# BLA Multi-Disciplinary Review and Evaluation

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| **Application Type** | Efficacy Supplement BLA – New Indication |
| **Application Number(s)** | 761055 s051 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | October 18, 2024 |
| **Received Date(s)** | October 18, 2024 |
| **PDUFA Goal Date** | April 18, 2025 |
| **Division/Office** | DPACC/OII |
| **Review Completion Date** | April 15, 2025 |
| **Established/Proper Name** | Dupilumab |
| **(Proposed) Trade Name** | Dupixent |
| **Pharmacologic Class** | Interleukin-4 receptor alpha antagonist (monoclonal antibody) |
| **Code name** | SAR231893/REGN668 |
| **Applicant** | Regeneron Pharmaceuticals Inc. |
| **Dosage form** | Subcutaneous injection |
| **Applicant proposed Dosing Regimen** | Adults (≥18 Years of Age):<br>• Initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W)<br><br>Pediatric Patients 12 to 17 Years of Age:<br>• Weight 30 kg to <60 kg: Initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W<br>• 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 12 years and older with chronic spontaneous urticaria (CSU) whose disease is not adequately controlled with 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) | Treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment |
| **Recommended SNOMED CT Indication Disease Term for each Indication** (if applicable) | 302162004 \| Chronic idiopathic urticaria (disorder) |
| **Recommended Dosing Regimen** | Same as proposed by Applicant |

# Table of Contents

# Table of Tables

# Table of Figures

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## Additional Reviewers of Application

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Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology

## Signatures

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# Glossary

| | |
|---|---|
| AAS | angioedema activity score |
| AAS7 | angioedema activity score over 7 days |
| AD | atopic dermatitis |
| ADA | antidrug antibody |
| AE | adverse event |
| AESI | adverse events of special interest |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| BLA | biologics license application |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CI | confidence intervalCICU chronic inducible cold urticaria |
| COPD | chronic obstructive pulmonary disease |
| COVID-19 | coronavirus disease 2019 |
| CRF | case report form |
| CRSwNP | chronic rhinosinusitis with nasal polyposis |
| CSU | chronic spontaneous urticaria |
| DARRTS | Document Archiving, Reporting and Regulatory Tracking System |
| DPACC | Division of Pulmonology, Allergy and Critical Care |
| EoE | eosinophilic esophagitis |
| EOS | end of study |
| E-R | exposure-response |
| FDA | Food and Drug Administration |
| HIV | human immunodeficiency virus |
| HSS | Hives Severity Score |
| HSS7 | Hives Severity Score over 7 days |
| H1AH | H1-antihistamines |
| IA | interim analysis |
| ICF | informed consent form |
| IgE | immunoglobulin E |
| IgG4 | immunoglobulin G subclass 4 |
| IL | interleukin |
| IMP | investigational medical product |
| IND | investigational new drug |
| iPSP | initial pediatric study plan |
| ISS | Itch Severity Score |
| ISS7 | Itch Severity Score over 7 days |
| ITT | intent-to-treat |
| LD | loading dose |
| LS | least-squares |

| | |
|---|---|
| MAP | maximum *a posteriori* |
| MedDRA | Medical Dictionary for Regulatory Activities |
| M-M | Michaelis-Menten |
| NAb | neutralizing antibody |
| NDA | new drug application |
| OCP | Office of Clinical Pharmacology |
| OCS | oral corticosteroid |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PN | prurigo nodularis |
| popPK | population PK |
| PRO | patient-reported outcome |
| Q2W | every other week |
| Q4W | every 4 weeks |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SE | standard error |
| TB | tuberculosis |
| TE | treatment-emergent |
| TEAE | treatment-emergent adverse event |
| UAS | Urticaria Activity Score |
| UAS7 | Urticaria Activity Score over 7 days |
| UCT | Urticaria Control Test |
| ULN | upper limit of normal |
| VPC | visual predictive check |
| WOCBP | woman of childbearing potential |
| WOCF | worst-observation carried forward |

# 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 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 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:

1. Atopic Dermatitis (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
2. 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 subtype or oral corticosteroid (OCS)-dependent
    b. Approval: Oct 20, 2021, Add-on maintenance moderate-to-severe asthma 6 to 11 years of age with eosinophilic subtype or OCS-dependent
3. 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
4. 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
5. 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

6. 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

On December 22, 2022, the Applicant submitted a supplemental biologics license application (sBLA), under BLA 761055 (Supplement 051), to expand the indications for dupilumab to include the "treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) whose disease is not adequately controlled with H1 antihistamine treatment." In support of this efficacy supplement, the Applicant conducted two Phase 3 pivotal efficacy and safety studies in adults and children 12 to 17 years of age with CSU (CUPID Study A and Study B). However, following Agency review, it was determined that substantial evidence of effectiveness had not been demonstrated based on the available clinical data and a Complete Response was issued on October 19, 2023.

This is a Class 2 resubmission that includes data from a third study (CUPID C) to support the proposed indication for the "treatment of adult and pediatric patients aged 12 years and older with CSU whose disease is not adequately controlled with H1-antihistamine treatment." The proposed dosing regimen for the CSU indication aligns with the approved doses for the atopic dermatitis indication:

- Adults: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week (Q2W)
- Adolescents 12 to 17 years of age weighing ≥ 60 kg: Initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W
- Adolescents 12 to 17 years of age weighing ≥ 30 kg to < 60 kg: Initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

To support this application, the Applicant completed three 24-week, randomized, double-blind, placebo-controlled safety and efficacy trials (CUPID Studies A, B, and C) of dupilumab in a total of 397 subjects with CSU inadequately controlled with H1-antihistamines (H1AH). The design of Studies A, B, and C were nearly replicate, with identical primary endpoints of change from baseline in Itch Severity Score over 7 days (ISS7) at Week 24; however, the study populations differed, specifically:

- Studies A and C included subjects 6 to 80 years of age with CSU not adequately controlled with H1AH treatment, and naïve to omalizumab (Study A: n=138; Study C: n=151)
- Study B included subjects who were 12 to 80 years of age with CSU not adequately controlled with H1AH treatment, and who were intolerant (n=4) or incomplete responders (n=104) to omalizumab

The results from Studies A and C demonstrated a statistically significant improvement in the primary endpoint, change from baseline in ISS7 at Week 24. For Study A, the least-squares (LS) mean change from baseline in ISS7 at Week 24 was -10.24 in the dupilumab arm and -6.01 in the placebo arm (LS mean difference -4.23 (95% CI: -6.63, -1.84, p=0.0005)). For Study C, the LS mean change from baseline in ISS7 at Week 24 was -8.64 in the dupilumab arm and -6.10 in the placebo arm (LS mean difference -2.54 (95% CI: -4.65, -0.43, p=0.0184)). These improvements in ISS7 were modest, but statistically significant and clinically meaningful. To further support demonstration of effectiveness, key secondary endpoints of change from baseline in Urticaria Activity Score over 7 days (UAS7) and Hives Severity Score over 7 days (HSS7) at Week 24, and improvements in clinically meaningful responder analysis endpoints at Week 24, including the proportion of subjects with well-controlled CSU (defined as a UAS7$\leq$6) and the proportion of subjects with a complete response (defined as UAS7=0), were also met. Study A included a multiplicity controlled assessment of change from baseline in ISS7 at Week 12 (LS mean difference -2.37 (95% CI: -4.60, -0.13, p=0.0377)) that was statistically significant. Assessment of change from baseline in ISS7 at Week 12 was not pre-specified in Study C.

Study B, in a CSU population not adequately controlled with H1AH and omalizumab treatment, met futility criteria at the predefined interim analysis (n=83), as defined in the Statistical Analysis Plan for the trial (see Multi-Disciplinary Review, dated October 18, 2023, for details).

The results from the two pivotal trials, Studies A and C, have met the standard for substantial evidence of effectiveness to demonstrate that dupilumab is an effective treatment for patients with CSU whose disease is inadequately controlled on H1AH. The recommended regulatory action is **Approval** of this sBLA.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

To support this application, the Applicant completed three 24-week, randomized, double-blind, placebo-controlled safety and efficacy trials (CUPID Studies A, B, and C) of dupilumab in a total of 397 subjects with CSU inadequately controlled with H1-antihistamines (H1AH). Studies A and C included subjects who were naïve to omalizumab (n=289), and Study B included subjects who were intolerant (n=4) or incomplete responders (n=104) to omalizumab. The primary endpoint for the trials was change from baseline in itch severity score over 7 days (ISS7) at 24 weeks. The results from Studies A and C demonstrate a statistically significant effect on the primary endpoint, the key secondary endpoint of change from baseline in UAS7 at Week 24, and other clinically meaningful endpoints, including the proportion of subjects with a complete response at 24 weeks (defined as UAS7=0). Study A included a multiplicity controlled assessment of change from baseline in ISS7 at Week 12 that was statistically significant, while assessment of change from baseline in ISS7 at Week 12 was not pre-specified in Study C. In both pivotal trials, improvements in ISS7 and UAS7 were modest and gradual; early timepoints (e.g. Week 4) were not included as multiplicity-controlled secondary endpoints. Although the angioedema activity score over 7 days (AAS7) was not multiplicity controlled, there was no difference in change from baseline in AAS7 between the treatment arms. Study B met futility criteria at the predefined interim analysis, as defined in the Statistical Analysis Plan for the trial.

Differences in baseline characteristics and disease severity may have contributed to the difference in the efficacy results between the three studies. The greater effect size for Study A compared to Study C may be a result of differences in disease severity between the two studies; the enrolled population in Study A, compared to Study C, had higher mean ISS7 at baseline, higher UAS7 at baseline, more subjects on 4-fold higher than approved antihistamine doses, and more subjects with angioedema. Study B represented a more severe CSU population, with inadequate response to omalizumab therapy. The differences in degree of recalcitrance between the omalizumab-refractory population compared to the omalizumab-naïve population may account for the lack of demonstrated efficacy of dupilumab in Study B.

The results from the two pivotal trials, Studies A and C, demonstrate substantial evidence of effectiveness for dupilumab as a treatment for patients with CSU whose disease is inadequately controlled on H1AH. However, dupilumab's role may be limited to patients with moderate disease, particularly given the gradual improvement following initiation of treatment.

Assessment of pooled safety from Studies A, B, and C was limited due to the small sample size (n=195 exposed to dupilumab) and the short study duration. The application included an assessment of adverse events of special interest, based on the known safety profile of dupilumab, including hypersensitivity reactions, conjunctivitis/keratitis, eosinophilic conditions, and helminthic infections. The safety profile for dupilumab in CSU was consistent with the known safety profile seen in the clinical development programs for the approved dupilumab indications,

including AD, asthma, CRSwNP, EoE, PN, and COPD, as well as in postmarketing safety reports. No new safety concerns were identified.

The benefit-risk assessment for dupilumab for patients with CSU inadequately controlled on H1AH is favorable. Studies A and C provide the basis for substantial evidence of effectiveness, and all three pivotal trials provide a supportive safety profile. The review team recommends **approval** of dupilumab for the treatment of adults and pediatric patients aged 12 and older with CSU inadequately controlled on H1AH.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • CSU is characterized by spontaneous and recurrent urticaria of at least 6 weeks duration and without an identifiable cause.<br>• The major feature of CSU is hives with prominent pruritus; some patients also present with angioedema, in addition to hives.<br>• Activation of mast cells and basophils is central to the pathogenesis of CSU.<br>• Most patients are treated successfully with antihistamines; however, 25% of patients are refractory to antihistamine therapy and require alternative treatments, such as omalizumab or systemic immunomodulators.<br>• CSU is self-limited in the majority of patients, with a 1-year spontaneous remission rate of 30 to 50%, and an average duration of two to five years. | • CSU causes significant morbidity in patients, with diminished quality of life.<br>• CSU is generally self-limited, resolving over several years, but some patients have more persistent disease. |
| Current Treatment Options | • Current guideline recommended treatment options for CSU include H1-receptor antihistamines (H1AH), at approved doses and up to 4-fold higher than approved doses.<br>• For adults and adolescents 12 years of age and older who remain symptomatic despite H1AH treatment, omalizumab is recommended by national and international treatment guidelines.<br>• Patients who are refractory to H1AH and are unresponsive to omalizumab may use off-label therapies, including cyclosporine, hydroxychloroquine, or systemic corticosteroids. The alternative treatments have significant adverse event profiles. | • Patients whose CSU is refractory to H1AH therapy require systemic immunomodulatory treatments, including omalizumab, with more complex side effect profiles.<br>• Additional treatment options with improved safety profiles are needed for patients with refractory CSU. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • To establish efficacy, three adequate and well-controlled, 24-week, randomized, double-blind, placebo-controlled trials were conducted in subjects with CSU with inadequate control despite antihistamine use.<br>– Studies A and C enrolled omalizumab-naïve subjects. These two trials demonstrated favorable efficacy results and met statistical significance for the primary endpoint (ISS7 at Week 24) and clinically meaningful secondary endpoints, including a significant improvement in the proportion of subjects with completely or well controlled CSU (UAS7=0 or UAS7≤6). Studies A and C establish SEE for dupilumab in CSU.<br>– Study B, which enrolled subjects who were intolerant or unresponse to omalizumab, met futility criteria at the prespecified interim analysis. It did not meet statistical significance for any primary or secondary endpoints.<br>• In the clinical trials, dupilumab demonstrated a statistically significant and clinically meaningful effects on the primary symptoms of CSU, itch and hives, in subjects whose CSU is refractory to H1AH therapy. Its efficacy has not been established in individuals whose CSU is refractory to omalizumab. | • Dupilumab demonstrates modest efficacy for the treatment CSU in patients who remain symptomatic despite H1AH treatment.<br>• Although efficacy was demonstrated at Week 24, the improvements in the primary and key secondary endpoints were gradual and progressive, with no pre-specified efficacy assessments at early timepoints (e.g. 4 weeks)<br>• Efficacy has not been established in individuals whose CSU is poorly responsive to omalizumab.<br>• Dupilumab provides an additional biologic treatment option for certain patients refractory to H1AH treatment. |
| Risk and Risk Management | • The safety profile for CSU was consistent with the known safety profile of dupilumab observed in the prior clinical trials for approved indicatiosn including AD, asthma, CRSwNP, EoE, PN, and COPD, as well as in postmarketing safety reports.<br>• There were no new safety signals identified. | • The safety profile for CSU is consistent with the known safety profile of dupilumab observed in approved indications.<br>• Safety can be adequately addressed through labeling and 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 | | |
| | | X | Patient reported outcome (PRO) | 8.1.3 |
| | | ☐ | Observer reported outcome (ObsRO) | |
| | | ☐ | Clinician reported outcome (ClinRO) | |
| | | ☐ | Performance outcome (PerfO) | |
| | ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Natural history studies | | |
| | ☐ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | ☐ | Other: (Please specify): | | |
| ☐ | **Patient experience data that were not submitted in the application, but were considered in this review:** | | | |
| | ☐ | Input informed from participation in meetings with patient stakeholders | | |
| | ☐ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | ☐ | Observational survey studies designed to capture patient experience data | | |
| | ☐ | Other: (Please specify): | | |
| ☐ | **Patient experience data was not submitted as part of this application.** | | | |

# 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 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. The pathophysiology of CSU is thought to be mediated by activated mast cells and basophils releasing mediators that cause itching, swelling, and redness. Approximately 1% of the general population is affected by CSU. It is more common in adults than children, most often presenting in the third to fifth decades of life (Adkinson et al. 2014). Women are more likely to develop CSU compared to men. CSU tends to be a self-limited condition in the majority of patients, with an average duration of less than five years and a 2-year spontaneous remission rate of 30 to 50% (Stepaniuk et al. 2020).

CSU is characterized by recurrent urticaria with or without angioedema. The urticarial lesions have three typical features: central swelling with surrounding erythema, pruritus, and a time course of up to 24 hours for each individual lesion (evanescent) without residual scarring or bruising of the skin. Angioedema, when present, manifests as episodic submucosal or subcutaneous swelling, often affecting areas of the body with loose connective tissue in an asymmetric pattern.

CSU leads to a decreased quality of life with impacts on sleep, fatigue, emotional factors, and work productivity (O'Donnell et al. 1997). Individuals with CSU reporting quality of life scores similar to individuals with coronary artery disease (O'Donnell et al. 1997). Individuals with CSU also have a higher prevalence of psychiatric disorders, particularly anxiety and depression, with severity of psychiatric disease correlating with severity of urticaria (Chu et al. 2020). The treatment goals of CSU include resolution or reduction of the signs and symptoms of active disease to provide relief and improve quality of life until remission occurs.

## 2.2. Analysis of Current Treatment Options

Approved treatments and therapies used off-label for the treatment of CSU are displayed in Table 1. First line therapy for CSU is a second generation H1AH at the approved dose, which is effective for the majority of patients (Bernstein et al. 2014). Practice guidelines from the American Academy of Allergy, Asthma, and Immunology and European Academy of Allergology and Clinical Immunology recommend that if patients do not respond to second generation H1AH at approved doses, then higher doses of H1AH, up to 4-fold higher than the approved dose, may provide improved efficacy (Bernstein et al. 2014; Zuberbier et al. 2018). In addition to the second-generation antihistamines that carry formal indications for CSU, all antihistamine

products, including many older first-generation sedating antihistamines (e.g., hydroxyzine, diphenhydramine, promethazine, etc.), are routinely used in clinical practice for the treatment of CSU. Many of the older products carry indications for more general urticaria related terms such as urticaria, chronic urticaria, etc. Approximately 25% of patients with CSU are inadequately controlled on H1AH therapy alone (Maurer et al. 2011). For these patients, guidelines recommend step-up therapy with omalizumab, which was approved on March 21, 2014, in adults and adolescents 12 years of age and older who remain symptomatic despite H1AH treatment (Zuberbier et al. 2018). Still, up to 30% of individuals with CSU may remain symptomatic despite H1AH and omalizumab therapy (Metz et al. 2020). For these patients, therapies with anti-inflammatory or immunosuppressant properties such as cyclosporine may be used off-label; however, these medications are not approved for urticaria and lack robust evidence for efficacy in CSU (Zuberbier et al. 2018).

**Table 1. Summary of Current Treatment Armamentarium for Chronic Spontaneous Urticaria**

| Product Name (Brand Name) | Mechanism of Action | Dosing/ Administration | Efficacy Information/ Labeling Indication | Important Safety and Tolerability Issues[1] |
|---|---|---|---|---|
| ***Approved Therapies*** | | | | |
| Loratadine (Claritin) | H1AH, 2nd generation | 10 mg PO | Can be used up to 4X approved dose for treatment of CSU.<br><br>Chronic idiopathic urticaria | May be sedating at higher than approved doses. |
| Fexofenadine (Allegra) | H1AH, 2nd generation | 180 mg PO | | |
| Cetirizine (Zyrtec) | H1AH, 2nd generation | 10 mg PO | | |
| Levocetirizine (Xyzal) | H1AH, 2nd generation | 10 mg PO | | |
| Diphenhydramine[3] | H1AH, 1st generation | 25 to 30 mg, PO | Uncomplicated allergic skin manifestations of urticaria and angioedema | Sedation, cardiovascular AEs (hypotension, palpitations, tachycardia, extrasystoles), epigastric distress, thickening of bronchial secretions |
| Hydroxyzine | H1AH, 1st generation | 10 to 25 mg, PO | Useful in the management of pruritus due to allergic conditions such as chronic urticaria and atopic and contact dermatoses, and in histamine-mediated pruritus. | QT prolongation/Torsade de Points (TdP), acute generalized exanthematous pustulosis (AGEP), drowsiness, hallucination. |
| Promethazine | H1AH, 1st generation | 12.5 mg PO, oral syrup available | Mild, uncomplicated allergic skin manifestations of urticaria and angioedema. | Significant: Anticholinergic effects, CNS depression, extrapyramidal symptoms, neuroleptic malignant syndrome, orthostatic hypotension, respiratory depression.<br><br>Significant drug interactions exist. |

| Product Name (Brand Name) | Mechanism of Action | Dosing/ Administration | Efficacy Information/ Labeling Indication | Important Safety and Tolerability Issues[1] |
|---|---|---|---|---|
| Cyproheptadine[3] | Includes H1AH, 1st generation properties | 4 mg PO | Mild, uncomplicated allergic skin manifestations of urticaria and angioedema; cold urticaria. | Sedation, cardiovascular AEs (hypotension, palpitations, tachycardia, extrasystoles), epigastric distress, thickening of bronchial secretions, acute labyrinthitis, tinnitus. |
| Clemastine | Includes H1AH, 1st generation properties | 1.34 mg PO | Relief of mild, uncomplicated allergic skin manifestations of urticaria and angioedema. | Significant drug interactions exist. |
| Additional unapproved therapies with first generation H1AH properties used off-label: chlorpheniramine, doxepin; this is not a complete list of medications with first generation H1AH properties that may be used off-label for symptom relief. | | | | |
| *Approved for Subjects Symptomatic Despite H1AH Treatment* | | | | |
| Omalizumab (Xolair) | Humanized recombinant IgG mAb that binds to free IgE and inhibits the interaction between IgE & the Fc region of the high-affinity receptor (FcεRI) on mast cells & basophils | 150 or 300 mg SC every 4 weeks | CSU in adults and adolescents ≥12 years of age who remain symptomatic despite H1AH treatment | US Boxed Warning: Anaphylaxis. Risk mitigation includes initiating treatment in healthcare setting and closely observe patients for an appropriate time after administration. Patients should carry emergency epinephrine for anaphylaxis risk. |

| Product Name (Brand Name) | Mechanism of Action | Dosing/ Administration | Efficacy Information/ Labeling Indication | Important Safety and Tolerability Issues[1] |
|---|---|---|---|---|
| ***Unapproved therapies that may be used for refractory subjects[2]*** | | | | |
| *Immunosuppressants* | | | | |
| Cyclosporine | Inhibits TH cells by blocking the production of pro-inflammatory cytokines | 4-6 mg/kg PO | May show efficacy in the H1AH and omalizumab refractory groups | Hypertension, renal insufficiency, hirsutism, gingival hyperplasia. |
| Mycophenolate Mofetil | Inhibitor of type I and type II (IMPDH) which inhibits de novo guanosine nucleotide synthesis and blocks DNA synthesis | 1000 mg BID and increased by 500 mg BID; maximal dose of 2000 mg BID | N/A | Significant adverse reactions include acute inflammatory syndrome, bone marrow suppression (anemia, pure red cell aplasia, leukopenia, thrombocytopenia), GI effects, infection, lymphoproliferative disorders. |
| Tacrolimus | Suppresses cellular immunity (inhibits T-lymphocyte activation) by binding to an intracellular protein, FKBP-12 and complexes with calcineurin dependent proteins to inhibit calcineurin phosphatase activity | 1 mg BID, maximum of 3 mg BID PO | N/A | US Boxed Warning: Malignancies and serious infection.<br><br>Significant adverse reactions include diabetes mellitus, drug- induced thrombotic microangiopathy, hyperkalemia, hypersensitivity reactions, hypertension, nephrotoxicity, neurotoxicity, pure red cell aplasia. |
| Azathioprine | Imidazolyl derivative of mercaptopurine; Metabolites are incorporated into replicating DNA and halt replication | 1 mg/kg/d PO | N/A | Significant adverse reactions include GI effects (nausea, vomiting, diarrhea), dose related hematologic toxicity (leukopenia, thrombocytopenia anemias), infections, liver dysfunction (hepatotoxicity), malignancy, pancreatitis. |

| Product Name (Brand Name) | Mechanism of Action | Dosing/ Administration | Efficacy Information/ Labeling Indication | Important Safety and Tolerability Issues[1] |
|---|---|---|---|---|
| *Anti-inflammatory* | | | | |
| Dapsone | Competitive antagonist of para-aminobenzoic acid (PABA) | 100 mg daily. CBC and LFT monitoring required | N/A | Significant adverse reactions include blood dyscrasias (methemoglobinemia, hemolytic anemia, neutropenia, agranulocytosis. Rare reports of aplastic anemia and pancytopenia), hepatic effects, hypersensitivity reactions (delayed). |
| Sulfasalazine | Unknown, inflammatory mediator modulation, leukotrienes | 500 mg once or BID, up to 1 gram BID | | Significant adverse reactions include blood dyscrasias (agranulocytosis, aplastic anemia, hemolytic anemia, leukopenia, immune thrombocytopenia), GI effects, hypersensitivity reactions (delayed). |
| Hydroxychloroquine | Inhibits locomotion of neutrophils and chemotaxis of eosinophils; impairs complement-dependent antigen-antibody reactions | 200 mg BID | | Significant adverse reactions include cardiomyopathy, G6PD deficiency, hypersensitivity reactions (delayed), hypoglycemia, neuromuscular effects, neuropsychiatric effects, QT prolongation, retinal toxicity. Several other toxicities and body systems may be affected. |
| Systemic Corticosteroids | Decreases inflammation by suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability; suppresses the immune system by reducing activity and volume of the lymphatic system | Dosing varies | Providers should try to limit exposure and use only for severe refractory symptoms | Adverse reactions by body system include (highlighting some major effects): Dermatologic (rashes, skin changes), ophthalmologic, cardiovascular, GI effects, bone and muscle effects, neuropsychiatric effects, metabolic and neuroendocrine effects, immune system effects, hematologic effects |

| Product Name (Brand Name) | Mechanism of Action | Dosing/ Administration | Efficacy Information/ Labeling Indication | Important Safety and Tolerability Issues[1] |
|---|---|---|---|---|
| Montelukast | Leukotriene receptor antagonist (LTRA) | 10 mg/d | May be added on with increased doses of antihistamines | US Boxed Warning: Serious neuropsychiatric events |

Source: Clinical Reviewer
[1] See drug labeling for complete list of possible adverse reactions.
[2] Unapproved therapies are used off-label, dosing varies. The CSU literature has been referenced for doses used in refractory CSU. Trial duration varies. Labs may be necessary prior to initiation due to toxicity of agents (Khan et al. 2021).
[3] Labeling information provided by drugs.com, FDA Prescriber Information summary
Abbreviations: BID, twice daily; CSU, chronic spontaneous urticaria; GI, gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase; H1, histamine-1 receptor; H1AH, H1-anthistamine; IgE, immunoglobulin E; IMPDH, inosine monophosphate dehydrogenase; LFT, liver function test; PO, per oral; SC, subcutaneous

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

For details regarding previously reviewed indications, refer to Section 1.1 and the unique Multi-disciplinary Reviews for each indication.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

The dupilumab CSU program was developed under the same IND as the asthma and CRSwNP indications (IND 105379). The key regulatory history for CSU is summarized in Table 2. Dupilumab is not approved for chronic spontaneous urticaria or other urticaria in any market.

Regarding related trials, the Applicant is conducting PKM16982, an ongoing 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 H1AH therapy. Study PKM16982 was originally submitted to the Division on April 12, 2022. At that time, the Applicant was also 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 who remained symptomatic despite H1AH therapy. 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.

**Table 2. Summary of Presubmission/Submission Regulatory Activity for Chronic Spontaneous Urticaria Indication**

| Interaction | Date | Remarks |
|---|---|---|
| EOP2 meeting | October 18, 2019 | Division recommended the Applicant to change the primary outcome measure (b) (4) to ISS7. Applicant agrees. |
| Master protocol EFC16461 (CUPID) submitted | October 30, 2019 | Adolescents included in the studies. |
| Agreed Amended iPSP | June 16, 2020 | Applicant maintained inclusion of children 6 to <12 years of age in the planned pediatric PK and safety study to mitigate against potential recruitment difficulties for patients 6 to <12 years of age in the ongoing Study A. |
| Protocol amendment version 4 | April 29, 2021 | Introduced IA for Study B due to COVID impact and associated difficulties to enroll patients in Study B |

| Interaction | Date | Remarks |
|---|---|---|
| Type C Meeting | October 14, 2021 | DPACC did not agree that (b) (4) ; acknowledged Study B was being conducted in omalizumab intolerant/incomplete responders. Meeting comments only, meeting cancelled. |
| Interim analysis and press release | Jan 19, 2022 (IA)<br>Feb 18, 2022 (PR) | IA for Study B met futility criteria and Study B is terminated. A press release with the results was released to the public with these results. |
| Pre-sBLA meeting | Dec 1, 2022 | Acknowledged two studies conducted in two distinct subsets of CSU populations; futility at IA for Study B with potential bias. Requested additional IA information. Meeting comments only. |
| BLA submission | Dec 22, 2022 | Applicant submitted supplement 51 to add a CSU indication: "treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) whose disease is not adequately controlled with H1 antihistamine treatment," based on Study A and Study B results. |
| Complete Response to sBLA | October 19, 2023 | Study A met statistical significant for the primary and key secondary endpoints. Study B met pre-specified futility criteria at IA. DPACC determined that results from a single adequate and well-controlled trial are not sufficient to establish SEE and that supportive data from an additional adequate and well-controlled trial was needed. |
| Protocol amendment version 5 | October 27, 2023 | Addition of Study C with a study population and design similar to the completed Study A. |
| Class 2 resubmission of sBLA | October 18, 2024 | Current review, based on results from Study A, Study B, and Study C |

Source: Clinical Reviewer
Abbreviations: DPACC, Division of Pulmonology, Allergy, and Critical Care; IA, interim analysis; IND, investigational new drug; iPSP, initial pediatric study plan; OCS, oral corticosteroid; SEE, substantial evidence of effectiveness

# 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 on the basis of efficacy or safety concerns 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 were submitted nor required for this supplemental BLA.

## 6 Clinical Pharmacology

### 6.1. Executive Summary

Dupilumab (Dupixent) solution for subcutaneous (SC) injection was originally approved under BLA 761055 on March 28, 2017, for the treatment of adult patients with moderate to severe atopic dermatitis (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 a human 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:

- 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)

- 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)
- Add-on maintenance treatment in adult and pediatric patients aged 12 years and older with inadequately controlled CRSwNP (S-014, S-066)
- Treatment of adult and pediatric patients aged 1 year and older, weighing at least 15 kg, with EoE (S-040, S-057)
- Treatment of adult patients with prurigo nodularis (S-044)
- Add-on maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype (S-064)

On December 22, 2022, the Applicant (Regeneron Pharmaceuticals, Inc.) submitted a supplemental biologics license application (sBLA) under BLA 761055 (Supplement 051), in which the Applicant proposed to expand the indication of dupilumab to include the treatment of adult and pediatric patients aged 12 years and older with CSU whose disease is not adequately controlled with H1 antihistamine treatment. In support of this efficacy supplement, the Applicant conducted two Phase 3 pivotal efficacy and safety studies in adults and children 12 to 17 years of age with CSU (EFC16461 (CUPID) Study A and Study B).

However, following Agency review, it was determined that substantial evidence of effectiveness was not demonstrated based on the available clinical data and a Complete Response was subsequently issued on October 19, 2023. Of note, the efficacy supplement and the proposed dosing regimen for adults and pediatrics patients aged 12 years and older were reviewed by Dr. Tao Liu and found to be approvable from a clinical pharmacology perspective. Refer to the BLA Multi-Disciplinary Review and Evaluation dated October 18, 2023 (Document Archiving, Reporting and Regulatory Tracking System [DARRTS] Reference ID: 5263308).

The present efficacy supplement is a Class 2 re-submission, in which the Applicant is again seeking to expand the indication of dupilumab to include the treatment of adult and pediatric patients aged 12 years and older with CSU whose disease is not adequately controlled with H1 antihistamine treatment. In support of the current re-submission, the Applicant has conducted a third Phase 3 pivotal efficacy and safety study in adult and pediatric patients aged 12 to 17 years of age with CSU (EFC16461 (CUPID) Study C). The proposed SC dosing regimens are the same as those previously proposed and reviewed by the clinical pharmacology team:

- **Adults and adolescents ≥12 to <18 years of age weighing ≥60 kg:** An initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W
- **Adolescents ≥12 to <18 years of age weighing ≥30 kg to <60 kg:** An initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W

The clinical pharmacology review for this sBLA focused on analysis of the pharmacokinetics (PK), pharmacodynamics (PD), exposure-response (E-R) relationship, and immunogenicity data in subjects with CSU to support the proposed indication. The major clinical pharmacology findings for this submission are as follows:

- Following SC administration of dupilumab at the proposed dosing regimen of 600 mg + 300 mg Q2W, the observed dupilumab trough concentrations in adults with CSU were comparable to those observed in adults with other approved indications, including AD, asthma, CRSwNP, etc.
- Following SC administration of dupilumab at the proposed dosing regimens of either 600 mg + 300 mg Q2W in adolescents weighing ≥ 60 kg, or 400 mg + 200 mg Q2W in adolescents weighing ≥ 30 kg and < 60 kg with CSU, the observed trough concentrations were comparable to those observed in adults with CSU. Comparable dupilumab systemic exposure between adolescents and adults is also supported by simulated data derived from population PK (popPK) modeling.
- The change from baseline in serum total immunoglobulin E (IgE) following SC administration of dupilumab in subjects with CSU was comparable to that observed in other approved indications, including moderate to severe asthma and PN. Change from baseline in serum IgE in adolescents was within the range of that observed in adults at the proposed dosing regimens.
- A significant exposure-dependent response could not be concluded based on the totality of data across clinical studies in CSU subjects.
- The observed incidence rates of development of treatment-emergent (TE) antidrug antibodies (ADAs) and neutralizing antibodies (NAbs) to dupilumab in subjects with CSU were comparable to those observed across other approved indications.
- Dupilumab exposure was reduced in subjects who tested positive for ADAs and NAbs. However, ADA status did not appear to induce a negative impact on key efficacy endpoints ISS7 or UAS7, nor was it associated with a clinically meaningful increase in safety events of interest.

**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-051. This efficacy supplement and the proposed dosing regimens for adults and adolescents aged 12 years and older 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 by Dr. Jie Wang during the original BLA review. Refer to the Office of Clinical Pharmacology Review dated December 19, 2016, for information regarding the clinical pharmacology data submitted in support of this supplemental BLA (DARRTS Reference ID 4030358).

In support of the current BLA supplement for the CSU indication, the Applicant has conducted three clinical efficacy and safety studies in patients with CSU under a master protocol design, all of which were 24-week, double-blind, placebo-controlled Phase 3 studies (Studies EFC16461-A, EFC16461-B, and EFC16461-C). Studies EFC16461-A and EFC16461-B were previously submitted by the Applicant and reviewed by the Agency following initial submission under BLA 761055/S-051. Both were pivotal efficacy and safety studies in adults and pediatrics with CSU who remain symptomatic despite the use of H1 antihistamine treatment, although EFC16461-A enrolled patients who were naïve to omalizumab and EFC16461-B enrolled patients who were intolerant or incomplete responders to omalizumab. For additional information and discussion regarding the results from these studies and the data supporting the Agency's Complete Response decision, refer to the BLA Multi-Disciplinary Review and Evaluation dated October 18, 2023 (DARRTS Reference ID 5263308).

In the current re-submission of this BLA supplement, the Applicant has submitted Study EFC16461-C for Agency review, which was of a similar design to EFC16461-A and enrolled adults (≥ 18 years), adolescents (aged ≥ 12 to < 18 years), and children (aged ≥ 6 to < 12 years) with CSU who were symptomatic despite the use of H1-antihistamine and who were naïve to omalizumab treatment. In addition to safety and efficacy assessments, the Applicant also evaluated the PK, PD (total serum IgE), and immunogenicity (ADAs and NAbs) following dupilumab SC administration.

A total of 151 subjects were randomized in an approximate 1:1 ratio to receive either dupilumab (N = 74) or placebo (N = 77). Of those randomized to the dupilumab arm, one was a child aged 6 to 11, three were adolescents aged 12 to 17, and all remaining subjects were adults aged 18 or older. Subjects randomized to receive dupilumab treatment received the following dosage regimens according to patient age and weight:

1. **Adults and Adolescents (≥ 12 to < 18 years of age) weighing ≥ 60 kg:** 600 mg SC Loading Dose (LD), followed by 300 mg SC Q2W (N = 72)
2. **Adolescents (≥ 12 to < 18 years of age) and Children (≥ 6 to < 12 years of age) weighing < 60 kg and ≥ 30 kg:** 400 mg SC LD, followed by 200 mg Q2W (N = 2)
3. **Children (≥ 6 to < 12 years of age) weighing < 30 kg and ≥ 15 kg:** 600 mg SC LD, followed by 300 mg every 4 weeks (Q4W; N = 0)

At the time of submission of this BLA supplement, Study EFC16461-C is ongoing. Approximately 91% (N = 67) and 66% (N = 49) of randomized subjects in the dupilumab arm have completed the study through Week 24 and Week 36, respectively. In the placebo group, approximately 90% (N = 69) and 68% (N = 52) of randomized subjects have completed the study through Week 24 and Week 36, respectively. In addition, there were a total of 15 and 18 treatment discontinuations in the dupilumab and placebo groups, respectively. Refer to the clinical review for additional details pertaining to the study design, key efficacy and safety endpoints, and demographics (Section 8).

