, 224, 252 and 280 days post-dose[a]
208021[2]	1	Chinese HVs	Depemokimab 100 or 300 mg in a single dose	SC	SSD	**PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168 and 182 days post-dose **BEC:** screening[b], pre-dose, 1, 2, 7, 14, 28, 56, 84, 126, 168, and 182 days post-dose **QTcF:** screening[b], day -1, pre-dose, 2, and 8 hours post-dose and 1, 2, 3, 4, 7, 14, 28, 56, 84, 126, 168, and 182 days post-dose
214099[3]	1	HVs	Depemokimab 100 mg in a single dose	SC	SSD or autoinjector	**PK:** 2 and 8h, and 1, 2, 4, 7, 14, 28, 56, 84, 126, 168 and 182 days post-dose **BEC:** screening[b], pre-dose, 7, 28, 56, 84, 168, and 182 days post-dose **QTcF:** screening[b], pre-dose and 1, 2, 7, 14, 84, and 182 days post-dose
206713[4]	3	Adult and adolescent (≥12 years) patients with asthma with BEC ≥300 cells/μL in the past 12 months prior to Visit 1 or ≥150 cells/μL at Screening Visit 1	Depemokimab 100 mg or placebo at Week 0 and Week 26	SC	SSD	**PK:** pre-dose, 14, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose **BEC:** screening[b], pre-dose, 14, 28, 56, 84, 140, 182, 196, 224, 280, 336 and 364 days post-first dose **QTcF:** screening[b], pre-dose, 14, 182, 196 and 364 days post-first dose
213744[5]	3	Adult and adolescent (≥12 years) patients with asthma with BEC ≥300 cells/μL in the past 12 months prior to Visit 1 or ≥150 cells/μL at Screening Visit 1	Depemokimab 100 mg or placebo at Week 0 and Week 26	SC	SSD	**PK:** pre-dose, 14, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose **BEC:** screening[b], pre-dose, 14, 28, 56, 84, 140, 182, 196, 224, 280, 336 and 364 days post-first dose **QTcF:** screening[b], pre-dose, 14, 182, 196 and 364 days post-first dose
217095[6]	3	Adult (≥18 years) CRSwNP patients with no specific BEC inclusion criteria	Depemokimab 100 mg or placebo at Week 0 and Week 26	SC	SSD	**PK:** pre-dose, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose **BEC:** screening[c], pre-dose, 28, 56, 84, 140, 182, 196, 224, 280, 336 and 364 days post-first dose **QTcF:** screening[c], pre-dose, 28, 56, 182, 196 and 364 days post-first dose
218079[7]	3	Adult (≥18 years) CRSwNP patients with no specific BEC inclusion criteria	Depemokimab 100 mg or placebo at Week 0 and Week 26	SC	SSD	**PK:** pre-dose, 28, 56, 84, 140, 182, 196, 224, 280 and 364 days post-first dose **BEC:** screening[c], pre-dose, 28, 56, 84, 140, 182, 196, 224, 280, 336 and 364 days post-first dose **QTcF:** screening[c], pre-dose, 28, 56, 182, 196 and 364 days post-first dose

Source: Applicant's Population PKPD report, Table 1
[a] After Week 26, PK sampling, blood eosinophil count and ECG measurements depended on the treatment group as follows: no more samples for the 10 mg treatment groups; PK sample, blood eosinophil count and ECG measurement on day 252 after dose for the 30 and 100 mg treatment groups; PK
samples, ECG and blood eosinophil count measurements on days 224 and 280 after dose for the 300 mg treatment group.
[b] Pre-screen up to 12 weeks before dosing, screening up to 4 weeks before randomization.
[c] Screening window was 28 days +/- 7 days i.e., maximum of 35 days from Day 1 and minimum of 21 days.
Abbreviations: BEC, baseline eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyps; ECG, electrocardiogram; HV, healthy volunteer; PD, pharmacodynamic; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device

Table 47. Summary of Baseline Covariates for PK Analysis

A: Continuous covariates

	China PK HV N=20	Device PK HV N=140	FTIH Asthma N=36	SWIFT Asthma N=493	ANCHOR CRSwNP N=272	Overall N=961
Body weight (kg)						
Mean (SD)	63.7 (7.21)	72.6 (11.0)	82.7 (10.2)	79.2 (19.7)	79.0 (16.0)	78.0 (17.4)
Median (min, max)	64.8 (50.9, 79.5)	72.3 (51.3, 101)	83.6 (64.6, 107)	77.0 (34.6, 161)	77.9 (45.9, 145)	76.0 (34.6, 161)
Age (years)						
Mean (SD)	29.7 (6.41)	35.5 (8.01)	43.9 (10.6)	53.7 (14.8)	52.4 (13.3)	49.8 (15.0)
Median (min, max)	27.2 (20.9, 43.5)	36.0 (18.0, 50.0)	46.0 (20.0, 63.0)	56.0 (12.0, 82.0)	53.0 (20.0, 93.0)	50.0 (12.0, 93.0)
Height (cm)						
Mean (SD)	167 (5.99)	169 (9.22)	178 (7.43)	167 (9.95)	171 (9.65)	169 (9.94)
Median (min, max)	169 (158, 178)	168 (147, 193)	178 (158, 194)	167 (144, 196)	172 (147, 197)	169 (144, 197)
BMI (kg/m^2)						
Mean (SD)	22.7 (2.24)	25.4 (2.84)	26.1 (2.94)	28.3 (5.91)	26.9 (4.47)	27.2 (5.16)
Median (min, max)	23.0 (19.3, 25.8)	25.4 (19.2, 30.1)	26.0 (20.7, 31.8)	27.6 (14.2, 52.6)	26.4 (18.2, 43.3)	26.6 (14.2, 52.6)
Albumin (g/L)						
Mean (SD)	46.4 (1.69)	45.2 (3.02)	44.2 (2.36)	45.4 (3.05)	45.8 (3.13)	45.4 (3.04)
Median (min, max)	46.0 (44.1, 50.3)	45.0 (36.0, 54.0)	45.0 (38.0, 48.0)	45.0 (34.0, 55.0)	46.0 (35.0, 55.0)	45.0 (34.0, 55.0)
Blood eosinophil count (cells/μL)						
Mean (SD)	132 (94.4)	144 (135)	361 (151)	431 (350)	453 (358)	387 (339)
Median (min, max)	105 (40.0, 440)	100 (5.00, 800)	310 (190, 890)	330 (5.00, 2360)	365 (5.00, 3440)	290 (5.00, 3440)
Alanine amino transferase (IU/L)						
Mean (SD)	21.6 (7.10)	17.7 (8.90)	21.8 (8.09)	22.3 (13.2)	21.4 (11.4)	21.4 (11.9)
Median (min, max)	20.0 (11.0, 35.0)	16.0 (5.00, 57.0)	20.5 (11.0, 45.0)	19.0 (5.00, 153)	18.5 (5.00, 97.0)	18.0 (5.00, 153)
Aspartate amino transferase (IU/L)						
Mean (SD)	21.3 (4.99)	18.0 (5.93)	22.4 (5.16)	20.7 (9.44)	20.5 (6.59)	20.3 (8.10)
Median (min, max)	21.5 (14.0, 31.0)	17.0 (9.00, 47.0)	22.0 (12.0, 40.0)	19.0 (9.00, 115)	19.0 (10.0, 49.0)	19.0 (9.00, 115)
Total bilirubin (μmol/L)						
Mean (SD)	13.8 (5.12)	9.57 (5.34)	11.1 (5.09)	7.34 (4.09)	8.06 (4.82)	8.14 (4.73)
Median (min, max)	13.8 (4.60, 29.6)	8.55 (1.71, 35.4)	10.0 (4.00, 28.0)	6.00 (2.00, 30.0)	7.00 (2.00, 42.0)	7.00 (1.71, 42.0)

	China PK HV N=20	Device PK HV N=140	FTIH Asthma N=36	SWIFT Asthma N=493	ANCHOR CRSwNP N=272	Overall N=961
Total protein (g/L)						
Mean (SD)	74.4 (3.07)	71.6 (4.86)	68.8 (3.60)	70.2 (4.58)	69.9 (4.44)	70.3 (4.60)
Median (min, max)	74.2 (69.7, 80.4)	72.0 (55.0, 84.0)	69.0 (61.0, 79.0)	70.0 (57.0, 91.0)	70.0 (55.0, 82.0)	70.0 (55.0, 91.0)
Serum creatinine (μmol/L)						
Mean (SD)	87.4 (8.00)	77.1 (17.8)	80.4 (10.4)	75.2 (18.9)	77.5 (14.9)	76.6 (17.3)
Median (min, max)	88.0 (69.0, 105)	74.3 (46.0, 127)	79.6 (53.9, 104)	72.0 (42.0, 202)	77.0 (44.0, 137)	74.3 (42.0, 202)
Creatinine clearance (mL/min)						
Mean (SD)	99.6 (14.0)	114 (21.7)	122 (22.2)	106 (37.8)	107 (32.0)	108 (33.6)
Median (min, max)	98.6 (77.1, 123)	114 (65.4, 174)	121 (81.4, 176)	98.4 (20.2, 259)	102 (46.5, 272)	104 (20.2, 272)
eGFR (mL/min/1.73m^2)						
Mean (SD)	103 (10.9)	104 (17.6)	100 (12.0)	89.5 (19.1)	92.2 (15.3)	93.0 (18.2)
Median (min, max)	102 (83.8, 123)	106 (58.7, 143)	101 (69.2, 120)	89.6 (24.9, 158)	93.1 (42.9, 134)	93.5 (24.9, 158)

B: Categorical covariates

	China PK HV N=20	Device PK HV N=140	FTIH Asthma N=36	SWIFT Asthma N=493	ANCHOR CRSwNP N=272	Overall N=961
Age category						
12-17 years old	0 (0%)	0 (0%)	0 (0%)	15 (3.0%)	0 (0%)	15 (1.6%)
18-64 years old	20 (100%)	140 (100%)	36 (100%)	351 (71%)	223 (82%)	770 (80%)
$\geq$ 65 years old	0 (0%)	0 (0%)	0 (0%)	127 (26%)	49 (18%)	176 (18%)
Sex						
Male	20 (100%)	65 (46%)	34 (94%)	195 (40%)	187 (69%)	501 (52%)
Female	0 (0%)	75 (54%)	2 (5.6%)	298 (60%)	85 (31%)	460 (48%)
Race						
American Indian or Alaska Native	0 (0%)	1 (0.71%)	0 (0%)	2 (0.41%)	1 (0.37%)	4 (0.42%)
Asian	20 (100%)	7 (5.0%)	1 (2.8%)	90 (18%)	64 (24%)	182 (19%)
Black or African American	0 (0%)	37 (26%)	2 (5.6%)	20 (4.1%)	6 (2.2%)	65 (6.8%)
White	0 (0%)	88 (63%)	33 (92%)	381 (77%)	196 (72%)	698 (73%)
Multiple or other	0 (0%)	7 (5.0%)	0 (0%)	0 (0%)	0 (0%)	7 (0.73%)
Unknown or not reported	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.37%)	1 (0.10%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (1.5%)	4 (0.42%)
Ethnicity						
Not hispanic or latino	20 (100%)	98 (70%)	36 (100%)	444 (90%)	235 (86%)	833 (87%)
Hispanic or latino	0 (0%)	42 (30%)	0 (0%)	49 (9.9%)	32 (12%)	123 (13%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (1.8%)	5 (0.52%)
Patient population						
HV	20 (100%)	140 (100%)	0 (0%)	0 (0%)	0 (0%)	160 (17%)
Asthma	0 (0%)	0 (0%)	36 (100%)	493 (100%)	0 (0%)	529 (55%)
CRSwNP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	272 (100%)	272 (28%)

	China PK HV N=20	Device PK HV N=140	FTIH Asthma N=36	SWIFT Asthma N=493	ANCHOR CRSwNP N=272	Overall N=961
Study						
208021 (China PK HV)	20 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (2.1%)
214099 (Device PK HV)	0 (0%)	140 (100%)	0 (0%)	0 (0%)	0 (0%)	140 (15%)
205722 (FTIH Asthma)	0 (0%)	0 (0%)	36 (100%)	0 (0%)	0 (0%)	36 (3.7%)
206713 (SWIFT-1 Asthma)	0 (0%)	0 (0%)	0 (0%)	250 (51%)	0 (0%)	250 (26%)
213744 (SWIFT-2 Asthma)	0 (0%)	0 (0%)	0 (0%)	243 (49%)	0 (0%)	243 (25%)
217095 (ANCHOR-1 CRSwNP)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	143 (53%)	143 (15%)
218079 (ANCHOR-2 CRSwNP)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	129 (47%)	129 (13%)
Device						
Safety syringe	20 (100%)	70 (50%)	36 (100%)	493 (100%)	272 (100%)	891 (93%)
Autoinjector	0 (0%)	70 (50%)	0 (0%)	0 (0%)	0 (0%)	70 (7.3%)
Injection site						
Upper arm	20 (100%)	47 (34%)	36 (100%)	468 (95%)	256 (94%)	827 (86%)
Thigh	0 (0%)	47 (34%)	0 (0%)	25 (5.1%)	14 (5.1%)	86 (8.9%)
Abdomen	0 (0%)	46 (33%)	0 (0%)	0 (0%)	0 (0%)	46 (4.8%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.74%)	2 (0.21%)
Anti-drug antibody status						
Positive at any point	0 (0%)	3 (2.1%)	9 (25%)	45 (9.1%)	21 (7.7%)	78 (8.1%)
Negative	20 (100%)	137 (98%)	27 (75%)	447 (91%)	251 (92%)	882 (92%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	1 (0.20%)	0 (0%)	1 (0.10%)
Maximal ADA titre[a]						
0	20 (100%)	137 (98%)	29 (81%)	451 (91%)	251 (92%)	888 (92%)
80	0 (0%)	1 (0.71%)	4 (11%)	32 (6.5%)	18 (6.6%)	55 (5.7%)
160	0 (0%)	0 (0%)	1 (2.8%)	8 (1.6%)	1 (0.37%)	10 (1.0%)
320	0 (0%)	0 (0%)	2 (5.6%)	1 (0.20%)	1 (0.37%)	4 (0.42%)
640	0 (0%)	1 (0.71%)	0 (0%)	0 (0%)	1 (0.37%)	2 (0.21%)
2560	0 (0%)	1 (0.71%)	0 (0%)	0 (0%)	0 (0%)	1 (0.10%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	1 (0.20%)	0 (0%)	1 (0.10%)

	China PK HV N=20	Device PK HV N=140	FTIH Asthma N=36	SWIFT Asthma N=493	ANCHOR CRSwNP N=272	Overall N=961
PK/ADA assay						
Rest of World Assay	0 (0%)	140 (100%)	0 (0%)	455 (92%)	238 (88%)	833 (87%)
China Assay	20 (100%)	0 (0%)	0 (0%)	38 (7.7%)	34 (12%)	92 (9.6%)
FTIH Asthma Assay	0 (0%)	0 (0%)	36 (100%)	0 (0%)	0 (0%)	36 (3.7%)
Maintenance OCS at baseline[b]						
Regular maintenance OCS treatment	0 (0%)	0 (0%)	0 (0%)	21 (4.3%)	0 (0%)	21 (2.2%)
No regular maintenance OCS treatment	20 (100%)	140 (100%)	36 (100%)	472 (96%)	272 (100%)	940 (98%)
Maintenance OCS dose at baseline[b]						
0 mg/day	20 (100%)	140 (100%)	36 (100%)	472 (96%)	272 (100%)	940 (98%)
5 mg/day	0 (0%)	0 (0%)	0 (0%)	11 (2.2%)	0 (0%)	11 (1.1%)
10 mg/day	0 (0%)	0 (0%)	0 (0%)	6 (1.2%)	0 (0%)	6 (0.62%)
(Missing)	0 (0%)	0 (0%)	0 (0%)	4 (0.81%)	0 (0%)	4 (0.42%)
Smoking status						
Never smoked	0 (0%)	0 (0%)	30 (83%)	372 (75%)	178 (65%)	580 (60%)
Current smoker	0 (0%)	0 (0%)	0 (0%)	1 (0.20%)	0 (0%)	1 (0.10%)
Former smoker	0 (0%)	0 (0%)	6 (17%)	120 (24%)	94 (35%)	220 (23%)
(Missing)	20 (100%)	140 (100%)	0 (0%)	0 (0%)	0 (0%)	160 (17%)
Country in North East Asia						
China	20 (100%)	0 (0%)	0 (0%)	38 (7.7%)	34 (12%)	92 (9.6%)
Japan	0 (0%)	0 (0%)	0 (0%)	41 (8.3%)	29 (11%)	70 (7.3%)
Taiwan	0 (0%)	0 (0%)	0 (0%)	8 (1.6%)	0 (0%)	8 (0.83%)
Rest of World	0 (0%)	140 (100%)	36 (100%)	406 (82%)	209 (77%)	791 (82%)
Renal impairment[c]						
Normal	17 (85%)	105 (75%)	29 (81%)	242 (49%)	155 (57%)	548 (57%)
Mild loss	3 (15%)	34 (24%)	7 (19%)	226 (46%)	110 (40%)	380 (40%)
Mild to moderate loss	0 (0%)	1 (0.71%)	0 (0%)	23 (4.7%)	7 (2.6%)	31 (3.2%)
Severe loss	0 (0%)	0 (0%)	0 (0%)	2 (0.41%)	0 (0%)	2 (0.21%)

Source: Applicant's Population PK report, Tables 3 and 4.
Numbers represent the number of subjects in each category; percentages represent the corresponding percentage of total number of subjects, specified in the column header.
[a] Maximal observed value per subject, during the study period.
[b] Prednisolone equivalent dose.
[c] Renal impairment categories were defined based on estimated glomerular filtration rate (eGFR) as follows: Normal >= 90 mL/min/1.73m2; Mild >= 60 and < 90 mL/min/1.73 m2; Mild to moderate >= 30 and < 60 mL/min/1.73 m2; Severe < 30 mL/min/1.73 m2.
Abbreviations: ADA, anti-drug antibody; BMI, body mass index; CRSwNP, chronic rhinosinusitis with nasal polyps; eGFR, estimated glomerular filtration rate; HV, healthy volunteer; OCS, oral corticosteroids; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation

Table 48. Summary of Baseline Covariates for PK/PD Analysis

A: Continuous covariates

	FTIH Asthma N=48	SWIFT Asthma N=748	ANCHOR CRSwNP N=528	Overall N=1324
Body weight (kg)				
Mean (SD)	82.9 (11.6)	79.4 (19.7)	79.4 (16.8)	79.5 (18.4)
Geometric mean (%CV)	82.1 (14.3)	77.1 (24.6)	77.7 (21.4)	77.5 (23.1)
Median (min, max)	84.7 (57.8, 107)	77.0 (34.6, 161)	77.6 (40.0, 149)	77.4 (34.6, 161)
Age (year)				
Mean (SD)	44.0 (11.2)	53.2 (15.1)	52.0 (13.3)	52.4 (14.4)
Geometric mean (%CV)	42.4 (29.3)	50.3 (38.4)	50.2 (28.5)	49.9 (34.6)
Median (min, max)	46.0 (19.0, 65.0)	55.0 (12.0, 82.0)	52.0 (19.0, 93.0)	54.0 (12.0, 93.0)
Blood eosinophil count (cells/μL)				
Mean (SD)	366 (147)	433 (374)	456 (551)	440 (449)
Geometric mean (%CV)	342 (36.6)	315 (101)	333 (99.0)	323 (98.0)
Median (min, max)	330 (190, 890)	320 (5.00, 4440)	360 (5.00, 10600)	335 (5.00, 10600)

B: Categorical covariates

	FTIH Asthma N=48	SWIFT Asthma N=748	ANCHOR CRSwNP N=528	Overall N=1324
Age group				
Adult	48 (100%)	719 (96%)	528 (100%)	1295 (98%)
Adolescent	0 (0%)	29 (3.9%)	0 (0%)	29 (2.2%)
Sex				
Male	46 (96%)	293 (39%)	365 (69%)	704 (53%)
Female	2 (4.2%)	455 (61%)	163 (31%)	620 (47%)
Race				
American Indian or Alaska Native	0 (0%)	3 (0.40%)	2 (0.38%)	5 (0.38%)
Asian	2 (4.2%)	133 (18%)	120 (23%)	255 (19%)
Black or African American	2 (4.2%)	32 (4.3%)	11 (2.1%)	45 (3.4%)
White	43 (90%)	579 (77%)	382 (72%)	1004 (76%)
Multiple or other	1 (2.1%)	1 (0.13%)	0 (0%)	2 (0.15%)
Unknown or not reported	0 (0%)	0 (0%)	5 (0.95%)	5 (0.38%)
(Missing)	0 (0%)	0 (0%)	8 (1.5%)	8 (0.60%)
Participant population				
Asthma	48 (100%)	748 (100%)	0 (0%)	796 (60%)
CRSwNP	0 (0%)	0 (0%)	528 (100%)	528 (40%)
Study population				
FTIH Asthma	48 (100%)	0 (0%)	0 (0%)	48 (3.6%)
SWIFT Asthma	0 (0%)	748 (100%)	0 (0%)	748 (56%)
ANCHOR CRSwNP	0 (0%)	0 (0%)	528 (100%)	528 (40%)
Neutralizing antibody status				
Positive at any point	0 (0%)	2 (0.27%)	1 (0.19%)	3 (0.23%)
Negative	48 (100%)	744 (99%)	525 (99%)	1317 (99%)
(Missing)	0 (0%)	2 (0.27%)	2 (0.38%)	4 (0.30%)
Maintenance OCS at baseline				
Regular maintenance OCS treatment	0 (0%)	40 (5.3%)	0 (0%)	40 (3.0%)
No regular maintenance OCS treatment	48 (100%)	708 (95%)	528 (100%)	1284 (97%)

	FTIH Asthma N=48	SWIFT Asthma N=748	ANCHOR CRSwNP N=528	Overall N=1324
Seasonal month at day of 1st dose[a]				
January	3 (6.2%)	61 (8.2%)	43 (8.1%)	107 (8.1%)
February	0 (0%)	88 (12%)	35 (6.6%)	123 (9.3%)
March	5 (10%)	94 (13%)	57 (11%)	156 (12%)
April	2 (4.2%)	46 (6.1%)	58 (11%)	106 (8.0%)
May	3 (6.2%)	35 (4.7%)	59 (11%)	97 (7.3%)
June	10 (21%)	49 (6.6%)	57 (11%)	116 (8.8%)
July	2 (4.2%)	48 (6.4%)	48 (9.1%)	98 (7.4%)
August	10 (21%)	54 (7.2%)	24 (4.5%)	88 (6.6%)
September	0 (0%)	70 (9.4%)	35 (6.6%)	105 (7.9%)
October	9 (19%)	61 (8.2%)	37 (7.0%)	107 (8.1%)
November	4 (8.3%)	58 (7.8%)	41 (7.8%)	103 (7.8%)
December	0 (0%)	84 (11%)	34 (6.4%)	118 (8.9%)
Country in North East Asia[b]				
China	0 (0%)	58 (7.8%)	63 (12%)	121 (9.1%)
Japan	0 (0%)	59 (7.9%)	55 (10%)	114 (8.6%)
Taiwan	0 (0%)	13 (1.7%)	0 (0%)	13 (0.98%)
Rest of World	48 (100%)	618 (83%)	410 (78%)	1076 (81%)

Source: Applicant's Population PKPD report, Tables 3 and 4
Numbers represent the number of subjects in each category; percentages represent the corresponding percentage of total number of subjects, specified in the column header.
[a] Seasonal month corresponds to the seasonal month at time of first dose, normalized to the Northern hemisphere, expressed in integer months.
[b] The categories of country in North East Asia are: China, Japan, Taiwan and Rest of World.
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; CV, coefficient of variation; OCS, oral corticosteroids; PD, pharmacodynamic; PK, pharmacokinetic; SD, standard deviation

17.4.1.3.2. Base Model

PK Base Model

The population PK model was developed using a non-linear mixed-effects modeling approach with the first-order conditional estimation with interaction method in NONMEM (Version 7.5). A one-compartment PK model with first-order absorption and first-order elimination was developed as the base model. In this model, weight effects with estimated on clearance and volume of distribution were included.

IIV was modelled assuming a log-normal distribution for patient level random effects. Residual variability was described using additive error model on the log-transformed concentration data. The quality of the model fit were assessed by diagnostic plots.

PK/PD Base Model

After the PK model was developed, an indirect response drug-effect (inhibition of kin) was developed as the base model for describing profiles of blood eosinophil count in subjects who received depemokimab.

IIV and residual variability were modeled similar to those in the PK based model.

17.4.1.3.3. Covariate Analysis

Mechanistic covariates were included in the base model without statistical testing. Structural covariates were then investigated conditionally on the mechanistic covariates. Subsequently, the impact of the exploratory covariates was investigated conditionally on the mechanistic and the identified structural covariates. The stepwise covariate model building procedure with adaptive scope reduction was used for the evaluation of structural and exploratory covariate-parameter relationships. The forward selection and backward elimination p-values were, respectively, 0.01 and 0.001. Primary covariates evaluated in the development of PK and PK/PD models were included in Table 49 and Table 50, respectively.

Table 49. Covariate-Parameter Relationships Evaluated in Depemokimab PK Model

Parameter	Type	Covariate
Clearance	Mechanistic	body weight[a]
	Structural	albumin, anti-drug antibody[b]
	Exploratory	age,[c] estimated glomerular filtration rate[c], sex, race[d], baseline eosinophil count, alanine amino transferase, total bilirubin, participant population[e], study population[e], 2 mg dose level[f]
Volume of distribution	Mechanistic	body weight[a]
	Structural	
	Exploratory	age, sex, race[d], participant population[e], study population[e]
First-order absorption rate constant	Mechanistic	
	Structural	body weight[a], administration device[g], injection site[g]
	Exploratory	age, sex, race[d], participant population[e], study population[e]
Bioavailability	Mechanistic	
	Structural	administration device[g], injection site[g]
	Exploratory	age, sex, race[d], participant population[e], study population[e], 2 mg dose level[f]

Source: Applicant's Population PK report, Table 5
[a] Included allometrically, i.e., exponents estimated according to a power model.
[b] Subject's overall (time-invariant) ADA status was tested as a dichotomous covariate.
[c] Age and estimated glomerular filtration rate were both tested on clearance (CL).
[e] Participant population and Study population together consist of five groups with participant population I) HV, II) asthma and III) CRSwNP patients, as well as study differences for IV) China PK HV and V) FTIH Asthma studies. The remaining three study populations are the reference groups for the three groups in participant population, and therefore not tested for study effects, due to complete confounding with participant population.
[f] Based on higher dose-normalized concentration profile over time compared to other dose groups observed in study 205722 report10.
[g] Only tested for injection sites (thigh or abdomen, versus upper arm) or administration device (autoinjector (AI) versus safety syringe device (SSD)) if the graphical analysis of the Device PK HV study (study 214099) showed a clear trend.
Abbreviations: PK, pharmacokinetic

Table 50. Covariate-Parameter Relationships Evaluated in Depemokimab PD (Blood Eosinophil Count) Model

Parameter	Type	Covariate
Baseline	Mechanistic	
	Structural	participant population[a], study population[a], oral corticosteroids treatment[b]
	Exploratory	age, sex, race/ethnicity[c], body weight, seasonal month[d]
Placebo response	Mechanistic	
	Structural	baseline eosinophil count[e]
	Exploratory	participant population[a], study population[a], oral corticosteroids treatment[b], age, sex, race/ethnicity[c], body weight
Half-life for drug on-/offset[f]	Mechanistic	
	Structural	
	Exploratory	age, body weight, baseline eosinophil count[e]
Maximum effect	Mechanistic	
	Structural	baseline eosinophil count[e]
	Exploratory	participant population[a], study population[a], oral corticosteroids treatment[b], age, sex, race/ethnicity[c], body weight, NAb[g]
Concentration at half maximum effect	Mechanistic	
	Structural	baseline eosinophil count[e]
	Exploratory	participant population[a], study population[a], oral corticosteroids treatment[b], age, sex, race/ethnicity[c], body weight, NAb[g]

Source: Applicant's Population PKPD report, Table 8
[a]Participant population and Study population together consists of three groups with participant population I) asthma and II) CRSwNP patients, as well as study differences for III) FTIH Asthma study.
[b]Information about oral corticosteroids (OCS) treatment will be tested as a time invariant yes/no in SCM.
[c]Race/ethnicity categories will be driven by the number of participants in each of the seven studies in the analysis dataset and will be defined in the data definition table (DDT) for the corresponding derived datafile.
[d]Hemisphere-corrected month, explored as a time-varying covariate, with an inflection point mid-July, according to: CovEffseason = 1+θseason● |season–7.5|, where season is a continuous variable ranging between 1 and 13.
[e]If identified by SCM, the observed baseline as covariate may be replaced by the individually-predicted baseline, post SCM.
[f]The covariates to be tested on on-/offset half-life are informed by FTIH study only, since Phase 3 data did not collect early or washout samples to inform this parameter.
[g]Subject's overall (time-invariant) NAb status will be tested as a dichotomous covariate in the exploratory SCM search. If found significant, two alternative NAb covariates may be tested manually (in model finalization): NAb as time-varying (dichotomous) and NAb as time varying with positive carried forward (so that subject does not go back to negative status after a positive sample).
Abbreviations: PD, pharmacodynamic

17.4.1.4. Final Model

17.4.1.4.1. PK Final Model

A 1-compartment model with first-order absorption and first-order elimination adequately described depemokimab PK (Figure 16, Figure 17). The exponents of body weight on clearance and volume of distribution in the final model were estimated. Other statistically significant covariate effects on PK model parameters were the followings: albumin, eGFR, Study population FTIH Asthma, Study population China PK HV, 2 mg dose, and participant population

CRSwNP on clearance; Asian race and Participant population HV on volume of distribution; abdomen injection site, age, participant population HV, Study population FTIH Asthma, and Study population China PK HV on ka; Study population FTIH Asthma and participant population CRSwNP on Frel. Sex, ADA, ALT, aspartate aminotransferase, total bilirubin are not significant covariates. The parameter estimates for the final covariate model are listed in Table 51. The relative standard error (RSE) for all parameters except the covariate effect of 2 mg dose on clearance were <32%. The relative high RSE for covariate effect of 2 mg dose on clearance (71%) may be related to the small number of subjects who received 2 mg dose (n=6). Low to moderate eta-shrinkage was observed for all parameters.

The effects of body weight, participant population, race, age, albumin, eGFR, injection site on the $AUC_{tau,ss}$ of depemokimab are explored in Figure 18. The effects of evaluated intrinsic factors (body weight, participant population, race, age, albumin, eGFR) are generally small, and unlikely to be clinically meaningful. Compared to a typical subject with body weight of 76 kg, participants with 95th percentile of body weight (108 kg) had a decrease of 25% in $AUC_{tau,ss}$, while participants with 5th percentile of body weight (54 kg) had an increase of 33% in $AUC_{tau,ss}$. The distribution of secondary PK parameters simulated for a virtual adolescent population was generally consistent with the predicted values of these parameters based on empirical Bayes estimates (EBEs) for adolescent patients, and both sets of parameter values for adolescent patients were comparable to the secondary PK parameters predicted based on EBEs for adult patients (Figure 19). The predicted exposure metrics, including average concentration during a dosing interval at steady state in patients with asthma and CRSwNP, were consistent with slightly lower exposure in patients with CRSwNP (Table 52). The individual post-hoc estimates of primary and secondary PK parameters from the final PK model were comparable across renal impairment groups, though the sample size of severe renal impairment group is limited (n=2) (Table 53).

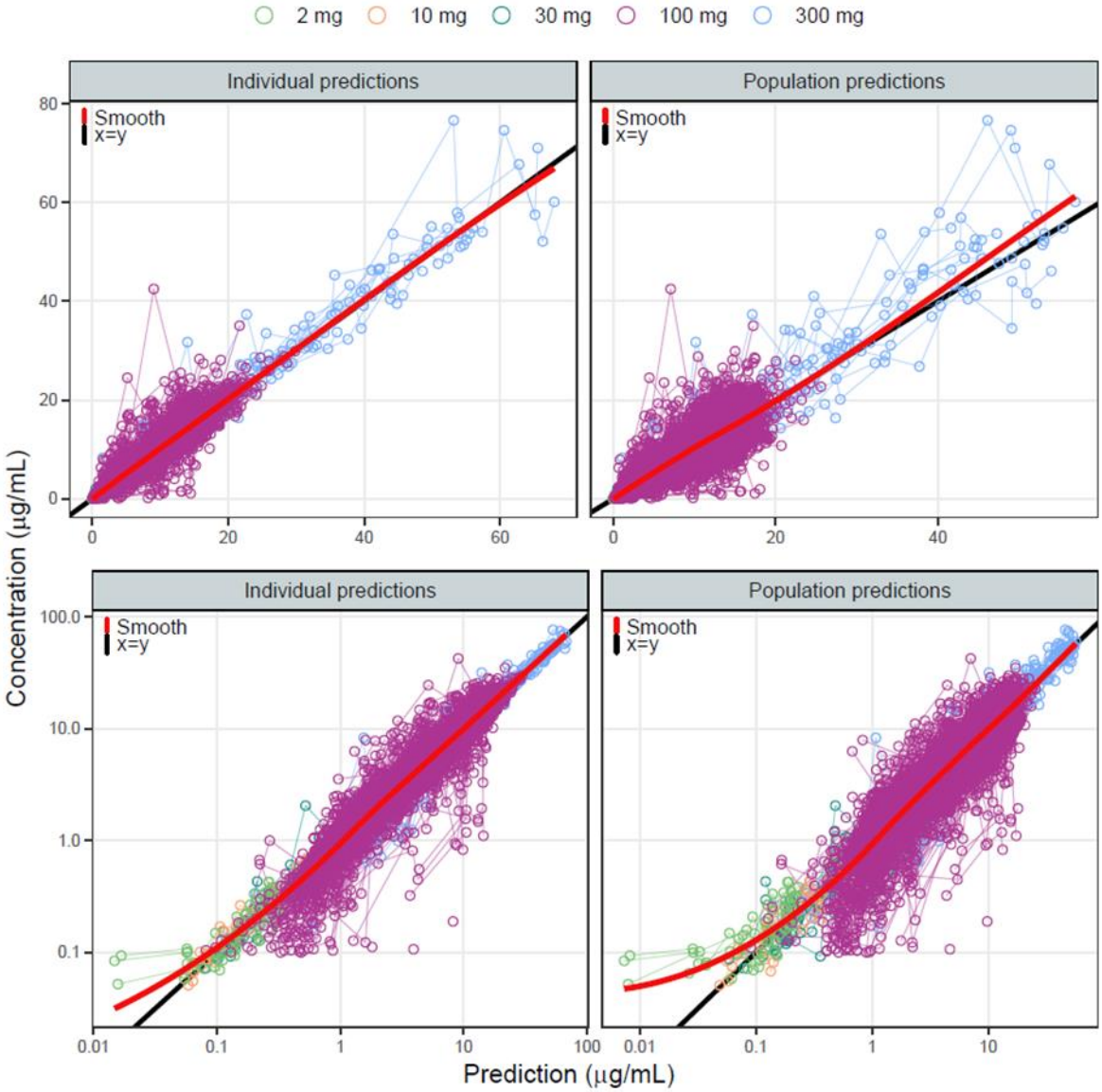
The geometric mean of apparent clearance, apparent volume of distribution, and terminal half-lives of depemokimab based on individual post-hoc PK estimates from the final model for patients in the SWIFT Asthma and ANCHOR CRSwNP studies were 0.0955 L/day, 6.55 L, and 47.5 days, respectively (Table 53).

