NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplemental BLA – SE-5 New or Significantly Altered Patient Population
Application Number(s)	BLA 761055/S-074
Priority or Standard	Standard
Submit Date(s)	June 27, 2025
Received Date(s)	June 27, 2025
PDUFA Goal Date	April 27, 2026
Division/Office	DPACC/OII
Review Completion Date	April 20, 2026
Established/Proper Name	Dupilumab
(Proposed) Trade Name	Dupixent
Pharmacologic Class	Interleukin-4 receptor alpha antagonist (monoclonal antibody)
Code name	REGN668 (SAR231893)
Applicant	Regeneron Pharmaceuticals Inc.
Dosage form	Subcutaneous injection
Applicant proposed Dosing Regimen	Pediatric Patients 2 to 5 Years of Age: • Weight 5 kg to < 15kg: Initial dose 200 mg (one injection 200mg injection), followed by 200 mg Q4W • Weight 15 kg to <30 kg: Initial dose 300 mg (one injection 200mg injection), followed by 300 mg Q4W Pediatric Patients 6 to 17 Years of Age and Older: • Weight 15 kg to <30 kg: Initial dose 600 mg (two 300 mg injections), followed by 300 mg Q4W • Weight 30 kg to <60 kg: Initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W • Weight 60 kg or more: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients aged 2 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	302162004 |Chronic idiopathic urticaria (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Same as proposed by Applicant
Recommended SNOMED CT Indication Disease	302162004 |Chronic idiopathic urticaria (disorder)|

Term for each Indication (if applicable)	
Recommended Dosing Regimen	Same as proposed by Applicant

Table of Contents

Table of Tables 5
Table of Figures 7
Reviewers of Multi-Disciplinary Review and Evaluation 8
Glossary 11
1 Executive Summary 13
1.1. Product Introduction 13
1.2. Conclusions on the Substantial Evidence of Effectiveness 15
1.3. Benefit-Risk Assessment 16
1.4. Patient Experience Data 19
2 Therapeutic Context 20
2.1. Analysis of Condition 20
2.2. Analysis of Current Treatment Options 21
3 Regulatory Background 22
3.1. U.S. Regulatory Actions and Marketing History 22
3.2. Summary of Presubmission/Submission Regulatory Activity 22
4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 23
4.1. Office of Scientific Investigations 23
4.2. Product Quality 23
4.3. Clinical Microbiology 23
4.4. Devices and Companion Diagnostic Issues 23
5 Nonclinical Pharmacology/Toxicology 23
5.1. Executive Summary 23
6 Clinical Pharmacology 23
6.1. Executive Summary 23
6.2. Summary of Clinical Pharmacology Assessment 26
6.2.1. Pharmacology and Clinical Pharmacokinetics 26
6.2.2. General Dosing and Therapeutic Individualization 27
6.3. Comprehensive Clinical Pharmacology Review 29
6.3.1. Clinical Pharmacology Questions 29
7 Sources of Clinical Data and Review Strategy 45
7.1. Table of Clinical Studies 45
7.2. Review Strategy 47
8 Statistical and Clinical and Evaluation 47

8.1. Review of Relevant Individual Trials Used To Support Efficacy 47
8.1.1. Study PKM16982 47
8.1.2. Study Results 53
8.1.3. CUPID Studies A and C 58
8.1.4. Integrated Assessment of Effectiveness 58
8.2. Review of Safety 58
8.2.1. Safety Review Approach 58
8.2.2. Review of the Safety Database 59
8.2.3. Adequacy of Applicant's Clinical Safety Assessments 60
8.2.4. Safety Results 61
8.2.5. Analysis of Submission-Specific Safety Issues 63
8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability 63
8.2.7. Safety Analyses by Demographic Subgroups 63
8.2.8. Additional Safety Explorations 63
8.2.9. Safety in the Postmarket Setting 64
8.2.10. Integrated Assessment of Safety 64
8.3. Conclusions and Recommendations 64
9 Advisory Committee Meeting and Other External Consultations 65
10 Pediatrics 65
11 Labeling Recommendations 66
11.1. Prescription Drug Labeling 66
12 Risk Evaluation and Mitigation Strategies 67
13 Postmarketing Requirements and Commitment 67
14 Associate Director for Therapeutic Review (Clinical) Comments 67
15 Appendices 70
15.1. References 70
15.1.1. Literature 70
15.1.2. Guidances for Industry 72
15.1.3. Other 72
15.2. Financial Disclosure 73
15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations) 74
15.3.1. Population PK Analysis 74
15.4 Additional Clinical Outcome Assessment Analyses 93

Table of Tables

Table 1: Recommended Dosage in Pediatric Patients Aged 2 to 5 Years Old 13
Table 2: Recommended Dosage in Pediatric Patients Aged 6 to 17 Years Old 13
Table 3: Summary of Dupilumab Exposure in Pediatric Subjects 2 to < 12 Years of Age With CSU Across Clinical Trials 27
Table 4: Summary of Arithmetic Mean (SD) Dupilumab Serum Concentrations (mg/L) Over Time for Subjects Enrolled at CCHMC and Overall (Pooled PK Population)[a] 29
Table 5: Summary of Arithmetic Mean (SD) Dupilumab Serum Concentrations Over Time by Dosing Regimen (Pooled PK Population; Studies PKM16982, EFC16461-C, and EFC16461-A)[a] ... 31
Table 6: Summary of Arithmetic Mean (SD) Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in CSU Subjects Across Age Groups and Dosing Regimens[a,b] 32
Table 7: Summary of Population PK Model-Simulated Dupilumab Plasma Steady-State PK Parameters in Children 2 to <12 Years of Age With CSU, Using a Virtual Pediatric Population From NHANES Database (Study POH1231)[a] 36
Table 8: Summary of Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in Adults and Adolescents 12 to <18 Years of Age With CSU (Study POH1089) 37
Table 9: Summary of Total Serum IgE Change From Baseline in Children 2 to <12 Years of Age With CSU (Pooled Safety Population; Studies PKM16982, EFC16461-C, and EFC16461-A)..... 38
Table 10: Change From Baseline in ISS7 by PK Sub-Group of Observed $C_{trough,ss}$ at Week 24 in Children 2 to < 12 Years of Age With CSU (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b] 41
Table 11: Change From Baseline in mUAS7 by PK Sub-Group of Observed $C_{trough,ss}$ at Week 24 in Children 2 to < 12 Years of Age With CSU (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b] 41
Table 12: Comparison of Arithmetic Mean (SD) Observed Steady-State Dupilumab Exposures in Children < 12 Years of Age With CSU, AD, Asthma, and EoE 44
Table 13: Listing of Clinical Trials Relevant to This sBLA 46
Table 14: Dosage in Subjects Aged 2 to 5 Years Old, Study PKM16982 48
Table 15: Dosage in Subjects Aged 6 to 11 Years Old, Study PKM16982 48
Table 16: Demographic Characteristics, Study PKM16982 54
Table 17: C-DLQI Results, Study PKM16982 56
Table 18: mUAS7 Results, Study PKM16982 56
Table 19: ISS7 Results, Study PKM16982 57
Table 20: HSS7 Results, Study PKM16982 57
Table 21: Applicant's Population PK Analysis of Dupilumab in Subjects 2 to Less Than 12 Years of Age With CSU 77
Table 22: Summary of Potential Continuous Covariates at Baseline for Children 2 to < 12 Years of Age With CSU in Final Population PK Dataset (N = 18) 78
Table 23: Summary of Potential Categorical Covariates at Baseline for Children 2 to < 12 Years of Age With CSU in Final Population PK Dataset (N = 18) 79
Table 24: Summary of Arithmetic Mean (SD) Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in CSU Subjects Across Age Groups and Dosing Regimens[a,b] 84

Table 25: Arithmetic Mean (SD) Steady-State Exposures for Dupilumab in Children With CSU as a Function of Intrinsic and Extrinsic Factors 85
Table 26: Comparison of PK Parameters Between Different Regimens in Children 2 to < 12 Years of Age With CSU 89
Table 27: Descriptive Statistics of Weight and Age for Virtual Pediatric Population From NHANES According to Age and Body Weight Sub-Group 89
Table 28: Summary of Population PK Model-Simulated Dupilumab Plasma Steady-State PK Parameters in Children 2 to < 12 Years of Age With CSU, Using a Virtual Pediatric Population From NHANES Database[a] 91

Table of Figures

Figure 1: Arithmetic Mean (SD) Dupilumab Plasma Concentration-Time Profile (Pooled PK Population; Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b,c,d] 31
Figure 2: Arithmetic Mean (SD) Observed Dupilumab Plasma Trough Concentrations Over Time According to Age Group, Body Weight Category, and Dosing Regimen[a,b,c] 34
Figure 3: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU Following SC Administration of the Proposed Dosing[a] 35
Figure 4: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Adults and Adolescents With CSU Following SC Administration of the Approved Dosing[a] 35
Figure 5: Scatter Plot of ISS7 (Left) and mUAS7 (Right) Change From Baseline at Week 24 vs. Observed Plasma $C_{trough,ss}$ in CSU Subjects (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b,c] 40
Figure 6: PKM16982 Study Design 48
Figure 7: Schematic Structure of Final Asthma Pediatric Population PK Model for Dupilumab (Study POH0776) 80
Figure 8: Arithmetic Mean (SD) Observed Dupilumab Trough Concentration-Time Profiles Following SC Administration of 200 mg Q2W Pediatric Subjects With CSU vs. Asthma 81
Figure 9: GoF Plots for the Application of the Asthma Pediatric Population PK Model (Study POH0776) in Children 2 to < 12 Years of Age With CSU 82
Figure 10: VPC for Asthma Pediatric Population PK Model in Children 2 to < 12 Years of Age With CSU 83
Figure 11: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU Following SC Administration of the Proposed Dosing[a] 87
Figure 12: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Adults and Adolescents With CSU Following SC Administration of the Approved Dosing[a] 88
Figure 13: Simulated Median (90% CI) Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU According to Dosing Regimen[a,b] 90
Figure 14: Children's Dermatology Quality of Life Index 93
Figure 15: Infants' Dermatitis Quality of Life Index 94

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

Signatures

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Glossary

AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AFRS	allergic fungal rhinosinusitis
ALT	alanine aminotransferase
BLA	biologics license application
BP	bullous pemphigoid
CCHMC	Cincinnati Children's Hospital Medical Center
C-DLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CICU	chronic inducible cold urticaria
C_{max}	maximum plasma concentration at steady state
COPD	chronic obstructive pulmonary disease
CRSwNP	chronic rhinosinusitis with nasal polyposis
CSU	chronic spontaneous urticaria
C_{trough}	plasma trough concentration at steady state
DARRTS	Document Archiving Reporting and Regulatory Tracking System
DPACC	Division of Pulmonology, Allergy and Critical Care
EoE	eosinophilic esophagitis
ER	exposure-response
FcεRI	high-affinity IgE receptor
FDA	Food and Drug Administration
HSS7	Hive Severity Score over 7 days
IDQOL	Infant's Dermatitis Quality of Life Index
Ig	immunoglobulin
IL	interleukin
IL-4Rα	interleukin-4 receptor alpha
iPSP	initial pediatric study plan
IND	Investigational New Drug
ISS7	Itch Severity Score over 7 days
K_e	elimination rate constant
LD	loading dose
MAP	maximum a posteriori
MedDRA	Medical Dictionary for Regulatory Activities
M-M	Michaelis-Menten
mUAS7	modified weekly urticaria activity score
NDA	new drug application
NHANES	National Health and Nutrition Examination Survey
OCP	Office of Clinical Pharmacology
OSE	Office of Surveillance and Epidemiology

OSIS	Office of Study Integrity and Surveillance
PD	pharmacodynamic
PK	pharmacokinetic
PN	prurigo nodularis
PREA-PMR	Pediatric Research Equity Act Postmarketing Requirement
Q2W	every 2 weeks
Q4W	every 2 weeks
SAE	serious adverse event
sBLA	supplemental biologics license application
SC	subcutaneous
SD	standard deviation
SEE	substantial evidence of effectiveness
TEAE	treatment-emergent adverse event
UAS7	weekly urticaria activity score
V1	screening visit
V2	central compartment volume of distribution
V_{max}	maximum target-mediated rate of elimination

1 Executive Summary

1.1. Product Introduction

Dupilumab (proprietary name Dupixent) is a human immunoglobulin G subclass 4 (IgG4) monoclonal antibody that functions as an interleukin-4 receptor alpha (IL-4Rα) antagonist. It inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab was approved on April 17, 2025 for the "treatment of adult and pediatric patients aged 12 years and older with CSU who remain symptomatic despite H1 antihistamine treatment." Regeneron Pharmaceuticals Inc. now submits supplemental biologics license application (sBLA) 761055/S-074, in response to Pediatric Research Equity Act Postmarketing Requirement (PREA-PMR) 4843-1, to support expansion of the chronic spontaneous urticaria (CSU) indication to include pediatric patients aged 2 to <12 years of age, specifically, "for the treatment of adult and pediatric patients aged 2 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment."

The proposed dosing regimen for pediatric patients is based on age and weight, and is identical to that currently approved for the treatment of atopic dermatitis in patients 6 months of age and older:

Table 1: Recommended Dosage in Pediatric Patients Aged 2 to 5 Years Old

Body Weight	Initial and Subsequent Dosage
5 to less than 15 kg	200 mg Q4WK
15 to less than 30 kg	300 mg Q4WK

Table 2: Recommended Dosage in Pediatric Patients Aged 6 to 17 Years Old

Body Weight	Initial Loading Dose	Subsequent Dosage
15 to less than 30 kg	600mg (two 300 mg injections)	300 mg Q4WK
30 to less than 60 kg	400mg (two 200 mg injections)	200 mg Q2WK
60 kg or more	600mg (two 300 mg injections)	300 mg Q2WK

No new dosage forms are proposed with this sBLA. The proposed drug product is intended to be administered using approved presentations (i.e., 200mg and 300 mg prefilled syringe assembled with a safety system, and 200mg and 300 mg single-use prefilled pen).

Dupilumab received initial approval on March 28, 2017 for the treatment of moderate-to-severe atopic dermatitis in adult patients whose disease is not adequately controlled with

topical prescription therapies or when those therapies are not advisable. Dupilumab is currently approved for multiple indications:

AD (developed under IND 107969, reviewed by the Division of Dermatology and Dental)

a) Approval: March 28, 2017, Treatment of moderate-severe AD, adults
b) Approval: March 11, 2019, Treatment of moderate-to-severe AD, ≥12 years of age
c) Approval: May 22, 2020, Treatment of moderate-to-severe AD, ≥6 to <2years of age
d) Approval: June 7, 2022, Treatment of moderate-to-severe AD, ≥6 months to <6 years

Asthma (developed under IND 105379, reviewed by the Division of Pulmonology, Allergy and Critical Care [DPACC])

a) Approval: October 19, 2018, Add-on maintenance moderate-to-severe asthma 12 years of age and older with eosinophilic phenotype or oral corticosteroid-dependent asthma
b) Approval: Oct 20, 2021, Add-on maintenance moderate-to-severe asthma 6 to 11 years of age with eosinophilic phenotype or oral corticosteroid-dependent asthma

Chronic rhinosinusitis with nasal polyposis (CRSwNP) (developed under IND 105379, reviewed by DPACC)

a) Approval: June 26, 2019, Add-on maintenance treatment in adult patients with inadequately controlled CRSwNP

Eosinophilic esophagitis (EoE) (developed under IND 136142, reviewed by the Division of Gastroenterology)

a) Approval: May 20, 2022, Treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with EoE

Prurigo nodularis (PN) (developed under IND 107969, reviewed by the Division of Dermatology and Dental)

a) Approval, September 27, 2022, Treatment of adult patients with PN

Chronic obstructive pulmonary disease (COPD) (developed under IND 105379, reviewed by DPACC)

a) Approval, September 27, 2024, Treatment of adult patients with COPD with an eosinophilic phenotype

CSU (developed under IND 105379, reviewed by DPACC)

a) Approval, April 17, 2025, Treatment of adult and pediatric patients aged 12 years and older with CSU who remain symptomatic despite H1 antihistamine treatment

Bullous pemphigoid (BP) (developed under IND 107969, reviewed by the Division of Dermatology and Dental)

a) Approval, June 18, 2025, Treatment of adult patients with BP

Allergic fungal rhinosinusitis (AFRS) (developed under IND 105379, reviewed by DPACC)

a) Approval, February 24, 2026, Treatment of adult and pediatric patients aged 6 years and older with AFRS who have a history of sino-nasal surgery

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with evidence that supported SEE from a prior approval of the drug and was determined, through extrapolation, to provide SEE for the new use.

The pathophysiology, clinical presentation, and natural history of CSU are similar in children, adolescents, and adults (Section 2.1). As a result, SEE for dupilumab in the treatment of children aged 2 to <12 years old with CSU is established through pediatric extrapolation from the previous demonstration of efficacy in adolescents and adults, based on disease similarity, expected response to treatment, and comparable pharmacokinetic (PK) data.

This application is supported by Study PKM16982, a phase 3, single-arm, PK and safety study conducted in 15 children 2 to < 12 years of age with CSU. Following subcutaneous administration at proposed dosing regimens, dupilumab steady-state systemic exposure in children 2 to <12 years was generally comparable to or higher than that observed in adults and adolescents with CSU supporting extrapolation of efficacy. Descriptive efficacy data from the 15 pediatric subjects enrolled in Study PKM16982 provide additional support based on demonstration of improvements in quality of life measures and measures of CSU disease activity in children aged 2 to <12 years old that were generally consistent with results observed in the pivotal studies for CSU in adults and adolescents.

Therefore, substantial evidence of effectiveness for dupilumab in children aged 2 to <12 years old with CSU is established through extrapolation of efficacy from adolescents and adults based on similarity of disease pathophysiology and expected response to treatment across age groups, comparable PK data with matched systemic exposure and pharmacodynamic responses, and consistent treatment effects in the pediatric population (2 to <12 years old) that align with results in adults and adolescents.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The efficacy of dupilumab for the treatment of pediatric patients aged 2 to <12 years old with chronic spontaneous urticaria (CSU) inadequately controlled with H1-antihistamine treatment is supported by extrapolation of efficacy from adults and adolescents with CSU, based on PK matching. Pharmacokinetic data from Study PKM16982 demonstrate comparable or higher dupilumab steady-state systemic exposure in children 2 to <12 years than that observed in adults and adolescents with CSU, supporting extrapolation of efficacy from adults and adolescents to children with CSU.

Safety for dupilumab in the treatment of CSU in pediatric patients aged 2 to <12 years of age is extrapolated, based on PK matching, from the known safety profile of dupilumab observed in prior pediatric clinical trials for approved indications that included children 2 to <12 years of age, as well as from postmarketing safety reports. To support safety extrapolation, mean dupilumab trough dupilumab concentrations in pediatric CSU subjects (Study PKM16982) were similar to those observed in pediatric subjects across other approved dupilumab indications.

Descriptive efficacy data from Study PKM16982 demonstrated improvements in quality of life and disease activity measures in children aged 2 to <12 years that were generally consistent with improvements observed in the pivotal adult and adolescent studies for CSU. Similarly, descriptive safety data from Study PKM16982 demonstrated that dupilumab was well-tolerated with no new safety concerns identified.

Based on the totality of evidence, the benefit-risk assessment is favorable for dupilumab for the treatment of pediatric patients aged 2 to <12 years with CSU inadequately controlled with H1-antihistamine treatment. The review team, including clinical, clinical pharmacology, and CMC, recommends **approval** of dupilumab with the proposed dosing regimens for the "treatment of adult and pediatric patients aged 2 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CSU is characterized by spontaneous urticaria lasting longer than six weeks, with or without angioedema, and without an identifiable etiology. It can be diagnosed at any age but is uncommon in children younger than 2 years old. • CSU is generally self-limited, with an average disease duration of 2-5 years. • Children with CSU experience substantial impairment in quality of life with disrupted sleep, decreased school performance, and a higher prevalence of mood and anxiety disorders.	• CSU is a condition that significantly impacts children's quality of life.
Current Treatment Options	• First-line therapy consists of second-generation H1-antihistamines at approved doses, with dose escalation up to four-fold for inadequate responders. • Most children with CSU are treated successfully with antihistamines; however, 10% to 25% of pediatric patients are refractory to antihistamine therapy and require alternative treatments. • There are no biologic therapies approved for children <12 years of age.	• There is an unmet medical need for treatments for children <12 years of age with CSU inadequately controlled by H1-antihistamines.
Benefit	• The efficacy of dupilumab has previously been demonstrated in adults and adolescents with CSU in two pivotal phase 3 trials. • CSU is similar in adults, adolescents, and children aged 2 to <12 years old, based on support from the literature. • Dupilumab steady-state exposure in children 2 to <12 years old was comparable to or higher than in adults and adolescents with CSU, supporting extrapolation of efficacy from adults and adolescents to children 2 to <12 years of age with CSU. • Descriptive efficacy data from Study PKM16982 demonstrated improvements in quality of life and disease activity measures, generally consistent with results observed in adults and adolescents.	• Substantial evidence of effectiveness has been demonstrated for dupilumab in the treatment of CSU in children 2 to <12 years of age. • Dupilumab provides the first approved biologic treatment for pediatric patients aged 2 to <12 years old with CSU inadequately controlled with H1-antihistamines.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Although limited safety data were obtained from Study PKM16982 given the small size and lack of comparator arm, there were no new safety signals identified • Safety for dupilumab in the treatment of CSU in pediatric patients aged 2 to <12 years of age is extrapolated, based on PK matching, from the known safety profile of dupilumab observed in prior pediatric clinical trials for approved indications, as well as from postmarketing safety reports.	• No new safety signals were identified. • Safety can be adequately addressed through labeling and routine pharmacovigilance.

1.4. Patient Experience Data

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

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	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):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Chronic spontaneous urticaria, formerly known as chronic idiopathic urticaria, is a condition characterized by the spontaneous occurrence of urticaria, with or without angioedema, lasting longer than six weeks, and without an identifiable etiology. CSU is distinct from chronic urticaria and/or angioedema that occurs secondary to a known trigger or underlying disease, such as chronic inducible urticaria, hereditary angioedema, vasculitis, mastocytosis, autoimmune-mediated, etc.

CSU affects approximately 0.1% to 1% of the general population. In pediatric populations, the prevalence ranges from 0.1% to 0.6%, with a higher prevalence found in the adolescent age groups (Broder et al. 2015; Balp et al. 2018; Fricke et al. 2020). While CSU can develop at any age, it is rarely diagnosed before two years of age.

The pathophysiology of CSU is considered to be the same in adults, adolescents and children, with mast cell and basophil activation leading to release of mediators including histamine that cause itching, swelling, and redness (Kaplan 2017; Zuberbier et al. 2026). The underlying causes of CSU are similar in adults and children, including infections and autoreactivity mediated by anti-immunoglobulin-E (IgE) and anti-FcεRI autoantibodies, further supporting similarity of pathophysiology. Studies demonstrate a comparable prevalence of anti-FcεRI autoantibodies and positive autologous serum skin testing, an in vivo diagnostic tool to detect autoreactivity in patients with CSU, in adults and children (Hide et al. 1993; Du Toit et al. 2006; Özçeker et al. 2023). Likewise, the clinical presentation of CSU is similar across adult, adolescent, and pediatric populations; however, children have a higher incidence of atopic comorbidities and a lower incidence of angioedema (Özçeker et al. 2023).

The natural history of CSU in adults, adolescents, and children shows that the condition is generally self-limited. However, children have a shorter time to remission than adults with spontaneous remission occurring in 17% to 33% of children within the first year and 39% to 54% within three years (Eser et al. 2016). The average disease duration for all patients ranges from two to five years, though it may persist longer in cases with concurrent angioedema or more severe disease manifestations (Stepaniuk et al. 2020).

The quality of life impact of CSU is notable in adults, adolescents, and children. Children with CSU experience a substantial impairment in their quality of life, with effects comparable to other chronic childhood conditions as psoriasis and asthma (Beattie and Lewis-Jones 2006). Children with CSU experience disrupted sleep, decreased school performance, and a higher prevalence of mood and anxiety disorders compared to healthy controls (Hergüner et al. 2011; Gonçalo et al. 2021). The condition also affects caregivers and families through missed work, financial strain, and emotional burden (Gonçalo et al. 2021).

2.2. Analysis of Current Treatment Options

Current treatment guidelines for CSU in children follow a stepwise approach similar to that recommended for adults and adolescents (Bernstein et al. 2014; Zuberbier et al. 2022). First-line therapy consists of second-generation, non-sedating H1-antihistamines at approved doses. These medications are effective for the majority of patients and represent the foundation of CSU management across all age groups. For patients who do not achieve adequate symptom control with standard-dose H1-antihistamines, clinical practice guidelines recommend dose escalation up to four-fold higher than approved doses (Bernstein et al. 2014; Zuberbier et al. 2022). However, approximately 10% to 25% of pediatric patients continue to experience symptoms despite high-dose antihistamine therapy (Lee et al. 2016).

For adults and adolescents aged 12 years and older who remain symptomatic despite H1-antihistamine treatment, omalizumab and dupilumab are approved therapies. More recently, remibrutinib was approved for adults who remain symptomatic despite H1-antihistamine treatment. The lack of an approved biologic in children <12 years of age with CSU represents a therapeutic gap.

Patients with CSU refractory to H1-antihistamines and, when age-appropriate, omalizumab, may be treated with off-label therapies. These include cyclosporine, hydroxychloroquine, systemic corticosteroids (generally limited to short courses), and various immunomodulatory agents such as methotrexate, mycophenolate mofetil, dapsone, and sulfasalazine (Bernstein et al. 2014; Zuberbier et al. 2022). These alternative therapies have limited efficacy data in CSU and are associated with safety concerns, particularly in pediatric populations.

The current treatment landscape indicates an unmet medical need for children younger than 12 years with CSU inadequately controlled by H1-antihistamines. No biologic therapies are approved for this age group, necessitating off-label use of medications with less favorable safety profiles or limited evidence of efficacy, in H1-antihistamine refractory pediatric patients.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The dupilumab pediatric CSU program was developed under the same IND as the adult CSU, asthma and CRSwNP indications (IND 105379). The sBLA 761055/S-051 for dupilumab for the CSU indication in adults and adolescents was approved on April 17, 2025.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant submitted their initial pediatric study plan (iPSP) on December 17, 2019. On March 12, 2020, the Division requested revisions including enrollment of children down to age 6 years in Phase 3 studies, modification of the waiver rationale for children under 2 years to specify that treatment fails to represent meaningful therapeutic benefit over available therapies and is unlikely to be used in substantial numbers of children in this age group, and revision of the timeline for the open-label PK and safety study (PKM16982) in subjects aged 2 to <12 years. The iPSP was agreed to on June 15, 2020, incorporating pediatric subjects aged 6 to <18 years in pivotal studies, deferral of studies in the 2 to <6 years age group until completion of studies in subjects ≥6 years, and waiver for the under 2 years population.