#### 6.2.2. General Dosing and Therapeutic Individualization

**General Dosing**

The proposed dosing regimens of 600 mg + 300 mg Q2W/400 mg + 200 mg Q2W administered by SC administration were evaluated in adults and adolescents ≥ 12 to < 18 years of age with CSU in pivotal clinical studies EFC16461-C, EFC16461-A, and EFC16461-B.

**Therapeutic Individualization**

None.

**Outstanding Issues**

None.

### 6.3. Comprehensive Clinical Pharmacology Review

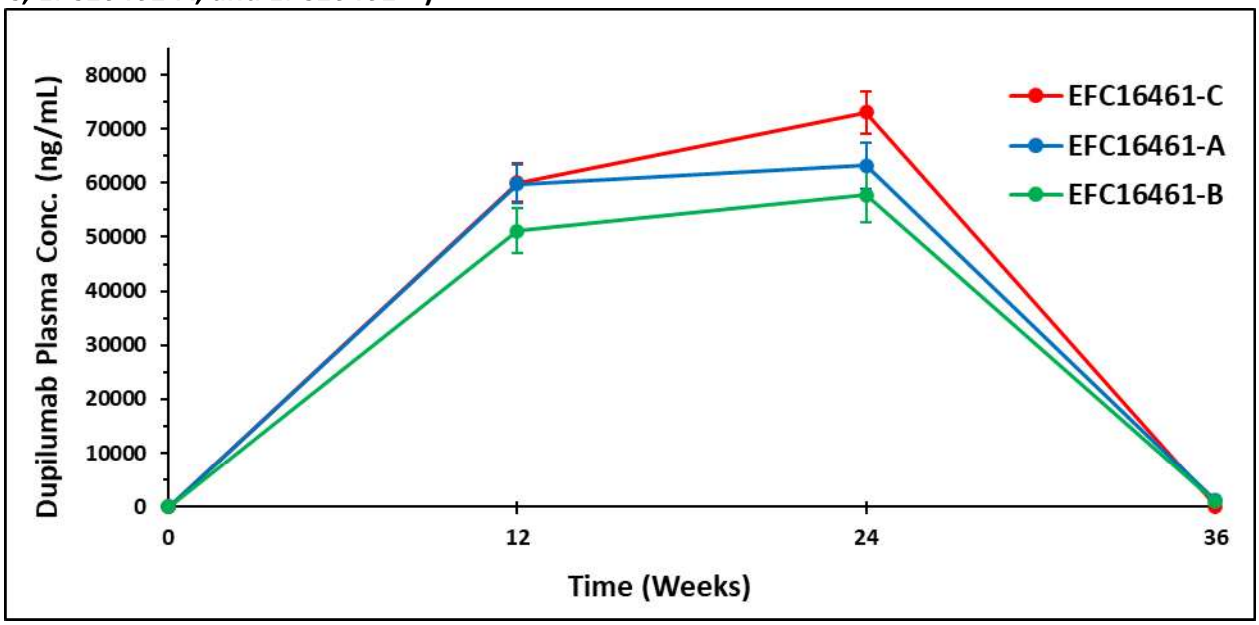
#### 6.3.1. Clinical Pharmacology Questions

**What are the pharmacokinetic characteristics of dupilumab following subcutaneous administration in patients with CSU?**

The PK of dupilumab was characterized in subjects with CSU using sparse sampling. Trough PK samples were collected at pre-dose on Day 0, Week 12, Week 24, and Week 36 following SC administration of dupilumab for 24 weeks in Studies EFC16461-C, EFC16461-A, and EFC16461-B. Plasma concentrations of dupilumab in all CSU studies were determined using a validated bioanalytical enzyme-linked immunosorbent assay (REGN668-AV-13074-VA-01V1), which was reviewed as part of the original BLA submission for AD. Refer to the Clinical Pharmacology and Biopharmaceutics Review by Dr. Jie Wang for additional information (DARRTS Reference ID: 4030358). The in-study bioanalysis results for Study EFC16461-C met acceptance criteria. In-study bioanalysis results for EFC16461-A and EFC16461-B were previously reviewed by Dr. Tao Liu during review of the Applicant's initial submission of this supplement under BLA 761055/S-051 and were found to be acceptable at that time (DARRTS Reference ID: 5263308).

The PK population for Study EFC16461-C included a total of 72 out of 74 subjects randomized to the dupilumab arm, all of whom had at least one post-baseline PK data point available. Of note, given that Study EFC16461-C is ongoing and 17 dupilumab-treated participants had yet to complete their scheduled follow-up visit through Week 36 at the time of this sBLA submission, the sample size is reduced at Week 36 compared to other timepoints. A summary of dupilumab plasma trough concentrations over time following SC administration of 300 mg SC Q2W in the PK population for clinical studies EFC16461-C, EFC16461-A, and EFC16461-B is depicted below in Figure 1 and Table 3.

**Figure 1. Mean (SE) Dupilumab Plasma Trough Concentration (ng/mL) Over Time (EFC16461-C, EFC16461-A, and EFC16461-B)[a,b,c,d]**




Source: Reviewer's analysis based on adpc.xpt for Studies EFC16461-A, EFC16461-B, and EFC16461-C
[a] A total of N=72, N=67, and N=51 subjects were included in the PK population for Studies EFC16461-C, EFC16461-A, and EFC16461-B, respectively
[b] EFC16461-C: Week 0 (N=68), Week 12 (N=72), Week 24 (N=59), Week 36 (N=42)
[c] EFC16461-A: Week 0 (N=63), Week 12 (N=67), Week 24 (N=64), Week 36 (N=60)
[d] EFC16461-B: Week 0 (N=48), Week 12 (N=51), Week 24 (N=47), Week 36 (N=47)
Abbreviations: Conc., concentration; N, number of subjects; PK, pharmacokinetic; SE, standard error

**Table 3. Summary of Dupilumab Trough Concentrations Following Administration at 300 mg SC Q2W Dosage Across Clinical Studies in CSU Population**

| | | Mean (SD) $C_{trough}$ (mg/L) | | | |
|---|---|---|---|---|---|
| **Clinical Study** | **Dupilumab Dose (N)[a]** | **Week 0** | **Week 12** | **Week 24** | **Week 36** |
| EFC16461-C[b] | 300 mg SC Q2W (72) | 0.00 (0.0) | 60.0 (30.8) | 73.0 (29.5) | 0.17 (0.73) |
| EFC16461-A[c] | 300 mg SC Q2W (67) | 0.00 (0.0) | 59.8 (30.1) | 63.2 (34.0) | 1.17 (3.55) |
| EFC16461-B[d] | 300 mg SC Q2W (51) | 0.00 (0.0) | 51.2 (31.7) | 57.8 (35.1) | 1.00 (3.37) |

Source: Reviewer's analysis based on adpc.xpt for Studies EFC16461-A, EFC16461-B, and EFC16461-C
[a] A total of N=72, N=67, and N=51 subjects were included in the PK population for Studies EFC16461-C, EFC16461-A, and EFC16461-B, respectively
[b] EFC16461-C: Week 0 (N=68), Week 12 (N=72), Week 24 (N=59), Week 36 (N=42)
[c] EFC16461-A: Week 0 (N=63), Week 12 (N=67), Week 24 (N=64), Week 36 (N=60)
[d] EFC16461-B: Week 0 (N=48), Week 12 (N=51), Week 24 (N=47), Week 36 (N=47)
Abbreviations: CSU, chronic spontaneous urticaria; $C_{trough}$, dupilumab plasma trough concentration; N, number of subjects; PK, pharmacokinetic; Q2W, every 2 weeks; SC, subcutaneous; SD, standard deviation

Given that the Applicant is seeking approval for treatment of CSU in both adults and adolescents down to 12 years of age, a summary of the observed dupilumab trough concentrations at steady state in both adult and adolescent subjects with CSU is provided below in Table 4.

**Table 4. Summary of Dupilumab Trough Concentrations at Steady State in Adults Versus Adolescents Across Clinical Studies in CSU Population**

| | | | Mean (SD) $C_{trough,ss}$ (mg/L) | |
|---|---|---|---|---|
| **Clinical Study** | **Age Group[a]** | **Dose** | **N** | **Observed[b]** |
| EFC16461-C | Adults | 300 mg Q2W | 55 | 73.7 (29.3) |
| | Adolescents (≥60 kg) | 300 mg Q2W | 2 | 55.6 (8.41) |
| | Adolescents (≥30 to <60 kg) | 200 mg Q2W | 1 | 44.9 |
| EFC16461-A | Adults | 300 mg Q2W | 62 | 63.5 (34.2) |
| | Adolescents (≥60 kg) | 300 mg Q2W | 1 | 78.8 |
| | Adolescents (≥30 to <60 kg) | 200 mg Q2W | 1 | 22.4 |
| EFC16461-B | Adults | 300 mg Q2W | 46 | 57.7 (35.5) |
| | Adolescents (≥60 kg) | 300 mg Q2W | 1 | 64.6 |

Source: Adapted from Summary of Clinical Pharmacology Studies, sBLA 761055-S-051 (Table 6)
[a] Adults defined as ≥ 18 years of age; Adolescents defined as ≥ 12 to < 18 years of age
[b] Observed $C_{trough,ss}$ at Week 24
Abbreviations: CSU, chronic spontaneous urticaria; $C_{trough,ss}$, dupilumab plasma trough concentration at steady state; N, number of subjects; Q2W, every 2 weeks; SD, standard deviation

In addition, the Applicant conducted a popPK analysis with data obtained across clinical studies in patients with CSU (Study POH1089). This popPK analysis incorporated prior information from a previously established global popPK model which was developed based on pooled data from healthy adult subjects, adult subjects with AD, and adult and adolescent subjects with asthma. For additional details, refer to the Pharmacometrics Review (Section 15.3). The popPK model

was previously applied to characterize the PK in patients with CRSwNP and was reviewed by Dr. Dipak Pisal under BLA 761055/S-014 (DARRTS Reference ID: 4454143).

The Applicant utilized this popPK model to compare dupilumab exposure across age groups and weight categories. A summary of the popPK model-derived estimates of individual steady-state exposure for subjects in Studies EFC16461-C, EFC16461-A, and EFC16461-B is displayed below according to subject age and weight category (Table 5). In addition, the mean (SD) observed steady-state plasma trough concentrations in adults and adolescents across all three clinical studies in CSU patients are provided for comparison.

**Table 5. Predicted and Observed Dupilumab Steady State Exposure by Age Category Across Clinical Studies in CSU Subjects[a]**

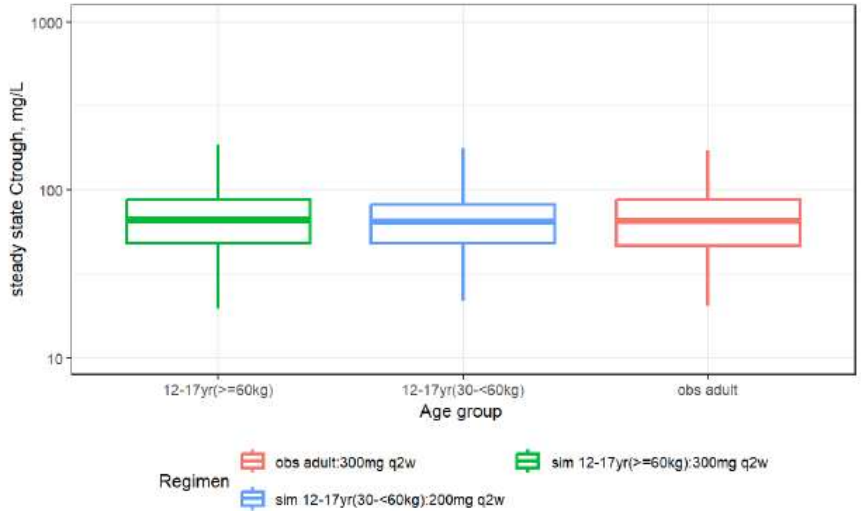
| Age Group | Dose | Predicted PK Parameters | | | | Observed PK Parameter | |
|---|---|---|---|---|---|---|---|
| | | N (median weight) | $AUC_{\tau,ss}$ (mg•day/L) | $C_{max,ss}$ (mg/L) | $C_{trough,ss}$ (mg/L) | N | $C_{trough,ss}$ (mg/L) |
| Adults | 300 mg q2w | 171 (75.0 kg) | 1130 (468) | 89.6 (34.9) | 67 (30.9) | 163 | 65.3 (33.5) |
| Adolescents ≥12 to <18 years | 300 mg q2w | 3 (72.0 kg) | 1100 (344) | 87.9 (26.3) | 64.5 (22.9) | 4 | 63.6 (12.0) |
| | 200 mg q2w | 2 (52.0 kg) | 770 (189) | 62.5 (14.1) | 43.7 (11.9) | 2 | 33.7 (15.9) |

Source: Summary of Clinical Pharmacology Studies, sBLA 761055-S-051 (Table 5)
[a] PK parameter values reported as mean (SD)
Abbreviations: $AUC_{\tau,ss}$: area under the plasma concentration-time curve of dupilumab over the dosing interval (τ) at steady state; $C_{max,ss}$: dupilumab maximum plasma concentration at steady state; CSU, chronic spontaneous urticaria; $C_{trough,ss}$: dupilumab plasma trough concentration at steady state; N, number of subjects; PK, pharmacokinetic; Q2W, every 2 weeks; SD, standard deviation

Based on these data, the steady state exposure observed in adolescents with CSU weighing ≥ 30 to < 60 kg (200 mg Q2W) and ≥ 60 kg (300 mg Q2W) appeared to be within the range of that observed for adults who received dupilumab 300 mg Q2W. Of note, the steady state dupilumab exposure was lower in adolescents weighing ≥ 30 to < 60 kg (200 mg Q2W) relative to adolescents weighing ≥ 60 kg (300 mg Q2W). The observed dupilumab exposure fell within the overall adolescent $5^{th}$ and $95^{th}$ percentiles of simuated steady state $C_{trough}$ for only 1 of the 2 lower body weight adolescents. However, this finding should be interpreted with caution, given the small sample size of adolescents for which PK data are available.

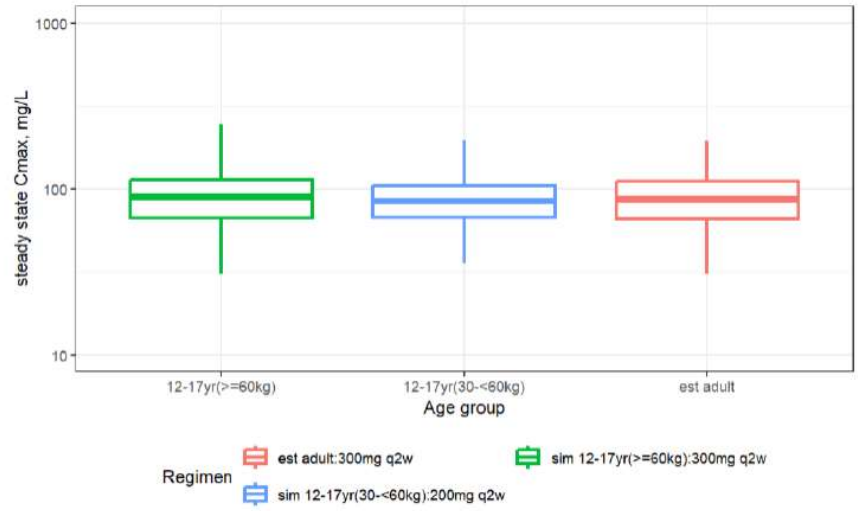
The simulated steady state dupilumab exposure ($C_{trough,ss}$ and $C_{max,ss}$) in adolescents with CSU weighing ≥ 30 to < 60 kg (200 mg Q2W) and ≥ 60 kg (300 mg Q2W) were comparable both to each other and to that observed in adults with CSU (300 mg Q2W) from Studies EFC16461-C, EFC16461-A, and EFC16461-B (Figure 2, Figure 3). See section 15.3.1 on Population PK Analysis for details.

**Figure 2. Boxplot of Dupilumab Plasma $C_{trough}$ (mg/L) at Steady State According to Age, Dupilumab Dose, and Body Weight Category in CSU Subjects, Study POH1089[a]**




Source: Population Pharmacokinetic Analysis Study Report POH1089 (Figure 10)
[a] PK data presented here are simulated (adolescents) and observed (adults)
Abbreviations: CSU, chronic spontaneous urticaria; $C_{trough}$, dupilumab plasma trough concentration; Obs, observed; PK, pharmacokinetic; Q2W, every 2 weeks; Sim, simulated; Yr, year

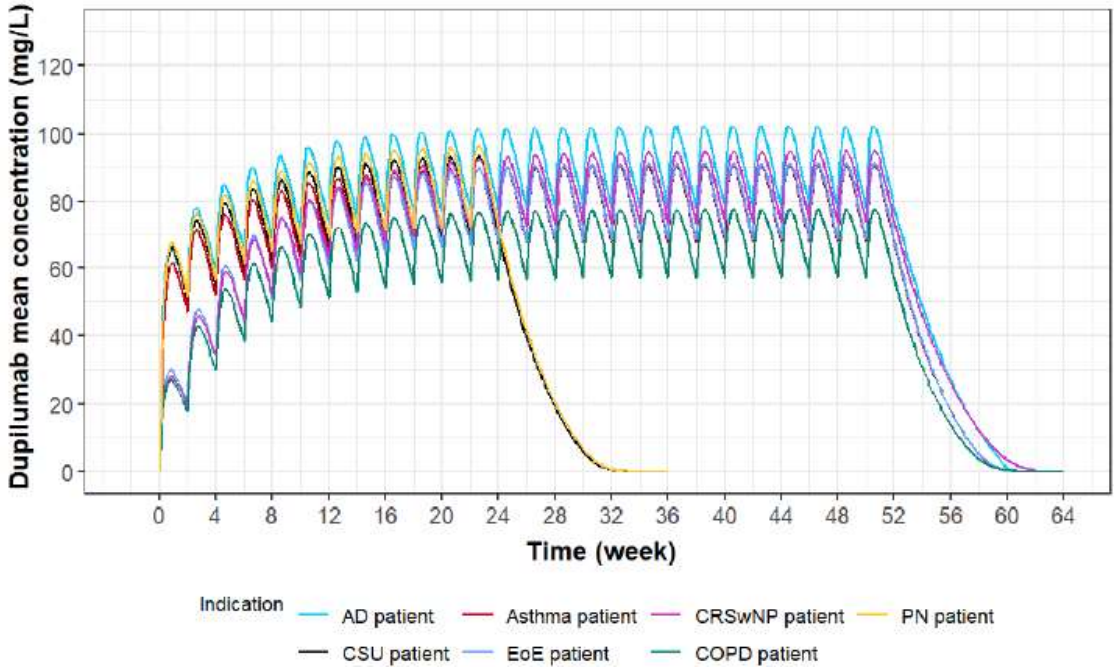
**Figure 3. Boxplot of Dupilumab Plasma $C_{max}$ (mg/L) at Steady State According to Age, Dupilumab Dose, and Body Weight Category in CSU Subjects, Study POH1089[a]**




Source: Population Pharmacokinetic Analysis Study Report POH1089 (Figure 11)
[a] PK data presented here are simulated (adolescents) and from post-hoc estimates of individual PK parameters generated by PopPK model (adults)
Abbreviations: $C_{max}$, dupilumab maximum plasma concentration; CSU, chronic spontaneous urticaria; Est, estimated; PK, pharmacokinetic; PopPK, population pharmacokinetic; Q2W, every 2 weeks; Sim, simulated; Yr, year

This popPK analysis was also used to compare PK characteristics of dupilumab between subjects with CSU and other approved indications. which demonstrated similar dupilumab PK across indications (Figure 4).

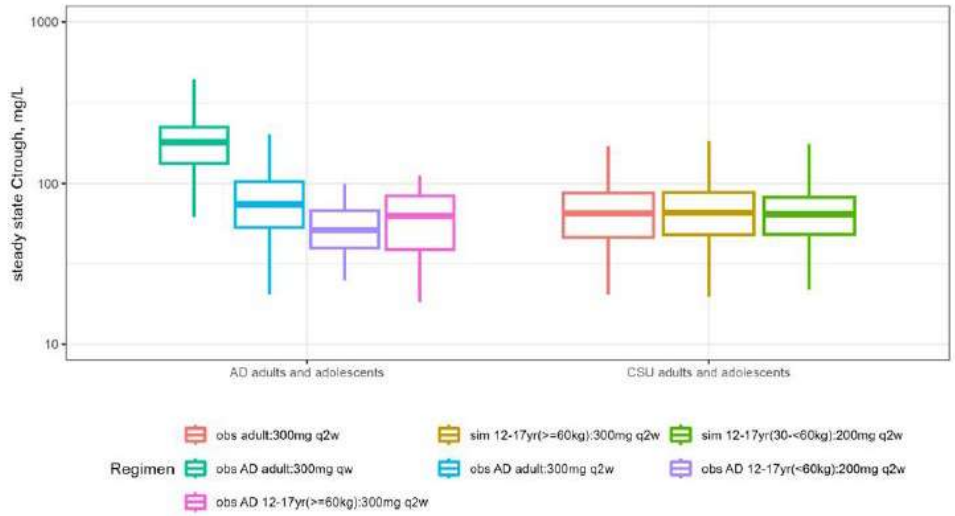
**Figure 4. Comparison of Dupilumab Typical Concentration-Time Profiles at 300 mg Q2W in Adult Patients With AD, Asthma, CRSwNP, EoE, PN, COPD, and CSU as Predicted by PopPK Model, Study POH1089**




Source: Population Pharmacokinetic Analysis Study Report POH1089 (Figure 9)
Abbreviations: AD, atopic dermatitis; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; PN, prurigo nodularis; PopPK, population pharmacokinetic; Q2W, every 2 weeks

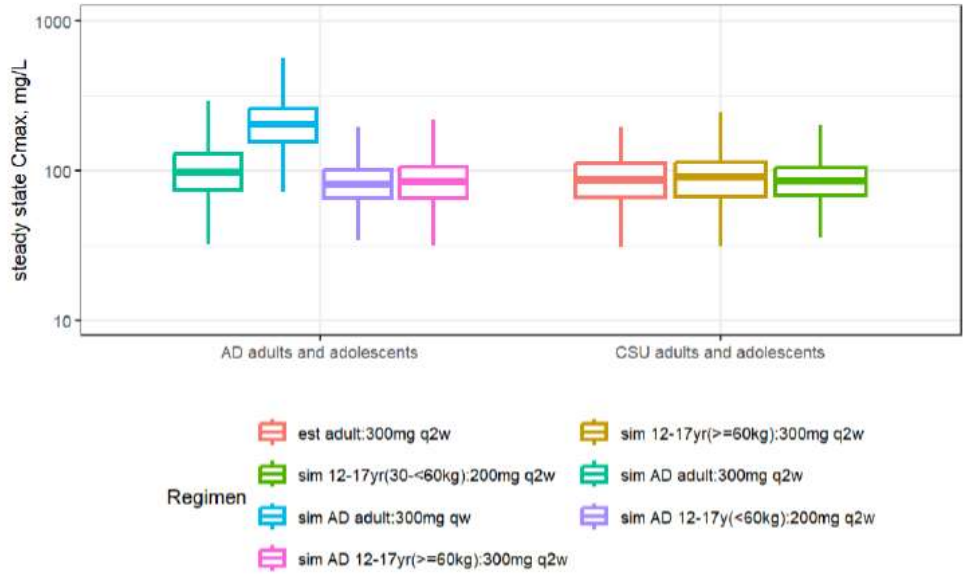
As further justification for efficacy extrapolation from adults to adolescents with CSU, the Applicant compared both observed and popPK-model predicted dupilumab exposure ($C_{trough,ss}$ and $C_{max,ss}$) in adults and adolescents with AD and CSU (Figure 5, Figure 6).

**Figure 5. Boxplot of Dupilumab $C_{trough}$ at Steady State by Treatment and Body Weight Groups in Patients With CSU or AD (Study POH1089)**




Source: Population Pharmacokinetic Analysis Study Report POH1089 (Figure 12)
Abbreviations: AD, atopic dermatitis; CSU, chronic spontaneous urticaria; $C_{trough}$, dupilumab plasma trough concentration; Obs, observed; QW, once weekly; Q2W, every 2 weeks; Sim, simulated; Yr, year

**Figure 6. Boxplot of Dupilumab $C_{max}$ at Steady State by Treatment and Body Weight Groups in Patients With CSU or AD**




Source: Population Pharmacokinetic Analysis Study Report POH1089 (Figure 13)
Abbreviations: AD, atopic dermatitis; $C_{max}$, dupilumab maximum plasma concentration; CSU, chronic spontaneous urticaria; Est, estimated; QW, once weekly; Q2W, every 2 weeks; Sim, simulated; Yr, year

Overall, both observed and simulated data appear to demonstrate similar PK between adolescent and adult populations with CSU at the proposed dosing regimens. In addition, these PK findings are generally consistent with those observed following administration of the same dosing regimens in adults and adolescents with AD.

**What are the pharmacodynamics characteristics of dupilumab following subcutaneous administration in patients with CSU?**

The PD of dupilumab (i.e., serum total IgE over time) was characterized in subjects with CSU. Trough PD samples were collected at pre-dose on Day 0, Week 12, Week 24, and Week 36 following SC administration of dupilumab for 24 weeks in Studies EFC16461-C, EFC16461-A, and EFC16461-B.

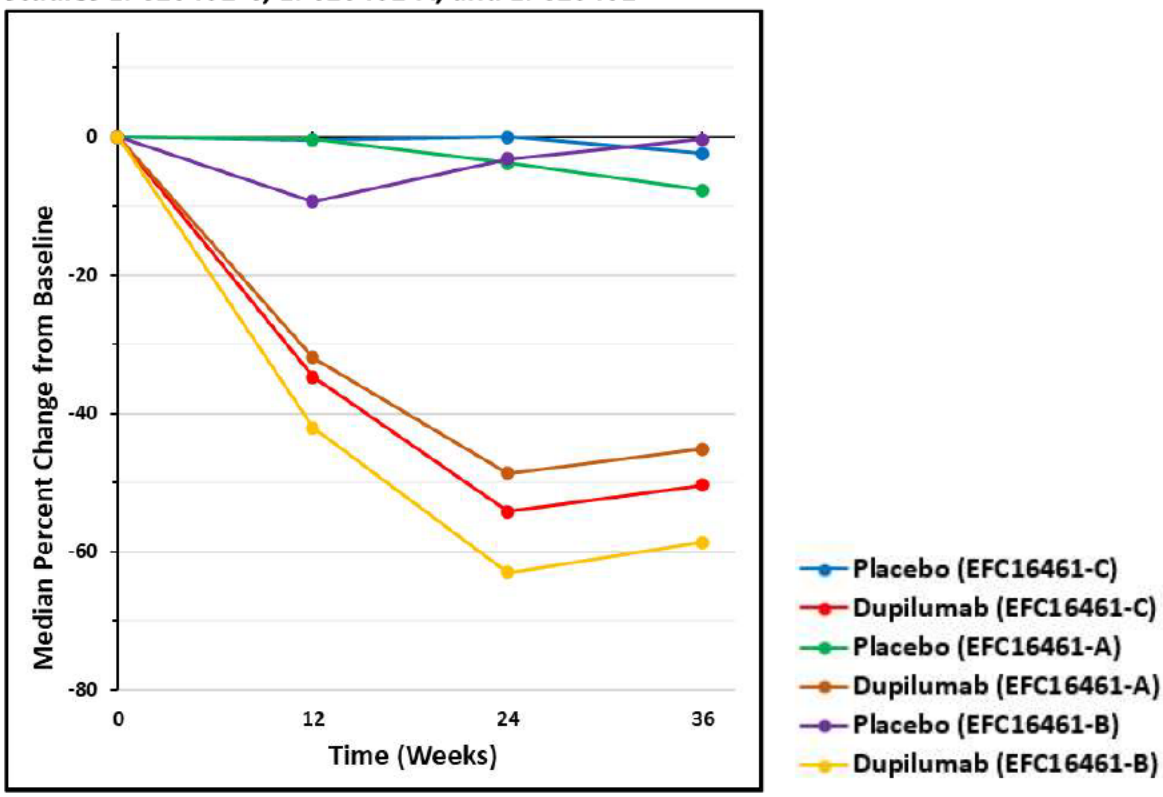
A summary of the change from baseline in plasma IgE concentration in clinical trials in subjects with CSU is depicted below in Table 6 and Figure 7. Of note, as previously discussed, given that Study EFC16461-C is ongoing and an additional 17 dupilumab-treated participants had yet to complete their scheduled follow-up visit at Week 36 at the time of this sBLA submission, the sample size is reduced at Week 36 compared to other timepoints.

**Table 6. Summary of Total Plasma IgE Change From Baseline in Subjects With CSU, Studies EFC16461-C, EFC16461-A, and EFC16461-B[a]**

| | | Timepoint | | | |
|---|---|---|---|---|---|
| **Clinical Study** | **Treatment Arm** | **Week 0** | **Week 12** | **Week 24** | **Week 36** |
| EFC16461-C[b] | Dupilumab | 0 | -43.1 (-34.7%) | -58.2 (-54.2%) | -65.4 (-50.3%) |
| | Placebo | 0 | -0.1 (-0.5%) | 0.0 (0%) | -1.0 (-2.4%) |
| EFC16461-A[c] | Dupilumab | 0 | -33.7 (-31.9%) | -51.5 (-48.7%) | -40.7 (-45.2%) |
| | Placebo | 0 | -0.6 (-0.4%) | -2.7 (-3.8%) | -3.0 (-7.7%) |
| EFC16461-B[d] | Dupilumab | 0 | -24.7 (-42.0%) | -41.2 (-63.0%) | -33.6 (-58.6%) |
| | Placebo | 0 | -2.4 (-9.3%) | -0.7 (-3.2%) | 0.25 (-0.4%) |

Source: Reviewer's analysis based on adlb.xpt for Studies EFC16461-C, EFC16461-A, and EFC16461-B
[a] Values reported as median absolute (%) change from baseline in total plasma IgE
[b] EFC16461-C: *Dupilumab Treatment Arm*: Week 0 (N=70), Week 12 (N=69), Week 24 (N=67), Week 36 (N=44); *Placebo*: Week 0 (N=74), Week 12 (N=73), Week 24 (N=66), Week 36 (N=49)
[c] EFC16461-A: *Dupilumab Treatment Arm*: Week 0 (N=66), Week 12 (N=65), Week 24 (N=61), Week 36 (N=58); *Placebo*: Week 0 (N=65), Week 12 (N=69), Week 24 (N=55), Week 36 (N=52)
[d] EFC16461-B: *Dupilumab Treatment Arm*: Week 0 (N=52), Week 12 (N=52), Week 24 (N=47), Week 36 (N=45); *Placebo*: Week 0 (N=52), Week 12 (N=53), Week 24 (N=42), Week 36 (N=42)
Abbreviations: CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; N, number of subjects

**Figure 7. Median Percent Change From Baseline in Total Plasma IgE in Subjects With CSU, Studies EFC16461-C, EFC16461-A, and EFC16461-B[a,b,c]**




Source: Reviewer's analysis based on adlb.xpt for Studies EFC16461-C, EFC16461-A, and EFC16461-B
[a] EFC16461-C: *Dupilumab Treatment Arm*: Week 0 (N=70), Week 12 (N=69), Week 24 (N=67), Week 36 (N=44); *Placebo*: Week 0 (N=74), Week 12 (N=73), Week 24 (N=66), Week 36 (N=49)
[b] EFC16461-A: *Dupilumab Treatment Arm*: Week 0 (N=66), Week 12 (N=65), Week 24 (N=61), Week 36 (N=58); *Placebo*: Week 0 (N=65), Week 12 (N=69), Week 24 (N=55), Week 36 (N=52)
[c] EFC16461-B: *Dupilumab Treatment Arm*: Week 0 (N=52), Week 12 (N=52), Week 24 (N=47), Week 36 (N=45); *Placebo*: Week 0 (N=52), Week 12 (N=53), Week 24 (N=42), Week 36 (N=42)
Abbreviations: CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; N, number of subjects

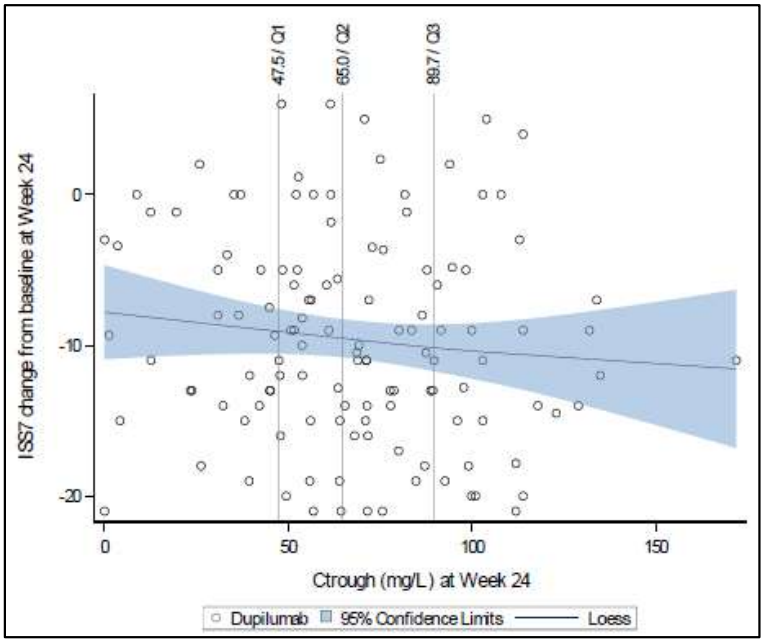
Total plasma IgE concentrations showed a progressive decline throughout the treatment period following dupilumab administration, compared with the placebo group for which no notable change from baseline was observed. In Study EFC16461-C, the median percent change from baseline in total serum IgE at Weeks 12 and 24 were -37.4% and -54.2%, respectively, for the dupilumab group, compared with -0.5% and 0% (no change), respectively, for the placebo group. This PD response is consistent with previous findings in subjects with moderate to severe asthma and PN, in which a 52% and 62% median reduction from baseline in total serum IgE was observed at Week 24, respectively (Studies DRI12544 [moderate to severe asthma] and EFC16460 [PN], respectively). In addition, the median change from baseline in serum IgE in dupilumab-treated adolescents with CSU across Studies EFC16461-C, EFC16461-A, and EFC16461-B was -62.2% at Week 24, which is within the range of that observed in the general population.

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

The proposed dupilumab dosing regimens of 600 mg + 300 mg Q2W/400 mg + 200 mg Q2W for adults and adolescents were administered by SC injection in all three clinical studies in subjects with CSU (Studies EFC16461-C, EFC16461-A, and EFC16461-B). 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 at Week 24. Refer to the clinical review by Dr. Anjeni Keswani for detailed discussion and assessment of the efficacy and safety data submitted to support this application (Section 8).

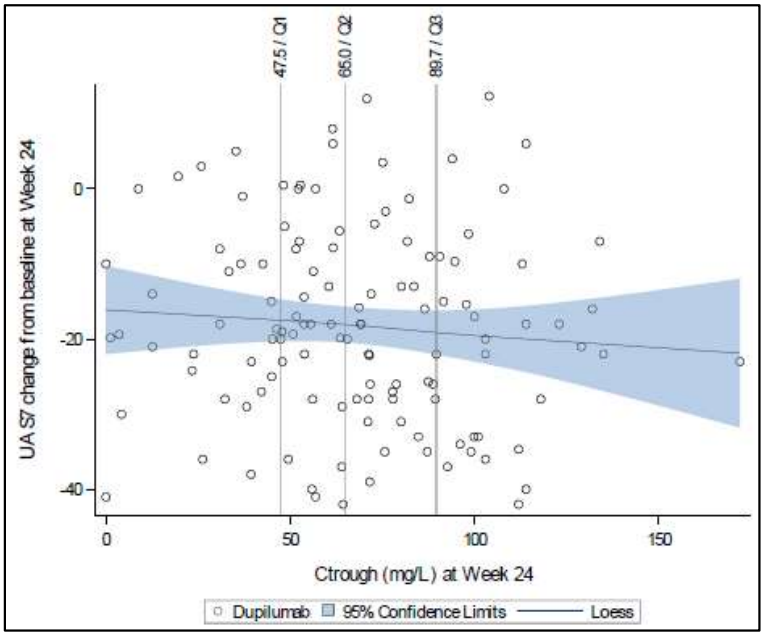
To support the proposed dupilumab dosing regimens in patients with CSU, the Applicant generated a PK/PD model using pooled data from Studies EFC16461-C and EFC16461-A and conducted an E-R analysis for both key efficacy endpoints ISS7 and UAS7 (Study CTS0083). Scatter plots depicting the change from baseline in ISS7 and UAS7 at Week 24 in dupilumab-treated subjects are presented below in Figure 8 and Figure 9, respectively.

