BLA Multi-Disciplinary Review and Evaluation

<table>
<tr><td>Application Type</td><td>BLA</td></tr>
<tr><td>Application Number</td><td>761055/S-020</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date</td><td>26 Nov 2019</td></tr>
<tr><td>Received Date</td><td>26 Nov 2019</td></tr>
<tr><td>PDUFA Goal Date</td><td>26 May 2020</td></tr>
<tr><td>Division/Office</td><td>DDDP/ODE III</td></tr>
<tr><td>Review Completion Date</td><td>22 May 2020</td></tr>
<tr><td>Established/Proper Name</td><td>Dupilumab</td></tr>
<tr><td>Trade Name</td><td>DUPIXENT</td></tr>
<tr><td>Pharmacologic Class</td><td>Interleukin-4 receptor alpha antagonist</td></tr>
<tr><td>Code Name</td><td></td></tr>
<tr><td>Applicant</td><td>Regeneron Pharmaceuticals, Inc.</td></tr>
<tr><td>Dosage Form</td><td>Injection, for subcutaneous use</td></tr>
<tr><td>Applicant Proposed Dosing Regimen</td><td>Pediatric Patients
<table>
<tr><th>Body Weight</th><th>Initial Dose</th><th>Subsequent Doses[a]</th></tr>
<tr><td>15 to less than 30 kg</td><td>600 mg (two 300 mg injections)</td><td>300 mg Q4W</td></tr>
<tr><td>30 to less than 60 kg</td><td>400 mg (two 200 mg injections)</td><td>200 mg Q2W</td></tr>
<tr><td>60 kg or more</td><td>600 mg (two 300 mg injections)</td><td>300 mg Q2W</td></tr>
</table>
[a] Q2W – every other week; Q4W – every 4 weeks</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>New patient population: patients with moderate-to-severe atopic dermatitis (AD) aged ≥6 to <12 years</td></tr>
<tr><td>Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication</td><td>24079001</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s) (if applicable)</td><td>Treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable</td></tr>
<tr><td>Recommended SNOMED CT Indication Disease Term for Each Indication (if applicable)</td><td>24079001</td></tr>
</table>

Recommended Dosing Regimen	Pediatric Patients

Body Weight	Initial Dose	Subsequent Doses[a]
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

[a] Q2W – every other week; Q4W – every 4 weeks

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Matthew White
Office of Clinical Pharmacology Reviewer(s)	Luke Oh, PhD / Da Zhang, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD / Jiang Liu, PhD
Clinical Reviewer	Brenda Carr, MD
Clinical Team Leader	Snezana Trajkovic, MD
Statistical Reviewer	Carin Kim, PhD
Statistical Team Leader	Mohamed Alosh, PhD
Cross-Disciplinary Team Leader	Snezana Trajkovic, MD
Deputy Director for Safety (DDD)	Tatiana Oussova, MD, MPH
Director (DDD)	Kendall A. Marcus, MD

Additional Reviewers of Application

DMPP	Sharon R. Mills, BSN, RN, CCRP / LaShawn Griffiths, MSHS-PH, BSN, RN
OPDP	Laurie Buonaccorsi, PharmD / Matthew Falter
OSI	Jenn Sellers, MD, PhD
OSE/DMEPA	James Schlick, MBA, RPh / Millie Shah, PharmD, BCPS

DDD=Division of Dermatology and Dentistry
DMPP=Division of Medical Policy Programs
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Luke Oh, PhD	OCP/DCP III	Section: 6, 14.4	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DCP III	Section: 6, 14.4	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Reviewer	Da Zhang, PhD	OCP/DPM	Section: 6, 14.4	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Section: 6, 14.4	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Carin Kim, PhD	OB/DB III	Section: 8	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Statistical team Leader	Mohamed Alosh, PhD	OB/DB III	Section: 8	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Clinical Reviewer	Brenda Carr, MD	OII/DDD	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 14.1, 14.2	**Select one:** _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Team Leader	Snezana Trajkovic, MD	OII/DDD	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 14.1, 14.2	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Deputy Director for Safety (DDD)	Tatiana Oussova, MD, MPH	OII/DDD	Sections: 1	**Select one:** ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

Glossary

AD	atopic dermatitis
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	Adverse Event of Special Interest
BLA	biologics license application
BSA	Body Surface Area
CMQ	customized MedDRA query
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
EOT	end of treatment
E-R	exposure-response
FAS	Full Analysis Set
FDA	Food and Drug Administration
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL-4	interleukin-4
IL-4Rα	IL-4 receptor alpha
IL-13	interleukin-13
IL-13Rα1	IL-13 receptor alpha 1
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified Full Analysis Set
NRS	Numeric Rating Scale
OLE	open-label extension
PCSV	Potentially clinically significant values
PDE-4	phosphodiesterase-4
PK	pharmacokinetics
PMR	postmarketing requirement
popPK	population PK
PREA	Pediatric Research Equity Act
PT	preferred term
QTW	every other week
QT4	every four weeks
SAE	serious adverse event
SAF	safety analysis set

SAP	statistical analysis plan
sBLA	supplemental biologics license application
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SMQ	standardized MedDRA query
SU	safety update
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
Th2	T helper 2 type

1 Executive Summary

1.1. Product Introduction

Dupilumab is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) sub-unit 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. It belongs to the pharmacologic class of immunomodulators, interleukin inhibitors.

Dupilumab is marketed under the proprietary name ”DUPIXENT” and is licensed for the following indications:

- for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

In this supplemental biologics license application (sBLA), the Applicant proposes extension of the age range for the atopic dermatitis indication to allow for the “treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.”

The proposed dosing regimens are:

- 15 to less than 30 kg: 600 mg, then 300 mg every 4 weeks (Q4W)
- 30 to less than 60 kg: 400 mg, then 200 mg every other week (Q2W)

With submission of this sBLA, it is recommended that postmarketing requirement (PMR) 3183-1 be considered fulfilled. That PMR required that the Applicant:

> Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 6 years to less than 12 years of age with severe atopic dermatitis.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the effectiveness of dupilumab in the treatment of severe atopic dermatitis (AD) in children 6 to < 12 years of age, the Applicant submitted results from a single randomized, multicenter, placebo-controlled Phase 3 Study R668-AD-1652 (1652), that evaluated 2 dosing frequencies: weight-based dosing every 2 weeks (Q2W) and non-weight-based dosing every 4 weeks (Q4W). The treatment period was 16 weeks.

Study 1652 randomized 367 subjects (6 to < 12 years of age) with severe AD, defined as having an Investigator's Global Assessment (IGA) score of 4, Eczema Area and Severity Index (EASI) ≥21, and Body Surface Area (BSA) ≥15% at baseline.

The primary endpoint was the proportion of patients with IGA score of 0 to 1 (on a 5-point scale) at Week 16. Secondary endpoints included the proportion of patients with reduction of weekly average of daily worst itch score ≥4 from baseline at Week 16.

Results for primary and all secondary efficacy endpoints were statistically significant ($p<0.001$).

The Applicant provided substantial evidence of effectiveness of dupilumab for treatment of children (6 to < 12 years of age) with severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

To support the proposed treatment of children with moderate disease, the Applicant analyzed safety data for the cohort of patients from the placebo group in Study 1652 who entered the open-label extension (OLE) Study R668-AD-1434 (1434), with moderate disease. Analyses included comparison of this group to all patients with moderate disease, all patients with severe disease, and all patients in the OLE. The safety profile in subjects with moderate disease was similar to that of patients with severe disease and to the overall OLE study population.

1.3.Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dupilumab is a recombinant human immunoglobulin-G4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is marketed under the proprietary name ”DUPIXENT,” and current licensed indications include:

- the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

The Applicant proposes expansion of the atopic dermatitis (AD) indication to allow for the “treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.”

To establish the effectiveness of dupilumab in the treatment of severe AD in children 6 to < 12 years of age, the Applicant submitted results from a single randomized, multicenter, placebo-controlled Phase 3 Study 1652), that evaluated 2 dosing frequencies: weight-based dosing every 2 weeks (Q2W) and non-weight based dosing every 4 weeks (Q4W). The treatment period was 16 weeks.

Study 1652 randomized 367 subjects (6 to < 12 years of age) with severe AD, defined as having an Investigator’s Global Assessment (IGA) score of 4, Eczema Area and Severity Index (EASI) ≥21, and Body Surface Area (BSA) ≥15% at baseline. The primary endpoint was the proportion of patients with IGA score of 0 to 1 (on a 5-point scale) at Week 16. Secondary endpoints included the proportion of patients with reduction of weekly average of daily worst itch score ≥4 from baseline at Week 16.

Results for primary and all secondary efficacy endpoints were statistically significant ($p<0.001$).

The Applicant comprehensively assessed the safety of dupilumab in patients 6 to <12 years old with severe AD. The safety evaluations were adequate in types and frequency to identify local and systemic treatment-emergent adverse events (TEAEs). In addition to routine safety assessments, the safety evaluations reflected what is known about dupilumab (e.g., mechanism of

action; protein product), its route of administration (subcutaneous), and its safety profile in the adolescent and adult AD populations (e.g., conjunctivitis). Pivotal Study 1652 provided the primary safety data.

Dupilumab was well tolerated in the development program. Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo, consistent with the known safety profile for dupilumab in the adolescent and adult AD populations. There were no systemic hypersensitivity reactions in patients 6 to <12 years of age that implicated dupilumab. TEAES were most commonly reported in the Infections and infestations system organ class (SOC), with the highest overall percentage being in the placebo group (51%). Nasopharyngitis was the most commonly reported event in this SOC and was reported at similar or higher frequencies in the dupilumab groups compared to the placebo group: placebo: 7%, Q4W: 13%, and Q2W: 7%. No new safety concerns were identified in children 6 to <12 years of age.

To support the proposed inclusion of moderate disease in the indication statement, the Applicant provided safety data for the cohort of patients from the placebo group in Study 1652, who entered the OLE Study 1434 with moderate disease (baseline IGA of 3). Analyses included comparison of this group to all patients with moderate disease, all patients with severe disease, and all patients in the OLE. The safety profile in subjects with moderate disease was similar to that of patients with severe disease and to the overall OLE study population.