The Applicant submitted the protocol for Study PKM16982 to the Division on April 12, 2022 as a phase 3, 24-week, single-arm, multicenter study to evaluate the pharmacokinetics and safety of dupilumab in pediatric subjects aged >2 to < 12 years of age with CSU or chronic inducible cold urticaria (CICU) inadequately controlled on H1 antihistamine therapy. At that time, the Applicant was conducting a second trial, Study EFC16720, a randomized, double-blind, placebo-controlled, multicenter, parallel-group study of dupilumab in adult and adolescents subjects with CICU. The Applicant notified the Agency on May 5, 2023 that the efficacy endpoints were not met in Study EFC16720. Based on these results, the decision was made to remove inclusion of pediatric subjects with CICU from study PKM16982 in a protocol amendment submitted on July 6, 2023.

The Applicant submitted sBLA 761055/S-051 for treatment of inadequately controlled CSU in adults and pediatric subjects aged 12 years and older on October 18, 2024. At that time, they proposed an amended iPSP requesting deferral for ages 2 to <12 years because the PK and safety study was incomplete at the time of the initial BLA submission for CSU in adults and adolescents. The Division agreed to the amended iPSP.

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

4.1. Office of Scientific Investigations

No clinical site inspections were requested as no sites of concern were identified.

4.2. Product Quality

The proposed drug product is intended to be administered using the approved presentations (i.e., 200mg and 300 mg prefilled syringe assembled with a safety system and 200mg and 300 mg single-use prefilled pen). No new product quality data were submitted for review to support the proposed indication.

4.3. Clinical Microbiology

No new microbiology data were submitted for review to support the proposed indication.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic test for review in support of this sBLA. The proposed presentations have been approved in prior submissions to the BLA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data was submitted with this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Background/Regulatory History

Dupixent (dupilumab) solution for SC injection was originally approved under BLA 761055 on March 28, 2017, for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The active pharmaceutical ingredient of Dupixent, dupilumab, is an IgG4 monoclonal antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit

shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Following a series of efficacy supplement approvals, the originally approved indication has been expanded to include the following:

1. The treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (S-012, S-020, S-042)
2. Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma (S-007, S-031)
3. Add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled CRSwNP (S-014, S-066)
4. Treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with EoE (S-040, S-057)
5. Treatment of adult patients with PN (S-044)
6. Add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype (S-064)
7. Treatment of adult and pediatric patients aged 12 years and older with CSU who remain symptomatic despite H1 antihistamine treatment (S-051)
8. Treatment of adult patients with BP (S-070)
9. Treatment of adult and pediatric patients aged 6 years and older with AFRS who have a history of sino-nasal surgery (S-075)

Overview of Current Submission (sBLA 761055/S-074)

On June 27, 2025, the Applicant (Regeneron Pharmaceuticals, Inc.) submitted an efficacy supplement under BLA 761055, in which they propose to expand the indication of dupilumab for the treatment of CSU in patients whose disease is not adequately controlled with H1 antihistamine treatment (currently approved for use in adults and adolescents under S-051) to include pediatric subjects 2 to < 12 years of age. In support of this application, the Applicant conducted a single-arm phase 3 study to assess efficacy, safety, and pharmacokinetics and pharmacodynamics of dupilumab in children 2 to < 12 years of age with CSU (Study PKM16982). Clinical data in children 6 to < 12 years of age are also provided from Phase 3 Studies EFC16461-C and EFC16461-A, which were previously reviewed under S-051 and supported approval of dupilumab for the treatment of CSU in adults and adolescents 12 years of age and older. Additional justification for the proposed dosing in children 2 to < 12 years of age with CSU is provided by population PK modeling and simulation analyses as part of an extrapolation approach to support efficacy and safety (Study POH1231). Furthermore, descriptive exposure-response (ER) analyses were conducted for key efficacy endpoints, Itch Severity Score over 7 days (ISS7) and weekly urticaria activity score (UAS7), based on observed data derived from Studies PKM16982, EFC16461-C, and EFC16461-A.

Proposed Dosing

The proposed SC dosing regimens for pediatric CSU subjects 2 to < 12 years of age are outlined below:

- **Children 2 to < 6 years of age (5 to < 15 kg):** 200 mg every 4 weeks (Q4W), no loading dose (LD)
- **Children 2 to < 6 years of age (15 to < 30 kg):** 300 mg Q4W, no LD
- **Children 6 to < 12 years of age (15 to < 30 kg):** 300 mg Q4W, with LD of 600 mg
- **Children 6 to < 12 years of age (30 to < 60 kg):** 200 mg every 2 weeks (Q2W), with LD of 400 mg
- **Children 6 to < 12 years of age (≥ 60 kg):** 300 mg Q2W, with LD of 600 mg

Of note, the proposed age- and weight-based dosing regimens for children 2 to < 12 years of age with CSU are identical to those currently approved for the treatment of AD in patients 6 months of age and older.

Major Clinical Pharmacology Review Findings

- Following SC administration at the proposed dosage regimens, the observed/simulated dupilumab steady-state systemic exposure in children 2 to < 12 years of age was generally comparable to or higher than that observed/simulated in adults and adolescents with CSU. Body weight was identified as the primary covariate influencing variability in systemic exposure between subjects.
- The change from baseline in serum total IgE following SC administration of dupilumab in children 2 to < 12 years of age was comparable to that observed in adults and adolescents with CSU. Reduction in serum IgE for children 2 to < 12 years of age with CSU was also similar to that observed in pediatric subjects 6 to < 12 years of age with moderate to severe asthma.
- Based on descriptive ER analyses, there appeared to be a slight trend toward larger reductions from baseline in the key efficacy endpoints (ISS7 and UAS7) at Week 24 with increasing plasma trough concentration at steady state ($C_{trough,ss}$) in children 2 to < 12 years of age with CSU, which aligns with findings in the adult/adolescent CSU population. However, given the limited enrollment of pediatric subjects, interpretability of these data is limited and a significant exposure-dependent response cannot be concluded based on the totality of data.
- Considering the higher dupilumab pharmacokinetics, comparable pharmacodynamic (PD) response (i.e., reduction in total serum IgE), and similar apparent exposure-efficacy relationship in children 2 to < 12 years of age with CSU as compared with adult and adolescents, extrapolation of efficacy from the adult/adolescent CSU population to support the proposed pediatric dosing appears reasonable from a clinical pharmacology perspective.

- Following SC administration of dupilumab at the proposed age- and weight-tiered dosing regimens in children 2 to < 12 years of age with CSU, mean observed/simulated dupilumab steady-state trough concentrations were comparable to and within the range of those observed in pediatric subjects less than 12 years of age across other dupilumab-approved indications, including AD, asthma, and EoE (subjects weighing ≥ 15 kg), thereby supporting extrapolation of safety data to the proposed pediatric CSU population.
- There were no positive anti-drug antibody (ADA) or neutralizing antibody (NAb) responses in any children 2 to < 12 years of age with CSU across any clinical trials, regardless of assigned treatment arm, thereby precluding any definitive assessments of the potential impact of immunogenicity on dupilumab pharmacokinetics, safety, and efficacy.

Recommendation

The Office of Clinical Pharmacology (OCP), Division of Inflammation and Immune Pharmacology, and Division of Pharmacometrics have reviewed the information submitted under sBLA 761055/S-074. This efficacy supplement and the proposed dosing regimens for children 2 to <12 years of age with CSU are approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The general clinical pharmacology program for dupilumab was reviewed following submission of the original BLA for the treatment of moderate-to-severe AD in adults (Refer to the Office of Clinical Pharmacology Review dated December 19, 2016 [DARRTS Reference ID: 4030358]).

In support of the current efficacy supplement, the Applicant has submitted clinical pharmacology data derived from three clinical trials for Agency review:

- **Study PKM16982:** Phase 3, single-arm, PK, efficacy, and safety study conducted in children 2 to < 12 years of age with CSU
- **Studies EFC16461-A and EFC16461-C:** Phase 3, randomized, double-blind, placebo-controlled trials conducted in adults, adolescents (12 to < 18 years of age), and children (6 to < 12 years of age) with CSU who remain symptomatic despite the use of H1 antihistamine treatment

All three studies evaluated dupilumab pharmacokinetics (i.e., trough concentrations), pharmacodynamics (i.e., serum IgE over time), and immunogenicity (i.e., ADAs and NAbs) over a 24-week treatment period. Study PKM16982 included a total of 15 children with CSU with body weight ranging from 14.5 to 55.7 kg to receive the following dosing regimens according to age and body weight:

- **Children 2 to < 6 years of age (5 to < 15 kg):** 200 mg SC Q4W, no LD (N = 1)
- **Children 2 to < 6 years of age (15 to < 30 kg):** 300 mg SC Q4W, no LD (N = 4)
- **Children 6 to < 12 years of age (15 to < 30 kg):** 300 mg SC Q4W, with LD of 600 mg (N = 2)
- **Children 6 to < 12 years of age (30 to < 60 kg):** 200 mg SC Q2W, with LD of 400 mg (N = 8)

Studies EFC16461-C and EFC16461-A were previously reviewed under sBLA 761055/S-051, for which they provided pivotal evidence to support for the approval of dupilumab for the treatment of CSU in adult and adolescent patients 12 years of age and older. These studies also included 5 pediatric subjects 6 to < 12 years of age (3 dupilumab, 2 placebo). Across all three studies, a total of 20 children 2 to < 12 years of age with CSU were enrolled and received treatment with either dupilumab (N = 18) or placebo (N = 2). A summary of enrollment of children 2 to < 12 years of age across the clinical trials completed in the CSU population is provided below in Table 3 according to study ID and assigned treatment arm.

Table 3: Summary of Dupilumab Exposure in Pediatric Subjects 2 to < 12 Years of Age With CSU Across Clinical Trials

Treatment Arm	Body weight (kg)	Age (years)	Dupilumab Dosing Regimen	Number of Subjects (N)			
				PKM16982	EFC16461-C	EFC16461-A	Total
Dupilumab	5 to < 15	2 to < 12	200 mg Q4W, no LD	1	0	0	1
	15 to < 30	2 to < 6	300 mg Q4W, no LD	4	0	0	4
		6 to < 12	300 mg Q4W + 600 mg LD	2	0	0	2
	30 to < 60	2 to < 12	200 mg Q2W + 400 mg LD	8	1	2	11
Dupilumab (Pooled)	5 to < 60	2 to < 12	Various dosing regimens	15	1	2	18
Placebo	30 to < 60	2 to < 12	Placebo	0	2	0	2

Source: Adapted from Summary of Clinical Pharmacology Studies (Table 2, pg. 16)
Abbreviations: CSU: Chronic Spontaneous Urticaria; N: Number of Subjects; Q4W: Every 4 Weeks; LD: Loading Dose; Q2W: Every 2 Weeks

Refer to Section 8 for additional details pertaining to the overall study design, key efficacy and safety endpoints, and subject demographics. Refer to Section 6.3.1 for detailed clinical pharmacology assessment of dupilumab pharmacokinetics, pharmacodynamics, and immunogenicity in children 2 to < 12 years of age with CSU across Studies PKM16982, EFC16461-C, and EFC16461-A, as well as the acceptability of the proposed dosing in this patient population.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed age- and weight-based dosing regimens for pediatric subjects 2 to < 12 years of age with CSU are outlined below:

- **Children 2 to < 6 years of age (5 to < 15 kg):** 200 mg SC Q4W, no LD
- **Children 2 to < 6 years of age (15 to < 30 kg):** 300 mg SC Q4W, no LD
- **Children 6 to < 12 years of age (15 to < 30 kg):** 300 mg SC Q4W, with LD of 600 mg
- **Children 6 to < 12 years of age (30 to < 60 kg):** 200 mg SC Q2W, with LD of 400 mg
- **Children 6 to < 12 years of age (≥ 60 kg):** 300 mg SC Q2W, with LD of 600 mg

Note that all of these dosing regimens were evaluated following SC administration across Studies PKM16982, EFC16461-C, and EFC16461-A, with the exception of the 300 mg SC Q2W + 600 mg LD dosing regimen in children 6 to < 12 years of age and weighing ≥ 60 kg, for which no observed clinical data are available in CSU patients.

Therapeutic Individualization

None.

Bioanalytical and Clinical Site Inspection by the Office of Study Integrity and Surveillance

A request for a biopharmaceutical inspection of the clinical and analytical sites for Study PKM16982 was submitted to the Office of Study Integrity and Surveillance (OSIS) on July 31, 2025. No objectional conditions were observed following inspection of the analytical site (i.e., Regeneron Pharmaceuticals, Tarrytown, NY). Based on inspection findings, there are no identified concerns regarding reliability of the data (refer to Bioequivalence Establishment Inspection Report Review Memorandum, dated February 5, 2026 [DARRTS Reference ID: 5741068]).

The OSIS also conducted an inspection of two of the clinical sites that enrolled the greatest number of subjects in Study PKM16982. These include Hamilton Allergy (Hamilton, Ontario, Canada), and Cincinnati Children's Hospital Medical Center (CCHMC, Cincinnati, OH). Objectionable conditions were observed and Form FDA 483 was issued for both sites. For additional details, refer to Bioequivalence Establishment Inspection Report Review Memorandum, dated February 3, 2026 (DARRTS Reference ID: 5739244). OSIS concluded that most of the identified issues are unlikely to impact the reliability of data for review. However, two issues were identified, both from CCHMC, that require further follow-up.

- PK and ADA serum samples were centrifuged for 10 minutes instead of 15 minutes as specified in the lab manual and it is possible that this deviation may have impacted the quality of the serum and the accuracy of the analytical results. OSIS recommends considering this sample processing deviation when reviewing PK data from the study.

- For one subject, (b) (6), the source document provides conflicting timelines for removal of IP from the refrigerator and IP administration. As a result, the exact time of IP administration is unclear. OSIS thus recommends not to accept data from subject (b) (6).

PK data are available from three subjects enrolled at CCHMC, including two subjects aged 6 to < 12 years and weighing ≥ 30 kg, both of whom received dupilumab 200 mg Q2W following a 400 mg LD; and one subject aged 2 to < 6 years and weighing 15 to < 30 kg who received 300 mg Q4W (Table 4).

Table 4: Summary of Arithmetic Mean (SD) Dupilumab Serum Concentrations (mg/L) Over Time for Subjects Enrolled at CCHMC and Overall (Pooled PK Population)[a]

Subject	Age Group	Body Weight	Dosing Regimen	W1	W2	W4	W12	W24
(b) (6)	2 to < 6 years	15 to < 30 kg[b]	300 mg Q4W, no LD	102	-	-	105	144
Overall				102, 150	101, 132	-	105	141 (30.1)
(b) (6)	6 to < 12 years	30 to < 60 kg[c]	200 mg Q2W + 400 mg LD	57.4	-	-	69.4	55.6
				-	75.2	-	71.0	77.3
Overall				86.5 (19.0)	73.0 (7.2)	88.5 (4.9)	91.9 (21.5)	80.9 (30.4)

Source: Reviewer's analysis based on adpc.xpt for Studies PKM16982, EFC16461-C, and EFC16461-A
Note that concentrations at Weeks 4, 12, and 24 are pre-dose trough concentrations.
[a] Individual concentrations reported for each subject or at timepoints at which N ≤ 2. For the pooled PK population, serum concentrations are reported as arithmetic mean (SD).
[b] **300 mg Q4W, no LD:** W1 (N = 2), W2 (N = 2), W4 (N = 0), W12 (N = 1), W24 (N = 3)
[c] **200 mg Q2W + 400 mg LD:** W1 (N = 5), W2 (N = 6), W4 (N = 3), W12 (N = 9), W24 (N = 9)
Abbreviations: CCHMC: Cincinnati Children's Hospital Medical Center; SD: Standard Deviation; PK: Pharmacokinetic; N: Number of Subjects; Q4W: Every 4 Weeks; LD: Loading Dose; Q2W: Every 2 Weeks

For all subjects enrolled at CCHMC, no consistent deviation of concentration values from the population mean values was observed. Among subjects aged 6 to < 12 years who received 200 mg Q2W following a 400 mg LD, most values fall within the range of reported serum concentration from Study PKM16982 (Week 1 [57.4, 108]; Week 2 [60.4, 82.2]; Week 12 [58.3, 126]; Week 24 [13.8, 115]). Meanwhile, for subject (b) (6), serum concentrations are comparable to those reported for subjects in other indications in the same weight band who received the same dosage of 300 mg Q4W (Table 12). Thus, the sample processing deviation resulting from shortening the centrifugation time does not appear to have introduced any systematic errors and is therefore unlikely to have affected serum dupilumab concentrations from subjects enrolled at CCHMC.

Serum dupilumab concentrations from subject (b) (6) were generally within the population range. For example, per the approved labeling for dupilumab, the mean (standard deviation [SD]) peak concentration following a 400 mg dose, measured 1 week post-dose, is 41.8 (12.4) mg/L. Meanwhile, the population PK simulated median (P5, P95) steady state trough concentration was 91.9 (52.7, 124) mg/L (Table 7). Therefore, PK data from subject (b) (6) is comparable to existing PK data for dupilumab and removal of data from subject (b) (6) is unlikely to yield large changes in the mean values.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

What Are the Pharmacokinetic Characteristics of Dupilumab Following Subcutaneous Administration in Children 2 to < 12 Years of Age With CSU?

Summary of Observed PK Data From Studies PKM16982, EFC16461-C, and EFC16461-A

The pharmacokinetics of dupilumab were characterized in children 2 to < 12 years of age with CSU using sparse sampling in Studies PKM16982, EFC16461-C, and EFC16461-A. In each study,

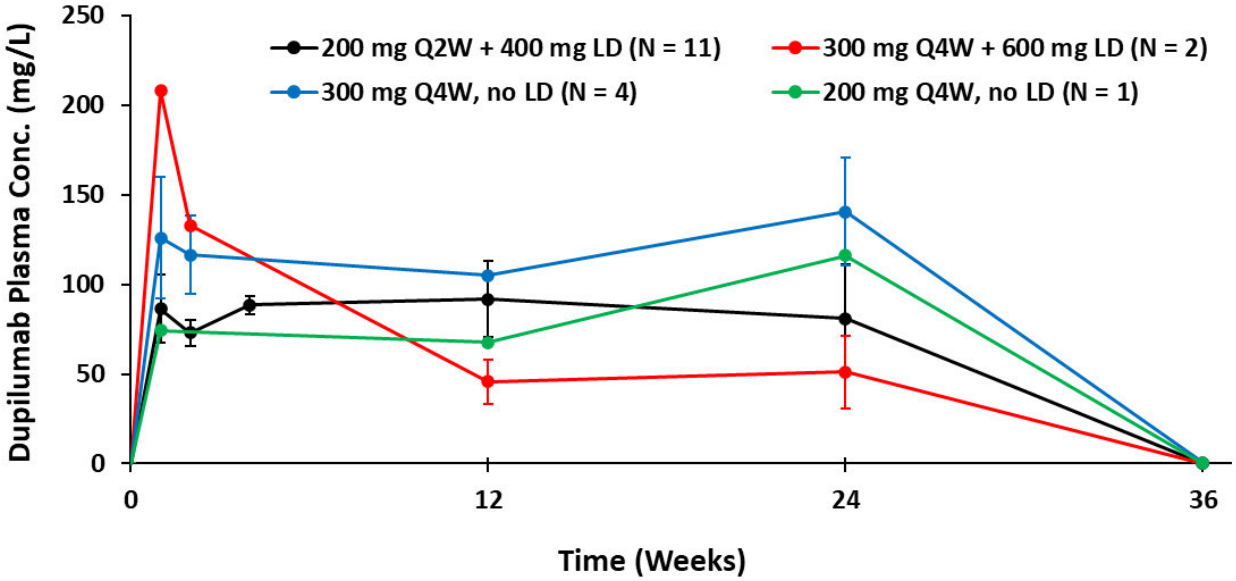
subjects received their assigned dupilumab treatment via SC injection for a total on-treatment period of 24 weeks. In Study PKM16982, subjects were randomized in a 1:1 ratio to PK schedule A (pre-dose trough samples collected at Weeks 0, 1, 12, and 24) or to PK schedule B (trough samples collected Weeks 0, 2, 12, and 24). In both EFC16461-C and EFC16461-A, pre-dose trough PK samples were collected at Weeks 0, 12, and 24. In all three studies, one additional sample was collected during the safety follow-up period at Week 36 (12 weeks after last dose).

Plasma concentrations of dupilumab in all three trials were determined using a previously validated bioanalytical enzyme-linked immunosorbent assay (REGN668-AV-13074), which was previously reviewed under the original BLA submission for the treatment of moderate-to-severe AD in adults, at which time it was found to be acceptable (Refer to the Office of Clinical Pharmacology Review dated December 19, 2016 [DARRTS Reference ID: 4030358]). The in-study bioanalysis results for Study PKM16982 met acceptance criteria. Additionally, method performance for Studies EFC16461-A and EFC16461-C was previously reviewed under sBLA 761055/S-051 and found to be acceptable (Refer to BLA Multi-Disciplinary Reviews and Evaluations dated October 18, 2023 [DARRTS Reference ID: 5263308] and April 16, 2025 [DARRTS Reference ID: 5572858]).

The pooled PK population for Studies PKM16982, EFC16461-C, and EFC16461-A included all 18 children 2 to < 12 years of age who received dupilumab treatment. However, both subjects from Study EFC16461-A (b) (6) withdrew from the study prior to completion, resulting in early treatment discontinuations on Day 28 and Day 70, respectively. Additionally, one subject from Study PKM16982 (b) (6) withdrew from the study on Day 12 and therefore only contributed one post-baseline PK sample. A summary of dupilumab plasma trough concentrations over time following SC administration for the pooled PK population is depicted below in Figure 1 and Table 5.

Overall, dupilumab trough concentrations increased over time throughout the treatment period, with near steady-state exposures achieved by Week 12. Except for a single participant weighing 17.1 kg and assigned to the 300 mg Q4W treatment group ((b) (6) Study PKM16982), dupilumab exposure decreased to below the lower limit of quantitation (0.078 mg/L) in all subjects by Week 36 following treatment discontinuation. Trough concentrations at Week 24 were highest in the lowest age and body weight sub-groups who received the dupilumab 200 mg/300 mg Q4W dosing regimens without a loading dose, although the interpretability of PK data in these dosing arms is limited by the small sample size.

Figure 1: Arithmetic Mean (SD) Dupilumab Plasma Concentration-Time Profile (Pooled PK Population; Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b,c,d]



Source: Reviewer's analysis based on adpc.xpt for Studies PKM16982, EFC16461-C, and EFC16461-A
[a] **200 mg Q2W + 400 mg LD:** W0 (N = 11), W1 (N = 5), W2 (N = 6), W4 (N = 3), W12 (N = 9), W24 (N = 9), W36 (N = 9)
[b] **300 mg Q4W + 600 mg LD:** W0 (N = 2), W1 (N = 1), W2 (N = 1), W4 (N = 0), W12 (N = 2), W24 (N = 2), W36 (N = 1)
[c] **300 mg Q4W, no LD:** W0 (N = 4), W1 (N = 2), W2 (N = 2), W4 (N = 0), W12 (N = 1), W24 (N = 3), W36 (N = 2)
[d] **200 mg Q4W, no LD:** W0 (N = 1), W1 (N = 1), W2 (N = 0), W4 (N = 0), W12 (N = 1), W24 (N = 1), W36 (N = 1)
Abbreviations: SD: Standard Deviation; PK: Pharmacokinetic; Conc. Concentration; Q2W: Every 2 Weeks; LD: Loading Dose; N: Number of Subjects; Q4W: Every 4 Weeks

Table 5: Summary of Arithmetic Mean (SD) Dupilumab Serum Concentrations Over Time by Dosing Regimen (Pooled PK Population; Studies PKM16982, EFC16461-C, and EFC16461-A)[a]

Age Group	BW (kg)	N	Dosing Regimen	Arithmetic Mean (SD) C_{trough} (mg/L)					
				W0	W1	W2	W4	W12	W24
2 to < 6 years	5 to < 15 kg[b]	1	200 mg Q4W, no LD	0.00	74.2	-	-	67.7	116
	15 to < 30 kg[c]	4	300 mg Q4W, no LD	0.00	102, 150	101, 132	-	105	141 (30.1)
6 to < 12 years	15 to < 30 kg[d]	2	300 mg Q4W + 600 mg LD	0.00	208	133	-	37.0, 54.6	36.9, 65.3
	30 to < 60 kg[e]	1 1	200 mg Q2W + 400 mg LD	0.00	86.5 (19.0)	73.0 (7.2)	88.5 (4.9)	91.9 (21.5)	80.9 (30.4)

Source: Reviewer's analysis based on adpc.xpt for Studies PKM16982, EFC16461-C, and EFC16461-A
[a] Individual concentrations reported for timepoints at which N ≤ 2
[b] **200 mg Q4W, no LD:** W0 (N = 1), W1 (N = 1), W2 (N = 0), W4 (N = 0), W12 (N = 1), W24 (N = 1)
[c] **300 mg Q4W, no LD:** W0 (N = 4), W1 (N = 2), W2 (N = 2), W4 (N = 0), W12 (N = 1), W24 (N = 3)
[d] **300 mg Q4W + 600 mg LD:** W0 (N = 2), W1 (N = 1), W2 (N = 1), W4 (N = 0), W12 (N = 2), W24 (N = 2)
[e] **200 mg Q2W + 400 mg LD:** W0 (N = 11), W1 (N = 5), W2 (N = 6), W4 (N = 3), W12 (N = 9), W24 (N = 9)
Abbreviations: SD: Standard Deviation; PK: Pharmacokinetic; N: Number of Subjects; Q4W: Every 4 Weeks; LD: Loading Dose; Q2W: Every 2 Weeks

Comparison of Observed vs. Predicted Dupilumab Pharmacokinetics

The Applicant conducted population PK analyses based on observed PK data in children 2 to < 12 years of age with CSU derived from Studies PKM16982, EFC16461-C, and EFC16461-A (Study

POH1231). Given the extensive clinical experience with dupilumab and the similar pharmacokinetics noted across other clinical programs including AD, asthma, EoE, COPD, and CSU, the Applicant evaluated dupilumab pharmacokinetics in CSU subjects with a maximum a posteriori (MAP) Bayesian approach using a previously established population PK model developed for the pediatric asthma population (Study POH0766). This model was developed based on PK data pooled from two phase 3 clinical studies (Studies EFC14153 and LTS14424), which included a total of 377 children 6 to < 12 years of age with asthma, and was previously reviewed and found to be acceptable under BLA 761055/S-031 (Refer to NDA/BLA Multi-Disciplinary Review and Evaluation dated October 21, 2021 [DARRTS Reference ID: 4875558]).