**Figure 8. Scatter Plot of ISS7 Change From Baseline Versus Observed Plasma $C_{trough}$ (mg/L) at Week 24 in CSU Subjects, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A**




Source: Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Figure 1)
Abbreviations: $C_{trough}$, dupilumab plasma trough concentration; CSU, chronic spontaneous urticaria; ISS7, Weekly Itch Severity Score; Loess, Locally-Estimated Scatterplot Smoothing; Q1, quartile 1 (<47.5 mg/L); Q2, quartile 2 (47.5 to < 65.0 mg/L); Q3, quartile 3 (65.0 to <89.7 mg/L); Q4, quartile 4 (≥89.7 mg/L)

**Figure 9. Scatter Plot of UAS7 Change From Baseline Versus Observed Plasma $C_{trough}$ (mg/L) at Week 24 in CSU Subjects, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A**




Source: Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Figure 3)
Abbreviations: CSU, chronic spontaneous urticaria; $C_{trough}$, dupilumab plasma trough concentration; Loess, Locally-Estimated Scatterplot Smoothing; Q1, quartile 1 (<47.5 mg/L); Q2, quartile 2 (47.5 to <65.0 mg/L); Q3, quartile 3 (65.0 to <89.7 mg/L); Q4, quartile 4 (≥89.7 mg/L); UAS7, Weekly Urticaria Activity Score

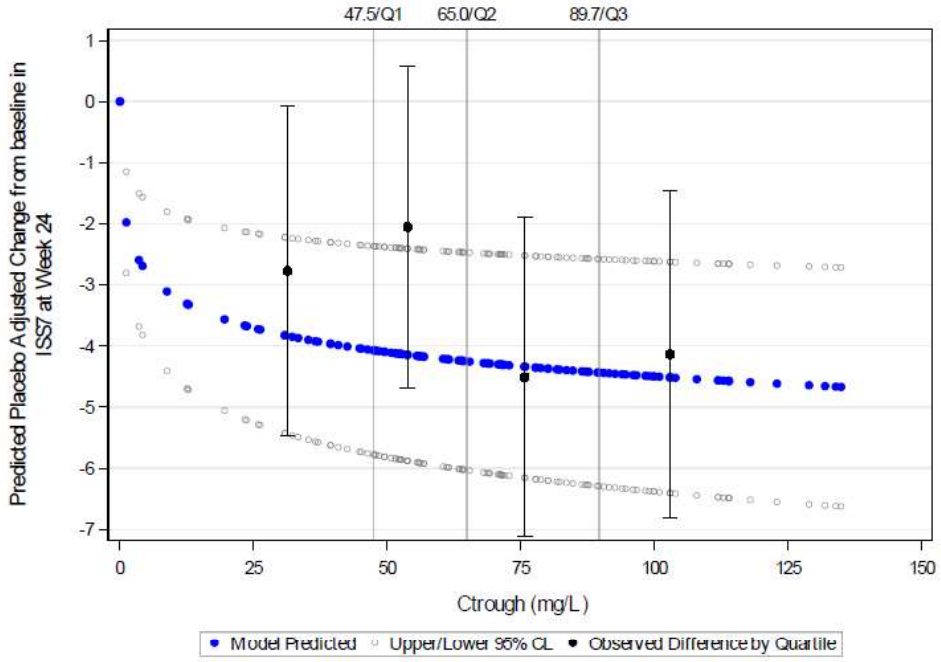
Furthermore, the Applicant compared the change from baseline in the key efficacy endpoints ISS7 and UAS7 at Week 24 between placebo and dupilumab treatment groups, stratified by observed dupilumab $C_{trough}$ quartiles. These comparisons are depicted below for ISS7 (Table 7, Figure 10) and UAS7 (Table 8, Figure 11).

**Table 7. Summary of ISS7 Change From Baseline at Week 24 in Placebo Group Compared With Dupilumab Treatment Stratified by Quartiles of Observed Plasma $C_{trough}$ (mg/L) in CSU Subjects, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A**

| Treatment Arm/ $C_{trough}$ Quartile (N) | Mean (SE) Dupilumab $C_{trough}$ (mg/L) | ISS7 Change From Baseline (CFB)[a] | |
|---|---|---|---|
| | | Mean (SE) CFB | Median (range) CFB |
| Placebo (127) | 0 | -6.1 (0.6) | -7.0 (-21.0, 10.0) |
| Dupilumab Q1 (29) | 27.0 (2.9) | -8.8 (1.2) | -9.3 (-21.0, 2.0) |
| Dupilumab Q2 (31) | 55.7 (1.0) | -8.7 (1.3) | -9.0 (-21.0, 6.0) |
| Dupilumab Q3 (32) | 77.1 (1.3) | -10.6 (1.1) | -11.0 (-21.0, 5.0) |
| Dupilumab Q4 (31) | 109.3 (3.1) | -10.2 (1.3) | -11.0 (-21.0, 5.0) |

Source: Adapted from Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Table 2)
[a] Values reported as absolute change from baseline in ISS7
Abbreviations: CSU, chronic spontaneous urticaria; CFB, change from baseline; $C_{trough}$, dupilumab plasma trough concentration; ISS7, Weekly Itch Severity Score; N, number of subjects; Q1, quartile 1 (<47.5 mg/L); Q2, quartile 2 (47.5 to <65.0 mg/L); Q3, quartile 3 (65.0 to < 89.7 mg/L); Q4, quartile 4 (≥ 89.7 mg/L); SE, standard error

**Figure 10. PK/PD Predicted Overlaying Observed ISS7 and Placebo-Ajusted Change From Baseline at Week 24, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A[a]**



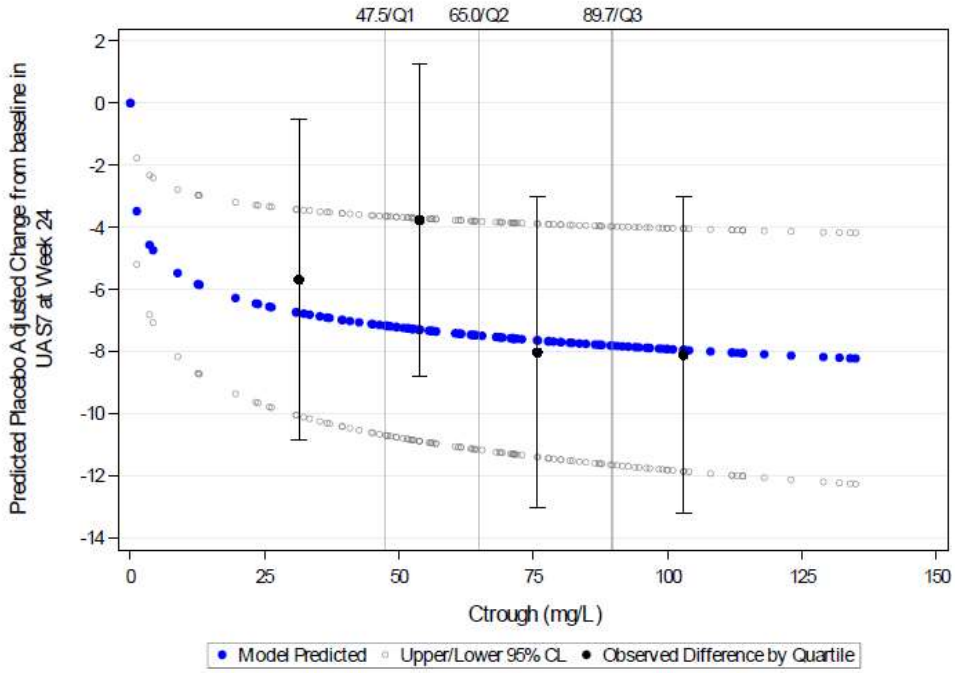

Source: Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Figure 2)
[a] Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed data at Week 24.
Abbreviations: CL, confidence level; $C_{trough,}$ Dupilumab Plasma Trough Concentration; ISS7, Weekly Itch Severity Score; PD, pharmacodynamic; PK, pharmacokinetic; Q1, quartile 1 (<47.5 mg/L); Q2, quartile 2 (47.5 to < 65.0 mg/L); Q3, quartile 3 (65.0 to < 89.7 mg/L); Q4, quartile 4 (≥ 89.7 mg/L)

**Table 8. Summary of UAS7 Change From Baseline at Week 24 in Placebo Group Compared With Dupilumab Treatment Stratified by Quartiles of Observed Plasma $C_{trough}$ (mg/L) in CSU Subjects, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A**

| Treatment Arm/ $C_{trough}$ Quartile (N) | Mean (SE) Dupilumab $C_{trough}$ (mg/L) | UAS7 Change From Baseline (CFB)[a] | |
|---|---|---|---|
| | | Mean (SE) CFB | Median (range) CFB |
| Placebo (127) | 0 | -11.7 (1.2) | -11.0 (-42.0, 21.0) |
| Dupilumab Q1 (29) | 27.0 (2.9) | -17.6 (2.3) | -19.4 (-41.0, 5.0) |
| Dupilumab Q2 (31) | 55.7 (1.0) | -16.3 (2.5) | -18.0 (-42.0, 8.0) |
| Dupilumab Q3 (32) | 77.1 (1.3) | -19.6 (2.2) | -22.1 (-39.0, 12.0) |
| Dupilumab Q4 (31) | 109.3 (3.1) | -19.4 (2.5) | -20.0 (-42.0, 12.3) |

Source: Adapted from Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Table 6)
[a] Values reported as absolute change from baseline in UAS7
Abbreviations: CFB, change from baseline; CSU, chronic spontaneous urticaria; $C_{trough}$, dupilumab plasma trough concentration; N, number of subjects; Q1, quartile 1 (< 47.5 mg/L); Q2, quartile 2 (47.5 to < 65.0 mg/L); Q3, quartile 3 (65.0 to < 89.7 mg/L); Q4, quartile 4 (≥ 89.7 mg/L); SE, standard error; UAS7, Weekly Urticaria Activity Score

**Figure 11. PK/PD Predicted Overlaying Observed UAS7 and Placebo-Adjusted Change From Baseline at Week 24, Study CTS0083; Pooled Studies EFC16461-C and EFC16461-A[a]**




Source: Amended Pharmacokinetic / Pharmacodynamic Study Report CTS0083 (Figure 4)
[a] Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed data at Week 24.
Abbreviations: CL, confidence level; $C_{trough}$, dupilumab plasma trough concentration; PD, pharmacodynamic; PK, pharmacokinetic; Q1, quartile 1 (< 47.5 mg/L); Q2, quartile 2 (47.5 to < 65.0 mg/L); Q3, quartile 3 (65.0 to <89.7 mg/L); Q4, quartile 4 (≥ 89.7 mg/L); UAS7, Weekly Urticaria Activity Score

The E-R analyses demonstrate a greater decrease from baseline in ISS7 and UAS7 for all dupilumab exposure quartiles compared with placebo. There appears to be a slight exposure-dependent trend for both key efficacy endpoints, which plateaued near dupilumab exposure at Quartile 3 (median $C_{trough}$ of 75.8 mg/L). Of note, the proposed dosing of dupilumab of 300 mg Q2W for adults with CSU is the same as that which is currently approved for adults with other approved indications, including AD, asthma, CRSwNP, PN, and COPD. Overall, these data are supportive of the Applicant's proposed dosing regimen in adult subjects.

However, despite these findings, there is a high degree of overlap in treatment effects between dupilumab exposure quartiles. Additionally, much of the apparent exposure-dependency of the treatment effects of dupilumab on ISS7 and UAS7 is driven by Study EFC16461-C. While the developed PK/PD models were able to describe the overall trend of placebo-adjusted efficacy endpoints versus dupilumab exposure ($C_{trough}$), indicating that higher exposure was associated with better efficacy, with efficacy reaching a plateau at higher concentrations (Q3 and Q4), the model-predicted values did not align well with observed data, particularly at lower concentrations, such as Q2. Overall, the exposure-efficacy relationship appeared relatively flat and not statistically significant. As previously noted by Dr. Tao Liu following review of this BLA supplement during initial submission, no exposure-dependent response was observed for ISS7

or UAS7 in Studies EFC16461-A and EFC16461-B (BLA Multi-Disciplinary Review and Evaluation for 761055/S-051; DARRTS Reference ID: 5263308). Therefore, a significant exposure-dependent response cannot be concluded based on the totality of available data.

**Proposed Dosing in Adolescents**

Across all clinical studies in CSU, a total of 12 adolescents were enrolled, of which 7 were randomized to receive dupilumab treatment. As discussed above, after accounting for differences in body weight, the systemic exposure of dupilumab in adolescents with CSU is comparable to that observed in adults following administration of the proposed dosing regimens based on both simulated and observed data. In addition, the change from baseline in serum IgE (PD biomarker) in dupilumab-treated adolescents was within the range of that observed in adults with CSU.

A similar change from baseline in key efficacy endpoints ISS7 and UAS7 at Week 24 was observed between adolescents and adults with CSU , although a definitive conclusion cannot be made based on the available data due to the limited adolescent sample size (Refer to Section 8.1 for detailed review of efficacy data in support of this sBLA). However, based on previous findings in subjects with asthma and AD, similar E-R relationships have been observed between pediatric and adult subjects. Additionally, the proposed dosing for adolescents aged ≥ 12 to < 18 with CSU in the current submission (300 mg Q2W/200 mg Q2W) is the same as that which is currently approved and has been found to be safe and effective for adolescents with asthma and AD.

Therefore, efficacy responses in adolescents with CSU following SC administration of the proposed 300 mg Q2W/200 mg Q2W dosing regimen are expected to be comparable to those observed in adults following SC administration of 300 mg Q2W.

**What is the incidence of the formation of ADAs and the impact of immunogenicity on dupilumab exposure and efficacy?**

Plasma samples were collected at Baseline, Week 12, Week 24, Week 36 (12 weeks after last dose), and early withdrawal (if applicable) for assessment of ADAs and NAbs to dupilumab in Studies EFC16461-C, EFC16461-A, and EFC16461-B. The bioanalytical methods used to identify both ADAs and NAbs were previously reviewed during marketing applications for asthma and AD and have been adequately validated (REGN668-AV-15153-VA-01V2 and REGN668-AV-13112-VA-01V1). The ADA population from Study EFC16461-C included 147 subjects (N = 72/74 and N = 75/77 in the dupilumab and placebo groups, respectively), all of whom had at least one post-baseline ADA data point available. A summary of immunogenicity results for the ADA population from Study EFC16461-C through the 36-week follow-up visit is provided below in Table 9.

**Table 9. Summary of ADA Incidence Through 36-Week Follow-Up Visit, Study EFC16461-C**

| | Treatment Group | |
|---|---|---|
| **ADA Parameter** | **Dupilumab (N=72)** | **Placebo (N=75)** |
| Pre-existing ADA+ | 0 (0%) | 2 (2.7%) |
| TE ADA+ (Total) | 3 (4.2%) | 0 (0%) |
| Persistent[a] | 0 (0%) | 0 (0%) |
| Indeterminate[b] | 2 (2.8%) | 0 (0%) |
| Transient[c] | 1 (1.4%) | 0 (0%) |
| Peak ADA titer | | |
| Low (< 1,000) | 3 (4.2%) | 2 (2.7%) |
| Moderate (1,000 to 10,000) | 0 (0%) | 0 (0%) |
| High (> 10,000) | 0 (0%) | 0 (0%) |
| NAb+ | 2 (2.8%) | 1 (1.3%) |
| Treatment-boosted response[d] | 0 (0%) | 0 (0%) |

Source: Reviewer's analysis based adis.xpt for Study EFC16461-C
[a] TE ADA-positive response with ≥ 2 consecutive ADA-positive sampling time points separated by > 12 weeks (i.e., >84 days), with no ADA-negative samples in between
[b] TE ADA-positive response with only the last collected sample positive in the ADA assay
[c] TE ADA-positive response that is not considered persistent or indeterminate
[d] A positive response in the ADA assay post first dose that is ≥ 4-fold over baseline titer levels, when baseline results are positive
Abbreviations: ADA, antidrug antibody; N, number of subjects; NAb, neutralizing antibody; TE, treatment-emergent

No persistent ADA responses (i.e., TE ADA-positive response with ≥ 2 consecutive ADA-positive sampling time points) were observed for any participants in Study EFC16461-C. In the dupilumab treatment arm, TE ADAs were observed in 4.2% (N = 3) of subjects. Of these, the ADA response was transiently positive at Week 12 for one subject and indeterminate (i.e., ADA response not classified as either persistent or transient) for the other two at Week 36. In the placebo group, there were no TE ADAs observed, although 2.7% (N = 2) of subjects were positive for pre-existing immunoreactivity. Titers were low (defined as max ADA titer < 1000) in all ADA-positive subjects in both treatment arms. All other participants in both dupilumab and placebo groups were ADA-negative at all timepoints.

The Applicant also further characterized ADA plasma samples for the presence of NAbs. In the dupilumab group, both subjects with indeterminate TE ADA responses were also NAb-positive at Week 36. In the placebo group, one subject with pre-existing immunoreactivity was NAb-positive at Week 12 only, after which all subsequent samples were NAb-negative.

Of note, in both EFC16461-A and EFC16461-B, an increased incidence of ADAs and NAbs was observed in the dupilumab group at Week 36 compared to Week 24, although this finding was not associated with new immunogenicity-related safety findings. In Study EFC16461-C, no increased rate of ADA or NAb formation was observed at Week 36 and overall incidence of ADAs and NAbs remained low throughout the entire study duration in both dupilumab and placebo groups, although data through Week 36 were only available for 68% (N = 49/72) of

dupilumab-treated participants in the ADA population at the time of submission of this BLA supplement. These immunogenicity findings generally align with those observed following dupilumab administration in other approved indications (Table 10).

**Table 10. Comparison of ADA and NAb Development Across Different Dupilumab Clinical Development Programs**

| Indication | Dosage | ADA+[a] | Persistent ADA[a,b] | NAb+[a] |
|---|---|---|---|---|
| AD | 300 mg Q2W for 52 weeks | 6% | 2% | 1% |
| Asthma | 300 mg Q2W for 52 weeks | 5% | 2% | 2% |
| | 200 mg Q2W for 52 weeks | 9% | 4% | 4% |
| CRSwNP | 300 mg Q2W for 52 weeks | 5% | 2% | 3% |
| EoE | 300 mg QW for 24 weeks | 1% | 0% | 0% |
| PN | 300 mg Q2W for 24 weeks | 8% | 1% | 3% |
| COPD | 300 mg Q2W for 52 weeks | 8% | 3% | 3% |
| CSU (proposed) | 300 mg Q2W for 24 weeks | 5% | 1% | 1% |

Source: Reviewer's analysis based on Dupixent USPI and adis.xpt for Studies EFC16461-C, EFC16461-A, and EFC16461-B; Adapted from Table 3 from clinical pharmacology review by Dr. Tao Liu in BLA Multi-Disciplinary Review and Evaluation for 761055/S-051 (DARRTS Reference ID: 5263308)

[a] The incidence rates for ADA, persistent ADA, and NAb included sampling time points up to 4 weeks after the last drug administration (except for CSU indication, which includes only incidence through 24-week treatment period)

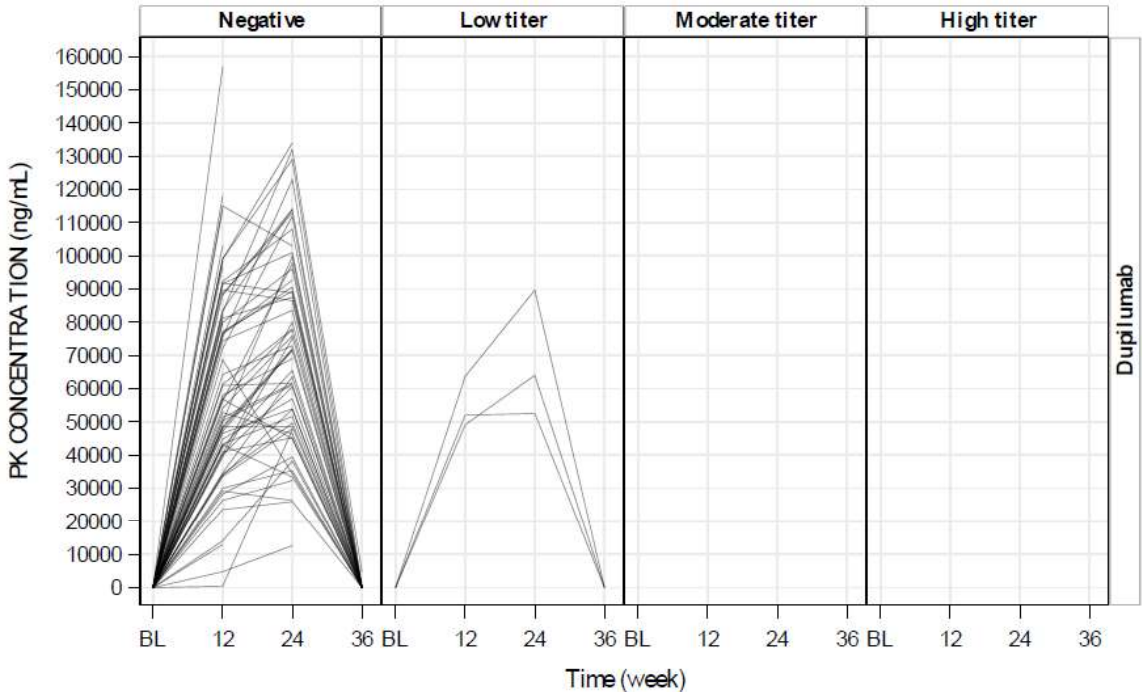
[b] TE ADA-positive response with ≥ 2 consecutive ADA-positive sampling time points separated by > 12 weeks (i.e., >84 days), with no ADA-negative samples in between

Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; BLA, biologics licensing application; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; EoE, eosinophilic esophagitis; NAb, neutralizing antibody; PN, prurigo nodularis; QW, once weekly; Q2W, every 2 weeks; TE, treatment-emergent; USPI, United States Prescribing Information

The impact of the development of ADAs on both dupilumab systemic exposure as well as efficacy responses (i.e., ISS7 and UAS7) in subjects with CSU was evaluated in Studies EFC16461-C, EFC16461-A, and EFC16461-B.

In Studies EFC16461-A and Study EFC16461-B, dupilumab systemic exposure was 71% and 57% lower in ADA-positive subjects at Week 12 and Week 24, respectively, according to the clinical pharmacology review by Dr. Tao Liu of the initial submission of this BLA supplement (BLA Multi-Disciplinary Review and Evaluation for 761055/S-051; DARRTS Reference ID: 5263308). In addition, based on the Applicant's popPK model, which incorporated all three CSU studies, predicted steady-state $AUC_{tau}$, $C_{max}$, and $C_{trough}$ were 37%, 34% and 40% lower, respectively, in ADA-positive compared to ADA-negative subjects. However, in Study EFC16461-C the individual dupilumab exposure in ADA-positive patients was generally within the exposure range of ADA-negative patients (Figure 12).

**Figure 12. Individual Concentration-Time Profiles of Dupilumab by ADA Titer Category Through Week 36 in Patients With CSU, Study EFC16461-C[a,b,c]**




Source: Summary of Clinical Pharmacology Studies, sBLA 761055-S-051 (Figure 12)
[a] Low titer defined as < 1,000
[b] Moderate titer defined as 1,000 to 10,000
[c] High titer defined as > 10,000
Abbreviations: ADA, antidrug antibody; BL, baseline; CSU, chronic spontaneous urticaria; PK, pharmacokinetic

In dupilumab-treated subjects in Study EFC16461-C, the mean change from baseline in key efficacy endpoints ISS7 and UAS7 at Week 24 were comparable between the ADA-positive (N = 3) and ADA-negative (N = 69) subjects. The mean (SD) change in ISS7 was -11.67 (7.02) and -9.19 (6.78) for ADA-positive and ADA-negative subjects, respectively. The mean (SD) change in UAS7 was -22.00 (15.00) and -16.93 (12.65) for ADA-positive and ADA-negative subjects, respectively. In addition, the Applicant conducted analyses of all treatment-emergent adverse events (TEAEs), with a focused analysis of anaphylaxis, hypersensitivity, and injection site reactions according to ADA status, for which no clear association was observed.

It was previously concluded by clinical pharmacology reviewer Dr. Tao Liu that no apparent negative impact of ADA status on efficacy was observed, based on data derived from Studies EFC16461-A and EFC16461-B (BLA Multi-Disciplinary Review and Evaluation for 761055/S-051; DARRTS Reference ID: 5263308). The results observed from Study EFC16461-C appear to support this conclusion. However, given the low incidence rate of TE ADAs across clinical studies in subjects with CSU, these findings should be interpreted cautiously.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

This sBLA includes data from three randomized, placebo-controlled, double-blind studies (Studies A, B, and C) conducted under one master protocol, EFC16461 (CUPID) (Table 11). Studies A and B were previously submitted and reviewed in the Multi-disciplinary Review dated October 18, 2023. Study C was submitted on October, 18, 2024, with this class 2 resubmission and is the focus of this review.

**Table 11. Listing of Clinical Trials Relevant to this NDA/BLA**

| Trial Identity NCT No. | Trial Design/ Duration | Study Population | Regimen/Schedule/Route | Study Endpoints | No. of Subjects Enrolled | No. of Centers and Countries |
|---|---|---|---|---|---|---|
| | ***Controlled Studies to Support Efficacy and Safety*** | | | | | |
| Master Protocol EFC16461 (CUPID) NCT04180488 Study A | R, DB, PC, PG, MC 24-week treatment, 12-week follow-up | Subjects ≥6 to 80 years of age with a diagnosis of CSU refractory to H1AH | All adults and adolescents ≥60 kg: 600 mg loading dose (Day 1) followed by 300 mg Q2W<br>Adolescents and children (≥6 to <12 years old) who weighed ≥30 to <60 kg at screening: 400 mg loading dose (Day 1) followed by 200 mg Q2W<br>Children aged ≥6 to <12 years ≥15 kg and <30 kg at screening: 600 mg loading dose (Day 1) followed by 300 mg Q4W | Primary endpoint: Change from baseline in ISS7 at Week 24<br>Key secondary endpoint: Change from baseline in UAS7 at Week 24 | 138 Total; dupilumab: 70, placebo: 68<br>Ages 6-11: 2 subjects in dupilumab group<br>Ages 12-17: 2 subjects each in the dupilumab group and placebo group | Study A: 9 countries Argentina, Canada, China, France, Hungary, Japan, Russia, Spain, USA; 55 active centers. |

| Trial Identity NCT No. | Trial Design/ Duration | Study Population | Regimen/Schedule/Route | Study Endpoints | No. of Subjects Enrolled | No. of Centers and Countries |
|---|---|---|---|---|---|---|
| Master Protocol EFC16461 (CUPID) NCT04180488 Study B | R, DB, PC, PG, MC 24-week treatment, 12-week follow-up | Subjects ≥12 to 80 years of age who had a diagnosis of CSU refractory to H1AH and intolerant or incomplete responder to omalizumab | All adults and adolescents ≥60 kg: 600 mg loading dose (Day 1) followed by 300 mg Q2W<br>Adolescents and children (≥6 to <12 years old) who weighed ≥30 to <60 kg at screening: 400 mg loading dose (Day 1) followed by 200 mg Q2W | Primary endpoint: Change from baseline in ISS7 at Week 24<br>Key secondary endpoint: Change from baseline in UAS7 at Week 24) | 108 Total; dupilumab: 54, placebo: 54<br>Ages 12-17: 1 subject each in the dupilumab group and placebo group | Study B: 11 countries including the same countries as Study A, with addition of Germany and the United Kingdom; 61 active centers. |
| Master Protocol EFC16461 (CUPID) NCT04180488 Study C | R, DB, PC, PG, MC 24-week treatment, 12-week follow-up | Subjects ≥6 to 80 years of age with a diagnosis of CSU refractory to H1AH | All adults and adolescents ≥60 kg: 600 mg loading dose (Day 1) followed by 300 mg Q2W<br>Adolescents and children (≥6 to <12 years old) who weighed ≥30 to <60 kg at screening: 400 mg loading dose (Day 1) followed by 200 mg Q2W<br>Children aged ≥6 to <12 years ≥15 kg and <30 kg at screening: 600 mg loading dose (Day 1) followed by 300 mg Q4W | Primary endpoint: Change from baseline in ISS7 at Week 24<br>Key secondary endpoint: Change from baseline in UAS7 at Week 24 | 151 Total; dupilumab: 74, placebo: 77<br>Ages 6-11: 1 subject in dupilumab group and 2 subjects in the placebo group<br>Ages 12-17: 3 subjects each in the dupilumab group and placebo group | Study C: 9 Countries Argentina, Canada, China, France, Germany, Hungary, Japan, Spain, and USA; 50 active centers |

Abbreviations: CSU, chronic spontaneous urticaria; DB, double-blind; H1AH, H1-anthistamine; ISS7, Weekly Itch Severity Score; MC, multicenter; PC, placebo-controlled; PG, parallel-group; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomized; UAS7, Weekly Urticaria Activity Score; USA, United States of America

### 7.2. Review Strategy

This review evaluates the efficacy and safety data submitted with this sBLA to support use of dupilumab for the treatment of CSU in patients whose disease is not adequately controlled on H1AH therapy. The sBLA includes data from three randomized, placebo-controlled, double-blind studies (Studies A, B, and C) conducted under one master protocol, EFC16461 (CUPID). Studies A and B were previously submitted and reviewed in the Multi-disciplinary Review dated October 18, 2023. Study C was submitted on October 18, 2024 with this class 2 efficacy supplement re-submission.

Section 8 includes a summary of the master protocol, an overview of the efficacy results of Studies A and B, comprehensive efficacy results for Study C, and the pooled safety results for Studies A, B, and C. Of note, an interim analysis (IA) was planned for Study B, which was conducted after the first 83 randomized subjects completed their Week 24 visit, as prespecified in the Statistical Analysis Plan. Futility criteria were met at the IA. On February 18, 2022, the Applicant informed Investigators and sites of the results and issued a press release stating that dupilumab did not reach statistical significance on IA and the study would be stopped due to futility. To minimize potential bias from public disclosure of the IA, efficacy results are based on review of data collected through the prespecified IA.

The clinical review was conducted by the primary clinical reviewer and the statistical analysis was conducted by the statistical team.

**Data Sources**

Data sources in this electronic submission included protocols, clinical study reports, narratives, and SAS transport datasets in legacy format.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used To Support Efficacy

### 8.1.1. Master Protocol EFC16461 (CUPID)

To support this application, the Applicant completed three 24-week, randomized, double-blind, placebo-controlled safety and efficacy trials under a master protocol EFC16461 (CUPID Studies A, B and C) in a total of 397 subjects with CSU not adequately controlled with H1AH.

Efficacy results from Studies A and B were reviewed previously in the Multi-disciplinary Review dated October 18, 2023 and will be briefly summarized here. Full efficacy results from Study C will be assessed in this Multi-disciplinary Review.

Study A was a 24-week, randomized, double-blind, placebo controlled, multicenter study of 138 subjects aged 6 to 80 years old with CSU not adequately controlled with H1AH treatment and naïve to omalizumab. The primary endpoint was change from baseline in ISS7 (range 0-21) at Week 24. Study A met its primary endpoint with the LS mean change from baseline of -10.24 in the dupilumab arm and -6.01 in the placebo arm. The LS mean difference between dupilumab and placebo was -4.23 (95% CI: -6.63, -1.84, p=0.0005), which represented a statistically significant and clinically meaningful improvement. The key secondary endpoint of change from baseline in Urticaria Activity Score over 7 days (UAS7) at Week 24 and other secondary endpoint of change from baseline in HSS7 were statistically significant and clinically meaningful for both the itch and hives components of CSU.

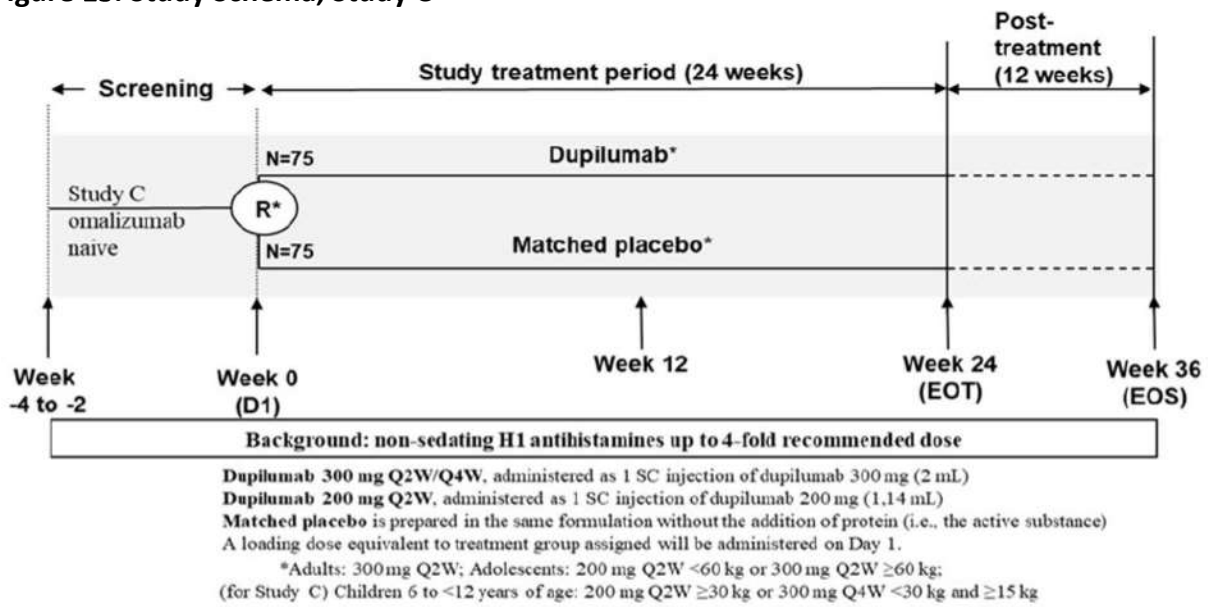
Study B was a 24-week, randomized, double-blind, placebo controlled, multicenter study of 108 subjects aged 12 to 80 years old with CSU not adequately controlled with H1AH treatment and unresponsive (n=104) or intolerant (n=4) to omalizumab. An interim analysis was conducted when the first 83 subjects completed their Week 24 visit. In the interim analysis, the LS mean change from baseline in ISS7 at Week 24 was -7.42 in the dupilumab arm versus -5.46 in the placebo arm; the difference was not statistically significant (-1.96, 95% CI: -5.53, -1.42, p=0.26). The results met the pre-specified futility criteria (p>0.10) determined in the Statistical Analysis Plan and the study was discontinued. The Applicant issued a press release stating that dupilumab did not reach statistical significance on IA and the study would be stopped due to futility.

### 8.1.2. CUPID Study C

**Trial Design**

Study C was a 24-week, phase 3, randomized, double-blind, placebo controlled, multicenter, parallel-group study comparing dupilumab to placebo in subjects aged 6 to 80 years old with CSU who remained symptomatic despite H1AH treatment and were naïve to omalizumab. The trial consisted of three periods: screening, treatment, and post-treatment. The study schema is displayed in Figure 13. The duration of the screening period was 2 to 4 weeks, the treatment period was 24 weeks ±3 days, and the post-treatment period was 12 weeks.

**Figure 13. Study Schema, Study C**




Abbreviations: EOS = End of study; EOT = End of treatment; R = randomization; SC = subcutaneous; Q2W = every 2 weeks; Q4W = every 4 weeks

Source: Clinical Study Report -CUPID Study C

**Trial Location**

Study C included 50 centers in Argentina, Canada, China, France, Germany, Hungary, Japan, Spain, and the United States.

**Study Population**

Subjects included patients with CSU who remained symptomatic despite the use of H1AH and were naïve to omalizumab. Subjects continued their established standard-of-care background therapy with a long-acting H1AH at up to 4-fold the recommended dose during the study.

**Eligibility Criteria**

Inclusion Criteria

- Subjects must be 6 years to 80 years of age at the time of signing the informed consent.
- Subjects who have a diagnosis of CSU refractory to H1AH at the time of randomization, as defined by all of the following:
  - Diagnosis of CSU >6 months prior to screening visit (Visit 1).
  - The presence of itch and hives for >6 consecutive weeks at any time prior to screening visit (Visit 1) despite the use of H1AH during this time period.

- Subjects using a study defined H1AH for CSU treatment (including cetirizine, levocetirizine dihydrochloride, fexofenadine, loratadine, desloratadine, bilastine, rupatadine, other H1AH after discussion with the Applicant).
  - Note: subjects should remain on their prescreening nonsedating H1AH dose. Only up to 4-fold the recommended dose is allowed. If subjects are on dose higher than 4-fold the recommended dose at screening, the Investigator can adjust the subject dose to the stipulated range at the screening visit (Visit 1). The H1AH dose should be stable for at least 3 consecutive days prior to the screening visit (Visit 1).
- During the 7 days before randomization:
  - UAS7>16
  - ISS7>8
    - Note: to be eligible for the study, subjects must have no missing electronic diary (e-diary) (UAS7 and ISS7) in the 7 days before randomization.