The medical officer concludes that the Applicant has established that the benefits of dupilumab for treatment of patients 6 to < 12 years of age with moderate-to-severe atopic dermatitis, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals. The prevalence of AD in the United States in individuals 4-8 years of age has been reported	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals, AD persists into the adult years. AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists. AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.	skin changes may distort the appearance of the skin. Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning. Sleep disturbance in the affected individual may also disrupt the sleep of family members. Affected children may also experience depression, anxiety, social isolation, and impaired psychosocial functioning.
Current Treatment Options	For the Applicant's target population, the only available Food and Drug Administration (FDA)-approved systemic treatment is corticosteroids. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment. Phototherapy is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children. Its drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage,	The medical need of children (6 to < 12 years) with moderate-to-severe AD is not currently being adequately met by available therapies. Approved or licensed systemic treatment options are extremely limited for this population. Approval of dupilumab would represent an important addition to the treatment options for children with moderate-to-severe AD that is not manageable by topical therapies. In the medical officer's opinion, dupilumab would considerably advance the state of the treatment armamentarium for these patients. It would represent the first systemic product

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	approved or licensed for treatment of AD in this population since corticosteroids. Dupilumab would represent a safe and effective alternative to corticosteroids, the only approved systemic treatment for this indication and a treatment that is generally not recommended for treatment of AD. Additionally, dupilumab would represent a safe and effective alternative to the several systemic immunomodulating agents that are used off-label for treatment of this population.
Benefit	To establish the effectiveness of dupilumab in the treatment of severe AD in children 6 to < 12 years of age, the Applicant submitted results from a single randomized, multicenter, placebo-controlled, Phase 3 Study 1652, that evaluated 2 dosing frequencies: weight-based every 2 weeks (Q2W) and non-weight-based dosing every 4 weeks (Q4W). The treatment period was 16 weeks. Study 1652 randomized 367 subjects (6 to < 12 years of age) with severe AD, defined as having an IGA score of 4, EASI ≥21, and BSA ≥15% at baseline. The primary endpoint was the proportion of patients with IGA score of 0 to 1 (on a 5-point scale) at Week 16. Secondary endpoints included the proportion of patients with reduction of weekly average of daily worst itch score ≥4 from baseline at Week 16. Results for primary and all secondary efficacy endpoints were statistically significant (p<0.001).	The medical officer concludes that the submitted evidence has met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that dupilumab is effective for treatment of the target AD population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The Applicant comprehensively assessed the safety of dupilumab in patients 6 to <12 years old with severe AD. The safety evaluations were adequate in types and frequency to identify local and systemic TEAEs. In addition to routine safety assessments, the safety evaluations reflected what is known about dupilumab (e.g., mechanism of action; protein product), its route of administration (subcutaneous (SC)), and its safety profile in the adolescent and adult AD populations (e.g., conjunctivitis). Pivotal Study 1652 provided the primary safety data (n= 362). Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo, consistent with the known safety profile for dupilumab in the adolescent and adult AD populations. There were no systemic hypersensitivity reactions in patients ≥6 to <12 years of age that implicated dupilumab. No new safety concerns were identified in children 6 to <12 years of age. To support the proposed inclusion of moderate disease in the indication statement, the Applicant provided safety data for the cohort of patients from the placebo in Study 1652 who entered the OLE Study 1434 with moderate disease (baseline IGA of 3). Analyses included comparison of this group to all patients with moderate disease, all patients with severe disease, and all patients in the OLE. The safety profile in subjects with moderate disease was similar to that of patients with severe disease and to the overall OLE study population.	The size of the safety database and the scope of the safety analyses were sufficient to characterize the safety profile of dupilumab in the target population. The safety evaluation identified no new signals or concerns; the safety profile in children 6 to <12 years of age was similar to that observed in adolescents and adults with AD. Dupilumab was generally well-tolerated by children 6 to <12 years of age with moderate-to-severe AD.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Section 8.1.2
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	Section 8.1.2
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Atopic dermatitis is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. In 60% of patients, the onset of disease is in the first year of life, with onset by the age of 5 years in approximately 85% of affected individuals.[1] Shaw et al. reported the prevalence of AD in the United States in individuals 4-8 years of age to be 10.63% and in those 9-12 years of age to be 9.96%.[2] For 10-30% of individuals, AD persists into the adult years.[3]

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In patients older than 2 years of age, the presentation is similar to that in adults. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, and volar aspects of the wrists.[1] AD may be generalized.

The pathogenesis involves a complex interplay of genetic, immunological, and environmental factors that result in abnormal skin barrier function and immune system dysfunction.[3] Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum which permits the penetration of environmental allergens.[4] The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[4]

Acute AD is associated with cytokines produced by T helper 2 type (Th2) cells (as well as other T-cell subsets and immune elements).[4] These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in

---

[1]Weston WL and Howe W. Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis. Dellavalle RP, Levy ML, Fowler J, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 15, 2020).

[2] Shaw TE et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. J Invest Dermatol. (2011) 131, 67–73.

[3]Eichenfield LF et al. Guidelines of care for the management of atopic dermatitis Section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 2014;70:338-51.

[4] Leung DYM, Guttman-Yassky E. Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches. J Allergy Clin Immunol 2014;134:769-79.

Th2 inflammation.[5] IL-4 has been shown to stimulate immunoglobulin E (IgE) production from B cells.[6] IL-13 expression correlates with disease severity and flares.[4] IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα, forming a signaling complex.[6] IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases.[6] Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4Rα subunit.[7]

Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.[1,3] Comorbidities involving the eyes include atopic keratoconjunctivitis,[1] a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD.[8] Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. The disruption in sleep could have carryover effects to impact behavior and neurocognitive functioning.[9] Sleep disturbance in the affected individual may also disrupt the sleep of family members, impacting the quality of life for all.[9] Affected children may experience depression and anxiety,[10] social isolation,[11] and impaired psychosocial functioning.[1, 11]

Patients with AD are predisposed to colonization or infection by microbes, particularly *Staphylococcus aureus* and herpes simplex virus. The susceptibility to *S. aureus* is related to multiple factors, including the abnormal skin barrier function and the production of serine proteases that degrade the skin barrier.[4]

The most common laboratory finding is an elevated IgE.[2] Up to 80% of the AD population has elevated IgE, often with accompanying eosinophilia.[1] IgE levels may fluctuate with disease severity; however, some patients with severe AD present with normal IgE levels.[1]

---

[5] Bao K and Reinhardt RL. The differential expression of IL-4 and IL-13 and its impact on type-2 Immunity.Cytokine 75 (2015) 25-37.
[6] May RD, Fung M. Strategies targeting the IL-4/IL-13 axes in disease. Cytokine 2015;75:89-116.
[7] DUPIXENT package insert.
[8] Hamrah P and Dana R. Atopic keratoconjunctivitis. Trobe J, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 16, 2020).
[9] Camfferman D et al. Eczema and sleep and its relationship to daytime functioning in children. Sleep Medicine Reviews 14 (2010) 359–369.
[10] Yaghmaie P et al. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.
[11] Drucker AM et al. The burden of atopic dermatitis: summary of a report for the National Eczema Association. J Invest Dermatol (2017) 137, 26-30.

2.2.Analysis of Current Treatment Options

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

Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[12] Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment.[12] Labels for systemic corticosteroids do not specify any limitations on the age of indication.

Topical corticosteroids (TCS) represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[13] Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

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

[12] Sidbury et al. Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol 2014;71:327-49.
[13] Eichenfeld et al. Guidelines of care for the management of atopic dermatitis. Section 1. Management and treatment with topical therapies. J Am Acad Dermatol 2014;71:116-32.

ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD).

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

Dupilumab is currently indicated for use in patients > 12 years of age with AD. The Applicant proposes broadening use of dupilumab to allow for the treatment of patients > 6 years of age who have failed topical therapies or when those therapies are inadvisable. Specifically, the Applicant proposes dupilumab for "patients 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable." FDA-approved systemic treatment options are extremely limited for this patient population, consisting only of corticosteroids; their limitations have been discussed above.

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including children.[12] However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts.[12] However, long-term risks from phototherapy treatment of AD in children have not been evaluated.[12] Narrowband UVB therapy may be considered first-line because of the safety profile relative to psoralen + UVA (PUVA).[12]

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

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Initial licensure for dupilumab was "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" on March 28, 2017. Licensure for the AD indication was extended to treatment of patients aged 12 and older on March 11, 2019 (S-012) ("treatment of patients aged 12 and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable").

Dupilumab is also licensed for the following indications:

- As an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
- As an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant has an agreed initial pediatric study plan with the letter of agreement dated November 10, 2015 which covers pediatric age cohorts down to 6 months.

The approval letter for the original biologics license application (BLA) (approval date: March 28, 2017) listed several pediatric assessments, required under the Pediatric Research Equity Act (PREA). Those PREA PMRs included the following:

3183-2 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in subjects 6 years to less than 12 years of age with severe atopic dermatitis.

3183-3 Conduct an open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis.

The pediatric study requirement for ages less than 6 months was waived because necessary studies are impossible or highly impracticable. This is because dupilumab is indicated for the treatment of moderate-to-severe atopic dermatitis in patients whose disease is not adequately controlled with topical prescription therapies or for whom those therapies are not advisable, and it will be impractical to make this determination in patients younger than 6 months of age.

The open-label study to address PMR 3183-3 is ongoing [R668-AD-1434 (1434)]; the Applicant submitted analyses of data only pertaining to subjects 6 to < 12 years in the supplement that is the subject of this review. Data from Study 1434 for subjects 12 to < 18 years were submitted in S-012, under which dupilumab was licensed for treatment of AD in adolescents.

The Applicant was granted Breakthrough Therapy designation of dupilumab for the treatment of moderate-to-severe [12 to <18 years of age] and severe [6 months to <12 years of age] atopic dermatitis in pediatric patients who are not adequately controlled with, or who are intolerant to topical medication on October 14, 2016.

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

4.1. Office of Scientific Investigation (OSI)

Study R668-AD-1652, entitled "A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab Administered Concomitantly with Topical Corticosteroids in Patients, ≥6 Years to <12 Years of Age, with Severe Atopic Dermatitis" was the pivotal study and a covered study.

Two sites were selected for inspection. The sites were chosen based on large enrollments, treatment effect size, protocol deviations, and no prior inspection histories.

Jeffrey Leflein, M.D., Ypsilanti, MI; Site #840328:

This site screened ten subjects and enrolled eight, all of whom completed the study.

The inspector reviewed the following: study records for all ten subjects study monitoring, ethics committee approval/communications, financial disclosures, FDA 1572s, and study staff background/training. The inspector verified all primary and secondary efficacy data points against the data listings provided by the Applicant and noted no discrepancies. Inspectors found no evidence of under-reporting of adverse events.

Jessica Kaffenberger, M.D. Gahanna, OH; Site #840311:

This site screened 12 subjects and enrolled 11, 9 of whom were randomized (2 subjects withdrew consent), and all 9 completed the study.