For the current submission, all model parameters were fixed to the values of the pediatric asthma population PK model to generate individual post hoc estimates of dupilumab PK parameters in children 2 to < 12 years of age with CSU according to age, body weight, and dosing regimen sub-groups. For additional details regarding the population PK analyses submitted in support of the current efficacy supplement, refer to Section 15.3.1. Predicted exposures in adults and adolescents were also generated based on the previously submitted population PK analyses for the adult and adolescent CSU population (Study POH1089), which were reviewed and found to be acceptable under sBLA 761055/S-051 (Refer to BLA Multi-Disciplinary Reviews and Evaluations dated October 18, 2023 [DARRTS Reference ID: 5263308] and April 16, 2025 [DARRTS Reference ID: 5572858]).

Simulated and observed exposures in children 2 to < 12 years of age with CSU were subsequently compared to verify the ability of the model to accurately describe dupilumab pharmacokinetics in this patient population (Table 6). Additionally, observed and predicted dupilumab PK parameters for adults and adolescents 12 years of age and older receiving 300 mg Q2W (≥ 60 kg) or 200 mg Q2W (30 to < 60 kg) are provided for comparison. Based on these data, the predicted dupilumab exposures were comparable to and within the range variability of those observed for children 2 to < 12 years of age with CSU, demonstrating robust model performance. Overall, the dupilumab pharmacokinetics of children 2 to < 12 years of age with CSU appears to be well-characterized by the pediatric asthma population PK model (Study POH0766).

Table 6: Summary of Arithmetic Mean (SD) Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in CSU Subjects Across Age Groups and Dosing Regimens[a,b]

			Predicted[c,d]			Observed	
Age Group	Dosing Regimen	N (BW)[a,b]	$AUC_{4\ weeks,ss}$ (mg*day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)	N (BW)[b]	$C_{trough,ss}$[e,f] (mg/L)
Adults	300 mg Q2W + 600 mg LD	171 (75.0)	2260 (936)	89.6 (34.9)	67.0 (30.9)	165 (75.1)	64.9 (33.5)
Adolescents (12 to < 18 yr)	300 mg Q2W + 600 mg LD (≥ 60 kg)	3 (72.0)	2200 (688)	87.9 (26.3)	64.5 (22.9)	4 (76.5)	63.6 (12.0)
	200 mg Q2W + 400 mg LD (30 to < 60 kg)	2 (47.1, 57.0)	1540 (378)	62.5 (14.1)	43.7 (11.9)	2 (47.1, 57.0)	22.4, 44.9

			Predicted[c,d]			Observed	
Age Group	**Dosing Regimen**	**N (BW)[a,b]**	**$AUC_{4\ weeks,ss}$ (mg*day/L)**	**$C_{max,ss}$ (mg/L)**	**$C_{trough,ss}$ (mg/L)**	**N (BW)[b]**	**$C_{trough,ss}$[e,f] (mg/L)**
Children (2 to < 12 yr)	200 mg Q2W + 400 mg LD (30 to < 60 kg)	10 (37.8)	3230 (441)	127 (16.5)	98.5 (14.4)	9 (38.6)	80.9 (30.4)
	300 mg Q4W + 600 mg LD (15 to < 30 kg, 6 to < 12 yr)	2 (25.1, 26.2)	2630 (451)	127 (19.3)	56.8 (12.2)	2 (25.1, 26.2)	36.9, 65.3
	300 mg Q4W, no LD (15 to < 30 kg, 2 to < 6 yr)	3 (18.7)	5440 (1020)	237 (42.3)	144 (29.4)	3 (18.7)	141 (30.1)
	200 mg Q4W, no LD (5 to < 15 kg)	1 (14.5)	3900	168	105	1 (14.5)	116

Source: Adapted from Summary of Clinical Pharmacology Studies (Table 3, pg. 30); Reviewer's analysis based on adpc.xpt and adsl.xpt for Studies PKM16982, EFC16461-A, EFC16461-B, and EFC16461-C

[a] For predicted PK exposures, of the 190 subjects included in the final PopPK dataset (Study POH1089), 185 subjects (181 adults and 4 adolescents) received 300 mg Q2W and 5 subjects (2 adolescents and 3 children 6 to < 12 years of age) received 200 mg Q2W. Due to early dose discontinuation, 10 adults receiving 300 mg Q2W, 1 adolescent receiving 300 mg Q2W, and 2 children (one receiving 200 mg Q2W + 400 mg LD, and the other receiving 300 mg Q4W, no LD) were excluded

[b] Reported as median body weight (kg); Individual body weight reported if N ≤ 2

[c] Predicted PK parameters derived based on post hoc estimates of individual steady state exposures for subjects enrolled in Studies EFC16461-A, EFC16461-B, EFC16461-C, and PKM16982 using PopPK studies POH1089 (adults and adolescents 12 to < 18 years of age) and POH1231 (children 2 to < 12 years of age)

[d] For Q2W dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24]; $AUC_{4\ weeks,ss}$ = $AUC_{\tau,ss}$ x 2; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24; For Q4W dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 20 – Week 24]; $AUC_{4\ weeks,ss}$ = $AUC_{\tau,ss}$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24

[e] Arithmetic mean (SD) observed $C_{trough,ss}$ at Week 24 reported for adults and adolescents 12 to < 18 years of age based on pooled PK population for Studies EFC16461-A, EFC16461-B, and EFC16461-C; Individual trough concentrations reported if N ≤ 2

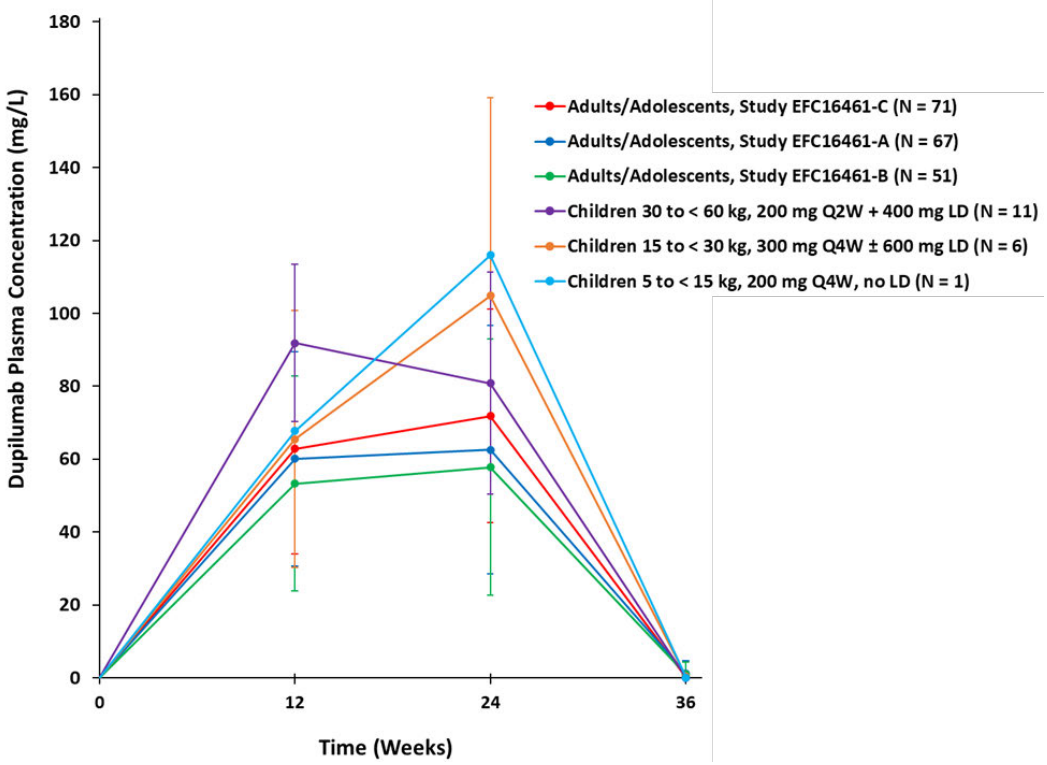
[f] Arithmetic mean (SD) observed $C_{trough,ss}$ at Week 24 reported for children 2 to < 12 years of age based on pooled PK population for Studies PKM16982, EFC16461-C, and EFC16461-A; Individual trough concentrations reported if N ≤ 2

Abbreviations: SD: Standard Deviation; PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; N: Number of Subjects; BW: Body Weight; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve Over 28 Days at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; Q2W: Every 2 Weeks; LD: Loading Dose; Yr: Years; Q4W: Every 4 Weeks; PopPK: Population Pharmacokinetic; $AUC_{\tau,ss}$: AUC Over the Dosing Interval at Steady State

Comparison of Dupilumab Pharmacokinetics Across Age Groups in CSU Subjects

The observed dupilumab plasma trough concentration-time profiles for children 2 to < 12 years of age with CSU are depicted below according to assigned maintenance dosing regimen, along with those for the adult/adolescent population from Studies EFC16461-C, EFC16461-A, and EFC16461-B (Figure 2). Of note, given the low sample size for pediatric subjects assigned to receive 300 mg Q4W with and without a 600 mg LD, these sub-groups have been pooled. Based on these data, dupilumab trough concentrations following SC administration in children 2 to < 12 years of age were generally higher at both Weeks 12 and 24 as compared with those observed in adults and adolescents with CSU.

Figure 2: Arithmetic Mean (SD) Observed Dupilumab Plasma Trough Concentrations Over Time According to Age Group, Body Weight Category, and Dosing Regimen[a,b,c]



Source: Reviewer's analysis based on adpc.xpt for Studies PKM16982, EFC16461-C, EFC16461-A, and EFC16461-B

[a] Observed dupilumab trough concentrations shown for adults and adolescents 12 years and older receiving either the 300 mg Q2W (≥ 60 kg) or 200 mg Q2W (30 to < 60 kg) dosing regimens from Studies EFC16461-C, EFC16461-A, and EFC16461-B

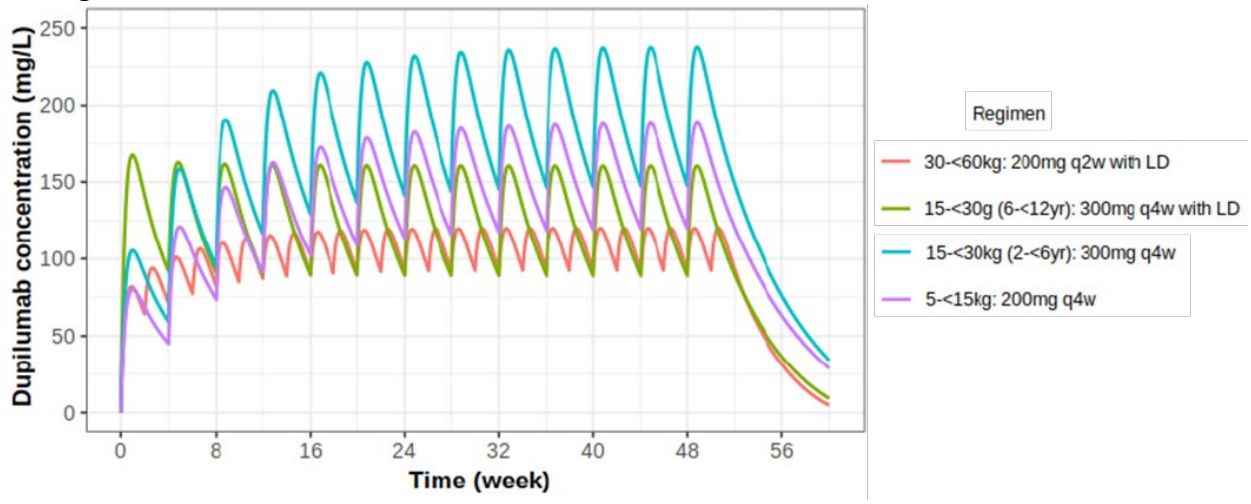
[b] Observed dupilumab trough concentrations shown for children 2 to < 12 years of age receiving assigned age- and weight-based dosing regimens in Studies PKM16982, EFC16461-C, and EFC16461-A (pooled)

[c] PK data for children 2 to < 12 years of age receiving dupilumab dosing regimens of 300 mg Q4W + 600 mg LD (N = 2) and 300 mg Q4W, no LD (N = 4) have been pooled for a total of 6 subjects receiving a maintenance dosage of 300 mg Q4W

Abbreviations: SD: Standard Deviation; N: Number of Subjects; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks

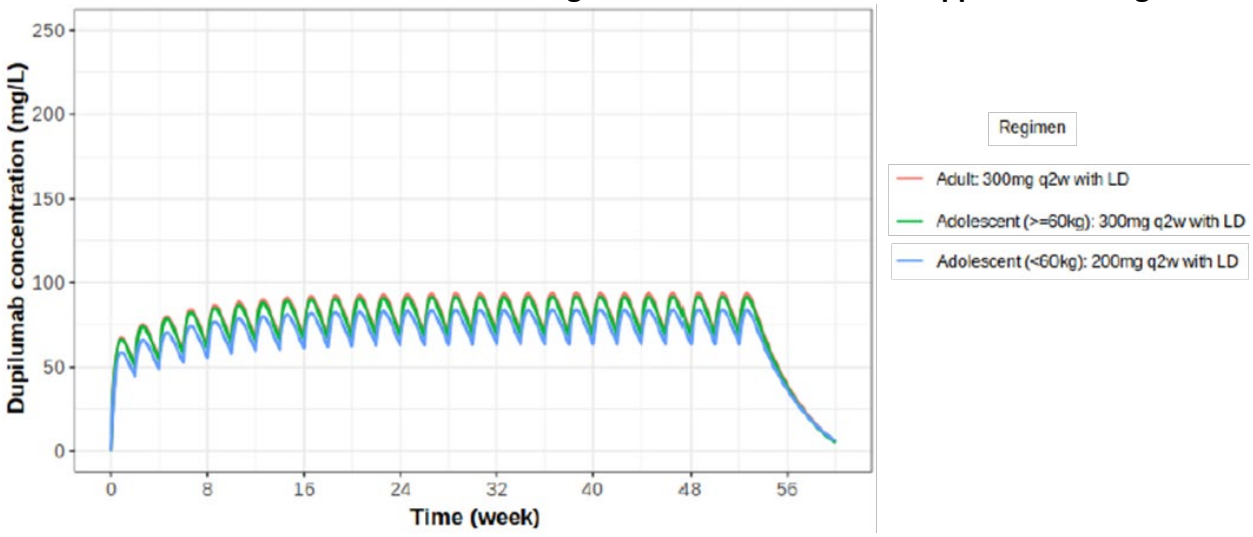
The Applicant used population PK modeling and simulation to further compare dupilumab pharmacokinetics in CSU subjects as a function of age. The typical dupilumab concentration-time profiles for children 2 to < 12 years of age and adults/adolescents with CSU are depicted below in Figure 3 and Figure 4, respectively.

Figure 3: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU Following SC Administration of the Proposed Dosing[a]



Source: Adapted from Summary of Clinical Pharmacology Studies (Figure 5, pg. 31)
[a] The typical profile simulation was conducted using asthma pediatric PopPK model (Study POH0766) for a typical pediatric subject 2 to < 12 years of age with CSU with median body weight of 38.6 kg (200 mg Q2W + 400 mg LD; N = 11), 25.7 kg (300 mg Q4W + 600 mg LD; N = 2), 17.9 kg (300 mg Q4W, no LD; N = 4), and 14.5 kg (200 mg Q4W, no LD; N = 1) based on final PopPK dataset (Study POH1231)
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; SC: Subcutaneous; Q2W: Every 2 Weeks; LD: Loading Dose; Yr: Year; Q4W: Every 4 Weeks; PopPK: Population PK

Figure 4: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Adults and Adolescents With CSU Following SC Administration of the Approved Dosing[a]



Source: Adapted from Summary of Clinical Pharmacology Studies (Figure 5, pg. 31)
[a] The typical profile simulation was conducted using the global PopPK base model (Study POH0668) for a typical adult or adolescent 12 to < 18 years of age with CSU with median body weight of 75.0 kg (adults; N = 184), 76.5 kg (adolescents weighing ≥ 60 kg; N = 4), and 52.1 kg (adolescents weighing 30 to < 60 kg; N = 2) based on final PopPK dataset (Study POH1089)
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; SC: Subcutaneous; Q2W: Every 2 Weeks; LD: Loading Dose; PopPK: Population PK

Additionally, the model-predicted dupilumab steady-state PK parameters for children 2 to < 12 years of age with CSU based on a virtual pediatric population using the National Health and Nutrition Examination Survey (NHANES) database are provided below in Table 7. A summary of

the observed/simulated steady-state dupilumab exposure (i.e., maximum plasma concentration at steady state [$C_{max,ss}$] and $C_{trough,ss}$) in adults and adolescents 12 to < 18 years of age, which was previously submitted and reviewed under sBLA 761055/S-051, is also included below in Table 8 for comparison.

Predicted steady-state trough concentrations are similar for children 2 to < 12 years of age with CSU receiving the 200 mg Q2W + 400 mg LD (30 to < 60 kg) and 300 mg Q4W + 600 mg LD (15 to < 30 kg, 6 to < 12 years) dosing regimens, although the predicted mean $C_{max,ss}$ is slightly higher (~1.5-fold) in those receiving the latter dosage as compared to the former. Notably, the median predicted dupilumab exposure (i.e., $C_{trough,ss}$ and $C_{max,ss}$) for children receiving the 200 mg Q2W + 400 mg LD (30 to < 60 kg) dosage falls within the 5th to 95th percentile of that predicted/observed for adults and adolescents with CSU receiving the 300 mg Q2W + 600 mg LD (≥ 60 kg) and 200 mg Q2W + 400 mg LD (30 to < 60 kg) dosing regimens, demonstrating comparable pharmacokinetics to adults and adolescents at this dose level. Median predicted $C_{trough,ss}$ for children 6 to < 12 years receiving the 300 mg Q4W + 600 mg LD (30 to < 60 kg) dosing regimen also falls within the 5th to 95th percentiles of observed/predicted values for adults and adolescents receiving 300 mg/200 mg Q2W, although median predicted $C_{max,ss}$ in children at this dosage exceeded the 95th percentile of that in adults and adolescents. The greater predicted $C_{max,ss}$ in children aged 6 to < 12 years and weighing 15 to < 30 kg relative to children weighing 30 to < 60 kg and adults and adolescents is likely due to the administration of a higher nominal dose (i.e., 300 mg vs. 200 mg) or due to the impact of lower body weight on dupilumab exposure.

Simulated steady-state dupilumab exposure for the lowest age and body weight pediatric sub-groups receiving the 300 mg Q4W (15 to < 30 kg, 2 to < 6 years) and 200 mg Q4W (5 to < 15 kg) dosage regimens was generally higher compared to the higher age and body weight subjects assigned to receive the 200 mg Q2W/300 mg Q4W dosing regimens with loading doses. Furthermore, the median predicted dupilumab exposure (i.e., $C_{trough,ss}$ and $C_{max,ss}$) for children receiving these dosage regimens equaled or exceeded the 95th percentile of those predicted/observed for adults and adolescents with CSU receiving the approved 300 mg/200 mg Q2W dosing. This higher model-predicted exposure in the lower age and body weight sub-groups is consistent with the observed data in CSU subjects and also aligns with previous PK findings reported in the AD patient population.

Table 7: Summary of Population PK Model-Simulated Dupilumab Plasma Steady-State PK Parameters in Children 2 to <12 Years of Age With CSU, Using a Virtual Pediatric Population From NHANES Database (Study POH1231)[a]

			$AUC_{4\ weeks,ss}$ (mg*day/L)[c,d]		$C_{max,ss}$ (mg/L)[c,d]		$C_{trough,ss}$ (mg/L)[c,d]	
Body Weight/ Age Group	**Dosing Regimen**	**N (BW)[b]**	**Mean (SD) [CV%]**	**Median [P5-P95]**	**Mean (SD) [CV%]**	**Median [P5-P95]**	**Mean (SD) [CV%]**	**Median [P5-P95]**
30 to < 60 kg	200 mg Q2W + 400 mg LD	667 (38.5)	3010 (684) [22.7]	3050 [1850-4020]	118 (25.6) [21.7]	120 [74.3-156]	90.5 (22.3) [24.7]	91.9 [52.7-124]
15 to < 30 kg, 6 to < 12 years	300 mg Q4W + 600 mg LD	546 (24.6)	3870 (658) [17.0]	3770 [3030-5130]	172 (26.3) [15.3]	168 [139-223]	97.8 (19.9) [20.3]	95.0 [72.9-136]

Body Weight/ Age Group	Dosing Regimen	N (BW)[b]	$AUC_{4\ weeks,ss}$ (mg*day/L)[c,d] Mean (SD) [CV%]	$AUC_{4\ weeks,ss}$ (mg*day/L)[c,d] Median [P5-P95]	$C_{max,ss}$ (mg/L)[c,d] Mean (SD) [CV%]	$C_{max,ss}$ (mg/L)[c,d] Median [P5-P95]	$C_{trough,ss}$ (mg/L)[c,d] Mean (SD) [CV%]	$C_{trough,ss}$ (mg/L)[c,d] Median [P5-P95]
15 to < 30 kg, 2 to < 6 years	300 mg Q4W, no LD	572 (18.0)	5180 (801) [15.5]	5240 [3730-6310]	224 (31.8) [14.2]	226 [166-268]	139 (24.7) [17.8]	140 [94-173]
5 to < 15 kg	200 mg Q4W, no LD	329 (13.4)	4660 (507) [10.9]	4560 [4070-5600]	198 (19.8) [10.0]	194 [175-234]	129 (16.0) [12.5]	125 [110-158]

Source: Adapted from Summary of Clinical Pharmacology Studies (Table 4, pg. 33)
[a] Dupilumab exposures for children 2 to < 12 years of age and weighing 5 to 60 kg were simulated using the asthma pediatric PopPK model (Study POH0766), based on a virtual pediatric population from NHANES database (N = 2114)
[b] Reported as median body weight (kg)
[c] For 200 mg Q2W + 400 mg LD dosing regimen: $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss} \times 2$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24
[d] For 200 mg Q4W, no LD and 300 mg Q4W ± 600 mg LD dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 20 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss}$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; NHANES: National Health and Nutrition Examination Survey; N: Number of Subjects; BW: Body Weight; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve Over 28 Days at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; SD: Standard Deviation; CV%: Coefficient of Variation; P5: 5th Percentile; P95: 95th Percentile; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; PopPK: Population Pharmacokinetic; $AUC_{\tau,ss}$: AUC Over the Dosing Interval at Steady State

Table 8: Summary of Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in Adults and Adolescents 12 to <18 Years of Age With CSU (Study POH1089)

Age Group	Study ID	Dosing Regimen	Predicted/Simulated $C_{max,ss}$ (mg/L) N (BW)[c]	Predicted/Simulated $C_{max,ss}$ (mg/L) Mean (SD)	Predicted/Simulated $C_{max,ss}$ (mg/L) P5-P95	Observed/Simulated $C_{trough,ss}$ (mg/L) N (BW)[c]	Observed/Simulated $C_{trough,ss}$ (mg/L) Mean (SD)	Observed/Simulated $C_{trough,ss}$ (mg/L) P5-P95
Adults[a]	EFC16461 Study C	300 mg Q2W + 600 mg LD	64 (72.1)	95.7 (32.9)	52.2-143	56 (73.0)	72.9 (29.6)	29.8-125
	EFC16461 Study A	300 mg Q2W + 600 mg LD	60 (75.1)	89.4 (36.0)	24.0-153	63 (63.0)	63.0 (34.2)	3.67-117
	EFC16461 Study B	300 mg Q2W + 600 mg LD	47 (80.0)	81.6 (35.1)	33.7-142	46 (79.6)	57.7 (35.5)	10.4-112
Adolescents (12 to < 18 years)[b]	POH1089	300 mg Q2W + 600 mg LD (≥ 60 kg)	1000 (73.7)	91.2 (35.7)	37.7-154	1000 (73.7)	68.6 (32.2)	22.2-125
		200 mg Q2W + 400 mg LD (30 to < 60 kg)	1000 (51.3)	87.6 (31.5)	43.4-144	1000 (51.3)	66.9 (28.1)	28.4-118

Source: Adapted from previously submitted Summary of Clinical Pharmacology Studies, sBLA 761055/S-051 (Table 9, pg. 59); Reviewer's analysis based on adpc.xpt and adsl.xpt for Studies EFC16461-C, EFC16461-A, and EFC16461-B
[a] Predicted $C_{max,ss}$ generated from PopPK model-predicted individual post hoc parameters using empirical Bayesian approach (Study POH1089); Observed $C_{trough,ss}$ at Week 24 for adults with CSU across Studies EFC16461-C, EFC16461-A, and EFC16461-B
[b] Dupilumab exposures for adolescents 12 to < 18 years of age with CSU were simulated using the global PopPK base model (Study POH0668), based on a virtual pediatric population from NHANES database (N = 2000)
[c] Reported as median body weight (kg)
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; BW: Body Weight; N: Number of Subjects; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; N: Number of Subjects; SD: Standard Deviation; P5: 5th Percentile; P95: 95th Percentile; Q2W: Every 2 Weeks; LD: Loading Dose; PopPK: Population Pharmacokinetic; NHANES: National Health and Nutrition Examination Survey

What Are the Pharmacodynamic Characteristics of Dupilumab Following Subcutaneous Administration in Children 2 to < 12 Years of Age With CSU?

The pharmacodynamics of dupilumab (i.e., serum total IgE over time) was characterized in children 2 to < 12 years of age with CSU in Studies PKM16982, EFC16461-C, and EFC16461-A, in which PD samples were collected at baseline and Week 24 following SC administration of dupilumab. Studies EFC16461-C and EFC16461-A also collected samples at Weeks 12 and 36 (12

weeks after last dose). A summary of the change from baseline in total serum IgE in dupilumab-treated children 2 to < 12 years of age with CSU according to dosing regimen is depicted below in Table 9.