- Subjects who are omalizumab naïve.
- Subjects must be willing and able to complete a daily symptom e-diary for the duration of the study.
- Male or female: Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- Female subjects
  - 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 (WOCBP)
      - OR
    - Is a WOCBP and agrees to use an acceptable contraceptive method as described in Appendix 4 of the protocol during the study (at a minimum until 12 weeks after the last dose of study intervention).
    - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) on Day 1 before the first dose of study intervention.
    - If a urine test on Day 1 cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.
- Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and the study protocol. Subjects ≥6 and <18 years of age must provide written informed assent, and their parent(s)/caregiver(s)/legally authorized representative(s) must sign the specific ICF. In countries where legal age of majority is >18 years, a specific ICF must also be signed by the subject's legally authorized representative.

**Exclusion Criteria**

- Weight is less than 30kg in adults and adolescents and 15kg in children aged ≥6 to <12 years of age.
- Clearly defined underlying etiology for chronic urticarias other than CSU (main manifestation being physical urticaria). This includes but is not limited to the following urticarias: urticaria, solar, cholinergic, heat, cold, aquagenic, vibratory angioedema, symptomatic dermographism, delayed pressure, or contact.
- Diseases with possible symptoms of urticaria or angioedema: systemic lupus erythematosus, urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer.
- Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes.
- Patients with active atopic dermatitis.
- 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 (hemoglobin A1c ≥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), active major autoimmune diseases (e.g., lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for subjects excluded under this criterion will be noted in study documents (chart notes, case report forms [CRF], etc.).
- Patients with active tuberculosis (TB) or nontuberculous mycobacterial infection, or a history of incompletely treated TB will be excluded from the study unless it is well documented by a specialist that the subject has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the Investigator and/or infectious disease specialist. Tuberculosis testing will be performed on a country-by-country basis, according to local guidelines if required by regulatory authorities or ethics boards.
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the screening visit and during the screening period.

- Known or suspected immunodeficiency, including history of invasive opportunistic infections (e.g., TB, 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.
- Active malignancy or history of malignancy within 5 years before the Baseline Visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.
- History of systemic hypersensitivity or anaphylaxis to omalizumab or any biologic therapy, including any excipients.
- Patient 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 patient's participation unreliable, or may interfere with study assessments. The specific justification for subjects excluded under this criterion will be noted in study documents (chart notes, CRF, etc.,).
- Current history of substance and/or alcohol abuse.
- Planned major surgical procedure during the patient's participation in this study.
- Exposure to another systemic or topical investigative drug (monoclonal antibodies as well as small molecules) within a certain time period prior to the screening visit (Visit 1), defined as follows: an interval of <6 months or <5 PK half-lives for investigative monoclonal antibodies, whichever is longer, and an interval of <30 days or <5 PK half-lives, whichever is longer, for investigative small molecules.
- Having used any of the following treatments within 4 weeks before the screening visit (Visit 1).
  - Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids [oral or parenteral - intravenous, intramuscular, SC]), cyclosporine, mycophenolate-mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, hydroxychloroquine, sulfasalazine, dapsone, colchicine, etc.).
  - Antifibrinolytic tranexamic acid and epsilon-aminocaproic acid.
  - Leukotriene receptor antagonists and H2 receptor antagonists. Note: patients taking stable leukotriene receptor antagonists and/or H2 receptor antagonists for diseases other than CSU (e.g., asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use.
  - Phototherapy, including tanning beds.

- Treatment with biologics as follows:
  - Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit (Visit 1).
  - Omalizumab within 4 months before the screening visit (Visit 1).
  - Other monoclonal antibodies (which are biological response modifiers): within 5 half-lives (if known) or 16 weeks before the screening visit (Visit 1), whichever is longer.
- Treatment with a live (attenuated) vaccine within 4 weeks before the screening visit (Visit 1).
  - Patient for whom administration of live (attenuated) vaccine can be safely postponed would be eligible to enroll into the study.
  - Patients who have their vaccination preponed can enroll in the study only after a gap of 4 weeks following administration of the vaccine.
    - Note: for subjects who have vaccination with live, attenuated vaccines planned during the course of the study (based on national vaccination schedule/local guidelines), it will be determined, after consultation with a physician, whether the administration of vaccine can be postponed until after the End Of Study, or preponed to before the start of the study, without compromising the health of the subject:
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to screening visit (Visit 1).
- Either intravenous immunoglobulin therapy and/or plasmapheresis within 30 days prior to screening visit (Visit 1).
- Planned or anticipated use of any prohibited medications and procedures during screening and study treatment period.
- Participation in prior dupilumab clinical study or have been treated with commercially available dupilumab.
- History of human immunodeficiency virus (HIV) infection or positive HIV 1/2 serology at the screening visit (Visit 1).
- Patients with any of the following result at the screening visit (Visit 1):
  - 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 antibody confirmed by positive hepatitis C virus RNA.
- Any country-related specific regulation that would prevent the subject from entering the study
- Individuals who are institutionalized, not suitable for participation due to medical or clinical conditions, or potentially at risk for non-compliance to study procedures

- Individuals who are dependent on the Applicant or Investigator, employees of the clinical study sites or other individuals directly involved in the conduct of the study or immediate family members of such individuals
- Individuals that have a sensitivity to any study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator that contraindicates participation in the study

**Study Treatments**

The dosing regimens studied for CSU are identical to the dosing regimen approved for adult and pediatric patients with moderate-to-severe AD. The Applicant's justification for dose selection included that CSU and AD have shared pathophysiology and target similar tissues (skin); the favorable benefit-risk profile of the approved dosing regimen for AD in adults and adolescents supported the selection of the same dosing regimen for CSU.

Adults and adolescents ≥12 years of age who weigh ≥60 kg:
- Dupilumab 300 mg given Q2W, after an initial loading dose of 600 mg

Adolescents ≥12 years of age and children ≥6 to <12 years of age who weigh ≥30 kg to <60 kg:
- Dupilumab 200 mg Q2W, after an initial loading dose of 400 mg

Children ≥6 to <12 years of age who weigh <30 kg and ≥15 kg:
- Dupilumab 300 mg given Q4W, after an initial loading dose of 600 mg

Subjects were randomized 1:1 to receive dupilumab or placebo and were treated with assigned study intervention. There were no subjects who were treated, but not randomized. Dupilumab and matching placebo were visually indistinguishable for each dose. Dose modification was not permitted in the study.

**Dietary Restrictions**

There were no dietary restrictions in the trial.

**Treatment Compliance**

Investigator or delegate ensured that the investigational medical product (IMP) was administered to each subject according to the labeling instructions. Subject compliance with study intervention was assessed at each visit. Compliance was assessed by returned kit/prefilled syringe. Deviation(s) from the prescribed dosage regimen was recorded in the eCRF.

**Concurrent Medications**

Subjects were permitted to be on up to 4-fold the approved non-sedating H1AH dose daily.

**Rescue Medication**

The initial maintenance H1AH dose at the time of randomization was to remain stable throughout the study, and subjects were to continue their maintenance dose once rescue treatments were no longer required.

All subjects on doses 1- to 3-fold the approved nonsedating H1AH dose (maintenance dose used at screening) were allowed to take additional doses of their H1AH medications as rescue therapy, as long as they did not exceed 4-fold the recommended dose during the screening, treatment, and follow-up periods. If symptoms were still uncontrolled after increase of H1AH to the maximum allowed dose, subjects were able to take a short course of OCS as rescue therapy during the treatment and follow-up periods. In order to ensure consistency, when possible, the recommended OCS duration was for 5 to 7 days, with a starting dose of oral prednisone 40 mg (or clinically comparable OCS), followed by taper per the Investigator's judgment.

The use of permitted rescue medications was to be delayed, if possible, for at least 8 weeks following the initiation of the investigational treatment. The date and time of rescue medication administration was recorded.

**Administrative Structure**

There was no Independent Data Monitoring Committee for this study.

**Procedures and Schedules**

Study procedures and schedules for Study C are displayed in Figure 14.

**Figure 14. Schedule of Activities, Study C**

| Procedures | Screening (2 to 4 weeks before Day 1) | Intervention period (Weeks) | | | Follow-up (12 weeks) | Notes |
|---|---|---|---|---|---|---|
| | | 0 (Day 1) | 12 | 24 | 36 | Visit window: ±3 days for Visits 3, 4, and 5 |
| **Visit** | **1** | **2[a]** | **3** | **4 (EOT)[b]** | **5 (EOS)** | |
| **Screening/baseline:** | | | | | | |
| Informed consent | X | | | | | |
| Medical history | X | | | | | |
| Prior and concomitant medication | X | X | X | X | X | Concomitant medication including rescue OCS taken since last visit will be collected throughout the study |
| Demographics | X | | | | | |
| Inclusion/exclusion criteria | X | X | | | | |
| Patient e-diary training | X | X | | | | |
| Randomization | | X | | | | |
| **Study intervention** | | | | | | |
| Call IVRS/IWRS | X | X | X | X | X | |
| IMP administration | | X[c] | | | | IMP will be administered every other week except (for study A and study C) for children <30 kg and ≥15 kg where it will be administered every 4 weeks. The planned last dose is at Week 22 except (for study A and study C) for children <30 kg and ≥15 kg where it will be administered at Week 20. Participants (or their care givers) are allowed to perform IMP injections at home. |
| Dispense/Upload electronic diary[d] | X | X | | | | Device is dispensed at Screening (including instructions for use). At the EOS, the e-diary is returned to the site. |
| **Safety[e]** | | | | | | |
| Physical examination[f] | X | X | | X | X | |
| Vital signs[g] | X | X | X | X | X | |
| Electrocardiogram (12 lead) | X | | | X | | ECG to be locally collected and read |

| Procedures | Screening (2 to 4 weeks before Day 1) | Intervention period (Weeks) | | | Follow-up (12 weeks) | Notes |
|---|---|---|---|---|---|---|
| | | 0 (Day 1) | 12 | 24 | 36 | Visit window: ±3 days for Visits 3, 4, and 5 |
| **Visit** | **1** | **2[a]** | **3** | **4 (EOT)[b]** | **5 (EOS)** | |
| Hematology, biochemistry, urine analysis[h] | X | X | X | X | X | |
| Hepatitis, HIV Serology, TB test[i] | X | | | | | |
| Pregnancy test[j] | Serum | Ur | Ur | Ur | Ur | In between visit urine pregnancy tests must be performed at home (Weeks 4, 8, 16, 20, 28, and 32) |
| AE reporting, including SAEs | X | X | X | X | X | |
| **Pharmacokinetics and ADA[e]** | | | | | | |
| Serum PK samples for dupilumab concentration[k] | | X | X | X | X | |
| Anti-dupilumab antibody[k] | | X | X | X | X | |
| **Biomarkers[e]** | | | | | | |
| Serum total IgE | | X | X | X | X | |
| Basophil activation test (optional sub-study) | | X | X | X | | For participants (except pediatric participants in Studies A and B and all Study C participants) who decide to participate and provide consent for the optional basophil activation test. |
| Skin biopsy (optional sub-study) | | X | | X | | For participants (except pediatric participants) who decide to participate and provide consent for the optional skin biopsy. Two biopsies will be taken from each participant, 1 from lesion and 1 from non-lesion. |
| Archive serum and plasma samples (optional) | | X | X | X | X | For participants (except pediatric participants) who decide to participate and consent for the optional archive serum and plasma sample. Archive serum and plasma samples (optional) are collected for future analysis of potential biomarkers of drug response, disease activity, safety and the Type 2 inflammation pathway. |

| Procedures | Screening (2 to 4 weeks before Day 1) | Intervention period (Weeks) | | | Follow-up (12 weeks) | Notes |
|---|---|---|---|---|---|---|
| | | 0 (Day 1) | 12 | 24 | 36 | Visit window: ±3 days for Visits 3, 4, and 5 |
| **Visit** | **1** | **2[a]** | **3** | **4 (EOT)[b]** | **5 (EOS)** | |
| DNA (whole blood) samples - Optional | | X | | | | For participants (except pediatric participants) who decide to participate and provide consent for the optional genomics sub-study (DNA sample collection). The DNA sample should be collected at the Day 1 visit, but can be collected at any visit during the study. |
| RNA (whole blood) samples - Optional | | X | | X | | For participants (except pediatric participants) who decide to participate and provide consent for the optional genomics sub-study (RNA sample collection). The RNA sample must be collected before the administration of the first dose of study drug and at Week 24 before the administration of study drug |
| **Efficacy[d, e]** | | | | | | |
| UAS7 | UAS7 (includes ISS7 and HSS7 as components), once daily from screening to EOS | | | | | To be recorded in e-diary on the same time of the day |
| AAS7 | AAS7, once daily from screening to EOS | | | | | To be recorded in e-diary on the same time of the day |
| UCT | | X | X | X | X | |
| DLQI/CDLQI | | X | X | X | X | |
| CU-Q2oL | | X | X | X | X | |
| PGIC | | | X | X | | |
| PGIS | X | X | X | X | | |
| EQ-5D-5L/EQ-5D-Y | | X | X | X | X | |
| Missed school/work days[l] | | X | X | X | X | |

| Procedures | Screening (2 to 4 weeks before Day 1) | Intervention period (Weeks) | | | Follow-up (12 weeks) | Notes |
|---|---|---|---|---|---|---|
| | | 0 (Day 1) | 12 | 24 | 36 | Visit window: ±3 days for Visits 3, 4, and 5 |
| **Visit** | **1** | **2[a]** | **3** | **4 (EOT)[b]** | **5 (EOS)** | |
| Photographs CSU representative area for commercial activities (at selected sites in selected countries) | | X | X | X | X | For participants (except pediatric participants in Studies A and B and all Study C participants) who decide to participate and provide consent for the photography, photographs will be taken of a representative area of CSU involvement for commercial activities. Instructions for taking the photographs are provided in the photography reference manual. |

Abbreviations: AAS7 = angioedema activity score over 7 days; ADA = anti-drug antibodies; AE = adverse events; CDLQI = children's dermatology life quality index; CU-Q2oL = chronic urticaria quality of life questionnaire; DLQI = dermatology life quality index; DNA = deoxyribonucleic acid; ECG = electrocardiogram; eCRF = electronic Case Report Form; EOS = End of study; EOT = End of treatment; EQ-5D 5L = 5-level EuroQol 5-dimensional questionnaire; EQ-5D-Y = EuroQol 5-dimensional questionnaire youth; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HCV Ab = hepatitis C virus antibodies; HIV = Human Immunodeficiency Virus; HSS7 = hives severity score over 7 days; IgE = immunoglobulin E; IMP = investigational medicinal product; ISS7 = weekly itch severity score; IVRS = interactive voice response system; IWRS = interactive web response system; OCS = oral corticosteroids; PGIC = patient global impression of change; PGIS = patient global impression of severity; PK = pharmacokinetic; q2w = every 2 weeks; RNA = ribonucleic acid; SAE = serious adverse event; SC = subcutaneous; TB = tuberculosis; UAS7 = urticaria activity score over 7 days; UCT = urticaria control test; Ur = urine.

*a* Randomization/baseline Visit is defined as Day 1. All assessments at Visit 2 (Day 1) are to be conducted pre-IMP dose with the exception of the assessment of local tolerability of subcutaneous (SC) injections.

*b* Participants who discontinue the study treatment prematurely (prior to completing the 24--week treatment period) will perform the EOT assessments at the time of discontinuation to assure a complete clinical assessment in close temporal proximity to the premature termination of study treatment In addition, to allow assessment of participant outcomes over the stipulated study period, participants will be asked and encouraged to complete all remaining study visits and participate in all assessments according to the visit schedule.

*c* Loading dose on Day 1 of 600 mg (2 SC injections of 300 mg) followed by 300 mg every 2 weeks (q2w) regimen for adults and adolescents ≥60 kg OR 400 mg (2 SC injections of 200 mg) followed by 200 mg q2w for adolescents <60 kg and children ≥30 kg (Study A and Study C) OR 600 mg (2 SC injections of 300 mg) followed by 300 mg q4w for children <30 kg and ≥15 kg (Study A and Study C) OR matched placebo.

*d* Electronic diary is used for daily recording of patient's answers to the urticaria activity score over 7 days (UAS7) and angioedema activity score over 7 days (AAS7) questionnaires as well as antihistamines medication use for the duration of the study. This device is dispensed at screening visit (Visit 1), including instructions for use. Electronic devices will be returned to the Sponsor after end of study (EOS). For urticaria control test (UCT), dermatology life quality index (DLQI [≥16 years old]) /children's dermatology life quality index (CDLQI [≥6 to <16 years old]), chronic urticaria quality of life questionnaire (CU-Q2oL), 5-level EuroQol 5-dimensional questionnaire (EQ-5D-5L [≥16 years old]) /EuroQol 5-dimensional questionnaire youth (EQ-5D-Y [≥6 to <16 years old]), patient global impression of change (PGIC), patient global impression of severity (PGIS), and missed school/work days questionnaires, the participant will fill in the questionnaires during their site visit on a tablet that will be provided to the site.

*e* Assessments/procedures should be conducted in the following order: participant-reported outcomes (other than participant assessment of injection pain), Investigator assessments, safety and laboratory assessments (including sample collection for anti-drug antibodies (ADA), pharmacokinetic (PK), biomarker, and optional DNA and RNA), and administration of study drug.

*f* Physical examinations will include skin, nasal cavities, eyes, ears, respiratory, cardiovascular, gastrointestinal, neurological, lymphatic, and musculoskeletal systems.

*g* Vital signs, including systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), axillary or oral temperature (same method of temperature measurement should be used during the course of the study) (°C), and respiratory rate will be measured at every visit in a semi-supine or sitting position after 5 minutes rest. Height (cm) will be measured at screening visit (Visit 1) only. Body weight (kg) will be measured at screening visit (Visit 1) and at end of treatment (EOT)/EOS Visits.

*h* Hematology will include hemoglobin, hematocrit, platelet count, total white blood cell count, differential count, and total red blood cell count. Serum chemistry will include creatinine, blood urea nitrogen, glucose, lactate dehydrogenase, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Urinalysis will include specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin. In case the urine dipstick test result is abnormal, a urine sample should be sent into the central laboratory for microscopic and macroscopic examination.

*i* Clinical laboratory testing at screening visit ( Visit 1) will include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies). In case of results showing HBs Ag (negative) and HBc Ab (positive), an HBV DNA testing will be performed and should be confirmed negative prior to randomization. In case of results showing HCV Ab (positive), an HCV RNA testing will be performed and should be confirmed negative prior to randomization. TB test will be performed locally if required and results noted in the eCRF.

*j* Only for women of childbearing potential. Pregnancy will lead to definitive treatment discontinuation in all cases. Pregnancy testing should be done monthly, female participants will be supplied with dipsticks for months with no site visits planned. In female participants who discontinue the study intervention, the pregnancy testing should continue for a minimum of 12 weeks after the last dose of study intervention.

*k* In the event of any SAE, any AE of severe injection site reaction lasting longer than 24 hours, or any AESI of anaphylactic reaction or systemic allergic reaction that is related to IMP and require treatment, PK and ADA samples will be collected at or near the onset of the event for any additional analysis if required or for archival purposes.

*l* Baseline version to be administered at Baseline; post-Baseline version to be administered at the subsequent visits.

**Subject Completion, Discontinuation, or Withdrawal**

A subject was considered to have completed the study if they completed all phases of the study, including the final end of study (EOS) visit. If a subject discontinued treatment period prematurely, but completed follow-up to the planned EOS Visit, they were considered a completer. Subjects who withdrew from the study could not be rerandomized (treated) in the study. Their inclusion and intervention numbers were not to be reused. Subjects who withdrew were not replaced. Subjects who discontinued study intervention were encouraged to remain in the study and complete the follow-up period the EOS visit.

**Study Endpoints**

Efficacy data were collected via electronic devices (electronic diary or e-diary). The e-diary was used for daily recording of patient-reported outcomes assessments and the use of H1AH medication. Copies of the instruments used in this study are provided in the Appendix 15.7 in the Multi-disciplinary Review dated October 18, 2023 and include the following instruments: Urticaria Activity Score (UAS) (which includes the ISS and HSS), Angioedema Activity Score (AAS), Urticaria Control Test (UCT), Dermatology Life Quality Index, Children's Dermatology Life Quality Index, Chronic Urticaria Quality of Life Questionnaire, Patient Global Impression of Change, Patient Global Impression of Severity, EuroQol 5-Dimensional Questionnaire Youth, 5-level EuroQol 5-Dimensional Questionnaire.

Baseline values for the patient-reported outcome (PRO) measurements were defined as the value obtained from the 7 days prior to randomization. Subjects must have had no missing e-diary assessments in those 7 days.

**Primary Endpoint:**

- Change from baseline in weekly ISS7 at Week 24. ISS7 range is 0 – 21.
    - ISS Daily Score assessment/24hours:
        - 0 = None
        - 1 = Mild (present but not annoying or troublesome)
        - 2 = Moderate (troublesome but does not interfere with normal daily activity or sleep)
        - 3 = Intense (interferes with normal daily activity or sleep)

    Note: The ISS7 is scored by the patient reflectively over the past 24 hours, at the same time of the day, and recorded in an e-diary. Scores were to be collected daily from screening to end of study.

**Secondary Endpoints:**

- Change from baseline in weekly UAS7 at Week 12 and Week 24. UAS7 range is 0 - 42.
    - UAS Daily Score is the sum of the daily HSS and the daily ISS.
- Change from baseline in HSS7 at Week 12 and Week 24. HSS7 range is 0 – 21.
    - HSS Daily Score assessment number of hives/24hours:
        - 0 = None
        - 1= <20 hives
        - 2= 20 to 50 hives
        - 3= >50 hives

    Note: The HSS7 was scored by the patient reflectively over the past 24 hours at the same time of the day and recorded in an e-diary. Scores were to be collected daily from screening to end of study.
- Time to reach ≥5 points reduction from baseline in ISS7 response
- Proportion of participants with ≥ 5 points reduction from baseline in ISS7 at Week 12 and Week 24
- Change from baseline in ISS7 at all time points (onset of action is assessed by the first $p<0.05$ that remains significant at subsequent measures until Week 24)
- Proportion of patients with UAS7≤6 at Week 12 and Week 24
- Proportion of patients with UAS7=0 at Week 12 and Week 24
- Change from baseline in angioedema activity score over 7 days (AAS7) at Week 12 and Week 24. AAS7 range is 0 – 105.

The primary endpoint and a subset of the secondary endpoints listed above are included in testing hierarchy (see "Multiplicity Adjustment" subheading under this section) and hence more important for this review. Review section 8.1.3 includes the result of the analyses of endpoints included in testing hierarchy.

**Statistical Analysis Plan**

The statistical analysis plan (SAP) for Study C was issued on April 12, 2024.

**Sample size calculation:**

Assumptions for sample size calculations for Study C were based on Study A ISS7 and UAS7 results. Based upon a standard deviation (SD) of 7.5 (pooled SD from the observed data in Study A), an assumed treatment difference of 4.23 in the ISS7 would correspond to an effect size of approximately 0.564. Based upon an SD of 14.3 (pooled SD from the observed data in Study A), an assumed treatment difference of 8.53 in the UAS7 would correspond to an effect size of approximately 0.597.

Based on this assumption, plus the assumption of a 10% dropout rate, it was estimated by the applicant that 75 participants per group would provide 90% power to detect an effect size of

0.564 or higher in the ISS7 between the dupilumab arm and placebo using a t-test with 2-sided alpha = 0.05. This was confirmed in the statistical review. This sample size estimate also applies to UAS7.

**Analysis Sets:**

The following populations for analyses are defined by the applicant:

- Efficacy population: The primary analysis population for the efficacy endpoints was the ITT (intent-to-treat) population, defined as the randomized participants. Participants were to be analyzed according to the intervention group allocated by randomization.
- Safety population: All participants randomly assigned to study intervention and who received at least 1 dose of study intervention. Participants were to be analyzed according to the intervention they actually received.
- PK population: all participants in the safety population with at least one non-missing result for functional dupilumab concentration in serum after first dose of the study intervention. Participants were to be analyzed according to the intervention actually received.
- ADA population: all participants in the safety population who have at least one non-missing ADA result after first dose of the study intervention. Participants were to be analyzed according to the intervention actually received.

**Primary Efficacy Analysis:**

Primary Estimands:

- Primary endpoint: Change from baseline in ISS7 at Week 24
- Treatment of interest: dupilumab + H1AH and placebo + H1AH.
- Population: Study participants with CSU who remain symptomatic despite the use of H1-antihistamine treatment and are omalizumab naive.
- Population-level summary: Least square mean difference between dupilumab and placebo.
- Intercurrent events : The intercurrent events and estimand strategies are listed in Table 12.

**Table 12. Intercurrent events and corresponding estimand strategies**

| Intercurrent Event (ICE) | Estimand Strategy |
|---|---|
| Treatment discontinuation (but no prohibited medication used) | Treatment policy strategy |
| Prohibited and/or rescue medications use | Composite strategy (data excluded and WOCF values assigned after ICE) |

Source: Adapted from Study C Statistical Analysis Plan. WOCF: worst-observation carried forward.

Primary Efficacy Analysis Model:

The primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model

with the baseline value of the primary endpoint, intervention group, presence of angioedema at baseline, and region as covariates, with intercurrent events and missing data handled by a hybrid method of the worst-observation carried forward (WOCF) and multiple imputation:

- For participants taking selected prohibited medications and/or rescue medications, their data after the medication start date were set to missing, and the worst post-baseline value on or before the time of the medication usage was used to impute missing Week 24 value (or the baseline value if all postbaseline values were missing).
- For participants who discontinued the treatment and did not take the selected prohibited medications and/or rescue medications, all data collected after treatment discontinuation were to be used in the analysis.
- Participants who discontinued the treatment prematurely were encouraged to follow the planned clinical visits. For these participants, missing data still happened despite all efforts to collect the data after treatment discontinuation.
- For participants who discontinued treatment due to lack of efficacy, all data collected after discontinuation were used in the analysis, and a WOCF approach was used to impute missing Week 24 value if needed.
- For participants who discontinued treatment due to reasons other than lack of efficacy, a multiple imputation approach was used to impute missing Week 24 value. This multiple imputation used all participants except participants who had taken the selected prohibited medications and/or rescue medications on or before Week 24 or participants who had discontinued due to lack of efficacy on or before Week 24. Each of the imputed complete data were analyzed by fitting an ANCOVA model as described above. Statistical inference obtained from all imputed data were combined using Rubin's rule.

Missing Data Sensitivity Analysis:

The following sensitivity analyses targeting the primary estimand were performed to assess the impact of the missing data assumptions.

- Pattern mixture model with copy increment from placebo after WOCF: After using the WOCF approach to impute data after taking the select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis), the primary endpoint was analyzed with imputed missing Week 24 values using a pattern mixture model with copy increment from placebo. This copy increment from placebo implied that when participants discontinued intervention early, they continued to take advantage of their previous therapy, but they progressed in the same way as participants in the placebo group. The imputed dataset was analyzed by fitting an ANCOVA model same as the one in the primary analysis. Descriptive statistics including number of participants, mean, standard error, and LS means was provided. In addition,

difference in LS means and the corresponding 95% CI were provided along with the p-values.

- Tipping point analysis: After using the WOCF approach to impute data after taking select prohibited/rescue medications and to impute missing data for participants who discontinue treatment due to lack of efficacy (as described for the primary analysis), a tipping point analysis was performed for the primary endpoint with imputed missing Week 24 values. Detailed description of the tipping point analysis steps is provided in Appendix 15.4 .

Supplementary Analyses:

- As-observed analysis (Including all data after taking selected prohibited and/or rescue medications): The data collected after taking the select prohibited medications and/or rescue medications were included in the supplementary analysis to evaluate the robustness of the primary analysis results with respect to the intercurrent event handling strategy while taking selected prohibited medications and/or rescue medications (e.g., treatment policy strategy). For missing data, a multiple imputation approach was used to impute missing Week 24 value, and this multiple imputation used all participants.

- Worst possible score analysis: For participants taking selected prohibited and/or rescue medications, their data after the medication start date were excluded from the analysis, and the worst possible score (21 for ISS7) was assigned to the Week 24 value. For missing data, a multiple imputation approach was used to impute missing Week 24 value, and this multiple imputation used all participants except participants who have taken the selected prohibited medications and/or rescue medications on or before Week 24.

Subgroup Analyses:

To assess the consistency of the treatment effects across various subgroups, subgroup analyses by demographic characteristics and by baseline disease characteristics were conducted for the primary endpoint. The analysis was performed based on imputed datasets from the primary analysis.

**Secondary Efficacy Analyses**

- Continuous secondary endpoints were analyzed using the same approach as the primary efficacy endpoint.
- Responder endpoints were analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by baseline disease severity, presence of angioedema at baseline, and region. The baseline disease severity was defined according to UAS7<28 or ≥28. Comparisons of the response rates between dupilumab and placebo were derived. Participants who received selected prohibited medications and/or rescue medications were considered as nonresponders for time points after medication usage. For other participants, all available data including those collected during the off-treatment period were to be used to determine the responder/nonresponder status. Subjects with missing data were considered as nonresponders.

**Multiplicity Adjustment**

The applicant specified a multiplicity adjustment procedure to control the overall type-I error rate for testing the primary and selected secondary endpoints. The overall alpha was 0.05. The comparisons with placebo were tested based on the hierarchical order below at 2-sided $\alpha$=0.05.

- Change from baseline in ISS7 at Week 24
- Change from baseline in UAS7 at Week 24
- Change from baseline in HSS7 at Week 24
- Proportion of participants with ≥ 5 points reduction from baseline in ISS7 at Week 24
- Proportion of patients with UAS7 ≤6 at Week 24
- Proportion of patients with UAS7 = 0 at Week 24
- Change from baseline in UCT at Week 24

**Protocol Amendments**

Studies A, B and C were included under the master protocol EFC16461 (CUPID). There were three global protocol amendments, and 2 country specific amendments (France and Japan). The major protocol amendments applicable to our review are summarized below.

- Amended Clinical Trial Protocol 01, February 10, 2020, version 1 (electronic 1.0): Japan only.
- Amended Clinical Trial Protocol 02, April 30, 2020, version 1 (electronic 2.0)
  - Increase the sample size of Study A (omalizumab naïve population) to power the studies using conservative assumptions with regards to treatment effect and variability (FDA recommendation).
  - Included children aged ≥6 to <12 years (for Study A only; FDA recommendation) with reflective changes to sample size, age stratification, informed consent requirements, dosing and administration clarifications, and other pertinent areas of protocol.
  - Clarification anticipation to enroll 30% to 40% of participants with angioedema in order to have a sufficient number of patients to assess effect of study intervention on CSU with angioedema.
  - Coronavirus disease 2019 (COVID-19) pandemic protocol amendments included.
- Amended Clinical Trial Protocol 03, October 9, 2020, version 1 (electronic 3.0): France only.
- Amended Clinical Trial Protocol 04, April 29, 2021, version 1 (electronic 4.0)
  - Plan for an IA for Study B when 80 randomized participants would have completed their 24-week treatment period. Applicant rationale included the following: Due to COVID impact and associated difficulties to enroll patients in Study B, an IA of will be performed to allow an earlier assessment of efficacy or stop for futility in this population.
  - Sample size calculations were updated to reflect the earlier IA using the O'Brien-Fleming approach.
  - At the IA, the study B is considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.021 (when p-value≤0.021) and

stops for futility if p-value>0.1. If Study B meets the criteria to continue at the interim analysis (when p-value>0.021 and p-value≤0.1), at the final analysis of Study B, it will be considered positive when the primary endpoint achieves statistical significance using 2-sided significance level 0.043.

- Amended Clinical Trial Protocol 05, March 17, 2022, version 1 (electronic 5.0)
  - Added Study C with a study population and design that is the same as the completed Study A, to provide data from two adequate and well-controlled clinical trials to support filing of a marketing application.
  - Key Study A results and information on the Study B prespecified interim analysis outcome (stop for futility outcome) have been added to this amended protocol.

### 8.1.3. Study Results

For study result subsections, the results for Study C are presented.

**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**

Patient disposition for Study C is summarized in Table 13. Of the 151 randomized and exposed patients, the overall early study intervention (24 weeks) discontinuation rate was 9.9%; the discontinuation rate was 10.4% in the placebo arm and 9.5% in the dupilumab arm. No patient in the dupilumab arm and 1 patient (1.3%) in the placebo arm discontinued the study intervention due to adverse events. Overall, study period (36 weeks) discontinuation rate was 11.9%; most patients who discontinued study intervention also discontinued from the study. The most common reason for study intervention (24 weeks) and study period (36 weeks) discontinuation was 'withdrawal by subject'.

**Table 13. Patient Disposition (ITT), Study C**

| Randomized and Exposed | Dupilumab (N = 74), n(%) | Placebo (N = 77), n(%) | All (N=151), n(%) |
|---|---|---|---|
| Completed the study intervention period | 67 (90.5) | 69 (89.6) | 136 (90.1) |
| Study intervention (24 weeks) discontinuation | 7 (9.5) | 8 (10.4) | 15 (9.9) |
| Adverse Event | 0 | 1 (1.3) | 1 (0.7) |
| Lack of Efficacy | 3 (4.1) | 0 | 3 (2.0) |
| Withdrawal by Subject | 4 (5.4) | 6 (7.8) | 10 (6.6) |

| Randomized and Exposed | Dupilumab (N = 74), n(%) | Placebo (N = 77), n(%) | All (N=151), n(%) |
|---|---|---|---|
| Adverse event | 0 | 1 (1.3) | 1 (0.7) |
| Study procedure | 0 | 1 (1.3) | 1 (0.7) |
| Lack of efficacy | 2 (2.7) | 2 (2.6) | 4 (2.6) |
| Other | 2 (2.7) | 2 (2.6) | 4 (2.6) |
| Other | 0 | 1 (1.3) | 1 (0.7) |
| Study period (36 weeks) discontinuation | 8 (10.8) | 10 (13.0) | 18 (11.9) |
| Adverse Event | 0 | 0 | 0 |
| Withdrawal by Subject | 6 (8.1) | 8 (10.4) | 14 (9.3) |
| Other | 2 (2.7) | 2 (2.6) | 4 (2.6) |

Source: Adapted from Study C Clinical Study Report Table 6, p.29.
Abbreviations: ITT, intent-to-treat population; N, number of subjects; n, number of subjects with specific disposition
Study period = study intervention period + post-intervention follow-up period

**Protocol Violations/Deviations**

Major Study C protocol deviations were reported in 31 (41.9%) subjects in the dupilumab group and 22 (28.6%) in the placebo group.

Twenty-one subjects had deviations in the "Concomitant medications/therapy" category. Most were related to background H1AH dosing with 11 subjects missing H1AH doses for between 4-7 days, 2 subjects missing H1AH doses for >7 days, and 2 subjects switching H1AH treatment. Three subjects had protocol deviations related to use of oral corticosteroids. One additional subject reported a protocol deviation related to prohibited therapy/medication/vaccine administered as he was administered evolocumab.

Fifteen subjects had deviations in the "randomization procedure – wrong stratum of randomization." Eleven (14.9%) subjects were in the dupilumab group and 4 (5.2%) in the placebo group. Ten (13.5%) subjects in the dupilumab group and 2 (2.6%) subjects in the placebo group had a baseline AAS7 equal to 0 and baseline AAS7 stratification (assessed by the Investigator) as "Yes". One (1.4%) subject in the dupilumab group and 2 (2.6%) subjects in the placebo group had a baseline AAS7 greater than 0 and baseline AAS7 stratification (assessed by the Investigator) as "No". Presence of angioedema at baseline based on subject's assessment was used as a covariate in the analysis, and the stratification errors made by the Investigator had no impact on the efficacy results. No subjects received the wrong IMP or wrong dose.

Ten subjects had deviations in "Informed consent procedures – Informed consent/Assent form not obtained for the substudy/exploratory analyses/DNA banking". Any samples collected without consent were destroyed.

Five subjects had deviations in "Inclusion/exclusion criteria, Subjects using a study defined H1AH for CSU treatment." Three subjects did not meet the study defined H1AH dose for CSU, one subject did not meet the Inclusion Criteria of UAS7$\geq$16 and ISS7$\geq$8 during the 7 days before randomization, and one subject had prior exposure to omalizumab and therefore, was not considered omalizumab naïve.

Five subjects had deviations related to UAS7/ISS7 examination not performed.

Four subjects had IMP related deviations: 2 subjects received 2 doses of dupilumab the same day, one subject was administered IMP that had a temperature excursion, and one subject did not discontinue the IMP injection although the subject reported malignancy (colorectal adenocarcinoma).