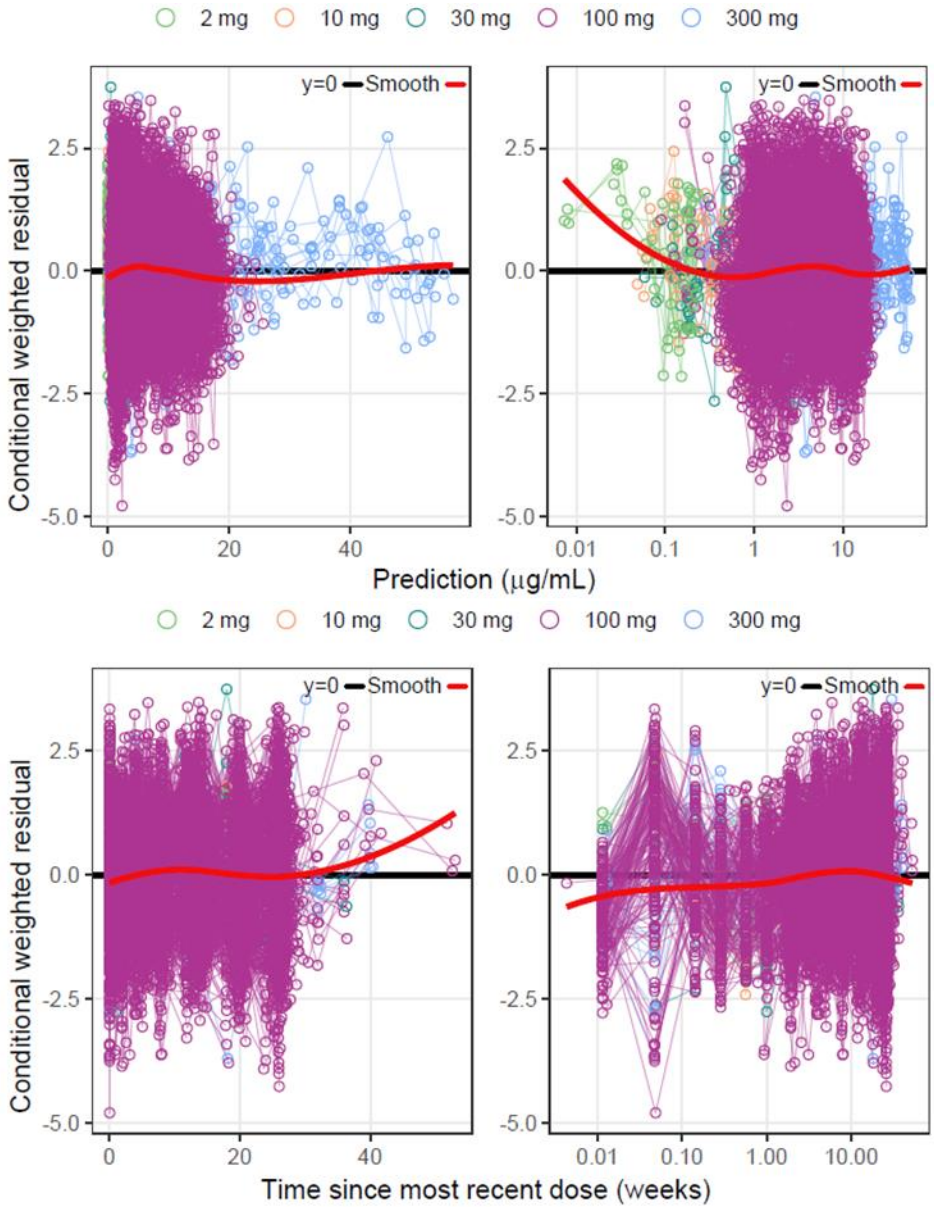
Table 51. Parameter Estimates for Final Population Pharmacokinetic Model

		Final PK model		
Run		11		
OFV		-15637.4		
Condition number		43.13		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL/F	(L/day)	0.0920	0.860	
V/F	(L)	6.29	0.997	
WT on CL	(allo. exponent)	0.841	3.78	
WT on V	(allo. exponent)	0.887	3.64	
F_{rel}		1.00	(FIX)	
k_a	(/day)	0.212	4.05	
TAD < 3h on RUV	†	5.18	7.58	
CRSwNP participant population on CL	(frac. change)	0.0625	16.3	
Albumin on CL	(frac. change per g/L)	-0.00684	23.2	
Estimated glomerular filtration rate on CL	(frac. change per mL/min/1.73 m^2)	0.00134	17.1	
Asian race on V	(frac. change)	0.0788	17.5	
CRSwNP participant population on F_{rel}	(frac. change)	-0.0509	29.3	
Age on k_a	(frac. change per year of age)	-0.00735	31.3	
Abdomen injection site on k_a	(frac. change)	0.520	23.9	
Study population FTIH Asthma on CL	(frac. change)	0.155	12.9	
Study population China PK HV on CL	(frac. change)	-0.219	8.79	
2 mg dose on CL	(frac. change)	-0.349	71.1	
Participant population HV on V	(frac. change)	-0.0513	24.9	
Study population FTIH Asthma on F_{rel}	(frac. change)	-0.173	17.2	
Participant population HV on k_a	(frac. change)	0.588	21.0	
Study population FTIH Asthma on k_a	(frac. change)	0.627	23.6	
Study population China PK HV on k_a	(frac. change)	0.405	27.9	
IIV CL	(CV)	0.101	6.06	10.2
IIV F_{rel}	(CV)	0.167	3.52	8.49
IIV k_a	(CV)	0.351	6.37	24.7
Correlation IIV F_{rel} - IIV k_a	(Cor)	0.638	6.74	
IIV RUV	(CV)	0.488	4.20	0.361
RUV	(CV)	0.178	1.95	2.04

Source: Applicant's Population PK report, Table A3-2
The estimated typical parameters are the values for a 75 kg, 50 years old, non-Asian SWIFT Asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 93.53 mL/min/1.73m2, receiving a dose of depemokimab, into the upper arm or thigh.
The IIV and RUV parameters are reported on the SD scale, which for exponential IIV and additive RUV on the log-scale corresponds to the approximate CV scale. The RSE for IIV and RUV parameters are reported on the approximate SD scale. The RSE for the correlation is reported for the square-root of the eta covariance. The continuous covariate effects are defined as the fractional change in parameter per one unit change in covariate. Allometric exponents are unitless as defined with power models.
Abbreviations: CL, clearance; CL/F, apparent clearance; CV, coefficient of variation; HV, healthy volunteer; IIV, interindividual variability; RSE, relative standard error; RUV, residual unexplained variability; SHR, subdistribution hazard ratio; V/F, volume of distribution; WT, wildtype.

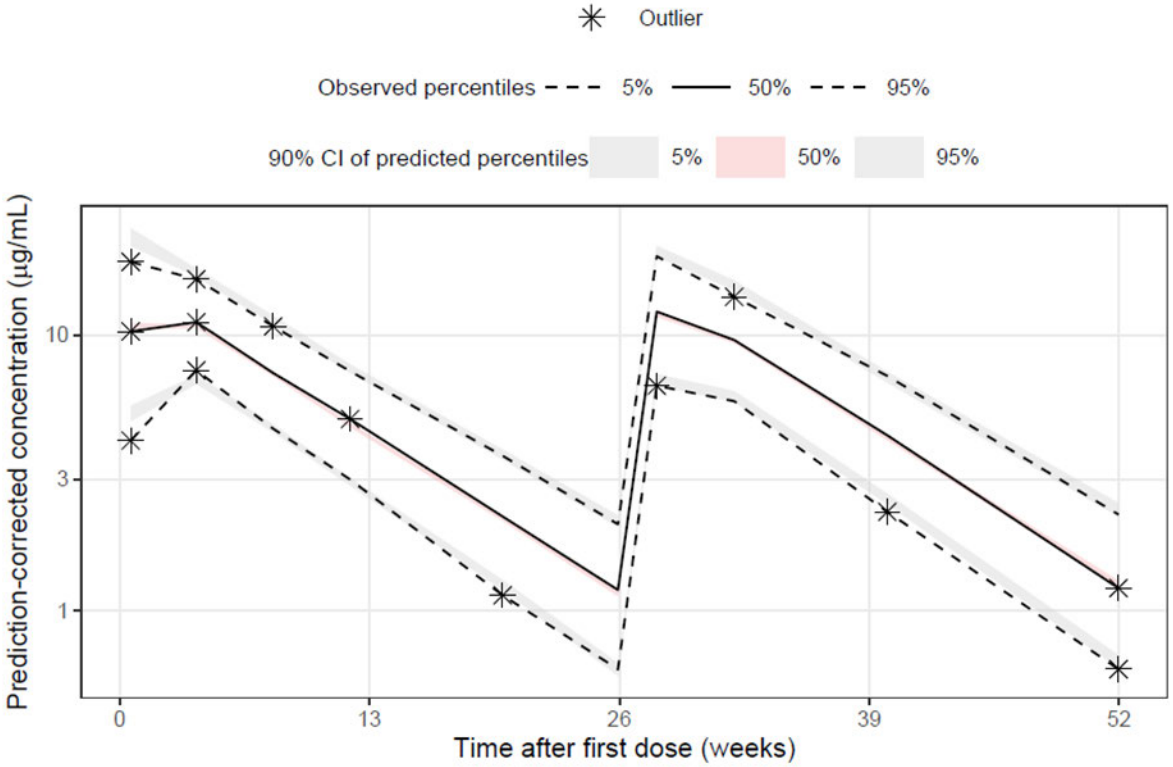
Figure 16. Goodness-of-Fit Plots for Final Population Pharmacokinetic Model





Source: Applicant's Population PK report, Figures A3-16, A3-18, and A3-20.

Figure 17. Prediction-Corrected Visual Predictive Check for Final Population Pharmacokinetic Model



Source: Applicant's Population PK report, Figure 11.
Data are presented on a semi-logarithmic scale.
Abbreviations: CI, confidence interval

Table 52. Summary Statistics of the Predicted Secondary PK Parameters Based on the Final Depemokimab PK Model for Subjects Receiving the Dose of 100 mg, Stratified by Study Populations of Interest

	SWIFT Asthma N=494	ANCHOR CRSwNP N=272	Overall N=766
$AUC_{\tau,ss}$ ($\mu g \cdot day/mL$)			
Mean (SD)	1120 (295.4)	982.0 (247.7)	1071 (286.9)
Geometric mean (%CV)	1081 (27.75)	950.3 (26.57)	1033 (28.06)
Median (min, max)	1090 (383.6, 2293)	968.0 (415.8, 1692)	1050 (383.6, 2293)
$C_{av,ss}$ (μg /mL)			
Mean (SD)	6.155 (1.623)	5.396 (1.361)	5.885 (1.577)
Geometric mean (%CV)	5.939 (27.75)	5.221 (26.57)	5.674 (28.06)
Median (min, max)	5.990 (2.108, 12.60)	5.319 (2.285, 9.297)	5.772 (2.108, 12.60)

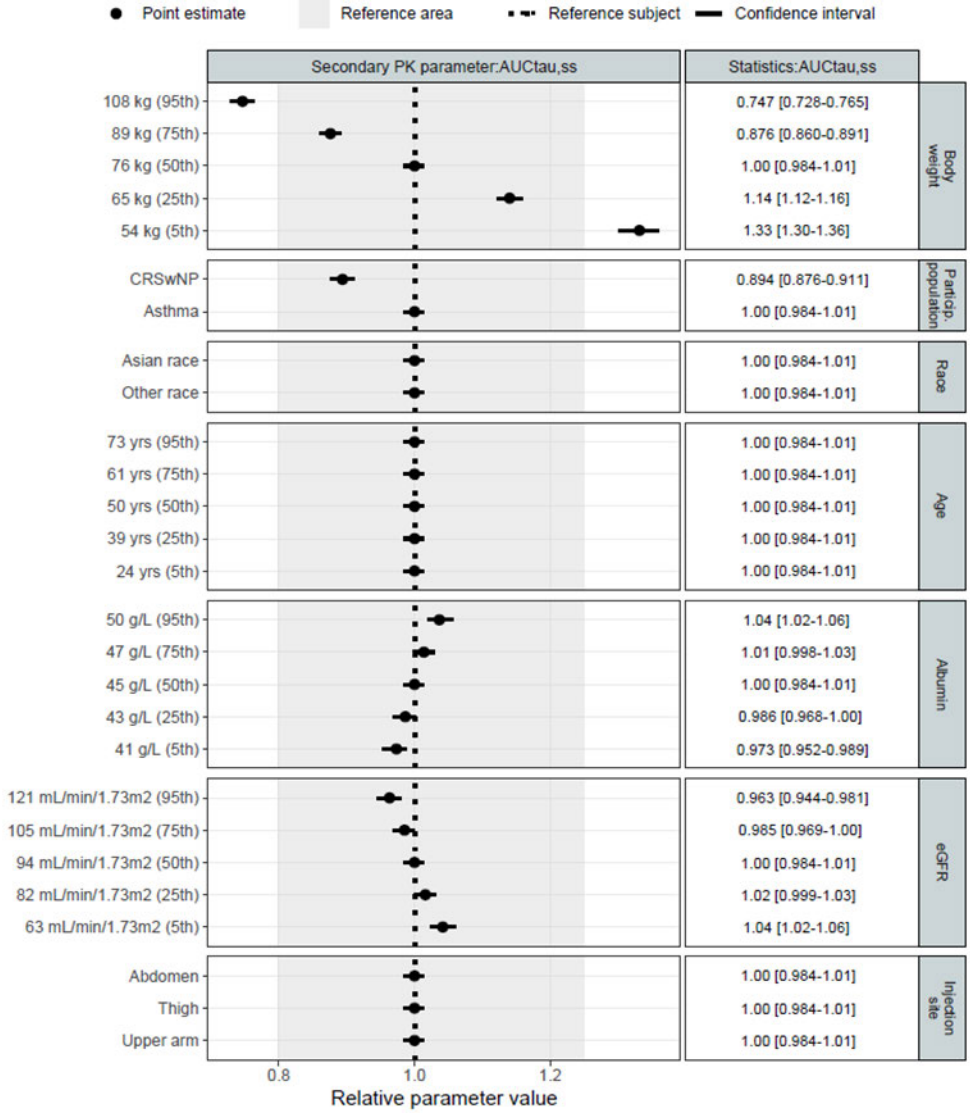
Source: Applicant's Population PK report, Tables S3.
Abbreviations: $AUC_{tau,ss}$, area under the curve over one dosing interval at steady state; $C_{av,ss}$, average plasma concentration at steady state; CRSwNP, chronic rhinosinusitis with nasal polyps; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviations

Table 53. Summary Statistics of the EBEs of the PK Parameters and Predicted Secondary PK Parameter Based on the Final Depemokimab PK Model for Subjects in SWIFT Asthma and ANCHOR CRSwNP Studies Stratified by Renal Impairment

	Normal N=398	Mild loss N=336	Mild to moderate loss N=30	Severe loss N=2	Overall N=766
CL/F (L/day)					
Mean (SD)	0.0976 (0.0229)	0.0975 (0.0196)	0.104 (0.0184)	0.0796 (0.0226)	0.0977 (0.0214)
Geometric mean (%CV)	0.0951 (23.1)	0.0956 (20.1)	0.102 (17.6)	0.0779 (29.5)	0.0955 (21.7)
Median (min, max)	0.0946 (0.0411, 0.198)	0.0967 (0.0514, 0.182)	0.102 (0.0747, 0.144)	0.0796 (0.0636, 0.0956)	0.0957 (0.0411, 0.198)
V/F (L)					
Mean (SD)	6.58 (1.39)	6.72 (1.20)	7.44 (1.24)	6.21 (2.02)	6.68 (1.32)
Geometric mean (%CV)	6.44 (20.7)	6.61 (18.0)	7.34 (16.7)	6.04 (34.0)	6.55 (19.6)
Median (min, max)	6.35 (3.42, 12.4)	6.59 (3.69, 11.8)	7.33 (4.93, 10.4)	6.21 (4.78, 7.63)	6.54 (3.42, 12.4)
k_a (/day)					
Mean (SD)	0.222 (0.0531)	0.199 (0.0461)	0.185 (0.0523)	0.194 (0.00333)	0.210 (0.0515)
Geometric mean (%CV)	0.215 (25.5)	0.194 (24.3)	0.178 (28.8)	0.194 (1.72)	0.204 (25.8)
Median (min, max)	0.217 (0.0981, 0.387)	0.198 (0.0949, 0.347)	0.170 (0.102, 0.308)	0.194 (0.191, 0.196)	0.208 (0.0949, 0.387)
F_{rel}					
Mean (SD)	0.998 (0.151)	0.994 (0.145)	1.03 (0.166)	1.08 (0.0445)	0.998 (0.149)
Geometric mean (%CV)	0.987 (15.6)	0.983 (15.1)	1.02 (16.1)	1.08 (4.14)	0.986 (15.4)
Median (min, max)	0.991 (0.574, 1.51)	0.998 (0.588, 1.38)	1.02 (0.776, 1.42)	1.08 (1.05, 1.11)	0.997 (0.574, 1.51)
$t_{1/2}$ (day)					
Mean (SD)	47.22 (4.742)	48.19 (4.541)	50.05 (4.908)	53.74 (2.278)	47.77 (4.707)
Geometric mean (%CV)	46.98 (10.14)	47.97 (9.652)	49.82 (9.905)	53.72 (4.242)	47.54 (10.01)
Median (min, max)	46.77 (32.09, 60.34)	48.34 (31.05, 60.33)	50.15 (39.69, 60.45)	53.74 (52.13, 55.35)	47.70 (31.05, 60.45)

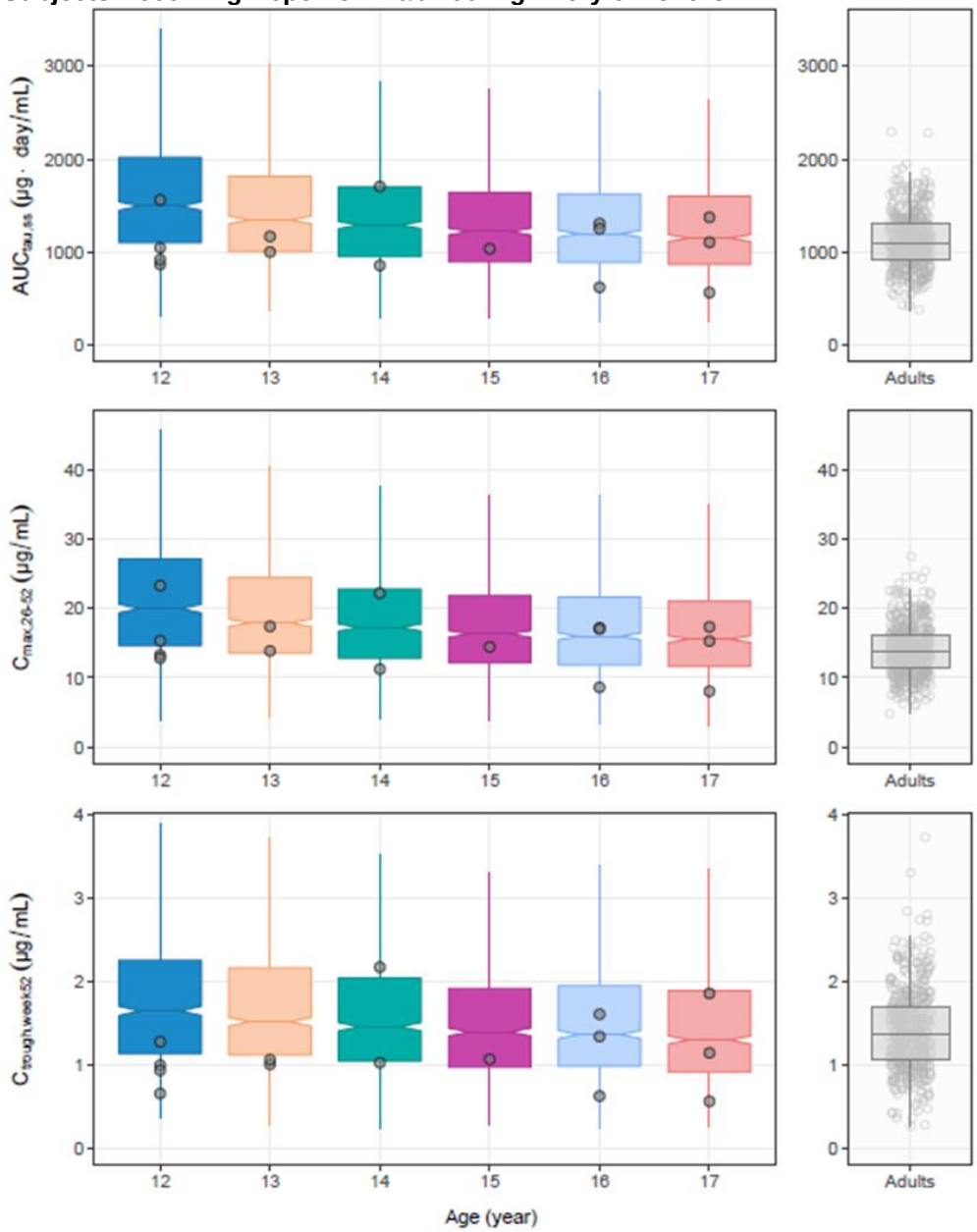
Source: Applicant's Population PK report, Tables A3-9, A3-10.
Abbreviations: CL/F, apparent clearance; CRSwNP, chronic rhinosinusitis with nasal polyps; CV, coefficient of variation; EBE, empirical Bayes estimates; Frel, relative bioavailability; PK, pharmacokinetic; SD, standard deviations; t1/2, terminal elimination half-life; V/F, apparent volume of distribution

Figure 18. Forest Plot for Covariate Effects on Depemokimab AUC_{ss} Relative to a Reference Subject



Source: Applicant's Population PK report, Figure S1.
Reference: 76 kg, 50 years, non-Asian asthma patient, with baseline albumin of 45 g/L and baseline eGFR of 94 mL/min/1.73m², receiving a dose of depemokimab 100 mg, into the upper arm.
Abbreviations: AUC_{ss}, area under the curve at steady state; $AUC_{tau,ss}$, area under the curve over one dosing interval at steady state; CRSwNP, chronic rhinosinusitis with nasal polyps; eGFR, estimated glomerular filtration rate; PK, pharmacokinetic

Figure 19. Box Plots of Simulated Depemokimab $AUC_{tau,ss}$, $C_{max,26-52}$ and $C_{trough,week52}$ for Adolescent Subjects Receiving Depemokimab 100 mg Every 6 Months



Source: Applicant's Population PK report, Figure 20.
Adolescents were sampled from the NHANES database (1000 subjects per age group). Overlayed grey dots are the predicted depemokimab $AUC_{t,ss}$, $C_{max,26-52}$ and $C_{trough,week52}$ for the adolescents from the prediction data file (N=15). As a comparator, box plots in grey represent the distribution of the predicted secondary PK metrics based on EBEs for the adult asthma patients from the prediction data file (N=479).
Abbreviations: $AUC_{tau,ss}$, area under the curve over one dosing interval at steady state; $C_{max,26-52}$, maximum plasma concentration from Week 26 to Week 52; $C_{trough,week\ 52}$, trough concentration at Week 52; EBE, empirical Bayes estimate; PK, pharmacokinetic

17.4.1.4.2. PK/PD Final Model

The final model was an indirect response drug-effect (inhibition of kin) model with the following covariates: predicted baseline blood eosinophils, CRSwNP participant population, age, weight, Asian race in Asthma population, and Asian race in CRSwNP population on Emax; FTIH Asthma

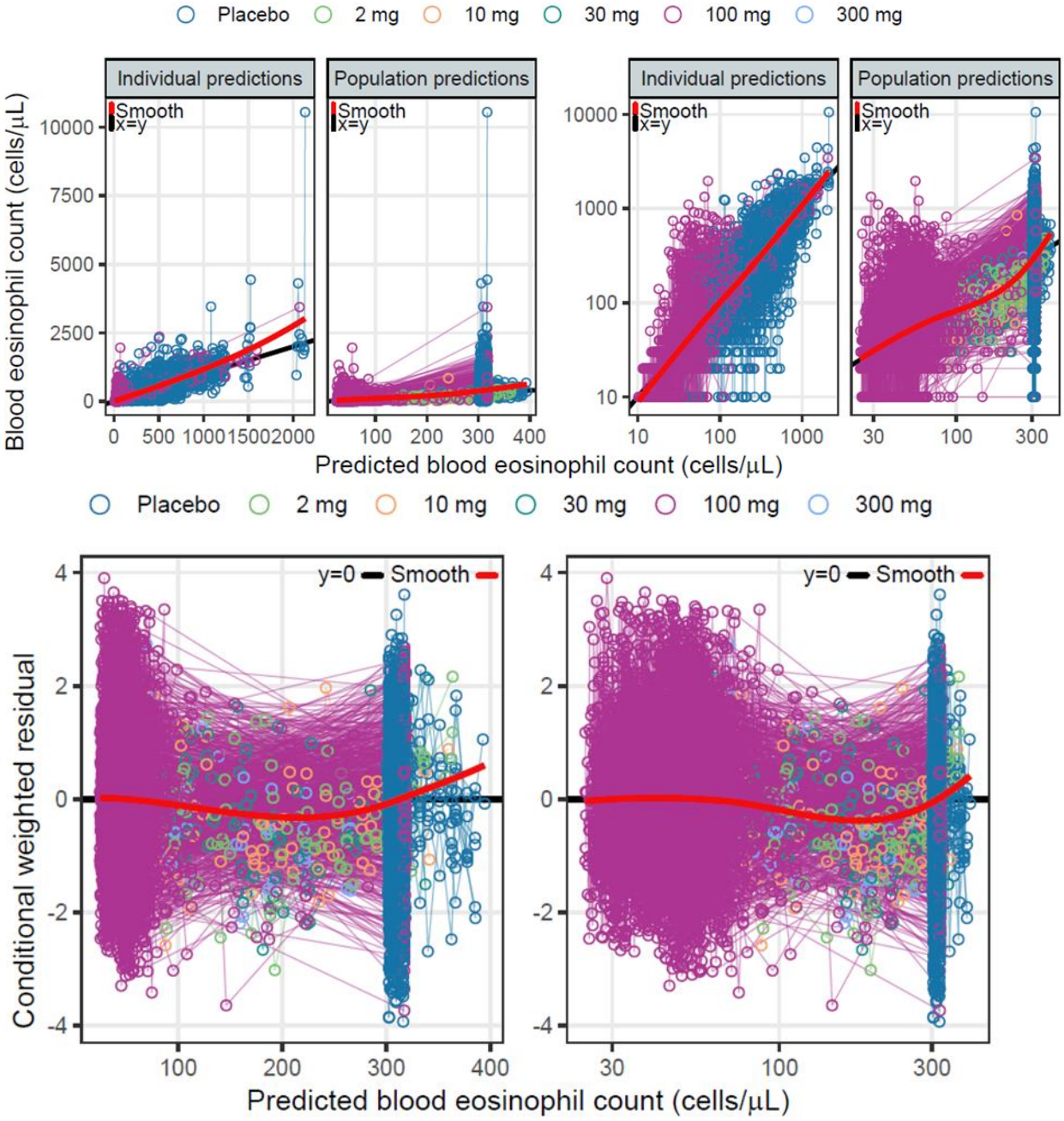
study population on EC_{50} and Pslp. The pooled PD data were adequately described by the final model (Figure 20, Figure 21). The parameter estimates for the final PD model are listed in Table 54. The RSE for all parameters except Asian race in CRSwNP population on Emax were <30%. The RSE for all the parameters were <41%. Overall, the precision of parameter estimates is reasonable. Eta-shrinkage was low for all the random effect parameters. The covariate effects of Asian race, predicted baseline blood eosinophil count (BEC), age, and body weight on the absolute BEC was small (Figure 22). The distribution of simulated PD metrics (absolute BEC and % BEC reduction at week 52) for the virtual adolescent population was generally consistent with those predicted based on EBEs for adolescent patients, and both sets of values for adolescent patients were comparable to the values of PD metrics predicted based on EBEs for adult patients (Figure 23).

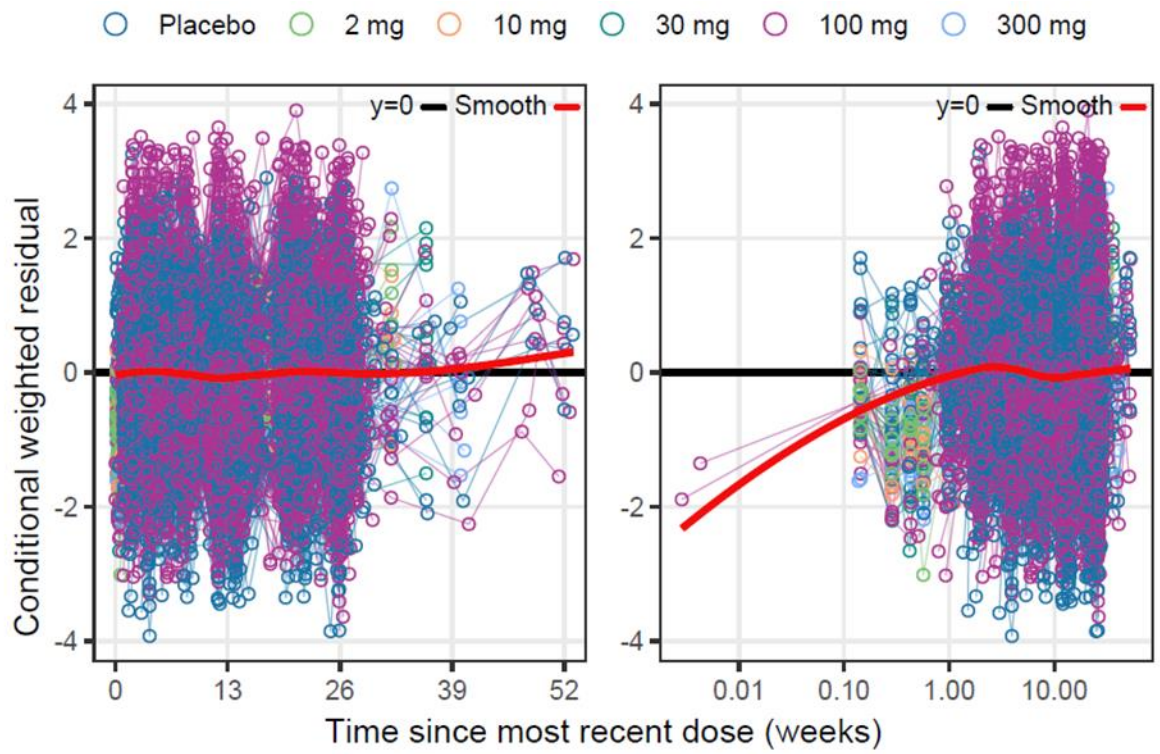
Table 54. Pharmacodynamic Parameter Estimates for Final Population Pharmacokinetic/ Pharmacodynamic Model

		Final model		
	Unit	Value	RSE (%)	SHR (%)
Baseline	cells/μL	317	2.05	
P_{slp} †	frac. change per year	-0.0466	29.5	
HL_{onset}	day	3.08	4.73	
E_{max} ††		0.848	0.564	
EC_{50} †	μg/mL	0.194	10.3	
Hill coefficient		1.64	6.11	
Predicted baseline blood eosinophils on E_{max} *	add. change on logit scale	0.834	4.93	
CRSwNP participant population on E_{max}	add. change on logit scale	0.320	14.7	
Age on E_{max}	add. change on logit scale per year of age	0.00660	21.4	
Weight on E_{max}	add. change on logit scale per kg	-0.00471	24.4	
Asian race in Asthma population on E_{max}	add. change on logit scale	0.450	15.3	
Asian race in CRSwNP population on E_{max}	add. change on logit scale	0.187	40.2	
FTIH Asthma study population on EC_{50}	frac. change	-0.561	9.12	
FTIH Asthma study population on P_{slp}	add. change	0.357	29.8	
Change in RUV for FTIH Asthma study population	frac. change	-0.242	17.9	
IIV RUV	CV	0.396	2.75	7.64
IIV Baseline	CV	0.646	2.89	6.94
IIV E_{max} ‡	SD	0.497	3.96	9.31
RUV†	CV	0.426	1.38	1.65

Source: Applicant's Population PK/PD report, Table 12.
The RSE for IIV and RUV parameters are reported on the approximate CV scale, except for IIV for Emax.
† The values represent the typical estimates for a subject belonging to the phase 3 studies.
†† The value represents the typical estimate for a non-Asian Asthma subject, with predicted baseline blood eosinophil count of 317 cells/mL, age of 54 years, and body weight of 77.4 kg.
* This represents the change in logit Emax per log unit change in predicted baseline blood eosinophil count centered around the log median.
‡ The IIV is presented as the SD on the logit scale. The corresponding CV for Emax was 0.0756, for the typical non-Asian patient from the SWIFT Asthma study. The CV was calculated using the following approximation: SD = $\theta\bullet(1-\theta)\bullet SD_{logit}$ and CV = SD/θ.
Add. and frac. stand for additive and fractional respectively.
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyps; CV, coefficient of variation; EC50, half-maximal effective concentration; E_{max}, maximal effective concentration; IIV, interindividual variability; RSE, relative standard error; RUV, residual unexplained variability; SD, standard deviation; SHR, sudistribution hazard ratio

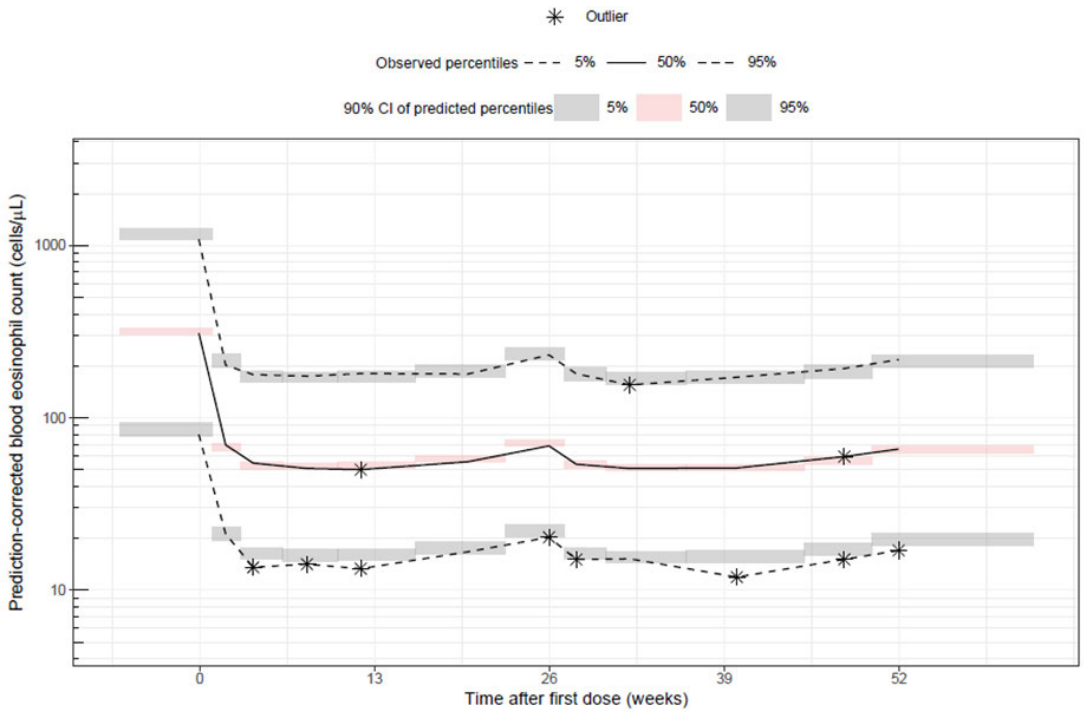
Figure 20. Goodness-of-Fit Plots for Final Population Pharmacokinetic/Pharmacodynamic Model



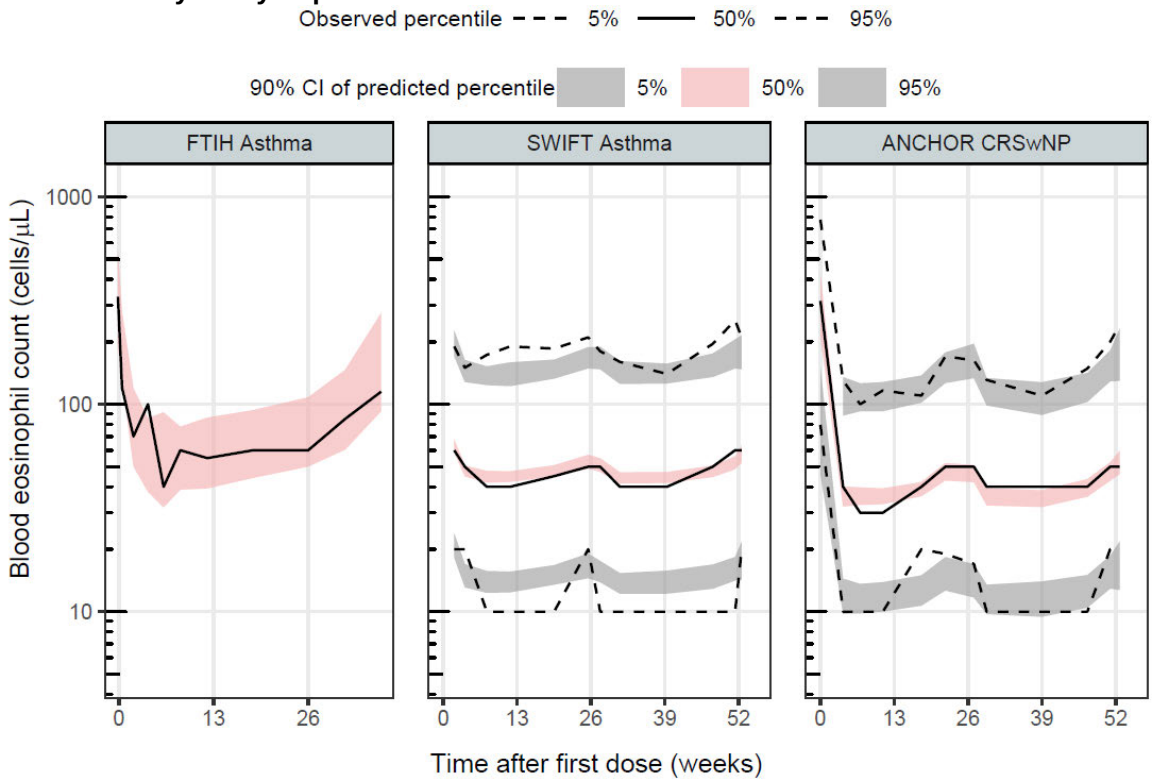


Source: Applicant's Population PK/PD report, Figures A3-5, A3-6 and A3-7.