The inspector reviewed the informed consent forms for all 12 screened subjects and other study records for all 11 enrolled subjects. These records included, but were not limited to, Independent Review Board approvals, training records, delegation of authority logs, financial disclosures, drug accountability, randomization scheme, study eligibility criteria, medical

histories, physical examinations, progress notes, topical corticosteroid dispensing log, concomitant medications, the primary and the secondary efficacy endpoint data, adverse events, and protocol deviations. The inspector verified all primary and secondary efficacy data points against the data listings provided by the Applicant and noted no discrepancies.

Overall assessment of the inspections: Inspectors concluded that the study appeared to have been conducted adequately at both sites, and the data generated by these sites appeared acceptable to support the indication.

4.2.Product Quality

A Product Quality review was not required for this supplement.

4.3.Clinical Microbiology

A clinical microbiology review was not required for this supplement.

4.4.Devices and Companion Diagnostic Issues

A device review was not required for this supplement.

5 Nonclinical Pharmacology/Toxicology

A nonclinical review was not required for this supplement.

6 Clinical Pharmacology

6.1.Executive Summary

In this sBLA, the Applicant has proposed to extend the currently approved age range for the AD indication to include children ≥6 to <12 years of age. The Applicant has proposed body weight-tiered dosing regimens in the pediatric population with AD as shown below:

Table 1. Body Weight Dosing Regimen, Pediatric Population

Body Weight of Patient	Initial Dose	Subsequent Doses
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 kg to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

For the initial dose, administer each of the 2 DUPIXENT injections at different injection sites.

To support the indication in subjects down to 6 years of age, the Applicant has submitted a Phase 3 study report (R668-AD-1652), an open-label extension study report (R668-AD-1434), a Phase 2 pharmacokinetics (PK) study report (R668-AD-1412) and population PK analysis (R668-PM-19142-SR-01V1). Clinical pharmacology review focuses on Phase 3 study which assessed efficacy, safety, and PK of dupilumab with concomitant TCS in subjects with severe AD aged ≥6 to < 12 years, population PK analyses report and exposure response analyses. Phase 2 PK study evaluated 2 mg/kg and 4 mg/kg doses in subjects with AD, which was an exploratory study to determine the doses and dosing regimen for Phase 3 trials. The observed PK results and PK simulations in relation to efficacy and safety were utilized to support the proposed dosing regimens in children with AD.

6.1.1. Recommendations

From a clinical pharmacology standpoint, the totality of data provided in this sBLA support the approval of the proposed target population down to 6 years of age and the proposed dosing regimens.

6.1.2. Postmarketing Requirement and Commitments

None.

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant evaluated PK data in 3 groups which were based on weight and dosing regimen and conducted a cross-study comparison to support the dupilumab treatment down to subjects 6 years of age with severe AD. The PK data from this study demonstrated that steady state was achieved prior to the time of primary endpoint assessment (i.e., Week 16); the Q2W dosing regimens achieved steady state by Week 8 and the Q4W dosing regimen achieved state by Week 12. At Week 16, mean ± standard deviation (SD) C_{trough} of dupilumab in subjects <30 kg with 300 mg Q4W regimen was 98.7 ± 33.2 mg/L, which was comparable to 86.0 ± 34.6 mg/mL in subjects ≥30 kg 200 mg Q2W regimen (Table 2 and Figure 1). Mean ± SD C_{trough} of dupilumab in subjects ≥30 kg with 300 mg Q4W regimen and in subjects <30 kg with 100 mg Q2W regimen were 53.9 ± 25.7 mg/L and 62.6 ± 32.3 mg/L, respectively (Table 2 and Figure 1).

Serum dupilumab concentrations in subjects 15 kg to <30 kg with 300 mg Q4W and in subjects ≥30 kg with 200 mg Q2W regimen were similar to the dupilumab concentration observed by the approved 300 mg Q2W regimen in adults and greater than the dupilumab concentration observed by the 100 mg Q2W regimen in pediatric subjects <30 kg and by the 300 mg Q4W regimen in pediatric subjects ≥30 kg (Figure 2). This data provided support towards selection of

the dosing regimen of 300 mg Q4W in subjects 15 kg to <30 kg and 200 mg Q2W in subjects ≥30 kg.

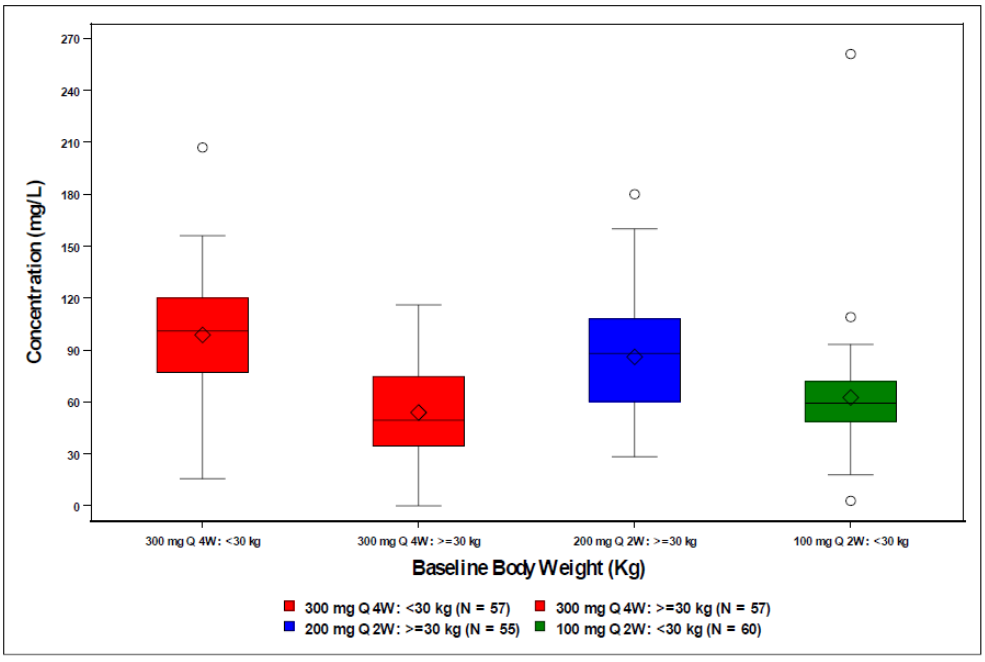
Table 2. Summary of Serum Dupilumab Concentration at Week 16 by Body Weight

	Concentrations of Functional Dupilumab in Serum (mg/L)									
	Placebo (N=116)		300 mg Q4W (N=114)		100 or 200 mg Q2W (N=117)		200 mg Q2W (N=56)		100 mg Q2W (N=61)	
Body Weight Category (Mean)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
<30 kg (23.9)	57	0 (0)	57	98.7 (33.2)	61	61.5 (33.1)	1	0 (---)	60	62.6 (32.3)
>=30 kg (39.3)	59	0 (0)	57	53.9 (25.7)	56	84.5 (36.2)	55	86.0 (34.6)	1	0 (---)

N = Number of patients contributing to each category, n = Number of samples per category; SD = Standard deviation, ET = Early termination, EOS = End of study
Note: Unscheduled Visits, ET and EOT/EOS are mapped to scheduled week based on analysis visit window.

Source: Clinical pharmacology report R668-AD-1652-CP-01V1

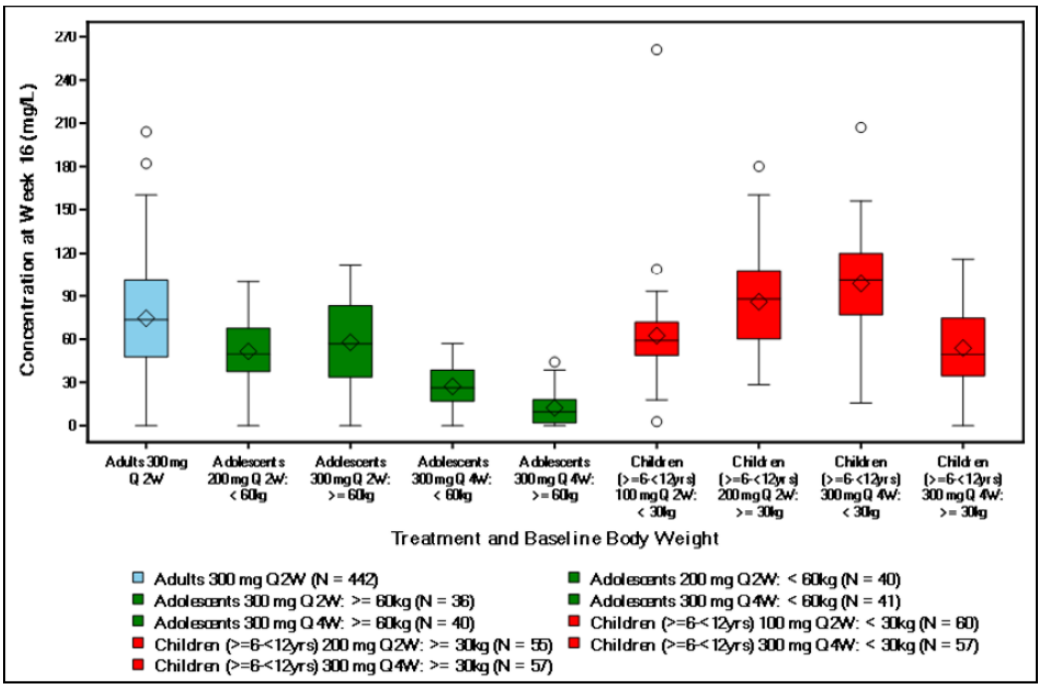
Figure 1. Serum Dupilumab Concentration at Week 16 by Treatment and Baseline Body Weight Category in Pediatric Subjects (≥6 to <12 Years of Age)



Note: Concentrations below the LLOQ were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); 2 Subjects with a baseline body weight greater than 30 Kg and less than 30 Kg and assigned to 100 Q2W and 200 Q2W respectively were excluded from analysis.
Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR],with IQR = Q3 - Q1.

Source: Figure 3 in Clinical Pharmacology report R668-AD-CP-01V1

Figure 2. Serum Dupilumab Concentration at Week 16 by Subject Age Group, Treatment and Baseline Body Weight Category



Note: BLQ values were set to 0.

Source: Figure 2 in 2.5 Clinical Overview

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The efficacy, safety, and PK results in Phase 3 trial R668-AD-1652 appear to support the acceptability of the proposed dosing regimens for subjects ≥6 to < 12 years of age:

Table 3. Proposed Dosing Regimens for Subjects ≥6 to <12 Years of Age

Body Weight	Initial Dose	Subsequent Doses
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

Abbreviations: Q2W = every other week, Q4W = every 4 weeks

Therapeutic Individualization

Body weight has been identified as a significant covariate on dupilumab PK; dupilumab concentrations were lower in subjects with higher body weight at a given dose. The efficacy and safety data from Phase 3 trial R668-AD-1652 as well as the cross-study and cross age-groups exposure-response (E-R) analyses support the proposed body weight-tiered dupilumab dosing regimens in children with AD.