Table 9: Summary of Total Serum IgE Change From Baseline in Children 2 to <12 Years of Age With CSU (Pooled Safety Population; Studies PKM16982, EFC16461-C, and EFC16461-A)

Dupilumab Dosing Regimen	N	Body Weight (kg)[a]	Serum Total IgE		
			Baseline (IU/mL)[a]	W24 (IU/mL)[a]	Median CFB (%)[b]
200 mg Q2W + 400 mg LD	9	37.8 (5.5)	296 (496)	85.4 (122)	-62.5%
300 mg Q4W + 600 mg LD	2	25.1, 26.2	45.6, 192	12, 57.4	-70.1%, -73.7%
300 mg Q4W, no LD	3	19.1 (2.2)	23.7 (30.7)	8.9 (11.1)	-71.9%
200 mg Q4W, no LD	0	-	-	-	-
Total	14	32.1 (9.3)	213 (408)	61.8 (102)	-66.3%

Source: Reviewer's analysis based on adlb.xpt for Studies PKM16982, EFC16461-C, and EFC16461-A

[a] Values reported as arithmetic mean (SD); Individual values reported for the 300 mg Q4W + 600 mg LD dosing arm since N ≤ 2

[b] Values reported as median percent change from baseline at Week 24; Individual percent change from baseline reported for the 300 mg Q4W + 600 mg LD dosing arm since N ≤ 2

Abbreviations: IgE: Immunoglobulin E; CSU: Chronic Spontaneous Urticaria; N: Number of Subjects; IgE: Immunoglobulin E; CFB: Change from Baseline; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; SD: Standard Deviation

Mean total serum IgE at baseline was notably lower for subjects assigned to the 300 mg Q4W dosing arm relative to those assigned to the 200 mg Q2W + 400 mg LD and 300 mg Q4W + 600 mg LD groups, although a high degree of variability was noted across treatment groups. Overall mean (SD) baseline total serum IgE across all subjects with evaluable PD data was 213 (408) IU/mL. The individual change from baseline ranged from -23.1% to -74.7% across dupilumab dosing arms, with an overall median change from baseline of -66.3%.

These PD findings in children 2 to < 12 years of age with CSU generally align with those observed in adults and adolescents with CSU, in which a progressive decline in serum IgE was noted throughout the entire 24-week treatment period. Specifically, in Studies EFC16461-C, EFC16461-A, and EFC16461-B, median percent change from baseline at Week 24 was -54.2%, -48.7%, and -63.0%, respectively. Additionally, this PD response in the pediatric CSU population also appears to be consistent with that observed for pediatric subjects 6 to < 12 years of age with moderate-to-severe asthma, in which the median percent reduction from baseline in total serum IgE at Week 24 was approximately 60.6% following SC administration of dupilumab 200 mg Q2W or 100 mg Q2W (Study EFC14153; note that 100 mg Q2W is not an approved dosage for dupilumab for the treatment of asthma in pediatric patients aged 6 to < 12 years).

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

The Applicant is proposing age- and weight-based dupilumab dosage regimens for the treatment of CSU in children 2 to < 12 years of age. The proposed dosing was evaluated in

Studies PKM16982, EFC16461-C, and EFC16461-A, in which a total of 18 children 2 to < 12 years of age received dupilumab treatment, including:

- **Children 2 to < 6 years of age (5 to < 15 kg):** 200 mg SC Q4W, no LD (N = 1)
- **Children 2 to < 6 years of age (15 to < 30 kg):** 300 mg SC Q4W, no LD (N = 4)
- **Children 6 to < 12 years of age (15 to < 30 kg):** 300 mg SC Q4W, with LD of 600 mg (N = 2)
- **Children 6 to < 12 years of age (30 to < 60 kg):** 200 mg SC Q2W, with LD of 400 mg (N = 11)

Of note, the Applicant is also proposing a dosage of 300 mg Q2W + 600 mg LD for children (b) (4) years and weighing ≥ 60 kg, although there are no clinical data available for children with CSU receiving this dosing regimen. However, this same dosage is currently approved for adolescents with CSU aged 12 years and older and weighing ≥ 60 kg, and for pediatric patients with AD aged 6 years and older and weighing ≥ 60 kg. In addition, a higher dosage of 300 mg once weekly is approved for adult and pediatric patients aged 1 year and older with EoE and weighing ≥ 40 kg. Across approved indications, including CSU, body weight has consistently been shown to be the primary covariate influencing dupilumab pharmacokinetics, whereas no clinically meaningful impact of age has been identified. In addition, dupilumab pharmacokinetics is consistent across approved indications. Therefore, given these considerations, the proposed 300 mg Q2W + 600 mg LD dosing regimen for children 6 to < 12 years and weighing ≥ 60 kg appears reasonable and no clinically significant differences in dupilumab pharmacokinetics, safety, and efficacy are expected as compared to adolescents and adults weighing ≥ 60 kg and receiving the same dosage.

The proposed age- and weight-tiered dosing regimens in children 2 to < 12 years of age with CSU and weighing 5 to < 60 kg are supported by the observed efficacy and safety data derived from Studies PKM16982, EFC16461-C, and EFC16461-A, which are discussed further in Section 8. Descriptive efficacy ER analyses were also conducted to provide further dosing support based on pooled data derived from these three clinical trials and are detailed below. However, given the limited enrollment of pediatric subjects across these trials, additional justification for the proposed dosing is furnished by an extrapolation approach, whereby the Applicant seeks to extrapolate (1) efficacy data from adults/adolescents with CSU and (2) safety data from other dupilumab-approved pediatric indications, including AD, asthma, and EoE.

Descriptive Exposure-Response Analyses for Key Efficacy Endpoints (ISS7 and UAS7/mUAS7)

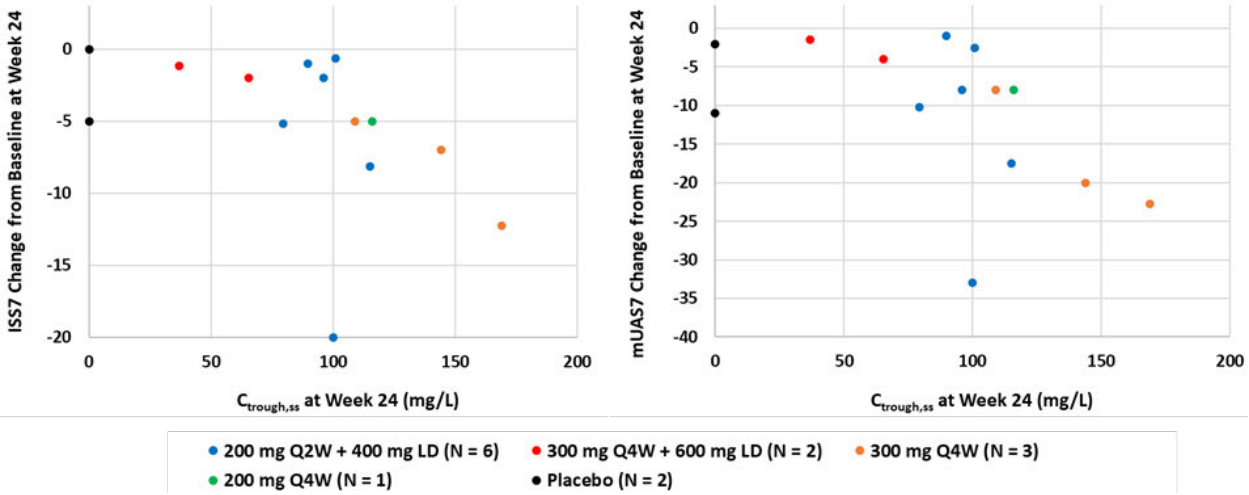
Descriptive efficacy ER analyses were conducted according to dupilumab trough concentrations observed in Studies PKM16982, EFC16461-C, and EFC16461-A, including low (< median $C_{trough,ss}$) and high (≥ median $C_{trough,ss}$) PK sub-groups. For each clinical study, the key primary efficacy endpoint was the change from baseline in ISS7 at Week 24, while the key secondary efficacy endpoint was change from baseline in UAS7 (modified UAS7 [mUAS7] for children 2 to < 12 years of age) at Week 24. Refer to Section 8 for detailed discussion and assessment of the efficacy data submitted to support this application.

Scatter plots depicting the individual change from baseline in ISS7 and mUAS7 at Week 24 with the corresponding observed $C_{trough,ss}$ values in dupilumab-treated children 2 to < 12 years of age

with CSU are presented below in Figure 5. Additionally, summaries of the change from baseline in ISS7 and mUAS7 at Week 24 for placebo- and dupilumab-treated subjects (according to PK sub-group) are depicted below in Table 10 and Table 11, respectively.

For both ISS7 and mUAS7, there appeared to be a slight trend towards higher efficacy responses with increasing $C_{trough,ss}$ at Week 24 in children 2 to < 12 years of age with CSU. This aligns with previous findings from the ER analyses conducted in the adult and adolescent CSU population based on pooled data from studies EFC16461-C and EFC16461-A (Study CTS0083), in which a slight ER trend was observed for both key efficacy endpoints at Week 24 with a plateau near dupilumab exposure at Quartile 3 (median $C_{trough,ss}$ of 75.8 mg/L). However, a significant exposure-dependent response was not concluded based on the totality of available data due to the high degree of overlap across exposure quantiles in addition to the relatively flat exposure-efficacy relationship (Refer to BLA Multi-Disciplinary Review and Evaluation for sBLA 761055/S-051 dated April 16, 2025 [DARRTS Reference ID: 5572858]).

Figure 5: Scatter Plot of ISS7 (Left) and mUAS7 (Right) Change From Baseline at Week 24 vs. Observed Plasma $C_{trough,ss}$ in CSU Subjects (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b,c]



Source: Reviewer's analysis based on adpc.xpt and adsl.xpt (Studies PKM16982, EFC16461-C, and EFC16461-A), adqs.xpt (Study PKM16982), and aded.xpt (Studies EFC16461-C and EFC16461-A)

[a] Descriptive ER analyses include 14 out of 20 children 2 to < 12 years of age enrolled across Studies PKM16982, EFC16461-C, and EFC16461-A; a total of 6 dupilumab-treated subjects were excluded due to either early dose discontinuation and missing trough concentration at Week 24 (N = 3) or missing efficacy data at Week 24 (N = 3)

[b] One subject from Study PKM16982 (b) (6) had missing information for baseline ISS7 and mUAS7 scores. For the descriptive ER analysis, missing baseline values of ISS7 and mUAS7 for this subject were imputed with those observed on Day 1.

[c] Last efficacy data for placebo-treated patients were collected at Week 22

Abbreviations: ISS7: Itch Severity Score over 7 Days; mUAS7: Modified Urticaria Activity Score Over 7 Days; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; CSU: Chronic Spontaneous Urticaria; Q2W: Every 2 Weeks; LD: Loading Dose; N: Number of Subjects; Q4W: Every 4 Weeks; ER: Exposure-Response

Table 10: Change From Baseline in ISS7 by PK Sub-Group of Observed $C_{trough,ss}$ at Week 24 in Children 2 to < 12 Years of Age With CSU (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b]

Treatment Group PK Sub-group/Subject ID	Mean (SD) $C_{trough,ss}$ (mg/L)[c]	Baseline Body Weight (kg)[d]	Baseline Mean ISS7	Mean (SD) CFB in ISS7[e]
Dupilumab				
Low (< median; N = 6)	77.9 (23.6)	34.7	11.7	-5.23 (7.39)
High (≥ median; N = 6)	126 (25.7)	20.1	8.22	-6.35 (3.86)
Placebo[f]				
(b) (6)	0	37.8	21	0
	0	32.7	14	-5

Source: Reviewer's analysis based on adpc.xpt and adsl.xpt (Studies PKM16982, EFC16461-C, and EFC16461-A), adqs.xpt (Study PKM16982), and aded.xpt (Studies EFC16461-C and EFC16461-A)

[a] Descriptive ER analysis includes 14 out of 20 children 2 to < 12 years of age enrolled across Studies PKM16982, EFC16461-C, and EFC16461-A; a total of 6 dupilumab-treated subjects were excluded due to either early dose discontinuation and missing trough concentration at Week 24 (N = 3) or missing efficacy data at Week 24 (N = 3)

[b] One subject from Study PKM16982 (b) (6) had missing information for baseline ISS7 score. For the descriptive ER analysis, missing baseline ISS7 for this subject was imputed with the observed value on Day 1.

[c] Median dupilumab $C_{trough,ss}$ of 100 mg/L at Week 52 among subjects included in ER analyses

[d] Reported as median body weight (kg)

[e] Last efficacy data for placebo patients were collected at Week 22

[f] Since only two children 2 to < 12 years of age were treated with placebo, data for these subjects is reported individually

Abbreviations: ISS7: Itch Severity Score over 7 Days; PK: Pharmacokinetic; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; CSU: Chronic Spontaneous Urticaria; SE: Standard Deviation; CFB: Change from Baseline; N: Number of Subjects

Table 11: Change From Baseline in mUAS7 by PK Sub-Group of Observed $C_{trough,ss}$ at Week 24 in Children 2 to < 12 Years of Age With CSU (Studies PKM16982, EFC16461-C, and EFC16461-A)[a,b]

Treatment Group PK Sub-group/Subject ID	Mean (SD) $C_{trough,ss}$ (mg/L)[c]	Baseline Body Weight (kg)[d]	Baseline Mean mUAS7	Mean (SD) CFB in mUAS7[e,f]
Dupilumab				
Low (< median; N = 6)	77.9 (23.6)	34.7	20.6	-9.62 (12.0)
High (≥ median; N = 6)	126 (25.7)	20.1	16.9	-13.1 (8.06)
Placebo[g]				
(b) (6)	0	37.8	42	-2
	0	32.7	30	-11

Source: Reviewer's analysis based on adpc.xpt and adsl.xpt (Studies PKM16982, EFC16461-C, and EFC16461-A), adqs.xpt (Study PKM16982), and aded.xpt (Studies EFC16461-C and EFC16461-A)

[a] Descriptive ER analysis includes 14 out of 20 children 2 to < 12 years of age enrolled across Studies PKM16982, EFC16461-C, and EFC16461-A; a total of 6 dupilumab-treated subjects were excluded due to either early dose discontinuation and missing trough concentration at Week 24 (N = 3) or missing efficacy data at Week 24 (N = 3)

[b] One subject from Study PKM16982 (b) (6) had missing information for baseline mUAS7 score. For the descriptive ER analysis, missing baseline mUAS7 for this subject was imputed with the observed value on Day 1.

[c] Median dupilumab $C_{trough,ss}$ of 100 mg/L at Week 52 among subjects included in ER analyses

[d] Reported as median body weight (kg)

[e] One subject with missing baseline value of mUAS7 was imputed with mUAS7 value at Day 1

[f] Last efficacy data for placebo patients were collected at Week 22

[g] Since only two children 2 to < 12 years of age were treated with placebo, data for these subjects is reported individually

Abbreviations: mUAS7: Modified Urticaria Activity Score Over 7 Days; PK: Pharmacokinetic; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; CSU: Chronic Spontaneous Urticaria; SD: Standard Deviation; CFB: Change from Baseline; N: Number of Subjects

Of note, one of the two placebo-treated subjects experienced a similar change from baseline in both ISS7 and UAS7 compared to both the low and high dupilumab PK sub-groups. Additionally, the changes from baseline reported in children 2 to < 12 years of age for both ISS7 and UAS7

were generally lower compared to the adult and adolescent CSU population. However, it should be acknowledged that dupilumab-treated subjects in Studies EFC16461-C and EFC16461-A had higher mean baseline ISS7 (15.3 and 16.1, respectively) and UAS7 (28.6 and 31.9, respectively) compared to those of the children 2 to < 12 years of age enrolled in Study PKM16982, for which mean baseline ISS7 and mUAS7 were 10 and 19.4, respectively. Given this difference in baseline disease severity between the two patient populations, comparisons of efficacy and ER trends should be interpreted with caution. Overall, based on these considerations and due to the small sample size of children 2 to < 12 years of age, no definitive conclusions can be drawn regarding exposure-dependency of efficacy findings or treatment response in the pediatric CSU population. Notably, study PKM16982 was designed as a PK and safety study to support the extrapolation of efficacy and safety data to pediatric patients with CSU aged 2 to < 12 years.

Extrapolation Approach to Support Dosing in Children 2 to < 12 Years of Age With CSU

In accordance with the ICH Guidance for Industry *E11A Pediatric Extrapolation* (December 2024), the Applicant is proposing the extrapolation of clinical data from adults and adolescents with CSU to children 2 to < 12 years of age based on the following collective evidence and assumptions:

- Similarity of CSU disease pathogenesis, progression and clinical manifestation in pediatric patients 2 to < 12 years old when compared to adults and adolescents
- Similar treatment guidelines and response to interventions for CSU in pediatric and adult patients
- Well-characterized PK profile of dupilumab with similar ER relationships between pediatric and adult patients with AD, asthma, and EoE

Therefore, the Applicant contends that this extrapolation approach, in addition to data generated from clinical trials in adults and adolescents with CSU (Studies EFC16461-C and EFC16461-A) as well as the overall dupilumab clinical and safety data derived from pediatric patients with AD, asthma, and EoE, is sufficient to support the efficacy and safety of the proposed dosing in children 2 to < 12 years of age with CSU. Assessment of the clinical pharmacology data submitted to justify the extrapolation of efficacy (from adults and adolescents with CSU) and safety (from AD, asthma, and EoE patient populations) in support of the proposed dosing in pediatric subjects 2 to < 12 years of age is presented below. Refer to Section 2 for discussion of the acceptability of the Applicant's justification of disease similarity and expected response to treatment between adults/adolescents and children 2 to < 12 years of age with CSU.

Extrapolation of Efficacy From Adults and Adolescents With CSU

As discussed above, the systemic exposure of dupilumab in children 2 to < 12 years of age with CSU is generally comparable to or higher than that observed/simulated in adults and adolescents following administration of the proposed dosing regimens. Regarding PD effects, the observed median percent reduction from baseline in serum total IgE in dupilumab-treated children was within the range of that observed in the overall adult/adolescent CSU population.

Additionally, although a significant ER relationship for efficacy could not be concluded based on the limited available data, there appeared to be a slight trend towards increased reduction from baseline in ISS7/mUAS7 at Week 24 with increasing dupilumab exposure in children 2 to < 12 years of age, which aligns with observations in the adult/adolescent CSU population. Notably, this is consistent with previous findings in patients with asthma and AD, for which similar ER relationships for pediatric and adult subjects were also observed.

Based on the totality of available evidence, dupilumab concentrations in children 2 to < 12 years of age with CSU following SC administration at the proposed dosing regimens are similar to or greater than those in adults and are expected to be efficacious for the treatment of CSU. Therefore, extrapolation of efficacy is reasonable from a clinical pharmacology perspective.

Extrapolation of Safety From Children With AD, Asthma, and EoE

The Applicant seeks to leverage the observed safety data across other dupilumab-approved pediatric indications, including AD, asthma, and EoE, to support the safety of the proposed dosing in children 2 to < 12 years of age with CSU. Of note, the proposed age- and weight-based dosing regimens for children with CSU are identical to those currently approved and shown to be safe and effective for pediatric subjects 6 months of age and older with AD. The approved dosages in children 6 to < 12 years of age with asthma are also similar to those proposed for CSU, although the highest approved pediatric dosage in asthma is 200 mg Q2W for subjects weighing ≥ 30 kg, whereas the proposed dosing in children with CSU includes a higher dosage of 300 mg Q2W for those weighing ≥ 60 kg. Regarding EoE, the approved dosages are higher than those proposed for children with CSU. Specifically, EoE is approved for adults and pediatric subjects 1 year of age and older and weighing 15 to < 30 kg, 30 to < 40 kg, and ≥ 40 kg at dosages of 200 mg Q2W, 300 mg Q2W, and 300 mg once weekly, respectively.

A summary of observed steady-state dupilumab trough concentrations following SC administration in pediatric subjects less than 12 years of age with CSU, AD, asthma, and EoE is provided below in Table 12. Based on these data, the mean (SD) observed steady-state dupilumab trough concentrations in children 2 to < 12 years of age with CSU are comparable to and within the range of observed variability of those in pediatric subjects < 12 years of age with AD, asthma, and EoE who received equivalent age- and weight-tiered dupilumab dosing regimens. Regarding EoE, pediatric subjects weighing 15 to < 30 kg and receiving the approved dosage of 200 mg Q2W had a notably higher (~1.6-fold higher) exposure compared to children with CSU in the same weight band receiving the proposed dosing regimen of 300 mg Q4W with or without a loading dose.

Table 12: Comparison of Arithmetic Mean (SD) Observed Steady-State Dupilumab Exposures in Children < 12 Years of Age With CSU, AD, Asthma, and EoE

Population	Study ID	Dupilumab Dosing Regimen	N	Body Weight (kg)[a]	$C_{trough,ss}$ (mg/L)[b]
CSU	Pooled PKM16982, EFC16461-A, and EFC16461-C	200 mg Q2W + 400 mg LD (2 to < 12 years, 30 to < 60 kg)	9	37.8 (5.5)	80.9 (30.4)
		300 mg Q4W ± 600 mg LD (2 to < 12 years, 15 to < 30 kg)	5	21.7 (3.9)	105 (54.4)
		200 mg Q4W, no LD (2 to < 12 years, 5 to < 15 kg)	1	14.5	116
AD	R668-AD-1652[c]	200 mg Q2W + 400 mg LD (6 to < 12 years, ≥ 30 kg)	52	38.8 (7.6)	88.3 (34.1)
		300 mg Q4W + 600 mg LD (6 to < 12 years, < 30 kg)	57	23.9 (3.1)	98.7 (33.2)
	R668-AD-1539 Part B	300 mg Q4W, no LD (6 mos to < 6 years, 15 to < 30 kg)	51	19.2 (3.6)	110 (42.8)
		200 mg Q4W, no LD (6 mos to < 6 years, 5 to < 15 kg)	24	12.3 (1.6)	109 (50.8)
Asthma	EFC14153	200 mg Q2W, no LD (6 to < 12 years, > 30 kg)	161	39.8 (7.0)	87.6 (43.7)
		100 mg Q2W, no LD[d] (6 to < 12 years, ≤ 30 kg)	86	25.0 (3.4)	59.1 (27.7)
EoE	R668-EE-1877 Part A	300 mg Q2W, no LD (1 to < 12 years, 30 to < 60 kg)	12	37.0 (6.0)	157 (46.9)
		200 mg Q2W, no LD (1 to < 12 years, 30 to < 60 kg)	7	39.9 (5.8)	89.8 (29.7)
		200 mg Q2W, no LD (1 to < 12 years, 15 to < 30 kg)	15	21.6 (5.9)	173 (73.8)
		300 mg Q4W, no LD (1 to < 12 years, 15 to < 30 kg)	16	23.3 (3.9)	85.2 (29.6)
		200 mg Q4W, no LD (1 to < 12 years, 5 to < 15 kg)	3	13.1 (1.0)	81.4 (36.6)

Source: Adapted from Summary of Clinical Pharmacology Studies (Table 5, pg. 35); Reviewer's analysis based on adpc.xpt and adsl.xpt for Studies PKM16982, EFC16461-C, EFC16461-A, R668-AD-1652, R668-AD-1539 Part B, EFC14153, and R668-EE-1877 Part A

[a] Reported as mean (SD) body weight (kg) of PK population; Individual body weight reported if N ≤ 2

[b] Reported as mean (SD) observed $C_{trough,ss}$ at Week 16 (AD and EoE populations) and Week 24 (asthma and CSU populations); Individual trough concentration reported if N ≤ 2

[c] To permit accurate comparison to the pediatric CSU population, a total of 3 children with AD and body weight > 60 kg who were randomized to the 200 mg Q2W dosing arm in Study R668-AD-1652 were excluded from the calculation of observed $C_{trough,ss}$ at Week 16. Under the proposed pediatric dosing for CSU, children weighing 30 to < 60 kg will receive 200 mg Q2W, while subjects weighing > 60 kg will receive 300 mg Q2W.

[d] 100 mg dose strength was discontinued and the associated 100 mg Q2W posology was subsequently withdrawn.

Abbreviations: SD: Standard Deviation; CSU: Chronic Spontaneous Urticaria; AD: Atopic Dermatitis; EoE: Eosinophilic Esophagitis; N: Number of Subjects; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; Mos; Months; PK: Pharmacokinetic

Overall, these data collectively demonstrate PK similarity between children 2 to < 12 years of age with CSU as compared to that of other dupilumab-approved indications in pediatric subjects < 12 years of age, given administration of similar age- and weight-tired dosing. Based on these considerations, extrapolation of safety data derived from all approved dosing regimens for pediatric subjects weighing 5 to < 60 kg with AD and asthma to children 2 to < 12 years of age with CSU is reasonable from a clinical pharmacology perspective. Regarding EoE, safety cannot be extrapolated to support the proposed 200 mg Q4W dosage for pediatric

subjects with CSU (5 to < 15 kg), as dupilumab is not approved in subjects with EoE weighing < 15 kg. However, given both the similar pharmacokinetics demonstrated between the EoE and CSU pediatric populations as well as the higher recommended dosing regimens approved for pediatric subjects 1 year of age and older and weighing ≥ 15 kg with EoE compared to those proposed for children 2 to < 12 years of age with CSU, additional support for systemic safety can be derived from all approved EoE dosing regimens for subjects weighing 15 kg or more.

What is the Incidence of the Formation of ADAs and the Impact of Immunogenicity on Dupilumab Exposure, Efficacy, and Safety?

Plasma samples were collected at baseline and Weeks 12, 24, and 36 (12 weeks after last dose) for assessment of ADAs and NAbs to dupilumab in PKM16982, EFC16461-C, and EFC16461-A. The bioanalytical methods used to identify both ADAs and NAbs were previously reviewed during marketing applications for adult and adolescents with asthma and have been adequately validated (REGN668-AV-15153-VA-01V2 and REGN668-AV-13112-VA-01V2).

There were no positive ADA samples among any children 2 to < 12 years of age with CSU who received either placebo or dupilumab across Studies PKM16982, EFC16461-C, and EFC16461-A. As a result, no assessment of the potential impact of immunogenicity on dupilumab pharmacokinetics, safety, or efficacy in the pediatric CSU population can be made. In adults and adolescents with CSU, overall incidence of development of ADAs was low (5%) and despite the lower systemic exposure observed in ADA-positive relative to ADA-negative subjects, no apparent negative impact of ADA status on efficacy or safety was observed (Refer to BLA Multi-Disciplinary Reviews and Evaluations dated October 18, 2023 [DARRTS Reference ID: 5263308] and April 16, 2025 [DARRTS Reference ID: 5572858]).