Figure 21. Prediction-Corrected Visual Predictive Check for Final Population Pharmacokinetic/Pharmacodynamic Model
A: All Subjects

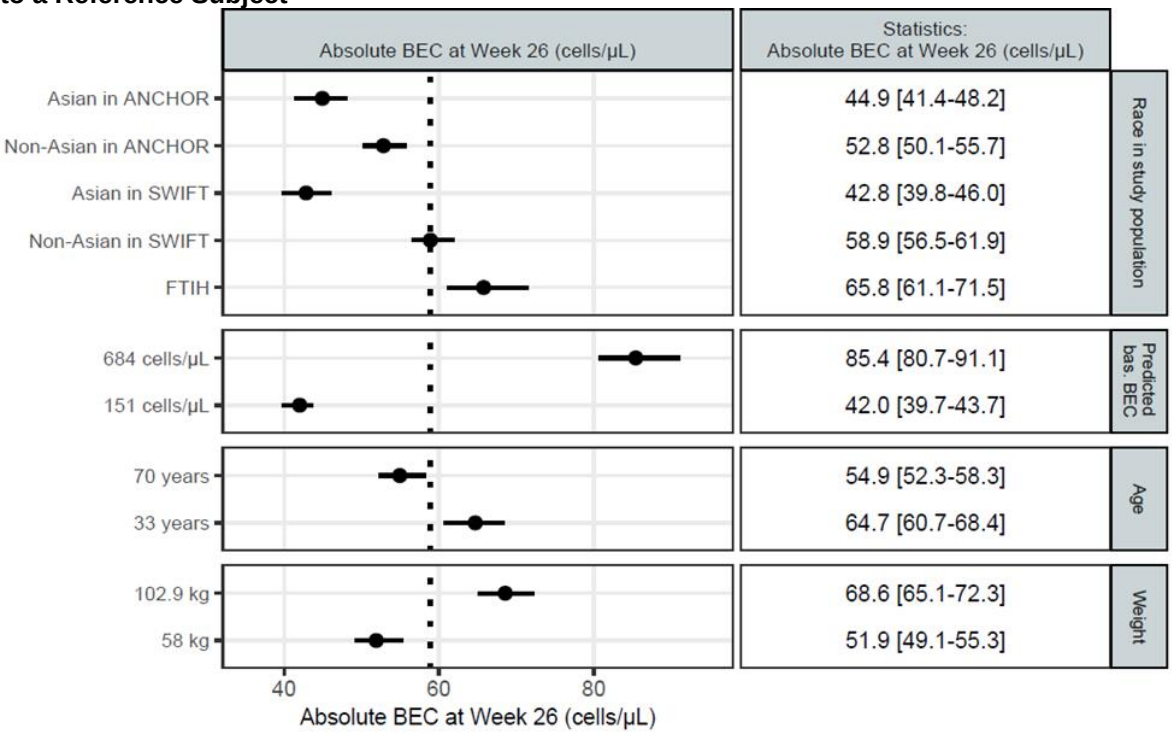


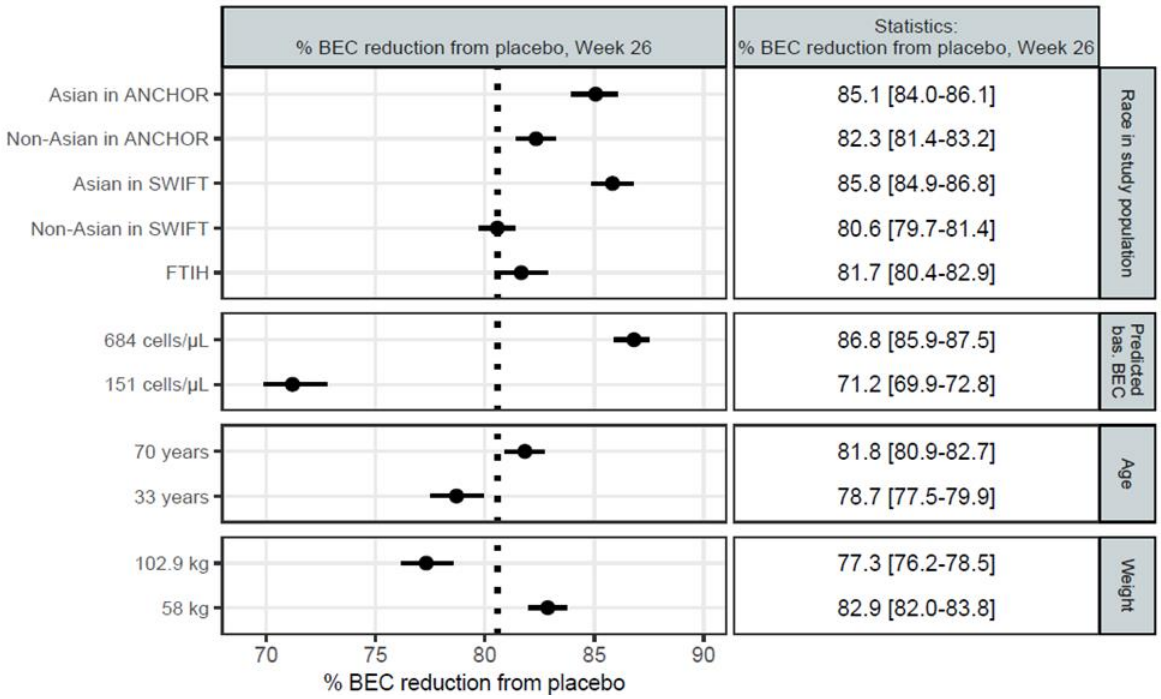
B: Stratified by Study Population



Source: Applicant's Population PK/PD report, Figures 19 and 21.
Abbreviations: CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps

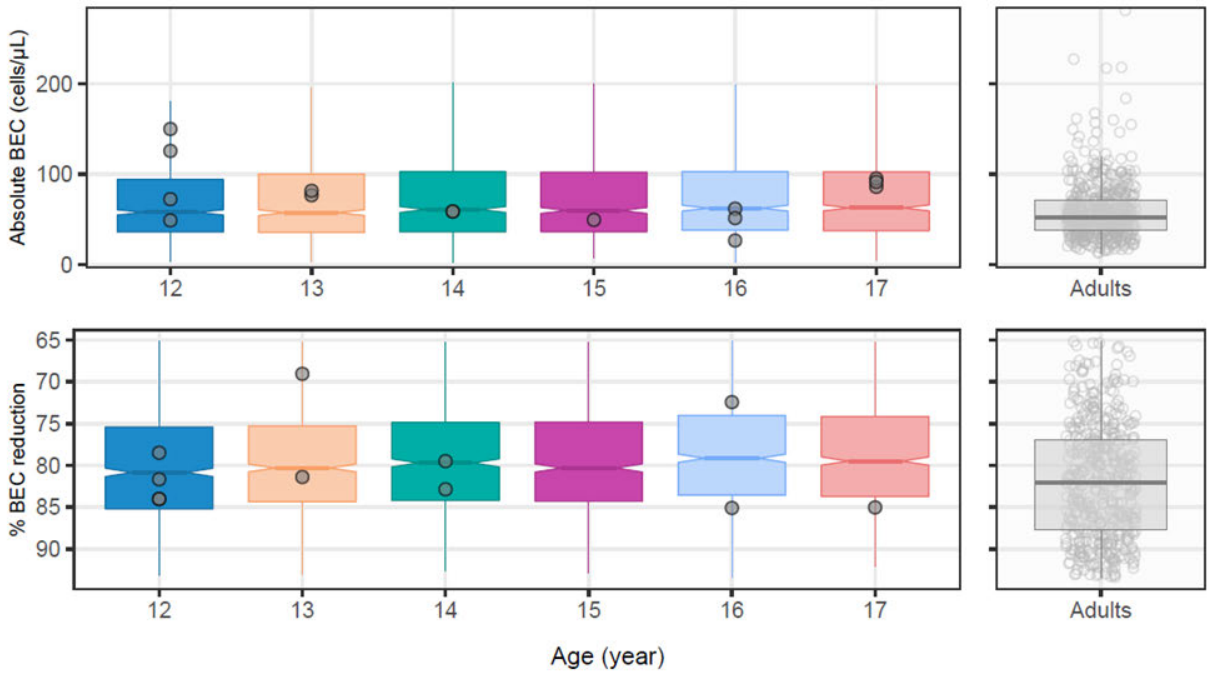
Figure 22. Forest Plot for Covariate Effect on Secondary Pharmacodynamic Parameters Relative to a Reference Subject





Source: Applicant's Population PK/PD report, Figure 24.
Reference: non-Asian in SWIFT study population, with 317 cells/µL at baseline, 54 y.o., 77.4 kg
Forest plots illustrating the effect of covariates on secondary PD parameters at Week 26, based on the final depemokimab PK and blood eosinophil count models and for a dosing regimen of 100 mg every 6 months. All covariates except predicted baseline blood eosinophil count impact both PK and PD parameters. The covariate values on the y-axis were used to generate the parameter predictions and represent the data either as the values of the categorical covariates or as the 10th and 90th percentiles of the continuous covariates. The specific values of the medians and 90% CIs shown in the Statistics box on the right-hand side of the parameter are calculated based on 250 sampled parameter vectors from the variance-covariance matrix of the final blood eosinophil count model, obtained from NONMEM. Hence, the concentrations derived from the depemokimab PK model are typical concentrations for each set of covariates (i.e., not including uncertainty nor IIV for PK). The parameter values for a reference subject (for whom covariate characteristics are provided below the plot) are shown by the dotted vertical line.
Abbreviations: BEC, blood eosinophil count

Figure 23. Box Plots of Simulated Depemokimab Secondary PD Metrics at Week 52 for Adolescents



Source: Applicant's Population PK/PD report, Figure 27.
The adolescent population was sampled from the NHANES database (1000 subjects per age group) overlayed with the corresponding predicted depemokimab secondary PD metrics for the adolescent patients in SWIFT Asthma population, randomized to active, of the analysis data file (N=15, grey dots), receiving depemokimab 100 mg every 6 months. As a comparator, box plots in grey represent the distribution of the predicted secondary PD metrics based on EBEs for the adults in SWIFT Asthma population, randomized to active, of the analysis data file (N=478). Simulations account for differences in race, age and body weight in PK and PD parameters, and include IIV.
Abbreviations: BEC, blood eosinophil count; EBE, empirical Bayes estimate; PD, pharmacodynamic; PK, pharmacokinetic

17.4.2. Exposure-Response Analysis

17.4.2.1. Review Summary

The ER analysis for primary efficacy endpoints in asthma is considered exploratory due to the limited range of exposure from one dose level. Among the patients with asthma who received depemokimab (100 mg every 6 months), there was no clear relationship between depemokimab PK/PD metrics and reduction in annualized asthma exacerbation rate. ER for safety analysis was not conducted as depemokimab has a favorable safety and tolerability profile.

17.4.2.2. Introduction

The primary objectives of Applicant's ER analysis were to conduct exposure-response analyses for the annualized rate of clinically significant exacerbations of asthma over the on- and post-treatment study periods.

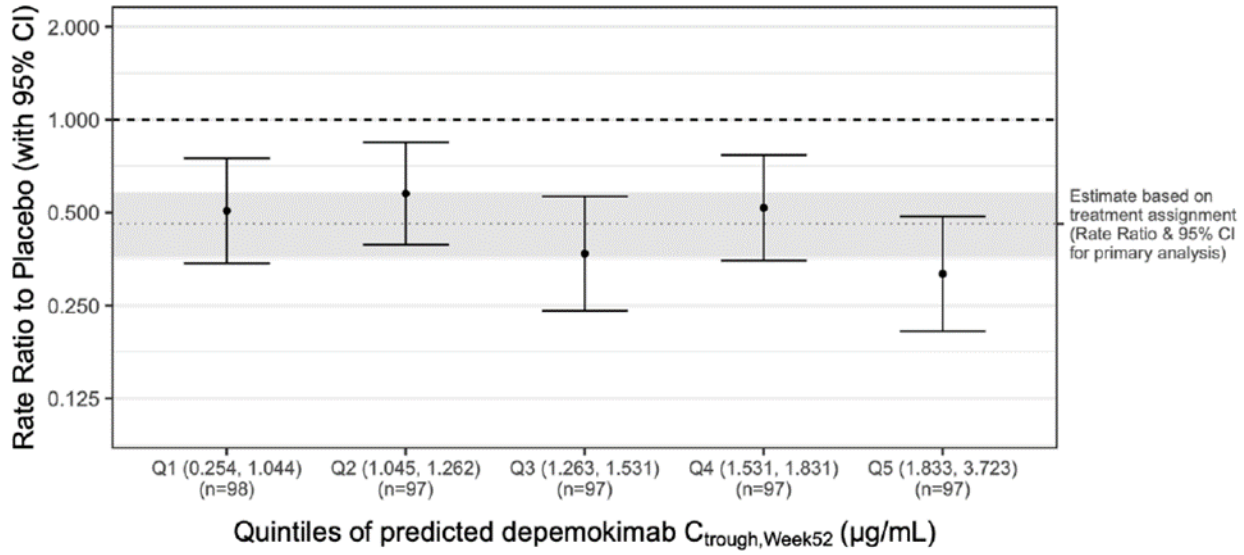
The following PK/PD metrics were evaluated in the ER analysis: $AUC_{tau,ss}$, $C_{trough,Week52}$, BEC_{Week52}, ratio to baseline BEC_{Week52} predicted based on post hoc parameter estimates from the final population PK/PD model, and observed $C_{trough,Week52}$, BEC_{Week52}, ratio to baseline BEC_{Week52}.

17.4.2.3. ER Analysis for Efficacy

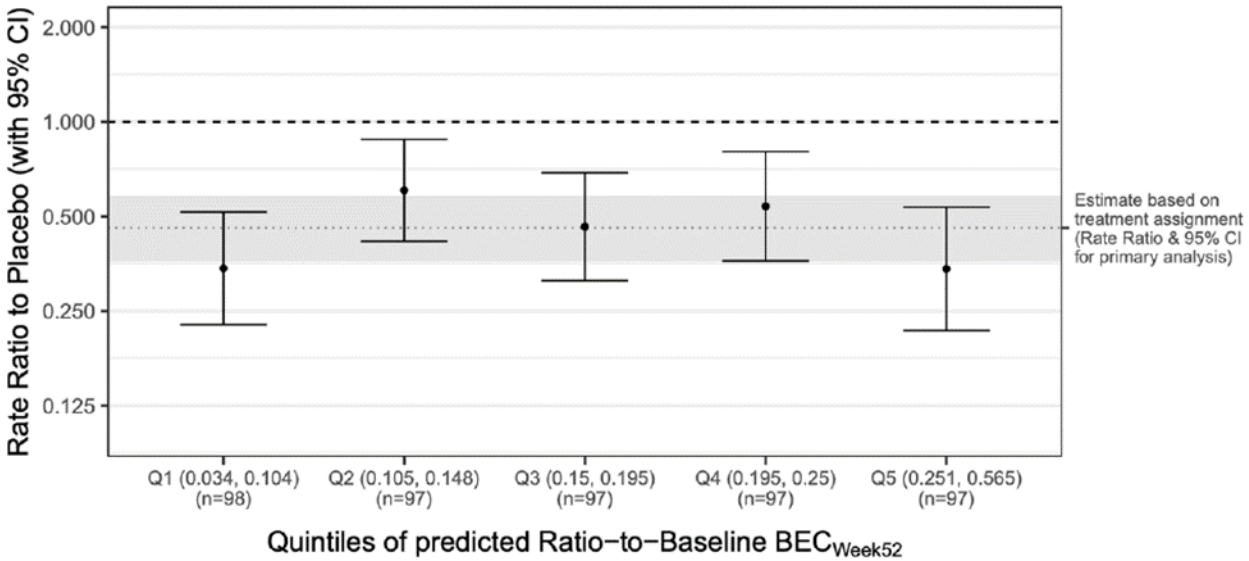
The efficacy endpoints is annualized rate of clinically significant exacerbations over the on- and posttreatment study periods (approximately 52+4 weeks). ER analysis was performed using exacerbation data from 742 participants (n=486/256 for depemokimab/placebo) in the Phase 3 studies (SWIFT-1 and SWIFT-2). The results from a negative binomial generalized linear model suggested that reduction in exacerbation rate compared to placebo was generally consistent across all quantiles of the assessed PK and PD metrics (Figure 24).

Figure 24. The Relationship Between PK/PD Metrics and Rate Ratio to Placebo for Annualized Rate of Clinically Significant Exacerbations of Asthma

A: Quintiles of predicted depemokimab $C_{trough,Week52}$



B: Quintiles of predicted Ratio-to-Baseline BEC_{Week52}



Source: Applicant's ER report, Figures 2 and 4.
Abbreviation: CI, confidence interval; $C_{trough, Week52}$, trough concentration at week 52; BEC_{Week52}, baseline eosinophil count at week 52; PD, pharmacodynamic; PK, pharmacokinetic18.5 Individual Study Reports

17.5. Individual Study Reports

17.5.1. Study 205722

Title

A randomized double-blind (sponsor open), placebo controlled, single ascending dose, first time in human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics, and pharmacodynamics of GSK3511294 [depemokimab] administered subcutaneously

Objectives

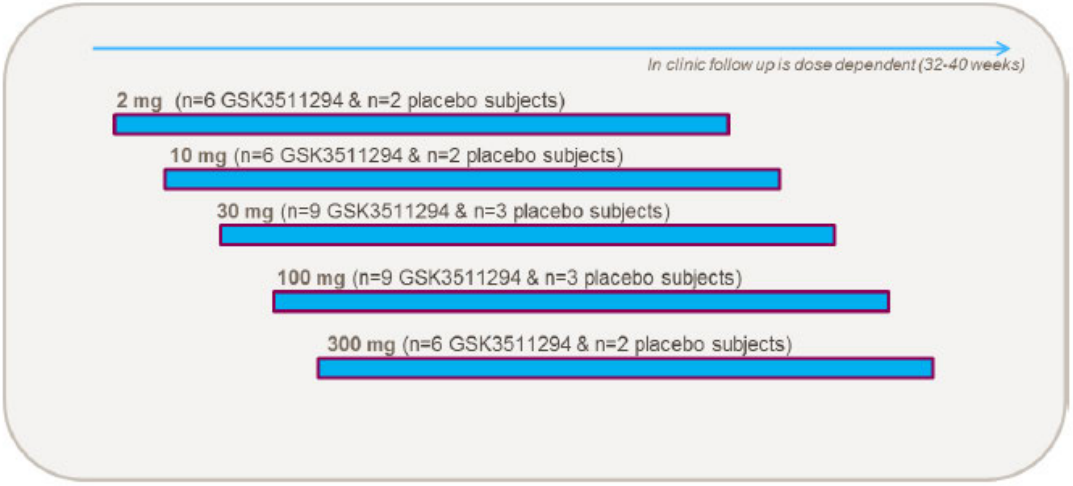
- **Primary:** Assess the safety and tolerability of single ascending doses of depemokimab administered as SC injection in subjects with mild to moderate asthma
- **Secondary:** Characterize depemokimab PK, PD (i.e., blood eosinophils), and immunogenicity following single ascending SC doses
- **Exploratory:** Assess serum total IL-5 and explore the PK/PD relationship of depemokimab following single ascending SC doses

Study Design

Study 205722 was a FIH, randomized, double-blind, placebo-controlled, parallel-group, single ascending dose study conducted in subjects with mild-to-moderate asthma (Figure 25). Subjects were randomized to receive single SC doses of 2, 10, 30, 100, and 300 mg depemokimab or placebo, after which they were followed for up to 40 weeks post-dose. Cohorts 1 (2 mg), 2 (10 mg) and 5 (300 mg) each consisted of 8 participants (6 depemokimab/2 placebo), while Cohorts 3 (30 mg) and 4 (100 mg) consisted of 12 participants (9 depemokimab/3 placebo). Of note, depemokimab was administered using the (b) (4) mg/mL formulation and the vialed presentation (not TBM).

This study enrolled male and female subjects aged 18 to 65 years (inclusive) with body weight ≥ 50 kg and body mass index (BMI) between 19 and 32 kg/m^2 (inclusive). Participants also had to have blood eosinophils ≥ 200 cells/µL at screening to be eligible for enrollment. Subjects were required to abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days or 5 half-lives (whichever was longer) prior to study medication administration and until completion of the follow-up visit. Permitted medications included acetaminophen (up to 2 grams per day) and hormone replacement therapy for women, along with standard of care for treatment of asthma, which was defined as SABA (i.e., albuterol, salbutamol as needed) and ICS alone, or ICS/LABA combination.

Figure 25. Overall Study Design for Study 205722



Source: CSR for Study 205722 (Figure 1, pg. 19)
Abbreviations: CSR, clinical study report; GSK3511294, depemokimab; N, number of subjects

PK, PD, and Immunogenicity Sampling

- PK samples were collected at pre-dose on Day 1, then post-dose at 2 h, 8 h, 24 h, 48 h, and 96 h, and at Weeks 1, 2, 4, 8, 12, 18, 24, 26, 32 (300 mg group only), 36 (30 and 100 mg groups only), and 40 (300 mg group only)
- PD samples (i.e., blood eosinophils) were collected at pre-dose on Day 1, then post-dose at 24 h, 48 h, 72 h, and 96 h, and at Weeks 1, 2, 4, 8, 12, 18, 24, 26, 32 (2, 10, and 300 mg groups only), 36 (30 and 100 mg groups only), and 40 (300 mg group only)
- Immunogenicity samples were collected at pre-dose on Day 1, then post-dose at Weeks 2, 4, 8, 12, 18, 24, 26, 32 (2, 10, and 300 mg groups only), 36 (30 and 100 mg groups only), and 40 (300 mg group only)

Subject Disposition and Demographics

A total of 48 subjects with mild to moderate asthma (FEV1 ≥ 60%, asthma maintained controlled on as-needed SABA and stable dose of ICS/stable dose of ICS/LABA combination therapy) were randomized, including 12 subjects who received placebo and 36 subjects who received a single SC dose of depemokimab 2 mg (N = 6), 10 mg (N = 6), 30 mg (N = 9), 100 mg (N = 9), and 300 mg (N = 6). All subjects completed the study as planned. There was some variation in baseline body weight between treatment groups, with a mean (SD) of ranging from 76.6 (7.7) kg for the 100 mg cohort up to 87.9 (6.9) kg for the 10 mg cohort.

PK/PD Analysis

PK and PD analyses were conducted based on the PK and PD populations, respectively, which consisted of all 36 subjects who received a single dose of depemokimab and had at least one quantifiable PK/PD sample for analysis. PK parameters were estimated using noncompartmental analyses (NCA) and summarized descriptively according to the dose of depemokimab received. Additionally, the Applicant analyzed depemokimab PK concentrations using a population PK/PD modeling approach, whereby post-hoc individual predicted plasma

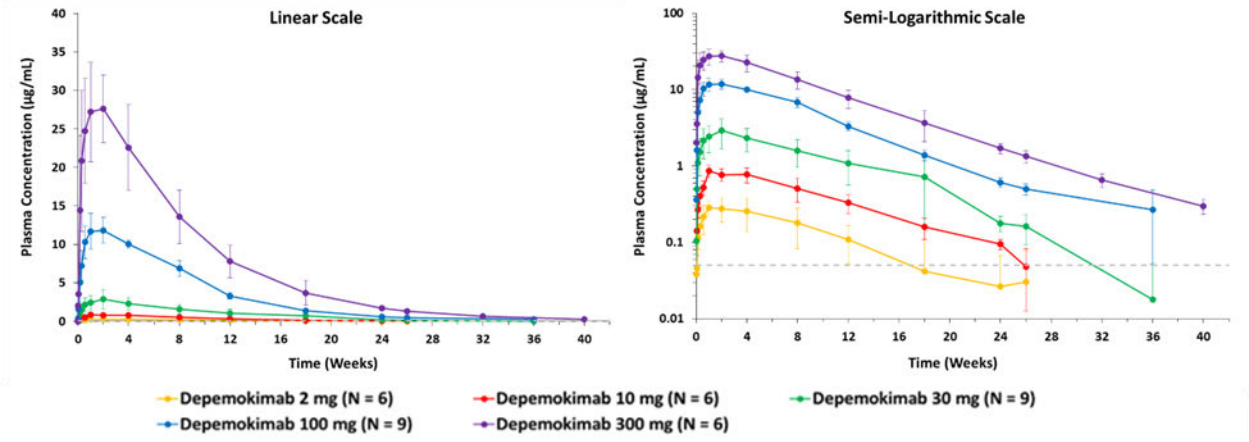
concentrations were merged with blood eosinophil data to assess ER and dose-response of depemokimab. Notably, these analyses supported the Applicant's phase 3 dose selection. Refer to Section 17.4 for additional discussion of the adequacy of the Applicant's population PK/PD and ER analyses.

Three subjects had measurable depemokimab plasma concentrations at pre-dose: two subjects in the 2 mg cohort (801 and 810) and one in the 300 mg cohort (247), with respective concentrations of 0.111 µg/mL, 0.117 µg/mL, and 0.154 µg/mL, representing 26.2%, 27.3%, and 0.5% of their C_{max}, respectively. None of these participants were excluded from the PK population. These measurable pre-dose concentrations were included without imputation in the plasma concentration summary statistics but were replaced by zero for the derivation of PK parameters. However, these three pre-dose concentrations were excluded from the population PK analysis.

PK Results

Arithmetic mean (SD) depemokimab concentration-time profiles by dose cohort are shown below in Figure 26. NCA-derived PK parameters for each depemokimab dose group are summarized below in Table 55. Depemokimab exposure (C_{max} and AUC) was approximately dose proportional across the dose range of 10 to 300 mg, with a less than dose proportional increase in exposure noted from 2 to 10 mg. Median T_{max} ranged from approximately 8 to 14 days, with geometric mean terminal half-life ranging from 38 to 53 days, neither of which appeared to be dose-dependent. Of note, given the large percentage of extrapolated AUC for the 2 mg cohort (> 20%), estimates of AUC_{inf}, terminal half-life, apparent clearance (CL/F), and apparent volume of distribution from this cohort should be interpreted with caution.

Figure 26. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile by Dose Group (PK Population; Study 214099)[a]



Source: Reviewer's analysis based on adpc.xpt for Study 205722
[a] Grey dashed line represents LLOQ of 0.05 µg/mL; Values below LLOQ were imputed as 0
Abbreviations: LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Table 55. Summary of Depemokimab PK Parameters Following SAD SC Dosing in Subjects With Mild to Moderate Asthma (PK Population; Study 205722)

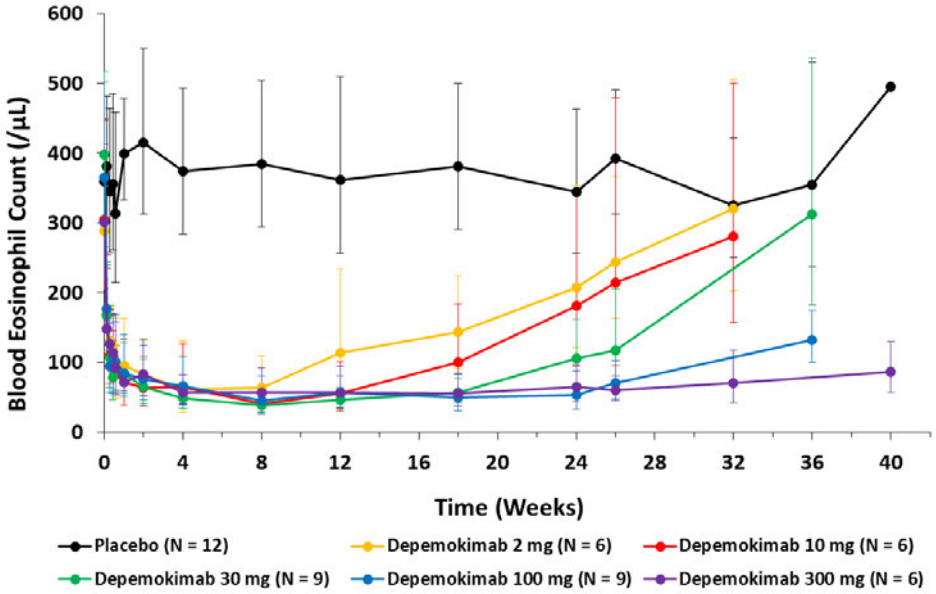
	Depemokimab Single SC Administration				
PK Parameter[a]	2 mg[b] (N=6)	10 mg (N=6)	30 mg (N=9)	100 mg (N=9)	300 mg (N=6)
AUC_{inf} (day*µg/mL)	24.8 (51.6)	68.9 (23.6)	208.3 (39.6)	846.7 (7.3)	1873.7 (25.5)
AUC_{last} (day*µg/mL)	18.4 (59.2)	62.1 (28.4)	201.4 (41.1)	830.2 (7.4)	1855.6 (25.8)
C_{max} (µg/mL)	0.34 (25.3)	0.88 (18.3)	2.81 (41.1)	12.25 (15.9)	28.60 (23.3)
CL/F (L/day)	0.0807 (51.6)	0.1451 (23.6)	0.1440 (39.6)	0.1181 (7.3)	0.1601 (25.5)
$t_{1/2}$ (day)	52.5 (37.3)	43.9 (16.2)	37.6 (10.7)	38.9 (11.7)	40.4 (6.3)
T_{max} (day)	11.0 (7.0, 28.0)	8.0 (7.0, 28.9)	13.9 (4.0, 28.0)	14.0 (4.0, 16.0)	13.9 (2.0, 15.0)
Vz/F (L)	6.1 (37.3)	9.2 (34.7)	7.8 (40.4)	6.6 (12.1)	9.3 (30.6)

Source. Reviewer's analysis based on adpp.xpt for Study 205722
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] Geometric mean %AUCex for the 2 mg dose group was approximately 24%
Abbreviations: %AUCex, percentage of AUC_{inf} obtained by extrapolation; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC from 0 to last timepoint sampled; C_{max}, maximum plasma concentration; CL/F, apparent clearance; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SAD, single ascending dose; SC, subcutaneous; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution during the terminal phase

PD Results

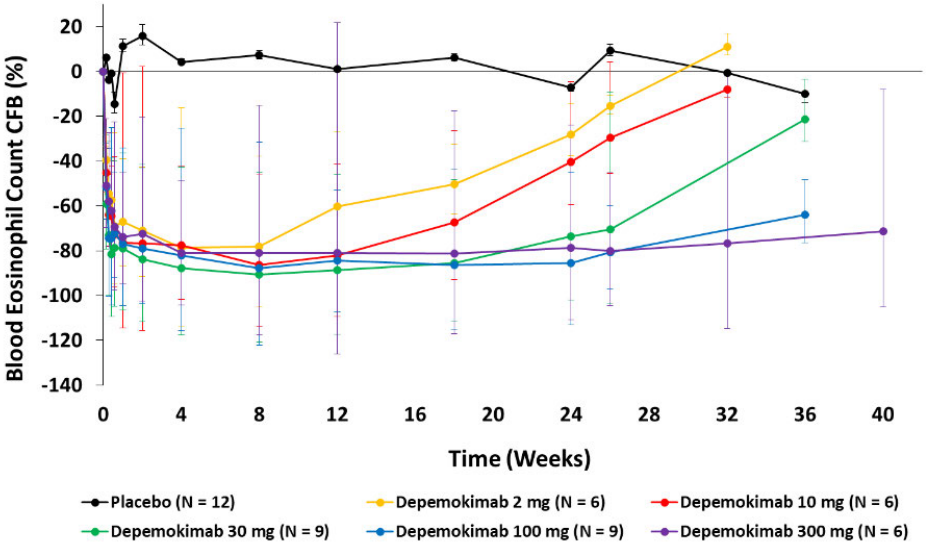
The geometric mean (95% CI) absolute and percent change from baseline blood eosinophil count over time for each treatment cohort is shown below in Figure 27 and Figure 28, respectively. The geometric mean baseline blood eosinophil count ranged from 288 to 398 cells/µL across the depemokimab groups, compared to 359 cells/µL in the placebo group. In all depemokimab dose cohorts, there was a notable reduction in eosinophils by the first post-dose assessment (Day 2), compared to minimal change in the placebo group. Peak eosinophil suppression was observed in most cohorts at Week 8, the magnitude of which was comparable across doses. However, the duration of eosinophil suppression appeared to be dose-dependent, with higher doses affording a more sustained inhibition of blood eosinophils. At 6 months post-dose (Week 26), both the 100 mg and 300 mg dose groups maintained a blood eosinophil reduction from baseline exceeding 80% (GMRs of 0.193 and 0.198, respectively).