Outstanding Issues

There are no outstanding issues that would preclude the approval of dupilumab for the treatment of AD in children ≥6 to <12 years of age from a Clinical Pharmacology perspective.

6.3.Comprehensive Clinical Pharmacology Review

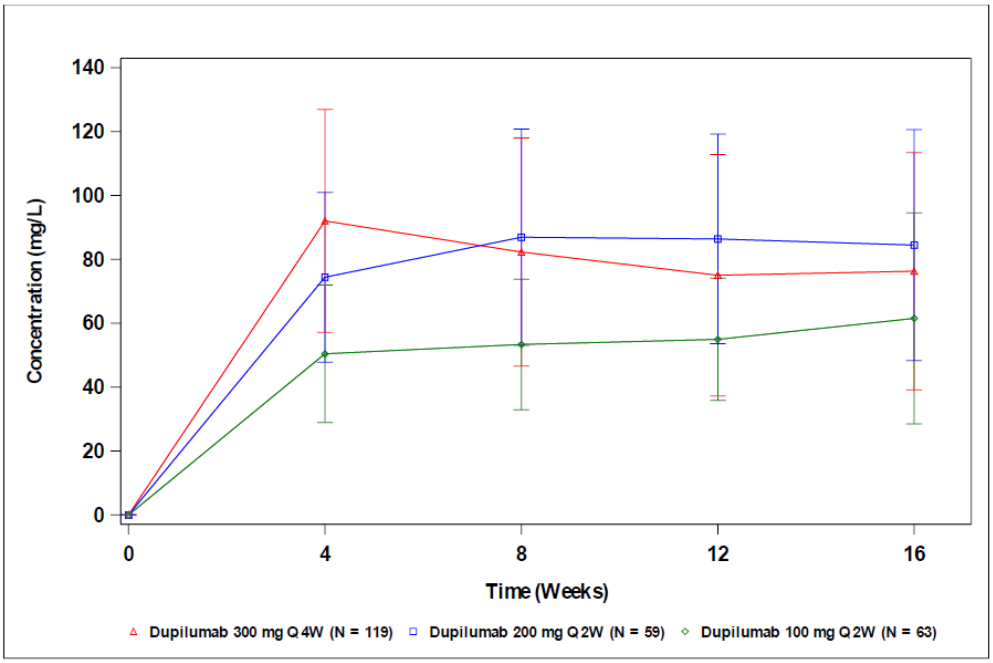
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics

The PK of dupilumab has been previously characterized in healthy subjects, adult and adolescent subjects with AD, and adult and adolescent subjects with asthma. Dupilumab exhibited nonlinear target-mediated PK with exposure increasing in a greater than dose-proportional manner.

The serum dupilumab concentrations observed in Study R688-AD-1652 are shown in Figure 3. The PK results showed that the steady state was achieved by Week 8 across the tested dosing regimens. At Week 16, the mean ± SD trough serum dupilumab concentrations were 76.3 ± 37.2 mg/L, 84.5 ± 36.2 mg/L, and 61.5 ± 33.1 mg/L for the 300 mg Q4W, 200 mg Q2W, and 100 mg Q2W dosing regimens, respectively.

Figure 3. Mean (±SD) Trough Concentration of Serum Dupilumab by Time and Treatment Group



N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were set to 0.

Source: Figure 1 in Clinical pharmacology report R668-AD-1652-CP-01V1

Immunogenicity

None of subjects in 300 mg Q4W group treatment exhibited anti-drug antibody (ADA) positivity and a total of 6 subjects (5.1%) in 100 mg Q2W, and 3 subjects in 200 mg Q2W groups exhibited ADA positivity with low titer (Table 4). Two subjects in placebo group showed ADA positivity (Table 4). Two subjects (3.3%) in 100 mg Q2W group and 1 subject (1.8%) in 200 mg Q2W group exhibited neutralizing antibody positivity (Table 5). There was no clinically meaningful impact of immunogenicity on serum dupilumab concentrations. It should be noted that the incidence of immunogenicity observed in this study in children ≥6 to <12 years of age is similar to adults.

Table 4. ADA Category and Maximum Titer Category

Maximum Titer Category	Placebo n (%)	Dupilumab					
		300 mg Q4W n (%)	100 or 200 mg Q2W n (%)	200 mg Q2W n (%)	100 mg Q2W n (%)	All Active Doses n (%)	Overall n (%)
ADA Analysis Set	116 (100%)	114 (100%)	118 (100%)	57 (100%)	61 (100%)	232 (100%)	348 (100%)
Negative*	114 (98.3%)	114 (100%)	112 (94.9%)	54 (94.7%)	58 (95.1%)	226 (97.4%)	340 (97.7%)
Treatment-Boosted Response	0	0	0	0	0	0	0
Treatment-Emergent Response	2 (1.7%)	0	6 (5.1%)	3 (5.3%)	3 (4.9%)	6 (2.6%)	8 (2.3%)
TE & TB							
Low (<1,000)	2 (1.7%)	0	6 (5.1%)	3 (5.3%)	3 (4.9%)	6 (2.6%)	8 (2.3%)
Moderate (1,000 to 10,000)	0	0	0	0	0	0	0
High (>10,000)	0	0	0	0	0	0	0

n = Number of patients contributing to each category; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre+) responses.

Source: Table 9 in Clinical pharmacology report R668-AD-1652-CP-01V1

Table 5. Summary of ADA Status and Neutralizing Ab (NAb) Status

ADA Status; NAb Status	Placebo	Dupilumab			
		300 mg Q4W	100 or 200 mg Q2W n (%)	200 mg Q2W	100 mg Q2W
NAb Analysis Set	116 (100%)	114 (100%)	118 (100%)	57 (100%)	61 (100%)
Pre+; NAb-	3 (2.6%)	4 (3.5%)	2 (1.7%)	1 (1.8%)	1 (1.6%)
Pre+; NAb+	0	0	0	0	0
TE & TB; NAb-	2 (1.7%)	0	3 (2.5%)	2 (3.5%)	1 (1.6%)
TE & TB; NAb+	0	0	3 (2.5%)	1 (1.8%)	2 (3.3%)

N = Number of patients contributing to each category; Pre+ = Pre-existing immunoreactivity; TE = Treatment-emergent; TB = Treatment-boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay

Source: Table 10 in Clinical pharmacology report R668-AD-1652-CP-01V1

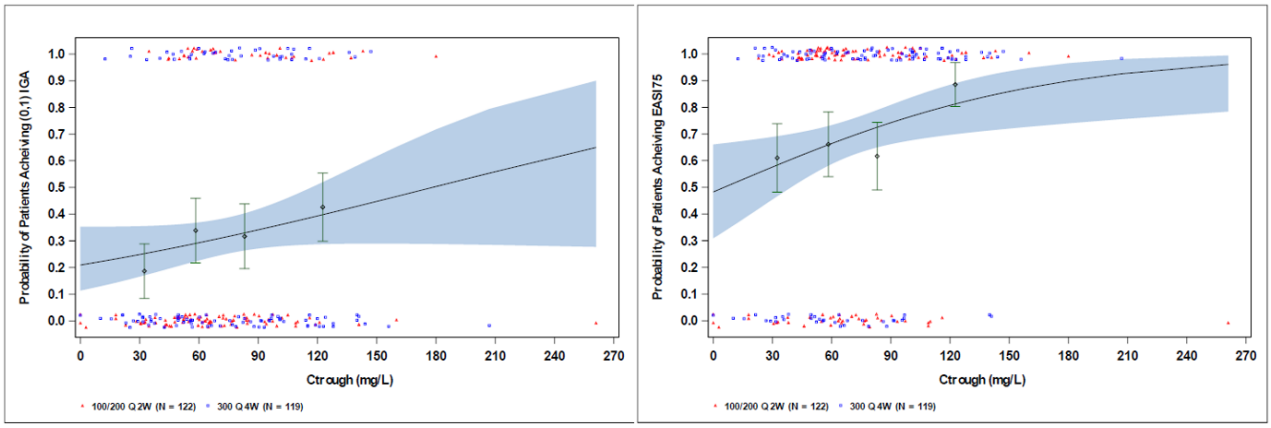
6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. the overall efficacy data from the Phase 3 trial R668-AD-1652 provide evidence that dupilumab is effective for the treatment of children with AD. See Section 8 of this multi-

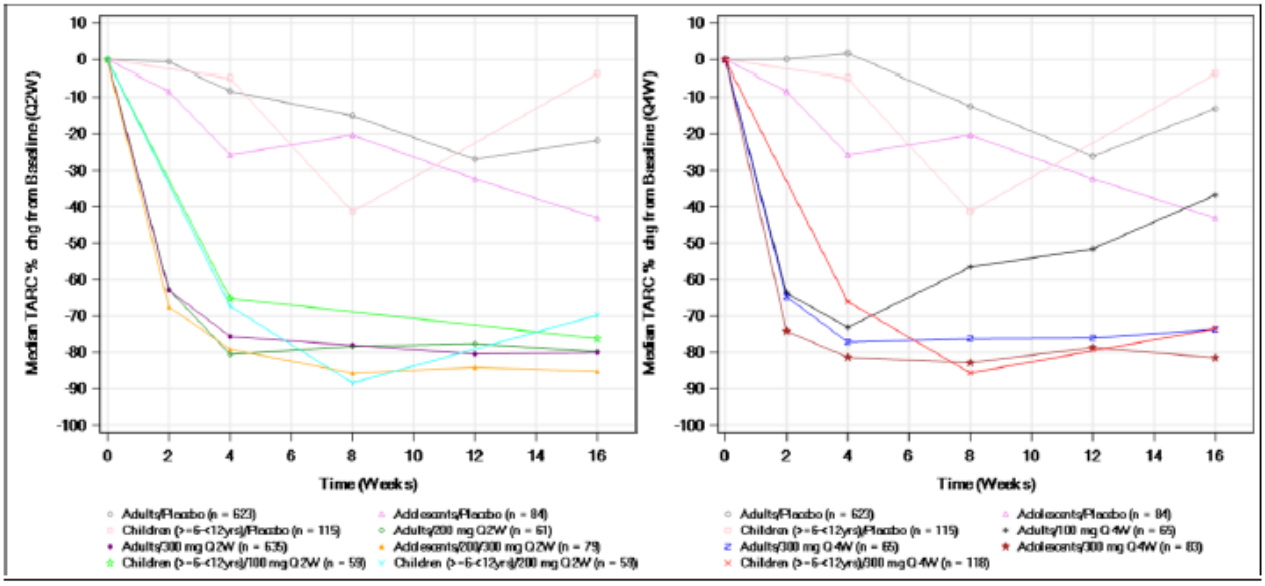
disciplinary review for details of the study design and efficacy results of the Phase 3 trial. The E-R relationships for efficacy provide supportive evidence of effectiveness (Figure 4). In children with AD, the E-R relationships revealed increasing drug effects with increasing dupilumab trough concentration in serum. The pharmacodynamic data on thymus and activation-regulated chemokine reduction also provide supportive evidence of effectiveness (Figure 5).