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant submitted results from Study PKM16982 to support the expansion of the CSU indication to include pediatric patients aged 2 to <12 years of age via pediatric extrapolation (Table 13). The results from Study PKM16982 are the focus of this review.

Efficacy and safety studies conducted in adults, adolescents, and children aged 6 to < 12 years of age with CSU (CUPID A, B, and C) were reviewed in the sBLA 761055/S-051 Multi-disciplinary Review dated April 16, 2025. Five pediatric subjects aged 6 to <12 years old were enrolled in CUPID Studies A and C, with 3 receiving dupilumab and 2 receiving placebo. Relevant findings from the 5 pediatric participants 6 to <12 years of age enrolled in CUPID A and C will be discussed as indicated throughout the review.

Table 13: Listing of Clinical Trials Relevant to This sBLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Study PKM16982 NCT05526521	Phase 3, multicenter, single-arm, open-label	Weight/age-tiered SC dosing: • 200mg Q4W (no loading dose) for 5 to <15 kg • 300mg Q4W (no loading dose) for 15 to < 30kg, ages 2 to <6 years • 300mg Q4W with 600mg loading dose for 15 to <30 kg, ages 6 to <12 years • 200mg Q2W with 400mg loading dose for 30 to <60 kg • 300mg Q2W with 600mg loading dose for >60 kg	**Primary:** Serum concentration of dupilumab over time including Ctrough at Week 12 and Week 24 **Secondary:** Safety (TEAEs/SAEs), immunogenicity (ADA), HRQoL (C-DLQI, IDQOL), urticaria activity (mUAS7, ISS7, HSS7)	24-week treatment duration/ 12 week follow-up	15 subjects	Male and female subjects aged ≥2 to <12 years of age with CSU, who remain symptomatic despite H1-antihistamine treatment	10 centers in 3 countries: Canada, Japan, and United States

7.2. Review Strategy

The efficacy and safety review of dupilumab for the treatment of CSU in pediatric patients aged 2 to <12 years of age whose disease is not adequately controlled on H1 antihistamine therapy is based on Study PKM16982, an phase 3, single-arm, open-label PK and safety study in 15 pediatric subjects aged 2 to <12 years old, and data from 5 pediatric subjects aged 6 to <12 years old enrolled in EFC16461 Studies A and C. A detailed clinical pharmacology review is located in Section 6.2.

FDA medical officer, Anjeni Keswani, MD MSCI, analyzed data from Study PKM16982 using the Analysis Studio Toolbox (Office of Computational Science). The descriptive efficacy data is presented in Section 8.1.2. The safety results presented in Section 8.2.4 represent the clinical reviewer's own analyses.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. Study PKM16982

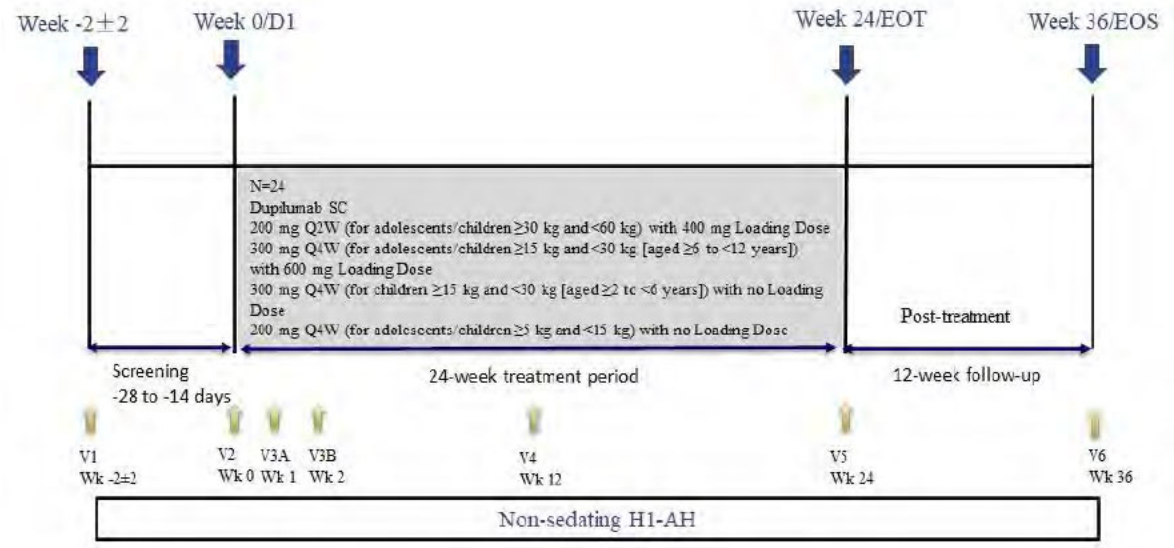
Trial Design

Study PKM16982 was a phase 3, multicenter, open-label, single-arm, 24-week treatment study designed to assess the pharmacokinetics and safety of dupilumab in subjects aged ≥2 to <12 years with CSU not adequately controlled with H1-antihistamine treatment.

As shown in Figure 6, the study consisted of three periods:

- Screening period of 2 to 4 weeks
- Treatment period of 24 weeks
- Post-treatment observational period of 12 weeks

Figure 6: PKM16982 Study Design



Abbreviations: D = day; EOT = End of Treatment; EOS = End of Study; H1-AH = H1-Antihistamines; N = number of participants; q2w = every 2 weeks; q4w = every 4 weeks; SC = subcutaneous; V = visit; Wk = week.

Subjects received dupilumab injections in a weight- and age-tiered dosing regimen for 24 weeks. The dosing regimens were as follows:

Table 14: Dosage in Subjects Aged 2 to 5 Years Old, Study PKM16982

Body Weight	Initial and Subsequent Dosage
5 to less than 15 kg	200 mg Q4WK
15 to less than 30 kg	300 mg Q4WK

Table 15: Dosage in Subjects Aged 6 to 11 Years Old, Study PKM16982

Body Weight	Initial Loading Dose	Subsequent Dosage
15 to less than 30 kg	600mg (two 300 mg injections)	300 mg Q4WK
30 to less than 60 kg	400mg (two 200 mg injections)	200 mg Q2WK
60 kg or more	600mg (two 300 mg injections)	300 mg Q2WK

No subjects in the 6 to 11 year age range weighed 60 kg or more were enrolled in Study PKM16982.

During the study, subjects continued their maintenance H1-antihistamine therapy.

For CSU exacerbations, a switch to another H1-antihistamine (up to 4-fold the licensed dose) was permitted. A short course of systemic corticosteroids could be given at the investigator's discretion.

Trial Location

Study PKM16982 included 10 centers that screened at least 1 subject in 3 countries: Canada, Japan, and the United States.

Study Population

Study PKM16982 enrolled participants aged ≥2 to <12 years with uncontrolled CSU.

Eligibility Criteria

Inclusion Criteria

1. Subject must be ≥2 years to <12 years of age, at the time of signing the informed consent.
2. Subjects who have history of a diagnosis of CSU prior to screening (V1) or symptoms consistent with a diagnosis of CSU for at least 3 months in the Investigator's opinion.
3. Subjects with CSU (characterized by recurrent itchy wheals with or without angioedema for >6 weeks) who remain symptomatic at the time of screening despite regular H1-antihistamine treatment.
4. Body weight within ≥5 kg to <60 kg.
5. For female subjects:
    - Contraceptive use by female subjects should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
    - A female subject is eligible to participate if she is not pregnant, or breastfeeding, and at least 1 of the following conditions applies:
        - Is not a woman of childbearing potential OR
        - Is post-menarche and agrees to use a contraceptive method that is highly effective, with a failure rate of <1% during the intervention period and for at least 12 weeks after the last dose of study intervention. A post-menarche female subject must have a negative highly sensitive pregnancy test on Day 1 before the first dose of study intervention. If a urine test cannot be confirmed as negative, a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
6. Subject's legally authorized representative capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and protocol. Subjects ≥6 years of age to <12 years of age as determined by the institutional review board/independent ethics committee and in accordance with the local regulations and requirements must provide written informed assent, and the subject's legally authorized representative must provide written informed consent.
7. Subject/parent(s)/caregiver(s)/subject's legally authorized representative, as appropriate, willing and able to comply with study visits and related procedures.
8. Subject/parent(s)/caregiver(s)/subject's legally authorized representative, as appropriate, must be able to understand and complete study-related questionnaires.

Exclusion Criteria

1. Underlying etiology for chronic urticarias other than CSU. This includes, but is not limited to the following conditions:
   - Inducible urticaria: acute urticaria, solar, cholinergic, heat, aquagenic, vibratory angioedema, symptomatic dermographism, delayed pressure, or contact.
   - Diseases with possible symptoms of urticaria or angioedema: hereditary alpha tryptasemia, systemic lupus erythematosus, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.
2. Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.
3. Subjects with a concurrent diagnosis of chronic inducible cold urticaria.
4. Subjects with active atopic dermatitis.
5. Severe concomitant illness(es) that, in the Investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to subjects with short life expectancy, subjects with uncontrolled diabetes (glycosylated hemoglobin ≥9%), subjects with cardiovascular conditions (e.g., Class III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (e.g., subjects on dialysis), hepato-biliary conditions (e.g., Child-Pugh class B or C), neurological conditions (e.g., demyelinating diseases), autoimmune diseases (e.g., lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary, psychiatric, or lymphatic diseases.
6. Subjects with active tuberculosis or non-tuberculous mycobacterial infection, or a history of incompletely treated tuberculosis unless well documented by a specialist that the subject has been adequately treated and can start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist.
7. Diagnosed with, suspected of, or at high risk of endoparasitic infection, and/or use of antiparasitic drug within 2 weeks before V1 or during the screening period.
8. History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at V1.
9. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 2 weeks before V1 or during the screening period.
10. Known or suspected immunodeficiency, including history of invasive opportunistic infections (e.g., histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution, or otherwise recurrent infections of abnormal frequency or prolonged duration suggesting an immune compromised status, as judged by the Investigator.
11. Active malignancy or history of malignancy within 5 years before the baseline visit.
12. History of systemic hypersensitivity or anaphylaxis to dupilumab including any excipient.
13. Known or suspected alcohol and/or drug abuse.
14. Subject with any other medical or psychological condition including relevant laboratory or electrocardiogram abnormalities at screening that, in the opinion of the Investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk

to the study subject as a result of his/her participation in this clinical trial, may make subject's participation unreliable, or may interfere with study assessments.

15. Planned or anticipated major surgical procedure during the subject's participation in this study.
16. Subject who has taken biologic therapy (disease modifiers)/systemic immunosuppressant/immunomodulator within 4 weeks before V1 or 5 half-lives, whichever is longer.
17. Prior use of omalizumab.
18. Treatment with a live (attenuated) vaccine within 4 weeks before V1.
    - Subjects for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
    - Subjects who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.
19. Either intravenous immunoglobulin therapy and/or plasmapheresis within 4 weeks before V1.
20. Use of any prohibited medications and procedures during screening period or planned use during screening or study treatment period.
21. Current participation to any clinical trial of an investigational drug or device or participation within 3 months before the screening visit or 5 half-lives of the investigational compound, whichever is longer.
22. Participation in prior dupilumab clinical study or have been treated with commercially available dupilumab.
23. Subjects with any of the following result at V1:
    - Positive (or indeterminate) hepatitis B surface antigen or,
    - Positive total hepatitis B core antibody confirmed by positive hepatitis B virus DNA or,
    - Positive hepatitis C virus antibodies confirmed by positive hepatitis C virus RNA.
24. Subjects are non-compliant with completion of e-diary by completing entries on less than 4 days out of 7 days immediately preceding the baseline visit (Visit 2).
25. Individuals accommodated in an institution because of regulatory or legal order; prisoners or subjects who are legally institutionalized.
26. Subject not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or subjects potentially at risk of noncompliance to study procedures.
27. Subject's legally authorized representative(s) are employees of the clinical study center or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.
28. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.
29. Any country-related specific regulation that would prevent the subject from entering the study.

Study Endpoints

Primary Endpoint

The primary endpoint for Study PKM16982 was:

- Concentration of dupilumab in serum over time including Ctrough at Week 12 and Week 24

Secondary Endpoints

The secondary endpoints were:

- Safety and tolerability assessments: Incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs)
- Incidence of ADA to dupilumab over time
- Change from baseline in Children's Dermatology Life Quality Index (C-DLQI) in children from 4 to less than 12 years of age at Week 24
- Change from baseline in Infant's Dermatitis Quality of Life Index (IDQOL) in children from 2 to less than 4 years of age at Week 24
- Change from baseline in mUAS7 at Week 24
- Change from baseline in the ISS7 at Week 24
- Change from baseline in the Hive Severity Score over 7 days (HSS7) at Week 24

Children's Dermatology Life Quality Index

The C-DLQI is a validated 10-item questionnaire measuring the impact of skin disease on the quality of life for children aged 4 to <16 (Figure 14). It covers the previous 7 days, assessing areas like symptoms, leisure, school, and relationships. Responses are on a 4-point scale (0-3), yielding a total score from 0 to 30, with higher scores indicating poorer quality of life.

Infants' Dermatitis Quality of Life Index

The IDQOL is a validated, caregiver-completed questionnaire for children aged 2 to <4 (Figure 15). It contains 11 questions covering the previous 7 days: ten 4-point Likert scale questions on quality of life and one 5-point Likert scale question on dermatitis severity. The total score from the quality-of-life questions ranges from 0 to 30, with higher scores indicating poorer quality of life.

Modified Urticaria Activity Score

The mUAS7 is an adaptation of the standard Urticaria Activity Score for children under 12, accounting for their smaller body surface area. It is the sum of daily scores from its two components: the Itch Severity Score and the Hive Severity Score, which are used to calculate the ISS7 and HSS7 below, respectively. While the Itch Severity Score component is unchanged from the adult scale (0-3), the Hive Severity Score component uses lower wheal count thresholds: 0 (absent), 1 (mild: 1 to <10 wheals/24h), 2 (moderate: 10 to 30

wheals/24h), and 3 (intense: >30 wheals/24h). Daily modified UAS scores (0-6) are summed over 7 days for a total mUAS7 score of 0 to 42, where higher scores indicate more severe disease. The tool was completed by the child or caregiver for subjects ≥4 years old and by the caregiver for subjects <4 years old.

Itch Severity Score

The ISS7 is the sum of daily scores recorded over a 7-day period. Subjects rate their itch severity daily on a scale from 0 (none) to 3 (intense). The total ISS7 score ranges from 0 to 21, with higher scores indicating greater itch severity.

Hive Severity Score

The HSS7 is the sum of daily scores recorded over a 7-day period. Subjects rate their hive severity daily on a scale from 0 (absent) to 3 (intense). For the modified version, "intense" is defined as >30 wheals/24 hours. The total HSS7 score ranges from 0 to 21, with higher scores indicating greater hive severity.

Statistical Analysis Plan

The statistical analysis plan was finalized before the database lock. All efficacy endpoints were analyzed descriptively. No formal hypothesis testing was planned for efficacy outcomes.

Protocol Amendments

One protocol amendment (Amended protocol 01, dated 31 May 2023) was implemented during the study. This amendment removed the inclusion of patients with CICU following the demonstration of lack of efficacy in adults with CICU in Study EFC16720. The amendment also modified the PK sampling schedule to increase flexibility and reduce subject burden. Due to a slow recruitment rate, enrollment was stopped at 15 subjects as this was deemed adequate for PK characterization when supplemented with data from other studies.

8.1.2. Study Results

Compliance With Good Clinical Practices

The study was performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice, and all applicable laws, rules, and regulations.

Financial Disclosure

See Appendix 15.2. There were no reported financial conflicts of interest that would be likely to influence study integrity.

Patient Disposition

A total of 15 subjects were enrolled and exposed to the dupilumab in Study PKM16982. Of these, 14 (93%) completed the 24-week treatment period. One subject (7%) withdrew consent due to "inconvenience of injection."

Protocol Violations/Deviations

No critical protocol deviations were reported. Major protocol deviations were reported in 8 (53%) subjects. The most frequent major deviations were:

- Planned PK sample not performed (4 subjects, 27%)
- Informed consent process deviation (3 subjects, 20%)
- Use of prohibited prior biologic/immunosuppressant therapy (2 subjects, 13%)
- Use of prohibited concomitant therapy (2 subjects, 13%)

Table of Demographic Characteristics

Of the 15 subjects enrolled in Study PKM16982, the mean age was 6.7 years, 73% were female, and 60% were White. The mean baseline body weight was 28.9 kg.

Table 16: Demographic Characteristics, Study PKM16982

Demographic Parameters	**Treatment Group** (N=15) n (%)
Sex	
Male	4 (27)
Female	11 (73)
Age	
Mean years (SD)	6.7 (2.9)
Median (years)	6.0
Min; max (years)	2; 11
Age Group	
≥2 to <6 years	4 (27)
≥6 to <12 years	11 (73)
Race	
White	9 (60)
Black or African American	1 (7)
Asian	4 (27)
Unknown	1 (7)
Ethnicity	
Hispanic or Latino	1 (7)
Not Hispanic or Latino	14 (93)

Demographic Parameters	**Treatment Group** (N=15) n (%)
Baseline Weight (kg)	
Mean (SD)	28.94 (9.89)
Median	30.80
Min ; Max	14.5 ; 44.7
Baseline Weight Group	
<15 kg	1 (7)
≥15 to <30 kg	6 (40)
≥30 to <60 kg	8 (53)
≥60 kg	0 (0)

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

Most subjects had a history of at least one allergic comorbidity, including allergic rhinitis (8 subjects, 53%), asthma (5 subjects, 33%), food allergy (4 subjects, 27%), allergic conjunctivitis (4 subjects, 27%), and atopic dermatitis (4 subjects, 27%)

Treatment Compliance and Concomitant Medications

Treatment compliance was 100% for all 15 subjects.

Regarding concomitant medications, all 15 subjects (100%) received concomitant systemic H1-antihistamines. Other frequently used concomitant medications included: ophthalmologic medications (80%), medications for obstructive airway disease (67%), antibacterials (47%), topical corticosteroids (40%), nasal sprays/preparations (40%) and systemic corticosteroids (33%).

Efficacy Results

Study PKM16982 demonstrated beneficial effects of dupilumab in children with CSU. Numerical improvements from baseline were observed in measures of quality of life, urticaria activity, itch, and hives from baseline through Week 24.

C-DLQI

C-DLQI data (total score range 0 to 30) were obtained for 12 subjects aged 4 to <12 years, with baseline scores ranging from 4 to 17 and an overall baseline mean (SD) of 9.5 (4.3).

Table 17: C-DLQI Results, Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=1)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=7)	All (N=11)
Baseline Mean (SD)	6.0	7.0	12.5 (4.9)	9.4 (4.6)	9.5 (4.3)
Week 24 Mean (SD)	3.0	1.0	2.0 (1.4)	2.0 (1.5)	2.0 (1.3)
Change from Baseline Mean (SD)	-3.0	-6.0	-10.5 (3.5)	-7.3 (4.3)	-7.4 (4.1)

Improvements in C-DLQI were observed across all dosing regimens at Week 24. The mean change from baseline was -3.0 in the dupilumab 200 mg Q4W group (N=1), -6.0 in the dupilumab 300 mg Q4W group (N=1), -10.5 (3.5) in the dupilumab 300 mg Q4W with 600 mg loading dose group (N=2), and -7.3 (4.3) in the dupilumab 200 mg Q2W with 400 mg loading dose group (N=7). The overall mean (SD) change from baseline was -7.4 (4.1).

IDQOL

IDQOL data (total score range 0 to 30) were obtained for 2 subjects aged 2 to <4 years at baseline and 1 subject at Week 24 in the dupilumab 300 mg Q4W without loading dose group. The mean IDQOL score at baseline was 4.0. The subject who completed 24 weeks of treatment had a baseline score of 6.0 and a change of -3.0 at Week 24, indicating improvement in quality of life.

mUAS7

Baseline mUAS7 data (total score range 0 to 42) were obtained for 14 subjects, with scores ranging from 1 to 32 and an overall baseline mean (SD) of 19.4 (10.4).

Table 18: mUAS7 Results, Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=2)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=5)	All (N=10)
Baseline Mean (SD)	14.0	18.3 (14.1)	21.3 (14.5)	20.1 (10.4)	19.4 (10.4)
Week 24 Mean (SD)	6.0	2.9 (5.1)	18.5 (16.3)	7.0 (7.1)	7.9 (9.1)
Change from Baseline Mean (SD)	-8.0	-21.4 (1.9)	-2.8 (1.8)	-7.8 (6.6)	-9.5 (8.0)

At Week 24, improvements in urticaria activity were observed across all dosing regimens. The mean change from baseline was -8.0 in the dupilumab 200 mg Q4W group (N=1), -21.4 (1.9) in the dupilumab 300 mg Q4W group (N=2), -2.8 (1.8) in the dupilumab 300 mg Q4W with 600 mg loading dose group (N=2), and -7.8 (6.6) in the dupilumab 200 mg Q2W with 400 mg loading dose group (N=5). The overall mean (SD) change from baseline was -9.5 (8.0).

ISS7

Baseline ISS7 data (total score range 0 to 21) were obtained for 14 subjects, with scores ranging from 1 to 18 and an overall baseline mean (SD) of 10.0 (5.3).

Table 19: ISS7 Results, Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=2)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=5)	All (N=10)
Baseline Mean (SD)	7.0	8.9 (7.8)	12.1 (4.4)	10.2 (5.4)	10.0 (5.3)
Week 24 Mean (SD)	2.0	1.8 (3.0)	10.5 (4.9)	4.2 (4.3)	4.5 (4.7)
Change from Baseline Mean (SD)	-5.0	-9.6 (3.7)	-1.6 (0.6)	-3.4 (3.2)	-4.4 (3.8)

At Week 24, improvements in itch severity were observed across all dosing regimens. The mean change from baseline was -5.0 in the dupilumab 200 mg Q4W group (N=1), -9.6 (3.7) in the dupilumab 300 mg Q4W group (N=2), -1.6 (0.6) in the dupilumab 300 mg Q4W with 600 mg loading dose group (N=2), and -3.4 (3.2) in the dupilumab 200 mg Q2W with 400 mg loading dose group (N=5). The overall mean (SD) change from baseline was -4.4 (3.8).

HSS7

Baseline HSS7 data (total score range 0 to 21) were obtained for 14 subjects, with scores ranging from 0 to 16 and an overall baseline mean (SD) of 9.5 (5.5).

Table 20: HSS7 Results, Study PKM16982

	200 mg Q4W (N=1)	300 mg Q4W (N=2)	300 mg Q4W, 600 mg LD (N=2)	200 mg Q2W, 400 mg LD (N=5)	All (N=10)
Baseline Mean (SD)	7.0	9.4 (7.1)	9.2 (10.1)	9.9 (5.1)	9.5 (5.5)
Week 24 Mean (SD)	4.0	1.2 (2.0)	8.0 (11.3)	2.8 (2.9)	3.4 (4.8)
Change from Baseline Mean (SD)	-3.0	-11.8 (1.8)	-1.2 (1.2)	-4.4 (3.6)	-5.1 (4.5)

At Week 24, improvements in hive severity were observed across all dosing regimens. The mean change from baseline was -3.0 in the dupilumab 200 mg Q4W group (N=1), -11.8 (1.8) in the dupilumab 300 mg Q4W group (N=2), -1.2 (1.2) in the dupilumab 300 mg Q4W with 600 mg loading dose group (N=2), and -4.4 (3.6) in the dupilumab 200 mg Q2W with 400 mg loading dose group (N=5). The overall mean (SD) change from baseline was -5.1 (4.5).

The effects of dupilumab on health-related quality of life and CSU activity and severity measures (mUAS7, ISS7, and HSS7) in children 2 to <12 years of age were generally consistent with results observed in adults and adolescents from EFC16461 CUPID Studies A and C.

Reviewer comment: The descriptive efficacy results from Study PKM16982 in pediatric subjects aged 2 to <12 years old (N=14) demonstrated modest improvements in CSU symptoms at Week

24, with considerable variability across the small dosing groups. When compared to the pivotal CUPID Studies A and C in adults and adolescents, the pediatric study data showed numerically smaller treatment effects for ISS7 and HHS7. However, there are significant limitations to cross-study comparisons of efficacy between Study PKM16982 and CUPID Studies A and C as Study PKM16982 had a limited sample size of 14 pediatric subjects for efficacy assessments, no placebo control arm, and did not include formal statistical testing of treatment effects. CUPID Studies A and C were adequately powered to demonstrate statistically significant treatment effects whereas Study PKM16982 was designed as a PK/safety study with only descriptive efficacy data.

Data Quality and Integrity

There were no significant issues with data integrity that prohibited review or required further action.

8.1.3. CUPID Studies A and C

A total of 5 children aged 6 to < 12 years old were enrolled across the pivotal CUPID Studies A and C, with 3 children receiving dupilumab and 2 receiving placebo. In the dupilumab arm, one subject with severe urticaria at baseline achieved complete symptom resolution at Week 12 and had well-controlled urticaria (UAS7 >1 to <6) at Week 24, while the other 2 subjects discontinued the study due to lack of efficacy at Week 4 and 10, respectively. In the placebo arm, one subject with severe urticaria at baseline achieved complete symptom resolution at Week 24, while the other subject showed no improvement at Week 24. Due to the extremely small sample size, no statistical conclusions about efficacy could be drawn for the 6 to < 12 years old age group based on the CUPID studies (see sBLA 761055/S-051 Multi-Disciplinary Review, dated April 16, 2025, for details).

8.1.4. Integrated Assessment of Effectiveness

Study PKM16982 demonstrated beneficial effects of dupilumab across multiple endpoints in children with CSU, including improvements in quality of life measures (C-DLQI and IDQOL) and disease activity measures (mUAS7, ISS7, and HSS7) at Week 24. The descriptive effects on health-related quality of life and CSU severity measures in children aged 2 to <12 years of age were generally consistent with results observed in adults and adolescents from the pivotal CUPID Studies A and C, supporting the validity of the extrapolation approach.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review is based on the 15 subjects 6-11 years old enrolled in Study PKM 16982 and the 3 pediatric subjects aged 6 to 11 years old enrolled in the pivotal trials EFC16461 A and C who received dupilumab. This review was conducted by FDA medical officer, Anjeni Keswani MD MSCI, and employed the Office of Computational Science Analysis Studio to independently

analyze safety data in the safety population, defined as all subjects who were randomized and received at least one dose of dupilumab.