Figure 27. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Dose Group (PD Population; Study 205722)



Source: Generated by reviewer from CSR for Study 205722 (Table 5.1, pg. 578-587)
Abbreviations: CI, confidence interval; CSR, clinical study report; N, number of subjects; PD, pharmacodynamic

Figure 28. Geometric Mean (95% CI) Percent Change From Baseline in Blood Eosinophil Count Over Time by Dose Group (PD Population; Study 205722)

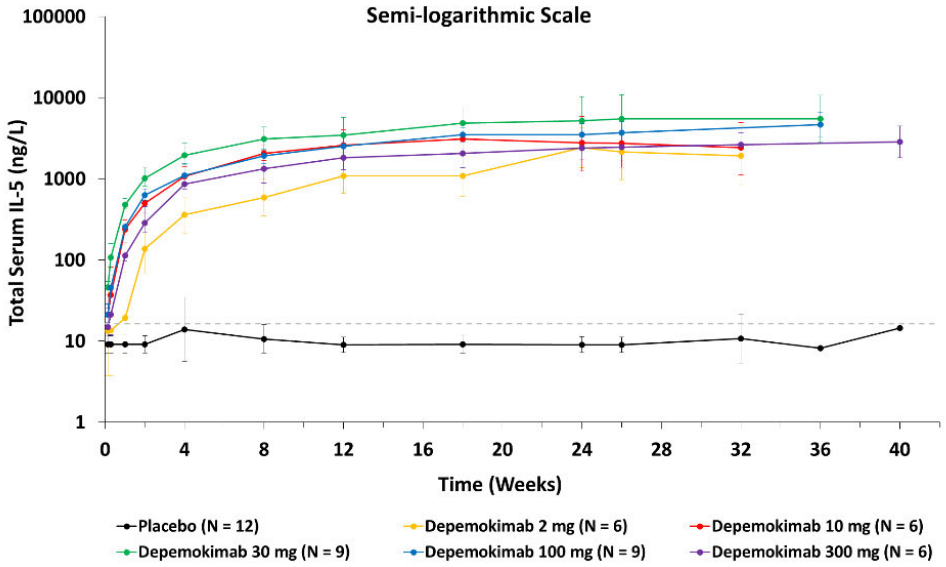


Source: Generated by reviewer from CSR for Study 205722 (Table 5.1, pg. 578-588)
Abbreviations: CFB, change from baseline; CI, confidence interval; CSR, clinical study report; N, number of subjects; PD, pharmacodynamic

The geometric mean (95%) total serum IL-5 (i.e., free IL-5 plus IL-5 bound to depemokimab) for each treatment cohort is depicted below in Figure 29. Baseline IL-5 was slightly lower in the placebo group (9.21 ng/L) compared to the depemokimab cohorts (10.38 to 15.11 ng/L), although most subjects had baseline values that were below the LLOQ (16.38 ng/mL). An increase from baseline in total serum IL-5 was observed post-dose for all depemokimab dose

groups, although no dose-dependent response was identified. Conversely, no notable change from baseline in total serum IL-5 was observed for placebo-treated subjects.

Figure 29. Geometric Mean (95% CI) Total Serum IL-5 Over Time by Dose Group (PD Population; Study 205722)[a]



Source: Generated by reviewer from CSR for Study 205722 (Table 5.7, pg. 622-626)
[a] Grey dashed line represents LLOQ of 16.38 µg/mL; Values below the LLOQ were imputed as LLOQ/2
Abbreviations: CI, confidence interval; CSR, clinical study report; IL-5, interleukin-5; LLOQ, lower limit of quantitation; N, number of subjects; PD, pharmacodynamic

Immunogenicity Results

A summary of immunogenicity results for all placebo- and depemokimab-treated subjects in Study 205722 is provided below in Table 56. All subjects were ADA-negative at baseline and all placebo-treated subjects remained ADA-negative at all timepoints throughout the study. A total of 25% (9/36) of depemokimab-treated subjects had a positive post-baseline ADA result, with the earliest ADA-positive timepoint occurring at Week 18 (Day 127). The majority of ADA-positive subjects were in the 30 mg dose group. Except for one subject with a transient ADA-positive result (defined as ADA detected only at one sampling time point during the treatment or at two or more sampling time points in a period less than 16 weeks, and the subject's last sampling time point is ADA-negative), all ADA-positive subjects had persistent responses (defined as ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples [irrespective of any negative samples in between] are separated by a period of 16 weeks or longer, or ADA detected only in the last sampling time point). Additionally, titers were generally low, ranging from 80 to 320. Immunogenicity samples were not assessed for the presence of NAbs in this study.

There did not appear to be any major differences in depemokimab PK or PD responses between ADA-positive and ADA-negative subjects. Regarding safety events, 22% (N = 2) and 33% (N = 3) of ADA-positive subjects reported headache and nasopharyngitis, respectively, compared to 26% (N = 7) and 37% (N = 10) among ADA-negative subjects, indicating no major difference in safety parameters as a function of ADA status.

Table 56. Summary of Immunogenicity Results (Safety Population; Study 205722)[a]

	Treatment Group					
ADA Parameter	Placebo (N=12)	2 mg (N=6)	10 mg (N=6)	30 mg (N=9)	100 mg (N=9)	300 mg (N=6)
Pre-existing ADA+	0	0	0	0	0	0
Postbaseline ADA+	0	0	1 (17%)	5 (56%)	2 (22%)	1 (17%)
Transient[b]	0	0	0	0	1 (11%)	0
Persistent[c]	0	0	1 (17%)	5 (56%)	1 (11%)	1 (17%)
ADA titer[d]	-	-	80 (80, 80)	160 (80, 320)	80 (80, 80)	80 (80, 80)

Source. Adapted from CSR for Study 205722 (Table 26, pg. 84-85)
[a] Safety population defined as all subjects who received at least one dose of study intervention (N = 48)
[b] Defined as ADA detected only at one sampling time point during the treatment or at two or more sampling time points in a period less than 16 weeks, and the subject's last sampling time point is ADA-negative
[c] Defined as ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or ADA detected only in the last sampling time point
[d] Reported as median (min, max)
Abbreviations: ADA, anti-drug antibody; CSR, clinical study report; N, number of subjects

17.5.2. Study 214099

Title

An open-label, randomized, single-dose, multicenter, parallel-group study to compare the pharmacokinetics of subcutaneous depemokimab when delivered with a safety syringe device or an autoinjector in healthy adult participants

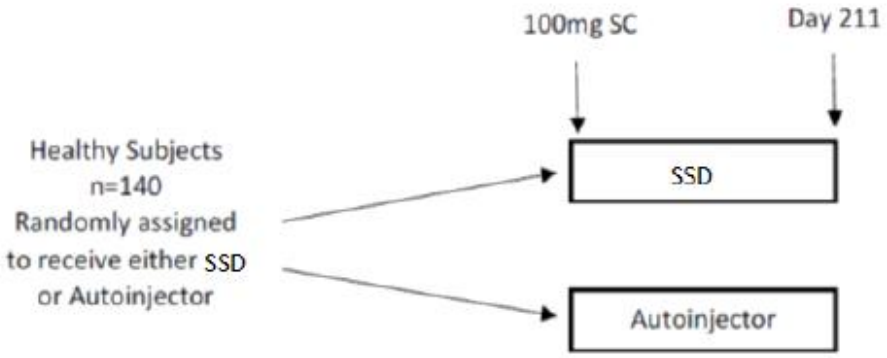
Objectives

- **Primary:** Characterize and compare the PK of depemokimab following a single SC injection administered via SSD or AI device presentations
- **Secondary:** Characterize the safety, tolerability, and immunogenicity of depemokimab following a single SC injection administered via SSD or AI device presentations
- **Exploratory:** Evaluate depemokimab PD (i.e., blood eosinophils) and compare depemokimab PK following single SC injection administered to different sites of injection, including the upper arm, thigh, and abdomen

Study Design

Study 214099 was a phase 1, randomized, open-label, parallel-group, single-dose study in healthy adult subjects (Figure 30). A parallel study design was considered acceptable due to the prolonged half-life of depemokimab (approximately 5 to 7 weeks), which limits the feasibility of a crossover study design. Subjects were stratified by body weight (i.e., < 70 kg, 70 to < 80 kg, and ≥ 80 kg) and then randomized in a 1:1:1:1:1:1 ratio to one of six groups according to device (i.e., SSD or AI) and injection site (i.e., abdomen, thigh, or upper arm). All subjects received a single 100 mg SC dose of depemokimab.

Figure 30. Overall Study Design for Study 214099



Source: CSR for Study 214099 (Figure 1, pg. 36)
Abbreviations: CSR, clinical study report; SC, subcutaneous; SSD, safety syringe device

The study enrolled male and female subjects aged 18 to 50 years (inclusive) with body weight ≥ 50 kg and BMI between 19 and 30 kg/m^2 (inclusive). Subjects were required to abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to study intervention until completion of the follow-up visit. Treatment with biologic agents (such as mAbs, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing was also prohibited. Acetaminophen (up to 2 grams per day) was permitted, along with any approved COVID-19 vaccine, provided it was received more than 14 days prior to depemokimab administration.

PK, PD, and Immunogenicity Sampling

- PK samples were collected at pre-dose on Day 1, then post-dose at 2 h, 8 h, 24 h, 48 h, and 96 h, and at Weeks 1, 2, 4, 8, 12, 18, 24, and 26
- PD samples (i.e., blood eosinophils) were collected at pre-dose on Day -1, then post-dose at Weeks 1, 4, 8, 12, 24, and 26
- Immunogenicity samples were collected at pre-dose on Day 1, then post-dose at Weeks 4, 8, 12, and 26

Subject Disposition and Demographics

A total of 140 healthy participants were randomized and received a single dose of depemokimab 100 mg SC, of which 70 subjects were assigned to both the SSD and AI groups. Within each device presentation arm, approximately 23 to 24 subjects were randomized to each injection site. The mean (SD) body weight at baseline was 71.9 (11.3) and 73.2 (10.9) kg in the SSD and AI groups, respectively. Within each device presentation arm, a larger proportion of subjects with body weight < 70 kg were enrolled compared with the 70 to < 80 kg and ≥ 80 kg body weight groups. A summary of subject allocation according to device presentation, injection site, and body weight category is provided below in Table 57.

Table 57. Subject Allocation According to Device Presentation, Injection Site, and Body Weight Group (Study 214099)

	Depemokimab SSD 100 mg SC (N=70)				Depemokimab AI 100 mg SC (N=70)			
Anatomical Location	<70 kg n (%)	70-80 kg n (%)	≥80 kg n (%)	Total n (%)	<70 kg n (%)	70-80 kg n (%)	≥80 kg n (%)	Total n (%)
Abdomen	11 (34.4)	6 (31.6)	6 (31.6)	23 (32.9)	10 (32.3)	7 (35.0)	6 (31.6)	23 (32.9)
Thigh	10 (31.2)	7 (36.8)	6 (31.6)	23 (32.9)	10 (32.3)	7 (35.0)	7 (36.8)	24 (34.3)
Upper arm	11 (34.4)	6 (31.6)	7 (36.8)	24 (34.2)	11 (35.4)	6 (30.0)	6 (31.6)	23 (32.9)
Total	32 (100.0)	19 (100.0)	19 (100.0)	70 (100.0)	31 (100.0)	20 (100.0)	19 (100.0)	70 (100.0)

Source. Compiled by Reviewer from CSR for 214099 (Table 1.8, pg. 137, 141, and 145)
Abbreviations: AI, autoinjector; CSR, clinical study report; N, number of subjects; SC, subcutaneous; SSD, safety syringe device

PK/PD Analysis

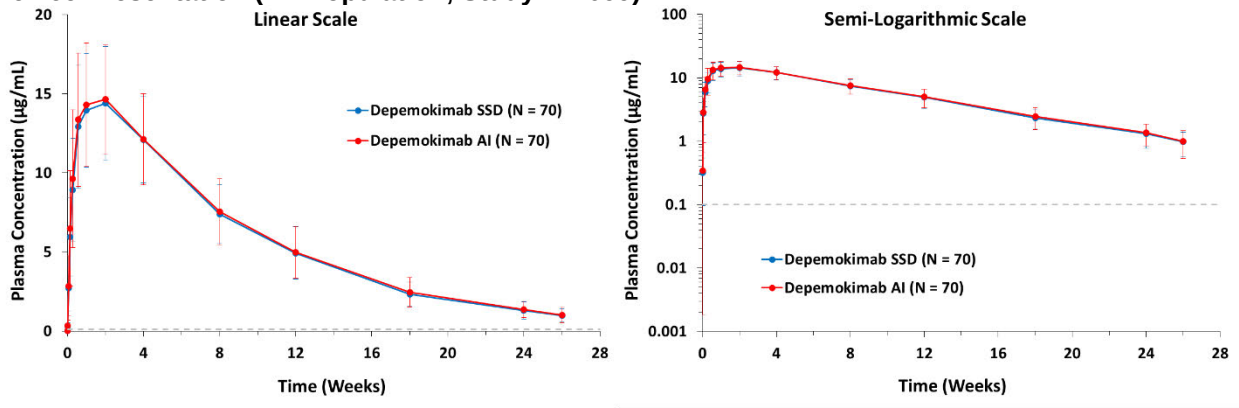
PK analyses were conducted based on the PK population, which consisted of all subjects who received a single dose of depemokimab 100 mg SC and had at least one quantifiable concentration measurement (N = 140). PK parameters were estimated using NCA. Point estimates and 90% confidence intervals (CIs) for GMRs were derived from log-transformed primary PK parameters (C_{max}, AUC_{inf}, and AUC_{last}). PD analyses were conducted based on the safety population, which consisted of all subjects who received at least one dose of study intervention (N = 140).

Of note, three subjects in the depemokimab AI treatment group were excluded from the primary statistical analysis. One subject (b) (6) withdrew between weeks 12 and 18, for which AUC_{inf} and AUC_{last} could not be reliably derived. Additionally, two subjects (b) (6) (b) (6) experienced events (pregnancy and severe pelvic inflammation) for which significant impact on the PK could not be excluded.

PK Results

The arithmetic mean (SD) depemokimab concentration-time profiles according to device presentation arm are shown in Figure 31. PK parameters for each device presentation are summarized in Table 58. A similar median T_{max} was observed for both treatment groups, ranging from approximately 12.4 to 13 days for the AI and SSD, respectively. Geometric mean (with coefficient of variation) half-life and CL/F were also similar between device presentations, at approximately 41.4 (24.5) days and 0.0942 (26.9) L/day, respectively, for the SSD group, and 41.2 (23.5) days and 0.0927 (28.4) L/day, respectively, for the AI group.

Figure 31. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile According to Device Presentation (PK Population; Study 214099)[a]



Source: Reviewer's analysis based on adpc.xpt for Study 214099
[a] Grey dashed line represents LLOQ of 0.1 µg/mL; Values below LLOQ were imputed as 0
Abbreviations: AI, autoinjector; LLOQ, lower limit of quantitation; N, number of subjects; PK, pharmacokinetic; SD, standard deviation; SSD, safety syringe device

Table 58. Summary of Depemokimab PK Parameters According to Device Presentation (PK Population; Study 214099)

	Device Presentation (100 mg SC)[b]	
PK Parameter[a]	**Depemokimab SSD (N=70)**	**Depemokimab AI (N=70)**
AUC_{inf} (day*µg/mL)	1061.0 (26.9)	1078.7 (28.4)[c]
AUC_{last} (day*µg/mL)	999.4 (26.1)	1014.3 (27.3)
C_{max} (µg/mL)	14.68 (24.2)	14.97 (23.3)
CL/F (L/day)	0.0942 (26.9)	0.0927 (28.4)[c]
$t_{1/2}$ (day)	41.4 (24.5)	41.2 (23.5)[c]
T_{max} (day)	13.0 (4.0, 28.9)	12.4 (3.9, 28.0)
Vz/F (L)	5.6 (25.0)	5.5 (27.2)[c]

Source. Reviewer's analysis based on adpp.xpt for Study 214099
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] Both treatment groups received a single 100 mg dose of depemokimab administered via SC injection in either upper arm, thigh, or abdomen
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC from 0 to last timepoint sampled; C_{max}, maximum plasma concentration; CL/F, apparent clearance; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution during the terminal phase; W12, Week 12

The statistical analysis of relative BA between device presentations based on the primary PK parameters C_{max}, AUC_{inf}, and AUC_{last} is depicted below in Table 59. Based on these data, BE criteria were met between the SSD and the AI device presentations.

Table 59. Statistical Analysis of Relative BA for Primary Depemokimab PK Parameters for SSD vs. AI Presentation Following Single 100 mg SC Dose (PK Population; Study 214099)

	Depemokimab SSD (N=70)		Depemokimab AI (N=70)		Test vs. Reference (AI / SSD)	
Parameter	**Geo LSMean (SE)**	**N**	**Geo LSMean (SE)**	**N**	**GMR**	**90% CI of GMR**
C_{max} (µg/mL)	14.68 (0.028)	70	14.94 (0.029)[a]	68	101.8	(95.3, 108.8)
AUC_{inf} (day*µg/mL)	1058.2 (0.033)	70	1071.5 (0.033)[a,b]	67	101.3	(93.7, 109.4)
AUC_{last} (day*µg/mL)	995.3 (0.032)	70	1009.5 (0.032)[a,b]	67	101.4	(94.1, 109.3)

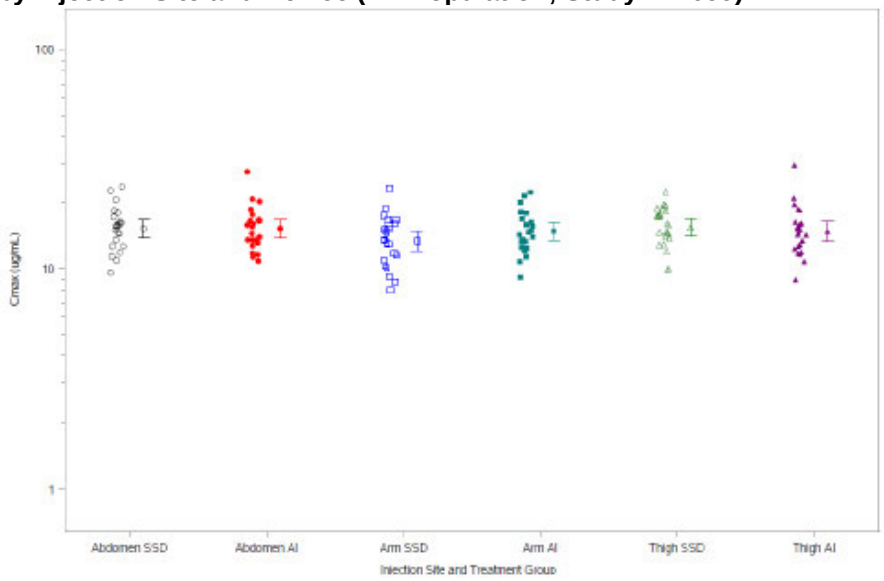
Source. Reviewer's analysis based on adpc.xpt for Study 214099
[a] Excluded two subjects (b) (6) due to an event (pregnancy and severe pelvic inflammation) for which significant impact on the PK could not be excluded
[b] Excluded one subject (b) (6) due to early withdrawal after the W12 visit
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC from 0 to last timepoint sampled; BA, bioavailability; C_{max}, maximum plasma concentration; CI, confidence interval; CV, coefficient of variation; Geo, geometric; GMR, geometric mean ratio; LSMean, least-squares mean; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SE, standard error; SSD, safety syringe device; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; W12, Week 12

This reviewer's statistical analysis was conducted using a univariate analysis of variance model to determine the GMRs and associated 90% CIs of C_{max}, AUC_{inf}, and AUC_{last}. The GMRs and 90% CIs for C_{max}, AUC_{inf}, and AUC_{last} when comparing the AI (test) to the SSD (reference) were 101.8 (95.3, 108.8), 101.3 (93.7, 109.4), and 101.4 (94.1, 109.3), respectively. This analysis corroborates the Applicant's conclusions that BE criteria were met between the SSD and AI.

PK According to Injection Site

The distribution of individual and geometric mean (95% CI) depemokimab C_{max} values based on injection site and device presentation is shown in Figure 32. Additionally, depemokimab PK parameters according to device presentation and injection site are displayed below in Table 60. Overall, PK parameters were similar across injection sites and between devices. It was noted that subjects who received depemokimab via SSD in the upper arm had a slightly lower geometric mean C_{max} and AUC_{inf} compared to other device-injection site combinations. However, given that the 95% CIs of depemokimab AUC_{inf} and C_{max} for all device-injection site combinations overlapped, this exposure difference appears to be minimal.

Figure 32. Individual Subject-Derived (With Geometric Mean [95% CI]) Plasma Depemokimab C_{max} by Injection Site and Device (PK Population; Study 214099)[a]



Source: CSR for Study 214099 (Figure 3, pg. 66)
[a] Labels on x-axis from left to right: Abdomen SSD, Abdomen AI, Arm SSD, Arm AI, Thigh SSD, Thigh AI
Abbreviations: AI, autoinjector; CI, confidence interval; C_{max}, maximum plasma concentration; CSR, clinical study report; PK, pharmacokinetic; SSD, safety syringe device

Table 60. Summary of Depemokimab PK Parameters by Treatment Group and Injection Site (PK Population; Study 214099)

		Device Presentation (100 mg SC)[b]	
Injection Site	**PK Parameter[a]**	**Depemokimab SSD (N=70)**	**Depemokimab AI (N=70)**
Arm	N	24	23
	AUC_{inf} (day*µg/mL)	976.0 (32.3)	1035.0 (29.7)
	C_{max} (µg/mL)	13.40 (26.2)	14.81 (22.7)
	T_{max} (day)	14.0 (4.0, 28.9)	14.0 (3.9, 25.9)
Abdomen	N	23	23
	AUC_{inf} (day*µg/mL)	1084.7 (22.7)	1156.7 (21.8)[c]
	C_{max} (µg/mL)	15.28 (22.7)	15.26 (22.6)
	T_{max} (day)	7.9 (4.0, 28.1)	7.0 (4.0, 15.0)
Thigh	N	23	24
	AUC_{inf} (day*µg/mL)	1132.5 (23.2)	1052.6 (32.2)
	C_{max} (µg/mL)	15.51 (21.3)	14.86 (25.4)
	T_{max} (day)	9.0 (4.0, 27.9)	7.0 (4.0, 28.0)

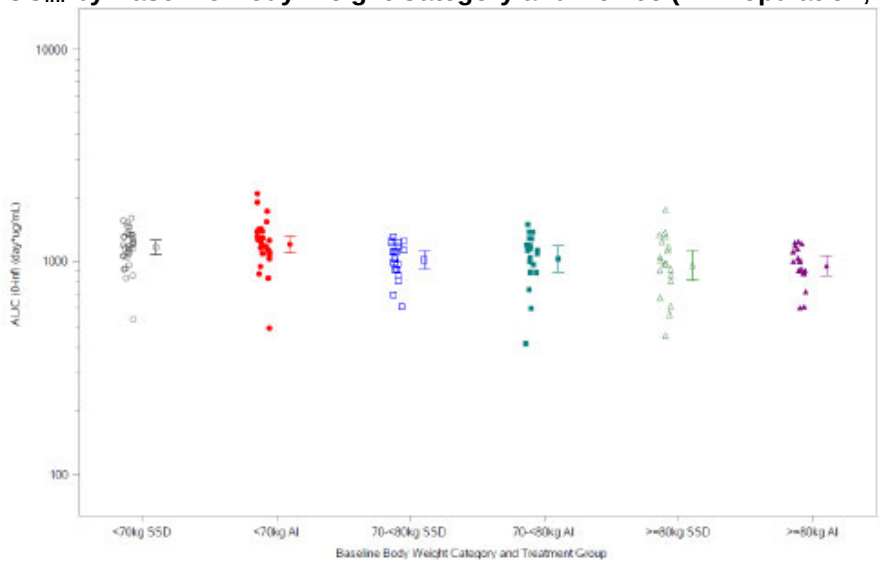
Source: Reviewer's analysis based on adpp.xpt for Study 214099
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] Both groups received a single 100 mg dose of depemokimab administered via SC injection in either upper arm, thigh, or abdomen
[c] PK parameter derived based on N = 22 due to early withdrawal of a single subject (b) (6) after the W12 visit
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; T_{max}, time to C_{max}; W12, Week 12

PK According to Injection Body Weight

The distribution of individual and geometric mean (95% CI) depemokimab AUC_{inf} values based on body weight group and device presentation is shown in Figure 33. Additionally, depemokimab PK parameters according to baseline body weight and device presentation are displayed below in Table 61. There was a trend towards slightly lower depemokimab exposure

(C_{max} and AUC) with increasing body weight category. However, depemokimab PK parameters were generally comparable with large overlap between body weight groups, regardless of device. Furthermore, within each body weight category, PK was similar between the SSD and AI.

Figure 33. Individual Subject-Derived (With Geometric Mean [95% CI]) Plasma Depemokimab AUC_{inf} by Baseline Body Weight Category and Device (PK Population; Study 214099)[a]



Source: CSR for Study 214099 (Figure 4, pg. 67)
[a] Labels on x-axis from left to right: < 70 kg SSD, < 70 kg AI, 70 - < 80 kg SSD, 70 - < 80 kg AI, ≥ 80 kg SSD, ≥ 80 kg AI
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; CI, confidence interval; CSR, clinical study report; PK, pharmacokinetic; SSD, safety syringe device

Table 61. Summary of Depemokimab PK Parameters by Treatment Group Baseline Body Weight Category (PK Population; Study 214099)

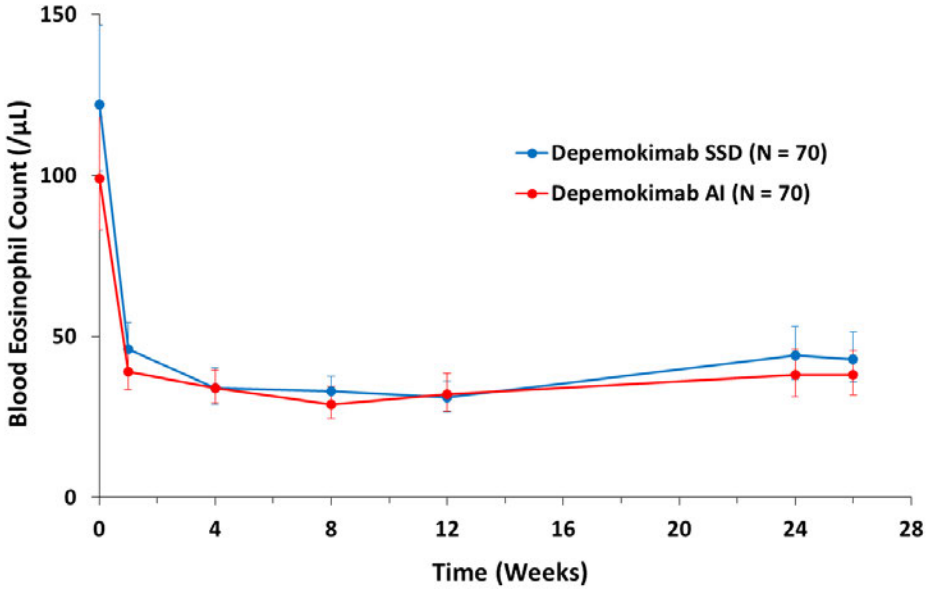
Body Weight Category	PK Parameter[a]	Device Presentation (100 mg SC)[b]	
		Depemokimab SSD (N=70)	Depemokimab AI (N=70)
<70 kg	N	32	31
	AUC_{inf} (day*µg/mL)	1161.3 (22.1)	1198.0 (26.5)
	C_{max} (µg/mL)	15.88 (19.5)	16.29 (25.5)
	T_{max} (day)	14.0 (4.0, 28.1)	12.9 (3.9, 28.0)
70 to <80 kg	N	19	20
	AUC_{inf} (day*µg/mL)	1013.8 (21.0)	1023.0 (31.2)
	C_{max} (µg/mL)	13.16 (21.6)	14.35 (19.9)
	T_{max} (day)	12.9 (4.0, 28.9)	10.0 (4.1, 25.9)
≥80 kg	N	19	19
	AUC_{inf} (day*µg/mL)	953.9 (34.6)	955.0 (22.2)[c]
	C_{max} (µg/mL)	14.35 (29.5)	13.65 (18.3)
	T_{max} (day)	7.1 (4.0, 15.0)	13.0 (4.0, 15.2)

Source. Reviewer's analysis based on adpp.xpt for Study 214099
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] Both groups received a single 100 mg dose of depemokimab administered via SC injection in either upper arm, thigh, or abdomen
[c] PK parameter derived based on N = 18 due to early withdrawal of a single subject (b) (6) after the W12 visit
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; T_{max}, time to C_{max}; W12, Week 12

PD Results

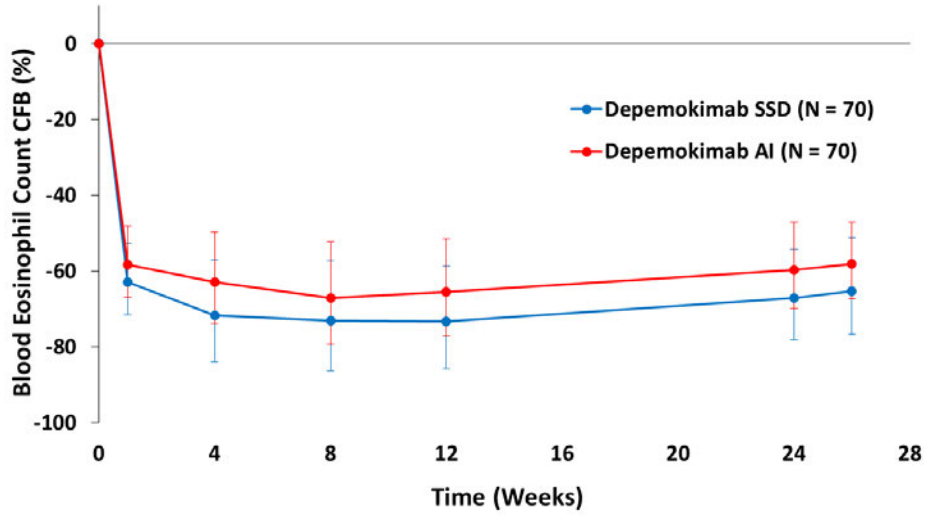
The geometric mean (95% CI) absolute and percent change from baseline blood eosinophil count over time following depemokimab treatment according to device presentation is displayed below in Figure 34 and Figure 35, respectively. Of note, subjects in the SSD arm had a slightly higher geometric mean baseline eosinophil count compared to the AI group (122 and 99 cells/µL, respectively). Absolute blood eosinophil counts over time were similar between the two treatment arms, with peak eosinophil suppression observed between Weeks 4 and 12 and a nadir of approximately 30 cells/µL. At all timepoints, a higher percent reduction from baseline was observed for the SSD group relative to the AI group, which is likely attributed to the higher baseline blood eosinophils in the SSD treatment arm. Overall, similar PD findings were observed for both device presentation arms.

Figure 34. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Device Presentation (Safety Population; Study 205722)[a]



Source: Generated by reviewer from CSR for Study 214099 (Table 4.4, pg. 524)
[a] Both treatment groups received a single dose of depemokimab 100 mg by SC injection
Abbreviations: AI, autoinjector; CI, confidence interval; CSR, clinical study report; N, number of subjects; SC, subcutaneous; SSD, safety syringe device

Figure 35. Geometric Mean (95% CI) Percent Change From Baseline in Blood Eosinophil Count Over Time by Device Presentation (Safety Population; Study 205722)a



Source. Generated by reviewer from CSR for Study 214099 (Table 4.5, pg. 525)
[a] Both treatment groups received a single dose of depemokimab 100 mg by SC injection
Abbreviations: AI, autoinjector; CI, confidence interval; CFB, change from baseline; CSR, clinical study report; N, number of subjects; SC, subcutaneous; SSD, safety syringe device

Immunogenicity Results

Across all 140 subjects who received a single dose of depemokimab 100 mg SC in this study, three participants (one AI and two SSD subjects) tested positive for ADAs). One subject (b) (6) in the SSD group tested positive for both ADAs and NAbs at baseline and remained positive throughout the entire study. However, this participant was considered negative for treatment-emergent ADAs, since the post-baseline titer values did not increase by > 4-fold relative to the baseline titer (2650). Both of the other two ADA-positive participants in the SSD and AI groups tested positive for ADAs at Week 26 only. The ADA-positive subject in the AI arm was also NAb-positive, while the SSD subject was NAb-negative.

Of the two ADA-positive subjects, one reported injection site bruising (SSD group) and the other had injection site erythema (AI group), which is consistent with safety findings in ADA-negative subjects. No other AEs were reported for ADA-positive participants. Overall, no observable impact of ADA status on PK, PD, or safety was observed, although the interpretability of these data is limited due to the low incidence of ADAs in this study.