Figure 4. Logistic Regression Relating Probability of Patients Achieving an (0,1) IGA Score (Panel A) or EASI-75 (Panel B) With Dupilumab Trough Concentrations at Week 16 in Children with Severe AD



Among 241 children with AD included in the E-R analysis, the percentage of patients achieving an IGA score of 0 or 1 or a 75% reduction in EASI score was higher in quartiles of higher dupilumab concentrations. The logistic regression analysis also identified dupilumab concentration at Week 16 and disease severity (baseline EASI total score) as significant covariates on both IGA (0,1) and EASI-75.
The figure shows mean Regression line - black, confidence area around regression line - blue. Non-responders (0) and responders (1) individual concentration values are jittered and represented at the bottom and top of the figure respectively. Means of response and confidence intervals (green vertical lines) around the means are presented in the figures by exposure quartiles, these vertical lines are placed at the means of interquartile ranges of an exposure on the x-axis.
Source: Figures 7, 8, Module 2.7.2 Summary of Clinical Pharmacology Studies

Figure 5. Comparison of the Median Percentage Change From Baseline in TARC by Dupilumab Treatment Group (Left Panel: Q2W vs. Placebo; Right Panel: Q4W vs. Placebo) Across Studies R668-AD-1021 (Adults), R668-AD-1334 (Adults), R668-AD-1416 (Adults), R668-AD-1526 (Children ≥6 to <12 Years of Age)



Abbreviations: n=Number of patients.
Common Nominal Time-points up to Week 16 are used for Analysis.
Adolescents: R668-AD-1526; Children (>=6 to <12 Years): R668-AD-1652; Adults: R668-AD-1021, R668-AD-1416, R668-AD-1334, R668-AD-1424
Placebo subjects from studies R668-AD-1021, R668-AD-1526 and R668-AD-1652 contribute to both panels, while the placebo subjects from the other studies only contribute to the Q2W panel since subjects in Q4W regimen are only in studies R668-AD-1021, R668-AD-1526 and R668-AD-1652.
n for Placebo is a sum of all placebo subjects from the age group contributing to both panels.
(Source: Figures 4., Module 2.7.2 Summary of Clinical Pharmacology Studies)

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

Yes. The efficacy and safety data from Phase 3 trial R668-AD-1652 overall support that the proposed body weight-tiered dosing regimens are appropriate for the AD indication in children ≥6 to <12 years. See Section 7 of this multi-discipline review for details of efficacy and safety results of the Phase 3 trial. The PK and E- R analysis results further support the proposed body weight-tiered dose of 300 mg Q4W for children ≥15 to <30 kg and 200 mg Q2W for children ≥30 kg.

- In Phase 3 trial R668-AD-1652, children ≥15 to <30 kg receiving 300 mg Q4W regimen and children ≥30 kg receiving 200 mg Q2W regimen achieved similar dupilumab concentrations at Week 16 (Figure 1), across study and across age groups. However, dupilumab exposure comparison based on popPK model simulations (Table 6) indicated that the dupilumab exposure (C_{trough}, C_{max} and AUC) with dosing regimen 300 mg Q4W in children <30 kg is higher than those predicted in adolescents (200/300 mg Q2W) and

adults (300 mg Q2W), whereas, the dupilumab exposure with dosing regimen 100 mg Q2W in children<30 kg is more comparable to the exposure predicted in adolescents and adults at approved doses. In order to address this drug exposure discrepancy, justifications based on E-R relationship comparisons among children, adolescents, and adults for efficacy and safety were conducted for the proposed dosing regimen of 300 mg Q4W for children ≥15 to <30 kg and ≥6 to <12 years of age.

- The probability of E-R relationships achieving IGA 0, 1, and EASI-75 versus C_{trough} at Week16 by age groups (Figure 30 and Figure 31) demonstrated that the mean C_{trough} exposure achieved by the proposed 300 mg Q4W regimen in children < 30 kg lies closer to the plateau of the respective E-R relationship compared to the 100 mg Q2W regimen which achieved lower mean Ctrough at steady-state.
- Logistic regression relating probability of children aged ≥6 to <12 years developing conjunctivitis with observed dupilumab Ctrough at Week 16 (Figure 8) showed a slight trend for an inverse E-R relationship with the highest probability of developing conjunctivitis observed at lower drug concentrations and the lowest probability at higher drug concentrations. This observation is consistent with the safety findings showing that the 100 mg Q2W dosing regimen (lower C_{trough} exposure) had a higher incidence of conjunctivitis events.

Positive E-R relationship for efficacy was observed in children with AD treated with dupilumab (Figure 4).

- The most commonly reported adverse event (AE) observed in the children pivotal Study R668- AD-1652 was conjunctivitis. In children ≥6 to < 12 years of age who weighed <30 kg, there was a trend towards a slightly higher number of TEAEs in the 100 mg Q2W dosing regimen as compared to 300 mg Q4W dosing regimen, driven by a higher incidence of conjunctivitis events in the 100 mg Q2W arm. The overall TEAE profile was comparable between the 300 mg Q4W dosing regimen and the approved dosing regimens in adolescents and adults. (Figure 8).

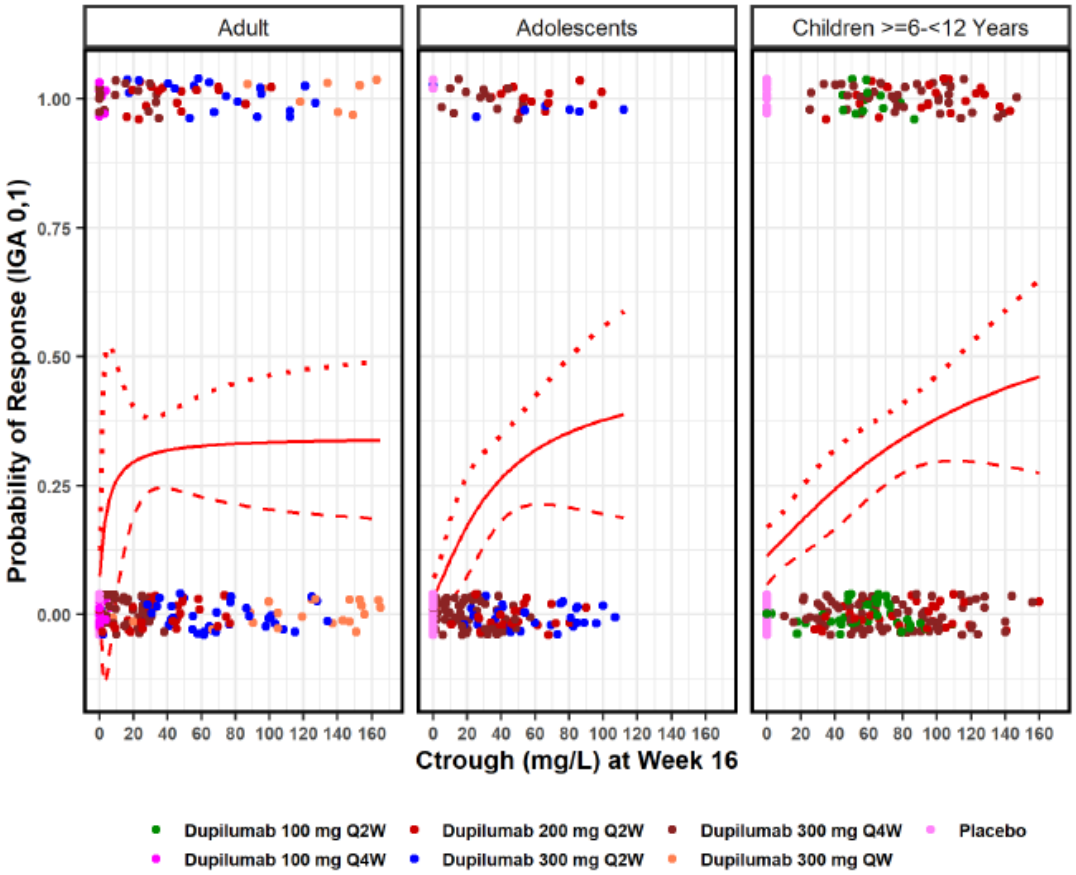
Table 6. Individual Predicted Exposure to Dupilumab in Children, Adolescents, and Adults at Steady State by Treatment, Age, and Weight Categories

Variable / Age Group			Treatment																			
			100 mg Q2W SC				200 mg Q2W SC				300 mg Q2W SC				300 mg Q4W SC				300 mg QW SC			
			Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95
CtroughSS (mg/L)	6-11 yo	1) <30 kg	59.6	28.3	59.0	93.3									79.8	40.1	77.5	128				
		2) >=30 kg					89.1	36.7	83.4	140					44.4	10.8	41.1	78.5				
	12-17 yo	3) <60 kg					54.9	26.5	52.6	84.9					23.3	3.74	21.5	43.6				
		4) >=60 kg									56.7	17.7	55.0	102	9.47	0.000784	6.68	26.6				
	Adults	5) All weights									69.6	24.7	67.0	122					181	85.1	175	295
CmaxSS (mg/L)	6-11 yo	1) <30 kg	86.8	48.6	86.6	125									175	111	175	241				
		2) >=30 kg					126	62.3	124	184					110	54.5	111	157				
	12-17 yo	3) <60 kg					82.4	46.6	80.2	119					71.8	45.2	70.1	106				
		4) >=60 kg									85.5	42.7	80.5	133	43.4	20.9	41.8	69.6				
	Adults	5) All weights									94.5	42.4	91.9	153					197	96.7	191	314
Monthly AUC (mg.day/L)	6-11 yo	1) <30 kg	2092	1112	2075	3084									3529	2117	3499	5076				
		2) >=30 kg					3075	1388	2935	4601					2139	876	2039	3276				
	12-17 yo	3) <60 kg					1965	1024	1892	2905					1310	606	1275	2005				
		4) >=60 kg									2037	882	1912	3309	718	251	638	1349				
	Adults	5) All weights									2353	975	2277	3935					5350	2573	5183	8596
Weight (kg)	6-11 yo	1) <30 kg	24.0	18.6	24.0	29.2									24.0	18.6	24.0	29.2				
		2) >=30 kg					39.2	30.5	36.2	58.5					39.2	30.5	36.2	58.5				
	12-17 yo	3) <60 kg					49.2	35.4	51.3	58.3					49.2	35.4	51.3	58.3				
		4) >=60 kg									80.4	60.0	75.4	117	80.4	60.0	75.4	117				
	Adults	5) All weights									76.5	52.0	74.6	108					76.5	52.0	74.6	108

Note: The steady-state AUC is calculated per week.