Major deviations pre-identified as potentially impacting the primary endpoint were reported in 4 (5.4%) subjects in the dupilumab group and 3 (3.9%) subjects in the placebo group. Of these, 5 were related to "Examination (UAS7/ISS7) not performed." The impact of these missing UAS7/ISS7 data on the primary efficacy endpoint was assessed as not significant based on the pre-planned sensitivity analyses using different approaches for handling of missing data. One subject in the placebo group did not meet Inclusion Criteria with an ISS7 of 3 and a UAS7 of 5 during the 7 days prior to randomization. One subject in the dupilumab group had an evolocumab injection 10 days after the 10$^{th}$ IMP injection at Week 16, but did not discontinue the study intervention.

**Demographic Characteristics**

Demographic characteristics for study C are shown in Table 14.

Demographics were similar for the dupilumab and placebo arms, with the largest difference noted in sex, with 63.5% female in the dupilumab arm and 76.6% female in the placebo arm. The mean age was 44.7 years old, with a minimum age of 8 years and a maximum age of 79 years. Most subjects were aged 18 to 64 years old. Most subjects in the study were white (46.4%) or Asian (41.1%); 1.3% were Black. 15.2% had Hispanic or Latino ethnicity. The majority of subjects were from Western Countries (60.9%) and Asia (33.1%). Weight and body mass index were similar between the dupilumab and placebo arms.

**Table 14. Demographic Characteristics of the Primary Efficacy Analysis, Study C – ITT Population**

| | Dupilumab N=74 | Placebo N=77 | Total N=151 |
|---|---|---|---|
| Age (years) | | | |
| Mean (SD) | 45.6 (17.09) | 44.0 (16.70) | 44.7 (16.86) |
| Median | 47.0 | 47.0 | 47.0 |
| IQR | 34.0, 55.0 | 31.0, 57.0 | 32.0, 57.0 |
| Min, Max | 11.0, 79.0 | 8.0, 77.0 | 8.0, 79.0 |
| Age Group (years) [n (%)] | | | |
| 6-11 | 1 (1.4) | 2 (2.6) | 3 (2.0) |
| 12-17 | 3 (4.1) | 3 (3.9) | 6 (4.0) |
| 18-39 | 26 (35.1) | 27 (35.1) | 53 (35.1) |
| 40-64 | 32 (43.2) | 36 (46.8) | 68 (45.0) |
| 65-74 | 8 (10.8) | 8 (10.4) | 16 (10.6) |
| 75+ | 4 (5.4) | 1 (1.3) | 5 (3.3) |
| Region [n (%)] | | | |
| Asia | 26 (35.1) | 24 (31.2) | 50 (33.1) |

| | Dupilumab N=74 | Placebo N=77 | Total N=151 |
|---|---|---|---|
| East Europe | 1 (1.4) | 1 (1.3) | 2 (1.3) |
| Latin America | 3 (4.1) | 4 (5.2) | 7 (4.6) |
| Western Countries | 44 (59.5) | 48 (62.3) | 92 (60.9) |
| Territory [n (%)] | | | |
| European Union | 18 (24.3) | 22 (28.6) | 40 (26.5) |
| North America | 27 (36.5) | 27 (35.1) | 54 (35.8) |
| Rest of World | 29 (39.2) | 28 (36.4) | 57 (37.7) |
| Sex [n (%)] | | | |
| Female | 47 (63.5) | 59 (76.6) | 106 (70.2) |
| Male | 27 (36.5) | 18 (23.4) | 45 (29.8) |
| Race [n (%)] | | | |
| American Indian or Alaska Native | 1 (1.4) | 0 | 1 (<1) |
| Asian | 33 (44.6) | 29 (37.7) | 62 (41.1) |
| Black or African American | 0 | 2 (2.6) | 2 (1.3) |
| White | 32 (43.2) | 38 (49.4) | 70 (46.4) |
| Multiple | 1 (1.4) | 2 (2.6) | 3 (2.0) |
| Missing | 7 (9.5) | 6 (7.8) | 13 (8.6) |
| Ethnicity [n (%)] | | | |
| Hispanic or Latino | 10 (13.5) | 13 (16.9) | 23 (15.2) |
| Not Hispanic or Latino | 62 (83.8) | 62 (80.5) | 124 (82.1) |
| Not Reported | 2 (2.7) | 1 (1.3) | 3 (2.0) |
| Unknown | 0 | 1 (1.3) | 1 (<1) |
| Weight (kg) | | | |
| Mean (SD) | 73.3 (16.96) | 73.7 (21.83) | 73.5 (19.53) |
| Median | 72.8 | 70.4 | 71.7 |
| IQR | 60.2, 82.5 | 60.2, 84.0 | 60.2, 83.3 |
| Min, Max | 45.3, 123.2 | 32.7, 156.4 | 32.7, 156.4 |
| Weight group (kg) | | | |
| <60 | 14 (18.9) | 19 (24.7) | 33 (21.9) |
| ≥ 60 | 60 (81.1) | 58 (75.3) | 118 (78.1) |
| BMI ($kg/m^2$) | | | |
| Mean (SD) | 26.4 (4.93) | 27.2 (7.15) | 26.8 (6.16) |
| Median | 26.0 | 26.0 | 26.0 |
| IQR | 22.8, 29.1 | 22.1, 30.1 | 22.5, 29.7 |
| Min, Max | 18.1, 41.6 | 17.3, 54.8 | 17.3, 54.8 |
| BMI group ($kg/m^2$) [n (%)] | | | |
| <30 | 59 (79.7) | 57 (74.0) | 116 (76.8) |
| ≥ 30 | 15 (20.3) | 20 (26.0) | 35 (23.2) |

Source: Statistical Reviewer Analysis; adsl.xpt;
Abbreviations: BMI, body mass index; IQR, interquartile range, ITT, Intent-to-treat population, max, maximum; min, minimum; N, number of subjects; SD, standard deviation

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Age of onset of CSU, time to diagnosis, baseline reporting of severity, medications used at baseline for CSU, and autoimmune disease history was reviewed in Table 15.

Baseline disease characteristics were similar between the dupilumab and placebo groups, particularly baseline ISS7 and UAS7 scores. There were fewer subjects with angioedema at baseline in the dupilumab group (16.2%) compared to the placebo group (28.6%), although the relevance of this disease characteristic to efficacy is unclear. Baseline total IgE levels were similar between the dupilumab and placebo groups. Regarding baseline H1AH use, there were fewer subjects using 4-fold standard dose antihistamines in the dupilumab group (6.8%) compared to the placebo group (14.3%), which may suggest a less refractory CSU disease course at baseline in the dupilumab group.

**Table 15. Baseline Disease Characteristics and Baseline Medications, Study C – ITT Population**

| Variable | Dupilumab N=74 | Placebo N=77 |
|---|---|---|
| Age at onset of CSU (years)- mean | 39.4 | 38.2 |
| Time since first diagnosis of CSU (years) - mean | 6.7 | 6.4 |
| Angioedema at baseline - Yes [n (%)] | 12 (16.2) | 22 (28.6) |
| Baseline ISS7 score - mean | 15.3 | 15.0 |
| Baseline UAS7 score - mean | 28.6 | 28.1 |
| Baseline HSS7 score - mean | 13.3 | 13.0 |
| Baseline UCT score - mean | 5.0 | 5.5 |
| Baseline total IgE (IU/mL) – mean | 304.7 | 318.7 |
| Baseline H1AH [n (%)] | | |
| Standard Dose | 40 (54.1) | 34 (44.2) |
| 2 to 3-Fold Standard Dose | 29 (39.2) | 32 (41.6) |
| 4-Fold Standard Dose | 5 (6.8) | 11 (14.3) |
| Baseline corticosteroid use for CSU | 20 (27.0) | 19 (24.7) |
| Autoimmune disease history | 2 (2.7) | 3 (3.9) |

Source: Statistical Reviewer Analysis; adsl.xpt;Abbreviations: IQR = interquartile range, ITT = Intent-to-treat population, SD = standard deviation

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

The mean treatment compliance rate was >99% and balanced between the dupilumab and placebo groups. No subject had a compliance rate <80%.

Concomitant medication use overall was similar between the dupilumab and placebo groups. Oral corticosteroids as a concomitant medication for treatment of a condition other than CSU were reported in 3 (4.1%) of the dupilumab group and 5 (6.5%) of the placebo group. Regarding omalizumab, 3 (4.1%) subjects in the dupilumab group and none in the placebo group received omalizumab (prohibited medication per protocol) during the study. One subject in the dupilumab group received evolocumab (PCSK9 inhibitor) for hypercholesterolemia and did not discontinue the study intervention. No AEs were reported following omalizumab or evolocumab

administration. Three subjects, 2 (2.7%) in the dupilumab group and 1 (1.3%) in the placebo group, received at least 1 dose of the COVID-19 vaccine. No AEs related to the COVID-19 vaccine were reported.

The overall number of subjects who required rescue treatment for CSU was low (Table 16). More subjects in the placebo group required any rescue treatment (7.8% in the placebo group vs 2.7% in the dupilumab group) and rescue with either H1AH or oral corticosteroids alone. This may suggest that the dupilumab group had better control of CSU than the placebo group.

**Table 16. Rescue Medications for CSU, Study C – ITT Population**

| Rescue | Dupilumab N=74 n (%) | Placebo N=77 n (%) |
|---|---|---|
| Any rescue medication | 2 (2.7) | 6 (7.8) |
| H1AH | 1 (1.4) | 2 (2.6) |
| OCS | 1 (1.4) | 5 (6.5) |

Source: Clinical Reviewer: Study C Clinical Study Report, Table 16.2.6.1.18.3
Abbreviations: CSU, chronic spontaneous urticaria; H1AH, H1-antihistamines; N, number of subjects; n, number of subjects with specific rescue medications

**Efficacy Results – Primary Endpoint**

Table 17 shows results for the primary efficacy endpoint of change from baseline in ISS7 at Week 24. The LS mean change from baseline in ISS7 at Week 24 was -8.64 in the dupilumab arm versus -6.10 in the placebo arm; the LS mean difference for dupilumab versus placebo was statistically significant (-2.54, 95% CI: -4.65, -0.43, p=0.0184).

**Table 17. Primary Analysis of Change From Baseline in ISS7 at Week 24, Study C – ITT Population**

| ISS7 | Dupilumab N=74 | Placebo N=77 |
|---|---|---|
| Baseline | | |
| n | 74 | 77 |
| Mean (SD) | 15.25 (3.63) | 15.03 (3.95) |
| Week 24 | | |
| n | 69 | 69 |
| Mean (SD) | 6.37 (6.53) | 8.51 (6.64) |
| Change from baseline | | |
| n (observed/imputed[1]) | 69 (64/5) | 69 (64/5) |
| LS mean (SE)[2] | -8.64 (1.41) | -6.10 (1.40) |
| LS mean difference vs. placebo (95% CI)[2] | -2.54 (-4.65, -0.43) | |
| p-value[2] | 0.0184 | |

Source: Statistical Reviewer Analysis
**1** Missing data after study intervention discontinued for lack of efficacy or data post select prohibited/rescue medication use were imputed by WOCF.
**2** Data collected after study intervention discontinuation were included. Other missing data were imputed by multiple imputation. Imputed data were analyzed using an ANCOVA model with baseline value, treatment group, presence of angioedema at baseline and regions as covariates.
Abbreviations: CI, confidence interval; ISS7, itchy severity score; ITT, intent-to-treat; LS, Least Squares; MI: multiple imputation; N, number of subjects; n, number of subjects in the analysis; SE, standard error; WOCF, worst observation carried forward.

To examine the robustness of the primary endpoint analysis result to missing data, pattern mixture models with copy increment from placebo (Table 18) and a tipping point analysis (Appendix 15.4) were conducted by the applicant. The LS mean difference versus placebo remained statistically significant under the pattern mixture models (Table 18), indicating that the impact of the missing-at-random assumption on overall missing data are not likely considerable.

**Table 18. Sensitivity Analysis of Change From Baseline in ISS7 at Week 24, Study C (PMM With Copy Increment From Placebo After WOCF) – ITT Population**

| ISS7 | Dupilumab N=74 | Placebo N=77 |
|---|---|---|
| Baseline mean (SD) | 15.25 (3.63) | 15.03 (3.95) |
| Week 24 mean (SD) | 6.37 (6.53) | 8.51 (6.64) |
| Change from baseline | | |
| LS mean (SE)[1] | -8.62 (1.40) | -6.11 (1.39) |
| LS mean difference vs. placebo (95% CI)[1] | -2.51 (-4.58, -0.43) | |
| p-value[1] | 0.0177 | |

Source: Study C Efficacy and Biomarker Response Data Table 16.2.6.1.5.2, p. 15.
1 Missing data after study intervention discontinued for lack of efficacy or data post select prohibited/rescue medication use were imputed by WOCF. Data collected after study intervention discontinuation were included. Other missing data were imputed by PMM with copy increment from placebo. Imputed data were analyzed using an ANCOVA model with baseline value, treatment group, presence of angioedema at baseline and regions as covariates.
Abbreviations: CI, confidence interval; ISS7, itchy severity score; ITT, intent-to-treat; LS, Least Squares; MI, multiple imputation; N, number of subjects; PMM, pattern mixture model; SE, standard error; WOCF, worst observation carried forward

In the tipping point analyses on change from baseline in ISS7 at Week 24 after WOCF (Table 41 in Appendix 15.4), the LS mean difference versus placebo remained statistically significant ($p<0.05$) under most scenarios after multiple missing data imputations and adding shift variables (1 to 9 in the dupilumab arm; -1 to -9 in the placebo arm), except under a few implausible extreme shifting scenarios. This finding, along with the results from the pattern mixture models, suggests that the primary analysis result is robust to underlying missing data assumption (missing-at-random).

In addition, under two supplementary analyses using as-observed data and the worst possible score, the LS mean difference versus placebo remained statistically significant ($p<0.05$), which suggests that the primary analysis result is robust to using alternative intercurrent event handling strategies.

- As-observed analysis: LS mean difference versus placebo (95% CI) = -2.75 (-4.76, -0.73); p=0.0075.

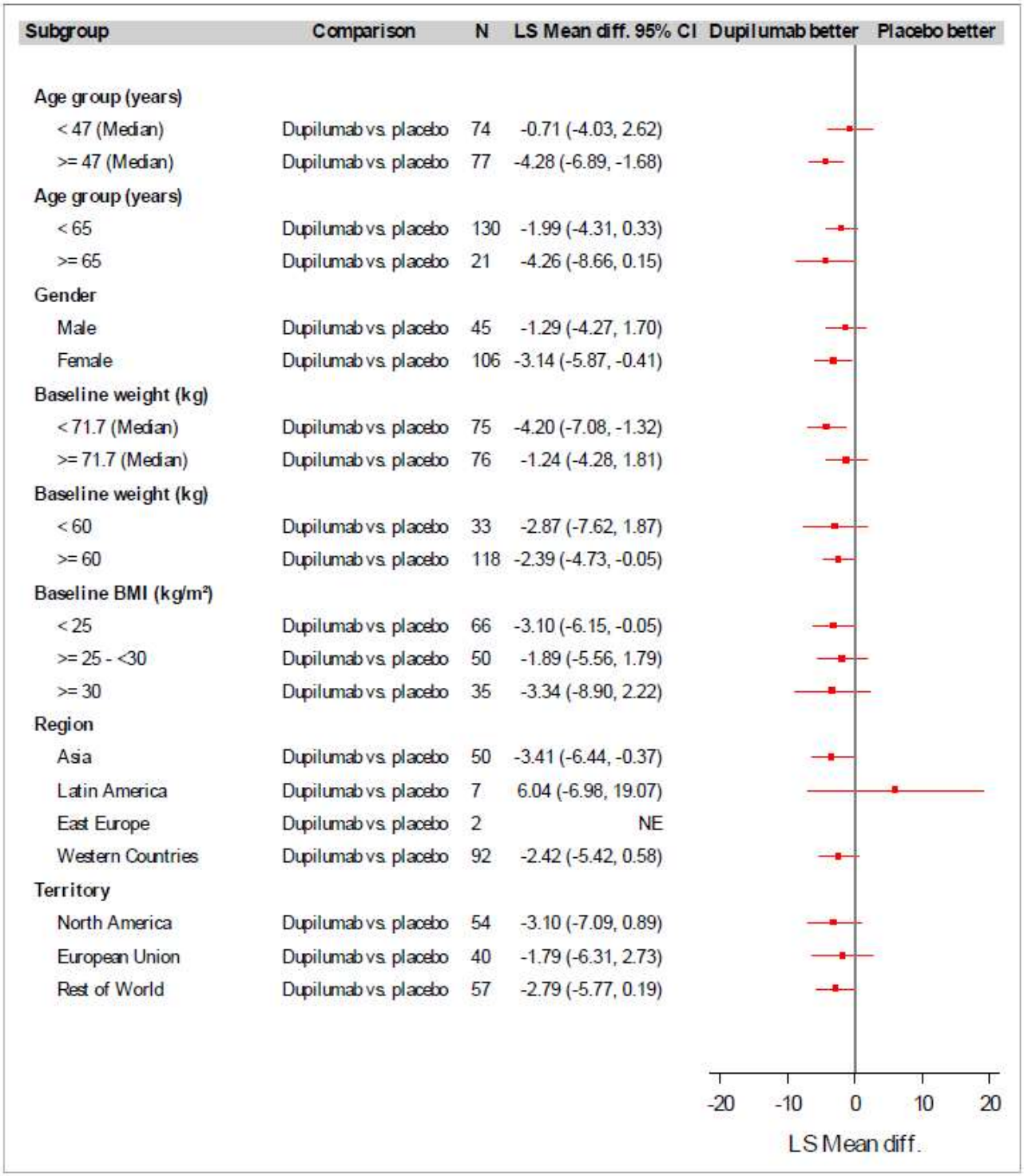
- Worst possible score analysis: LS mean difference versus placebo (95% CI) = -2.78 (-4.92, -

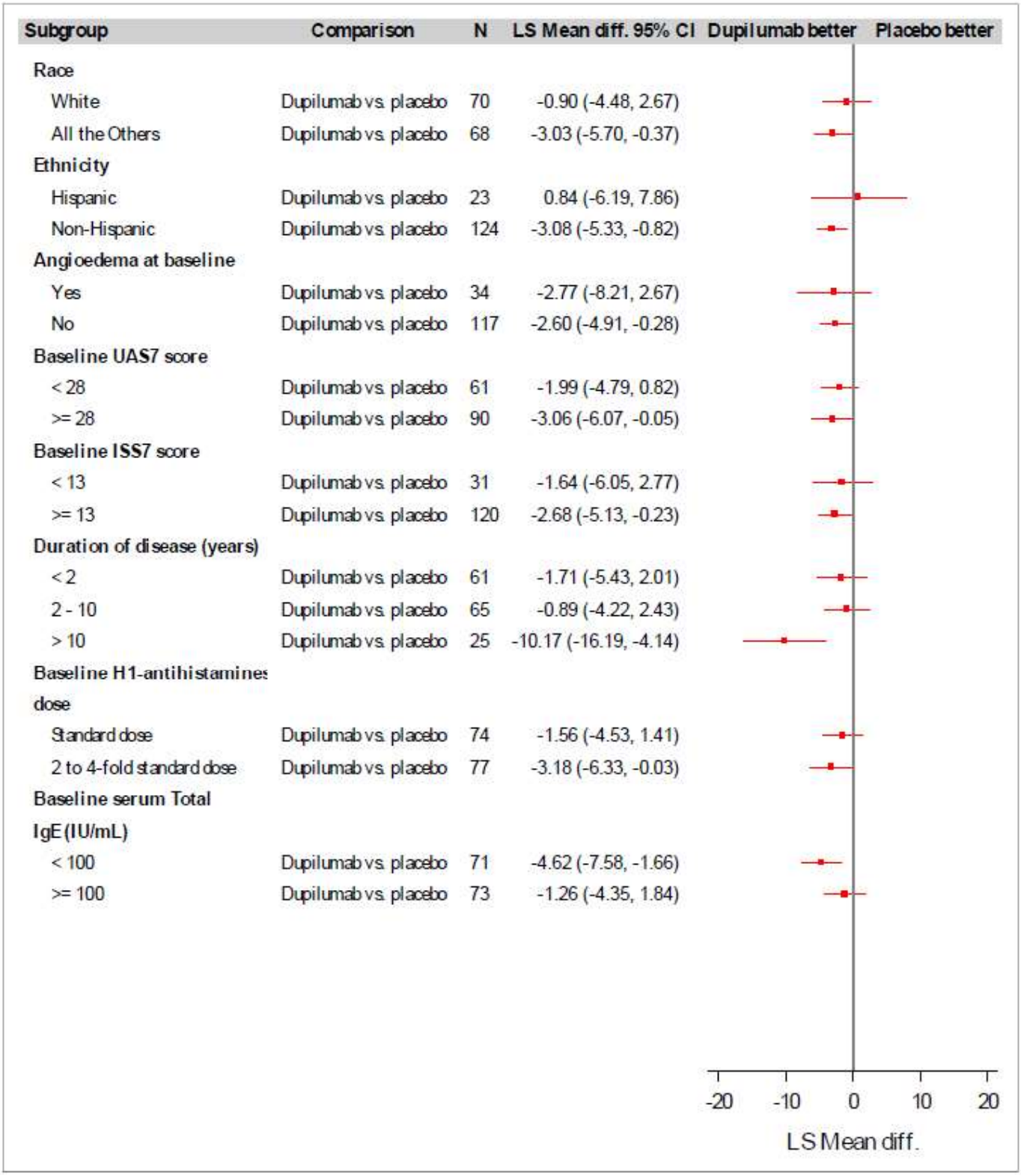
0.64); p=0.0110.

Subgroup Analysis for Primary Efficacy Endpoint

The subgroup analyses by demographics and baseline characteristics (Figure 15) showed that the results in subgroups were generally consistent with the overall treatment effect in ISS7, except for 2 subgroups (the Latin America and Hispanic subgroups). For these two subgroups, the treatment effects were in the opposite direction and had wide confidence intervals, likely due to limited sample size in these subgroups.

**Figure 15. Plot of treatment effect on change from baseline in ISS7 at Week 24 by subgroups, Study C - ITT population**




Subgroup
Comparison
N
LS Mean diff. 95% CI
Dupilumab better
Placebo better
Race
White
Dupilumab vs. placebo
70
-0.90 (-4.48, 2.67)
All the Others
Dupilumab vs. placebo
68
-3.03 (-5.70, -0.37)
Ethnicity
Hispanic
Dupilumab vs. placebo
23
0.84 (-6.19, 7.86)
Non-Hispanic
Dupilumab vs. placebo
124
-3.08 (-5.33, -0.82)
Angioedema at baseline
Yes
Dupilumab vs. placebo
34
-2.77 (-8.21, 2.67)
No
Dupilumab vs. placebo
117
-2.60 (-4.91, -0.28)
Baseline UAS7 score
< 28
Dupilumab vs. placebo
61
-1.99 (-4.79, 0.82)
>= 28
Dupilumab vs. placebo
90
-3.06 (-6.07, -0.05)
Baseline ISS7 score
< 13
Dupilumab vs. placebo
31
-1.64 (-6.05, 2.77)
>= 13
Dupilumab vs. placebo
120
-2.68 (-5.13, -0.23)
Duration of disease (years)
< 2
Dupilumab vs. placebo
61
-1.71 (-5.43, 2.01)
2 - 10
Dupilumab vs. placebo
65
-0.89 (-4.22, 2.43)
> 10
Dupilumab vs. placebo
25
-10.17 (-16.19, -4.14)
Baseline H1-antihistamines dose
Standard dose
Dupilumab vs. placebo
74
-1.56 (-4.53, 1.41)
2 to 4-fold standard dose
Dupilumab vs. placebo
77
-3.18 (-6.33, -0.03)
Baseline serum Total IgE (IU/mL)
< 100
Dupilumab vs. placebo
71
-4.62 (-7.58, -1.66)
>= 100
Dupilumab vs. placebo
73
-1.26 (-4.35, 1.84)
-20
-10
0
10
20
LS Mean diff.

Source: Study C Clinical Study Report Figure 3

**Data Quality and Integrity**

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

**Efficacy Results – Secondary endpoints under multiplicity control**

Secondary endpoints under type I error control were tested sequentially in the order specified in Section 8.1.2 under "Multiplicity Adjustment" subheading in the ITT population. The comparison of dupilumab vs. placebo for change from baseline in UAS7 and HSS7 at Week 24 achieved statistical significance, respectively (Table 19). Additionally, dupilumab demonstrated statistically significant odds ratio compared to placebo for the three binary endpoints of proportion of participants with at least 5 points reduction from baseline in ISS7, with UAS7≤6 and with UAS7=0 at Week 24 (Table 20).

**Table 19. Analyses of UAS7 and HSS7, Study C – ITT Population**

| Secondary Endpoints | Dupilumab N=74 | Placebo N=77 | Difference for Dupilumab vs. Placebo (95% CI) | p-value |
|---|---|---|---|---|
| Change from baseline in UAS7 at Week 24 | -15.86 (2.66) | -11.21 (2.65) | -4.65 (-8.65, -0.65) | 0.02 |
| Change from baseline in HSS7 at Week 24 | -7.27 (1.32) | -5.11 (1.31) | -2.17 (-4.15, -0.19) | 0.03 |

Source: Statistical Reviewer Analysis
For these secondary endpoints, values presented in "Dupilumab" and "Placebo" columns are LS mean change (SE) from baseline and value presented in "Difference for dupilumab vs. Placebo (95% CI)" column is LS mean difference (95% CI). These endpoints were analyzed using an ANCOVA model with baseline value, treatment group, presence of angioedema at baseline and region as covariates. Missing data after study intervention discontinued for lack of efficacy or discontinued for prohibited/rescue medication use was imputed by WOCF; other missing data were imputed by multiple imputation.
Abbreviations: CI, confidence interval; HSS7, Hives-Severity Score over 7 days (0-21); ITT, intent-to-treat population; N, number of subjects; UAS7, urticaria activity score over 7 days (0-42); WOCF, worst outcome carried forward;SE: standard error.

**Table 20. Analyses of Binary Secondary Endpoints, Study C – ITT Population**

| Secondary Endpoints (Binary) | Dupilumab N=74 | Placebo N=77 | Odds Ratio for Dupilumab vs. Placebo (95% CI) | p-value |
|---|---|---|---|---|
| Proportion of participants with ≥ 5 points reduction from baseline in ISS7 at Week 24 | 52 (70.3%) | 40 (51.9%) | 2.51 (1.23, 5.11) | 0.01 |
| Proportion of participants with UAS7 ≤ 6 at Week 24 | 30 (40.5%) | 18 (23.4%) | 3.14 (1.37, 7.18) | <0.01 |
| Proportion of participants with UAS7 = 0 at Week 24 | 22 (29.7%) | 14 (18.2%) | 2.68 (1.13, 6.36) | 0.02 |

Source: Statistical Reviewer Analysis
For these secondary endpoints, values presented in "Dupilumab" and "Placebo" columns are number (%) of responders and value presented in "Odds Ratio for dupilumab vs. Placebo (95% CI)" column is CMH odds ratio. These endpoints were calculated using Cochran-Mantel-Haenszel test adjusted for baseline severity, presence of angioedema at baseline, and region. Participants who received prohibited medications are considered as nonresponders for timepoints after medication usage. Missing data are considered as nonresponders.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; ITT, intent-to-treat populationN, number of subjects.

For the last secondary endpoint of change from baseline in UCT at Week 24 in the testing hierarchy, the estimated least squares mean change was 5.09 (SE of 0.95) in the dupilumab arm and 4.16 (SE of 0.94) in the placebo arm. The LS mean difference of dupilumab vs. placebo was 0.93 (95% CI: -0.48, 2.34, p-value of 0.19), which was not statistically significant.

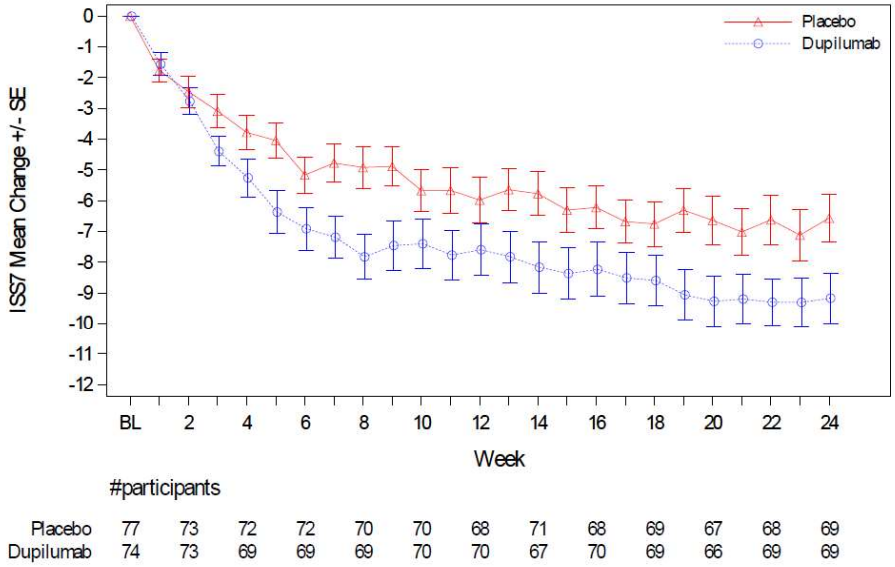
**Dose/Dose Response**

Dose response was not evaluated in Study C.

**Durability of Response**

There was a trend toward continued improvement in change from baseline in ISS7 during the 24-week treatment period in the dupilumab group compared to the placebo group (Figure 16).

**Figure 16. Plot of Mean Change From Baseline in ISS7 Over Time, Study C – ITT Population**




Source: Study C Clinical Study Report Figure 5

**Efficacy Results – Secondary Clinical Outcome Assessment (PRO) Endpoints**

Angioedema activity was measured by the AAS, a validated PRO measure for assessing angioedema status. The AAS7 is the sum of daily AAS (range 0-15) over 7 days with a total range of 0-105. At baseline, 12 (16.2%) subjects in the dupilumab group and 22 (28.6%) subjects in the placebo group had active angioedema, defined as an AAS7 score >0, with a median AAS7 score of 48.7 and 38.0, respectively. At Week 24, the LS mean change (decrease) from baseline in AAS7 was -28.85 in the dupilumab group and -24.04 in the placebo group, demonstrating no difference between the two groups.

### 8.1.4. Assessment of Efficacy Across Trials

Under a master protocol, the Applicant completed three 24-week, randomized, double-blind, placebo-controlled safety and efficacy trials (CUPID Studies A, B, and C) of dupilumab in a total of 397 subjects with CSU inadequately controlled with H1AH. Study A enrolled 138 subjects aged 6 and older with CSU not adequately controlled with H1AH and naïve to omalizumab. Similarly, Study C enrolled 151 subjects aged 6 and older with CSU not adequately controlled with H1AH and naïve to omalizumab. In contrast, Study B enrolled a different study population of 108 subjects aged 12 and older with CSU not adequately controlled with H1AH and unresponsive or intolerant to omalizumab.

**Primary, Secondary and Other Endpoints**

Study A and Study C establish the basis for substantial evidence of effectiveness for dupilumab in CSU. The results fom Study A are discussed in detail in the original Multi-disciplinary Review, dated October 18, 2023, and the results from Study C are discussed above.

Table 20 summarizes the results of the primary and secondary endpoints from Study A and Study C (ITT population). Both Study A and Study C enrolled subjects with CSU refractory to H1AH treatment, but who were omalizumab naïve. Both studies achieved statistical significance for their primary endpoint (change in baseline in ISS7 at Week 24), as well as secondary endpoints of change in baseline in UAS7 and HSS7, proportion of participants with UAS7≤6, and proportion of participants with UAS7=0, all at Week 24. Only change from baseline in UCT at 24 weeks in Study C was not significant. In general, the effect size for Study A was larger than for Study C across the primary and secondary endpoints.

**Table 21. Summary of the Primary and Secondary Endpoints, Study A and Study C – ITT Population**

| | Study A | | | | Study C | | | |
|---|---|---|---|---|---|---|---|---|
| Endpoints | Dupilumab N=70 | Placebo N=68 | Compared to Placebo (95% CI) | p-value | Dupilumab N=74 | Placebo N=77 | Compared to Placebo (95% CI) | p-value |
| Change from baseline in ISS7 at Week 24[1] | -10.24 (0.91) | -6.01 (0.94) | 4.23 (-6.63, 1.84) | **<0.01** | -8.64 (1.41) | -6.10 (1.40) | -2.54 (-4.65, -0.43) | **0.02** |
| Change from baseline in UAS7 at Week 24[1] | -20.53 (1.76) | -12.00 (1.81) | -8.53 (-13.16, -3.90) | **<0.01** | -15.86 (2.66) | -11.21 (2.65) | -4.65 (-8.65, -0.65) | **0.02** |
| Proportion of participants with UAS7 ≤ 6 at Week 24[2] | 32 (45.71%) | 16 (23.53%) | 2.85 (1.30, 6.23) | **0.01** | 30 (40.5%) | 18 (23.4%) | 3.14 (1.37, 7.18) | **<0.01** |
| Proportion of participants with UAS7 = 0 at Week 24[2] | 22 (31.43%) | 9 (13.24%) | 2.91 (1.17, 7.21) | **0.02** | 22 (29.7%) | 14 (18.2%) | 2.68 (1.13, 6.36) | **0.02** |
| Change from baseline in HSS7 at Week 24[1] | -10.28 (0.91) | -5.90 (0.93) | -4.38 (-6.78, -1.98) | **<0.01** | -7.27 (1.32) | -5.11 (1.31) | -2.17 (-4.15, -0.19) | **0.03** |
| Change from baseline in ISS7 at Week 12[1] | -8.37 (0.84) | -6.01 (0.85) | -2.37 (-4.60, -0.13) | **0.04** | - | - | - | - |
| Change from baseline in UAS7 at Week 12[1] | -16.81 (1.62) | -11.79 (1.64) | -5.02 (-9.32, -0.72) | **0.02** | - | - | - | - |
| Proportion of subjects with UAS7 ≤ 6 at Week 12[2] | 24 (34.29%) | 12 (17.65%) | 2.64 (1.15, 6.06) | **0.02** | - | - | - | - |
| Proportion of participants with ≥ 5 points reduction from baseline in ISS7 at Week 24[2] | 51 (72.86%) | 29 (42.65%) | 3.41 (1.60, 7.30) | **<0.01** | 52 (70.3%) | 40 (51.9%) | 2.51 (1.23, 5.11) | **0.01** |
| Proportion of participants with ≥ 5 points reduction from baseline in ISS7 at Week 12[2] | 49 (70.00%) | 36 (52.94%) | 1.87 (0.89, 3.92) | 0.10 | - | - | - | - |
| Change from baseline in HSS7 at Week 12[1] | -8.39 (0.83) | -5.69 (0.83) | -2.70 (-4.90, -0.50) | 0.02 | - | - | - | - |
| Proportion of subjects with UAS7 = 0 at Week 12[2] | 11 (15.71%) | 6 (8.82%) | 1.97 (0.68, 5.74) | 0.22 | - | - | - | - |
| Change from baseline in UCT at Week 24[1] | 7.71 (0.59) | 4.88 (0.61) | 2.84 (1.27, 4.40) | <0.01 | 5.09 (0.95) | 4.16 (0.94) | 0.93 (-0.48, 2.34) | 0.19 |
| Change from baseline in UCT at Week 12[1] | 6.48 (0.57) | 4.62 (0.57) | 1.86 (0.35, 3.36) | 0.02 | - | - | - | - |

Source: Clinical Study Report Study A and C (Order of the endpoints in this table are based on testing hierarchy of study A. Study C results for endpoints ordered based on original testing hierarchy are listed in section 8.1.2 under "Multiplicity Adjustment" subheading). All p-values in bold font are significant according to the hierarchical testing procedure specific to the study.

1 For these endpoints, values presented in "Dupilumab" and "Placebo" columns are LS mean change (SE) from baseline and value presented in "Comparison with Placebo (95% CI)" column is LS mean difference (95% CI). These endpoints were analyzed using an ANCOVA model with baseline value, treatment group, presence of angioedema at baseline and region as covariates. Missing data after study intervention discontinued for lack of efficacy or discontinued for prohibited/rescue medication use was imputed by WOCF; other missing data were imputed by multiple imputation.

2 For these endpoints, values presented in "Dupilumab" and "Placebo" columns are number (%) of responders and value presented in "Comparison with Placebo (95% CI)" column is CMH odds ratio. These endpoints were calculated using Cochran-Mantel-Haenszel test adjusted for baseline severity, presence of angioedema at baseline, and region. Participants who received prohibited medications are considered as nonresponders for timepoints after medication usage. Missing data are considered as nonresponders.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel Haenszel; HSS7, Hives-Severity Score over 7 days (0-21); ISS7, itch-severity score over 7 days (0-21); ITT, intent-to-treat population; N, number of subjects; UAS7, urticaria activity score over 7 days (0-42); UCT, urticaria control test (0-16); WOCF, worst outcome carried forward.