17.5.3. Study 208021

Title

An open-label, single dose study to investigate the pharmacokinetics, safety, tolerability and immunogenicity of two dose levels of GSK3511294 [depemokimab] administered subcutaneously in Chinese healthy participants

Objectives

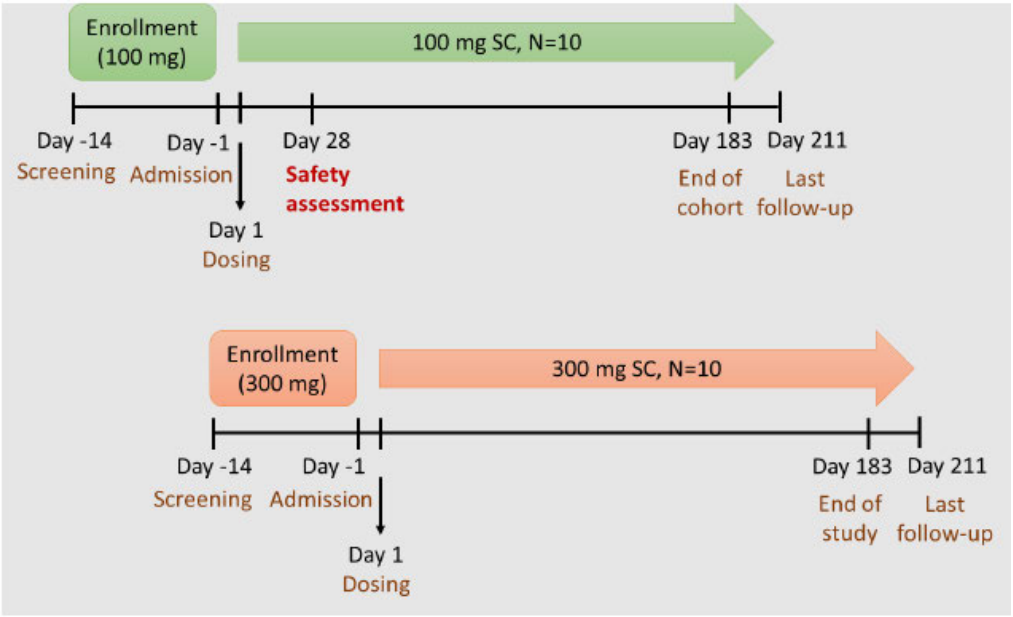
- **Primary:** Assess the PK of single SC doses of depemokimab (100 and 300 mg) administered in healthy Chinese adult subjects
- **Secondary:** Characterize the safety, tolerability, and immunogenicity of single SC doses of depemokimab administered in healthy Chinese adult subjects

Study Design

Study 208021 was a single-dose, open-label study designed to evaluate the PK, safety, tolerability, and immunogenicity following a single SC dose of depemokimab in healthy Chinese adult subjects (Figure 36). Subjects were randomized to one of two depemokimab dose cohorts (N = 10 subjects per cohort) to receive a single SC dose of 100 or 300 mg, after which they were followed for 30 weeks post-dose. All doses were administered using the 100 mg/mL formulation and the TBM SSD device presentation.

The study enrolled male and female subjects aged 18 to 45 years (inclusive) with body weight ≥ 50 kg (males) or 45 kg (females) and BMI between 19 and 26 kg/m^2 (inclusive). Subjects were required to abstain from taking prescription or nonprescription drugs, including vaccines, vitamins, herbal, and dietary supplements within 7 days (or 14 days for enzyme inducers) or 5 half-lives (whichever is longer) prior to the first dose until completion of the follow-up visit. Acetaminophen (up to 2 grams per day) was permitted, along with any approved COVID-19 vaccine, provided it was not administered within 14 days of receiving depemokimab.

Figure 36. Overall Study Design for Study 208021



Source: CSR for Study 208021 (Figure 1, pg. 14)
Abbreviations: CSR, clinical study report; N, number of subjects; SC, subcutaneous

PK and Immunogenicity Sampling

- PK samples were collected at pre-dose on Day 1, then post-dose at 2 h, 8 h, 24 h, 48 h, and 96 h, and at Weeks 1, 2, 4, 8, 12, 18, 24, and 26
- Immunogenicity samples were collected at pre-dose on Day 1, then post-dose at Weeks 4, 12, and 26

Subject Disposition and Demographics

A total of 20 healthy Chinese adult subjects were randomized to receive a single SC dose of depemokimab, including 10 subjects each into the 100 mg and 300 mg dose cohorts. A total of 19 participants completed the study as planned and 1 subject in the 300 mg group was lost to follow-up (b) (6) All enrolled subjects were healthy Chinese males. Additionally, baseline mean (SD) body weight was similar between the 100 mg and 300 mg dose groups (64.9 [8.1] and 62.6 [6.4], respectively).

PK Analysis

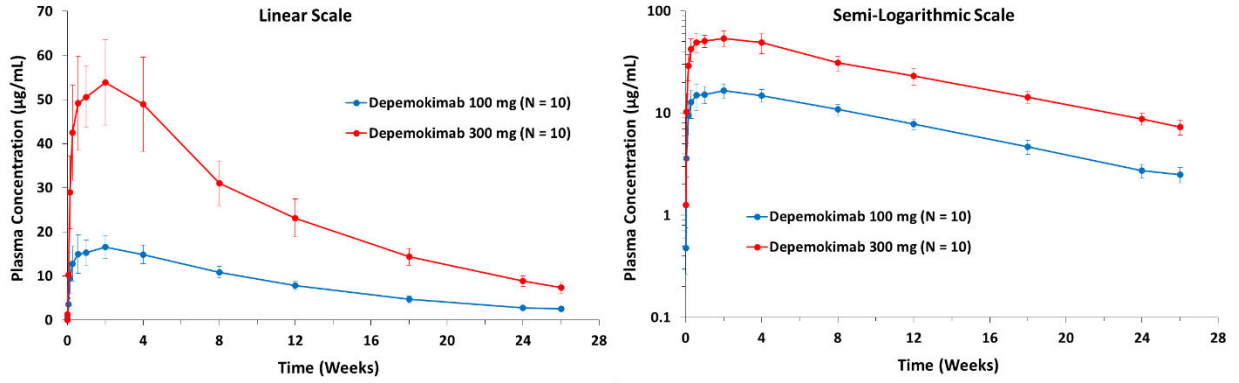
PK analyses were conducted based on the PK population, which consisted of all 20 subjects who received a single dose of depemokimab and had at least one quantifiable PK sample for analysis. PK parameters were estimated using NCA and summarized descriptively using both raw and log-transformed data for each depemokimab dose cohort. The one subject (b) (6) in the 300 mg cohort who was lost to follow-up had PK data through Week 8. Therefore, although λ_z-related parameters could not be determined, C_{max} and T_{max} were calculated and reported for this participant.

One subject (b) (6) in the 100 mg dose group had a measurable depemokimab plasma concentration of 0.111 µg/mL at pre-dose, which represented 0.49% of the C_{max}. However, this subject was not excluded from the PK population and the measurable pre-dose concentration was included in both the plasma concentration summary statistics as well as the derivation of PK parameters.

PK Results

The arithmetic mean (SD) depemokimab concentration-time profiles for each dose cohort are shown below in Figure 37. A summary of PK parameters derived for each depemokimab dose cohort is provided below in Table 62.

Figure 37. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile by Dose Group (PK Population; Study 208021)



Source: Reviewer's analysis based on adpc.xpt for Study 208021
Abbreviations: N, number of subjects; PK, pharmacokinetic; SD, standard deviation

Table 62. Summary of Depemokimab PK Parameters Following Single SC Dose of 100 mg and 300 mg in Healthy Chinese Subjects (PK Population; Study 208021)

	Depemokimab SC Administration	
PK Parameter[a]	**100 mg (N=10)**	**300 mg (N=10)**
AUC_{inf} (day*µg/mL)	1685.9 (12.6)	5224.1 (13.4)[b]
AUC_{last} (day*µg/mL)	1473.0 (12.6)	4604.9 (14.1)[b]
C_{max} (µg/mL)	16.82 (18.2)	55.04 (18.8)
CL/F (L/day)	0.0593 (12.6)	0.0574 (13.4)[b]
$t_{1/2}$ (day)	58.8 (8.1)	58.2 (8.2)[b]
T_{max} (day)	14.0 (4.0, 28.0)	14.0 (4.0, 28.0)
Vz/F (L)	5.0 (13.9)	4.8 (16.7)[b]

Source. Reviewer's analysis based on adpp.xpt for Study 208021
[a] All PK parameters reported as geometric mean (CV%), except for Tmax, which is reported as median (min, max)
[b] PK parameters derived based on N = 9 due to early withdrawal of a single subject (b) (6) after the W8 visit
Abbreviations: AI, autoinjector; AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; AUC_{last}, AUC_{last}, AUC from 0 to last timepoint sampled; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; PK, pharmacokinetic; SC, subcutaneous; SSD, safety syringe device; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}; Vz/F, apparent volume of distribution during the terminal phase; W8, Week 8

All depemokimab plasma concentrations were quantifiable through Day 183 (Week 26) and exposure (C_{max} and AUC) was approximately dose-proportional. Across both dose groups, median T_{max} was about 14 days, and geometric mean half-life was approximately 59 days. Additionally, CL/F and apparent volume of distribution appeared to be consistent between dose levels, with geometric mean values of 0.0574 to 0.0593 L/day and 4.827 to 5.033 L, respectively.

Immunogenicity Results

All subjects were ADA-negative at all timepoints throughout the duration of this study.

17.5.4. Studies 206713 and 213744 (SWIFT-1 and SWIFT-2)

Refer to Section 8.2 for details regarding the design and conduct of SWIFT-1 and SWIFT-2.

PK, PD, and Immunogenicity Sampling

- PK samples were collected on Day 1 (pre-dose), then post-dose at Weeks 2, 4, 8, 12, 20, 26 (pre-dose), 28, 32, 40, and 52
- PD samples (i.e., blood eosinophils) were collected on Day 1 (pre-dose), then post-dose at Weeks 2, 4, 8, 12, 20, 26 (pre-dose), 28, 32, 40, 48, and 52
- Immunogenicity samples were collected on Day 1 (pre-dose), then post-dose at Weeks 2, 4, 8, 12, 26, 28, 32, 36, 40, and 52

Subject Disposition and Demographics

For additional details, see Section 8.2.

Study 206713 (SWIFT-1): A total of 382 subjects were randomized in a 2:1 ratio to depemokimab (N = 250) or placebo (N = 132) treatment arms. Among adult subjects randomized to receive depemokimab (N = 247), the median (range) body weight was 77.8 (41.1, 152.8) kg. This study also enrolled 8 adolescent subjects ranging in age from 14 to 17 years, including 3 randomized to depemokimab and 5 to placebo. Among adolescent subjects who received depemokimab, the median (range) body weight was 73.0 (72.0, 97.9) kg.

Study 213744 (SWIFT-2): A total of 397 participants were randomized in a 2:1 ratio to depemokimab or placebo treatment arms, although only 380 subjects were included for further analysis, including N = 252 and N = 128 who received depemokimab and placebo, respectively. Of the 17 participants who were excluded, 12 were excluded due to concerns about data integrity and GCP violations at sites 250085 and 250523, and 5 were randomized in error but did not receive any study intervention. Among adult subjects randomized to receive depemokimab (N = 240), the median (range) body weight was 77.0 (34.6, 161.0) kg. The study also enrolled 22 adolescent subjects ranging in age from 12 to 17 years, including 12 randomized to depemokimab and 10 to placebo. Among adolescent subjects who received depemokimab, the median (range) body weight was 67.0 (39.7, 141.0) kg.

PK/PD Analysis

PK analyses were conducted based on the PK population, which consisted of all subjects in the FAS population for whom at least one PK sample was obtained, analyzed, and measurable. In SWIFT-1, the PK population consisted of all 250 subjects who were randomized to receive depemokimab treatment. However, three subjects were excluded from the PK population for SWIFT-2, resulting in a PK population consisting of 249 subjects. In total, 499 subjects were included in the integrated SWIFT-1/2 PK population, comprising 484 adults and 15 adolescents.

PD analyses were conducted based on the FAS population, which consisted of all subjects who received at least one dose of study intervention. For SWIFT-1, the FAS population included 250 and 132 subjects who received depemokimab and placebo, respectively, whereas for SWIFT-2, this included 252 and 128 subjects who received depemokimab and placebo, respectively. In total, 762 subjects were included in the SWIFT-1/2 pooled FAS population, comprising 502 and 260 subjects who received depemokimab and placebo, respectively. Additionally, the SWIFT-1/2 pooled FAS population included 30 adolescents (N = 15 depemokimab; N = 15 placebo).

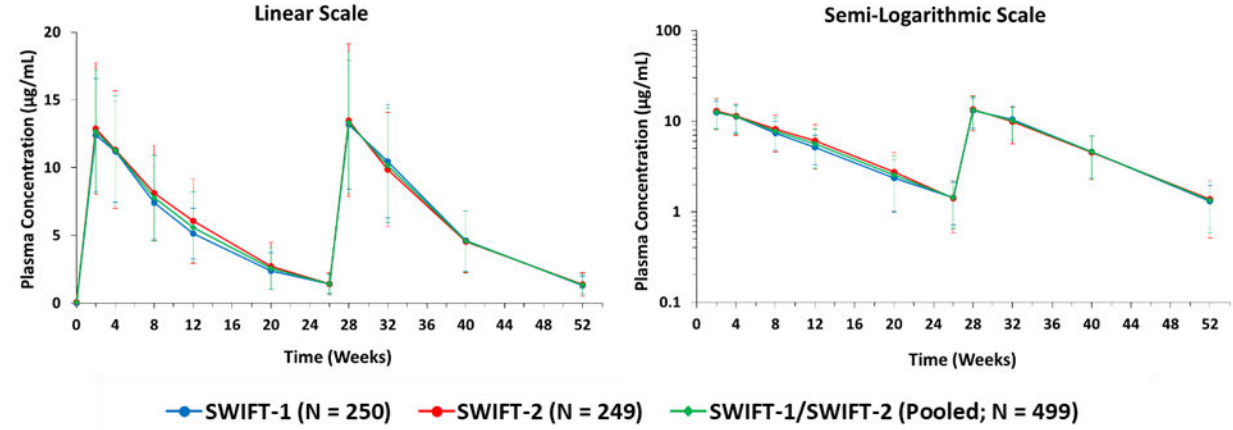
Depemokimab plasma concentrations for both studies were summarized by nominal time points and plotted on linear and semi-logarithmic scales using both pooled and unpooled data. NCA was not conducted. Absolute and percent change from baseline blood eosinophil count-time profiles were generated based on the SWIFT-1/2 pooled FAS population. All PK and PD data were also incorporated into the Applicant's longitudinal population PK/PD and ER analyses.

PK Results

The arithmetic mean (SD) depemokimab concentration-time profiles in both linear and semi-logarithmic scale for the individual and pooled SWIFT-1 and SWIFT-2 PK populations are shown below in Figure 38.

Following administration of depemokimab 100 mg SC, C_{max} was achieved at approximately 14 days post-dose on both Day 1 and Week 26, after which depemokimab concentrations gradually decreased in a monophasic manner. A similar mean depemokimab plasma trough concentration was observed at both Weeks 26 and 52 (1.42 and 1.34 µg/mL, respectively). Additionally, the observed mean depemokimab plasma concentrations at Weeks 2 and 28 (12.65 and 13.32 µg/mL, respectively), which represent the approximate C_{max} following the first and second dose, respectively, were also comparable. Based on these findings from the pooled SWIFT-1/2 PK population, there does not appear to be substantial accumulation at the proposed Q6M dosing interval in patients with severe asthma. Of note, in SWIFT-2, plasma concentrations in seven depemokimab-treated subjects at Site 251152 were below the LLOQ at all timepoints except for the Week 20 visit. These results were confirmed following sample re-analysis, although no root cause was identified.

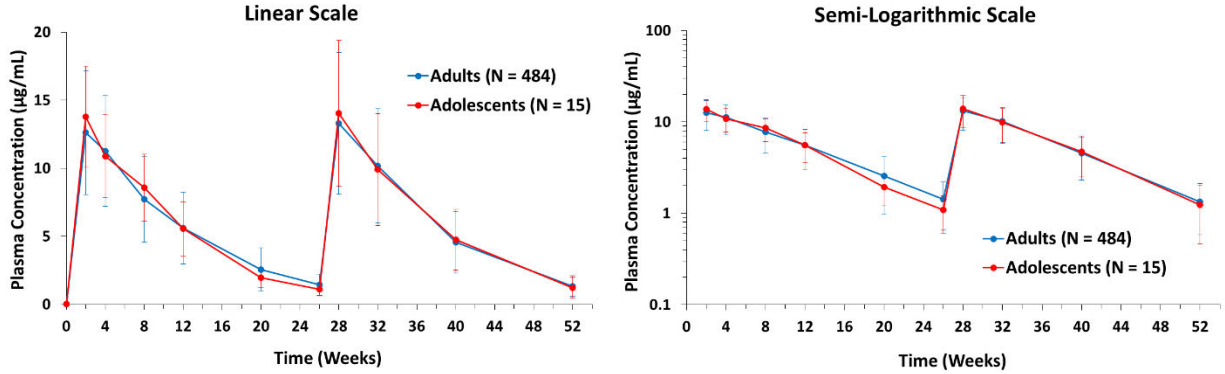
Figure 38. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile Following 100 mg SC Q6M Dosing (SWIFT-1/SWIFT-2, Pooled and Unpooled PK Populations)



Source: Reviewer's analysis based on adpc.xpt for Studies 206713 and 213744
Abbreviations: N, number of subjects; PK, pharmacokinetic; Q6M, every 6 months; SC, subcutaneous; SD, standard deviation

The arithmetic mean (SD) depemokimab concentration-time profiles for adults versus adolescents in the pooled SWIFT-1/2 PK population are shown below in Figure 39.

Figure 39. Arithmetic Mean (SD) Depemokimab Plasma Concentration-Time Profile Following 100 mg SC Q6M Dosing: Adults vs. Adolescents (Pooled SWIFT-1/2 PK Population)



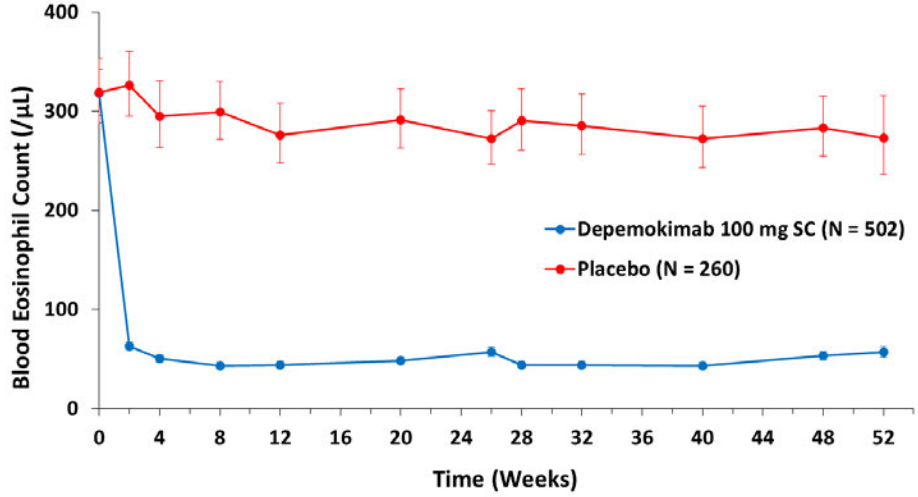
Source: Reviewer's analysis based on adpc.xpt for Studies 206713 and 213744
Abbreviations: N, number of subjects; PK, pharmacokinetic; Q6M, every 6 months; SC, subcutaneous; SD, standard deviation

The mean depemokimab plasma trough concentrations at Weeks 26 and 52 were slightly lower in adolescents (1.09 and 1.23 µg/mL, respectively) compared to adults (1.43 and 1.34 µg/mL, respectively). Additionally, the observed mean depemokimab plasma concentrations at Weeks 2 and 28 (approximate C_{max} after the first and second dose, respectively) were slightly higher in adolescents (13.78 and 14.03 µg/mL, respectively) compared to adults (12.61 and 13.30 µg/mL, respectively), which may be partially explained by the slightly lower body weight in adolescents. However, overall, the observed mean depemokimab exposure in adolescents was similar to and within the range of that in adults.

PD Results

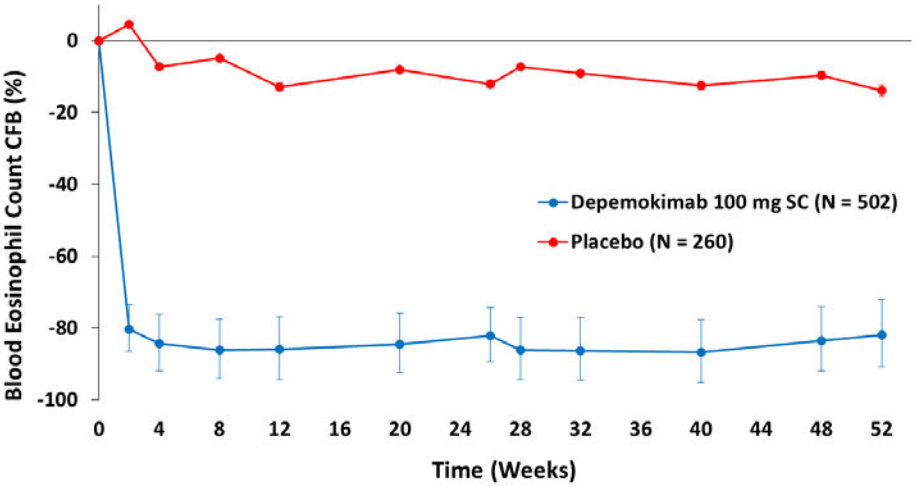
The geometric mean (95% CI) absolute and percent change from baseline blood eosinophil count over time is shown below in Figure 40 and Figure 41, respectively, for placebo- and depemokimab-treated subjects in the pooled SWIFT-1/2 FAS population. These data demonstrate a similar PD response to that observed in phase 1 studies 205722 and 214099, as well as in the phase 3 CRSwNP program. A substantial decline in blood eosinophil count was observed in depemokimab-treated subjects at the first post-dose visit (Week 2), after which peak reduction was reached around Week 8 post-dose, compared to no notable change from baseline in placebo-treated subjects. In the depemokimab group, the geometric mean ratio to baseline blood eosinophil count was 0.197 (80.3%) at Week 2, 0.178 (82.2%) at Week 26, and 0.180 (82.0%) at Week 52, indicating that (1) > 80% eosinophil suppression is sustained over the 26-week dosing interval, and (2) comparable PD effects are observed after single- and multiple-dosing.

Figure 40. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Treatment Group (Pooled SWIFT-1/2 FAS Population)



Source: Generated by reviewer based on ISE – Asthma (Table 4.1, pg. 2468-2491)
Abbreviations: CI, confidence interval; FAS, full analysis set; ISE, integrated summary of efficacy; N, number of subjects; SC, subcutaneous

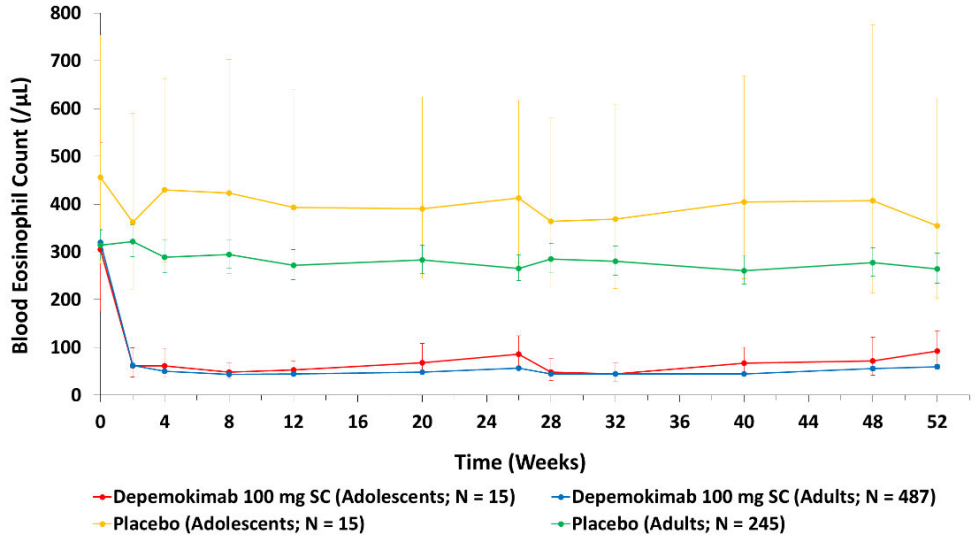
Figure 41. Geometric Mean (95% CI) Percent Change From Baseline in Blood Eosinophil Count Over Time by Treatment Group (Pooled SWIFT-1/2 FAS Population)



Source: Generated by reviewer based on ISE – Asthma (Table 4.1, pg. 2468-2491)
Abbreviations: CFB, change from baseline; CI, confidence interval; FAS, full analysis set; ISE, integrated summary of efficacy; N, number of subjects; SC, subcutaneous

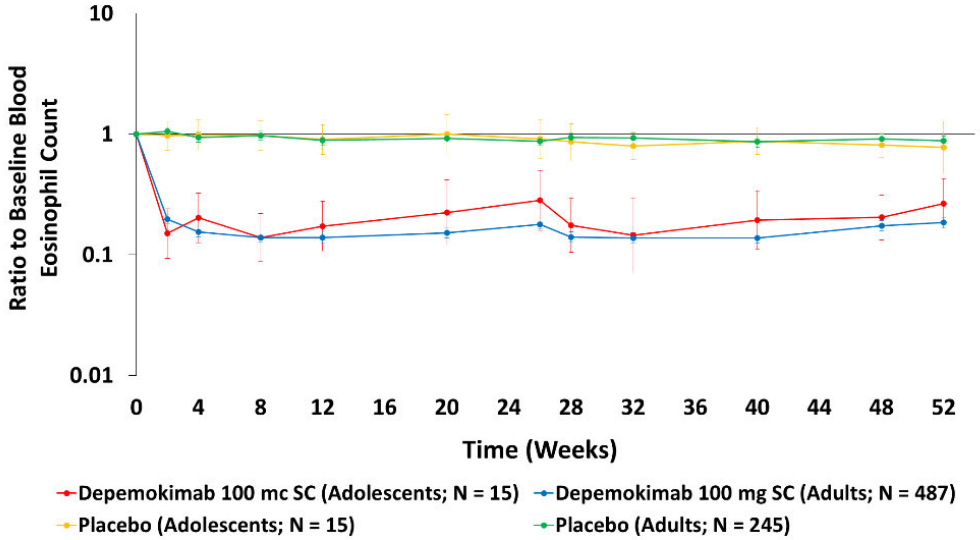
Figure 42 and Figure 43 show the geometric mean (95% CI) absolute and ratio to baseline blood eosinophil count over time, respectively, in adults versus adolescents in the pooled SWIFT-1/2 FAS population.

Figure 42. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Treatment Group: Adults vs. Adolescents (Pooled SWIFT-1/2 FAS Population)



Source: Reviewer's analysis based on adpd.xpt for Studies 206713 and 213744
Abbreviations: CI, confidence interval; FAS, full analysis set; N, number of subjects; SC, subcutaneous

Figure 43. Geometric Mean (95% CI) Ratio to Baseline Blood Eosinophil Count Over Time by Treatment Group: Adults vs. Adolescents (Pooled SWIFT-1/2 FAS Population)



Source: Reviewer's analysis based on adpd.xpt for Studies 206713 and 213744
Abbreviations: CI, confidence interval; FAS, full analysis set; N, number of subjects; SC, subcutaneous

There was no apparent difference in peak eosinophil suppression between the two age groups, although the rate of eosinophil recovery appeared to be slightly faster in adolescents compared to adults, as demonstrated by the higher geometric mean absolute eosinophil count at Weeks 26 and 52 in adolescents (86.1 and 92.5 cells/µL, respectively) relative to adults (56.2 and 59.7 cells/µL, respectively). This finding aligns with the slightly lower depemokimab plasma trough concentrations observed in adolescents compared to adults. However, in general, eosinophil suppression was comparable between depemokimab-treated adults and adolescents, with overlapping 95% CIs at all timepoints based on both absolute count and ratio to baseline.

Immunogenicity Results

A summary of immunogenicity results for all placebo- and depemokimab-treated subjects the SWIFT-1 and SWIFT-2 safety populations is provided below in Table 63. All placebo-treated subjects in both studies tested negative for ADAs at baseline and were not assessed further for ADA status at any timepoint post-baseline. ADA incidence in depemokimab-treated subjects was generally low across both studies, with a post-baseline ADA incidence rate of 12% (N = 31) and 5% (N = 13) in SWIFT-1 and SWIFT-2, respectively. Notably, among ADA-positive subjects in SWIFT-1, the majority of subjects who tested positive for ADAs were from China (N = 19/31), although the Applicant attributes this finding to the more sensitive ADA assay utilized for subjects from mainland China. Of those who developed anti-depemokimab ADAs, the majority had a persistent response. However, titers were low in ADA-positive subjects, ranging from 80 to 320 across both studies. Additionally, only two depemokimab-treated subjects (both in SWIFT-2) tested positive for NAbs (1 transient and 1 persistent response).

Table 63. Summary of Immunogenicity Results (SWIFT-1/SWIFT-2 Safety Populations)[a]

	Study ID			
	SWIFT-1 (Study 206713)		SWIFT-2 (Study 213744)	
ADA Parameter	Placebo (N=132)	Depemokimab (N=250)	Placebo (N=129)	Depemokimab (N=251)
Baseline ADA+	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Postbaseline ADA+	-	31 (12%)	-	13 (5%)
Transient[b]	-	8 (3%)	-	7 (3%)
Persistent[c]	-	23 (9%)	-	6 (2%)
ADA titer[d]	-	80 (80, 160)	-	80 (80, 320)
NAb+	-	0 (0%)	-	2 (1%)

Source. Compiled by reviewer from CSRs for Study 206713 (Table 37, pg. 139) and 213744 (Table 38, pg. 137)
[a] Safety population defined as all subjects who received at least one dose of their assigned study intervention
[b] Defined as ADA detected only at one sampling time point during the treatment or at two or more sampling time points in a period less than 16 weeks, and the subject's last sampling time point is ADA-negative
[c] Defined as ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or ADA detected only in the last sampling time point
[d] Reported as median (min, max)
Abbreviations: ADA, anti-drug antibody; CSR, clinical study report; N, number of subjects; Nab, neutralizing antibody

Regarding safety, in SWIFT-1, there was a greater frequency of AEs in depemokimab-treated subjects who were ADA-positive (94%; 29/31) compared to those who were ADA-negative (70%; 153/218). However, in SWIFT-2, a similar number of on-treatment AEs were reported for ADA-positive (77%; 10/13) and ADA-negative (72%; 170/237) participants. The most commonly reported AEs in both groups across both studies were COVID-19, nasopharyngitis and, upper respiratory infections. Overall, there did not appear to be any noticeable trends in AEs as a function of ADA status.

17.5.5. Study 212895 (AGILE)

Refer to Section 18.2 for details regarding the design and conduct of AGILE.

PD and Immunogenicity Sampling

- PD samples (i.e., blood eosinophils) were collected on Day 1 (pre-dose), then post-dose at Weeks 4, 8, 12, 20, 26 (pre-dose), 32, 40, and 52
- Immunogenicity samples were collected on Day 1 (pre-dose), then post-dose at Weeks 12, 26 (pre-dose), 40, and 52

Subject Disposition and Demographics

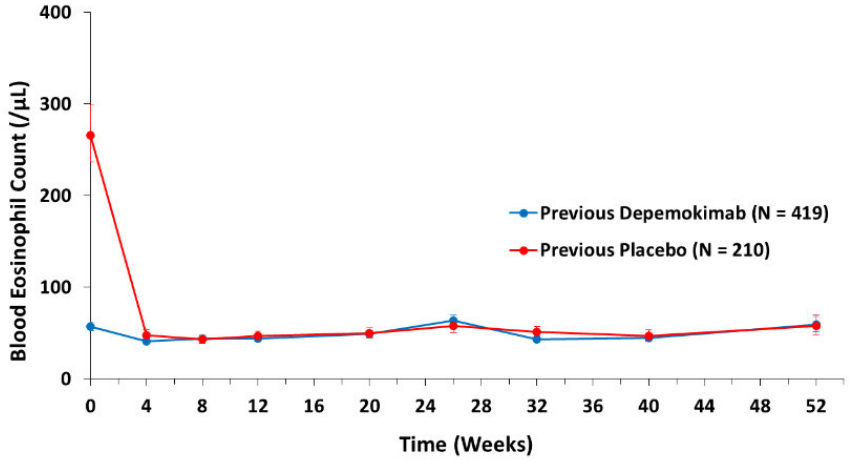
For details, see Section 18.2. A total of 640 subjects rolled over into AGILE from the SWIFT-1 and SWIFT-2 studies, including 428 and 213 subjects who previously received depemokimab and placebo, respectively. Of these, only 629 (N = 419 previous depemokimab; N = 210 previous placebo) were included for further analysis in the safety population, which was used for all efficacy, safety, immunogenicity, and PD analyses. Eleven subjects enrolled at sites 254404, 254803, and 254811 were excluded due to concerns about data integrity and GCP violations.

The majority of rollover subjects were of white race (78%; N = 490), although approximately one-fifth were of Asian descent (18%; N = 116). Among all subjects, the median (range) body weight at baseline was 76.8 (40.0, 171.0) kg. The study also enrolled 22 adolescents ranging in age from 13 to 17 years, consisting of 11 who previously received placebo and 11 who previously received depemokimab. Among adolescents, the median (range) body weight at baseline was 69.9 (43.6, 169.1) kg.

PD Results

The geometric mean (95% CI) absolute blood eosinophil count over time for depemokimab- and placebo-treated subjects in the AGILE safety population is shown below in Figure 44. Note that at baseline for AGILE (i.e., following completion of SWIFT-1 or SWIFT-2), geometric mean blood eosinophil counts were 57 and 266 cells/µL in subjects previously assigned to the depemokimab and placebo groups, respectively. However, by approximately Week 4 post-dose, the 95% CIs for the geometric mean absolute eosinophil counts overlap for all subsequent timepoints, regardless of previously assigned treatment in the SWIFT-1/2 parent trials. Additionally, in depemokimab-naïve subjects, the geometric mean ratio to baseline eosinophil count was 0.180 (-82.0%) at Week 4, 0.213 (-78.7%) at Week 26, and 0.232 (-76.8%) at Week 52, which is comparable to the percent change from baseline observed for depemokimab-treated subjects from the SWIFT-1/2 studies.

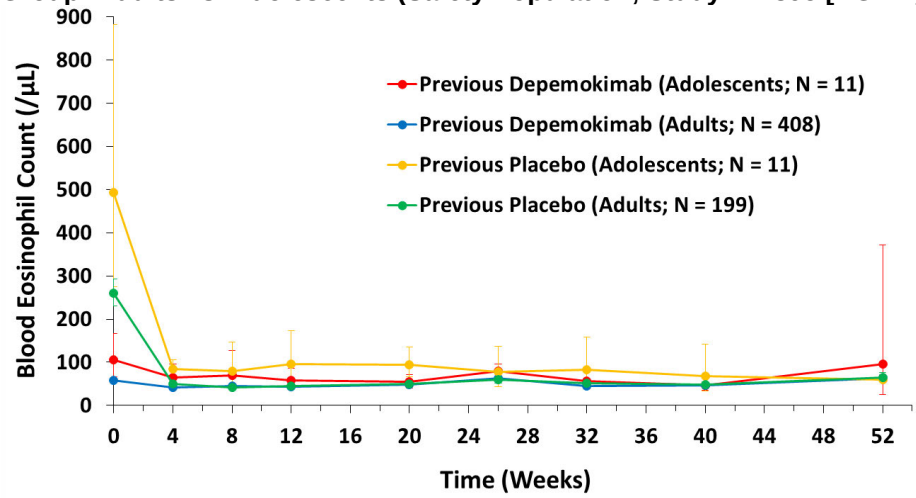
Figure 44. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Treatment Group (Safety Population; Study 212895 [AGILE])



Source: Generated by reviewer from CSR for Study 212895 (Table 5.1, pg. 932-939)
Abbreviations: CI, confidence interval; CSR, clinical study report; N, number of subjects; SC, subcutaneous

The geometric mean (95% CI) of the absolute blood eosinophil count over time in adolescents versus adults who rolled over into AGILE is shown below in Figure 45.