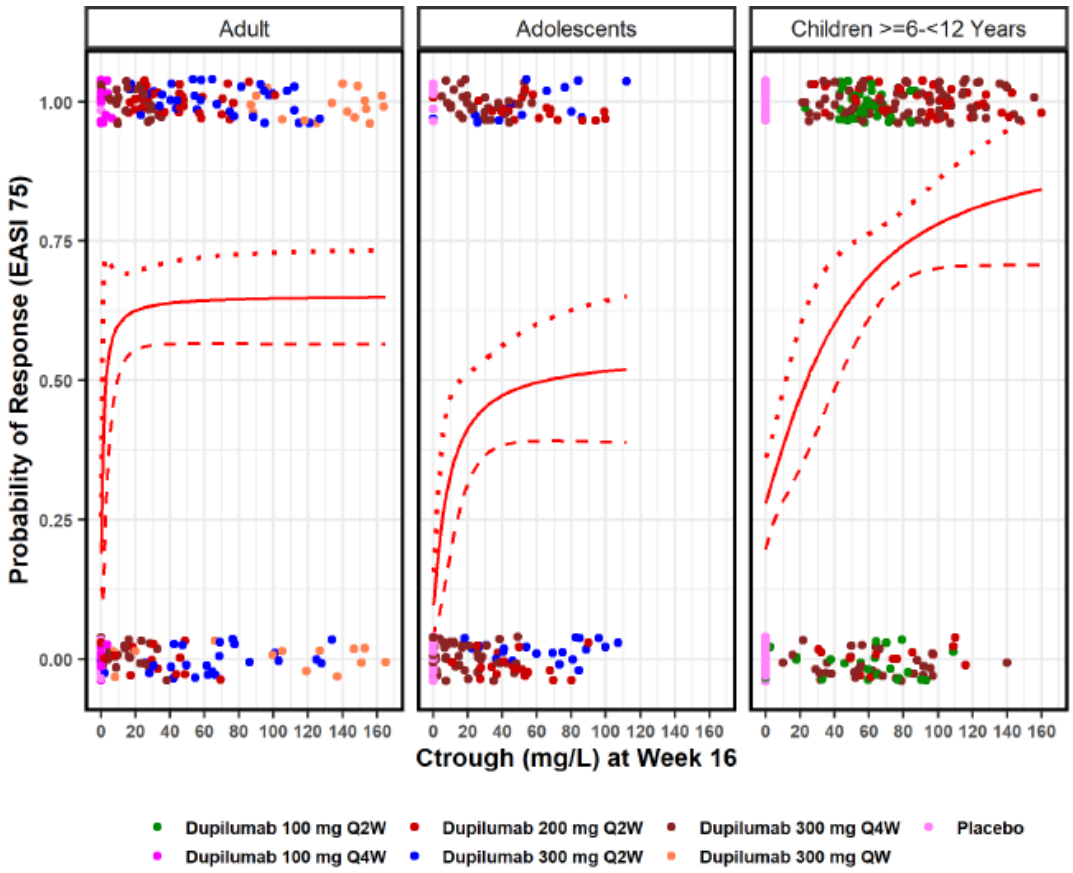
Source: Table 4. PK Memorandum (dated March 26th, 2020)

Figure 6. Probability of Response (IGA 0-1) vs. C_{trough} (mg/L) at Week 16 in Adults, Adolescents, and Children (≥6 to <12 Years)



Source: Figure 1., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

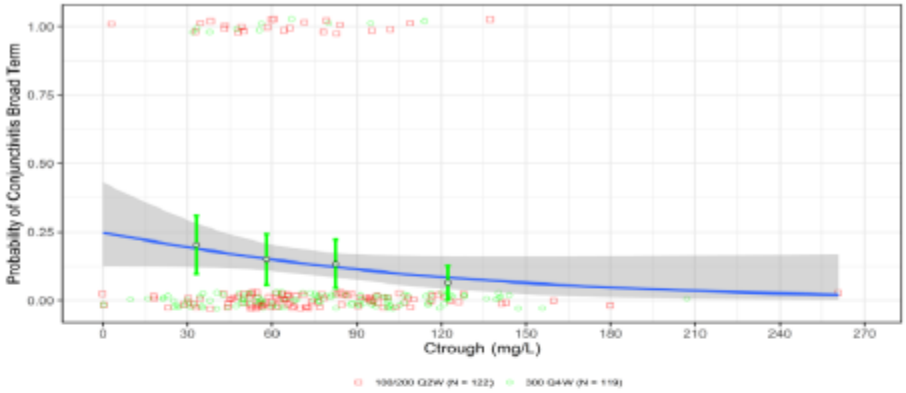
Figure 7. Probability of Response (EASI -75) vs. C_{trough} (mg/L) at Week 16 in Adults, Adolescents, and Children (≥6 to <12 Years)



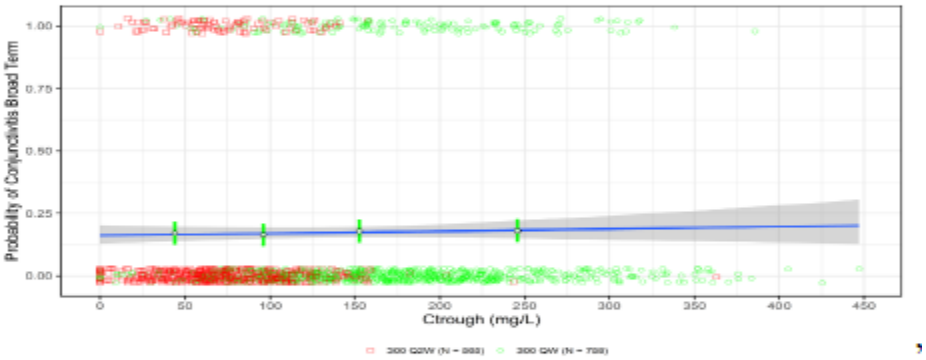
Source: Figure 2., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

Figure 8. Logistic Regression Relating Probability of Patients Developing Conjunctivitis With Dupilumab Trough Concentrations at Week 16 in Adults, Adolescents, and Children (≥6 to <12 Years)

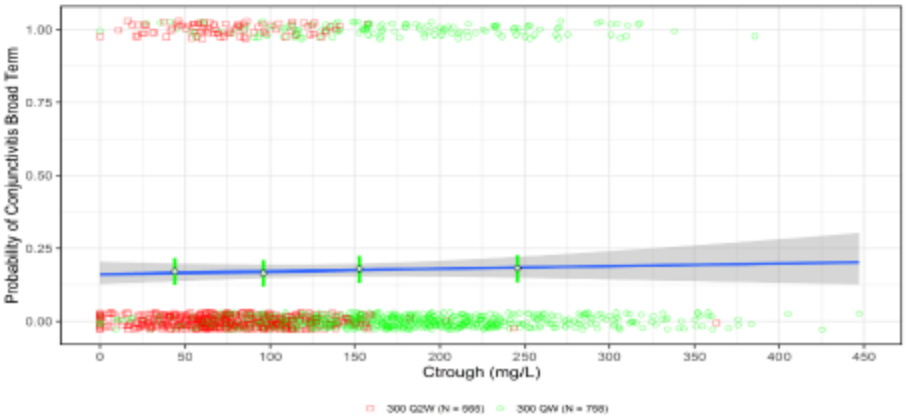
Patients ≥6 to <12 Years of Age with Severe AD



Adolescent Patients with Moderate-to-Severe AD (Study R668-AD-1526)



Adults (R668-AD-1416, R668-AD-1334, and R668-AD-1224)



Source: Figure 5., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

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

No. An alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors. Population PK model identified body weight as a significant covariate on dupilumab PK; therefore, body weight-tiered dupilumab dosing regimens was investigated and proposed as 300 mg Q4W for children ≥15 to <30 kg and 200 mg Q2W for children ≥30 kg. The relative higher dupilumab exposure with the proposed 300 mg Q4W dosing regimen in children ≥15 to <30 kg compared to those seen in adolescents and adults was justified based on efficacy, safety and exposure response analyses. A further dose adjustment is not needed

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

Food-drug interactions are not applicable as dupilumab is administered by SC injection. Drug interaction potential for dupilumab with CYP450 substrates is described in Section 12.3 of dupilumab product labeling. There is no additional drug interaction information in the current sBLA to update the drug interaction potential for dupilumab.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant provided data from 3 studies:

- R668-AD-1412 (1412): an open-label, PK/safety Phase 2a study; single dose followed by 4-week repeat dose treatment (patients ≥6 to <12 years old: n= 37).
- R668-AD-1652 (1652): the pivotal, randomized, double-blind, placebo-controlled Phase 3 study; the primary safety data (n= 362).
- R668-AD-1434 (1434): an ongoing Phase 3, open-label extension, long-term safety study (n= 368). The data cutoff date for the sBLA was July 22, 2019.

Subjects from Studies 1652 and 1412 could be “rolled over” into Study 1434, into which all pediatric subjects (≥6 Months to <18 Years) from the AD program may ultimately be enrolled.

For this efficacy supplement, the Applicant only submitted analyses of data from patients who were 6 to <12 years old at the screening visit for the OLE. The Applicant termed the analyses from Study 1652 the “second-step analysis.” The first-step analysis was done on data from adolescent patients in Study 1652 and was reviewed under S-012.