**Subpopulations**

CUPID Studies A, B, and C had unique baseline populations. All studies enrolled subjects with CSU who were inadequately controlled with H1AH. Studies A and C enrolled subjects naïve to omalizumab therapy and Study B enrolled subjects intolerant or unresponsive to omalizumab therapy as well. Given their failure to respond to omalizumab, subjects enrolled in Study B had more refractory CSU compared to subjects enrolled in Studies A and C. We analyzed subject characteristics at baseline, including age, baseline CSU severity scores (ISS7/HSS7/UAS7), baseline IgE level, autoimmune disease history, baseline concomitant medication use including antihistamines, oral corticosteroids, and immunosuppression, to assess how CSU disease severity may have affected study results.

*Study A/C vs Study B*
Subjects enrolled in Study B had a longer mean duration of CSU of 9.1 years compared to subjects in Studies A and C who had mean disease durations of 5.7 and 6.5 years, respectively. The population in Study B had a lower mean IgE of 223.2 IU/ml compared to mean IgE levels of 540.3 IU/ml and 311.9 IU/ml in Studies A and C, respectively. This may indicate that subjects enrolled in Study B may have had a different underlying pathophysiology driving their CSU compared to subjects enrolled in Studies A and C. Higher than standard doses of H1AH at baseline were reported in a larger proportion of Study B subjects (63.5% on 2-to 4-fold on higher than dose) than subjects in Study A (47.9%) and Study C (51.0%). Baseline systemic corticosteroid use for CSU was higher in Study B subjects (38.0%) versus Studies A (23.2%) and C (25.8%) subjects. Baseline immunosuppression use was also higher in Study B subjects (14.8%) versus Studies A (5.1%) and C (3.3%) subjects. The greater medication needs for CSU treatment for subjects in Study B, in addition to inadequate response to omalizumab treatment, may indicate that subjects enrolled in Study B had more severe/refractory CSU than those subjects enrolled in Studies A and C. The different baseline characteristics taken together may imply that subjects enrolled in Study B had a different driver for their CSU disease than subjects enrolled in Studies A and C, leading to the difference in study results.

*Study A vs Study C*
There were less notable differences between the subjects enrolled in Study A and Study C that may explain the greater effect size observed in Study A. The greater effect size for Study A compared to Study C may be a result of the differences in disease severity between the two studies as the enrolled population in Study A had higher mean ISS7 at baseline, higher UAS7 at baseline, and more subjects on 4-fold higher than approved antihistamine doses (16.7% in Study A vs 10.6% in Study C). The enrolled population in Study A also had more subjects with angioedema (44.9% in Study A vs 22.5% in Study C). These differences in baseline characteristics in the enrolled populations of Study A and Study C may be suggestive of differences in disease severity with the greater disease severity in Study A potentially explaining the greater effect size seen in Study A.

#### 8.1.5. Integrated Assessment of Effectiveness

Substantial evidence of effectiveness has been demonstrated for dupilumab for adults and adolescents 12 years and older with CSU.

The results from Studies A and C demonstrate a statistically significant improvement in the primary endpoint, change from baseline in ISS7 at Week 24. Key secondary endpoints of change from baseline in UAS7 and HSS7 at Week 24 were also met. Additional clinically meaningful responder analysis endpoints were also met. Study B met futility criteria at the predefined interim analysis (n=83), as defined in the Statistical Analysis Plan for the trial, and the trial was discontinued. Differences in baseline characteristics and disease severity may have contributed to the difference in the efficacy results between the three studies.

The results from the two pivotal trials, Studies A and C, have met the standard for substantial evidence of effectiveness to demonstrate that dupilumab is an effective treatment for patients with CSU whose disease is inadequately controlled on H1AH. However, no conclusion on effectiveness can be made for dupilumab in the treatment of CSU that is inadequately controlled on H1AH and unresponsive to omalizumab therapy.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The three safety and efficacy studies, CUPID Studies A, B, and C, were conducted under individual protocols as separate studies outlined in Section 8.1. For our safety review, the safety data for CUPID Studies A, B, and C are pooled using MedDRA version 27.0. All three studies had a duration of 24 weeks of treatment and 12 weeks of follow-up. Subjects in all three studies had the same dupilumab dosing regimen and equivalent placebo. The safety population was defined as all subjects randomly assigned to study intervention and who received at least 1 dose of study intervention. Subjects in this group were analyzed according to the intervention they received. Adverse events (AEs) were reported through the end of the follow-up period. The review tools used to conduct the safety analyses by the clinical reviewer included JMP Clinical, MAED, and Analysis Studio.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

The overall exposure for dupilumab and placebo from CUPID Studies A, B, and C combined is shown in Table 21. The exposures in Studies A, B, and C are of similar duration.

**Table 22 Safety Population, Size, and Denominators for CUPID Studies A, B, and C, Overall Exposure**

| | Dupilumab | Placebo |
|---|---|---|
| Total Subjects | n=198 | n=199 |
| Duration of study treatment (days) | | |
| Mean (SD) | 161.0 (28.7) | 150.9 (41.1) |
| Min, max | 15, 194 | 15, 177 |
| Study A | n=70 | n=68 |
| Duration of study treatment (days) | | |
| Mean (SD) | 161.2 (27.4) | 140.6 (50.0) |
| Min, max | 33, 174 | 15, 175 |
| Study B | n=54 | n=54 |
| Duration of study treatment (days) | | |
| Mean (SD) | 157.8 (35.5) | 153.6 (35.2) |
| Min, max | 29, 176 | 42, 177 |
| Study C | n=74 | n=77 |
| Duration of study treatment (days) | | |
| Mean (SD) | 163.2 (24.2) | 158.1 (34.5) |
| Min, max | 15, 194 | 15, 176 |
| Duration of IMP exposure by category | | |
| ≤4 weeks | 1 (0.5) | 3 (1.5) |
| >4 and ≤8 weeks | 5 (2.5) | 10 (5.0) |
| >8 and ≤12 weeks | 1 (0.5) | 9 (4.5) |
| >12 and ≤16 weeks | 7 (3.5) | 11 (5.5) |
| >16 and ≤20 weeks | 2 (1.0) | 2 (1.0) |
| >20 and ≤24 weeks +3 days | 28 (14.1) | 21 (10.6) |
| >24 and ≤24 weeks +3 days | 142 (71.7) | 134 (67.3) |
| >24 weeks +3 days | 12 (6.1) | 9 (4.5) |

Adapted by the Clinical Reviewer from the following sources: Integrated Summary of Safety, Appendix 3, Table 3.1.2; CUPID Study A Clinical Study Report, Table 12; CUPID Study B Clinical Study Report, Table 12; Study C Clinical Study Report, Table 12; ISS Appendix 3, Dosing Data CSU, Table 3.1.2.
Abbreviations: IMP, investigational medical product; max, maximum; min, minimum; SD, standard deviation

**Adequacy of the safety database:**

Overall, the safety database is of sufficient size and duration for CSU to assess the safety of the proposed doses of dupilumab. The safety assessment also takes into consideration the previous safety data collected for the approved indications of asthma, atopic dermatitis, CRSwNP, PN, and EoE. Dupilumab has an extensive safety database, including in pediatric patients aged ≥6 months to <18 years. As of March 28, 2024, 15,834 subjects were enrolled into the development program for dupilumab (per the Applicant's Development Safety Update Report submitted May 24, 2024).

### 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 supplemental BLA based on an Office of Computational Science Core Data Fitness analysis.

**Categorization of Adverse Events**

AEs were captured from the signing of informed consent through the final follow-up visit. The Applicant provided definitions of AEs and serious adverse events (SAEs) consistent with 21CFR312.32. TEAEs were defined as any adverse event (AE) that increased in severity or that was newly developed at or after receiving the first dose of study drug through the final follow-up visit. AEs were coded using the MedDRA dictionary version 27.0. The Applicant's coding of verbatim terms to preferred terms was appropriate.

**Routine Clinical Tests**

Routine clinical testing included hematology, serum chemistry, electrolytes, bicarbonate, creatine phosphokinase, and urinalysis. Refer to Figure 14, the Schedule of Activities, for the timing, frequency, and details of the testing.

### 8.2.4. Safety Results

**Deaths**

One subject in the placebo group experienced a TEAE that led to death in Study A. This subject completed suicide.

There were no deaths in Studies B and C.

**Serious Adverse Events**

An SAE is a medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent disability/incapacacity or is a congenital anomaly/birth defect.

Overall, 18 (4.5%) of subjects had a treatment-emergent SAE. A total of 10 SAEs occurred in the dupilumab arm in 10 subjects (5.1%), and a total of 10 SAEs occurred in the placebo arm in 8 subjects (4.0%). One subject in the placebo arm experienced 3 SAEs on the same day. The pooled SAEs are summarized in Table 22.

**Table 23. All Individual Subject SAEs, Safety Population, Pooled Analyses**

| Study Arm | Subject ID | Sex | Age (Years) | Dosing Duration Days) | Study Day of SAE | SAE | |
|---|---|---|---|---|---|---|---|
| | | | | | | MedDRA Preferred Term | Verbatim Term |
| Dupilumab | (b) (6) | F | 24 | 169 | 114 | Depression | Acute depressive episode |
| Dupilumab | | F | 70 | 169 | 107 | Colorectal adenocarcinoma | Adenocarcinoma of the rectosigmoid colon |
| Dupilumab | | F | 47 | 169 | 58 | Pneumonia bacterial | Pneumonia (bacterial) |
| Dupilumab | | M | 37 | 169 | 230 | Hepatic steatosis | Fatty Liver |
| Dupilumab | | F | 73 | 169 | 87 | Angina unstable | Unstable Angina Pectoris |
| Dupilumab | | M | 25 | 127 | 20 | Hemorrhoids | Mixed hemorrhoids |
| Dupilumab | | F | 37 | 30 | 30 | Chronic spontaneous urticaria | Generalized chronic spontaneous urticaria exacerbation |
| Dupilumab | | F | 22 | 194 | 147 | Concussion | Unknown suspected concussion |
| Dupilumab | | F | 53 | 168 | 252 | Intestinal obstruction | Intestinal obstruction (adhesive, food induced) |
| Dupilumab | | F | 29 | 169 | 113 | Idiopathic angioedema | Exacerbation of urticaria with angioedema (etiology unknown) |
| Placebo | | M | 54 | 48 | 48 | Completed suicide | Completed suicide |
| Placebo | | M | 42 | 46 | 42 | Dermatitis atopic | Atopic dermatitis |
| Placebo | | F | 55 | 15 | 1 | Asthma | Bronchial asthma (acute attack) |
| Placebo | | F | 53 | 169 | 17 | Angioedema | Angioedema |
| Placebo | | F | 39 | 43 | 37 | COVID-19 pneumonia | Bilateral pneumonia, COVID-19 |
| Placebo | | F | 61 | 169 | 251 | Abdominal pain upper | Epigastric pain of unknown origin |
| Placebo | | F | 61 | 169 | 251 | Dyspnea | Shortness of breath of unknown origin |
| Placebo | | F | 61 | 169 | 251 | Nausea | Nausea of unknown origin |
| Placebo | | F | 58 | 82 | 34 | Osteoarthritis | Arthrosis of the left foot |
| Placebo | | M | 50 | 92 | 91 | Pain in extremity | Worsening pain in extremity of unknown origin |

Source: Clinical Reviewer, and JMP Clinical 17.1
Note: dosing duration is the number of days the subject was dosed and study day of SAE is the day in which the SAE was reported. Dosing was up to Week 24 and AE reporting was up to Week 36. SAEs may have been reported after dosing was complete.
Filters: dataset adae, adsl, TRAT01, AESER (Y); AGE, SEX,
ADSL dataset: TRTDURD: Total Treatment Duration (Days)
ADAE dataset TRAT01, AESER (Y); ASTDY: Analysis Start Relative Day
Abbreviations: COVID-19, coronavirus disease 2019; F, female; M, male; SAE, severe adverse event

**Dropouts and/or Discontinuations Due to Adverse Effects**

TEAEs leading to permanent treatment discontinuation in Studies A and C were infrequent. There were no TEAEs leading to intervention discontinuation in Study B. In Study A, a total of 6 subjects (2.4%) had TEAEs leading to permanent treatment discontinuation, with 2 (0.8%) of these subjects in the dupilumab group. In Study C, 1 subject (0.7%) in the placebo group and no subjects in the dupilumab group had a TEAE leading to permanent treatment discontinuation. Each event leading to discontinuation occurred in only one person. Pooled TEAEs leading to discontinuations are displayed in Table 23.

**Table 24. Events Leading to Treatment Discontinuation Dupilumab Greater Than Placebo, Safety Population, Pooled Analysis**

| Body System or Organ Class<br>Preferred Term | Dupilumab (N=193)<br>n (%) | Placebo (N=195)<br>n (%) |
|---|---|---|
| Subjects with at least one AEs | 2 (1.0%) | 4 (2.1%) |
| Pregnancy, puerperium and perinatal conditions | | |
| Pregnancy | 1 (0.5%) | 0 |
| Psychiatric disorders | | |
| Depression | 1 (0.5%) | 0 |
| Borderline personality disorder | 1 (0.5%) | 0 |

Source: Clinical Reviewer, JMP Clinical 17.1., Modified version of Table 10 from Summary of Clinical Safety.
Filters: TRAT01, TRTEM (Y), AEACN, Drug withdrawn
Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with specific event

**Significant Adverse Events**

The assessment of intensity of adverse events was defined as mild, moderate, or severe.

- Mild: an event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: an event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: an event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Four severe event AE terms occurred more in the dupilumab arm than the placebo arm. Each severe event occurred in only one person. None of the severe events was deemed related to IMP.

- One subject with a medical history of previous abdominal surgery was hospitalized for an intestinal obstruction on Day 252 (98 days after the last dose of IMP injection). The subject underwent an surgical lysis of intestinal adhesions and was discharged without complicaton. The subject was recovering at his End of Study visit. The AE was deemed not related to the IMP.

- One subject with a 3-year medical history of hepatic steatosis was hospitalized for hepatic steatosis 76 days after the last dose of the IMP. The subject recovered from the AE 7 days later and was discharged from the hospital. The AE was deemed not related to the IMP.
- One subject with a 9-year history of hypertension and a 2-year history of coronary artery disease with coronary artery stent insertion developed angina, unstable requiring hospitalization on Day 119, with coronary artery stent insertion on Day 122. The subject recovered from the AE and completed the treatment period per protocol. The AE was deemed not related to the IMP.
- One subject had a fall on Day 147 after his jacket caught on a door handle, and the AE concussion was reported. He was hospitalized overnight for monitoring. The subject recovered from the concussion and fall on Day 148 and completed the treatment period per protocol. The AE was deemed not related to the IMP.

**Table 25. Severe AEs Dupilumab Greater Than Placebo, Safety Population, Pooled Analysis**

| Preferred Term | Dupilumab (N=193) n (%) | Placebo (N=195) n (%) |
|---|---|---|
| Subjects with at least one severe AE | 6 (3.1%) | 6 (3.1%) |
| Intestinal obstruction | 1 (0.5%) | 0 |
| Concussion | 1 (0.5%) | 0 |
| Hepatic steatosis | 1 (0.5%) | 0 |
| Angina unstable | 1 (0.5%) | 0 |

Source: Clinical Reviewer, JMP Clinical 17.1, Filters: TRAT01, AESEV, Severe
Abbreviations: AE, adverse event; N, number of subjects; n, number of subjects with specific adverse event

**Treatment Emergent Adverse Events and Adverse Reactions**

Pooled TEAEs for Studies A, B, and C are displayed in Table 25. Common AE incidence was similar across treatment groups.

Injection site reactions (high level term encompassing injection site erythema, injection site reaction, injection site pain, injection site induration, injection site dermatitis, injection site hermatoma, injection site pruritus, and injection site swelling) were reported in 20 (10.1%) of subjects in the dupilumab group and 16 (8.0%) in the placebo group.

There were a total of 7 subjects with abnormal alanine aminotransferase (ALT) testing during the 3 studies (6 (3%) in the dupilumab group and 1 (0.5%) in the placebo group); none met the adverse events of special interest (AESI) criteria for elevated liver function tests. Six subjects' elevated liver function tests were considered not related by investigators. Two subjects in the dupilumab group had TEAEs of potential drug-related hepatic disorder that were assessed as related to the study intervention per the Investigator's judgment:

- Subject 016461-[redacted] (b) (6) (Study B) had an elevated post-baseline ALT of 3.73× upper limit of normal (ULN) at Week 12, which recovered and returned to baseline status with no disruption of the treatment schedule and no intervention before the last dose of study intervention.

- Subject 016461-[redacted] (b) (6) (Study C) had an elevated post-baseline ALT of 1.61x ULN thirteen days after the last administration of dupilumab as planned, which resolved and returned to baseline.

There were no events of Hy's law, cholestatic, or Temple's corollary cases.

**Table 26. TEAEs Occurring in Greater Than 2% of Subjects, and Greater in Dupilumab Than Placebo, Pooled Safety Population**

| Body System or Organ Class<br>Preferred Term | Dupilumab (N=198)<br>n, (%) | Placebo (N=199)<br>n, (%) | Risk Difference<br>(95% CI) |
|---|---|---|---|
| Infections and Infestations | | | |
| COVID-19 | 12 (6.1%) | 10 (5.0%) | 0.00 (-0.05, 0.05) |
| Pharyngitis | 5 (2.5%) | 2 (1.0%) | 0.02 (-0.02, 0.06) |
| Influenza | 4 (2.0%) | 3 (1.5%) | 0.01 (-0.03, 0.05) |
| General disorders and administration site conditions | | | |
| Injection site reaction | 8 (4.0%) | 4 (2.0%) | 0.02 (-0.02, 0.07) |
| Injection site pain | 5 (2.5%) | 4 (2.0%) | 0.01 (-0.03, 0.05) |
| Immune system disorders | | | |
| Urticaria[1] | 12 (6.1%) | 12 (6.0%) | -0.01 (-0.06, 0.04) |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | 9 (4.5%) | 4 (2.0%) | 0.03 (-0.02, 0.07) |
| Investigations | | | |
| Alanine aminotransferase increased | 6 (3.0%) | 1 (0.5%) | 0.03 (-0.01, 0.07) |

Source: Sponsor Table 15 in Summary of Clinical Safety, recreated and summarized by Clinical Reviewer, Analysis Studio, Safety Explorer, JMP and JMP Clinical 8.1.
Filters: TRAT01, TRTEM (Y)
[1] "Urticaria" includes the Dictionary-Derived Terms "Chronic Spontaneous Urticaria" and "Urticaria" from Body or System Organ Class "Immune system disorders" and "Skin and subcutaneous tissue disorders." Filtered by USUBJID to avoid duplicates.
Abbreviations: CI, confidence interval; N, number of subjects; n, number of subjects with specific event; TEAE, treatment-emergent adverse event

**Laboratory Findings**

There were no clinically meaningful changes observed in mean values of white blood cells, red blood cells, and platelets between the dupilumab and placebo groups throughout the treatment period. There was a minor increase in the change from baseline in mean blood eosinophil count in the dupilumab group (+15 cells/mcL [absolute 235 cells/mcl with adult ULN of 800 cells/mcl]), which returned to baseline value at Week 36 (178 cells/mcl). No change from baseline in mean blood eosinophil count was observed in the placebo group. Minor increases in blood eosinophil counts have also been observed in development programs for atopic dermatitis, asthma, CRSwNP and COPD. Six (3.0%) subjects in the dupilumab group and 1 (0.5%) subject in the placebo group had a peak blood eosinophil count between >1100 and <2000 cells/mcl. No subjects had a peak blood eosinophil count of $\geq$5000 cells/mcl.

There were no clinically meaningful changes observed in mean metabolic parameters, electrolyte levels, and renal function parameters between the dupilumab and placebo groups throughout the treatment period.

There were no clinically meaningful changes observed in mean liver function parameters between the dupilumab and placebo groups throughout the treatment period. No subjects had

liver function abnormalities that met laboratory criteria for Hy's Law. Four (2.1%) subjects in the dupilumab group and 2 (1.0%) subjects in the placebo group had ALT >3xULN. Of these, 2 (1.1%) subjects in the dupilumab group and 1 (0.5%) subject in the placebo group had ALT >5xULN. ALT values returned to <3xULN in 2 subjects in the dupilumab group and 1 subject in the placebo group without treatment discontinuation before the last dose of dupilumab.

**Vital Signs**

Vital sign measurements included blood pressure (mm Hg), pulse rate (beats per minute), respiration rate (breaths per minute), auxiliary or oral body temperature (degrees Celsius), and body weight (kg) prior to IMP at each visit. Height was measured at screening (in cm). There were no notable abnormalities in vital signs

**Electrocardiograms**

Electrocardiograms (12-lead) were performed at multiple time points (see Figure 14) to monitor for abnormalities. There were no notable abnormalities in electrocardiograms.

**QT**

There were no notable QT abnormalities in electrocardiograms.

**Immunogenicity**

ADA formation did not correlate with safety findings. There was no apparent pattern or increase in TEAE incidence in the ADA-positive subjects compared to ADA-negative subjects.

### 8.2.5. Analysis of Submission-Specific Safety Issues

AESIs were prespecified based on the known safety profile of dupilumab and the adverse drugs reactions in the label. AESIs included anaphylactic reactions, systemic hypersensitivity reactions, helminthic infections, any severe type of conjunctivitis or blepharitis, keratitis, clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms), significant ALT elevation - defined as ALT >5 × the ULN in subjects with baseline ALT ≤2 × ULN or ALT >8 × ULN if baseline ALT >2 × ULN, pregnancy in a female study subject or a female partner of a male subject, and symptomatic overdose.

Other selected AE groupings were prespecified in the SAP and included: serious injection-site reactions or severe injection site reactions that last longer than 24 hours, severe or serious infection, drug-related hepatic disorder, injection site reaction, malignancy, conjunctivitis (narrow, broad, FDA), and keratitis (FDA). The Applicant analyzed Standardized MedDRA Queries for anaphylaxis, systemic hypersensitivity reactions, drug-related hepatic disorders, and malignancy.

## Anaphylaxis

No cases of anaphylaxis were reported in this study.

## Systemic Hypersensitivity Reactions

Treatment-emergent AESIs of systemic hypersensitivity reactions were reported in 2 subjects, one in the dupilumab arm and one in the placebo arm. These were confirmed by medical review; both were associated with receipt of a COVID-19 vaccine. The subject in the dupilumab arm presented with a systemic hypersensitivity event (preferred term urticaria, reported as "hives and itching all over the body in reaction to the COVID-19 vaccine" 1-day after receiving the first dose of a COVID-19 vaccine, which was treated with 1 dose of OCS and recovered without recurrence on the second COVID-19 vaccine dose). The subject in the placebo arm experienced generalized urticaria 48 hours after receiving a vaccine for COVID-19, which was treated with 5 days of OCS and recovered without recurrence on the second and third COVID-19 vaccine doses. These hypersensitivity reactions were deemed unlikely to be related to the investigational medical product. No treatment discontinuations occurred.

## Helminthic Infections

No cases of helminthic infections were reported in this study.

## Severe Conjunctivitis or Blepharitis, Keratitis

Ocular safety issues including conjunctivitis, blepharitis, dry eye, and hyperemia, which were identified in previously reviewed dupilumab programs (atopic dermatitis and CRSwNP), were not seen in the CSU program.

## Clinically Symptomatic Eosinophilia

No clinically symptomatic eosinophilia events were reported.

## Significant ALT Elevation

AESI for significant ALT elevation as defined as ALT >5 × the ULN in subjects with baseline ALT ≤2 × ULN; or ALT >8 × ULN if baseline ALT >2 × ULN. No subjects met these criteria.

## Pregnancy

AESI of pregnancy was defined as pregnancy in a female study subject or a female partner of a male subject. Two pregnancy events occurred, one in the dupilumab group and one in the placebo group.

- Subject No. 016461-(b) (6) (Study A, dupilumab group): On Day 42 (13 days after the Week 6 IMP injection), pregnancy was reported (as detected on Day 83 by urinary test) despite using oral contraception. The IMP was permanently discontinued due to pregnancy (as per protocol) and the last IMP administration was on Day 68 (Week 10). No adverse events related to the pregnancy were reported. The pregnancy went to term (normal delivery) and the baby was born on Day 324. The newborn's condition was not reported.

- Subject No. 016461-(b) (6) (Study B, placebo group): The study subject had the last menstrual period on Day 226 (71 days after the last injection of IMP), and pregnancy was considered to have started on the same day. Between Day 215 and Day 242, an adverse event of subchorionic hematoma (mild) was reported, diagnosed via uterine ultrasound. In addition, noninvasive prenatal testing was performed, which was reported to be normal. The pregnancy resulted in a normal delivery.

**Symptomatic Overdose**

No events of symptomatic overdose were reported.

### 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 safety differences were noted in the subgroups based on baseline characteristics. There were no specific safety concerns noted in adolescent or geriatric subgroups.

### 8.2.8. Specific Safety Studies/Clinical Trials

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

Subject No. (b) (6) (Study C) developed colorectal adenocarcinoma. On Day 75 post-first IMP treatment, the subject had a positive fecal immunochemical test. On Day 107, the subject underwent a colonscopy with biopsy and was diagnosed with colorectal adenocarcinoma. The polyp with adenocarcinoma was removed with appropriate margins during colonoscopy and no further treatment was given. The subject completed the treatment period per protocol. The AE of colorectal adenocarcinoma was deemed not related to the IMP.

No malignancies were reported in CUPID Studies A and B.

**Human Reproduction and Pregnancy**

See the Pregnancy subsection above for reports on 2 pregnancies in the study.

**Pediatrics and Assessment of Effects on Growth**

Effects of growth were not evaluated in the 17 pediatric subjects (n=5 for 6-11 years of age and n=12 for 12-17 years of age).

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

Accidental overdose was defined as administration of at least twice the planned dose during an interval of less than 11 days. Nine (4.5%) subjects in the dupilumab group and 4 (2.0%) subjects in the placebo group had an accidental overdose. All subjects were asymptomatic. No safety events were reported for these cases of overdose.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

No new safety findings were identified in the post-marketing data in the Periodic Benefit Risk Evaluation Report covering the period from March 29, 2023 to March 28, 2024.

### 8.2.11. Integrated Assessment of Safety

The pooled 36-week safety data included the 397 subjects from the safety and efficacy studies CUPID Studies A, B, and C. No new safety signals were identified, and the AEs observed were consistent with the labeling for dupilumab. Overall, the safety profile for dupilumab is favorable for the CSU indication.

## 8.3. Statistical Issues

In summary, the results from Study C demonstrated a statistically significant effect on the primary efficacy endpoint (change from baseline in ISS7 at Week 24), the key secondary efficacy endpoint (change from baseline in UAS7 at Week 24), as well as on most of the other secondary endpoints included in testing hierarchy (except the last endpoint in hierarchy, UCT). The endpoint of change from baseline in UCT at Week 24 is not statistically significant. The sensitivity analyses and the supplementary analyses for the primary endpoint demonstrated that the primary analysis result is robust to underlying missing data assumption and robust to using alternative intercurrent event handling strategies. Overall, there are no statistical issues identified in the review of study C. Study A was previously reviewed in the Multi-disciplinary Review dated 12/22/2022 and no statistical issues were identified for Study A.

## 8.4. Conclusions and Recommendations

The recommended regulatory action from a clinical and statistical perspective is approval of dupilumab in adults and adolescents aged 12 to 17 years old with CSU inadequately controlled with H1AH as substantial evidence of effectiveness has been demonstrated and no major safety concerns were identified.
To support this application, the Applicant completed three 24-week, randomized, double-blind, placebo-controlled safety and efficacy trials (Studies A, B, and C) of dupilumab in a total of 397 subjects with CSU inadequately controlled with H1AH. Studies A and C included subjects who

were naïve to omalizumab, and Study B included subjects who were intolerant or incomplete responders to omalizumab.

Studies A and C demonstrated statistically significant and clinically meaningful improvements in the primary endpoint, change from baseline in ISS7 at Week 24, and the key secondary endpoint of change from baseline in UAS7 at Week 24 indicating a benefit in both the itch and hives components of CSU. The results from Studies A and C have met the standard for substantial evidence of effectiveness to demonstrate that dupilumab is an effective treatment for patients with CSU whose disease is inadequately controlled on H1AH.

Study B met futility criteria at the predefined interim analysis, as defined in the Statistical Analysis Plan for the trial. The difference in study results between Studies A and C and Study B may be attributed to the different study populations as Study B enrolled a more severe, treatment-refractory population compared to Studies A and C.

The safety profile for dupilumab use in CSU was consistent with the known safety profile seen in the clinical development programs for the approved dupilumab indications, including AD, asthma, CRSwNP, EoE, PN, and COPD. No new safety concerns were identified.

Adolescents were included in Studies A, B, and C; however, the adolescent subgroup was not powered to detect a statistically significant difference between the dupilumab and placebo arms in this age group. The approval of dupilumab for adolescents with CSU is based on extrapolation of efficacy from adults based on similarity of disease pathophysiology and expected response to treatment in adults and adolescents, similarity of systemic exposure in adolescents and adults at the proposed dose, and reassuring safety data from dupilumab use in adolescents in other indications.

The benefit-risk assessment for dupilumab is favorable for adults and adolescents with CSU inadequately controlled on H1AH. Studies A and C provide the basis for substantial evidence of effectiveness, and all three studies in CSU provide a supportive safety profile.

# 9 Advisory Committee Meeting and Other External Consultations

The review team did not identify any challenging, controversial, or precedent setting issues as outlined in the CDER Advisory Committee Decision Aid. Dupilumab does not provide a major advance in the treatment of patients with CSU and there were no major clinical trial design, conduct, efficacy, safety, or benefit/risk assessment issues identified 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 iPSP to the Applicant on March 12, 2020, requesting 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. The timeline for completion of the PK and safety study in subjects aged ≥2 to <12 years old was estimated to be Quarter 2 of 2024.

Amended iPSP

When the Applicant submitted their BLA, 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 BLA submission. Per the Applicant, the study would be completed in February 2025 and the final report would be submitted in July 2025. The Division agreed to the amended iPSP.

Pediatric Efficacy and Safety Overview

The Applicant conducted three 24-week studies, CUPID Studies A, B, and C, in support of this licensing application. Studies A and C were used to support substantial evidence of effectiveness in adults and adolescents with CSU inadequately controlled on H1AH. Fifteen pediatric subjects were enrolled in these two trials: 10 adolescents aged ≥12 to < 18 years old and 5 children aged >6 to <12 years old.

Of the 10 adolescents enrolled in Studies A and C, 5 were exposed to dupilumab and 5 were in the placebo arm. In the dupilumab arm:

- 1 subject achieved complete symptom resolution at Week 12 and remained symptom-free through Week 24
- 1 subject achieved complete symptom resolution at Week 12 but had moderate urticaria, defined as UAS7 >16 to <27, at Week 24
- 1 subject had improvement in urticaria activity from severe (UAS7≥28) to mild (UAS7>6 to <16) at Week 24
- 1 subject had improvement in urticaria activity from severe (UAS7≥28) to mild (UAS7>6 to <16) at Week 22 but did not complete assessments at Weeks 23 and 24
- 1 subject discontinued after Week 22 due to lack of efficacy

In the placebo arm:

- 3 subjects with moderate to severe urticaria activity at baseline achieved complete symptom resolution at Weeks 12 and 24
- 1 subject had improvement in urticaria activity from moderate (UAS7 >16 to <27) to well-controlled (UAS7>1 to <6)
- 1 subject discontinued due to lack of efficacy

Of the 5 children aged ≥6 to <12 years old enrolled in Studies A and C, 3 were exposed to dupilumab and 2 were in the placebo arm. In the dupilumab arm:

- 1 subject with severe urticaria at baseline had complete symptom resolution at Week 12 and well-controlled urticaria (UAS7>1 to <6) at Week 24
- 2 subjects discontinued due to lack of efficacy

In the placebo arm:

- 1 subject with severe urticaria at baseline had complete symptom resolution at Week 24
- 1 subject with severe urticaria at baseline did not achieve any improvement at Week 24

The subgroups of adolescents and children aged ≥6 to <12 years old were not powered to detect a statistically significant difference between the dupilumab and placebo arms in these ages. No statistical conclusions about efficacy of dupilumab in adolescents and children aged ≥6 to < 12 years old can be made.

The safety pool for adolescents and children aged ≥6 to < 12 years old for dupilumab in CSU consists of 12 adolescents (6 in the dupilumab arm and 6 in the placebo arm) and 5 children (3 in the dupilumab arm and 2 in the placebo arm) in CUPID Studies A, B, and C. In the 12 adolescents, TEAEs were reported in 1 subjects in the dupilumab arm (nasopharyngitis) and 3 subjects in the placebo group (COVID-19, post-procedural fever due to COVID vaccine injection, and dermatitis). None were serious, severe, or assess as related to the IMP. In the 5 children aged ≥6 to < 12 years old, there were no TEAEs reported in subjects in the dupilumab arm and two TEAEs (diarrhea, tonsillitis streptococcal) were reported in 1 subject in the placebo arm.

The approval of dupilumab for adolescents with CSU inadequately controlled on H1AH is based on extrapolation of efficacy from adults based on similarity of disease pathophysiology and expected response to treatment in adults and adolescents, similarity of systemic exposure in adolescents and adults at the proposed dose, and reassuring safety data from dupilumab use in adolescents in other indications. Assessment of the efficacy and safety of dupilumab in children ≥6 to < 12 years old with CSU is deferred until completion of the PK and safety study in this age group.