Figure 45. Geometric Mean (95% CI) Absolute Blood Eosinophil Count-Time Profile by Treatment Group: Adults vs. Adolescents (Safety Population; Study 212895 [AGILE])



Source: Reviewer's analysis based on adlb.xpt for Study 212895
Abbreviations: CI, confidence interval; N, number of subjects; SC, subcutaneous

There is a high degree of variability in PD response for adolescents, given the relatively small number who participated in this study. Additionally, as of the data cut-off date, blood eosinophil count at Week 52 is only available for 4 adolescent subjects (3 previous depemokimab and 1 previous placebo), which makes it difficult to draw definitive conclusions from these data. However, overall, these data appear to demonstrate a similar long-term PD response between adolescents and adults.

Immunogenicity Results

A summary of immunogenicity results for the AGILE safety population as of the data cut-off is provided below in Table 64.

Table 64. Summary of Immunogenicity Results as of Interim Data Cut-Off (Safety Population; Study 212895 [AGILE])[a]

	Previously Assigned Treatment Arm From SWIFT-1/SWIFT-2	
ADA Parameter	**Previous Placebo (N=210)**	**Previous Depemokimab (N=419)**
Baseline ADA+	0 (0%)	12 (3%)
Postbaseline ADA+	7 (4%)	36 (9%)
Transient[b]	0 (0%)	6 (2%)
Persistent[c]	7 (4%)	30 (8%)
ADA titer[d]	80 (80, 160)	80 (80, 160)
NAb+	0 (0%)	3 (7%)

Source. Adapted from Clinical Study Report for Study 212895 (Table 31, pg. 95)
[a] Safety population defined as all subjects who received at least one dose of study intervention
[b] Defined as ADA detected only at one sampling time point during the treatment or at two or more sampling time points in a period less than 16 weeks, and the subject's last sampling time point is ADA-negative
[c] Defined as ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer, or ADA detected only in the last sampling time point
[d] Reported as median (min, max)
Abbreviations: ADA, anti-drug antibody; CSR, clinical study report; N, number of subjects; Nab, neutralizing antibody

For subjects who previously received placebo, all subjects were considered ADA-negative at baseline, as post-baseline placebo samples from SWIFT-1 and SWIFT-2 studies were not analyzed for ADA status. A total of 4% (7) of these subjects had a positive post-baseline ADA result, all of which were categorized as persistent ADA responses. For subjects who previously received depemokimab, 3% (N = 12) were ADA-positive at baseline, with an incidence of positive post-baseline ADA responses of 9% (N = 36). Of the ADA-positive results in previous depemokimab-treated subjects, 8% (N = 30) and 2% (N = 6) were categorized as persistent and transient responses, respectively. Across all AGILE subjects, the overall incidence of post-baseline ADA-positive results was 7% (N = 43), of which 7% (N = 3) were also NAb-positive (all NAb-positive samples were from previous depemokimab-treated subjects).

18 Trial Design

18.1. SWIFT-1 and SWIFT-2

18.1.1. Schedule of Assessments

Table 65. Schedule of Assessments

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
General Eligibility Assessments																					
Informed consent [a]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote a.
Genetic sample informed consent [d]	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; See footnote d.
Demography data collection	X	(X)																			Conduct at Visit 1 if not completed at Visit 0; All females must be assessed at Visit 1 to determine childbearing potential.
Inclusion/Exclusion criteria	X	X																			
Historical blood eosinophil count		X																			See footnote e.
Medical history		X																			Include cardiovascular (CV), CV risk factors, asthma, exacerbations, vasculitis, allergies and anaphylaxis.
Smoking status		X																			

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Parasite screening		X															X				Only required in regions with high-risk or for participants who have visited a high-risk region in the past 6 months. Use local laboratories for this test. For details refer to study reference manual (SRM).
eDiary registration and training		X																			Conduct thorough eDiary training at Screening Visit 1 and throughout the study on as-needed basis.
Randomisation criteria			X																		Assess prior to randomisation; see footnote e.
Efficacy Assessments																					
Review for exacerbations		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Collection of exacerbations at Visit 1 is historical data.
Spirometry (pre- and post-bronchodilator FEV_1)[h]		X	X								X							X	X		FEV_1=Forced expiratory volume in 1 second; Spirometry should not be conducted for participants with confirmed/suspected COVID-19 (see Section 8.2.3).
ACQ-5			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		ACQ-5=Asthma Control Questionnaire-5

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Review eDiary (asthma symptoms, PEF summary)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PEF=Peak expiratory flow
HRQoL: PRO and Health Outcomes Assessments																					
SGRQ			X		X		X				X				X			X	X		SGRQ=St. George's Respiratory Questionnaire
PROMIS (fatigue items)			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		PROMIS= Patient-reported outcomes measurement information system
SNOT-22			X								X							X	X		SNOT-22=Sino-nasal Outcomes Test-22 Questionnaire
Complete ADSD/ANSD		←========= daily =========→							X	X	X	X	X	X	X	X	X	X			ADSD/ANSD=Asthma Daily/Nightly Symptom Diary; To be completed daily during Run-in phase through Week 16, then to be completed for 1 full week during the week preceding each visit thereafter.
Clinician-rated response to therapy							X				X				X			X	X		

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Patient-rated response to therapy							X				X				X			X	X		
PGI-S		X	X				X		X		X				X			X	X		PGI-S: Patient Global Impression of Severity (of asthma)
PGI-C							X		X		X				X			X	X		PGI-C: Patient Global Impression of Change (from baseline of asthma severity)
Safety Assessments																					
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Ensure maintenance asthma medications from the year prior to Screening Visit 1, all medications within the 3 months prior to Screening Visit 1 and all current medications are reviewed.
Physical Examination		X																X	X		Include height and weight for the complete physical exam at Screening Visit 1. Height can be omitted for subsequent visits.
Vital Signs		X	X			X			X		X	X			X		X	X	X		

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
12-lead ECG		X	X	X							X	X						X	X		ECG must be performed and assessed pre-dose. Twelve-lead ECG central over-read values should be used at all visits with the exception of Visit 2 and Visit 10 where 12-lead ECG machine read values should be used.
AE/SAE Assessment	X [g]	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	AE=Adverse events; SAE=Serious adverse events; see footnote g.
Laboratory Assessments																					
Haematology with white blood cells count [f]		X [e]	X	X	X	X	X		X		X	X	X		X		X	X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing; see footnotes e and f.
Total IgE			X																		
Clinical Chemistry		X	X		X	X	X		X		X	X			X		X	X	X		Include liver chemistry.
Pregnancy Test (WOCBP only)		X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	Serum pregnancy test should be done at screening Visit 1 and Exit Visit/ Withdraw from study visit; urine pregnancy tests should be done for all other assessments; WOCBP=Women of childbearing potential; See Section 8.3.5 for additional information.

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Urinalysis		X	(X)								X							X	X		Conduct at Visit 2 if not completed at Visit 1. Note: dipstick, send for analysis if abnormality is identified by dipstick **China Only:** For China sites the urine specimen may be sent to the central laboratory for routine urinalysis instead of performing a local urine dipstick. Urinalysis should be performed at Visit 1 so that results are available before randomisation at Visit 2. Urine pregnancy test must still be performed at the site.
Anti-MPO antibody, anti-PR3 antibody, ANA, and anti-dsDNA antibody			X																		ANA=antinuclear antibodies; MPO=myeloperoxidase; PR3=proteinase 3. Collected baseline sample will be stored and may be tested if necessary (see Section 7.5).
Complement C3 and C4			X				X				X				X			X	X		
PK sample			X	X	X	X	X		X		X	X	X		X			X	X		For dosing days (Week 0 and Week 26), obtain sample prior to dosing.

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Immunogenicity sample			X	X	X	X	X				X	X	X	X	X			X	X		
Blood biomarker sample			X				X				X				X			X			Sample will be stored and may be analysed for exploratory biomarkers (see Section 8.7.3) **China only:** Blood samples for exploratory biomarkers will not be collected from participants in China.
Genetics sample			←========== The genetics sample can be collected at Visit 2 or any visit after ==========→																		See footnote d.
Study intervention																					
Administer study intervention			X								X										Study intervention will only be administered in the clinic. Any scheduled assessments or sample draws should be performed beforehand. Monitor participant for at least 2h after administration (see Section 6.5).
eCRF/worksheets/other																					
Dispense Rescue medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Protocol Activity	Pre-Screening	Screening/Run-in	Intervention Period and Exit Visit (visit window is ±7 days)																Follow-up /Withdraw (±7 days)		Notes
Visit	V0 [a]	Visit 1 [a]	V2[b] R*	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	Exit V17	WS[c]	FU	R* =Randomisation WS=Withdraw from study visit (see footnote c) FU=Follow-up visit/call (only required for participants not entering OLE study)
Study Week	-8 to -6	-6 to -1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	26 or 52	56	
Study Day	-56 to -42	-42 to -7	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364		392	
Register Visit in the IRT system		X	X								X								X		IRT=interactive response technology
Provide worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				The worksheet is a medical problems and healthcare utilisation worksheet.
Review worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
eDiary close out																		X	X		
Complete eCRF	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		eCRF=electronic Case Report Form

a. Informed Consent must be obtained prior to initiating any study assessments. Pre-screening Visit 0 can occur any time from 0 to 14 days before Screening Visit 1.
b. Randomisation Visit 2 is 1 week after Screening Visit 1 but can be extended to up to 6 weeks after Visit 1 if, for example, a participant has an exacerbation during the run-in period. Results from Screening Visit 1 procedures must be available for review of randomisation criteria.
c. If a participant withdraws from the study, then the Withdraw from Study (WS) Visit should be conducted 26 weeks after the last administered dose of study intervention, i.e., at Week 26 if the second dose of study intervention was not received, or at Week 52 if the second dose of study intervention was received. A follow-up visit/call should also be conducted 30 weeks after the last dose of study intervention for AE/SAE assessments and pregnancy testing.
d. Informed Consent for optional genetics research must be obtained before collecting a sample. **China only:** Genetic Informed Consent will not be collected from participants in China. Genetic blood samples will not be collected from participants in China.
e. To be randomised, participants without a historical blood eosinophil count of ≥300 cells/μL in the 12 months prior to Screening Visit 1, must have a blood eosinophil count of ≥150 cells/μL at Screening Visit 1. If the Screening Visit test result does not meet the blood eosinophil count eligibility criteria, the laboratory assessment may be repeated, at the discretion of the investigator, if it is judged to be likely in the eligible range for study inclusion within the run-in period prior to Visit 2.
f. For haematology samples collected after Randomisation, the absolute and differential (%) values of eosinophils, lymphocytes, basophils, neutrophils and monocytes will not be reported to site staff and Sponsor (to maintain the treatment blind). However, sites will be sent total white blood counts throughout the study. Samples should be taken prior to dosing at Week 0 and Week 26 visits.
g. SAEs must be collected from signing of Informed Consent if considered related to study procedures
h. If a patient fails the protocol-specified reversibility criterion or FEV_1 inclusion criteria, spirometry retest is allowed during the run-in period.

Source: SWIFT-1 protocol amendment 2, p. 15-23; SWIFT-2 protocol amendment 2, p.15-20.

18.1.2. Adverse Event Definition

Figure 46. Adverse Event Definition

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Source: SWIFT-1 protocol amendment 2, p. 95; SWIFT-2 protocol amendment 2, p. 91.
Abbreviations: AE, adverse event; ECG, electrocardiogram; SAE, serious adverse event

Figure 47. Adverse Event Severity Grading Scale

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilised for rating the intensity of an event; and both AE and SAE can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Source: SWIFT-1 protocol amendment 2, p. 98; SWIFT-2 protocol amendment 2, p. 94.
Abbreviations: AE, adverse event; SAE, serious adverse event

18.1.3. Patient Reported Outcome Instruments

Figure 48. St. George's Respiratory Questionnaire

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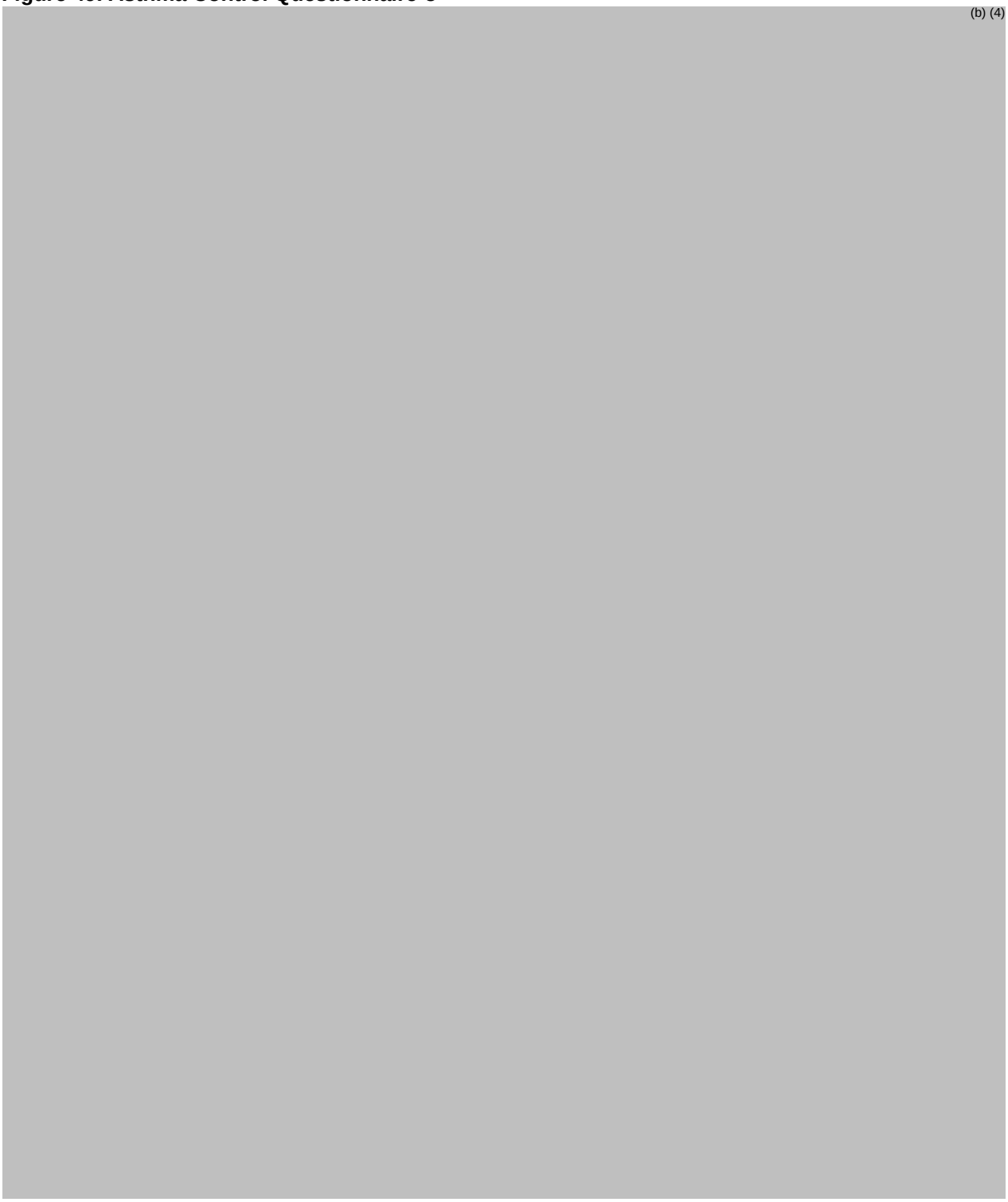
Figure 49. Asthma Control Questionnaire-5



Source: Applicant PRO Evidence Dossier, p. 39-40.

Figure 50. Asthma Daily/Nightly Symptom Diary

(b) (4)

Source: Applicant PRO Evidence Dossier, p. 50-51.
Abbreviations: ADSD, Asthma Daily Symptom Diary; ANSD, Asthma Nightly Symptom Diary

18.2. Trial 212895 (AGILE)

Table 66. Trial Summary, AGILE

Parameter	Details
Title	A multi-center, single arm, open-label extension study to evaluate the long-term safety of GSK3511294 (Depemokimab) in adult and adolescent participants with severe asthma with an eosinophilic phenotype from studies 206713 or 213744
Study Initiation	March 1, 2022
Database lock	July 17, 2024
Interim Data Report	June 14, 2024
Interim Report Final	October 3, 2024
EudraCT	2020-004334-38
IND Number	146742
Countries (% of subjects enrolled)	156 centers in 14 countries. Australia (<1%), Canada (2%), China (7%), Czech Republic (9%), France (<1%), Germany (5%), Hungary (2%), Italy (3%), Japan (9%), Poland (19%), Spain (17%), Taiwan (2%), United Kingdom (2%), United States (23%).

Source: clinical reviewer created based on the clinical study report.
Note: The Applicant provided a final CSR report dated July 24, 2025; however, clinical safety (Section 20.2) is primarily based on the interim data cut-off.
Abbreviations: EudraCT, European Union drug regulating authorities clinical trials database; IND, investigational new drug

18.2.1. Design and Conduct

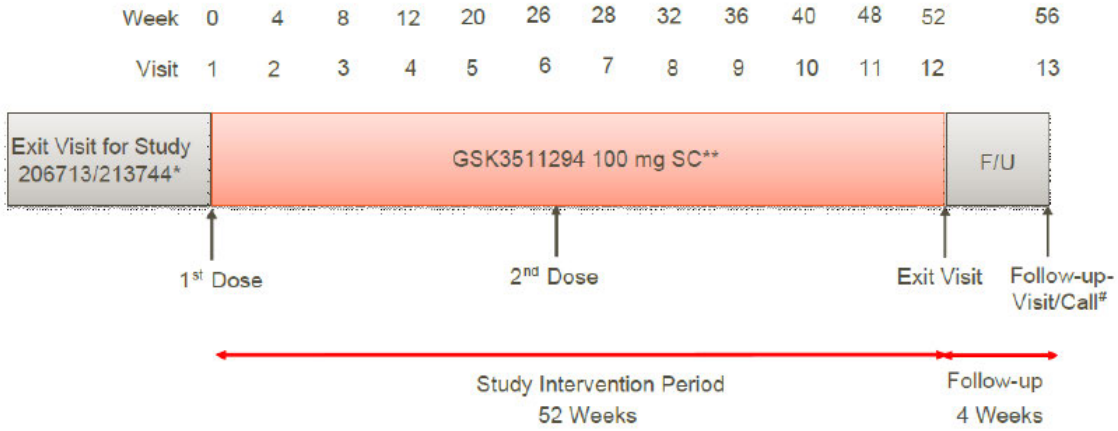
AGILE was a 52-week, open-label, single arm, multi-center extension, Phase 3 trial evaluating the long-term safety and efficacy of 100 mg depemokimab administered subcutaneously (SC) via a pre-filled safety syringe device Q6M in conjunction with continued asthma maintenance therapy in adults and adolescents aged ≥12 years with severe, uncontrolled, eosinophilic asthma who completed SWIFT-1 or SWIFT-2 trials. The following sections will primarily focus on review of safety to provide additional support for the pivotal SWIFT-1 and SWIFT-2 trials.

After obtaining informed consent (or assent for minors), eligibility was assessed at Visit 1 (Baseline Visit). Assessments from the Exit Visit of the SWIFT trials could be used for AGILE if they occurred on the same day or within 7 days of AGILE Visit 1. In contrast, if Visit 1 was >7 days and a maximum of 14 days after the Exit Visit in the SWIFT trials, assessments were completed prior to dosing at Visit 1. Notably, a delayed administration of study drug for a maximum of 4 weeks could be considered in discussion with the medical monitor.

Subjects who met all of the inclusion criteria and none of the exclusion criteria entered the 52-week treatment period and received two doses of depemokimab 100 mg subcutaneously (SC) at Weeks 0 and Week 26. Subsequently, subjects completed a follow-up visit or call 4 weeks after the Exit Visit (Figure 51).

There were no notable differences in the trial design, conduct, and population of AGILE compared to the SWIFT-1 and SWIFT-2 trials. Of note, in order to continue blinding from the SWIFT trials, white blood cell differential was blinded up to Week 4.

Figure 51. Trial Design, AGILE



**The Exit Visit in 206713/213744 will serve as the Baseline Visit (Visit 1) for this study (212895)*

*** Participants will remain on standard of care asthma therapy, which may be adjusted during the study at the discretion of their physician.*

 # Follow-up phone call is only applicable for male and WONCBP

Source: AGILE clinical study protocol, p. 16.

18.2.2. Eligibility Criteria

To be eligible for AGILE, subjects were required to receive both doses of IMP, complete the Exit Visit, and not meet study drug discontinuation criteria during the SWIFT-1/2 trials. In addition, subjects had to meet the following inclusion and exclusion criteria.

Key Inclusion Criteria

- ≥12 years of age (except in the United Kingdom and Germany in which subjects ≥18 years of age were recruited)

Key Exclusion Criteria

- Clinically significant change in health status during the SWIFT-1/2 trials causing the subject to be unsuitable for AGILE based on Investigator discretion
- Subjects with the following liver abnormalities based on Week 48 assessments in SWIFT-1/2 trials, or later assessment: a) ALT > 2x ULN, b) total bilirubin > 1.5x ULN
- Known parasitic infection within 6 months prior to Visit 1 or required to be appropriately treated prior to start of IMP
- Current vasculitis
- Current smokers
- Other clinically significant medical conditions uncontrolled with standard of care therapy causing the subject to be unsuitable for AGILE based on Investigator discretion

18.2.3. Trial Treatment and Concomitant Medications

IMP consisted of open-label depemokimab 100 mg administered SC Q6M by the investigator or designee at the clinical trial study site. Permitted and prohibited medications were consistent with SWIFT-1 and SWIFT-2 trials.

18.2.4. Trial Endpoints

The primary endpoint included the incidence of AEs/SAEs and the incidence of immunogenicity over 52 weeks. Since the trial is not intended to support efficacy for the asthma indication, the only secondary endpoint related to efficacy presented in this review is the annualized rate of clinically significant asthma exacerbations over 52 weeks (see Section 19.8).

18.3. Trial 206785 (NIMBLE)

Table 67. Trial Summary, NIMBLE

Parameter	Details
Title	A 52-week, randomized, double-blind, double-dummy, parallel group, multi-center, non-inferiority study assessing exacerbation rate, additional measures of asthma control and safety in adult and adolescent severe asthmatic participants with an eosinophilic phenotype treated with GSK3511294 (depemokimab) compared with mepolizumab or benralizumab
Trial Initiation	January 26, 2021
Interim Data Cut-off	July 15, 2024
Database Lock	August 12, 2024
Final Interim Report	October 21, 2024
EudraCT	2020-003612-28
IND Number	146742
Countries	404 sites in 20 countries at the time of the interim data cut-off

Source: clinical reviewer created based on the clinical study report.
Abbreviations: EudraCT, European Union drug regulating authorities clinical trials database; IND, investigational new drug

18.3.1. Design and Conduct

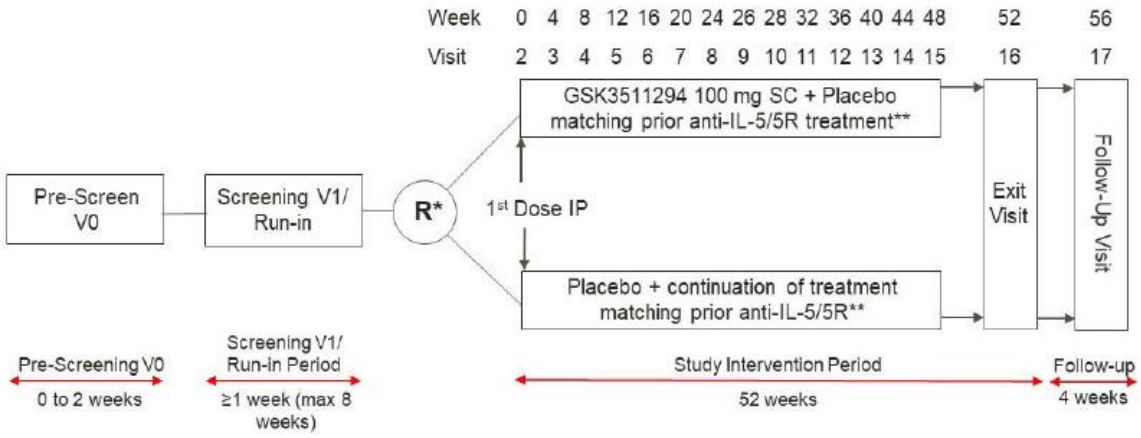
NIMBLE was a 52-week, randomized, double-blind, double-dummy, parallel group, multi-center, non-inferiority trial of 100 mg depemokimab administered subcutaneously (SC) via a pre-filled safety syringe device Q6M on top of continued asthma maintenance therapy compared to continuation of mepolizumab 100 mg SC every 4 weeks or benralizumab 30 mg SC every 8 weeks with continued asthma maintenance therapy in adults and adolescents aged ≥12 years with severe, uncontrolled, eosinophilic asthma. Since NIMBLE is ongoing and a non-inferiority trial, efficacy results are not presented to support the asthma indication. Rather, the following sections will primarily focus on review of safety to provide additional support for the safety observed in SWIFT-1 and SWIFT-2.

The trial consisted of a 0-2 week Pre-Screening period, a 1-8 week Screening and Run-in period, a 52-week Treatment period, and a 4 week follow-up Period. After obtaining informed consent (or assent for minors), eligibility was assessed at Screening. Those who met all of the inclusion

criteria and none of the exclusion criteria entered in the Run-in period. Subjects who met the randomization criteria at the end of the Run-in period were then randomized 1:1 to receive depemokimab or continuation of their anti-IL-5/5R therapy (mepolizumab or benralizumab) during the 52-week Treatment period. A follow-up visit was then completed at Week 56 (Figure 52). Of note, subjects who had an asthma exacerbation during the Run-in period were treated and remained in the Run-in Period until they reached their baseline asthma status for ≥1 week. The Run-in period could be up to 8 weeks in NIMBLE, compared to up to 6 weeks in the SWIFT-1 and SWIFT-2 trials.

The trial was stratified by baseline anti-IL-5/5R therapy with a minimum enrollment of 40% on either mepolizumab or benralizumab.

Figure 52. Trial Design, NIMBLE



** R = Randomisation*
*** Participants randomised to GSK3511294 will receive placebo treatment matching their prior anti-IL-5/5R medication while subjects randomised to receive placebo matching GSK3511294 will receive active treatment matching their prior anti-IL-5/5R (either mepolizumab 100 mg every 4 weeks or benralizumab 30 mg every 8 weeks). All injections will be administered by a prefilled safety syringe (PFS)*

Source: clinical trial protocol amendment 1, p. 12.
Abbreviations: IL-5, interleukin-5; IP, investigational product; SC, subcutaneous; V, visit

18.3.2. Eligibility Criteria

The inclusion and exclusion criteria were generally consistent with the SWIFT-1 and SWIFT-2 trials, thus criteria specific to NIMBLE are presented below. Notably, the SWIFT-1 and SWIFT-2 trials did not specify the use of alternative smoking products (e.g., pipes and/or cigars) as exclusionary and the prohibited period for reslizumab prior to Visit 1 was longer. Moreover, Tezepelumab was not explicitly listed as an excluded biologic in the SWIFT-1 and SWIFT-2 protocols. Randomization criteria were consistent with the SWIFT-1 and SWIFT-2 trials.

Key Inclusion Criteria

- Adults and adolescents ≥12 years of age. In Germany, UK, and Norway only adults ≥18 years-old; in Austria only subjects ≥16 years of age.
- Prior use of mepolizumab 100 mg SC or benralizumab 30 mg SC for ≥1 year prior to Screening with documented benefit.

Demonstration of clinical benefit to prior anti-IL-5/5R therapy was defined as either:

- ≥50% reduction in exacerbation frequency since initiation of an anti-IL-5/5R therapy or
- ≥50% reduction in maintenance oral corticosteroid use since initiation of an anti-IL-5/5R therapy or
- No asthma exacerbations in the past 6 months while receiving an anti-IL-5/5R therapy and an ACQ-5 score of ≤1.5 at Screening

Key Exclusion Criteria

- Prior use of omalizumab, dupilumab, reslizumab, or tezepelumab within 130 days prior to Visit 1
- Current or former smokers with a smoking history of ≥20 pack years. Pipes and/or cigars and/or electronic cigarettes/vaping cannot be used to determine pack-year history; however, current and former use of these is exclusionary. Note: although the SWIFT-1/2 trials list an exclusion criterion of ≥10 pack years, the calculation for number of pack years is the same between SWIFT-1/2 and NIMBLE.

18.3.3. Trial Treatment and Concomitant Medications

IMP consisted of depemokimab 100 mg administered SC Q6M , mepolizumab 100 mg administered SC once every 4 weeks, and benralizumab 30 mg administered SC once every 8 weeks with matching placebo for each. During the Run-in Period, participants received their last dose of mepolizumab and benralizumab 4 and 8 weeks prior to randomization, respectively.

Depemokimab, mepolizumab, benralizumab, and matching placebo were administered at the site by the investigator or designee. The Applicant notes that participants on depemokimab and benralizumab had adequate eosinophil suppression through the week 56 follow-up period. In comparison, mepolizumab participants received their last dose on week 48 and missed their week 52 dose. The Applicant anticipates minimal effect on eosinophil level, but notes that the investigator could administer commercial mepolizumab at their discretion on week 52 if the subject was at risk of AEs due to a missed mepolizumab dose.

Maintenance asthma medications were consistent with SWIFT-1 and SWIFT-2 trials. Among the prohibited medications prior to Screening or during the trial, in addition to those listed for SWIFT-1 and SWIFT-2, NIMBLE also included troleandomycin, and noted that hydrocortisone to treat or prevent adrenal crises when tapering off steroids for asthma may be allowed in consultation with the medical monitor. Additionally, short term use of corticosteroids (≤5 days up to and including 4 courses throughout the trial) was allowed. For rescue therapy, in contrast to the SWIFT-1 and SWIFT-2 trials, reliver therapy as part of MART (ICS/formoterol) or ICS/SABA was allowed if part of a subject's maintenance regimen at Screening. MART was only allowed in recruited subjects after protocol amendment 2 was implemented.

18.3.4. Trial Endpoints

Since NIMBLE is intended to provide support for safety, the associated endpoints were the incidence of AEs/SAEs, laboratory parameters, vital signs, ECG assessments, and incidence of immunogenicity. Efficacy endpoints and results are not discussed within this review.

19 Additional Efficacy Information

19.1. Interim Analysis (SWIFT-1 and SWIFT-2)

The IA was based on the predictive probability of meeting the 'end of program' success criteria: achieving statistical significance for the primary endpoint at a two-sided alpha of 5% in each trial. If the predictive probability of success was ≤0.25, the trials would be stopped early for futility. The methodology for this approach involved predicting the remainder of the primary endpoint data for participants that had not yet completed or been randomized into the trials. The primary analysis (described in Section 8.2.7) was then performed separately for each trial on a "complete" dataset comprised of observed pre-interim data and predicted post-interim data, and the success criteria above was applied. To account for the uncertainty in parameters at the IA (and thus the uncertainty in the predicted remaining data due to the limited data available at the time of the IA), this step was performed >1000 times, and the proportion of samples (iterations) that met the success criteria above yielded the predictive probability of success. An overview of the procedure is provided below:

1. Data on the primary endpoint was pooled across SWIFT-1 and SWIFT-2 to predict the post-interim data, as these were replicate trials and to allow for a more precise estimate of the overall treatment effect and improved operating characteristics. Only participants in the trials for at least one month at the time of the IA were included.
2. The primary analysis using the pooled data across both trials was fit (with an additional term for trial number) in a Bayesian framework (non-informative priors were defined for all model parameters). Posterior distributions for the model and dispersion parameters were obtained from >1000 sets of samples (iterations) taken from these posteriors. Predictions for the post-interim data were based on the interim posterior distribution.
3. The pre-interim observed data (one set) was combined with each set of post-interim data (>1000 sets) to create >1000 'end of trial' datasets.
4. The primary analysis was then applied to each 'end of trial' dataset for each trial separately, and the p-value for the observed treatment effect (rate ratio) was obtained. Subsequently, each dataset was flagged as a success or failure.
5. Finally, the mean of the above flags was calculated to obtain the predictive probability of success for comparison to the pre-specified futility threshold of 0.25.

19.2. Protocol Deviations (SWIFT-1 and SWIFT-2)

The frequency and percentage of SWIFT-1 and SWIFT-2 participants who experienced an IPD are summarized in Table 68.

In SWIFT-1, a similar proportion of participants on depemokimab (28%) and placebo (30%) had at least one IPD. The most commonly reported IPDs were related to study drug administration (out of window administrations and participants not being monitored in clinic for at least two hours post-administration), informed consent, and study procedures.

In SWIFT-2, a similar proportion of participants on depemokimab (25%) and placebo (31%) had at least one IPD. The most commonly reported IPDs were related to study drug administration (one participant was administered an incorrect treatment), informed consent (biomarker samples were drawn for participants who did not provide informed consent for optional biomarker research), and concomitant medication.

Table 68. Protocol Deviations (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1			SWIFT-2		
Protocol Deviation	**Depemokimab N=250**	**Placebo N=132**	**Overall N=382**	**Depemokimab N=252**	**Placebo N=128**	**Overall N=380**
Participants with at least 1 IPD, n (%)	70 (28)	39 (30)	109 (29)	64 (25)	40 (31)	104 (27)
Study drug administration	20 (8)	11 (8)	31 (8)	17 (7)	26 (20)	43 (11)
Informed consent and process	18 (7)	10 (8)	28 (7)	25 (10)	9 (7)	34 (9)
Study procedures	18 (7)	8 (6)	26 (7)	4 (2)	3 (2)	7 (2)
Concomitant medication	6 (2)	6 (5)	12 (3)	13 (5)	8 (6)	21 (6)
Visit schedule	8 (3)	2 (2)	10 (3)	5 (2)	2 (2)	7 (2)
Blinding	5 (2)	2 (2)	7 (2)	3 (1)	7 (5)	10 (3)
Laboratory assessment	3 (1)	3 (2)	6 (2)	1 (<1)	1 (1)	2 (1)
Safety	1 (<1)	5 (4)	6 (2)	2 (1)	2 (2)	4 (1)
Inclusion criteria	3 (1)	1 (1)	4 (1)	7 (3)	4 (3)	11 (3)
Exclusion criteria	3 (1)	0 (0)	3 (1)	4 (2)	4 (3)	8 (2)
Randomization	1 (<1)	1 (1)	2 (1)	0 (0)	0 (0)	0 (0)

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
Notes: This table reflects all IPDs reported in the SWIFT-1 and SWIFT-2 Clinical Study Reports. Additional IPDs of interest reported post-hoc in the SWIFT-1 and SWIFT-2 Clinical Study Report Errata are provided in Section 12. The majority of participants in SWIFT-1/2 with a concomitant medication IPD were due to SCS. One placebo subject in SWIFT-1 received the concomitant medication mepolizumab. Two placebo subjects in SWIFT-2 received the concomitant medication benralizumab; 1 depemokimab subject in SWIFT-2 received omalizumab.
Abbreviations: IPD, important protocol deviation; N, number of participants in the full analysis set; n, number of participants in the respective group.