8.2.2. Review of the Safety Database

Overall Exposure

In study PKM16982, 15 subjects aged 6 to 11 years old were enrolled and 14 subjects (93%) were exposed to dupilumab for 24 weeks at the following doses:

- 200 mg Q4weeks: 1 subject
- 300 mg Q4weeks: 4 subjects
- 300 mg Q4weeks with 600mg loading dose: 2 subjects
- 200 mg Q2weeks with 400mg loading dose: 8 subjects

Of the 15 subjects, 14 (93%) completed the study period and 1 (7%) subject in the 300mg Q4W group withdrew at Week 4 due to "inconvenience of injection." There were no subject discontinuations due to adverse events (AEs) or poor compliance.

In EFC16461 Study A, 2 subjects aged 6 to 11 years old were enrolled and both were exposed to dupilumab 200mg Q2W with a loading dose of 400mg. Both subjects permanently discontinued dupilumab after Week 4 and Week 10 due to lack of efficacy.

In EFC16461 Study A, 3 subjects aged 6 to 11 years old was enrolled. One subject was exposed to dupilumab 200mg Q2W with a loading dose of 400mg for 24 weeks and completed the study period.

Adequacy of the Safety Database

As of March 28, 2025, 12,596 adult and pediatric subjects aged ≥6 months to <18 years were exposed to dupilumab across the overall clinical development program (per the Applicant's Development Safety Update Report submitted May 19, 2025).

Eighteen pediatric subjects aged 2 to < 12 years old and 195 adults and adolescent subjects were exposed to dupilumab in the development program for CSU. The pediatric CSU safety database is of limited value due to the small sample size and absence of a comparator arm. Thus, the safety assessment also takes into consideration the previous safety data collected in pediatric patients aged 2 to <12 years old for the approved indications of asthma, atopic dermatitis, and EoE. Therefore, the safety database for dupilumab for CSU in pediatric patients aged 2 to <12 years of age is adequate based on extrapolation from the from the extensive safety database from other pediatric development programs, with PK bridging (see Section 6.2).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this sBLA. The submission is appropriately indexed and complete to permit review.

Categorization of Adverse Events

The Applicant provided definitions of AEs and SAEs consistent with regulatory standards.

- An AE was defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention, which could include any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
- An SAE was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, or is a congenital anomaly/birth defect.

The Investigators assessed the intensity of each AE and SAE using three categories:

- Mild: easily tolerated, causing minimal discomfort and not interfering with everyday activities
- Moderate: causing sufficient discomfort and interfering with normal everyday activities
- Severe: preventing normal everyday activities

Adverse events of special interest (AESI) were prospectively identified based on the pharmacological properties and mechanism of action of dupilumab, requiring ongoing monitoring and immediate notification by the Investigator to the Applicant within 24 hours. These AESIs included anaphylactic reactions, systemic hypersensitivity reactions, helminthic infections, any severe conjunctivitis or blepharitis, keratitis, and clinically symptomatic eosinophilia or eosinophilia associated with clinical symptoms. Additional AESIs included pregnancy in a female subject, alanine aminotransferase (ALT) elevation >5 times the upper limit of normal in subjects with normal baseline ALT or >8 times the upper limit of normal in subjects with baseline ALT >2 times the upper limit of normal, and symptomatic overdose with either investigational or non-investigational medicinal products.

AEs were coded using the MedDRA dictionary version 27.1. The Applicant's coding of verbatim terms to preferred terms was appropriate.

Routine Clinical Tests

Routine clinical testing included hematology, serum chemistry, electrolytes, liver function tests, urinalysis and human chorionic gonadotropin pregnancy tests (for females of childbearing potential).

8.2.4. Safety Results

Deaths

There were no TEAEs leading to death reported in pediatric patients aged ≥2 to <12 years with CSU in Study PKM16982 or in the 3 dupilumab treated pediatric subjects aged 6 to < 12 years old included in EFC16461 Study A and Study C.

Serious Adverse Events

There were no treatment-emergent SAEs reported in pediatric patients aged ≥2 to <12 years with CSU in Study PKM16982 or in the 3 dupilumab treated pediatric subjects included in EFC16461 Study A and Study C.

Dropouts and/or Discontinuations Due to Adverse Effects

There were no TEAEs leading to permanent study intervention discontinuation reported in pediatric patients aged ≥2 to <12 years with CSU in Study PKM16982 or in the 3 dupilumab treated pediatric subjects included in EFC16461 Study A and Study C.

Significant Adverse Events

There were no adverse events classified as severe by intensity in the 15 pediatric subjects enrolled in Study PKM16982 or in the 3 dupilumab treated subjects in EFC16461 Study A and Study C.

Treatment Emergent Adverse Events and Adverse Reactions

Study PKM16982 (N=15)

The proportion of subjects who experienced at least one TEAE during the 24-week treatment period was 80% (12 subjects). Three subjects (20%) experienced 4 mild TEAEs deemed related to dupilumab (preferred terms of abdominal discomfort and diarrhea in one subject, insomnia in one subject and injection site reaction in one subject).

The most frequently reported TEAEs at the System Organ Class level (≥2 subjects overall) were:

- Infections and infestations: 9 subjects (60%)
- Gastrointestinal disorders: 4 subjects (27%)
- General disorders and administration site conditions: 2 subjects (13%)
- Respiratory, thoracic and mediastinal disorders: 2 subjects (13%)

At the preferred term level, TEAEs that occurred in more than 1 subject were:

- Viral upper respiratory tract infection: 4 subjects (27%)
- Influenza: 2 subjects (13%)
- Nasopharyngitis: 2 subjects (13%)
- Vomiting: 2 subjects (13%)

Treatment-Related TEAEs

Four nonserious TEAEs of mild intensity reported by 3 subjects were considered related to the investigational medicinal product by the Investigator:

- Abdominal discomfort (1 subject)
- Diarrhea (1 subject, same subject as abdominal discomfort)
- Insomnia (1 subject)
- Injection site reaction (1 subject)

EFC16461 Study A and Study C

There were no TEAEs reported in the 3 children who received dupilumab in these studies. In the placebo group, TEAEs of diarrhea and tonsillitis streptococcal were reported in 1 child; both events were assessed as nonserious, mild, and resolved.

Laboratory Findings

In the hematology assessments across the three studies, no children experienced hematological abnormalities that were classified as treatment-emergent SAEs or that led to permanent discontinuation of the study intervention.

In Study PKM16982, no subjects had clinically significant abnormalities for red blood cells, platelets, or coagulation parameters. Two subjects receiving dupilumab 200 mg Q2W with a loading dose of 400 mg developed a low white blood cell count, but these changes were not deemed clinically significant and were not reported as adverse events.

Similarly, in EFC16461 Study A and Study C, three hematologic abnormalities were noted: one child on dupilumab 200 mg Q2W had a low white blood cell count in Study A, while in Study C, one child on placebo had a high hematocrit and one child on dupilumab 300 mg Q2W had a high white blood cell count. None of these laboratory changes were considered clinically significant or reported as adverse events.

There were no clinically meaningful changes in renal function parameters, electrolytes, or liver function parameters in children across the three studies. No subjects had liver function abnormalities that met laboratory criteria for Hy's Law.

Vital Signs

There were no clinically meaningful findings in vital sign measurements. Vital sign measurements included systolic and diastolic blood pressure (mm Hg), respiratory rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg). There were no clinically meaningful changes over time in vital signs observed throughout the course of the study. There were no subjects with potentially clinically significant abnormalities for systolic and diastolic blood pressure, respiratory rate, and body temperature.

Immunogenicity

There were no positive ADA samples among children aged 2 to <12 years of age in studies PKM16982, EFC16461-C, and EFC16461-A. There was no impact on safety from immunogenicity in the studied pediatric CSU population (see Section 6.3).

8.2.5. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

There were no reported treatment-emergent AESIs, including anaphylactic reaction, systemic hypersensitivity reaction, helminthic infections, severe type of conjunctivitis or blepharitis, keratitis, clinically symptomatic eosinophilia, pregnancy, significant ALT elevation, or symptomatic overdose.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

No clinical outcome assessment analyses informed safety and tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

No subgroup analysis was performed due to the limited sample size and lack of a comparator group.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in subjects enrolled in study PKM16982 during the study period.

Human Reproduction and Pregnancy

No pregnancies in female subjects were reported in Study PKM16982.

Pediatrics and Assessment of Effects on Growth

Effects on growth were not evaluated in Study PKM16982.

Overdose, Drug Abuse Potential, Withdrawal, and **Rebound**

In Study PKM16982, overdose was defined as any dose of dupilumab greater than twice the intended dose during an interval of less than 11 days (for the Q2W regimen) or 25 days (for the Q4W regimen). One subject who received dupilumab 200mg Q2W with a 400mg loading dose had an accidental overdose (8 days between 2 injections) which was asymptomatic. No safety event was reported for this case of overdose.

There is no known abuse potential for dupilumab. Withdrawal or rebound effects were not formally evaluated in Study PKM16982; however, no concerning signals for withdrawal or rebound were identified.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

No new safety findings were identified in the post-marketing data in the Development Safety Update Report covering the period from March 29, 2024 to March 28, 2025.

On April 16, 2026, the United States Prescribing Information was revised to include the addition impairment including blindness associated with conjunctivitis, keratitis, or blepharitis and the potential resultant need for discontinuation of dupilumab and/or surgical intervention in Section 5.2 of Warnings and Precautions as well as inclusion of Ocular Disorders: ectropion, cicatricial disease/cicatricial ectropion, punctal stenosis/canalicular obstruction, symblepharon, and temporary or ongoing vision loss, including visual impairment and blindness associated with conjunctivitis, keratitis, or blepharitis to Section 6.2 Postmarketing Experience.

8.2.10. Integrated Assessment of Safety

Dupilumab is an approved biologic with a well characterized safety profile in children and adults. No new safety signals were identified in Study PKM16982, and the AEs observed were consistent with the labeling for dupilumab. Overall, the safety profile for dupilumab is favorable for the proposed indication.

8.3. Conclusions and Recommendations

Efficacy and safety of dupilumab for CSU in pediatric patients aged 2 to <12 years old is supported through pediatric extrapolation from adult and adolescent CSU populations, based on disease similarity, comparable clinical pharmacology data, and corroborative findings from Study PKM16982. CSU demonstrates consistent pathophysiology across age groups, characterized by mast cell and basophil activation with histamine release, a high prevalence of autoantibody-mediated autoreactivity, and comparable clinical presentations and quality-of-life impacts. Clinical pharmacology data demonstrate that steady-state dupilumab exposure at proposed pediatric dosing regimens is comparable to or exceeds that in adults and adolescents with CSU, supporting efficacy extrapolation, while mean trough concentrations align with those

in pediatric patients across other approved dupilumab indications, supporting safety extrapolation. Descriptive efficacy data from Study PKM16982 showed improvements in quality-of-life and disease activity measures consistent with pivotal adult and adolescent trials, and safety data demonstrated dupilumab was well-tolerated without new safety signals. The review team recommends approval of dupilumab for children from ages 2 to < 12 years old with H1-antihistamine-refractory CSU.

9 Advisory Committee Meeting and Other External Consultations

The review team did not identify any major clinical trial design, conduct, efficacy, safety, or benefit/risk assessment issues that would benefit from discussion at an Advisory Committee meeting. Therefore, no Advisory Committee meeting was requested.

10 Pediatrics

Agreed Initial Pediatric Study Plan

The Applicant submitted their initial pediatric study plan (iPSP) on December 17, 2019. The Division sent a written response to the Applicant on March 12, 2020, requesting revisions to the iPSP, specifically inclusion of children down to the age of 6 years in Phase 3 studies, revision of the reason for waiver for the <2 years of age group to state that the treatment fails to represent a meaningful therapeutic benefit over available therapies for pediatric patients and is unlikely to be used in a substantial number of children <2 years of age, and revision of the timeline for start of the open-label PK and safety study in subjects aged >2 to <12 years old (PKM16982). The iPSP was agreed to on June 15, 2020 with inclusion of pediatric subjects aged >6 to <18 years old in the pivotal studies, deferral of pediatric studies in the >2 to <6 year old population until studies enrolling individuals >6 years of age are completed, and waiver of pediatric studies in the <2 year old population.

Amended iPSP

When the Applicant submitted sBLA 761055/S-051 for the treatment of inadequately controlled CSU in adult and pediatric subjects aged 12 years and older, they proposed an amended iPSP for a deferral in the age groups >2 to <12 years of age as the PK and safety study was not complete at the time of initial BLA submission for treatment of CSU in adults and adolescents. The Division agreed to the amended iPSP.

Pediatric Efficacy and Safety Overview

The Applicant has fulfilled PREA-PMR 4843-1 by submission of this supplement (074) to BLA 761055 to extend dupilumab's indication for CSU inadequately controlled by H1 antihistamines to include pediatric patients aged 2 to <12 years. Approval of dupilumab for CSU in pediatric

patients aged 2 to <12 years old is supported through pediatric extrapolation from adult and adolescent CSU populations, based on disease similarity, comparable clinical pharmacology data, and descriptive efficacy and safety findings from Study PKM16982 and 3 pediatric subjects enrolled in the pivotal adult and adolescent trials.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE	DUPIXENT is indicated for the treatment of adult and pediatric patients aged 2 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment. *The indication statement was expanded to include pediatric patients aged 2 to 11 years.*
2 DOSAGE AND ADMINISTRATION	The recommended dosage of DUPIXENT for pediatric patients is based on weight and the recommended dosage was revised to provide dosage for two groups of pediatric patients based on age and weight. Pediatric patients aged 2 to 5 years do not require a loading dose, and the dosage is based on weight in these patients. Dosage for pediatric patients aged 6 to 17 years is based on weight with an initial loading dose followed by subsequent dosage for maintenance.
6 ADVERSE REACTIONS	In the *Clinical Trials Experience* subsection, the adverse reactions of DUPIXENT in patients with CSU were separated by age. The common adverse reactions were based on pooled safety data among adult and pediatric patients aged 12 years and older. Safety of DUPIXENT in pediatric patients aged 2 to 11 years was assessed in patients who received DUPIXENT based on weight, and no new safety signals were observed.

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	**8.4 Pediatric Use** The Pediatric Use statement and the evidence supporting the use of DUPIXENT was revised to reflect the new pediatric population, pediatric patients aged 2 to 11 years. The use of DUPIXENT expanded to pediatric patients aged 2 years and older supported by clinical trials in adults and pediatric patients aged 12 years older with additional pharmacokinetic data in pediatric patients aged 2 years and older and safety data in pediatric patients in other indications.
12 CLINICAL PHARMACOLOGY	**12.3 Pharmacokinetics** Updated this subsection to include PK data among pediatric patients aged 2 to 11 years with CSU.

12 Risk Evaluation and Mitigation Strategies

The Division did not find any safety issues that require a Risk Evaluation and Mitigation Strategy. Safety findings present in the clinical studies can be adequately addressed through labeling and will be followed with routine pharmacovigilance.

13 Postmarketing Requirements and Commitment

The Applicant has fulfilled PREA-PMR 4843-1 by submission of this supplement sBLA 761055/S-074 to extend dupilumab's indication for CSU inadequately controlled by H1 antihistamines to include pediatric patients aged 2 to <12 years.

There are no new safety or efficacy issues identified in this review that warrant a postmarketing requirement or postmarketing commitment.

14 Associate Director for Therapeutic Review (Clinical) Comments

Dupilumab was approved for the treatment of CSU in adults and adolescents ≥12 years inadequately controlled by H1 antihistamines on April 17, 2025. Regeneron Pharmaceuticals submitted efficacy supplement sBLA 761055/S-074 to extend dupilumab's indication for CSU to include pediatric patients aged 2 to <12 years. This submission fulfills PREA-PMR 4843-1 and proposes age- and weight-tiered dosing regimens that mirror those currently approved for atopic dermatitis in patients ≥6 months of age. The application employs a scientifically rigorous

pediatric extrapolation strategy supported by a single-arm Phase 3 PK and safety study (PKM16982) enrolling 15 children aged 2 to <12 years, along with population pharmacokinetic modeling and exposure-response analyses.

The basis for demonstration of substantial evidence of effectiveness through pediatric extrapolation rests on disease similarity across age groups, robust clinical pharmacology support, and consistent treatment effects across age groups. CSU demonstrates comparable pathophysiology, clinical presentation, and quality of life impact in children, adolescents, and adults. Pathophysiology is consistent across age groups, involving mast cell and basophil activation leading to release of mediators including histamine. The underlying causes are similar, including autoreactivity mediated by anti-IgE and anti-FcεRI autoantibodies, with studies demonstrating comparable prevalence of anti-FcεRI autoantibodies and positive autologous serum skin testing in adults and children. While children demonstrate a higher incidence of atopic comorbidities and a lower incidence of angioedema compared to adults, the core disease manifestations remain consistent. CSU is generally self-limited across all age groups with an average disease duration of 2-5 years, though children demonstrate a shorter time to remission with spontaneous remission. Children with CSU experience substantial impairment in quality of life comparable to other chronic childhood conditions, such as psoriasis and asthma, with specific impacts including disrupted sleep, decreased school performance, and a higher prevalence of mood and anxiety disorders compared to healthy controls.

The clinical pharmacology assessment demonstrated that steady-state dupilumab exposures in children aged 2 to <12 years receiving the proposed dosing regimens were generally comparable to or higher than those observed in adults and adolescents with CSU, with body weight identified as the primary determinant of exposure variability. Pharmacodynamic responses assessed through serum total IgE changes were comparable between pediatric CSU patients and both adult/adolescent CSU populations and pediatric asthma patients, supporting mechanistic consistency across age groups and indications. Descriptive exposure-response analyses suggested trends consistent with findings in adults and adolescents and mean steady-state trough concentrations in pediatric CSU patients fell within the range observed across other approved pediatric indications, supporting cross-indication safety extrapolation. Descriptive efficacy data from Study PKM16982 demonstrated improvements in quality of life measures and measures of CSU disease activity in children aged 2 to <12 years that were generally consistent with results observed in the pivotal studies for CSU in adults and adolescents.

The safety profile for CSU in pediatric patients aged 2 to <12 years was consistent with the known safety profile of dupilumab observed across multiple approved indications. No new safety signals were identified in the pediatric CSU population. The extensive pediatric safety database across multiple indications, combined with comparable drug exposures in the target population and mean steady-state trough concentrations similar to those observed in pediatric subjects across other approved dupilumab indications, provides substantial reassurance regarding the safety profile and supports cross-indication extrapolation.

This application addresses a significant unmet medical need, as approximately 10-25% of pediatric patients with CSU remain refractory to antihistamine therapy and no biologic therapies are currently approved for children younger than 12 years. While the limited enrollment of pediatric subjects (18 treated with dupilumab across all CSU studies) represents an inherent limitation, the totality of evidence—including comparable or higher exposures, consistent pharmacodynamic responses, similar exposure-efficacy trends, and alignment with established pediatric safety profiles—provides adequate support for the proposed indication expansion. Based on the totality of evidence, including disease similarity, clinical pharmacology data supporting the dosing strategy, descriptive efficacy and safety data, and the established benefit-risk profile for CSU in adults and adolescents, the benefit-risk assessment is favorable for dupilumab for the treatment of pediatric patients aged 2 to <12 years with CSU inadequately controlled with H1-antihistamine treatment. I agree with the review team's recommendation of **approval** of this supplemental application.

15 Appendices

15.1. References

15.1.1. Literature

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15.1.2. Guidances for Industry

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15.1.3. Other

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PKM16982

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 41		
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: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ Not applicable	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Population PK Analysis

15.3.1.1. Executive Summary

Overview

In this application, the Applicant submitted a population PK analysis study report (Study POH1231) entitled "*Population Pharmacokinetic and Descriptive Exposure-Response Analysis of Dupilumab in Children ≥ 2 to < 12 Years of Age with Chronic Spontaneous Urticaria.*" Per the Applicant, the primary objectives of these population PK analyses were the following:

1. Apply a previously developed dupilumab population PK model (Study POH0766) to PK data in children 2 to < 12 years of age with CSU and assess its ability to characterize dupilumab pharmacokinetics in this population
2. Generate individual dupilumab post hoc PK exposures in children 2 to < 12 years of age with CSU and assess the influence of intrinsic and extrinsic factors on dupilumab pharmacokinetics in this population
3. Conduct descriptive ER analyses for efficacy endpoints in children 2 to < 12 years of age with CSU

No new population PK models were developed for the current submission. Instead, dupilumab pharmacokinetics in children 2 to < 12 years of age with CSU were characterized through the application of a previously developed pediatric asthma population PK model (Study POH0776), which was a two-compartment model with first order absorption, parallel linear and nonlinear (i.e., Michaelis-Menten [M-M]) elimination, and time-varying body weight included as a significant covariate on central compartment volume of distribution (V2), maximum target-mediated rate of elimination (V_{max}), and elimination rate constant (K_e).

Adequacy and Application of Population PK Analyses

The asthma pediatric population PK model (Study POH0776) was applied to sparse PK data for children 2 to < 12 years of age with CSU from Studies PKM16982, EFC16461-C, and EFC16461-A through a MAP Bayesian approach. All parameter estimates were fixed to the values of the asthma pediatric population PK model in order to generate individual post hoc dupilumab PK exposure parameters for children 2 to < 12 years of age with CSU. The adequacy of the model to describe dupilumab pharmacokinetics in the pediatric CSU population was assessed via standard diagnostic criteria, including comparison of model-predicted and observed steady-state exposures, goodness-of-fit plots, quality criteria, and visual predictive checks.

Following confirmation of model suitability, the Applicant assessed the potential impact of selected intrinsic and extrinsic factors of interest on dupilumab pharmacokinetics in the pediatric CSU patient population. Additionally, typical dupilumab PK profiles and predicted PK parameters with descriptive statistics were simulated for children 2 to < 12 years of age with

CSU for comparison with adults and adolescents 12 years of age and older. Due to the relatively small sample size of children enrolled across Studies PKM16982, EFC16461-C, and EFC16461-A, simulations to support the proposed pediatric dosing regimens were conducted based on a virtual pediatric population obtained from the NHANES database.

Results of Population PK Analyses

The asthma pediatric population PK model (Study POH0776) was determined to be adequate to characterize the pharmacokinetics of dupilumab in children 2 to < 12 years of age with CSU. Based on PK simulations, the predicted dupilumab exposure in children 2 to < 12 years of age with CSU at the proposed age- and weight-based dosing regimens is generally comparable to or higher than that observed/predicted in adults and adolescents receiving the approved dosage of 300 mg Q2W. Body weight was identified at the main source of variability affecting dupilumab pharmacokinetics, which is consistent with previous findings across other patient populations. Other covariates, including age, race, ethnicity, sex, and baseline disease severity, did not appear to have a clinically meaningful impact on dupilumab pharmacokinetics based on post hoc assessment of the limited available data.

Pharmacometrics Review Conclusions

In general, the Applicant's population PK analyses are acceptable for the purpose of estimating the pharmacokinetics and exposure parameters of dupilumab in children 2 to < 12 years of age with CSU. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. The results of the population PK analyses were used to support the proposed dosage regimens in children 2 to < 12 years of age based on the extrapolation of (1) efficacy data in adults and adolescents with CSU and (2) safety data in pediatric subjects with asthma, AD, and EoE. Refer to Section 6.3.1 for additional discussion of overall acceptability of the proposed pediatric extrapolation approach and dupilumab dosing regimens, along with assessment of descriptive ER analyses for efficacy and safety.

15.3.1.2. Population PK Assessment Summary

Overall Population PK Modeling and Simulation Approach

The Applicant's population PK analyses were performed based on sparse PK data in 18 children 2 to < 12 years of age with CSU derived from three clinical trials, including PKM16982 (N = 15), EFC16461-A (N = 2), and EFC16461-C (N = 1). The initial dataset included a total of 77 dupilumab concentrations across 18 study participants. After exclusion of pre- and post-dose below limit of quantitation records, the final dataset included a total of 50 dupilumab concentrations obtained from 18 subjects. Observed PK data derived from Studies PKM16982, EFC16461-C, and EFC16461-A were not included in the asthma pediatric population PK model development but were evaluated through a MAP Bayesian approach for external validation.

Summary of Population PK Models Utilized in the Current Application

The asthma pediatric population PK model (Study POH0766) was a two-compartment model with first order absorption, parallel linear and nonlinear (i.e., M-M) elimination, and time-varying body weight as a covariate on V2, V_{max}, and K_e. The model was developed with pooled data from two phase 3 studies in 377 children 6 to < 12 years of age with asthma (body weight ranged from 16.4 kg to 67.2 kg). The typical values of absorption rate constant, K_e and V2 of dupilumab were 0.252 day^{-1}, 0.0564 day^{-1}, and 2.35 L, respectively. For the M-M elimination, the typical values of V_{max} and K_m were 1.48 mg/L/day and 2.52 mg/L, respectively. Refer to the NDA/BLA Multi-Disciplinary Review and Evaluation dated October 21, 2021 for additional details pertaining to the development, validation, and application of this model to support approval of dupilumab as add-on maintenance treatment of moderate-to-severe asthma in pediatric subjects 6 years of age and older under sBLA 761055/S-031 DARRTS Reference ID: 4875558).

Major Population PK Model Outputs

Details of the Applicant's population PK analyses are summarized below in Table 21.

Post hoc patient-level dupilumab exposure metrics (steady-state area under the concentration-time curve, $C_{max,ss}$, $C_{trough,ss}$) were derived for children 2 to < 12 years of age with CSU for determination of model adequacy and for subsequent comparison as a function of intrinsic/extrinsic factors. Covariates of interest which were evaluated included the following: age, body weight, sex, race, ethnicity, baseline albumin, and baseline disease characteristics, including ISS7, UAS7, and HSS7 scores (Table 22, Table 23). The overall mean (SD) predicted $C_{trough,ss}$ (102 [29.8] mg/L) was comparable to the observed $C_{trough,ss}$ at Week 24 (91.2 [39.4] mg/L). Additionally, PK simulations were conducted to support the proposed age- and weight-based dosing recommendations for adolescents and children 6 to < 12 years of age with CSU using a virtual pediatric population from the NHANES database.