# 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 | The Applicant's proposed indication statement was modified to align with the indication statement of an approved product, along with the Limitations of Use (LOU). LOU was applicable to DUPIXENT because the indication was specific for spontaneous urticaria and no other forms of urticaria.<br><br>An additional LOU to convey the concern and/or uncertainty of the risk-benefit profile of the use of DUPIXENT in patients with CSU who were symptomatic despite anti-IgE treatment (Study B) was considered and discussed, but not included in labeling. However, CUPID Study B was succinctly described in Section 14 to inform healthcare providers that DUPIXENT has not been demonstrated to be effective in patients who were symptomatic despite anti-IgE treatment.<br><br>*Proposed*: DUPIXENT is indicated for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) whose disease is not adequately controlled with H1 antihistamine treatment.<br><br>*Approved*: DUPIXENT is indicated for the treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment.<br><br><u>Limitations of Use</u>:<br>DUPIXENT is not indicated for treatment of other forms of urticaria. |
| 2 DOSAGE AND ADMINISTRATION | New subsection added to provide the Recommended Dosage for Chronic Spontaneous Urticaria in adult and pediatric patients aged 12 years and older. The recommended dosage for adults is an initial dose of 600 mg, followed by 300 mg every 2 weeks. Recommended dosage for pediatric patients aged 12 years and older is based on weight (i.e., 30 kg to less than 60 kg and 60 kg or more) and provided in a table.<br><br>Administration instructions were updated to include CSU in the |

| Full Prescribing Information Sections | Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI) |
|---|---|
| | applicable instructions for administration of DUPIXENT. |
| 5 WARNINGS AND PRECAUTIONS | Updated the Conjunctivitis and Keratitis information to reflect the similar incidence of conjunctivitis between the DUPIXENT and placebo treated subjects in the clinical trials for CSU. |
| 6 ADVERSE REACTIONS | Safety of DUPIXENT in adult and pediatric patients aged 12 years and older were pooled from three clinical trials (Study A, Study B, and Study C) under the master protocol, CUPID. The pooled safety population received an initial dose of DUPIXENT 600 mg or 400 mg, followed by DUPIXENT 300 mg or 200 mg, respectively, or matching placebo, administered subcutaneously every 2 weeks. The only adverse reaction with an incidence of ≥2% with DUPIXENT in the CUPID trial was injection site reactions.<br><br>The Specific Adverse Reactions such as conjunctivitis, herpes zoster, and an increase from baseline in blood eosinophil were updated to convey the occurrence of these adverse reactions from the CUPID trial. Of note, adverse reactions for which the placebo rate equals or exceeds the rate of the drug should not be included in the ADVERSE REACTIONS section, which was the case for conjunctivitis (DUPIXENT group (1%) was slightly lower compared to the placebo group (1.5%)). However, the information of conjunctivitis reaction was included without incidence in labeling for consistency of providing conjunctivitis adverse reaction for all indications. |
| 8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment) | Pediatric Use was revised to reflect the indication statement and the evidence to the support the use of DUPIXENT in pediatric patients aged 12 years and older with CSU. The use of DUPIXENT was supported by evidence from 2 adequate and well-controlled studies in adults, with additional pharmacokinetic data in 6 pediatric patients aged 12 years and older, and safety data in pediatric patients in other approved indications.<br><br>There was no evidence to support safety and effectiveness of DUPIXENT in pediatric patients younger than 12 years of age with CSU and/or pediatric patients weighing less than 30 kg. The language for no evidence to support safety and effectiveness was |

| Full Prescribing Information Sections | Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI) |
|---|---|
| | revised to include weight since the recommended dosage in pediatric patients is based on weight. |
| 12 CLINICAL PHARMACOLOGY | Mechanism of Action subsection was updated to include CSU as an indication that is affected by inflammation driven by IL-4 and IL-13 and 'basophils', which play a role in urticaria.<br><br>Pharmacodynamics subsection was updated with the inclusion of language that conveys the observed decline of total IgE in serum in CSU trials, consistent with the dupilumab mechanism of action of inhibition of IL-4 and IL-13 signaling.<br><br>Pharmacokinetics subsection was updated to indicate that the PK of dupilumab PK in patients with CSU were similar to that in other approved indications. In addition, PK information among 6 pediatric patients aged 12 years and older was included. Updated labeling indicates similar steady-state trough concentrations between these pediatric patients and adults with CSU.<br><br>Immunogenicity was updated for CSU to reflect the incidence observed in CSU trials. |
| 14 CLINICAL STUDIES | The efficacy of DUPIXENT for CSU was evaluated in a master protocol (CUPID) that included 3 studies (Study A, Study B, and Study C). CUPID Study A and C were described in Section 14 to inform efficacy from the two studies in a patient population who were naïve to anti-IgE treatment, while CUPID Study B did not. Additionally, CUPID Study A and C (b) (4) were removed from the efficacy results (b) (4). Therefore, efficacy of DUPIXENT was evaluated from CUPID Study A and C that included adult and pediatric patients 12 years of age and older with CSU (Itch Severity Score over 7 days (ISS7) ≥8 on a scale of 0 to 21 and Urticaria Activity Score over 7 days (UAS7) ≥16 on a scale of 0 to 42) who were symptomatic despite the use of H1 antihistamines, but who were anti-IgE treatment naïve.<br><br>Efficacy results for the primary endpoint (change from baseline in ISS7) are provided in a table, along with a figure to show the change from baseline in ISS7 over 24 weeks. Results for secondary |

| Full Prescribing Information Sections | Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI) |
|---|---|
| | endpoints are also included in the table.<br><br>In addition to the efficacy results, Section 14 included the outcome of CUPID Study B that included adult and pediatric patients 12 years and older with CSU who were adequate responders to H1 antihistamines and anti-IgE treatments. CUPID Study B was included to convey to healthcare providers that DUPIXENT has not been demonstrated to be effective in patients who were unresponsive to anti-IgE therapy since CUPID Study B did not meet statistical significance for reduction of ISS7 (primary endpoint) in this patient population. |

# 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

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

# 14 Associate Director for Therapeutic Review (Clinical) Comments

Chronic spontaneous urticaria is characterized by the spontaneous and recurrent occurrence of urticaria, with or without angioedema, persisting for more than six weeks without an identifiable cause. Uncontrolled CSU, particularly due to pruritus, can significantly impair quality of life and daily functioning, potentially affecting academic and occupational performance, and may be associated with comorbid psychiatric disorders. The condition affects approximately 1% of the general population, with higher prevalence in adults compared to children. CSU is often self-limiting, with a 1-year spontaneous remission rate of 30% to 50% and an average duration of two to five years.

The therapeutic goals for CSU include reduction or resolution of active disease symptoms to provide symptomatic relief and improve quality of life until remission occurs. Current treatment

guidelines recommend second-generation H1-antihistamines at doses up to 4-times the approved doses, followed by omalizumab for patients who do not respond adequately to H1-antihistamines. For patients who fail to respond to H1-antihistamines and omalizumab, off-label use of immunomodulators such as cyclosporine, dapsone, or oral corticosteroids is recommended. There remains an unmet medical need for additional treatment options for patients with severe and refractory CSU, particularly therapies with improved safety profiles.

Dupilumab is a human 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 was initially approved on March 28, 2017, under BLA 761055, for the treatment of adult patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Subsequent efficacy supplement approvals have expanded the labeling to include indications for pediatric atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, prurigo nodularis, and chronic obstructive pulmonary disease.

The Applicant has completed a development program to support an indication for the "treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) whose disease is not adequately controlled with H1-antihistamine treatment." On December 22, 2022, the Applicant submitted a supplemental biologics license application (sBLA), under BLA 761055 (Supplement 051), to expand the labeling of dupilumab to include the CSU indication. The application was supported by two Phase 3 pivotal efficacy and safety studies in adults and adolescents aged 12 to 17 years with CSU (EFC16461-A (Study A) and EFC16461-B (Study B)). Study A enrolled CSU subjects inadequately controlled with H1-antihistamine treatment and naïve to omalizumab. Study B enrolled CSU subjects inadequately controlled with H1-antihistamine treatment who were intolerant to (n=4) or incomplete responders to omalizumab (n=104) treatment.

Following Agency review, it was determined that substantial evidence of effectiveness was not demonstrated based on the available clinical data, and a Complete Response was issued on October 19, 2023. Specifically, although Study A met statistical significance for the primary and key secondary endpoints, Study B met futility criteria at the pre-specified interim analysis. The Agency determined that the positive results from a single adequate and well-controlled trial were not sufficient to provide substantial evidence of effectiveness for approval of this new indication.

The present efficacy supplement is a Class 2 re-submission, seeking to support expansion of dupilumab labeling to include the indication for the treatment of adult and pediatric patients aged 12 years and older with CSU whose disease is not adequately controlled with H1-antihistamine treatment. In support of the current re-submission, the Applicant has conducted a third Phase 3 pivotal efficacy and safety study in adult and pediatric subjects aged 12 to 17 years with CSU who were inadequately controlled with H1-antihistamine treatment and naïve to omalizumab (EFC16461-C (Study C)).

The results from Study A, submitted with the original sBLA, demonstrated a statistically significant effect on the primary endpoint:

- The LS mean change from baseline in ISS7 at Week 24 was -10.24 in the dupilumab arm versus -6.01 in the placebo arm (LS mean difference -4.23, 95% CI: -6.63, -1.84, p=0.0005).
- Study A also demonstrated statistically significant effects on key secondary endpoints, including change from baseline in UAS7 at Week 24 (p<0.01), proportion of participants with UAS7≤6 at Week 24 (p=0.01), proportion of participants with UAS7=0 at Week 24 (p=0.02), change from baseline in HSS7 at Week 24 (p<0.01), change from baseline in ISS7 at Week 12 (p=0.04), change from baseline in UAS7 at Week 12 (p=0.02), and proportion of participants with UAS7≤6 at Week 12 (p=0.02).

The results from Study C, submitted with the current Class 2 re-submission, demonstrated a statistically significant effect on the primary endpoint:

- The LS mean change from baseline in ISS7 at Week 24 was -8.64 in the dupilumab arm versus -6.10 in the placebo arm (LS mean difference -2.54, 95% CI: -4.65, -0.43, p=0.02).
- Study C also demonstrated statistically significant effects on key secondary endpoints, including change from baseline in UAS7 at Week 24 (p=0.02), proportion of participants with UAS7≤6 at Week 24 (p<0.01), proportion of participants with UAS7=0 at Week 24 (p=0.02), and change from baseline in HSS7 at Week 24 (p=0.03). Primary and secondary endpoints at 12 weeks were not under type I error control and were not tested in Study C.

Overall, the pivotal trials (Study A and Study C) demonstrate efficacy in CSU patients who are symptomatic despite H1-antihistamine treatment. Primary and secondary endpoints at 24 weeks were met. While the improvements in primary and secondary endpoints with dupilumab treatment at 24 weeks were modest, they were statistically significant and clinically meaningful. Multiplicity-controlled endpoints in Study A demonstrated efficacy as early as 12 weeks, but earlier timepoints (e.g., 4 weeks) were not assessed in either study. Improvements in ISS7, UAS7, and HSS7 with dupilumab treatment appear to be gradual and progressive. As a result, while efficacy has been adequately demonstrated, delays in response and modest effect size may limit patient selection for treatment.

The results from Study B, submitted with the original sBLA , met futility criteria at the predefined interim analysis (n=83), as defined in the Statistical Analysis Plan for the trial, in subjects inadequately controlled with H1-antihistamine and omalizumab treatment. The results from Study B did not demonstrate a statistically significant effect on the primary or key secondary endpoint:

- The LS mean change from baseline in ISS7 at Week 24 was -7.42 in the dupilumab arm versus -5.46 in the placebo arm; the difference was not statistically significant (-1.96, 95% CI: -5.53, 1.42, p=0.26) at the prespecified alpha level of 0.021 by O'Brien-Fleming approach.

- The LS mean change from baseline in UAS7 at Week 24 (key secondary endpoint) was -13.26 in the dupilumab arm versus -10.12 in the placebo arm; the difference was not statistically significant (-3.15, 95% CI: -9.79, 3.49, p=0.35) at the prespecified alpha level of 0.021 O'Brien-Fleming approach.

The interim analysis results for both endpoints exceeded the predefined futility boundary of p=0.1. Consequently, the outcome of this interim analysis met the prespecified criteria for futility. The Independent Data Monitoring Committee recommended discontinuation of the study due to futility on January 19, 2022. Subsequently, on February 18, 2022, the Applicant notified Investigators and study sites, providing instructions to contact participants still receiving study treatment and arrange early end-of-treatment visits. A public disclosure of the interim analysis futility results was issued via press release on the same date.

The safety profile of dupilumab in chronic spontaneous urticaria, based on pooled data from Studies A, B, and C, was consistent with the established safety profile observed in clinical development programs for approved dupilumab indications, including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, and prurigo nodularis. No new safety signals were identified.

In conclusion, the dupilumab CSU program has demonstrated substantial evidence of effectiveness, based on the results from Studies A and C in subjects who are symptomatic despite H1-antihistamine treatment and naïve to omalizumab treatment. The review team's assessment indicating a favorable benefit-risk profile is supported by the data. Based on these findings, I concur with the review team's recommendation for regulatory approval of this supplemental Biologics License Application.

# 15 Appendices

## 15.1. References

Bernstein, JA, DM Lang, DA Khan, T Craig, D Dreyfus, F Hsieh, J Sheikh, D Weldon, B Zuraw, DI Bernstein, J Blessing-Moore, L Cox, RA Nicklas, J Oppenheimer, JM Portnoy, CR Randolph, DE Schuller, SL Spector, SA Tilles, and D Wallace, 2014, The diagnosis and management of acute and chronic urticaria: 2014 update, J Allergy Clin Immunol, 133(5):1270-1277.

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## 15.2. Financial Disclosure

The Applicant's compliance with the Final Rule on lot refff Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this biologic license application (BLA). Details of the financial disclosure are outlined below. The Applicant submitted Food and Drug Administration (FDA) Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 Code of Federal Regulations (CFR) Part 54.

Twenty-three investigators disclosed their financial interests/arrangements. The Sponsor implemented appropriate actions to protect the studies from potential bias. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application and do not affect the review or recommendation for action.

**Covered Clinical Study (Name and/or Number): EFC16461 (CUPID), Studies A, B, and C**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 430. There were 235 unique investigators in Study A, 277 unique investigators in Study B, and 198 unique investigators in Study C. There were 59 investigators who participated in all three studies (A, B, and C). | | |
| 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): 23 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 0<br>Proprietary interest in the product tested held by investigator: 0<br>Significant equity interest held by investigator in 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 | Yes ☐ | No ☐ (Request explanation |

| | | |
|---|---|---|
| reason: | | from Applicant) |

# 15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

## 15.3.1. Population PK Analysis

### 15.3.1.1. Executive Summary

In this application, the Applicant submitted a population PK report (POH1089) entitled "Population Pharmacokinetic Analysis of Dupilumab Using Pooled Data from Three Phase 3 studies in Patients with Chronic Spontaneous Urticaria" to characterize the pharmacokinetics of dupilumab in CSU patients from EFC16461 Study A, Study B and Study C. No new population PK models were developed. A previously developed global Population PK base model was assessed for the adequacy in describing observed dupilumab concentrations in CSU patients and applied to derive exposure for comparing exposures across various disease populations. The effect of selected intrinsic and extrinsic factors on dupilumab PK in CSU patients were also assessed.

Dupilumab exhibits nonlinear PK. The global population PK model for dupilumab was a two-compartment model with first order absorption, parallel linear and Michaelis-Menten (M-M) elimination, and body weight as a significant covariate on V2, Vmax, and Ke. The model was found adequate in describing the PK of dupilumab in CSU patients and was used to predict individual exposures of patients with CSU.

The PK of dupilumab in patients with CSU were comparable to those of AD, asthma, CRSwNP, EoE, COPD and PN patients, which confirmed PK similarity of dupilumab across the different disease populations. PK simulations demonstrated that 300 mg q2w dose regimen (≥60 kg) and 200 mg q2w (30 to <60 kg) in adolescents with CSU would achieve dupilumab exposure similar to that for 300 mg q2w dose regimens in adult patients with CSU, and similar to the exposure observed in adult and adolescent patients with AD treated with the approved dose regimens 200 mg q2w (30 to <60 kg) and 300 mg q2w (≥60 kg).

In general, the Applicant's population PK analysis is acceptable for the purpose of estimating the PK and exposure parameters of dupilumab in adult and adolescent patients with CSU, despite some uncertainties for exposure in children due to the small sample size in adolescent (12-17 yo) and children (6-11 yo) populations. 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 regimen regarding PK parameters of dupilumab and assess the effects of the selected intrinsic and extrinsic factors.

### 15.3.1.2. PopPK Assessment Summary

The Applicant's popPK analysis was performed with PK data from 190 CSU patients (72 patients in Study C, 67 patients in Study A, and 51 patients in Study B), with a total of 374 dupilumab concentrations (135 PK samples in Study C, 137 PK samples in Study A, and 102 PK samples in Study B)(Table 27). The global popPK base model was developed with pooled data from Phase 1 to Phase 3 studies in healthy subjects (adults) and in patients with AD (adults) and asthma(adults and adolescents) in Study POH0668. Data from Study C, Study A and Study B were not included in the global popPK model development but were evaluated through a maximum *a posteriori* (MAP) Bayesian approach for external validation.

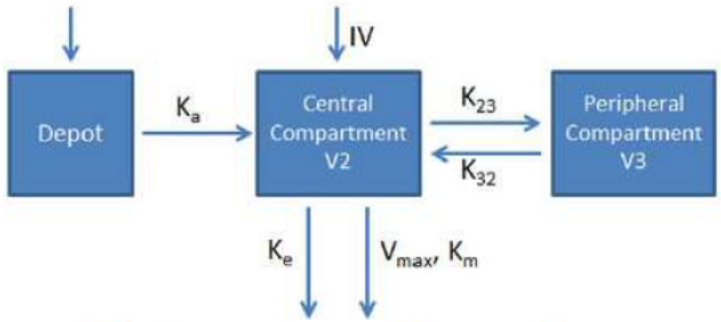
The global base popPK model was a two-compartmentmodel with first order absorption, parallel linear and M-M elimination, and body weight as a covariate on V2, Vmax, and Ke. The model was applied to sparse data to estimate PK parameters of dupilumab in CSU patients.The typical values of Ke and Vc of dupilumab were 0.041 1/day and 2.79 L, respectively. For the M-M elimination, the typical values of Vmax and Km were 1.48 mg/L/day, 2.52 mg/L, respectively.

Based on the goodness-of-fit plots and visual predictive checks (VPCs), the popPK model was considered adequate to derive the patient-level exposure metrics ($AUC_{\tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) for subsequent comparative analyses of exposure. The exposure metrics were used to compare dupilumab exposures between the sub-groups of interests.

The sub-groups of interests included Dose regimen (200 mg q2w vs. 300 mg q2w), race (Asian vs. non-Asian), age (<18 yr vs. ≥ 18 yr), weight (<=60 kg vx >60 kg), sex (Male vs. Female), Stationary ADA (Negative ADA vs. Positive ADA)(Table 30). Steady-state exposures in patients with CSU after 300 mg q2w treatment were highly comparable among EFC16461 Study A, Study B and Study C. The mean [SD] predicted Ctrough,ss (66.8 [30.6] mg/L) of these three studies was close to the observed Ctrough,ss (65.8 [33.0] mg/L). Details of the Applicant's population PK analysis are summarized in the table below.

| **General Information** | | |
|---|---|---|
| Objectives of PPK Analysis | | (1) To characterize dupilumab PK in CSU patients by applying the global Pop PK base model to CSU patients; (2)To generate individual dupilumab post hoc exposures and assess the influence of selected intrinsic and extrinsic factors on dupilumab PK in CSU patients. |
| Study Included | | Three Phase 3 studies (EFC16461 Study A, Study B and Study C) in Patients with CSU after subcutaneous (SC) |
| Dose(s) Included | | 300 mg q2w for body weight >= 60 kg, 200 mg q2w for body weight 30 to < 60 kg. |
| Population Included | | Adult, adolescent, and children( >=6 to < 12 years of age) CSU patients with body weight >=30 kg, |
| Population Characteristics (Table 3, Table 4) | General | The pooled population was 37.9% male and the age ranged from 8 to 79 years, with a range of weight of 32.5 to 136 kg |
| | Organ Impairment | None |
| | Pediatrics (if any) | The PK data in adolescents and children with CSU was limited and only available in six adolescents and three children; No children with body weight 15 to <30 kg enrolled, so no data for the dupilumab 300 mg q4w dose regimen were available in this analysis |
| No. of Patients, PK Samples, and BLQ | | The final dataset contained 374 dupilumab concentrations from 190 patients with CSU (67 patients for EFC16461 Study A, 51 for Study B and 72 patients for Study C). Pre-dose (N=193) and post-dose (N=133) BLQ samples were flagged in the dataset and excluded in Pop PK analysis. |

| | | |
|---|---|---|
| Sampling Schedule | Rich Sampling | No rich PK sampling in Study A, Study B, and Study C. |
| | In ITT Population | Sparse PK sampling were scheduled at baseline, trough at Weeks 12, and 24 during treatment, and at Week 36 during safety follow-up period |
| Covariates Evaluated | Static | [redacted], Race (Caucasian 60.5%, Black 2.11%, Asian 30%, Other 2.63%, Missing 4.74%), Stationary ADA (Negative vs. Positive), Stationary ADA (Negative, Pre-existing, Treatment-emergent), AD(With vs Without), H1AH, Body weight (32.5-136 kg), Age (8-79 years), CLCR for adults Albumin, ISS7, UAS7, HSS7, CSU patient population (Naïve to omalizumab, with omalizumab) see Table 27 and Table 28 |
| | Time-varying | None |

| **Final Model** | **Summary** | **Acceptability [FDA's comments]** |
|---|---|---|
| Software and Version | Analysis dataset creation was conducted by using SAS® Version 9.4 software (SAS Institute, Cary, North Carolina); The population PK analysis was conducted by using NONMEM version 7.4.1 based upon concentration data pooled from three Phase 3 studies as described in Section 3.1.1. R statistical software (version 3.6.1) (4) was used for data tabulation/visualization/simulation activities. | Acceptable |
| Model Structure | The global model is a two-compartment model with a first order absorption, and parallel linear and nonlinear elimination. The absorption process is parameterized in terms of first order absorption rate constant (Ka, day-1). The elimination process is described by the linear pathway parameterized in terms of linear elimination rate constant (Ke, day-1) and nonlinear Michaelis-Menten elimination represented by the two parameters Vmax (mg · day/L) and Km (mg/L). The two compartments are represented by a distribution volume of central compartment (V2) and inter-compartment distribution<br>**Figure 2 - Schematic structure of dupilumab Pop PK model**<br>  <br><br>Abbreviation: $K_a$: absorption rate constant; $V_2$: central compartment volume; $V_3$: peripheral compartment volume; $K_{23}$, $K_{32}$: inter-compartmental rate constants; $K_e$: elimination rate constant; $V_{max}$: maximum target-mediated rate of elimination; $K_m$: Michaelis constant. | Acceptable |
| Model Parameter Estimates | See the popPK Report POH0668 submitted for CRSwNP | Acceptable |
| Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap) | See the popPK Report POH0668 submitted for CRSwNP | Acceptable |
| BLQ for Parameter Accuracy | Pre-dose (N=193) and post-dose (N=133) BLQ samples were flagged in the dataset and excluded in Pop PK analysis | |
| GOF, VPC | See Figure 18 for GOF and Figure 19 for VPC | Acceptable |
| Significant Covariates and Clinical Relevance | Post hoc covariate effect assessment was conducted. Consistent with the finding in other populations, body weight was identified as the primary factor explaining dupilumab PK variability in CSU patients. All other tested factors, including baseline demographics ([redacted], age, and race), baseline lab parameters (creatinine clearance and albumin), immunogenicity, ethnicity, patient population (with or without omalizumab treatment), baseline biomarker and disease characteristics (ISS7, UAS7, | Acceptable |

| | | |
|---|---|---|
| | HSS7) and concomitant medication (H1AH) had no apparent effect on dupilumab PK exposure in patients with CSU based on available data. | |
| Analysis Based on Simulation (optional) | Typical concentration-time profiles for dupilumab in patients with CSU after 300 mg q2w SC treatment were simulated using the global Pop PK base model. The simulations were conducted for a typical patient with the median weight in the Final Dataset. Simulated typical dupilumab concentrations over time profiles for 300 mg q2w dose regimen in adult patients with AD, asthma, CRSwNP, EoE, PN, COPD and CSU were compared (Table 32 and Table 33). | Acceptable |
| **Labeling Language** | **Description** | **Acceptability [FDA's comments]** |
| 12.3 PK | | |

**Table 27. Summary of Potential Continuous Covariates for Patients with CSU in the Final Dataset**

| Covariate candidate | EFC16461 Study A, Study B and Study C | | |
|---|---|---|---|
| | N | Mean (SD) | Median (Min, Max) |
| Weight (kg) | 190 | 76.6 (18.9) | 74.8 (32.5, 136) |
| Age (year) | 190 | 44.6 (16.8) | 45 (8, 79) |
| CLCR for adults (mL/min) [a] | 181 | 137 (46.6) | 128 (45.7, 342) |
| CLCR for patients <18 years old (mL/min/1.73 m²)[a] | 9 | 175 (39.6) | 169 (136, 266) |
| Albumin (g/L) | 190 | 46 (2.75) | 46 (39, 53) |
| ISS7 | 190 | 15.6 (3.85) | 15 (8, 21) |
| UAS7 | 190 | 30.2 (7.41) | 31 (16, 42) |
| HSS7 | 190 | 14.5 (4.37) | 14 (2, 21) |

**Abbreviations**: CLCR: creatinine clearance;; HSS7: weekly hive severity score; ISS7: weekly itch severity score; N: subject number; SD: standard deviation; UAS7: weekly urticaria activity score.

a For adults, CLCR value was derived using the equation of Cockroft and Gault. For patients <18 years old, CLCR value was derived using the equation of glomerular filtration rate (GFR) Bedside Schwartz.

Source: Adapted from Table 3 on page 26 of Applicant's population PK report

**Table 28. Summary of Potential Categorical Covariates for Patients with CSU in the Final Dataset**

| Covariate candidate | Subgroup | EFC16461 Study A, Study B and Study C N (%) |
|---|---|---|
| [redacted] | Male | 72 (37.9%) |
| | Female | 118 (62.1%) |
| Race[a] | Caucasian | 115 (60.5%) |
| | Black | 4 (2.11%) |
| | Asian | 57 (30%) |
| | Other | 5 (2.63%) |
| | Missing | 9 (4.74%) |
| Stationary ADA[1] | Negative | 167 (87.9%) |
| | Pre-existing | 2 (1.05%) |
| | Treatment-emergent | 21 (11.05%) |
| Stationary ADA[2] | Negative | 167 (87.9%) |
| | Positive | 23 (12.1%) |
| AD | With | 12 (6.3%) |
| | Without | 178 (93.7%) |
| H1AH | Without | 6 (3.2%) |
| | Standard dose | 69 (36.3%) |
| | 2-3-fold standard dose | 76 (40%) |
| | 4-fold standard dose | 39 (20.5%) |
| CSU patient population | CSU patients naive to omalizumab (Study A) | 67 (35.3%) |
| | CSU patients with omalizumab treatment (Study B) | 51 (26.8%) |
| | CSU patients naive to omalizumab (Study C) | 72 (37.9%) |

**Abbreviations**: AD: atopic dermatitis; ADA:anti-drug antibody; CSU: : chronic spontaneous urticaria; H1AH: H1-antihistamines.

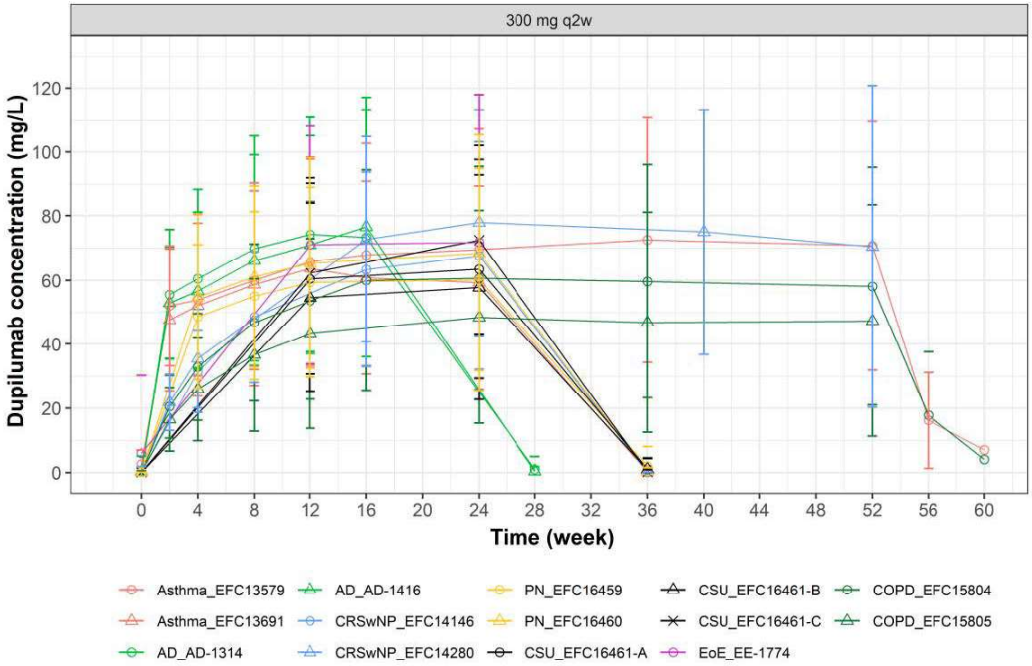
a One patient from EFC16461 Study A , one patient from EFC16461Study B and seven patient in EFC16461 Study C had missing information for race. In the post hoc analysis, the missing race values were imputed using the categorical value of the majority of the population (i.e., Caucasian).

Source: Adapted from Table 4 on page 27 of Applicant's population PK report

**Comparison of observed PK data across different populations**

Figure 17 demonstrated that observed dupilumab PK profiles for patients with CSU who received 300 mg q2w in studies EFC16461 Study A, Study B and Study C were comparable to the observed PK profiles for adult AD, asthma, CRSwNP, EoE, PN and COPD patients who received 300 mg q2w from 9 Phase 3 studies (AD-1314, AD-1416, EFC13579, EFC13691, EFC14146 and EFC14280, EE-1774, EFC16459, EFC16460, EFC15804 and EFC15805). The observed mean concentration-time profiles were similar across different populations, except for a slower rise of the initial profiles in patients with CRSwNP, COPD and EoE, due to the absence of a loading dose. The observed dupilumab steady-state exposures (trough concentrations) were similar across all populations regardless of treatment durations.

**Figure 17. Mean (SD) Observed Trough Concentration-Time Profiles of Dupilumab at 300 mg Q2W in Adult Patients With AD, Asthma, CRSwNP, EoE, PN, COPD and CSU**




Source: Figure 4 on page 28 of Applicant's population PK report
Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; Q2W, every 2 weeks; SD, standard deviation

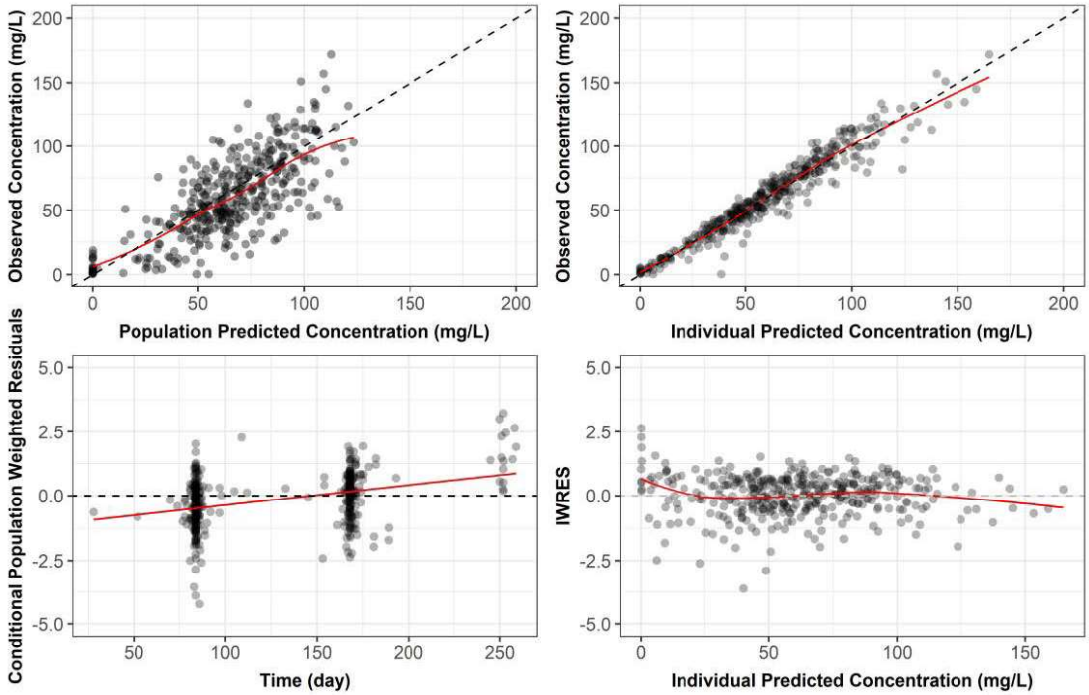
**Population PK Model**

The global Pop PK base model was applied to sparse data in patients with CSU from EFC16461 Study A, Study B and Study C by fixing the population parameter estimates. The individual PK parameters and exposure estimates for patients with CSU was generated by MAP estimation (i.e.,MAP Bayesian approach).

**Model Evaluation**

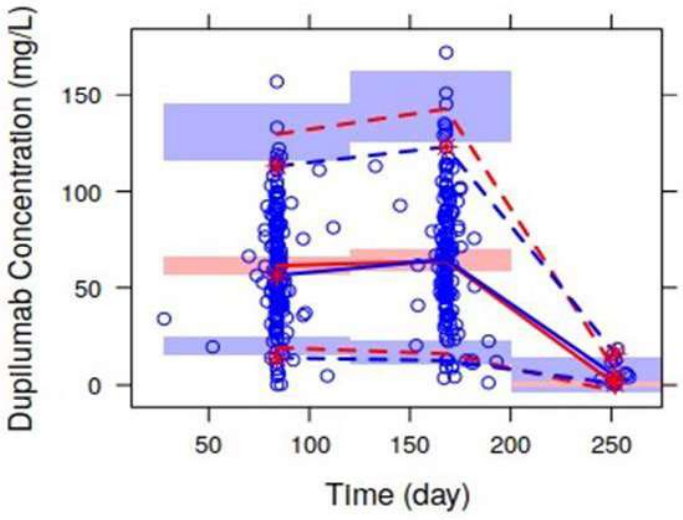
The goodness-of-fit plots for applying the global popPK base model with CSU patients are presented in Figure 18. The VPC plots that demonstrate the observed and model-predicted concentrations of dupilumab are shown in Figure 19. Overall, The VPC results indicated that individual observed concentrations of dupilumab in patients with CSU were adequately fitted with the global popPK base model.

**Figure 18. Goodness-of-Fit Plots for Applying Global PopPK Base Model in Patients With CSU**




Source: Figure 5 on page 29 of Applicant's population PK report
Abbreviations: CSU, chronic spontaneous urticaria; PK, pharmacokinetic; popPK, population PK

**Figure 19. Visual Predictive Checks for Global PopPK Base Model in Patients With CSU**




Source: Figure 6 on page 29 of Applicant's population PK report
Notes: Legend: blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.
Abbreviations: CSU, chronic spontaneous urticaria; PK, pharmacokinetic; popPK, population PK

**Exposure Estimates from the global population PK Model**

The global popPK base model was used to generate post-hoc estimates of individual steady-state exposures for each patient with CSU. Summary statistics of exposure estimates of dupilumab by study and dose regimen are presented in Table 29.

**Table 29. Mean (SD)[CV%] Predicted and Observed Steady-State Exposures of Dupilumab in Patients With CSU by Study and Dose Regimen, EFC16461 Study A, Study B and Study C**

| Study | Dose regimen[a] | Predicted | | | | Observed | |
|---|---|---|---|---|---|---|---|
| | | N[b] (median weight) | $AUC_{\tau,SS}$[c] (mg•day/L) | $C_{max,SS}$[c] (mg/L) | $C_{trough,SS}$[c] (mg/L) | N[d] (median weight) | $C_{trough,SS}$[e] (mg/L) |
| EFC16461 Study A | 300 mg q2w | 61 (75.0 kg) | 1130 (479) [42.3%] | 89.8 (35.8) [39.9%] | 67.1 (31.9) [47.6%] | 60 (75.0 kg) | 65.5 (33.6) [51.4%] |
| | 200 mg q2w | 1 (57.0 kg) | 637 | 52.5 | 35.3 | 1 (57.0 kg) | 22.4 |
| | All | 62 (75.0 kg) | 1120 (479) [42.6%] | 89.2 (35.8) [40.1%] | 66.5 (31.9) [48.0%] | 61 (75.0 kg) | 64.8 (33.8) [52.2%] |
| EFC16461 Study B | 300 mg q2w | 48 (79.6 kg) | 1030 (471) [45.9%] | 81.8 (34.8) [42.5%] | 60.3 (31.2) [51.8%] | 47 (79.2 kg) | 57.8 (35.1) [60.7%] |
| EFC16461 Study C | 300 mg q2w | 65 (72.6 kg) | 1200 (440) [36.5%] | 95.2 (33.0) [34.6%] | 71.6 (28.8) [40.2%] | 56 (73.0kg) | 73.3 (29.2) [39.9%] |
| | 200 mg q2w | 2 (46.2 kg) | 1170 (383) [32.6%] | 92.2 (28.0) [30.3%] | 70.1 (25.5) [36.4%] | 2 (46.2 kg) | 72.4 (38.9) [53.7%] |
| | All | 67 (71.6 kg) | 1200 (435) [36.2%] | 95.1 (32.6) [34.3%] | 71.6 (28.5) [39.9%] | 58 (73.0 kg) | 73.2 (29.2) [39.8%] |
| Total | 300 mg q2w | 174 (75.0 kg) | 1130 (465) [41.2%] | 89.6 (34.7) [38.7%] | 66.9 (30.8) [46%] | 163 (75.1 kg) | 65.9 (33.0) [50.0%] |
| | 200 mg q2w | 3 (47.1 kg) | 995 (412) [41.4%] | 79 (30.3) [38.3%] | 58.5 (27) [46.2%] | 3 (47.1 kg) | 55.7 (39.9) [71.5%] |
| | All | 177 (74.5 kg) | 1130 (463) [41.1%] | 89.4 (34.6) [38.7%] | 66.8 (30.6) [45.9%] | 166 (75.1kg) | 65.8 (33.0) [50.2%] |

**Abbreviations**: N: number of patients; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CV: coefficient of variation; q2w: every two weeks; SD: standard deviation.

*a* 200 mg q2w with an initial loading dose of 400 mg and 300 mg q2w with an initial loading dose of 600 mg.

*b* For predicted PK exposures, out of 190 patients as PK population in Final Dataset, 185 patients (181 adults and 4 adolescents) received 300 mg q2w and 5 patients (2 adolescents and 3 children 6 to <12 years of age) received 200 mg q2w. Due to dose discontinuation before Week 22, 10 adult and 1 adolescents patients receiving 300 mg q2w, and 2 children 6 to <12 years of age receiving 200 mg q2w were exclude in this post assessment.

*c* $AUC_{\tau,ss}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A ,Study B and Study C.

*d* For observed PK exposure, out of 190 patients as PK population in Final Dataset, 168 patients with CSU (1162 adults and 6 adolescents) had measurable PK concentrations at Week 24 . Two measurable PK concentrations at Week 24 for two adult patient (Patient No. 016461-(b) (6) with last received dose at Week 12 and 016461-(b) (6) with last received dose at Week 18) were excluded from observed PK summary here. The first PK sample was also identified as outlier due to CWRES>5 and excluded from Bayesian analysis and post hoc assessment.