19.3. Intercurrent Events (SWIFT-1 and SWIFT-2)

The frequency and percentage of SWIFT-1 and SWIFT-2 participants who experienced a pre-specified ICE are summarized in Table 69.

Table 69. Intercurrent Events (Full Analysis Set, SWIFT-1 and SWIFT-2)

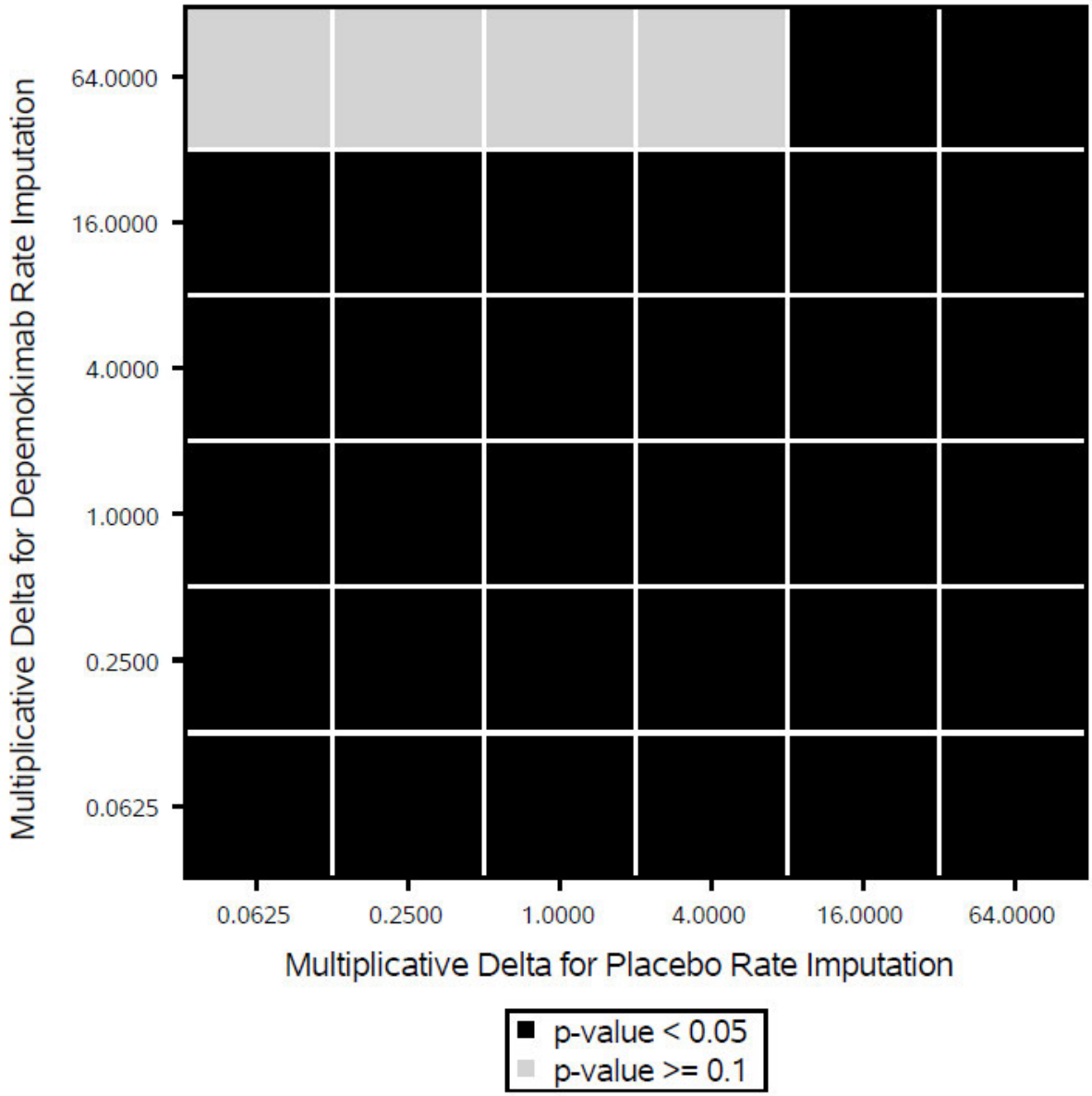
	SWIFT-1			SWIFT-2		
Intercurrent Event	**Depemokimab N=250**	**Placebo N=132**	**Overall N=382**	**Depemokimab N=252**	**Placebo N=128**	**Overall N=380**
Change in asthma maintenance therapy, n (%)	1 (<1)	1 (1)	2 (1)	7 (3)	2 (2)	9 (2)
Treatment discontinuation related to COVID-19, n (%)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Treatment discontinuation unrelated to COVID-19, n (%)	13 (5)	6 (5)	19 (5)	13 (5)	3 (2)	16 (4)
Use of concomitant/prohibited medications, n (%)	6 (2)	6 (5)	12 (3)	13 (5)	9 (7)	22 (6)

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
Note: This table reflects all intercurrent events reported in the SWIFT-1 and SWIFT-2 Clinical Study Reports. Based on the post-hoc intercurrent events reported in the SWIFT-2 Clinical Study Report Errata, there were an additional 3 participants who used concomitant/prohibited medications during the trial.
Abbreviations: N, number of participants in the full analysis set; n, number of participants in the respective group.

19.4. Sensitivity Analysis Plots for the Primary Endpoint (SWIFT-1 and SWIFT-2)

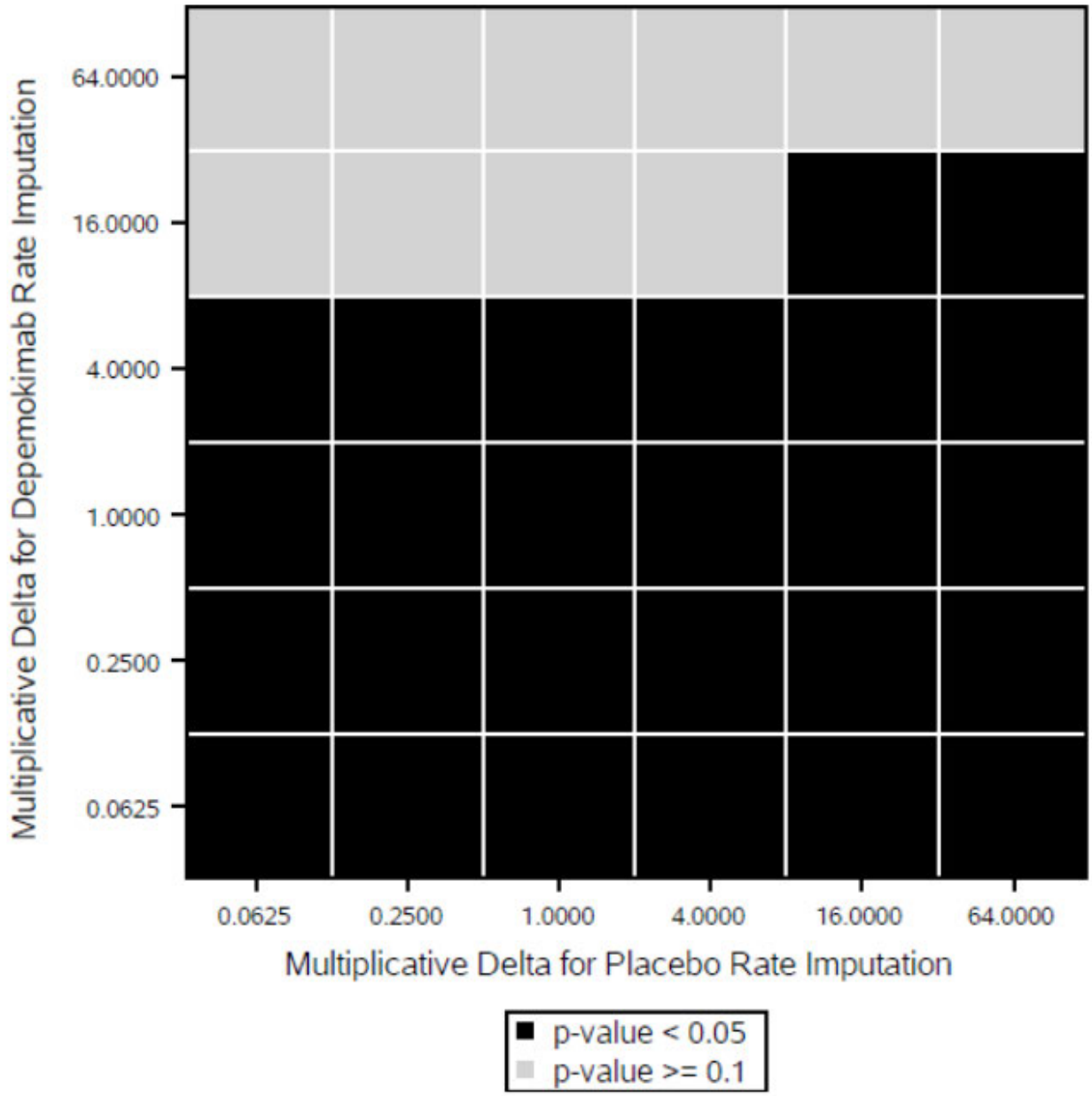
Results for the tipping point sensitivity analyses used to assess the impact of missing data in the primary analysis of the annualized rate of clinically significant asthma exacerbations over 52 weeks in SWIFT-1 and SWIFT-2 are summarized in Figure 53 and Figure 54, respectively. Ultimately, missing data did not substantially impact the primary analysis results in either trial.

Figure 53. Tipping Point Sensitivity Analysis for the Primary Endpoint of Annualized Rate of Clinically Significant Asthma Exacerbations Over 52 Weeks (Full Analysis Set, SWIFT-1)



Source: SWIFT-1 Clinical Study Report, Figure 3
Notes: Analysis performed using a negative binomial model identical to the primary analysis (see Section 8.2.9). Based on 1000 iterations.

Figure 54. Tipping Point Sensitivity Analysis for the Primary Endpoint of Annualized Rate of Clinically Significant Asthma Exacerbations Over 52 Weeks (Full Analysis Set, SWIFT-2)



Source: SWIFT-2 Clinical Study Report, Figure 3
Notes: Analysis performed using a negative binomial model identical to the primary analysis (see Section 8.2.9). Based on 1000 iterations.

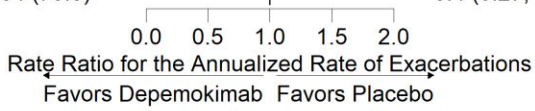
19.5. Subgroup Analysis Plots for the Primary Endpoint (SWIFT-1 and SWIFT-2)

For SWIFT-1 and SWIFT-2, subgroup analyses were conducted for the primary endpoint (annualized rate of clinically significant asthma exacerbations over 52 weeks) by age, sex, race, ethnicity, geographical region, and baseline ICS dose, peripheral blood eosinophil count, and

ACQ-5 score (Figure 55; Figure 56). For both trials, the subgroup analysis results were generally consistent with the overall (FAS) population.

Figure 55. Subgroup Analyses for the Primary Endpoint of Annualized Rate of Clinically Significant Asthma Exacerbations Over 52 Weeks (Full Analysis Set, SWIFT-1)

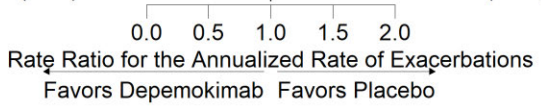
Variable	Depemokimab N = 250	Placebo N = 132	Rate Ratio (95% CI)
Overall, n (%)	249 (100)	132 (100)	0.42 (0.3, 0.6)
Sex, n (%)			
Female	143 (57.4)	79 (59.8)	0.4 (0.26, 0.61)
Male	106 (42.6)	53 (40.2)	0.46 (0.26, 0.79)
Race, n (%)			
White	206 (82.7)	109 (82.6)	0.51 (0.35, 0.75)
Asian	38 (15.3)	20 (15.2)	0.15 (0.07, 0.3)
Age Group, n (%)			
18 - 64	184 (73.9)	91 (68.9)	0.43 (0.28, 0.66)
>= 65	62 (24.9)	36 (27.3)	0.36 (0.2, 0.64)
Region, n (%)			
Rest of World	59 (23.7)	29 (22)	0.23 (0.12, 0.44)
Europe	158 (63.5)	85 (64.4)	0.54 (0.35, 0.83)
Ethnicity, n (%)			
Not Hispanic or Latino	238 (95.6)	121 (91.7)	0.45 (0.32, 0.63)
Hispanic or Latino	11 (4.4)	11 (8.3)	0.06 (0, 0.61)
Baseline ICS Dose, n (%)			
High	132 (53)	71 (53.8)	0.47 (0.3, 0.72)
Medium	117 (47)	61 (46.2)	0.36 (0.21, 0.62)
Baseline Eosinophil Subgroup 1, n (%)			
< 0.15 (GI/L)	42 (16.8)	25 (18.9)	0.45 (0.17, 1.22)
>= 0.15 (GI/L)	207 (83.1)	107 (81.1)	0.42 (0.29, 0.61)
Baseline Eosinophil Subgroup 2, n (%)			
< 0.3 (GI/L)	97 (39.0)	56 (42.4)	0.59 (0.35, 0.99)
>= 0.3 (GI/L)	152 (61.0)	76 (57.6)	0.32 (0.2, 0.51)
Baseline ACQ-5 Score, n (%)			
< 1.5	55 (22.1)	28 (21.2)	0.47 (0.22, 0.99)
>= 1.5	194 (77.9)	104 (78.8)	0.4 (0.27, 0.6)



Source: Statistical analyst; SWIFT-1 (p. 95) Clinical Study Report; Responses to Information Request received on July 21, 2025.
Note: One SWIFT-1 participant on depemokimab was excluded from analysis due to missing covariate data at Week 52 (this participant did not have any asthma exacerbations).
Abbreviations: ACQ-5, asthma control questionnaire (5-item version); CI, confidence interval; GI/L, number of eosinophils per gigaliter; ICS, inhaled corticosteroids; N, number of participants in the full analysis set; n, number of participants in the respective group

Figure 56. Subgroup Analyses for the Primary Endpoint of Annualized Rate of Clinically Significant Asthma Exacerbations Over 52 Weeks (Full Analysis Set, SWIFT-2)

Variable	Depemokimab N = 252	Placebo N = 128	Rate Ratio (95% CI)
Overall, n (%)	252 (100)	128 (100)	0.51 (0.36, 0.73)
Sex, n (%)			
Female	160 (63.5)	81 (63.3)	0.52 (0.33, 0.82)
Male	92 (36.5)	47 (36.7)	0.42 (0.24, 0.72)
Race, n (%)			
Black or African American	17 (6.7)	11 (8.6)	1.22 (0.2, 6.84)
White	181 (71.8)	91 (71.1)	0.45 (0.3, 0.66)
Age Group, n (%)			
18 - 64	169 (67.1)	93 (72.7)	0.57 (0.38, 0.84)
12 - 17	12 (4.8)	10 (7.8)	0.7 (0.19, 2.43)
>=65	71 (28.2)	25 (19.5)	0.36 (0.14, 0.87)
Region, n (%)			
Rest of World	54 (21.4)	25 (19.5)	0.54 (0.25, 1.13)
US	90 (35.7)	46 (35.9)	0.5 (0.23, 1.05)
Europe	108 (42.9)	57 (44.5)	0.52 (0.35, 0.76)
Ethnicity, n (%)			
Not Hispanic or Latino	207 (82.1)	108 (84.4)	0.55 (0.39, 0.77)
Hispanic or Latino	45 (17.9)	20 (15.6)	0.2 (0.01, 1.51)
Baseline ICS Dose, n (%)			
High	158 (62.7)	68 (53.1)	0.58 (0.38, 0.89)
Medium	94 (37.3)	60 (46.9)	0.45 (0.24, 0.81)
Baseline Eosinophil Subgroup 1, n (%)			
< 0.15 (GI/L)	39 (15.4)	15 (11.7)	0.72 (0.24, 2.17)
>= 0.15 (GI/L)	213 (84.5)	113 (58.3)	0.5 (0.35, 0.73)
Baseline Eosinophil Subgroup 2, n (%)			
< 0.3 (GI/L)	105 (41.7)	59 (46.1)	0.45 (0.26, 0.78)
>= 0.3 (GI/L)	147 (58.3)	69 (53.9)	0.55 (0.35, 0.86)
Baseline ACQ-5 Score, n (%)			
< 1.5	63 (25.0)	30 (23.4)	0.45 (0.21, 0.97)
>= 1.5	184 (73.0)	95 (74.2)	0.53 (0.36, 0.79)



Source: Statistical analyst; SWIFT-2 (p. 91) Clinical Study Report; Responses to Information Request received on July 21, 2025.
Abbreviations: ACQ-5, asthma control questionnaire (5-item version); CI, confidence interval; GI/L, number of eosinophils per gigaliter; ICS, inhaled corticosteroids; N, number of participants in the full analysis set; n, number of participants in the respective group

19.6. ANSD and ADSD Analyses (SWIFT-1 and SWIFT-2)

For both trials, changes from baseline in ANSD and ADSD weekly mean scores at Week 52 were evaluated using MMRMs similar to the secondary analyses (see Section 8.2.7), conducted in the FAS. In SWIFT-1 and SWIFT-2, treatment with depemokimab resulted in a very small numerical improvement in the absolute change from baseline in ANSD weekly mean score at Week 52 compared to placebo, with LS mean differences of -0.09 (95% CI: -0.05, 0.31) and -0.21 (95% CI: -0.52, 0.09), respectively (Table 70). In both trials, the conclusions for ADSD were similar (Table 71).

Table 70. Additional Efficacy Analyses: Change From Baseline in ANSD Weekly Mean Score at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=128**
Number of evaluable participants[a], n (%)	185 (74)	95 (72)	232 (92)	117 (91)
LS mean (SE)	1.49 (0.12)	1.58 (0.17)	1.24 (0.09)	1.45 (0.13)
Difference[b]	-0.09		-0.21	
95% CI	-0.05, 0.31		-0.52, 0.09	
P-value	0.65		0.173	

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] Number of participants with analyzable data for one or more timepoints.
[b] Calculated as: LS mean in depemokimab arm – LS mean in placebo arm.
Note: All results were obtained from an MMRM with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, baseline value, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: ANSD, Asthma Nighttime Symptom Diary; CI, confidence interval; N, number of participants in the full analysis set; n, number of evaluable participants; SE, standard error.

Table 71. Additional Efficacy Analyses: Change From Baseline in ADSD Weekly Mean Score at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=128**
Number of evaluable participants[a], n (%)	206 (82)	110 (83)	249 (99)	126 (98)
LS mean (SE)	1.36 (0.1)	1.44 (0.14)	1.14 (0.08)	1.35 (0.11)
Difference[b]	-0.08		-0.21	
95% CI	-0.42, 0.26		-0.48, 0.07	
P-value	0.647		0.138	

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] Number of participants with analyzable data for one or more timepoints.
[b] Calculated as: LS mean in depemokimab arm – LS mean in placebo arm.
Note: All results were obtained from an MMRM with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, baseline value, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: ADSD, Asthma Daytime Symptom Diary; CI, confidence interval; N, number of participants in the full analysis set; n, number of evaluable participants; SE, standard error.

19.7. Additional Efficacy Analyses (SWIFT-1 and SWIFT-2)

Time to First Clinically Significant Asthma Exacerbation Over 52 Weeks

This endpoint was analyzed exploratorily using a Cox proportional hazards model with terms for treatment arm, asthma exacerbation history (2, 3, or ≥4 in the past year), baseline ICS dose (medium or high), geographical region (Europe, US, or rest of the world), and baseline pre-BD ppFEV1. The exact method was used to handle potential ties, and the proportional hazards assumption was examined graphically. The hazard ratio and percent reduction in the hazard rate relative to placebo with associated 95% CIs and p-values were reported. Kaplan-Meier cumulative incidence curves were also reported for each treatment arm. For participants who discontinued IMP due to reasons related to COVID-19 (only one case in SWIFT-1), observed data after this ICE were excluded from the analysis and assumed to be MAR. Data following withdrawals were also assumed to be MAR.

In SWIFT-1 and SWIFT-2, treatment with depemokimab resulted in a numerical reduction in the risk of a first clinically significant asthma exacerbation compared to placebo, with hazard ratios of 0.56 (95% CI: 0.40, 0.79) and 0.53 (95% CI: 0.38, 0.74), respectively (Table 72).

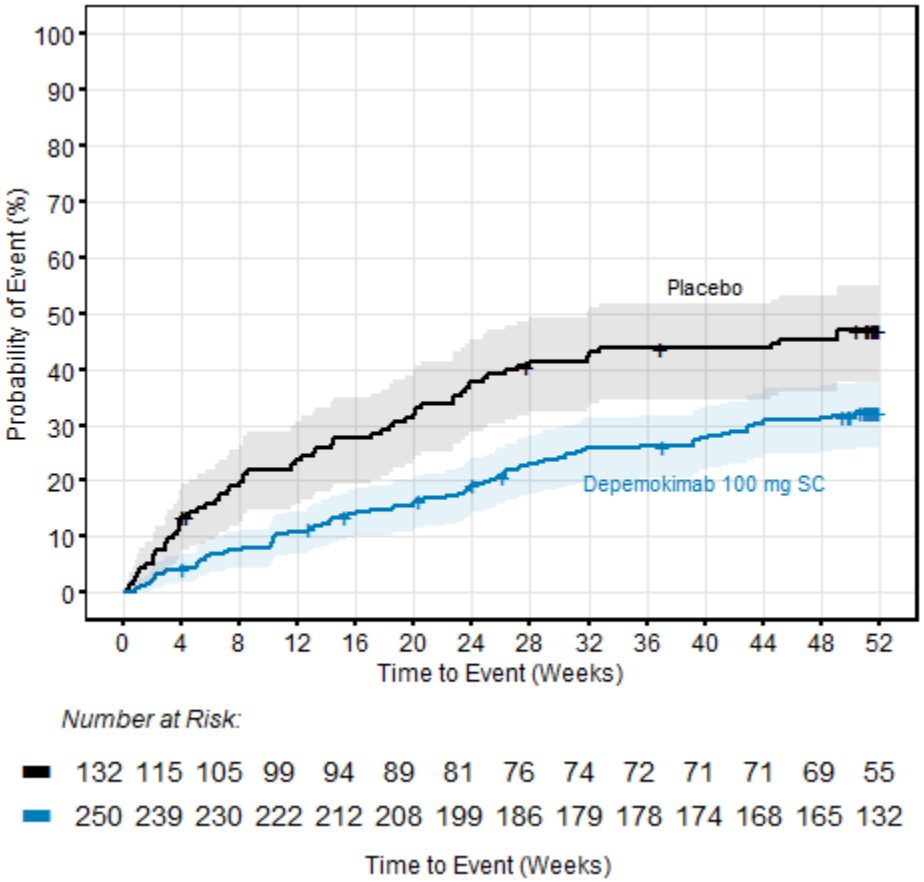
Table 72. Additional Efficacy Results: Time to First Clinically Significant Asthma Exacerbation Over 52 Weeks (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	**Depemokimab N=250**	**Placebo N=132**	**Depemokimab N=252**	**Placebo N=128**
Number of evaluable participants[a], n (%)	249 (>99)	132 (100)	252 (100)	128 (100)
Hazard ratio[b]	0.56		0.53	
95% CI	0.40, 0.79		0.38, 0.74	

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] One SWIFT-1 participant on depemokimab was excluded from analysis due to missing covariate data at Week 52 (this participant did not have any clinically significant asthma exacerbations).
[b] Calculated as: hazard rate in depemokimab arm / hazard rate in placebo arm.
Note: All results were obtained from a Cox PH model with terms for treatment arm, asthma exacerbation history, baseline ICS dose, geographical region, and baseline pre-bronchodilator ppFEV1.
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; N, number of participants in the full analysis set; n, number of participants in the respective group; PH, proportional hazards; ppFEV1, percent predicted forced expiratory volume in 1 second.

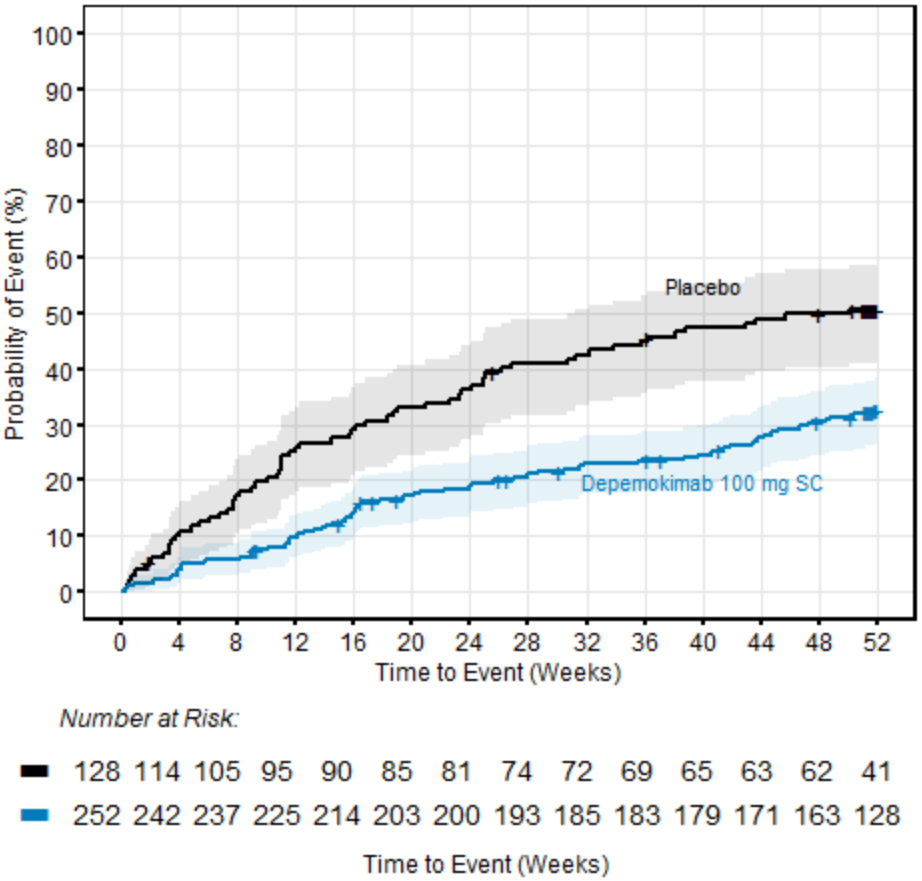
The above results are supported by the separation of the cumulative incidence curves for the depemokimab and placebo arms in SWIFT-1 (Figure 57) and SWIFT-2 (Figure 58).

Figure 57. Additional Efficacy Results: Kaplan-Meier Cumulative Incidence Curves for Time to First Clinically Significant Asthma Exacerbation (Full Analysis Set, SWIFT-1)



Source: Statistical analyst; SWIFT-1 Clinical Study Report.
Note: Shaded areas represent the 95% CI.
Abbreviations: CI, confidence interval; SC, subcutaneously.

Figure 58. Additional Efficacy Results: Kaplan-Meier Cumulative Incidence Curves for Time to First Clinically Significant Asthma Exacerbation (Full Analysis Set, SWIFT-2)



Source: Statistical analyst; SWIFT-2 Clinical Study Report.
Note: Shaded areas represent the 95% CI.
Abbreviations: CI, confidence interval; SC, subcutaneously.

ACQ-5 Responder Status

This endpoint was defined as achieving a ≥0.5-point reduction from baseline at Week 52 and was evaluated using a generalized linear mixed model with terms for treatment arm, baseline ICS dose (medium or high), asthma exacerbation history (2, 3, or ≥4 in the past year), geographical region (Europe, US, or rest of the world), visit, participant (random effect), baseline ACQ-5 total score, baseline ppFEV1, and interactions for baseline ACQ-5 total score and visit and for treatment arm and visit. An unstructured variance-covariance matrix was assumed. Pearson residuals were plotted for model checking and diagnostics. The frequencies and percentages of responders and the odds ratios relative to placebo with associated 95% CIs and p-values were reported. For participants who discontinued IMP due to reasons related to COVID-19 (only one case in SWIFT-1), observed data after this ICE were excluded from the analysis and assumed to be MAR. Data following withdrawals were also assumed to be MAR.

In SWIFT-1 and SWIFT-2, treatment with depemokimab did not result in a meaningful improvement in the proportion of ACQ-5 responders (Table 73). ACQ-5 responder rates have been commonly included as a PRO to support labeling claims for other asthma biologics (e.g.,

mepolizumab) and thus will also be labeled for depemokimab for consistency and comparability among therapeutics.

Table 73. Additional Efficacy Results: ACQ-5 Responder Status at Week 52 (Full Analysis Set, SWIFT-1 and SWIFT-2)

	SWIFT-1		SWIFT-2	
Analysis Statistic	Depemokimab N=250	Placebo N=132	Depemokimab N=252	Placebo N=128
Number of evaluable participants[a], n (%)	241 (96)	129 (98)	247 (98)	125 (98)
Proportion of responders, n (%)	131 (54)	71 (55)	134 (54)	66 (53)
Odds ratio[b]	0.95		1.06	
95% CI	0.6, 1.52		0.67, 1.69	

Source: SWIFT-1 and SWIFT-2 Clinical Study Reports.
[a] 12 SWIFT-1 participants (9 on depemokimab and 3 on placebo) and 8 SWIFT-2 participants (5 on depemokimab and 3 on placebo) were excluded from analysis due to lack of ACQ-5 data for one or more timepoints.
[b] Calculated as: odds in depemokimab arm / odds in placebo arm.
Notes: All results were obtained from a generalized linear mixed model with terms for treatment arm, baseline ICS dose, asthma exacerbation history, geographical region, visit, participant (random effect), baseline value, baseline ppFEV1, and interactions for baseline value and visit and for treatment arm and visit.
Abbreviations: ACQ-5, Asthma Control Questionnaire – 5-item version; CI, confidence interval; ICS, inhaled corticosteroid; N, number of participants in the full analysis set; n, number of participants in the respective group; ppFEV1, percent predicted forced expiratory volume in 1 second.

19.8. Efficacy Analyses (AGILE; Study 212895)

The Applicant is conducting an ongoing, multicenter, single-arm, open-label extension study (Study 212895; AGILE) with a 52-week Treatment Period and 4-week Follow-up Period to evaluate the long-term safety and efficacy of depemokimab 100 mg administered SC via PFS device on top of standard of care (continued asthma maintenance therapy [medium- or high-dose ICS plus at least one additional asthma controller medication with or without maintenance oral corticosteroids]) in adults and adolescents (aged ≥12 years) with severe, uncontrolled, eosinophilic asthma who completed SWIFT-1 or SWIFT-2. All SWIFT-1 and SWIFT-2 completers had the opportunity to roll into AGILE, and the baseline demographics and clinical characteristics of participants in AGILE did not substantially differ from SWIFT-1 and SWIFT-2. The primary endpoints for this study are focused on safety (see Section 20.2), while the secondary endpoints are focused on efficacy, including evaluation of the annualized rate of clinically significant asthma exacerbations (using the same estimand and exacerbation definitions that were pre-specified for SWIFT-1 and SWIFT-2).

Safety (see Section 20.2) and efficacy results were submitted based on an IA (data cutoff date: June 14, 2024) of 629 participants (Safety Set) who either continued on depemokimab after completing SWIFT-1 or SWIFT-2 (419 participants) or were depemokimab-naïve (210 participants). At the data cutoff date, 298 participants (47%) completed the study, 309 participants (49%) were ongoing, and 22 participants (3%) withdrew from the study.

Among the 419 participants who continued on depemokimab after completing SWIFT-1 or SWIFT-2, the estimated annualized rate of clinically significant asthma exacerbations was 0.47 (95% CI: 0.39, 0.56), providing some evidence of durability of the treatment effects observed for the primary endpoint in SWIFT-1 and SWIFT-2 (Table 74). Additionally, the estimated exacerbation rate among the 210 depemokimab-naïve participants was 0.49 (95% CI: 0.38,

0.64) and also congruent with the results from SWIFT-1 and SWIFT-2. However, due to the lack of a control arm and blinding, these results should be interpreted with caution.

Table 74. Annualized Rate of Clinically Significant Asthma Exacerbations (Safety Set, AGILE)

Analysis Statistic	Previous Depemokimab N=419	Previous Placebo N=210	Total N=629
Annualized rate of clinically significant asthma exacerbations	0.47	0.49	0.48
95% CI	0.39, 0.56	0.38, 0.64	0.41, 0.56

Source: Statistical analyst; AGILE Interim Clinical Study Report.
Abbreviations: CI, confidence interval; N, number of participants in the safety set; n, number of participants in the respective group.