Table 7. Listing of Clinical Trials Relevant to This sBLA

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population
R668-AD-1412	Open-label, ascending dose, sequential cohort	- For dose cohort 1: 2 mg/kg at day 1 as single dose in Part A, then weekly at day 1 to Week 3 in Part B as repeat doses -For dose cohort 2: 4 mg/kg at day 1 as a single dose in Part A, then weekly at day 1 to Week 3 in Part B as repeat doses	**Primary Objective:** to characterize the PK profiles of dupilumab in pediatric AD patients aged ≥6 to <18 years. **Secondary Endpoints**: -Incidence of treatment-emergent adverse events (TEAEs) -Percent change from baseline in Eczema Area and Severity Index -Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) score -Percent change from baseline in Pruritus Numerical Rating Scale (NRS) -Percentage of patients with an IGA score of 0 or 1 -Change from baseline in % body surface area affected by AD	The study included Part A (including a single-dose treatment followed by an 8-week semi-dense PK sampling period), and Part B (including a 4-week repeat dose treatment period [4 weekly doses] followed by an 8-week follow-up period)	78 38 patients were 6 to <12 years of age	Pediatric patients with moderate-to-severe AD (for adolescents aged ≥12 to <18 years at the time of baseline) or severe AD (for children aged ≥6 to <12 years at the time of baseline) that was not adequately controlled with topical medications
R668-AD-1652	Randomized, double-blind, placebo-controlled	- Dupilumab every 2 weeks (Q2W) treatment group: 100 mg for patients <30 kg or 200 mg for patients ≥30 kg -Dupilumab every 4-weeks (Q4W) treatment group: 300 mg -Placebo group	Primary Endpoint: -The proportion of patients with IGA 0 or 1 at Week 16 was the primary endpoint for the U.S. Key Secondary Endpoints: -Proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16 (this was a co-primary	16 weeks treatment/ 12 weeks follow-up	251	Pediatric patients (aged ≥6 to <12 years at the time of baseline) with severe AD that could not be adequately controlled with topical AD medications or for whom topical treatment was medically inadvisable.

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population
		16 weeks treatment/ 12 weeks follow-up	endpoint ex-U.S.) -Percent change in EASI score from baseline to Week 16 -Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS			
R668-AD-1434	Open-label extension study	Based on protocol amendment 1, all patients at the time of enrollment started on a dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at Week 16 as follows: - Patients weighing ≥60 kg: 300 mg Q2W - Patients weighing <60 kg: 200 mg Q2W Note: Prior to amendment 1, subjects from Study R668-AD-1412 received weight based dosing regimens of 2 mg/kg or 4 mg/kg.	Primary Endpoint: -The incidence and rate of treatment-emergent adverse events (TEAEs) from baseline through the last study visit. Secondary Endpoints: -Incidence of treatment-emergent serious adverse events (SAEs) from baseline through the last study visit -Incidence of TEAEs of special interest from baseline through the last study visit -Proportion of patients with an IGA score of 0 or 1 (clear or almost clear) at all in clinic visits post-baseline -Proportion of patients with Eczema Area and Severity Index-75 (≥75% reduction in EASI from baseline of parent study) response at all in-clinic visits post-baseline	The study will be conducted until regulatory approval of the product for the age group of the subject in his/her geographic region, and a 12-week follow-up period.	368 pediatrics patients ≥6 to <12 years of age	Pediatric patients with AD, aged ≥6 months to <18 years at the time of screening with moderate-to-severe AD who had also completed a prior dupilumab clinical study.

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-Up	No. of Patients Enrolled	Study Population
			-Change and percent change from baseline in EASI at all in-clinic visits postbaseline -Change from baseline in body surface area affected by AD at all in-clinic visits post-baseline -Percent change from baseline in SCORAD at all in-clinic visits postbaseline -Change from baseline in Children's Dermatology Life Quality Index for patients ≥4 years of age at all in-clinic visits post-baseline in which the assessments are planned to be performed			

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of dupilumab for the proposed indication included final study reports submitted by the Applicant, datasets [Study Data Tabulation Model and Analysis Data Model]. This application was submitted in electronic common technical document format and entirely electronic. The electronic submission including the protocol, the statistical analysis plan (SAP), the clinical study report, the SAS transport datasets in Study Data Tabulation Model, and Analysis Data Model format were in the following network path:

\\cdsesub1\evsprod\bla761055\0700\m5\datasets\r668-ad-1652\

Pivotal Study R668-AD-1652 was reviewed for efficacy.

The Applicant provided safety data from 3 studies:

- R668-AD-1652 (1652): the pivotal, randomized, double-blind, placebo-controlled Phase 3 study; the primary safety data (n= 362).

Supportive safety data were provided from:

- R668-AD-1434 (1434): ongoing Phase 3, OLE, long-term safety study (n= 368). Discuss original dosing regimen. The data cutoff date for the sBLA was July 22, 2019.
- R668-AD-1412 (1412): open-label, PK/safety Phase 2a study; single dose followed by 4-week repeat dose treatment (patients 6 to <12 years old: n= 37).

The safety review focused on the data from pivotal trial Study 1652, as this was the primary safety data. Only serious adverse events (SAEs) will be discussed from Study 1412, as the dosing regimen differed significantly from Studies 1652 and 1434 (the dosing in those studies align more with proposed labeled dosing).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Pivotal Phase 3 Trial (R668-AD-1652)

Trial Design and Endpoints

The Applicant conducted a single Phase 3 trial (R668-AD-1652) to support the application.

The key inclusion criteria that defined the study population were as follows:

- Male or female ≥ 6 to <12 years of age
- Diagnosis of AD according to the American Academy of Dermatology consensus criteria
- Chronic AD diagnosed at least 1 year prior to the screening visit
- IGA score of 4 at screening and baseline visits. See Figure 9 for the IGA scale.
- EASI ≥ 21 at the screening and baseline visits
- BSA ≥ 15% at screening and baseline visits
- With documented recent history (within 6 months before the baseline visit) of inadequate response to topical AD medication(s)
- Had applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit

Figure 9. Applicant's Investigator's Global Assessment (IGA) Scale

Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Proposed Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

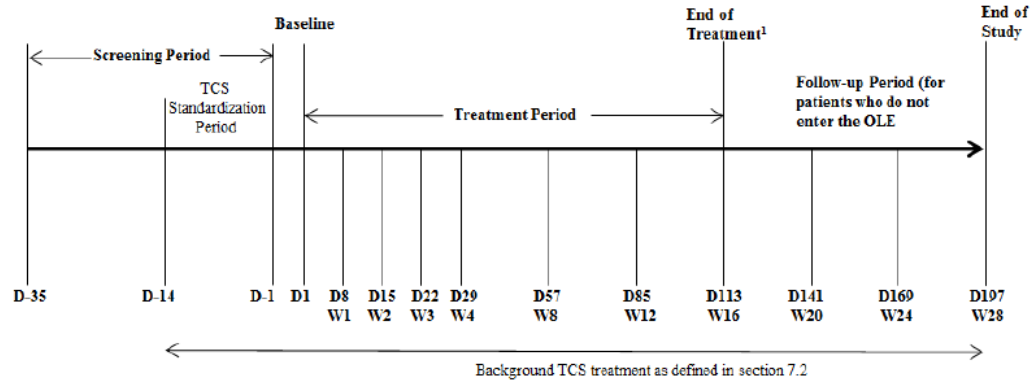
Figure 10 presents the study flow diagram for Trial R668-AD-1652. The Phase 3 trial was a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with TCS in subjects ≥ 6 to <12 years of age with severe AD. Using the Interactive Voice/Web Response System, the Applicant randomized a total of 367 subjects to one of the following groups in a 1:1:1 ratio.

- Dupilumab Q2W group:
  - 100 mg Q2W for subjects <30 kg (loading dose of 200 mg) or
  - 200 mg Q2W for subjects ≥30 kg (loading dose of 400 mg)
- Dupilumab Q4W group: 300 mg Q4W (loading dose of 600 mg), irrespective of weight

- Placebo
  - Subjects <30 kg will receive placebo (matching 100 mg dupilumab)
  - Subjects ≥30 kg will receive placebo (matching 200 mg dupilumab)

Randomization was stratified by baseline weight group (<30 kg and ≥30 kg) and region (North America/Europe).

Figure 10. Study Flow Diagram



D = study day; W = study week
Note: The length of the screening period is not fixed, but must not exceed 35 days. The length of the TCS standardization period is fixed at 14 days.
[1]For patients who enter the OLE, week 16 is the end of study.

Source: Applicant's protocol

Table 8 lists the primary and the secondary endpoints as well as the hierarchical order of testing of these endpoints (α= 0.05, two-sided).

Table 8. Endpoints and Hierarchical Order of Testing

	Endpoints	Dupilumab q4w group	Dupilumab q2w group
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	7	1
Co-primary endpoint for EMA and EMA Reference Market Countries only, key secondary for US	Proportion of patients with EASI-75 (>=75% improvement from baseline) at week 16	8	2
Secondary endpoints	Percent change in EASI score from baseline to week 16	9	3
	Proportion of patients with EASI-50 at week 16	10	4
	Percent change from baseline to week 16 in weekly average of daily worst itch score	11	5
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline at week 16	12	6
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline at week 16	15	13
	Proportion of patients with EASI-90 at week 16	16	14
	Change from baseline to week 16 in POEM	20	17
	Change from baseline to week 16 in CDLQI	21	18
	Percent change from baseline to week 16 in SCORAD	22	19

Source: Applicant's Statistical Analysis Plan (SAP; page 38)

Statistical Methodologies

The primary efficacy analysis was conducted in Full Analysis Set (FAS) defined as all randomized subjects, and the FAS was the primary analysis set.

For the analysis of the primary endpoint and the binary secondary endpoints, the protocol was specified using the Cochran Mantel Haenszel test stratified by weight (<30 kg versus ≥30 kg) and region (North America/Europe). The protocol specified that to account for the impact of rescue treatment on the efficacy effect, if a subject used rescue treatment, the subject would be specified as a non-responder from the time the rescue is used. For the continuous secondary endpoints, the protocol specified the analysis of covariance model with the treatment group, the baseline value, and the randomization strata as the primary analysis method.

For handling of missing data for the binary endpoints, the protocol specified using No Response Imputation approach, and considered the missing data as failures. For the continuous secondary endpoints, the protocol specified that multiple imputation would be used as the primary imputation method. As sensitivity analyses for handling missing data for endpoints for both the binary and continuous endpoints, the protocol specified using the last observation carried forward, and using all observed data regardless if rescue treatment was used or data were collected after withdrawal from study treatment.

In addition to the FAS, the Applicant also conducted sensitivity analyses using the modified FAS (mFAS) defined as all randomized subjects excluding 68 subjects as the Applicant noted that a packing list included a description of the Investigational Product, which according to the Applicant, might have potentially unblinded the patients. The Applicant noted that this "inadvertent operation error" was initially communicated to the Agency on November 21, 2018, and at that time the Applicant proposed to conduct sensitivity analyses by excluding these subjects.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the submitted clinical studies were conducted in accordance with the ethical principles consistent with the International Council for Harmonisation guidelines for Good Clinical Practice.