Table 21: Applicant's Population PK Analysis of Dupilumab in Subjects 2 to Less Than 12 Years of Age With CSU

General Information	
Objectives of Population PK Analysis	1. Apply a previously developed dupilumab population PK model (Study POH0766) to PK data in children 2 to < 12 years of age with CSU and assess its ability to characterize dupilumab PK in this population 2. Generate individual dupilumab post hoc PK exposures in children 2 to < 12 years of age with CSU and assess the influence of intrinsic and extrinsic factors on dupilumab pharmacokinetics in this population 3. Conduct descriptive ER analyses for efficacy endpoints in children 2 to < 12 years of age with CSU
Clinical Studies Included	Three phase 3 studies including PKM16982, EFC16461-C, and EFC16461-A
Number of Subjects, PK Samples, and BLQ	The initial PK dataset included 77 dupilumab PK records from 18 study participants across three clinical trials (Studies PKM16982 [N = 15], EFC16461-A [N = 2], and EFC16461-C [N = 1]) • Pre-dose (N = 18) and post-dose (N = 9) BLQ samples were flagged in the dataset and excluded in PopPK analysis. • No outlier PK data were identified After exclusions, the final population PK dataset consisted of 50 dupilumab PK samples collected from 18 subjects. **PK Sampling Schedule:** No rich PK sampling conducted in Studies PKM16982, EFC16461-A, or EFC16461-C. Instead, pharmacokinetics of dupilumab were characterized in children 2 to < 12 years of age with CSU using sparse sampling as follows: • **Study PKM16982:** Subjects were randomized in a 1:1 ratio to PK schedule A (pre-dose trough samples collected at Weeks 0, 1, 12, and 24) or to PK schedule B (trough samples collected Weeks 0, 2, 12, and 24) during 24-week on-treatment period. One additional sample was collected at Week 36 during the safety follow-up period. • **Studies EFC16461-A and EFC16461-C:** Pre-dose trough PK samples collected at Weeks 0, 12, and 24 during 24-week on-treatment period. One additional sample was collected at Week 36 during the safety follow-up period.

<table>
<tr><td>Dose(s) Included</td><td>Four dose levels were included according to subject age and weight:
• Children 2 to < 12 years of age (5 to < 15 kg): 200 mg SC Q4W, no LD (N = 1)
• Children 2 to < 6 years of age (15 to < 30 kg): 300 mg SC Q4W, no LD (N = 4)
• Children 6 to < 12 years of age (15 to < 30 kg): 300 mg SC Q4W, with LD of 600 mg (N = 2)
• Children 2 to < 12 years of age (30 to < 60 kg): 200 mg SC Q2W, with LD of 400 mg (N = 11)

Of note, the Applicant also proposed a dosage of 300 mg Q2W + 600 mg LD for children (b) (4) weighing ≥ 60 kg. However, no children weighing 60 kg or higher were enrolled, so there are no clinical data available for this dosing regimen in this analysis.</td></tr>
<tr><td>Population Included</td><td>Children 2 to < 12 years of age and weighing 5 to < 60 kg with CSU (N = 18)</td></tr>
<tr><td>Population Baseline Characteristics</td><td>A summary of the continuous and categorical baseline characteristics of the subjects included in the final population PK dataset is provided below in Table 22 and Table 23, respectively. A total of 18 subjects were included in the final dataset, with only one subject weighing 5 to < 15 kg and receiving the proposed 200 mg Q4W dosage.

Table 22: Summary of Potential Continuous Covariates at Baseline for Children 2 to < 12 Years of Age With CSU in Final Population PK Dataset (N = 18)
<table>
<tr><th>Baseline Covariate</th><th colspan="3">Total</th></tr>
<tr><th></th><th>N</th><th>Mean (SD)</th><th>Median (Min, Max)</th></tr>
<tr><td>Body weight (kg)</td><td>18</td><td>31.5 (11.5)</td><td>31.8 (14.5, 55.7)</td></tr>
<tr><td>Age (year)</td><td>18</td><td>7.22 (2.90)</td><td>8 (2, 11)</td></tr>
<tr><td>eGFR (mL/min/1.73 m^2)</td><td>18</td><td>197 (33.4)</td><td>191 (143, 266)</td></tr>
<tr><td>Albumin (g/L)</td><td>18</td><td>47.4 (1.38)</td><td>47 (45, 50)</td></tr>
<tr><td>ISS7[a]</td><td>17</td><td>10.7 (5.57)</td><td>9 (1, 21)</td></tr>
<tr><td>UAS7[a]</td><td>17</td><td>20.8 (10.5)</td><td>20 (1, 35)</td></tr>
<tr><td>HSS7[a]</td><td>17</td><td>10.1 (5.40)</td><td>12 (0, 17)</td></tr>
</table>
Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 3, pg. 31)
[a] One subject from Study PKM16982 (b) (6) had missing information for baseline ISS7, UAS7 and HSS7 scores. For the descriptive ER analysis, missing baseline values of ISS7, UAS7 and HSS7 for this subject were imputed with those observed on Day 1.
Abbreviations: CSU: Chronic Spontaneous Urticaria; PK: Pharmacokinetic; N: Number of Subjects; SD: Standard Deviation; Min: Minimum; Max: Maximum; eGFR: Estimated Glomerular Filtration Rate; ISS7: Weekly Itch Severity Score; UAS7: Weekly Urticaria Activity Score; HSS7: Weekly Hive Severity Score; ER: Exposure-Response</td></tr>
</table>

Table 23: Summary of Potential Categorical Covariates at Baseline for Children 2 to < 12 Years of Age With CSU in Final Population PK Dataset (N = 18)

Baseline Covariate	Sub-Group	N (%)
Sex	Male	6 (33.3%)
	Female	12 (66.7%)
Race[a]	Caucasian	12 (66.7%)
	Black	1 (5.56%)
	Asian	4 (22.2%)
	Other	0 (0%)
	Missing	1 (5.56%)
Stationary ADA	Negative	18 (100%)
	Positive	0 (0%)

Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 4, pg. 31)
[a] One subject from Study PKM16982 (b) (6) had missing information for race. In the post hoc assessment, the missing race value for this subject was imputed using the categorical value of the majority of the population (i.e., Caucasian).
Abbreviations: CSU: Chronic Spontaneous Urticaria; PK: Pharmacokinetic; N: Number of Subjects; ADA: Anti-Drug Antibody

Covariates Evaluated	Refer to Table 22 and Table 23 above.
Final Model	**Summary**
Software and Version	The PopPK analysis was performed with NONMEM (version 7.5.1) based upon concentration data pooled from three phase 3 studies (PKM16982, EFC16461-A, and EFC16461-C). Analysis dataset creation was conducted by using SAS® Version 9.4 software (SAS Institute, Cary, North Carolina). R statistical software (version 4.2.3) was used for data tabulation/visualization/simulation activities.
Model Structure	The asthma pediatric population PK model was a two-compartment model with a first order absorption, and parallel linear and nonlinear (i.e., M-M) elimination (Figure 7). The absorption process was parameterized in terms of the first order absorption rate constant (K_a, day^{-1}). The elimination process was described by the linear pathway parameterized in terms of the linear elimination rate constant (K_e, day^{-1}) and nonlinear M-M elimination represented by the two parameters V_{max} (mg*day/L) and K_m (mg/L). The two compartments are represented by a distribution volume of the central compartment (V2) and the peripheral compartment (V3), with inter-compartmental distribution rate constants (K_{23} and K_{32}).

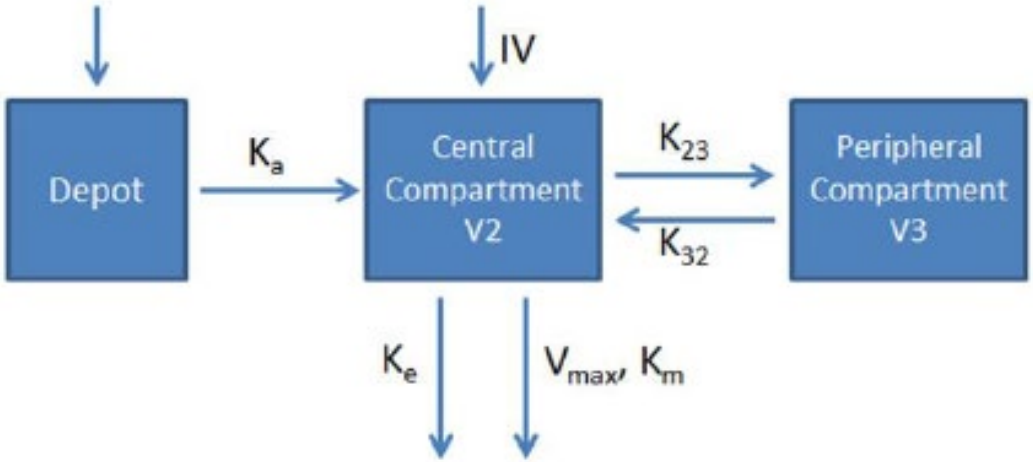
	Figure 7: Schematic Structure of Final Asthma Pediatric Population PK Model for Dupilumab (Study POH0776)  **Source.** Applicant's Population PK Analysis Study Report POH1231 (Figure 2, pg. 23) **Abbreviations:** PK: Pharmacokinetic; K_a: Absorption Rate Constant; IV: Intravenous; V2: Central Compartment Volume; V3: Peripheral Compartment Volume; K_{23}, K_{32}: Inter-Compartmental Distribution Rate Constants; K_e: Elimination Rate Constant; V_{max}: Maximum Target-Mediated Rate of Elimination; K_m: Michaelis-Menten Constant
Model Parameter Estimates	See Population PK Analysis Study Report POH0776 submitted for pediatric asthma under sBLA 761055/S-031.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	See Population PK Study Analysis Report POH0776 submitted for pediatric asthma under sBLA 761055/S-031.
BLQ for Parameter Accuracy	Pre-dose (N = 18) and post-dose (N = 9) BLQ samples were flagged in the dataset and excluded in Population PK analysis.
Comparison of Observed PK Data (Asthma vs. CSU)	Prior to conducting the population PK analyses described herein, the Applicant compared the dupilumab trough concentration-time profile observed in children with CSU (weighing 30 to < 60 kg) to those with asthma (weighing > 30 kg) following administration of the 200 mg Q2W dosing regimen (Figure 8). Apart from the time to reach steady state, which was shorter in CSU subjects due to the administration of an initial 400 mg loading dose, PK profiles were generally similar. The mean (SD) steady-state trough concentrations at Week 24 in children with CSU (80.9 [30.4] mg/L, N = 9) and asthma (87.6 [43.7] mg/L, N = 161) were also comparable, supporting PK similarity between patient populations.

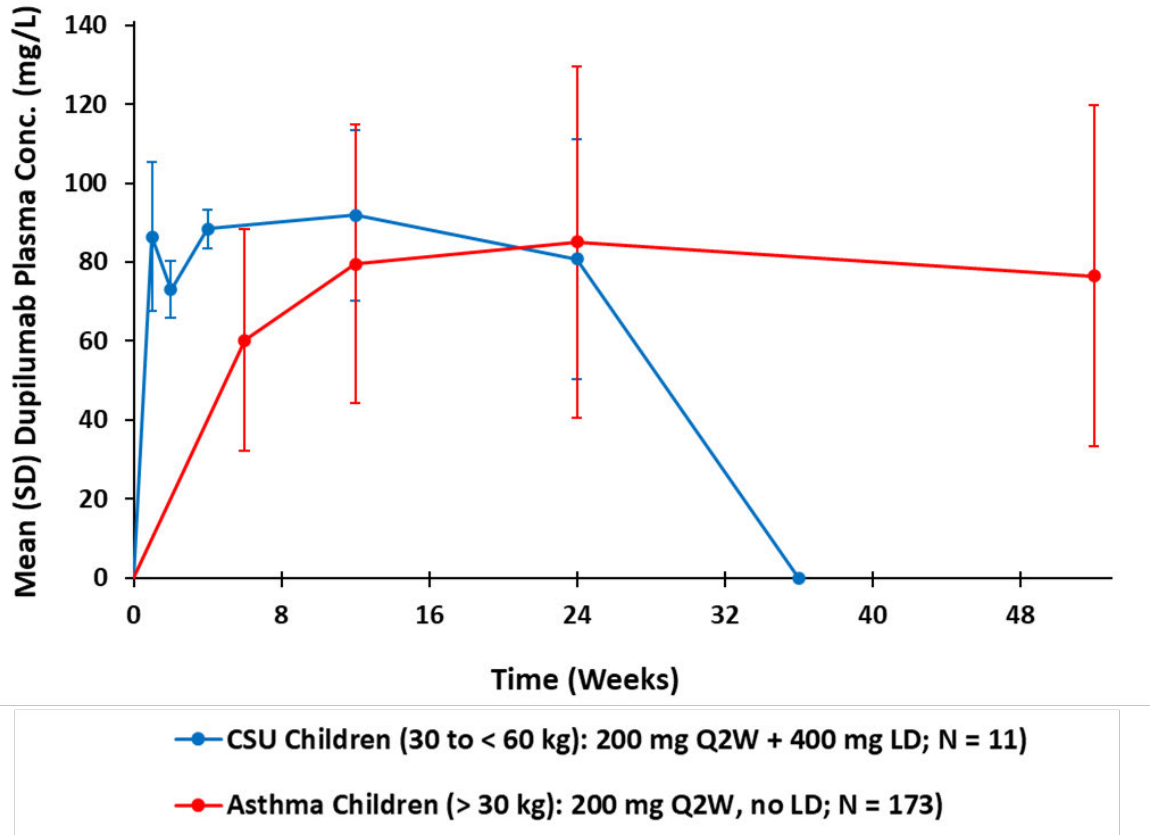
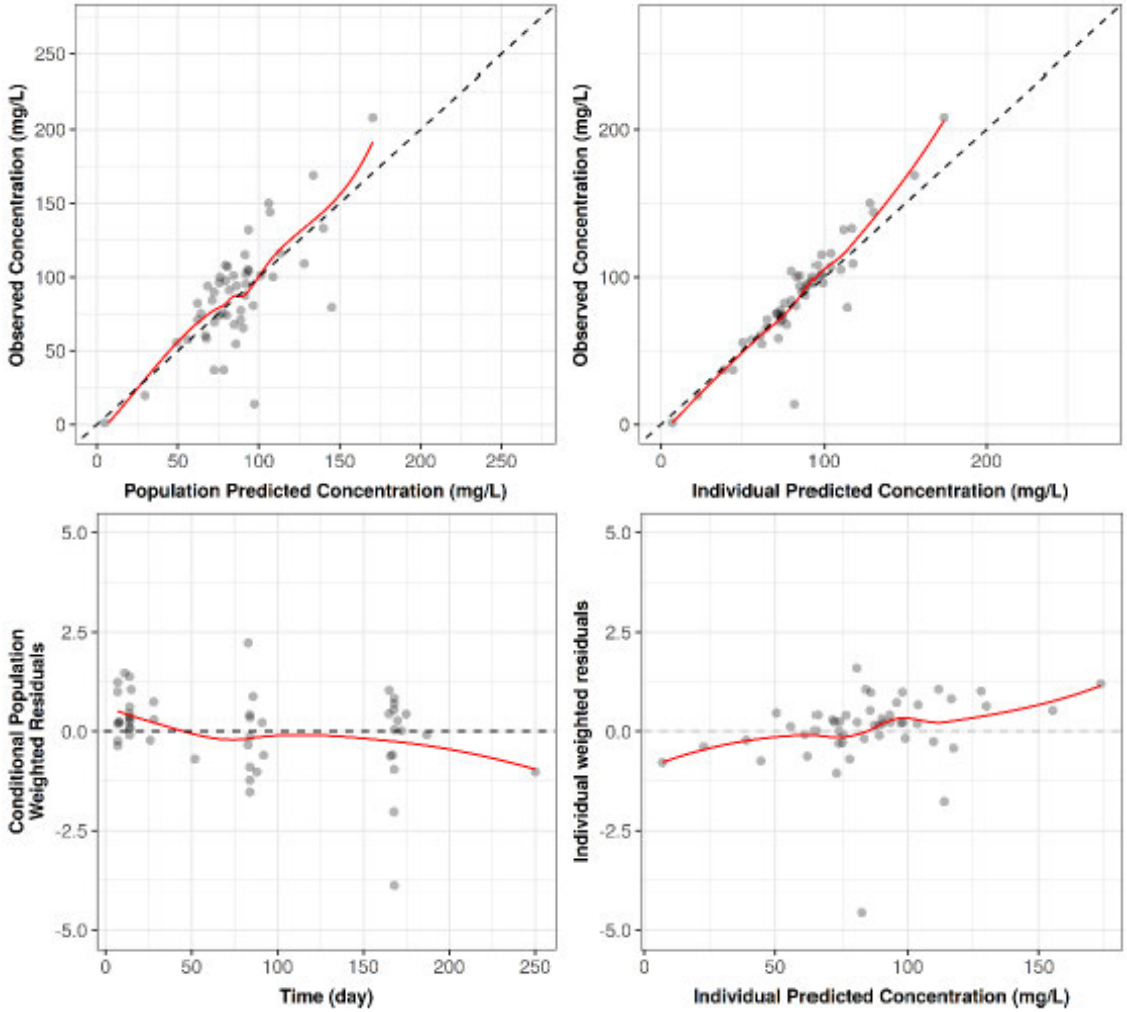
	Figure 8: Arithmetic Mean (SD) Observed Dupilumab Trough Concentration-Time Profiles Following SC Administration of 200 mg Q2W Pediatric Subjects With CSU vs. Asthma  **Source.** Reviewer's analysis based on adpc.xpt for Studies PKM16982, EFC16461-C, EFC16461-A, and EFC14153 [a] Mean observed trough concentration-time profile for CSU pediatric population was summarized from Studies PKM16982, EFC16461-C, and EFC16461-A; Mean observed trough concentration-time profile for asthma pediatric population was summarized from Study EFC14153. **Abbreviations:** SD: Standard Deviation; SC: Subcutaneous; Q2W: Every 2 Weeks; CSU: Chronic Spontaneous Urticaria; LD: Loading Dose; N: Number of Subjects
Goodness-of-Fit (GoF), Visual Predictive Checks (VPC), Observed vs. Predicted PK	GoF plots for the application of the asthma pediatric population PK model in children 2 to < 12 years of age with CSU are provided below in Figure 9. Overall, good agreement was demonstrated between observed and predicted dupilumab concentrations.

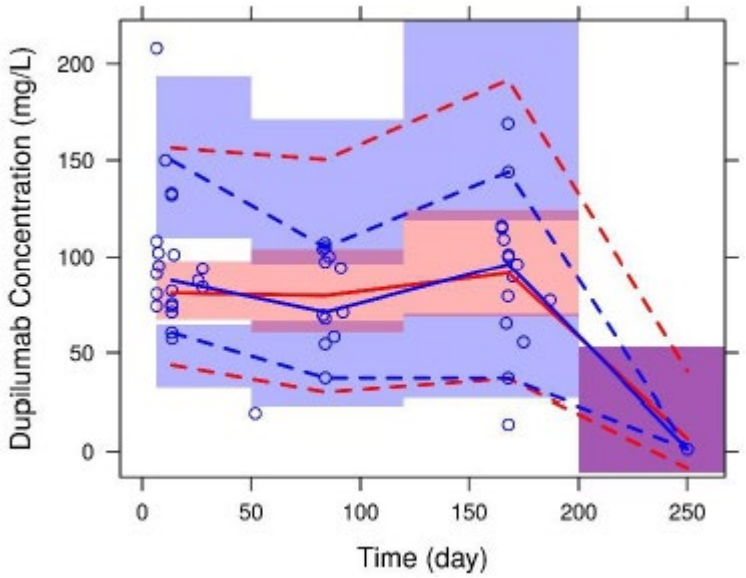
Figure 9: GoF Plots for the Application of the Asthma Pediatric Population PK Model (Study POH0776) in Children 2 to < 12 Years of Age With CSU



Source. Applicant's Population PK Analysis Study Report POH1231 (Figure 7, pg. 33)
Note: Each grey dot represents a PK record. Black dashed line is line of identity or zero line; Red line is a smoothing function
Abbreviations: GoF: Goodness-of-Fit; PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria

Additionally, predictive performance of the asthma population PK model for children 2 to < 12 years of age with CSU across studies was evaluated using VPC of dupilumab pharmacokinetics versus time (Figure 10). Based on the VPC results, the majority of observed concentrations were within the 5th to 95th percentile of the predicted exposure. Two individual concentrations at Days 53 (19.6 mg/L) and 169 (13.8 mg/L) fell below the 5th percentile of predicted concentrations, with another sample at Day 8 (208 mg/L) falling above the 95th percentile. Overall, the final model appears to reasonably describe the observed data.

Figure 10: VPC for Asthma Pediatric Population PK Model in Children 2 to < 12 Years of Age With CSU



Source. Applicant's Population PK Analysis Study Report POH1231 (Figure 7, pg. 33)
Note: Blue dots are individual observations; Blue solid and dashed lines are the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; Red solid and dashed lines are the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; Pink and light blue shaded areas are confidence intervals of median and percentiles of predicted concentrations at each time bin.
Abbreviations: VPC: Visual Predictive Check; PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria

After confirming the suitability of the asthma pediatric population PK model to describe dupilumab pharmacokinetics in the pediatric CSU population, the model was used to generate post hoc estimates of individual steady-state exposures for children 2 to < 12 years of age with CSU (Table 24). Model-predicted steady-state trough exposures were comparable to those observed in Studies PKM16982, EFC16461-A, or EFC16461-C, supporting robust model performance.

Table 24: Summary of Arithmetic Mean (SD) Observed/Simulated Dupilumab Plasma Steady-State PK Parameters in CSU Subjects Across Age Groups and Dosing Regimens[a,b]

		Predicted[c,d]				Observed[e]	
Dupilumab Dosing Regimen	**Age/Body Weight Group**	**N (BW)[a,b]**	**$AUC_{4\ weeks,ss}$ (mg*day/L)**	**$C_{max,ss}$ (mg/L)**	**$C_{trough,ss}$ (mg/L)**	**N (BW)[b]**	**$C_{trough,ss}$ (mg/L)**
200 mg Q2W + 400 mg LD	6 to < 12 years, 30 to < 60 kg	10 (37.8)	3230 (441)	127 (16.5)	98.5 (14.4)	9 (38.6)	80.9 (30.4)
300 mg Q4W + 600 mg LD	6 to < 12 years, 15 to < 30 kg	2 (25.1, 26.2)	2630 (451)	127 (19.3)	56.8 (12.2)	2 (25.1, 26.2)	36.9, 65.3
300 mg Q4W, no LD	2 to < 6 years, 15 to < 30 kg	3 (18.7)	5440 (1020)	237 (42.3)	144 (29.4)	3 (18.7)	141 (30.1)
200 mg Q4W, no LD	2 to < 6 years, 5 to < 15 kg	1 (14.5)	3900	168	105	1 (14.5)	116

Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 5, pg. 35); Reviewer's analysis based on adpc.xpt and adsl.xpt for Studies PKM16982, EFC16461-A, and EFC16461-C

[a] Due to early dose discontinuation, two participants from Studies EFC16461-A (Subject (b) (6); 200 mg Q2W + 400 mg LD, last dose on Day 28) and PKM16982 (Subject (b) (6); 300 mg Q4W, no LD, last dose on Day 1) were excluded in this post hoc assessment. One participant in EFC16461-A (Subject (b) (6); 200 mg Q2W + 400 mg LD, last dose on Day 70) was included in this summary of post hoc steady-state PK exposures, as PK at 200 mg Q2W with LD reached steady state at Week 10 (based on simulation).

[b] Reported as median body weight (kg); Individual body weight reported if N ≤ 2

[c] For 200 mg Q2W + 400 mg LD dosing regimen: $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss} \times 2$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24

[d] For 200 mg Q4W, no LD and 300 mg Q4W ± 600 mg LD dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 20 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss}$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24

[e] Arithmetic mean (SD) observed $C_{trough,ss}$ at Week 24 reported based on pooled PK population for Studies PKM16982, EFC16461-A, and EFC16461-C; Individual trough concentration reported if N ≤ 2

Abbreviations: SD: Standard Deviation; PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; N: Number of Subjects; BW: Body Weight; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over 28 Days at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; $AUC_{\tau,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over the Dosing Interval at Steady State

Significant Covariates and Clinical Relevance

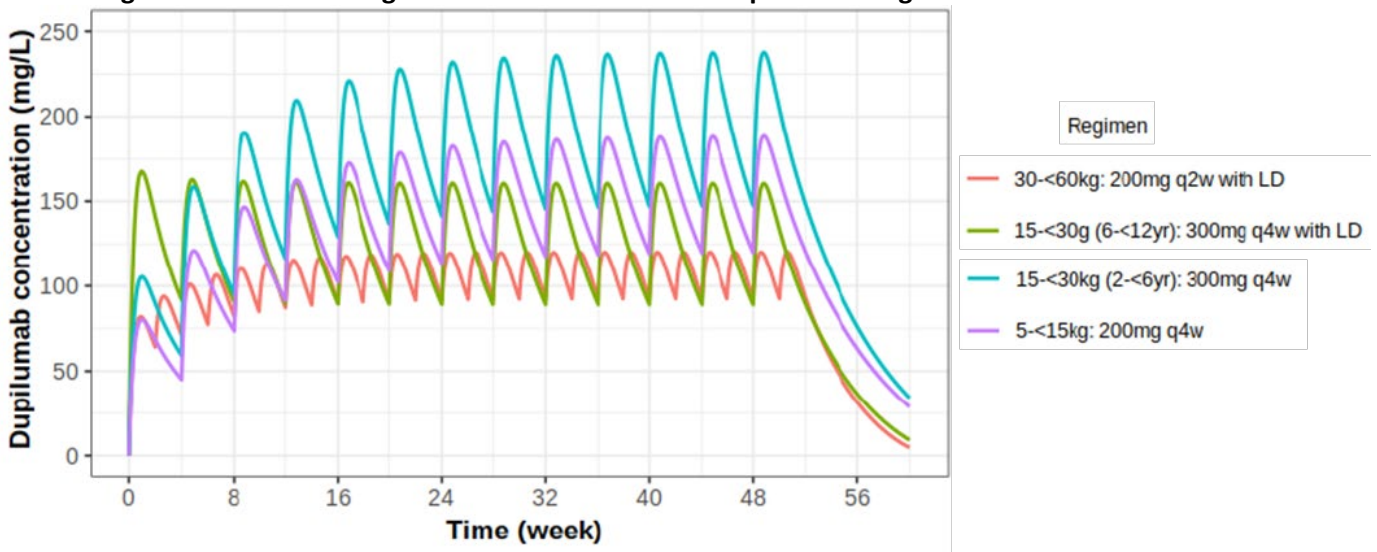
Post hoc covariate effect assessments were conducted and are summarized below in Table 25. Consistent with findings in other patient populations, body weight was identified as the primary factor explaining dupilumab PK variability in children 2 to < 12 years of age with CSU, such that increasing body weight is associated with decreasing dupilumab concentrations. All other tested factors, including baseline demographics (, age, and race), baseline albumin, ethnicity, and baseline disease characteristics (i.e., ISS7, UAS7, and HSS7) had no apparent effect on dupilumab PK exposure based on available limited data (N = 16). The impact of ADA status and renal impairment on dupilumab pharmacokinetics was not evaluated, as all subjects were ADA-negative and with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2).