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20.1. SWIFT-1 and SWIFT-2

Table 75. Serious Adverse Events More Common Than Placebo by System Organ Class and OND Custom Medical Query (Narrow), Pooled Safety Population, SWIFT-1 and SWIFT-2

System Organ Class OCMQ (Narrow)	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Cardiac disorders (SOC)			
Acute coronary syndrome	1 (0.2)	0	0.2 (-1.3, 1.1)
Myocardial ischemia	1 (0.2)	0	0.2 (-1.3, 1.1)
Endocrine disorders (SOC)			
Hypoglycemia	1 (0.2)	0	0.2 (-1.3, 1.1)
Gastrointestinal disorders (SOC)			
Abdominal pain	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatobiliary disorders (SOC)			
Cholecystitis	2 (0.4)	0	0.4 (-1.1, 1.4)
Hepatic injury	1 (0.2)	0	0.2 (-1.3, 1.1)
Musculoskeletal and connective tissue disorders (SOC)			
Tendinopathy	2 (0.4)	0	0.4 (-1.1, 1.4)
Arthritis	1 (0.2)	0	0.2 (-1.3, 1.1)
Nervous system disorders (SOC)			
Seizure	2 (0.4)	0	0.4 (-1.1, 1.4)
Stroke and TIA	1 (0.2)	0	0.2 (-1.3, 1.1)

System Organ Class OCMQ (Narrow)	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Vascular disorders (SOC)			
Thrombosis	2 (0.4)	0	0.4 (-1.1, 1.4)
Thrombosis arterial	2 (0.4)	0	0.4 (-1.1, 1.4)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
For specific preferred terms under each OCMQ, see the table "Serious Adverse Events by System Organ Class, OND custom medical query (Narrow) and Preferred Term…"
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in OND custom medical query (Narrow)…"
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; OCMQ, Office of New Drugs custom medical query; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

Table 76. Severe Adverse Events More Common Than Placebo by System Organ Class, OCMQ (Narrow) and Preferred Term, Pooled Safety Population, SWIFT-1 and SWIFT-2

System Organ Class OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference (%) (95% CI)
Gastrointestinal disorders (SOC)			
Abdominal Pain (OCMQ)	1 (0.2)	0	0.2 (-1.3, 1.1)
Abdominal pain	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatobiliary disorders (SOC)			
Cholecystitis (OCMQ)	2 (0.4)	0	0.4 (-1.1, 1.4)
Cholecystitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Cholecystitis acute	1 (0.2)	0	0.2 (-1.3, 1.1)
Hepatic Injury (OCMQ)	1 (0.2)	0	0.2 (-1.3, 1.1)
Alanine aminotransferase increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Aspartate aminotransferase increased	1 (0.2)	0	0.2 (-1.3, 1.1)
Infections and infestations (SOC)			
Bronchiolitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Bacterial Infection (OCMQ)	2 (0.4)	1 (0.4)	0.0 (-1.8, 1.1)
Cholecystitis	1 (0.2)	0	0.2 (-1.3, 1.1)
Cholecystitis acute	1 (0.2)	0	0.2 (-1.3, 1.1)
Musculoskeletal and connective tissue disorders (SOC)			
Tendinopathy (OCMQ)	2 (0.4)	0	0.4 (-1.1, 1.4)
Rotator cuff syndrome	1 (0.2)	0	0.2 (-1.3, 1.1)
Tenosynovitis stenosans	1 (0.2)	0	0.2 (-1.3, 1.1)
Myalgia (OCMQ)	1 (0.2)	0	0.2 (-1.3, 1.1)
Myalgia	1 (0.2)	0	0.2 (-1.3, 1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)			
Malignancy (OCMQ)	2 (0.4)	0	0.4 (-1.1, 1.4)
Metastases to peritoneum	1 (0.2)	0	0.2 (-1.3, 1.1)
Ovarian cancer	1 (0.2)	0	0.2 (-1.3, 1.1)
Small intestine adenocarcinoma	1 (0.2)	0	0.2 (-1.3, 1.1)

System Organ Class OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference (%) (95% CI)
Nervous system disorders (SOC)			
Headache (OCMQ)	1 (0.2)	0	0.2 (-1.3, 1.1)
Headache	1 (0.2)	0	0.2 (-1.3, 1.1)
Seizure (OCMQ)	1 (0.2)	0	0.2 (-1.3, 1.1)
Epilepsy	1 (0.2)	0	0.2 (-1.3, 1.1)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Includes AE records assessed by investigator as "Severe" and also includes 3 records that are not labelled "Severe" but are labelled life-threatening.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in OND custom medical query (Narrow)…"
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; OCMQ, Office of New Drugs custom medical query; SOC, system organ class

Table 77. Adverse Events by System Organ Class and Preferred Term More Common Than Placebo, Showing Terms Occurring in at Least 1% of Subjects in Any Arm, Pooled Safety Population, SWIFT-1 and SWIFT-2

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Any AE	362 (72.3)	198 (75.9)	-3.6 (-9.9, 3.1)
Blood and lymphatic system disorders (SOC)	10 (2.0)	5 (1.9)	0.1 (-2.6, 2.1)
Anaemia	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
Ear and labyrinth disorders (SOC)	11 (2.2)	4 (1.5)	0.7 (-1.8, 2.6)
Eye disorders (SOC)	22 (4.4)	6 (2.3)	2.1 (-0.9, 4.6)
Conjunctivitis allergic	11 (2.2)	4 (1.5)	0.7 (-1.8, 2.6)
Gastrointestinal disorders (SOC)	64 (12.8)	31 (11.9)	0.9 (-4.3, 5.6)
Diarrhoea	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Toothache	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Abdominal pain	7 (1.4)	2 (0.8)	0.6 (-1.5, 2.2)
Abdominal pain upper	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
General disorders and administration site conditions (SOC)	39 (7.8)	22 (8.4)	-0.6 (-5.1, 3.3)
Influenza like illness	9 (1.8)	1 (0.4)	1.4 (-0.4, 3.1)
Pyrexia	11 (2.2)	4 (1.5)	0.7 (-1.8, 2.6)
Chest pain	7 (1.4)	2 (0.8)	0.6 (-1.5, 2.2)
Infections and infestations (SOC)	280 (55.9)	153 (58.6)	-2.7 (-10.0, 4.7)
Pharyngitis	18 (3.6)	3 (1.1)	2.4 (-0.0, 4.7)
Upper respiratory tract infection	46 (9.2)	20 (7.7)	1.5 (-2.9, 5.4)
Acute sinusitis	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Influenza	24 (4.8)	11 (4.2)	0.6 (-2.9, 3.5)
Urinary tract infection	10 (2.0)	5 (1.9)	0.1 (-2.6, 2.1)
Conjunctivitis	6 (1.2)	3 (1.1)	0.0 (-2.2, 1.7)
Injury, poisoning and procedural complications (SOC)	42 (8.4)	21 (8.0)	0.3 (-4.1, 4.2)
Ligament sprain	6 (1.2)	0	1.2 (-0.3, 2.6)
Investigations (SOC)	21 (4.2)	13 (5.0)	-0.8 (-4.4, 2.2)
Alanine aminotransferase increased	6 (1.2)	2 (0.8)	0.4 (-1.6, 2.0)

System Organ Class Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)	66 (13.2)	42 (16.1)	-2.9 (-8.6, 2.2)
Pain in extremity	9 (1.8)	1 (0.4)	1.4 (-0.4, 3.1)
Osteoarthritis	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Arthralgia	19 (3.8)	8 (3.1)	0.7 (-2.4, 3.3)
Nervous system disorders (SOC)	63 (12.6)	31 (11.9)	0.7 (-4.5, 5.4)
Dizziness	10 (2.0)	2 (0.8)	1.2 (-0.9, 3.0)
Psychiatric disorders (SOC)	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Respiratory, thoracic and mediastinal disorders (SOC)	85 (17.0)	44 (16.9)	0.1 (-5.8, 5.5)
Rhinitis allergic	29 (5.8)	7 (2.7)	3.1 (-0.1, 5.9)
Dyspnoea	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Rhinorrhoea	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Skin and subcutaneous tissue disorders (SOC)	35 (7.0)	17 (6.5)	0.5 (-3.7, 4.0)
Urticaria	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 78. Adverse Events Occurring in at Least 0.5% of Subjects in Any Arm and More Common Than Placebo by System Organ Class, OND Custom Medical Query (Narrow) and Preferred Term, Pooled Safety Population, Trials 206713 and 213744

System Organ Class OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)			
Anemia (OCMQ)	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
Anaemia	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
Cardiac disorders (SOC)			
Arrhythmia (OCMQ)	9 (1.8)	4 (1.5)	0.3 (-2.2, 2.1)
Endocrine disorders (SOC)			
Hyperglycemia (OCMQ)	12 (2.4)	8 (3.1)	-0.7 (-3.7, 1.6)
Type 2 diabetes mellitus	3 (0.6)	0	0.6 (-0.9, 1.7)
Gastrointestinal disorders (SOC)			
Abdominal pain (OCMQ)	16 (3.2)	6 (2.3)	0.9 (-2.0, 3.2)
Abdominal pain	7 (1.4)	2 (0.8)	0.6 (-1.5, 2.2)
Abdominal pain upper	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
Diarrhea (OCMQ)	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Diarrhoea	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Dyspepsia (OCMQ)	9 (1.8)	3 (1.1)	0.6 (-1.7, 2.4)
Dyspepsia	3 (0.6)	0	0.6 (-0.9, 1.7)
Abdominal pain upper	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)

System Organ Class OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)			
Dizziness (OCMQ)	13 (2.6)	4 (1.5)	1.1 (-1.5, 3.1)
Dizziness	10 (2.0)	2 (0.8)	1.2 (-0.9, 3.0)
Pyrexia (OCMQ)	11 (2.2)	4 (1.5)	0.7 (-1.8, 2.6)
Pyrexia	11 (2.2)	4 (1.5)	0.7 (-1.8, 2.6)
Fatigue (OCMQ)	7 (1.4)	3 (1.1)	0.2 (-2.0, 1.9)
Local administration reaction (OCMQ)	5 (1.0)	2 (0.8)	0.2 (-1.8, 1.7)
Injection site reaction	5 (1.0)	0	1.0 (-0.5, 2.3)
Fall (OCMQ)	3 (0.6)	1 (0.4)	0.2 (-1.6, 1.4)
Fall	3 (0.6)	1 (0.4)	0.2 (-1.6, 1.4)
Hepatobiliary disorders (SOC)			
Hepatic injury (OCMQ)	9 (1.8)	4 (1.5)	0.3 (-2.2, 2.1)
Alanine aminotransferase increased	6 (1.2)	2 (0.8)	0.4 (-1.6, 2.0)
Immune system disorders (SOC)			
Hypersensitivity (OCMQ)	6 (1.2)	2 (0.8)	0.4 (-1.6, 2.0)
Hypersensitivity	3 (0.6)	1 (0.4)	0.2 (-1.6, 1.4)
Infections and infestations (SOC)			
Bacterial infection (OCMQ)	35 (7.0)	15 (5.7)	1.2 (-2.8, 4.7)
Cystitis	3 (0.6)	0	0.6 (-0.9, 1.7)
Periodontitis	3 (0.6)	0	0.6 (-0.9, 1.7)
Tooth abscess	3 (0.6)	0	0.6 (-0.9, 1.7)
Urinary tract infection	10 (2.0)	5 (1.9)	0.1 (-2.6, 2.1)
Purulent material (OCMQ)	4 (0.8)	0	0.8 (-0.7, 2.0)
Tooth abscess	3 (0.6)	0	0.6 (-0.9, 1.7)
Viral infection (FMQ)	121 (24.2)	64 (24.5)	-0.4 (-7.0, 5.9)
Influenza	24 (4.8)	11 (4.2)	0.6 (-2.9, 3.5)
Viral infection	4 (0.8)	1 (0.4)	0.4 (-1.4, 1.7)
Viral upper respiratory tract infection	4 (0.8)	1 (0.4)	0.4 (-1.4, 1.7)
Nasopharyngitis (FMQ)	163 (32.5)	93 (35.6)	-3.1 (-10.3, 3.9)
Rhinitis allergic	29 (5.8)	7 (2.7)	3.1 (-0.1, 5.9)
Pharyngitis	18 (3.6)	3 (1.1)	2.4 (-0.0, 4.7)
Upper respiratory tract infection	46 (9.2)	20 (7.7)	1.5 (-2.9, 5.4)
Acute sinusitis	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Musculoskeletal and connective tissue disorders (SOC)			
Arthritis (OCMQ)	17 (3.4)	1 (0.4)	3.0 (1.0, 5.1) *
Arthritis	5 (1.0)	0	1.0 (-0.5, 2.3)
Osteoarthritis	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Spinal osteoarthritis	3 (0.6)	0	0.6 (-0.9, 1.7)
Arthralgia (OCMQ)	19 (3.8)	8 (3.1)	0.7 (-2.4, 3.3)
Arthralgia	19 (3.8)	8 (3.1)	0.7 (-2.4, 3.3)
Psychiatric disorders (SOC)			
Depression (OCMQ)	4 (0.8)	1 (0.4)	0.4 (-1.4, 1.7)
Depression	3 (0.6)	1 (0.4)	0.2 (-1.6, 1.4)
Renal and urinary disorders (SOC)			
Renal & urinary tract infection (OCMQ)	15 (3.0)	6 (2.3)	0.7 (-2.2, 3.0)
Cystitis	3 (0.6)	0	0.6 (-0.9, 1.7)
Urinary tract infection	10 (2.0)	5 (1.9)	0.1 (-2.6, 2.1)

System Organ Class OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)			
Dyspnea (OCMQ)	13 (2.6)	4 (1.5)	1.1 (-1.5, 3.1)
Dyspnoea	12 (2.4)	4 (1.5)	0.9 (-1.7, 2.9)
Cough (OCMQ)	19 (3.8)	9 (3.4)	0.3 (-2.9, 3.0)
Productive cough	4 (0.8)	1 (0.4)	0.4 (-1.4, 1.7)
Skin and subcutaneous tissue disorders (SOC)			
Rash (OCMQ)	16 (3.2)	5 (1.9)	1.3 (-1.5, 3.5)
Urticaria	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Dermatitis contact	3 (0.6)	0	0.6 (-0.9, 1.7)
Pruritus (OCMQ)	9 (1.8)	2 (0.8)	1.0 (-1.1, 2.8)
Pruritus	5 (1.0)	2 (0.8)	0.2 (-1.8, 1.7)
Urticaria (OCMQ)	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Urticaria	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OND custom medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in OND custom medical query (Narrow)…"
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; OCMQ, Office of New Drugs custom medical query; PT, preferred term; SOC, system organ class

Table 79. Adverse Event Assessment of Arthritis OCMQ (Narrow), Pooled Safety Population, SWIFT-1 and SWIFT-2

OCMQ (Narrow) Preferred Term	Depemokimab N=501 n (%)	Placebo N=261 n (%)	Risk Difference % (95% CI)
Arthritis (OCMQ)	17 (3.4)	1 (0.4)	3.0 (1.0, 5.1) *
Arthritis	5 (1.0)	0	1.0 (-0.5, 2.3)
Gout	1 (0.2)	0	0.2 (-1.3, 1.1)
Osteoarthritis	6 (1.2)	1 (0.4)	0.8 (-1.0, 2.3)
Periarthritis	2 (0.4)	0	0.4 (-1.1, 1.4)
Polyarthritis	1 (0.2)	0	0.2 (-1.3, 1.1)
Rheumatoid arthritis	1 (0.2)	0	0.2 (-1.3, 1.1)
Spinal osteoarthritis	3 (0.6)	0	0.6 (-0.9, 1.7)

Source: adae.xpt; Software: R
On-treatment adverse events defined as AEs occurring after the study treatment start date and within 182 days of the last dose of study treatment.
Duration is 52 weeks.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Relatedness is determined by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; OCMQ, Office of New Drugs custom medical query

Table 80. Maximum QTcF and QT Post-Baseline, Safety Population, Pooled Trials SWIFT-1 and SWIFT-2

Test (Units), n (%) Category	Depemokimab (N=501)	Placebo (N=261)
QTcF interval, aggregate (msec), n	497	260
Decrease, no change or increase to ≤450	482 (97)	253 (97)
Increase to >450 to ≤480	14 (3)	7 (3)
Increase to >480 to ≤500	0	0
Increase to >500 to ≤530	1 (<1)	0
Increase to >530	0	0
QT interval, aggregate (msec), n	497	260
No change or decrease to <600	497 (100)	260 (100)
Increase to ≥600	0	0

Source: Applicant ISS Table 3.154

Table 81. Maximum Increase in QTcF Post-Baseline, Safety Population, Pooled ANCHOR-1 and ANCHOR-2

Test (Units), n (%) Category	Depemokimab (N=501)	Placebo (N=261)
QTcF interval, aggregate (msec), n	497	260
Increase of ≤30 msec	355 (71)	183 (70)
Increase of 31-60 msec	7 (1)	6 (2)
Increase of >60 msec	0	0

Source: Applicant ISS Table 3.156

20.2. AGILE

The open-label extension period of AGILE provided an additional 52 weeks of safety data for participants who completed the SWIFT-1 and SWIFT-2 trials. Data was analyzed in particular for participants who were previously treated with depemokimab in the SWIFT-1 and SWIFT-2 trials and then received additional depemokimab therapy as part of the AGILE trial, referred to as the depemokimab-to-depemokimab treatment group, to determine longer term safety information. General safety, AESIs, and safety review issues identified for SWIFT-1 and SWIFT-2 (e.g., pregnancy, hypersensitivity reactions) were assessed in AGILE.

General Safety, Laboratory Findings, and Assessment of Drug-Induced Liver Injury

AEs in the depemokimab-to-depemokimab treatment group (63.2%) were comparable to the placebo-to-depemokimab treatment group (61.4%) and were primarily of mild-moderate severity. SAEs also occurred with similar incidence (7.4% and 7.6% in the depemokimab-to-depemokimab and placebo-to-depemokimab arms, respectively) and there were no on-treatment fatalities. There was no single SAE commonly associated with prolonged depemokimab exposure in the depemokimab-to-depemokimab treatment group. Review of AEs by SOC and OCMQ (narrow) identified a marginal notable treatment difference in the OCMQs systemic hypertension (2.6% depemokimab-to-depemokimab; 1.0% placebo-to-depemokimab) and stroke and transient ischemic attack (1.7% depemokimab-to-depemokimab; 0% placebo-to-depemokimab), though a safety signal was not identified for these AEs in the SWIFT-1/2 trials and the AGILE results are based on interim data. Common AEs occurring with ≥3% frequency in the depemokimab-to-depemokimab and placebo-to-depemokimab treatment groups were nasopharyngitis (11% and 8.1%), upper respiratory tract infection (9.5% and 10%), bronchitis

(5% and 3.3%), COVID-19 (4.8% and 7.1%), headache (4.1% and 2.9%), respiratory tract infection (3.6% and 0.5%), and pneumonia (3.1% and 2.4%). Of these, AEs that were more common in the depemokimab-to-depemokimab treatment group were nasopharyngitis, bronchitis, headache, respiratory tract infection, and pneumonia. Upper respiratory tract infection was observed in both the SWIFT-1/2 trials and AGILE, though incidence was nearly equal in the depemokimab-to-depemokimab and placebo-to-depemokimab arms, suggesting that prolonged exposure does not increase risk.

Outlier analysis of general chemistry, liver chemistry, and hematology did not identify any clinically significant findings. Notably, the reduction in total leukocyte counts observed in SWIFT-1/2 due to eosinophil suppression was not as pronounced in AGILE. There were no cases of potential Hy's law. Of mention, the AGILE interim clinical study report errata (dated November 22, 2024) details nine total leukocyte counts in depemokimab participants that were analyzed, but not reported to the investigators or Applicant. Four were outside the normal range (2 below 3.8 GI/L and 2 above 10.8 GI/L) with one of these considered an outlier (12.7 GI/L).

AESIs and Herpes Infection

AESIs were as defined in the SWIFT-1/2 trials. There were no AESIs of anaphylaxis or Type III hypersensitivity reaction (immune complex disease/vasculitis). The Applicant categorized one participant in the placebo-to-depemokimab cohort with a Type I allergic hypersensitivity reaction based on the preferred term of pruritus, which occurred 14 days after the first dose of depemokimab. Overall hypersensitivity reactions by OCMQ (narrow) were balanced between depemokimab-to-depemokimab (1.2%) and placebo-to-depemokimab (1.4%) participants. Other systemic reactions were comparable among the depemokimab-to-depemokimab and placebo-to-depemokimab cohorts (<1% incidence each) while injection site reactions were only observed in the depemokimab-to-depemokimab treatment arm at a 1% incidence Further, the majority of participants in either treatment arm had a decrease, no change, or increase to ≤450 msec and maximum increase from baseline of ≤30 msec of their QTcF interval. In the interim clinical study report errata, the Applicant mentions that baseline ECG data from SWIFT-2 participants enrolled in AGILE were missing. Nevertheless, the overall conclusion regarding QTcF assessment remains consistent. There were no depemokimab-to-depemokimab participants with an AE preferred term of QT prolongation based on participant listing. In general, there were no AESIs that occurred with prolonged depemokimab use.

Regarding herpes zoster and herpes infection, one placebo-to-depemokimab participant with the PT 'herpes zoster' had IMP interrupted. Two participants in the depemokimab-to-depemokimab arm were also diagnosed with 'herpes zoster', one of whom required drug interruption. Four additional depemokimab-to-depemokimab participant had AEs of oral herpes. Consistent with the SWIFT-1 and SWIFT-2 trials, a risk of herpes zoster was not observed.

Pregnancy

There was one pregnancy in the depemokimab-to-depemokimab treatment group which was electively terminated with no apparent congenital anomaly present. There was an additional pregnancy in the placebo-to-depemokimab treatment group which was ongoing at the time of the interim data cut-off, but reported as delivered with no congenital anomaly present in the final CSR. See Section 22 for pregnancy associated PMRs to be conducted.

20.3. NIMBLE

The non-inferiority NIMBLE trial provides an additional 52 weeks of supportive safety data for depemokimab and a comparison with other approved anti-IL-5/5R therapies (mepolizumab and benralizumab). General safety, AESIs, and safety review issues identified for SWIFT-1 and SWIFT-2 (e.g., pregnancy, hypersensitivity reactions) were assessed in NIMBLE.

General Safety, Laboratory Findings, Vital Signs, and Assessment of Drug-Induced Liver Injury

AEs were comparable between the depemokimab (83.3%), mepolizumab (80.6%), and the benralizumab treatment groups (81.2%), with the majority being mild to moderate severity. SAEs in the depemokimab treatment arm (8.6%) were more common than for mepolizumab (5.9%), but not for benralizumab (10.4%), and comparable to the combined mepolizumab/benralizumab group (8.0%). There were no on-treatment fatalities. There were no SAEs that were observed at a clinically relevant disproportionate rate in depemokimab participants based on SOC, PT, and OCMQ. Common AEs with ≥5% frequency and more common in the depemokimab arm compared to the combined mepolizumab and benralizumab arms were pyrexia (5.6% and 3.0%), cough (7.4% and 5.2%), hypertension (5.4% and 3.2%), bronchitis (4.8% and 2.8%), respiratory tract infection (6.3% and 4.5%), dyspnea (5.2% and 4.3%), and sinusitis (6.1% and 5.8%). Of these, pyrexia had a notable imbalance towards depemokimab (5.6%) when compared to the mepolizumab arm (3.1%), benralizumab arm (2.8%), and the combined mepolizumab and benralizumab arm (3.0%). A similar trend was observed for cough, but with a lower difference between the depemokimab (7.4%) and mepolizumab arm (5.6%) than all other comparator arms.

Outlier analysis of general chemistry, hematology, and vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) did not identify any clinically significant findings. Notably, in a clinical study report errata (dated November 21, 2024) the Applicant notes 21 total leukocyte counts (blinded) that were analyzed, but not reported to the investigators or Applicant. Of these, five were outside the normal range (3 below 3.8 GI/L, 2 above 10.8 GI/L). There were no potential Hy's law cases in the depemokimab or mepolizumab arm, but one potential case in the benralizumab arm.

AESIs and Herpes Infection

There were no AESIs of anaphylaxis or Type III hypersensitivity reactions (immune complex disease/vasculitis). One depemokimab participant had a Type I hypersensitivity reaction (rash), though this occurred with placebo matching benralizumab administration. An additional

depemokimab participant had two SAEs of anaphylaxis to an unknown trigger and peanut allergen, respectively. Incidence of hypersensitivity by OCMQ (narrow) was balanced between the depemokimab (1.3%) and combined mepolizumab/benralizumab arm (0.9%) with no particular preferred term at a notably disproportionate rate. Other systemic reactions were comparable between the depemokimab cohort (2%) and the combined mepolizumab/benralizumab cohort (<1%) as were local injection site reactions (1% and 3%, respectively, in depemokimab and combined mepolizumab/benralizumab participants). The majority of depemokimab and combined mepolizumab/benralizumab participants had a decrease, no change, or increase to ≤450 msec and maximum increase from baseline of ≤30 msec of their QTcF interval. There were no AEs of QTc prolongation by participant listing. Overall, there were no notable AESIs observed with depemokimab compared to other anti-IL-5/5R therapies.

Incidence of herpes zoster was 0.7% in the depemokimab arm, 1.0% in the mepolizumab arm, 0.8% in the benralizumab arm, and 0.9% in the combined mepolizumab/benralizumab cohort. Moreover, three depemokimab subjects experienced an AE of oral herpes based participant listings. In general, herpes zoster was not more common in depemokimab participants.

Pregnancy

There were two pregnancies reported in depemokimab participants which resulted in a spontaneous and elective abortion, respectively. See Section 22 for pregnancy associated PMRs to be conducted.

20.4. Overall Safety (Placebo-Controlled Pool; SWIFT-1/2, ANCHOR-1/2)

The overall safety of depemokimab in all placebo-controlled Phase 3 completed trials across the asthma and CRSwNP indications were evaluated to assess the general safety of depemokimab irrespective of indication and trial population. The four trials (SWIFT-1, SWIFT-2, ANCHOR-1, and ANCHOR-2) were of 52-weeks duration, double-blind, and placebo controlled with depemokimab doses administered subcutaneously at Weeks 0 and 26. Of note, randomization differed between the trials with ratios of 2:1 and 1:1 in the asthma and CRSwNP indications, respectively.

Based on Applicant provided safety data, on-treatment AEs and SAEs were more common in placebo participants (78% and 10%) compared to depemokimab participants (73% and 5%). Common AEs at ≥4% incidence and more common in the depemokimab treatment arm were allergic rhinitis (3.9% v. 1.7%), upper respiratory tract infection (9.6% v. 9.5%), and COVID-19 (14.2% v. 13.2%). There were no adverse events of special interest related to allergic Type 1 hypersensitivity reactions, including anaphylaxis, or Type III hypersensitivity reactions (immune complex disease/vasculitis) seen in either treatment arm. Other systemic reactions was comparable among treatment groups (1% in depemokimab participants, <1% in placebo participants) as were local injection site reactions (1% in depemokimab participants, <1% in

placebo participants). Evaluation of the abbreviated safety data provided for the placebo-controlled pool did not identify any overarching safety signals.

20.5. 120-Day Safety Update

The Applicant submitted a 120-day safety report on April 9, 2025 which covered trials AGILE and NIMBLE.

AGILE

As of December 11, 2024, 8% and 9% of participants experienced SAEs in the depemokimab-to-depemokimab and placebo-to-depemokimab treatment groups, respectively, with no particular SAE by PT occurring at a notably disproportionate rate in either arm. There were 8 new SAEs across 7 participants between August 27, 2024 until December 16, 2024 with no patterns identified and no fatalities. Moreover, there were no AEs leading to treatment discontinuation or study withdrawal, AESIs, or liver stopping events from June 14, 2024 through December 11, 2024. Lastly, there were no new pregnancy cases as of December 16, 2024. In general, the safety profile of longer term depemokimab use remained reassuring.

NIMBLE

There were 23 new blinded SAEs across 16 participants between August 27, 2024 to December 16, 2024 with no fatalities. Of these, pneumonia was the most common event reported by SAE and PT. No patterns were identified based on SAEs. No blinded participants not included within the interim analysis met liver stopping criteria as of December 11, 2024. Further, there were no new pregnancy cases as of December 16, 2024 or significant follow-up pregnancy information. Overall, no new safety concerns were identified; however, interpretation was limited based on the blinded treatment allocation.

21 Labeling: Key Changes

Table 82 provides a high-level summary of the Prescribing Information (PI) and rationale for major changes as compared to the Applicant's draft PI. The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare provider.

Table 82. Key Labeling Changes and Considerations

Full PI Sections	Rationale for Major Changes Incorporated into the Finalized PI
1 INDICATIONS AND USAGE	(b) (4) , the approved indication is as follows: *EXDENSUR is indicated for the add on maintenance treatment of severe asthma characterized by an eosinophilic phenotype in adult and pediatric patients aged 12 years and older.* *Limitations of Use* *EXDENSUR is not indicated for the relief of acute bronchospasm or status asthmaticus [see Warnings and Precautions (5.2)].* The indication statement was revised to replace 'Type 2 inflammation' with the more specific and clinically relevant term 'eosinophilic phenotype' that is consistent with other product labeling. Description of background asthma therapy received during the pivotal trials is detailed in Section 14 and thus removed from Section 1.
2 DOSAGE AND ADMINISTRATION	The recommended dosage remain unchanged as follows: *The recommended dosage is 100 mg once every 6 months administered by subcutaneous (SC) injection into the upper arm, thigh, or abdomen avoiding 2 inches (5 cm) around the navel [see Dosage and Administration (2.2)].* The Preparation and Administration Instructions for EXDENSUR subsection was revised to provide instructions (b) (4) since EXDENSUR should be administered by healthcare providers (HCP) only. (b) (4) this subsection was revised to include all instructions necessary for HCPs to administer EXDENSUR.
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	5.1 Hypersensitivity Reactions Although no IgE-mediated hypersensitivity reactions were observed in SWIFT-1/2, the Warnings and Precautions related to hypersensitivity reactions was retained as they are expected to occur. Associated information (b) (4) was removed, however. 5.3 Risk Associated with Abrupt Reduction of Corticosteroid Dosage Revised with risk specific to reduction of corticosteroid dosage, (b) (4), for consistency with class labeling. 5.4 Parasitic (Helminth) infection Recommended that patients discontinue, (b) (4), treatment if they develop an unresponsive parasitic infection. This is consistent with class labeling.

Full PI Sections	Rationale for Major Changes Incorporated into the Finalized PI
6 ADVERSE REACTIONS	In the *Clinical Trials Experience* subsection, the safety of EXDENSUR was informed from a pooled safety population of two clinical trials (SWIFT-1 and SWIFT-2). (b) (4) were removed. The common adverse reactions table was revised to include all AEs more common than placebo occurring with 4% or greater frequency. Specific adverse reactions (e.g., injection site reactions) are described in text; however, (b) (4) were removed as these did not occur with greater incidence in the depemokimab group or (b) (4) . (b) (4)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Pediatric Use, Geriatric Use)	8.1 Pregnancy and 8.2 Lactation subsections were revised to highlight specific risks related to the YTE-modification, in particular the potential for higher and prolonged fetal and infant exposure through placental transfer if given to pregnant women as well as the uncertain clinical impact of EXDENSUR transmission to the fetus so that prescribers may consider the risks and benefits of administration during pregnancy. Based on nonclinical data, including language in Section 8.1 (along with highlights) and Section 17 were considered sufficient to inform prescribers without the need for a Warning and Precaution. 8.4 Pediatric Use (b) (4) . Similarity of PK and safety data in pediatric patients aged 12 years and older and adults was included. 8.5 Geriatric Use Geriatric use was provided consistent with the Geriatric Information in Human Prescription Drug and Biological Product Labeling.
10 OVERDOSAGE	Human overdosage data was not available to inform this section, but language to contact the Poison Help center for overdose management was included.

Full PI Sections	Rationale for Major Changes Incorporated into the Finalized PI
12 MECHANISM OF ACTION	12.1 Mechanism of action The mechanism of action was modified to ensure consistency with class labeling (e.g., mepolizumab). Literature provided by the Applicant were (b) (4) . 12.2 Pharmacodynamics Pharmacodynamic results were limited to the pivotal SWIFT-1/2 trials. 12.3 Pharmacokinetics (b) (4) was removed.
13 NONCLINICAL TOXICOLOGY	No major changes were made to this section. This section includes a statement that no genotoxicity or carcinogenicity studies were conducted and a summary of animal fertility and reproductive performance.
14 CLINICAL STUDIES	This section includes the summary of SWIFT-1/2 to evaluate the efficacy of EXDENSUR. The clinical trial design, study population, and results are provided. The following major changes were made to this section: • (b) (4) • Time to first clinically significant asthma exacerbation was described individually, (b) (4), for SWIFT-1 and SWIFT-2 with associated Kaplan Meier curves. • (b) (4) • (b) (4) was removed from Table 3 of PI as it may artificially inflate the treatment differences and was considered promotional. • (b) (4) ACQ-5 responder analysis was allowed, consistent with class labeling. • (b) (4) • (b) (4) Section 14 generally includes trials that provide primary support for effectiveness, rather than uncontrolled, unblinded, open-label extension data. • Data from (b) (4) were removed.
17 PATIENT COUNSELING INFORMATION	Revised to ensure consistency with Section 5 and statement regarding use in pregnancy was added.

Full PI Sections	Rationale for Major Changes Incorporated into the Finalized PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	These sections are consistent with Product Quality Information.

Source: Labeling Discussion Comments dated November 7, 2025, November 21, 2025, December 8, 2025, and December 11, 2025.
Abbreviations: ACQ-5, asthma control questionnaire-5; DPMH, Division of Pediatrics and Maternal Health; ED, emergency department; HCP, healthcare provider; (b) (4) PI, Prescribing Information; PT, preferred term; (b) (4); W&P, Warnings and Precautions

21.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will also be FDA-approved:

- Prescribing Information (PI)
- Patient Package Insert
- Carton and Container

22 Postmarketing Requirements and Commitments

PMR 4920-1

Conduct a 52-week, open-label, pharmacokinetic, pharmacodynamic, and safety study of depemokimab in pediatric patients 6 years to 11 years of age with severe asthma characterized by an eosinophilic phenotype.

Final protocol submission: June 2025 (submitted)
Study Completion: June 2029
Final report submission: December 2029

PMR 4920-2

Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to depemokimab during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant

outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.

Draft Protocol Submission:	June 2026
Final protocol submission:	December 2026
Interim study report:	December 2028
Interim study report:	December 2030
Interim study report:	December 2032
Interim study report:	December 2034
Interim study report:	December 2036
Study/Trial completion	December 2036
Final report submission:	June 2037

PMR 4920-3

Perform a lactation study (milk-only or mother-infant pair study) in lactating women who have received depemokimab to measure concentrations of depemokimab and its major metabolites in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.

Draft protocol submission:	September 2026
Final protocol submission:	March 2027
Study completion:	December 2028
Final report submission:	June 2029

PMC 4920-4
Qualification of a new Working Reference Standard.

Final Report Submission Date: December 31, 2026

PMC 4920-5
Conduct an additional bacterial retention study, including differential pressure monitoring and submit the final report in a CBE-30 supplement.

Final Report Submission Date: February 28, 2026

PMC 4920-6
Repeat the container closure integrity testing validation for AI and SSD by dye ingress, revise the acceptance criteria (b) (4) as expected and submit the final report in a CBE-0 supplement.

Final Report Submission Date: January 31, 2026

23 Financial Disclosure

Table 83. Financial Disclosures for SWIFT-1

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified (excluding those with zero enrollment): 144 centers across 12 countries including Canada, China, Czech Republic, France, Germany, Ireland, Italy, Poland, Russia, Spain, the United Kingdom, and the United States. 19 U.S. investigators across multiple centers.		
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): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: • Principal Investigator, (b) (6), received payments totaling $58,337.50. The site recruited (b) (6) subjects. • Sub-investigator, (b) (6), received payments totaling $43,225.00. The site recruited (b) (6) subjects. • Principal Investigator, (b) (6), received payments totaling $101,957.00. The site recruited (b) (6). Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 84. Financial Disclosures for SWIFT-2

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified (excluding those with zero enrollment): 187 centers across 11 countries including Australia, Canada, Czech Republic, France, Hungary, Italy, Japan, Poland, Spain, Taiwan, and the United States. 52 U.S. investigators across multiple sites.		
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): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: • Principal Investigator, (b) (6), received payments totaling $39,275.00. The site recruited (b) (6) subjects. • Principal Investigator, (b) (6), received payments totaling $194,039.00. The site recruited (b) (6). • Principal Investigator, (b) (6), received payments totaling $125,656.00. The site recruited (b) (6) subjects. • Sub-investigator, (b) (6), received payments totaling $81,300.00. The site recruited (b) (6) subjects. • Sub-investigator, (b) (6), received payments totaling $81,300.00. The site recruited (b) (6) subjects. Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator: Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Note: Form FDA 3454 for SWIFT-2 had 3 sub-investigators for which required information could not be obtained. None of the sub-investigators are those with disclosable financial interests.

24 References

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Guidance for Industry

Guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators* (February 2013)

Guidance for industry *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* (July 2009)

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Guidance for Industry *M10 Bioanalytical Method Validation and Study Sample Analysis* (November 2022)

Web Pages

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