*e* Observed $C_{trough,ss}$ was summarized based on observed data at Week 24 in Pop PK dataset. For EFC16461 Study A, compared to clinical study report (N=64 with observed concentration at Week 24), three patients due to outlier concentrations at Week 24 (N=2) and all BLQ data (N=1) were excluded from the summary of observed $C_{trough,ss}$ at Week 24 here. For EFC16461 Study C, compared to clinical study report (N=59 with observed concentration at Week 24), one patients due to outlier concentrations at Week 24 (N=1) were excluded from the summary of observed $C_{trough,ss}$ at Week 24 here.

Source: Table 5 on page 31 of Applicant's population PK report

**Effect of Covariates**

The mean and SD of steady-state exposures (i.e., AUCτ,ss, Cmax,ss, and Ctrough,ss) of dupilumab in patients with CSU in EFC16461 Study A, Study B and Study C as a function of selected intrinsic/extrinsic factors were provided in Table 30. Among the evaluated factors, only body weight exerted a primary effect explaining variability source in dupilumab PK in patients with CSU. Patients in lower body weight group exhibited higher exposures of dupilumab. The summary of predicted dupilumab steady-state exposures by age and dose regimen were presented in Table 30.

**Table 30. Mean (SD) Predicted Steady-State Exposures for Dupilumab in Patients With CSU as a Function of Intrinsic/Extrinsic Factors**

| Tested covariates | | N[a] (mean weight) | $AUC_{\tau,ss}$[b] (mg.day/L) | $C_{max,ss}$[b] (mg/L) | $C_{trough,ss}$[b] (mg/L) |
|---|---|---|---|---|---|
| All | | 177 (76.6 kg) | 1130 (463) | 89.4 (34.6) | 66.8 (30.6) |
| Dose regimen[c] | 200 mg q2w | 3 (49.8 kg) | 995 (412) | 79.0 (30.3) | 58.5 (27.0) |
| | 300 mg q2w | 174 (77.0 kg) | 1130 (465) | 89.6 (34.7) | 66.9 (30.8) |
| Age (year) | <18 yr | 6 (61.4 kg) | 1050 (344) | 83.4 (25.8) | 61.5 (22.6) |
| | ≥18 yr | 171 (77.1 kg) | 1130 (468) | 89.6 (34.9) | 67.0 (30.9) |
| Weight (kg) | <=60 kg | 39 (54.3 kg) | 1560 (473) | 122 (34.5) | 94.7 (31.7) |
| | >60 kg | 138 (82.8 kg) | 1000 (380) | 80.1 (28.4) | 58.9 (25.4) |
| Stationary ADA | Negative ADA | 156 (75.4 kg) | 1180 (455) | 93.2 (33.9) | 70.1 (30.1) |
| | Positive ADA | 21 (85.1 kg) | 748 (337) | 61.3 (25.7) | 41.9 (22.1) |
| Sex | Male | 68 (81.9 kg) | 1130 (365) | 89.6 (27.2) | 67.3 (24.3) |
| | Female | 109 (73.2 kg) | 1120 (517) | 89.3 (38.6) | 66.4 (34.1) |
| Race 1[d] | White | 112 (79.6 kg) | 1080 (478) | 85.5 (35.4) | 63.6(31.7) |
| | Black | 4 (84.7 kg) | 1000 (190) | 79.9 (13.8) | 58.7 (13.1) |
| | Asian | 56 (68.8 kg) | 1250 (447) | 98.8 (33.6) | 74.3 (29.5) |
| | Other | 5 (89.0 kg) | 1010 (205) | 80.1 (15.5) | 59.1 (13.1) |
| Race 2[d] | Asian | 56 (68.8 kg) | 1250 (447) | 98.8 (33.6) | 74.3 (29.5) |
| | No-Asian | 121 (80.2 kg) | 1070 (462) | 85.1 (34.3) | 63.3 (30.6) |

**Abbreviations**: AD: atopic dermatitis; ADA: anti-drug antibody; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; CLCR: creatinine clearance; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CSU: chronic spontaneous urticaria ; H1AH: H1-antihistamines; HSS7: weekly hive severity score; ISS7: weekly itch severity score; N: subject number; q2w: every two weeks; RI: renal impairment; SD: standard deviation; UAS7: weekly urticaria activity score.

a For predicted PK exposures, out of 190 patients as PK population in Final Dataset, 185 patients (181 adults and 4 adolescents) received 300 mg q2w and 5 patients (2 adolescents and 3 children 6 to <12 years of age) received 200 mg q2w. Due to dose discontinuation before Week 22, 10 adult and 1 adolescents patients receiving 300 mg q2w, and 2 children 6 to <12 years of age receiving 200 mg q2w were exclude in this post assessment.

b $AUC_{\tau,ss}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A, Study B and Study C.

c 200 mg q2w with an initial loading dose of 400 mg or 300 mg q2w with an initial loading dose of 600 mg.

d One patient in Study B and 6 patients in Study C (out of 177 patients) had missing values for race, which had been imputed as White in this post hoc summary.

*Continued*

*Table 30, continued*

| Tested covariates | | N[a] (mean weight) | $AUC_{\tau,ss}$[b] (mg.day/L) | $C_{max,ss}$[b] (mg/L) | $C_{trough,ss}$[b] (mg/L) |
|---|---|---|---|---|---|
| Albumin (g/L) | 30 - <40 | 3 (86.7 kg) | 773 (571) | 62.8 (41.9) | 44.0 (37.9) |
| | 40 - <50 | 154 (76.1 kg) | 1120 (463) | 89.3 (34.5) | 66.6 (30.6) |
| | ≥ 50 | 20 (78.5 kg) | 1200 (451) | 94.7 (33.7) | 71.4 (29.7) |
| Renal function[c] | Normal | 153 (78.4 kg) | 1090 (437) | 86.3 (32.7) | 64.0 (28.8) |
| | Mild renal impairment | 22 (65.3 kg) | 1340 (511) | 105 (37.3) | 80.6 (34.7) |
| | Moderate RI (ml/min) | 2 (60.4 kg) | 1980 (779) | 153 (58.0) | 125 (46.0) |
| AD | With | 12 (68.4 kg) | 1440 (581) | 113 (43.1) | 87.5 (38.2) |
| | Without | 165 (77.1 kg) | 1100 (447) | 87.7 (33.4) | 65.3 (29.6) |
| ISS7 | <13 | 35 (78.4 kg) | 1120 (458) | 89.3 (34.5) | 66.5 (30.0) |
| | ≥13 | 142 (76.1 kg) | 1130 (466) | 89.5 (34.7) | 66.8 (30.9) |
| UAS7 | <28 | 56 (76.0 kg) | 1190 (511) | 93.8 (38.1) | 70.5 (33.7) |
| | ≥28 | 121 (76.8 kg) | 1100 (439) | 87.4 (32.8) | 65.0 (29.1) |
| HSS7 | <13 | 52 (76.0 kg) | 1200 (491) | 94.9 (36.5) | 71.5 (32.4) |
| | ≥13 | 125 (76.8 kg) | 1100 (450) | 87.2 (33.6) | 64.8 (29.8) |
| H1AH | without | 5 (88.2 kg) | 928 (521) | 75.3 (38.6) | 54.7 (32.6) |
| | standard dose | 63 (71.7 kg) | 1260 (511) | 99.8 (38.2) | 75.9 (33.9) |
| | 2-3 fold standard dose | 72 (79.8 kg) | 1020 (406) | 81.7 (30.2) | 59.9 (27.0) |
| | 4 fold standard dose | 37 (76.9 kg) | 1120 (430) | 88.8 (32.0) | 66.2 (28.3) |

**Abbreviations**: AD: atopic dermatitis; ADA: anti-drug antibody; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; CLCR: creatinine clearance; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CSU: chronic spontaneous urticaria ; H1AH: H1-antihistamines; HSS7: weekly hive severity score; ISS7: weekly itch severity score; N: subject number; q2w: every two weeks; RI: renal impairment; SD: standard deviation; UAS7: weekly urticaria activity score.

*a* For predicted PK exposures, out of 190 patients as PK population in Final Dataset, 185 patients (181 adults and 4 adolescents) received 300 mg q2w and 5 patients (2 adolescents and 3 children 6 to <12 years of age) received 200 mg q2w. Due to dose discontinuation before Week 22, 10 adult and 1 adolescents patients receiving 300 mg q2w, and 2 children 6 to <12 years of age receiving 200 mg q2w were exclude in this post assessment.

*b* $AUC_{\tau,ss}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A, Study B and Study C.

*c* For adults, CLCR value (mL/min) was derived using the euqation of Cockroft and Gault and renal function categories were based on the following creteria: Normal: CLCR ≥ 90 mL/min; Mild renal impairment: 60 ≤ CLCR < 90 mL/min; Moderate renal impairment: 30≤CLCR < 60 mL/min. For adolescents, CLCR value (mL/min/1.73 $m^2$) was derived using the equation of GFR Bedside Schwartz and same renal function catogories were used: Normal: CLCR ≥ 90 mL/min/1.73 $m^2$; Mild renal impairment: 60 ≤ CLCR < 90 mL/min/1.73 $m^2$; Moderate renal impairment: 30≤CLCR < 60 mL/min/1.73 $m^2$.

Source: Table 6 on pages 33-34 of Applicant's population PK report

**Table 31. Mean (SD)[CV%] Predicted Steady-State Exposures of Dupilumab in Patients With CSU by Age and Dose Regimen, EFC16461 Study A, Study B, and Study C**

| | Category | Dose regimen[a] | Predicted N[b] (median weight) | Predicted $AUC_{\tau,SS}$[c] (mg•day/L) | Predicted $C_{max,SS}$[c] (mg/L) | Predicted $C_{trough,SS}$[c] (mg/L) |
|---|---|---|---|---|---|---|
| Age | Adults | 300 mg q2w | 171 (75.0 kg) | 1130 (468) [41.4%] | 89.6 (34.9) [38.9%] | 67 (30.9) [46.2%] |
| | Adolescents (12-17 year) | 300 mg q2w | 3 (72.0 kg) | 1100 (344) [31.2%] | 87.9 (26.3) [29.9%] | 64.5 (22.9) [35.5%] |
| | | 200 mg q2w | 2 (52.0 kg) | 770 (189) [24.5%] | 62.5 (14.1) [22.5%] | 43.7 (11.9) [27.2%] |
| | Children (6-11 year) | 200 mg q2w | 1 (45.3 kg) | 1440 | 112 | 88.1 |

**Abbreviations**: N: number of patients; $AUC_{\tau,SS}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,SS}$: maximum concentration at steady state; $C_{trough,SS}$: minimum concentration at steady state; CV: coefficient of variation; q2w: every two weeks; SD: standard deviation.

a 200 mg q2w with an initial loading dose of 400 mg and 300 mg q2w with an initial loading dose of 600 mg.

b For predicted PK exposures, out of 190 patients as PK population in Final Dataset, 185 patients (181 adults and 4 adolescents) received 300 mg q2w and 5 patients (2 adolescents and 3 children 6 to <12 years of age) received 200 mg q2w. Due to dose discontinuation before Week 22, 10 adult and 1 adolescents patients receiving 300 mg q2w, and 2 children 6 to <12 years of age receiving 200 mg q2w were exclude in this post assessment.

c Predicted $AUC_{\tau,SS}$ = AUC[Week 24 – Week 22] for 200 mg q2w and 300 mg q2w. $C_{max,SS}$ and $C_{trough,SS}$ were calculated over Week 22 and Week 24 for 200 mg q2w and 300 mg q2w in EFC16461 Study A, Study B and Study C.

Source: Table 7 on page 36 of Applicant's population PK report

**Table 32. Model-Predicted and Observed Steady State Exposure of Dupilumab in Patients With CSU and AD**

| Population | Age group | Study identifier | Dose | Median body weight (kg) | Predicted/Simulated $C_{max,ss}$ (mg/L)[a] N | Mean (SD) | P5-P95 | Observed/Simulated $C_{trough,ss}$ (mg/L)[a] N | Mean (SD) | P5-P95 |
|---|---|---|---|---|---|---|---|---|---|---|
| CSU | Adults | EFC16461 Study A[a] | 300 mg q2w | 75.1 | 60 | 89.4 (36.0) | 24.0-153 | 62 | 63.5 (34.2) | 3.63-117 |
| | | EFC16461 Study B[a] | 300 mg q2w | 80.0 | 47 | 81.6 (35.1) | 33.7-142 | 46 | 57.7 (35.5) | 10.4-112 |
| | | EFC16461 Study C[a] | 300 mg q2w | 72.1 | 64 | 95.7 (32.9) | 52.2-143 | 55 | 73.7 (29.3) | 30.5-125 |
| AD | Adults | R668-AD-1334 R668-AD-1416[b] | 300 mg qw | 75.2 | 5000 | 216 (84.3) | 108-371 | 417 | 183 (77.0) | 66.0-325 |
| AD | Adults | R668-AD-1334 R668-AD-1416[b] | 300 mg q2w | 75.0 | 5000 | 105 (43.2) | 48.3-186 | 438 | 75.0 (40.3) | 12.4-141 |
| CSU | Adolescents | POH0861[c] | 300 mg q2w (≥60 kg) | 73.7 | 1000 | 91.2 (35.7) | 37.7-154 | 1000 | 68.6 (32.2) | 22.2-125 |
| | | | 200 mg q2w (30-<60 kg) | 51.3 | 1000 | 87.6 (31.5) | 43.4-144 | 1000 | 66.9 (28.1) | 28.4-118 |
| AD | Adolescents | R668-AD-1526[b] | 300 mg q2w (≥60 kg) | 80.3 | 4140 | 87.0 (31.8) | 41.0-144 | 36 | 57.9 (30.0) | 13.7-102 |
| | | | 200 mg q2w (<60 kg) | 49.0 | 3860 | 86.1 (28.8) | 49.2-142 | 41 | 51.6 (24.0) | 10.8-94.3 |

**Abbreviations**: $C_{max}$: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; N: number of patients; q2w: every 2 weeks; q4w: every 4 weeks; SD: standard deviation, P5: 5th percentile; P95: 95th percentile

a Predicted $C_{max,ss}$ generated from Pop PK model predicted individual post hoc parameters using bayesian approach; observed $C_{trough,ss}$ for adult patients with CSU

b Simulated $C_{max,ss}$; observed $C_{trough,ss}$ for adults and adolescents with AD

c Simulated $C_{trough,ss}$ and $C_{max,ss}$ based on Pop PK model for 300 mg q2w and 200 mg q2w in adolescents with CSU (≥60 kg) and (30 to <60 kg), respectively, using virtual pediatric population from NHANES.

**Source**: observed $C_{trough,ss}$ and simulated $C_{max,ss}$ in adults and adolescents with CSU in this study and observed $C_{trough,ss}$ for adults and adolescents with AD (R668-AD-1334-CP-01V1, R668-AD-1416-CP-01V1, R668-AD-1526-CP-01V2). Simulated $C_{max,ss}$ of 300 mg q2w / 300 mg qw in adults with AD, (Study R668-PM-19142-SR-01V1); Simulated $C_{max,ss}$ 300 mg q2w / 200 mg q2w in adolescents with AD (Study R668-PM-18124-SR-01V1)

Source: Table 8 on page 49 of Applicant's population PK report

***Reviewer's comments:*** *The population PK modeling analyses for dupilumab in CSU patients are deemed acceptable. The reviewer was able to repeat and verify the Applicant's analyses with no significant discrepancies identified. Overall, the global population PK base model appeared*

*adequate for characterizing the PK of dupilumab administered subcutaneously in adult and adolescent patients with CSU, as indicated in the Applicant's goodness-of-fit plots and VPC plots. The results of the population PK analyses were used to support the proposed dosage regimen regarding PK parameters of dupilumab and the effects of intrinsic and extrinsic factors.*

*There were some uncertainties and limitations in the assessment of dupilumab PK in adolescents and children with CSU, as PK data were only available in six adolescents and three children, and no children weighing 15 to <30 kg enrolled in the studies.*

### 15.3.2. Exposure-Response Analysis

#### 15.3.2.1. E-R (Efficacy) Assessment Summary

The Applicant submitted an E-R analysis report entitled "Empirical Exposure-Response Modeling for Dupilumab in Participants with Chronic Spontaneous Urticaria (CSU)" to explore the relationships between exposure ($C_{trough}$) of dupilumab and key efficacy endpoints (ISS7, UAS7, and HSS7), to support the proposed dosage regimen used in the pivotal studies (EFC16461 Studies A and C).

The summary of baseline body weight and H1AH dose is shown in Table 34. Based on a total of 130 participant (58 participants for Study A, 72 for Study C) with a $C_{trough}$ at Week 24 (or at Week 12 if Week 24 was missing), plots by the concentration quartiles and placebo arm and corresponding summary statistics were conducted for ISS7, UAS7, and HSS7 changes from baseline at Week 24. A base PK/PD model was used to select an E/R relationship form from linear, log-linear and Emax models. Covariate effects were also explored in the modeling analyses.

Model-based analysis for EFC16461 pooled studies A and C showed a greater reduction in ISS7 with increasing dupilumab $C_{trough}$ at Week 24 and appeared to plateau at the exposure of the 3rd quartile Q3 (median Ctrough of 75.8 mg/L) (Figure 10 and Table 35 ). The model-predicted ISS7 responses are consistent with the clinical observation in EFC16461 pooled studies A and C.

Model-based analysis for EFC16461 pooled studies A and C showed a greater decrease in UAS7 with increasing dupilumab Ctrough at Week 24 and appeared to plateau at the exposure of the 3rd quartile Q3 (median Ctrough of 75.8 mg/L) (Figure 11 and Table 36). The model-predicted HSS7 responses are consistent with the descriptive observation in EFC16461 pooled studies A and C.

Model-based analysis for EFC16461 pooled studies A and C showed a greater decrease in HSS7 with increasing dupilumab Ctrough at Week 24 and appeared to plateau at the exposure of the 3rd quartile Q3 (median Ctrough of 75.8 mg/L) (Table 37 and Figure 20). The model-predicted HSS7 responses are consistent with the descriptive observation in EFC16461 pooled studies A and C.

The Applicant's analyses were repeated and deemed acceptable. The model-based PK/PD

analyses indicated that a greater increase of efficacy response with an increase in concentrations and reached to plateau around $C_{trough}$ concentration of 75.8 mg/L, which approximately corresponds to the median Ctrough of the 3rd quartile, for all endpoints.

The Applicant's E-R analyses results are summarized in detail below.

**Table 33. Summary of Baseline Body Weight and H1-AH Dose by Quartiles of Observed Trough Concentration at Week 24 and Placebo Arm in Participants with CSU in EFC16461, Study CTS0083**

**Study A**

| Treatment arm | $C_{trough}$ quartile | N | $C_{trough}$ Mean (SE) (mg/L) | Weight BL Mean (SE) (Giga/L) | H1-AH BL Dose Mean (SE) (% Standard Dose) |
|---|---|---|---|---|---|
| Placebo | NA | 58 | 0 | 73.5 ( 2.4) | 179.3 (14.9) |
| Dupilumab | 1 | 13 | 15.7 ( 3.9) | 98.0 ( 6.7) | 200.0 (34.0) |
| Dupilumab | 2 | 13 | 50.5 ( 1.3) | 82.5 ( 5.4) | 223.1 (32.3) |
| Dupilumab | 3 | 14 | 66.4 ( 1.4) | 73.4 ( 4.2) | 207.1 (30.5) |
| Dupilumab | 4 | 15 | 100.7 ( 6.4) | 60.7 ( 3.5) | 193.3 (30.0) |

BL: baseline; $C_{trough}$: trough concentration; H1-AH: H1-antihistamine; SE: standard error. Quartiles groups: Q1 (<40.9 mg/L), Q2(40.9-<56.2 mg/L), Q3(56.2-<75.7 mg/L), Q4(>=75.7 mg/L).

**Study C**

| Treatment arm | $C_{trough}$ quartile | N | $C_{trough}$ Mean (SE) (mg/L) | Weight BL Mean (SE) (Giga/L) | H1-AH BL Dose Mean (SE) (% Standard Dose) |
|---|---|---|---|---|---|
| Placebo | NA | 69 | 0 | 74.5 ( 2.7) | 192.8 (12.8) |
| Dupilumab | 1 | 17 | 37.6 ( 2.4) | 83.3 ( 4.7) | 188.2 (24.1) |
| Dupilumab | 2 | 17 | 62.6 ( 1.7) | 78.5 ( 3.2) | 160.5 (19.0) |
| Dupilumab | 3 | 17 | 85.0 ( 1.6) | 71.7 ( 2.0) | 147.1 (12.5) |
| Dupilumab | 4 | 17 | 112.6 ( 2.8) | 58.2 ( 2.3) | 161.8 (23.3) |

BL: baseline; $C_{trough}$: trough concentration; H1-AH: H1-antihistamine; SE: standard error. Quartiles groups: Q1 (<40.9 mg/L), Q2(40.9-<56.2 mg/L), Q3(56.2-<75.7 mg/L), Q4(>=75.7 mg/L).

Source: Table 1 on page 19 of Applicant's E-R report (cts0083)

**Table 34. ISS7 Change from Baseline at Week 24: Observed and PK/PD Model Predicted Treatment Differences by $C_{trough}$ at W24 Quartiles Group, EFC16461 Pooled Studies A and C, Study CTS0083**

| Quartile Comparison vs Placebo | Observed PD LS Mean Difference (95% CI) from ANCOVA Model | Predicted Mean Difference (95% CI) from PK/PD Model | Median $C_{trough}$ (mg/L) at Week 24 |
|---|---|---|---|
| Q1 | -2.77 (-5.47, -0.07) | -3.98 (-5.59, -2.38) | 31.4 |
| Q2 | -2.05 (-4.68, 0.57) | -3.37 (-5.10, -1.63) | 53.9 |
| Q3 | -4.51 (-7.12, -1.90) | -4.51 (-6.33, -2.69) | 75.8 |
| Q4 | -4.14 (-6.80, -1.47) | -4.80 (-6.70, -2.91) | 103.0 |

Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed Change from baseline in ISS7 at Week 24 as response and the treatment arm, baseline ISS, presence of angioedema, region (Asia, East Europe, Latin America and Western Countries), and study (A vs C), as covariates.

Source: Adapted from Table 5 on page 27 of Applicant's E-R report (cts0083)
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; $C_{trough}$, dupilumab plasma trough concentration; ISS7, Itch Severity Score over 7 days; LS, least-squares; PD, pharmacodynamic; PK, pharmacokinetic; Q(X), quartile X (X=1, 2, 3, 4)

**Table 35. UAS7 Change from Baseline at Week 24: Observed and PK/PD Model Predicted and Placebo-Adjusted Treatment Differences by $C_{trough}$ at W24 Quartiles Group, EFC16461 Pooled Studies A and C, Study CTS0083**

| Quartile Comparison vs Placebo | Observed PD LS Mean Difference (95% CI) from ANCOVA Model | Predicted Mean Difference (95% CI) from PK/PD Model | Median $C_{trough}$ (mg/L) at Week 24 |
|---|---|---|---|
| Q1 | -5.68 (-10.84, -0.52) | -6.48 (-9.80, -3.17) | 31.4 |
| Q2 | -3.76 (-8.78, 1.26) | -7.10 (-10.68, -3.52) | 53.9 |
| Q3 | -8.02 (-13.01, -3.03) | -7.80 (-11.55, -4.05) | 75.8 |
| Q4 | -8.10 (-13.20, -3.00) | -8.69 (-12.60, -4.79) | 103.0 |

Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed Change from baseline in UAS7 at Week 24 as response and the treatment arm, baseline UAS, presence of angioedema, region (Asia, East Europe, Latin America and Western Countries), and study (A vs C), as covariates.

Source: Adapted from Table 9 on page 34 of Applicant's E-R report (cts0083)
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; $C_{trough}$, dupilumab plasma trough concentration; LS, least-squares; PD, pharmacodynamic; PK, pharmacokinetic; Q(X), quartile X (X=1, 2, 3, 4); UAS7, Urticaria Activity Score over 7 days

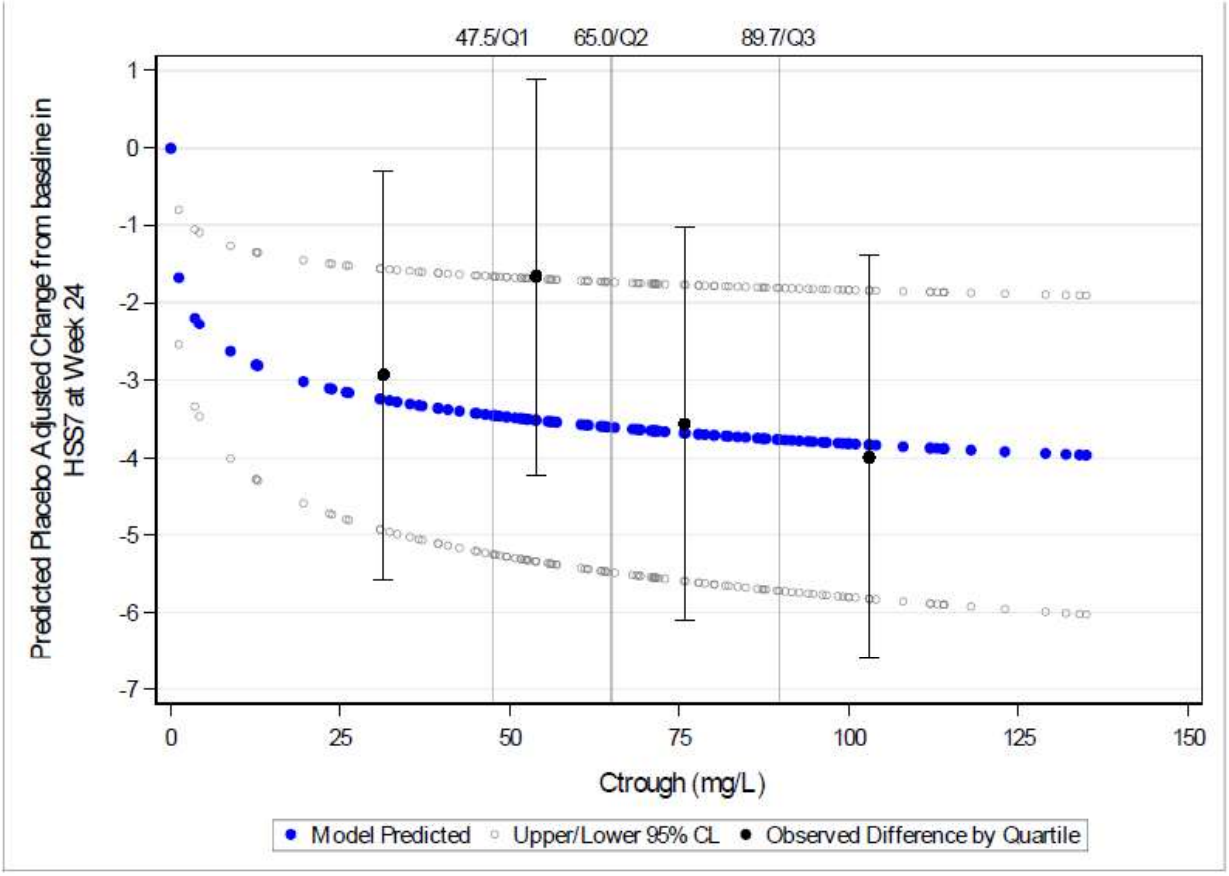
**Table 36. HSS7 Change from Baseline at Week 24: Observed and PK/PD Model Predicted Treatment Differences by $C_{trough}$ at W24 Quartiles Group, EFC16461 Pooled Studies A and C, Study CTS0083**

| Quartile Comparison vs Placebo | Observed PD LS Mean Difference (95% CI) from ANCOVA Model | Predicted Mean Difference (95% CI) from PK/PD Model | Median $C_{trough}$ (mg/L) at Week 24 |
|---|---|---|---|
| Q1 | -2.94 (-5.57, -0.30) | -3.07 (-4.76, -1.38) | 31.4 |
| Q2 | -1.66 (-4.22, 0.90) | -3.40 (-5.22, -1.57) | 53.9 |
| Q3 | -3.57 (-6.11, -1.02) | -3.72 (-5.63, -1.81) | 75.8 |
| Q4 | -3.99 (-6.59, -1.40) | -4.19 (-6.18, -2.20) | 103.0 |

Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed Change from baseline in HSS7 at Week 24 as response and the treatment arm, baseline HSS, presence of angioedema, region (Asia, East Europe, Latin America and Western Countries), and study (A vs C), as covariates.

Source: Table 13 on page 41 of Applicant's E-R report (cts0083)
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; $C_{trough}$, dupilumab plasma trough concentration; HSS7, Hives Severity Score over 7 days; LS, least-squares; PD, pharmacodynamic; PK, pharmacokinetic; Q(X), quartile X (X=1, 2, 3, 4)

**Figure 20. PK/PD Predicted Overlaying Observed and Placebo-Adjusted HSS7 Change From Baseline at Week 24 in EFC16461 Pooled Studies A and C, Study CTS0083**




Predicted based on the final PK/PD model and median baseline covariates. Observed effects were based on PD analysis of observed data at Week 24.

Source: Figure 6 on page 40 of Applicant's E-R report (cts0083)
Abbreviations: $C_{trough}$, dupilumab plasma trough concentration; HSS7, Hives Severity Score over 7 days; PD, pharmacodynamic; PK, pharmacokinetic; Q(X), quartile X (X=1, 2, 3)

*Reviewer's comment: The reviewer acknowledges that the developed PK/PD models were able to describe the overall trend of placebo-adjusted efficacy endpoints versus dupilumab exposure ($C_{trough}$), showing that higher exposure was associated with better efficacy, with efficacy reaching a plateau at higher concentrations (Q3 and Q4). However, the model-predicted values did not align with the observed data well, particularly at lower concentrations such as Q2. Overall, the exposure-efficacy relationship appeared relatively flat and not significant.*

## 15.4. Additional Biostatistical Information

**Tipping Point Analysis**

The steps of the tipping point analysis described in "Missing Data Sensitivity Analysis" subsection under section 8.1.2 are as follows:

- Step 1. Monotone missing pattern was induced by Markov Chain Monte Carlo method using PROC multiple imputation: for participants who had intermediate missing values, the intermediate missing values were imputed assuming a multivariate normal distribution over observations from all visits. Forty datasets with a monotone missing pattern were obtained using this method.
- Step2. For each of the imputed dataset with monotone missing pattern obtained in Step 1, the remaining missing data were imputed using the regression method for the monotone pattern with adjustment for covariates including response variable, intervention groups, angioedema at baseline, region, and baseline value of the corresponding endpoint. All available data in the monotone missing pattern data were used. One imputed dataset was obtained for each of the imputed dataset at Step 1. So, 40 fully imputed datasets were obtained altogether.
- Step 3. The imputed values in dupilumab group were added by a positive amount d for each imputed data set.
- Step 4. The imputed values in placebo group were subtracted by a positive amount p for each imputed data set.
- Step 5. Change from baseline in endpoint was analyzed using ANCOVA model same as the one in primary analysis. Then the SAS MIANALYZE procedure was used to generate statistical inferences by combining results from the 40 analyses using Rubin's formula.

Step 3 to Step 5 were repeated iteratively until the p-value for treatment effect of dupilumab compared to placebo estimated in Step 5 is >0.05 (reviewer's note: SAP had a typo of 0.043). LS mean difference between dupilumab and placebo in change from baseline in primary endpoint at Week 24 and the corresponding p-values were provided for each combination of shift parameters.

**Table 37. Sensitivity analysis: LS Mean Difference (p-Value) Based on Tipping Point Analysis of Change From Baseline in ISS7 at Week 24, Study C, ITT Population**

| Shift in Dupilumab Arm (L)[a] | Shift in Placebo Arm (L)[b] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0** | **-0.5** | **-1** | **-1.5** | **-2** | **-2.5** | **-3** | **-3.5** | **-4** |
| 0 | -2.54 | -2.49 | -2.43 | -2.38 | -2.32 | -2.27 | -2.21 | -2.16 | -2.10 |
| | (0.0184) | (0.0212) | (0.0244) | (0.0280) | (0.0321) | (0.0367) | (0.0420) | (0.0479) | (0.0545) |
| 0.5 | -2.51 | -2.45 | -2.40 | -2.34 | -2.29 | -2.23 | -2.18 | -2.12 | -2.07 |
| | (0.0200) | (0.0230) | (0.0264) | (0.0303) | (0.0346) | (0.0396) | (0.0452) | (0.0514) | (0.0584) |
| 1 | -2.48 | -2.42 | -2.37 | -2.31 | -2.26 | -2.20 | -2.15 | -2.09 | -2.04 |
| | (0.0217) | (0.0249) | (0.0286) | (0.0327) | (0.0374) | (0.0427) | (0.0486) | (0.0553) | (0.0627) |
| 1.5 | -2.44 | -2.39 | -2.33 | -2.28 | -2.22 | -2.17 | -2.11 | -2.06 | -2.00 |
| | (0.0236) | (0.0271) | (0.0310) | (0.0354) | (0.0404) | (0.0460) | (0.0523) | (0.0594) | (0.0672) |
| 2 | -2.41 | -2.35 | -2.30 | -2.24 | -2.19 | -2.13 | -2.08 | -2.02 | -1.97 |
| | (0.0257) | (0.0294) | (0.0336) | (0.0383) | (0.0436) | (0.0496) | (0.0563) | (0.0638) | (0.0721) |
| 2.5 | -2.38 | -2.32 | -2.27 | -2.21 | -2.16 | -2.10 | -2.05 | -1.99 | -1.94 |
| | (0.0279) | (0.0319) | (0.0364) | (0.0414) | (0.0471) | (0.0534) | (0.0605) | (0.0685) | (0.0772) |
| 3 | -2.34 | -2.29 | -2.23 | -2.18 | -2.12 | -2.07 | -2.01 | -1.96 | -1.90 |
| | (0.0303) | (0.0346) | (0.0394) | (0.0448) | (0.0508) | (0.0576) | (0.0651) | (0.0735) | (0.0827) |
| 3.5 | -2.31 | -2.26 | -2.20 | -2.15 | -2.09 | -2.04 | -1.98 | -1.93 | -1.87 |
| | (0.0330) | (0.0375) | (0.0426) | (0.0484) | (0.0548) | (0.0620) | (0.0700) | (0.0788) | (0.0886) |
| 4 | -2.28 | -2.22 | -2.17 | -2.11 | -2.06 | -2.00 | -1.95 | -1.89 | -1.84 |
| | (0.0358) | (0.0407) | (0.0462) | (0.0523) | (0.0591) | (0.0667) | (0.0752) | (0.0845) | (0.0948) |
| 4.5 | -2.25 | -2.19 | -2.14 | -2.08 | -2.03 | -1.97 | -1.92 | -1.86 | -1.81 |
| | (0.0389) | (0.0441) | (0.0499) | (0.0565) | (0.0637) | (0.0718) | (0.0807) | (0.0906) | (0.1015) |
| 5 | -2.21 | -2.16 | -2.10 | -2.05 | -1.99 | -1.94 | -1.88 | -1.83 | -1.77 |
| | (0.0422) | (0.0478) | (0.0540) | (0.0609) | (0.0687) | (0.0772) | (0.0867) | (0.0971) | (0.1085) |
| 5.5 | -2.18 | -2.12 | -2.07 | -2.01 | -1.96 | -1.90 | -1.85 | -1.79 | -1.74 |
| | (0.0458) | (0.0517) | (0.0584) | (0.0658) | (0.0739) | (0.0830) | (0.0930) | (0.1039) | (0.1159) |

| **Shift in Dupilumab Arm (L)[a]** | **Shift in Placebo Arm (L)[b]** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **0** | **-0.5** | **-1** | **-1.5** | **-2** | **-2.5** | **-3** | **-3.5** | **-4** |
| 6 | -2.15 | -2.09 | -2.04 | -1.98 | -1.93 | -1.87 | -1.82 | -1.76 | -1.71 |
| | (0.0497) | (0.0560) | (0.0631) | (0.0709) | (0.0796) | (0.0891) | (0.0996) | (0.1112) | (0.1238) |
| 6.5 | -2.11 | -2.06 | -2.00 | -1.95 | -1.89 | -1.84 | -1.78 | -1.73 | -1.67 |
| | (0.0538) | (0.0606) | (0.0681) | (0.0764) | (0.0856) | (0.0956) | (0.1067) | (0.1188) | (0.1321) |

a Imputed values in the Dupilumab group are added by the shifting variable
b Imputed values in the placebo group are decreased by the shifting variable
Abbreviations: ISS7, Itch Severity Score over 7 days; ITT, intent-to-treat; LS, least-squares

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/s/

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KELLY D STONE
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