Table 25: Arithmetic Mean (SD) Steady-State Exposures for Dupilumab in Children With CSU as a Function of Intrinsic and Extrinsic Factors

Intrinsic/Extrinsic Factor	Sub-Group	N (BW)[a,b]	Predicted PK Parameters[c,d]		
			$AUC_{4week,ss}$ (mg*day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
Overall (Total)[e]		16 (31.0)	3610 (1080)	150 (48.8)	102 (29.8)
Age (year)	**< 6 years**	3 (19.1)	5440 (1020)	237 (42.3)	144 (29.4)
	6 to < 12 years	13 (33.7)	3190 (508)	130 (19.1)	92.6 (20.6)
Weight (kg)	**5 to < 15 kg**	1 (14.5)	3900	168	105
	15 to < 30 kg	5 (21.7)	4320 (1720)	193 (67.6)	109 (52.6)
	30 to < 60 kg	10 (37.3)	3230 (441)	127 (16.5)	98.5 (14.4)
Sex	**Male**	5 (34.1)	3880 (1580)	157 (73.4)	114 (38.2)
	Female	11 (29.6)	3490 (838)	147 (37.3)	97.2 (25.6)
Race[f]	**Caucasian**	11 (32.2)	3660 (1300)	152 (59.0)	104 (34.1)
	Black	1 (31.2)	3300	130	100
	Asian	4 (27.6)	3560 (431)	149 (13.2)	99.4 (23.2)
Ethnicity	**Japanese**	3 (26.1)	3470 (482)	149 (16.1)	93.4 (24.3)
	Non-Japanese	13 (32.1)	3640 (1190)	150 (54.2)	104 (31.4)
Albumin (g/L)	**40 to < 50**	14 (30.3)	3780 (1050)	156 (49.3)	108 (26.7)
	≥ 50	2 (26.2, 44.7)	2440 (180)	108 (8.71)	62.5 (20.2)
Baseline ISS7[g]	**< 9**	7 (28.3)	3970 (657)	164 (35.9)	114 (12.4)
	≥ 9	9 (33.1)	3330 (1290)	139 (56.7)	93.5 (36.7)

				Predicted PK Parameters[c,d]		
	Intrinsic/Extrinsic Factor	**Sub-Group**	**N (BW)[a,b]**	**$AUC_{4week,ss}$ (mg*day/L)**	**$C_{max,ss}$ (mg/L)**	**$C_{trough,ss}$ (mg/L)**
	Baseline UAS7[g]	**< 20**	8 (30.2)	3680 (531)	152 (26.3)	105 (17.8)
		≥ 20	8 (31.7)	3550 (1490)	148 (66.4)	99.7 (39.7)
	Baseline HSS7[g]	**< 12**	8 (30.2)	3680 (531)	152 (26.3)	105 (17.8)
		≥ 12	8 (31.7)	3550 (1490)	148 (66.4)	99.7 (39.7)
	Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 6, pg. 36); Reviewer's analysis based on adlb.xpt and adsl.xpt for Studies PKM16982, EFC16461-A, and EFC16461-C [a] Due to early dose discontinuation, two participants from Studies EFC16461-A (Subject (b) (6); 200 mg Q2W + 400 mg LD, last dose on Day 28) and PKM16982 (Subject (b) (6); 300 mg Q4W, no LD, last dose on Day 1) were excluded in this post assessment. One participant in EFC16461-A (Subject (b) (6); 200 mg Q2W + 400 mg LD, last dose on Day 70) was included in this summary of post hoc steady-state PK exposures, as PK at 200 mg Q2W with LD reached steady state at Week 10 (based on simulation). [b] Reported as arithmetic mean body weight (kg); Individual body weight reported if N ≤ 2 [c] For 200 mg Q2W + 400 mg LD dosing regimen: $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24]; $AUC_{4\ weeks,ss}$ = $AUC_{\tau,ss}$ x 2; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 [d] For 200 mg Q4W, no LD and 300 mg Q4W ± 600 mg LD dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 20 – Week 24]; $AUC_{4\ weeks,ss}$ = $AUC_{\tau,ss}$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24 [e] All subjects had normal renal function at baseline (eGFR ≥ 90 mL/min/1.73m^2) [f] One subject in Study PKM16982 (b) (6) had missing value for race, which was imputed as Caucasian in this post assessment summary. The mean body weight for non-Asian subjects (N = 12) is 32.1 kg. [g] One subject from Study PKM16982 (b) (6) had missing values for baseline ISS7, UAS7 and HSS7, which were imputed with ISS7, UAS7 and HSS7 values on Day 1 for this patient in this post hoc summary. **Abbreviations:** SD: Standard Deviation; CSU: Chronic Spontaneous Urticaria; N: Number of Subjects; BW: Body Weight; PK: Pharmacokinetic; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over 28 Days at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; ISS7: Weekly Itch Severity Score; UAS7: Weekly Urticaria Activity Score; HSS7: Weekly Hive Severity Score; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; $AUC_{\tau,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over the Dosing Interval at Steady State; eGFR: Estimated Glomerular Filtration Rate					
Analysis Based on Simulation (optional)	The typical dupilumab concentration-time profiles for children 2 to < 12 years of age and adults/adolescents with CSU are depicted below according to dosing regimen in Figure 11 and Figure 12, respectively. Overall, predicted dupilumab exposure in the pediatric CSU population at the proposed dosing is comparable to or slightly higher than that simulated in adults and adolescents at the approved dosing.					

Figure 11: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU Following SC Administration of the Proposed Dosing[a]

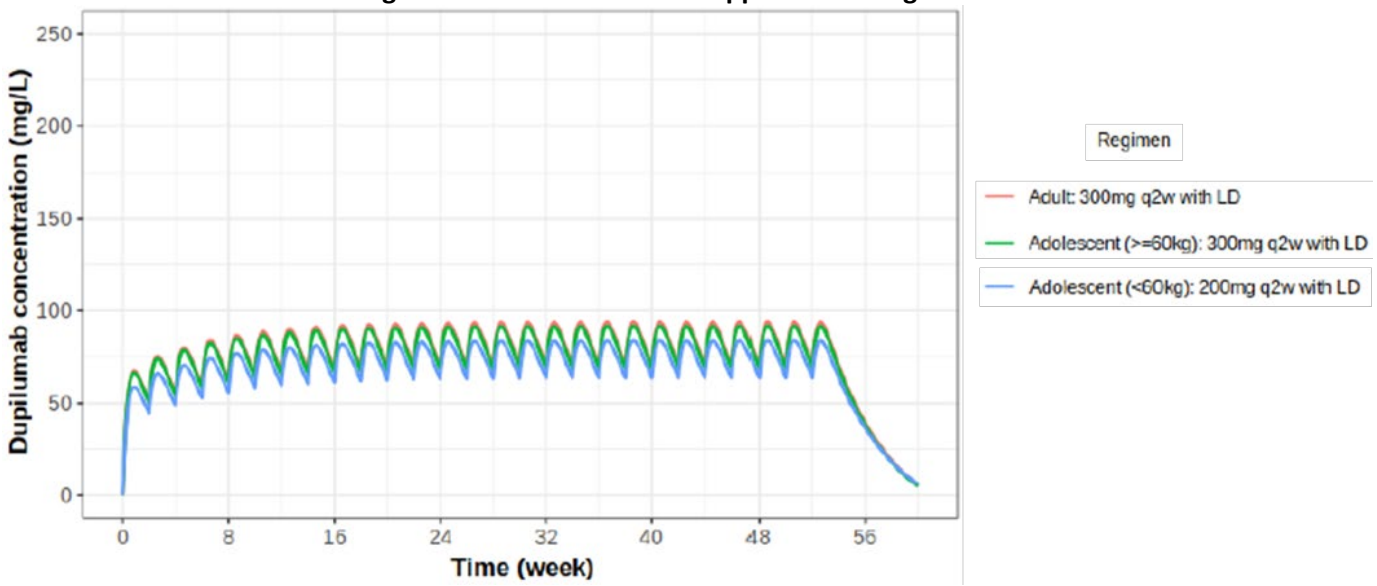


Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Figure 9, pg. 37)

[a] The typical profile simulation was simulated using the asthma pediatric PopPK model (Study POH0766) for a typical pediatric subject 2 to < 12 years of age with CSU with median body weight of 38.6 kg (200 mg Q2W + 400 mg LD; N = 11), 25.7 kg (300 mg Q4W + 600 mg LD; N = 2), 17.9 kg (300 mg Q4W, no LD; N = 4), and 14.5 kg (200 mg Q4W, no LD; N = 1) based on final PopPK dataset (Study POH1231)

Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; SC: Subcutaneous; Q2W: Every 2 Weeks; LD: Loading Dose; Yr: Year; Q4W: Every 4 Weeks; PopPK: Population PK

Figure 12: Typical Population PK Model-Predicted Dupilumab Concentration-Time Profiles in Adults and Adolescents With CSU Following SC Administration of the Approved Dosing[a]



Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Figure 10, pg. 38)

[a] The typical profile simulation was simulated using the global PopPK base model (Study POH0668) for a typical adult or adolescent 12 to < 12 years of age with CSU with median body weight of 75.1 kg (adults; N = 181), 76.5 kg (adolescents weighing ≥ 60 kg; N = 4), and 52.1 kg (adolescents weighing 30 to < 60 kg; N = 2) based on final PopPK dataset (Study POH1089)

Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; SC: Subcutaneous; Q2W: Every 2 Weeks; LD: Loading Dose; PopPK: Population PK

Additionally, based on the completed simulations in children 2 to < 12 years of age with CSU, the typical time to steady state and washout period following the last dose at steady state were estimated (Table 26). As expected, dosing regimens which include an initial loading dose have a shorter time to reach steady-state compared to those without a loading dose.

Table 26: Comparison of PK Parameters Between Different Regimens in Children 2 to < 12 Years of Age With CSU

Dupilumab Dosing Regimen	Age/Body Weight Sub-Group	Median BW (kg)	PK Parameters[a]	
			Time to Steady State	Wash-out time from last dose at steady state
200 mg Q2W + 400 mg LD	30 to < 60 kg	38.6	10 weeks	14 weeks
300 mg Q4W + 600 mg LD	6 to < 12 years, 15 to < 30 kg	25.7	4 weeks	18 weeks
300 mg Q4W, no LD	2 to < 6 years, 15 to < 30 kg	17.9	20 weeks	22 weeks
200 mg Q4W, no LD	5 to < 15 kg	14.5	20 weeks	22 weeks

Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 7, pg. 38)
[a] Reported as the model-predicted typical value
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; BW: Body Weight; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks

To inform the proposed age- and weight-based dupilumab dosing regimens, a virtual pediatric population of subjects 2 to less than 12 years of age was generated based on the National Health and Nutrition Examination Survey (NHANES) database, which included subjects with body weights ranging from 9.6 to 59.8 kg (N = 2114). The demographic characteristics of the virtual pediatric population are summarized below (Table 27).

Table 27: Descriptive Statistics of Weight and Age for Virtual Pediatric Population From NHANES According to Age and Body Weight Sub-Group

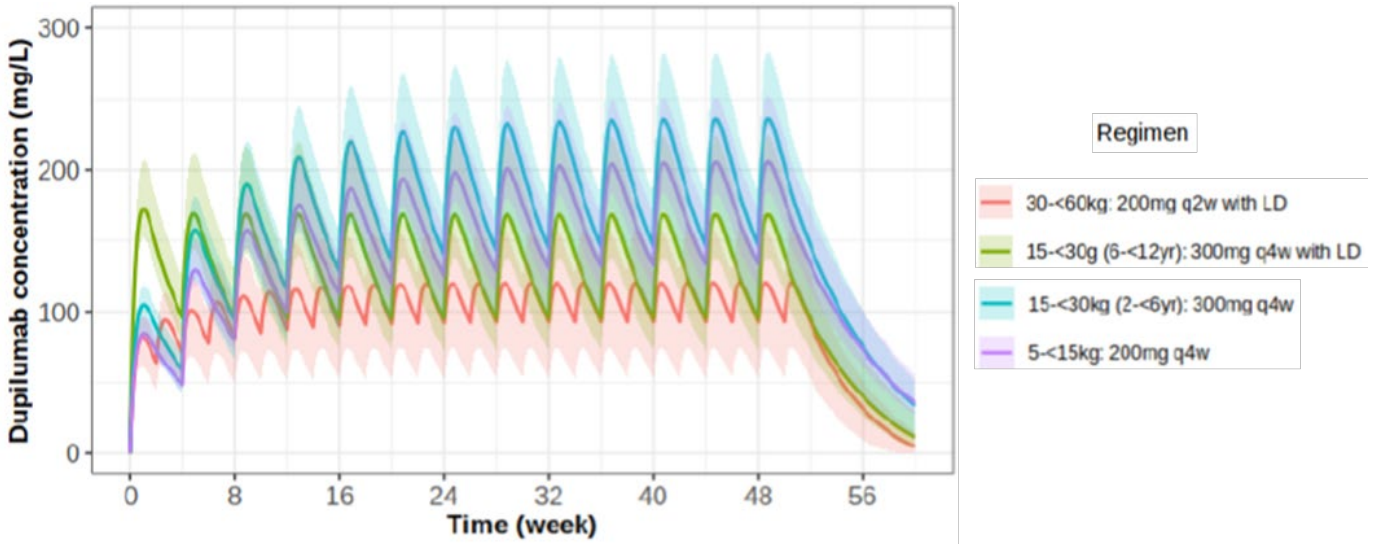
Demographic Characteristic	Age/Body Weight Sub-Group	Dupilumab Dosing Regimen	Virtual Patients		
			N	Mean (SD)	Median (Min, Max)
Body Weight (kg)	30 to < 60 kg	200 mg Q2W + 400 mg LD	667	40.4 (7.99)	38.5 (30.0, 59.8)
	15 to < 30 kg, 6 to < 12 years	300 mg Q4W + 600 mg LD	546	24.6 (3.26)	24.6 (16.4, 29.9)
	15 to < 30 kg, 2 to < 6 years	300 mg Q4W, no LD	572	18.6 (2.89)	18.0 (150., 29.2)
	5 to < 15 kg	200 mg Q4W, no LD	329	13.2 (1.21)	13.4 (9.60, 14.9)
Age (year)	30 to < 60 kg	200 mg Q2W + 400 mg LD	667	9.2 (1.57)	9 (3, 11)
	15 to < 30 kg, 6 to < 12 years	300 mg Q4W + 600 mg LD	546	7.2 (1.23)	7 (6, 11)
	15 to < 30 kg, 2 to < 6 years	300 mg Q4W, no LD	572	3.8 (0.996)	4 (2, 5)
	5 to < 15 kg	200 mg Q4W, no LD	329	2.4 (0.664)	2 (2, 5)

Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 8, pg. 39)
Abbreviations: NHANES: National Health and Nutrition Examination Survey; N: Number of Subjects; SD: Standard Deviation; Min: Minimum; Max: Maximum; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks

Using the final population PK model and the virtual pediatric population from NHANES, simulated median (90% CI) dupilumab concentration-time profiles were generated according to the proposed age- and weight-based dosing

regimen (Figure 13). Additionally, the model-predicted dupilumab steady-state PK parameters with descriptive statistics are provided below in Table 28.

Figure 13: Simulated Median (90% CI) Dupilumab Concentration-Time Profiles in Children 2 to < 12 Years of Age With CSU According to Dosing Regimen[a,b]



Source. Adapted from Applicant's Population PK Analysis Study Report POH1231 (Figure 11, pg. 40)

[a] The typical median PK profile with 5th to 95th percentile was simulated using the asthma pediatric PopPK model (Study POH0766) for children 2 to < 12 years of age and weighing 5 to < 60 kg, using a virtual pediatric population from NHANES database (N = 2114)

[b] The median body weight was 38.5 kg for children weighing 30 to < 60 kg (200 mg Q2W + 400 mg LD; N = 667), 24.6 kg for children 6 to < 12 years of age and weighing 15 to < 30 kg (300 mg Q4W + 600 mg LD; N = 546), 18.0 kg for children 2 to < 6 years of age and weighing 15 to < 30 kg (300 mg Q4W, no LD; N = 572), and 13.4 kg for children weighing 5 to < 15 kg (200 mg Q4W, no LD; N = 329)

Abbreviations: CI: Confidence Interval; CSU: Chronic Spontaneous Urticaria; Q2W: Every 2 Weeks; LD: Loading Dose; Yr: Year; Q4W: Every 4 Weeks; PK: Pharmacokinetic; PopPK: Population PK; NHANES: National Health and Nutrition Examination Survey; N: Number of Subjects

Table 28: Summary of Population PK Model-Simulated Dupilumab Plasma Steady-State PK Parameters in Children 2 to < 12 Years of Age With CSU, Using a Virtual Pediatric Population From NHANES Database[a]

Age/Body Weight Group	Dosing Regimen	N (BW)[b]	$AUC_{4\ weeks,ss}$ (mg*day/L)[c,d] Mean (SD) [CV%]	$AUC_{4\ weeks,ss}$ (mg*day/L)[c,d] Median [P5-P95]	$C_{max,ss}$ (mg/L)[c,d] Mean (SD) [CV%]	$C_{max,ss}$ (mg/L)[c,d] Median [P5-P95]	$C_{trough,ss}$ (mg/L)[c,d] Mean (SD) [CV%]	$C_{trough,ss}$ (mg/L)[c,d] Median [P5-P95]
30 to < 60 kg	200 mg Q2W + 400 mg LD	667 (38.5)	3010 (684) [22.7]	3050 [1850-4020]	118 (25.6) [21.7]	120 [74.3-156]	90.5 (22.3) [24.7]	91.9 [52.7-124]
15 to < 30 kg, 6 to < 12 years	300 mg Q4W + 600 mg LD	546 (24.6)	3870 (658) [17.0]	3770 [3030-5130]	172 (26.3) [15.3]	168 [139-223]	97.8 (19.9) [20.3]	95.0 [72.9-136]
15 to < 30 kg, 2 to < 6 years	300 mg Q4W, no LD	572 (18.0)	5180 (801) [15.5]	5240 [3730-6310]	224 (31.8) [14.2]	226 [166-268]	139 (24.7) [17.8]	140 [94-173]
5 to < 15 kg	200 mg Q4W, no LD	329 (13.4)	4660 (507) [10.9]	4560 [4070-5600]	198 (19.8) [10.0]	194 [175-234]	129 (16.0) [12.5]	125 [110-158]

Source: Adapted from Applicant's Population PK Analysis Study Report POH1231 (Table 9, pg. 41)

[a] Steady-state dupilumab PK parameters were simulated using the asthma pediatric PopPK model (Study POH0766) for children 2 to < 12 years of age and weighing 5 to 60 kg, using a virtual pediatric population from NHANES database (N = 2114)

[b] Reported as median body weight (kg)

[c] For 200 mg Q2W + 400 mg LD dosing regimen: $AUC_{\tau,ss}$ = AUC [Week 22 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss} \times 2$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24

[d] For 200 mg Q4W, no LD and 300 mg Q4W ± 600 mg LD dosing regimens: $AUC_{\tau,ss}$ = AUC [Week 20 – Week 24]; $AUC_{4\ weeks,ss} = AUC_{\tau,ss}$; $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 20 and Week 24

Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; NHANES: National Health and Nutrition Examination Survey; N: Number of Subjects; BW: Body Weight; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over 28 Days at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; SD: Standard Deviation; CV%: Coefficient of Variation; P5: 5th Percentile; P95: 95th Percentile; Q2W: Every 2 Weeks; LD: Loading Dose; Q4W: Every 4 Weeks; PopPK: Population Pharmacokinetic; $AUC_{\tau,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over the Dosing Interval at Steady State

Adequacy of the above-described PK simulations to support the proposed pediatric dosing regimens in children 2 to < 12 years of age with CSU, as well as the acceptability of the overall extrapolation approach of efficacy and safety for pediatric subjects with CSU, is discussed further in Section 6.3.1.

Language	Description
, Pediatric Use	The following language in red has been added to the labeling: Chronic Spontaneous Urticaria The safety and effectiveness of DUPIXENT for the treatment of CSU in patients who remain symptomatic despite H1 antihistamine treatment have been established in pediatric patients 2 years of age and older. Use of DUPIXENT

	in this indication is supported by evidence from two adequate and well-controlled studies in adults and pediatric patients aged 12 years and older [see Clinical Studies (14.7)] with the following additional data: • Pharmacokinetic (PK) data in 6 pediatric patients 12 to 17 years of age, • PK data in 18 pediatric patients 2 to 11 years of age, and safety data in pediatric patients in other indications [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)] Safety and effectiveness of DUPIXENT have not been established in pediatric patients younger than 2 years of age, and/or weighing less than 5 kg, with CSU.
12.3, Pharmacokinetics	The following language in red has been added to the labeling: Chronic Spontaneous Urticaria A total of 12 pediatric subjects 12 to 17 years of age with CSU were enrolled in CUPID (Study A, B, and C), including 6 subjects who received DUPIXENT 200 mg Q2W (≥ 30 to < 60 kg) and 300 mg Q2W (≥ 60 kg). At week 24, the mean ± SD observed steady-state trough concentration was 53.6 ± 19.4 mcg/mL, which was within the range of steady-state trough concentrations in adult subjects with CSU who received DUPIXENT 300 mg Q2W. A total of 20 pediatric subjects 2 to 11 years of age with CSU were enrolled in clinical trials and pharmacokinetic Study PKM16982, including 18 subjects who received DUPIXENT 200 mg Q4W (≥ 5 to < 15 kg), 300 mg Q4W (≥ 15 to < 30 kg), or 200 mg Q2W (≥ 30 to < 60 kg). At week 24, the mean ± SD steady-state trough concentration was 91.1 ± 39.4 mcg/mL.

Source. Applicant's Population PK Analysis Study Report (Study POH1231); Summary of Clinical Pharmacology Studies, m2.7.2
Abbreviations: PK: Pharmacokinetic; CSU: Chronic Spontaneous Urticaria; ER: Exposure-Response; BLQ: Below the Limit of Quantitation; N: Number of Subjects; SC: Subcutaneous; Q4W: Every 4 Weeks; LD: Loading Dose; Q2W: Every 2 Weeks; SD: Standard Deviation; Min: Minimum; Max: Maximum; eGFR: Estimated Glomerular Filtration Rate; ISS7: Weekly Itch Severity Score; UAS7: Weekly Urticaria Activity Score; HSS7: Weekly Hive Severity Score; ADA: Anti-Drug Antibody; NONMEM: Nonlinear Mixed Effects Modeling; SAS: Statistical Analysis Software; M-M: Michaelis-Menten; K_a: Absorption Rate Constant; K_e: Elimination Rate Constant; V_{max}: Maximum Target-Mediated Rate of Elimination; K_m: Michaelis-Menten Constant; V2: Central Compartment Volume; V3: Peripheral Compartment Volume; K_{23}, K_{32}: Inter-Compartmental Distribution Rate Constants; BLA: Biologics Licensing Application; RSE: Relative Standard Error; IIV: Inter-Individual Variability; GoF: Goodness-of-Fit; VPC: Visual Predictive Check; BW: Body Weight; $AUC_{4\ weeks,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over 28 Days at Steady State; $AUC_{\tau,ss}$: Area Under the Plasma Concentration-Time Curve of Dupilumab Over the Dosing Interval at Steady State; $C_{max,ss}$: Maximum Plasma Concentration at Steady State; $C_{trough,ss}$: Plasma Trough Concentration at Steady State; Yr: Year; PopPK: Population PK; NHANES: National Health and Nutrition Examination Survey; CV%: Coefficient of Variation; P5: 5th Percentile; P95: 95th Percentile

15.4 Additional Clinical Outcome Assessment Analyses

Figure 14: Children's Dermatology Quality of Life Index

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI SCORE:
Age:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, "**scratchy**", **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** **OR** was it **holiday time?**	**If school time**: Over the last week, how much did your skin problem affect your **school work**? **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Prevented school ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?		Very much Quite a lot Only a little Not at all
9.	Over the last week, how much has your **sleep** been affected by your skin problem?		Very much Quite a lot Only a little Not at all
10.	Over the last week, how much of a problem has the **treatment** for your skin been?		Very much Quite a lot Only a little Not at all

Please check that you have answered EVERY question. Thank you.

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Source: Lewis-Jones and Finlay (1993)

Figure 15: Infants' Dermatitis Quality of Life Index

Draft 7 **INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)**

Name: **Date:** **IDQOL**
Address: **SCORE**

The aim of this chart is to record how your child's dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please could you answer every question.

Dermatitis Severity

Over the last week, **how severe** do you think your child's dermatitis has been?; i.e. how red, scaly, inflamed or widespread.	Extremely severe	☐
	Severe	☐
	Average	☐
	Fairly good	☐
	None	☐

Life Quality Index

1.	Over the last week, how much has your child been **itching and scratching**?	All the time	☐
		A lot	☐
		A little	☐
		None	☐
2.	Over the last week, what has your child's **mood** been?	Always crying, extremely difficult	☐
		Very fretful	☐
		Slightly fretful	☐
		Happy	☐
3.	Over the last week approximately how much **time** on average has it taken **to get your child off to sleep** each night?	More than 2 hrs	☐
		1 - 2 hrs	☐
		15mins - 1 hr	☐
		0-15mins	☐
4.	Over the last week, what was the **total time** that your child's **sleep was disturbed** on average each night?	5 hrs or more	☐
		3 - 4 hrs	☐
		1 - 2 hrs	☐
		Less than 1 hour	☐
5.	Over the last week, has your child's eczema interfered with **playing or swimming**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
6.	Over the last week, has your child's eczema interfered with your child **taking part in** or **enjoying other family activities**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
7.	Over the last week, have there been problems with your child at **mealtimes** because of the eczema?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
8.	Over the last week, have there been problems with your child caused by the **treatment**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
9.	Over the last week, has your child's eczema meant that **dressing and undressing** the child has been **uncomfortable**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐
10.	Over the last week how much has your child having eczema been a problem at **bathtime**?	Very much	☐
		A lot	☐
		A little	☐
		None	☐

Please can you check that you have answered every question.

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Source: Lewis-Jones and Finlay (2000)

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