Financial Disclosure

The Applicant identified pivotal Study 1652 as a covered clinical study. Regeneron and Sanofi adequately disclosed financial arrangements with clinical investigators. They implemented the following measures to protect the study from potential bias:

- Study 1652 was double-blind for the collection of safety and efficacy data.
- Subjects were randomly assigned to treatment arms via an Interactive Voice Response System.
- A central clinical team blinded to the treatment arm followed the quality of data reported by investigators and adherence to the protocol.

The disclosed interests/arrangements did not raise concerns about data integrity due to the above measures taken by the Applicant to protect the study from potential bias.

Patient Disposition and Demographic Characteristics

The Phase 3 trial randomized a total of 367 subjects from 57 centers. Table 9 presents the disposition of subjects, and shows that approximately 96% of the subjects completed the study treatment with very few subjects having discontinued the study.

Table 9. Subject Disposition

Completed Study Treatment	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Yes	119 (97.5%)	118 (96.7%)	114 (92.7%)
No	3 (2.5%)	4 (3.3%)	9 (7.3%)
Adverse Event	1 (0.8%)	0	1 (0.8%)
Lack of Efficacy	0	0	2 (1.6%)
Other	2 (1.6%)	4 (3.3%)	6 (4.9%)

Source: Applicant's Table 2 (Study report; page 45)

The baseline demographics and baseline disease characteristics are presented in Table 10 and Table 11, respectively. The demographics and baseline disease characteristics were generally balanced across the treatment arms. Approximately 50% of the subjects were male, 69% of the subjects were white, 48% of subjects were 6 to <9 years of age, and 50% of the subjects were <30 kg. All but one randomized subject in dupilumab Q4W +TCS had IGA score of severe (4) at baseline, and approximately 99% of the enrolled subjects had baseline worst average itch on the Numeric Rating Scale (NRS) ≥4.

Table 10. Baseline Demographics

Demographics	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Age			
≥6 to <9	58 (47.5%)	60 (49.2%)	57 (46.3%)
≥9 to <12	64 (52.5%)	62 (50.8%)	66 (53.7%)
Sex			
Male	65 (53.3%)	57 (46.7%)	61 (49.6%)
Female	57 (46.7%)	65 (53.3%)	62 (50.4%)
Race			
White	88 (72.1%)	89 (73.0%)	77 (62.6%)
Black	20 (16.4%)	19 (15.6%)	23 (18.7%)
Asian	10 (8.2%)	5 (4.1%)	13 (10.6%)
Other	4 (3.2%)	9 (7.4%)	10 (8.1%)
Weight (kg)			
<30 kg	63 (51.6%)	61 (50.0%)	61 (49.6%)
≥30 kg	59 (48.4%)	61 (50.0%)	62 (50.4%)
Mean (SD)	32.07 (10.79)	30.98 (9.40)	31.46 (10.82)
Median	29.50	29.7	30.0
Min, Max	(17.7, 79.1)	(18.3, 65.8)	(15.3, 68.0)

Demographics	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Region			
Europe	43 (35.2%)	43 (35.2%)	44 (35.8%)
North America	79 (64.8%)	79 (64.8%)	79 (64.2%)

Source: Applicant's table (page 53)

Table 11. Baseline Disease Severity

Disease Severity	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
IGA at baseline			
4 (severe)	122 (100%)	121 (99.2%)	123 (100%)
3 (moderate)	0	1[(1)] (0.8%)	0
EASI			
Mean (SD)	37.3 (10.86)	37.4 (12.45)	39.0 (12.01)
Median	35.3	35.3	38.3
Min-max	17.5[(2)] -66.0	21.1-69.6	17.7[(3)] -72.0
Weekly average worst itch			
≥4	120 (98.4%)	120 (98.4%)	122 (99.2%)
<4	0	2 (1.6%)	1 (0.8%)

Source: Applicant's table (page 55)

[1] subject R668-AD-1652-(b) (6) had IGA of 3 and EASI score of 21.2 at baseline;
[2] subject R668-AD-1652-(b) (6) had an IGA of 4 and EASI score of 17.5 at baseline
[3] subject R668-AD-1652-(b) (6) had IGA of 4 and EASI score of 17.7 at baseline.

Efficacy Results

Table 12 and Table 13 present the results of the efficacy analyses as specified in the study protocol (i.e., by dosing regimen Q2W, Q4W, and placebo). Results for primary and all secondary efficacy endpoints were statistically significant ($p<0.001$). The responses were numerically higher for the Q4W regimen compared to the Q2W for the endpoints based on investigator's assessment; however, for the Patient Reported Outcomes (i.e., itch) endpoints based on the NRS, the Q2W regimen provided numerically higher (better) responses compared to those of the Q4W regimen. Note that in Sections 8.1.3 of this review, we consider analyses by weight and its potential impact on dose selection for labeling.

Table 12. Efficacy Results at Week 16 (FAS)

Endpoints	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Loading dose	200 mg then 100 mg (<30 kg) 400 mg then 200 mg (≥30 kg) [1]	600 mg then 300 mg [2]	
IGA 0 or 1	36 (29.5%)	40 (32.8%)	14 (11.4%)
EASI 75	82 (67.2%)	85 (69.7%)	33 (26.8%)
EASI 90	37 (30.3%)	51 (41.8%)	9 (7.3%)
EASI 50	101 (82.8%)	111 (91.0%)	53 (43.1%)
NRS≥4	70 (58.3%)	61 (50.8%)	15 (12.3%)
NRS≥3	81 (67.5%)	73 (60.3%)	26 (21.1%)
% change in EASI (LS mean, SE)	-78.4 (2.35)	-82.1 (2.37)	-48.6 (2.46)
% change in weekly average daily worst itch (LS mean, SE)	-57.0 (2.77)	-54.6 (2.89)	-25.9 (2.90)

Source: Applicant's table (page 70)
[1] Same as the currently approved dose for adolescent subjects <60 kg
[2] Same as the currently approved dose for adults and adolescent subjects ≥ 60 kg

To investigate the potential impact of unblinding of the 68 subjects on the efficacy results, the Applicant conducted sensitivity analyses by excluding these subjects from the analysis (mFAS). Table 13 shows that similar responses to those using the FAS were seen using the mFAS.

Table 13. Sensitivity Analyses of Efficacy Results at Week 16 Excluding the 68 Unblinded Subjects (mFAS)

Endpoints	Dupilumab Q2W + TCS N=92	Dupilumab Q4W+ TCS N=103	Placebo + TCS N=104
IGA 0 or 1	29 (31.3%)	33 (32.0%)	14 (13.5%)
EASI 75	65 (70.7%)	75 (72.8%)	32 (30.8%)
EASI 90	32 (34.8%)	47 (45.6%)	9 (8.7%)
EASI 50	77 (83.7%)	93 (90.3%)	47 (45.2%)
NRS≥4	51 (56.7%)	51 (50.5%)	14 (13.6%)
NRS≥3	58 (64.4%)	62 (60.8%)	22 (21.2%)
% change in EASI (LS mean, SE)	-79.2 (2.54)	-82.1 (2.41)	-52.6 (2.60)
% change in weekly average daily worst itch (LS mean, SE)	-54.8 (3.18)	-54.3 (2.89)	-25.3 (3.11)

Source: Applicant's table (page 70); mFAS (modified Full Analysis Set) excludes the 68 subjects from the Full Analysis Set (FAS) that were unblinded due to packaging error.

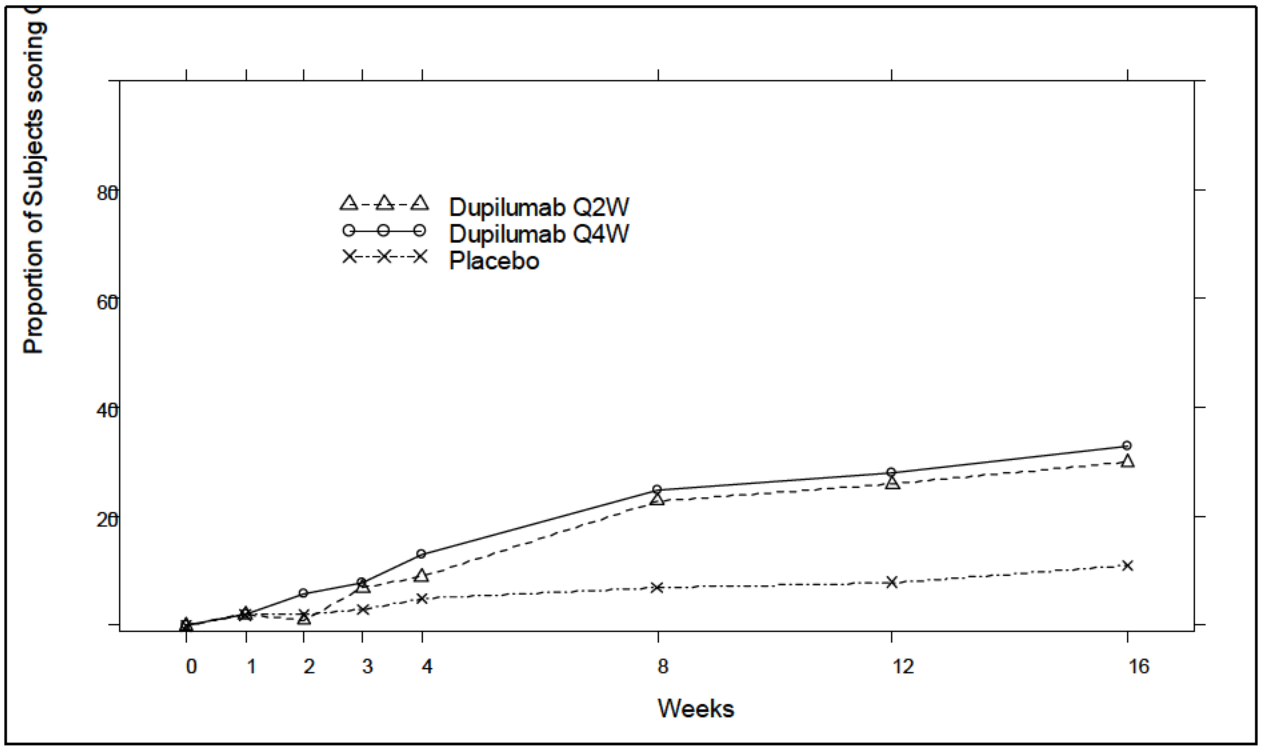
Data Quality and Integrity

In general, the data submitted by the Applicant to support the efficacy and safety of dupilumab for the proposed indication appeared adequate.

Efficacy Over Time

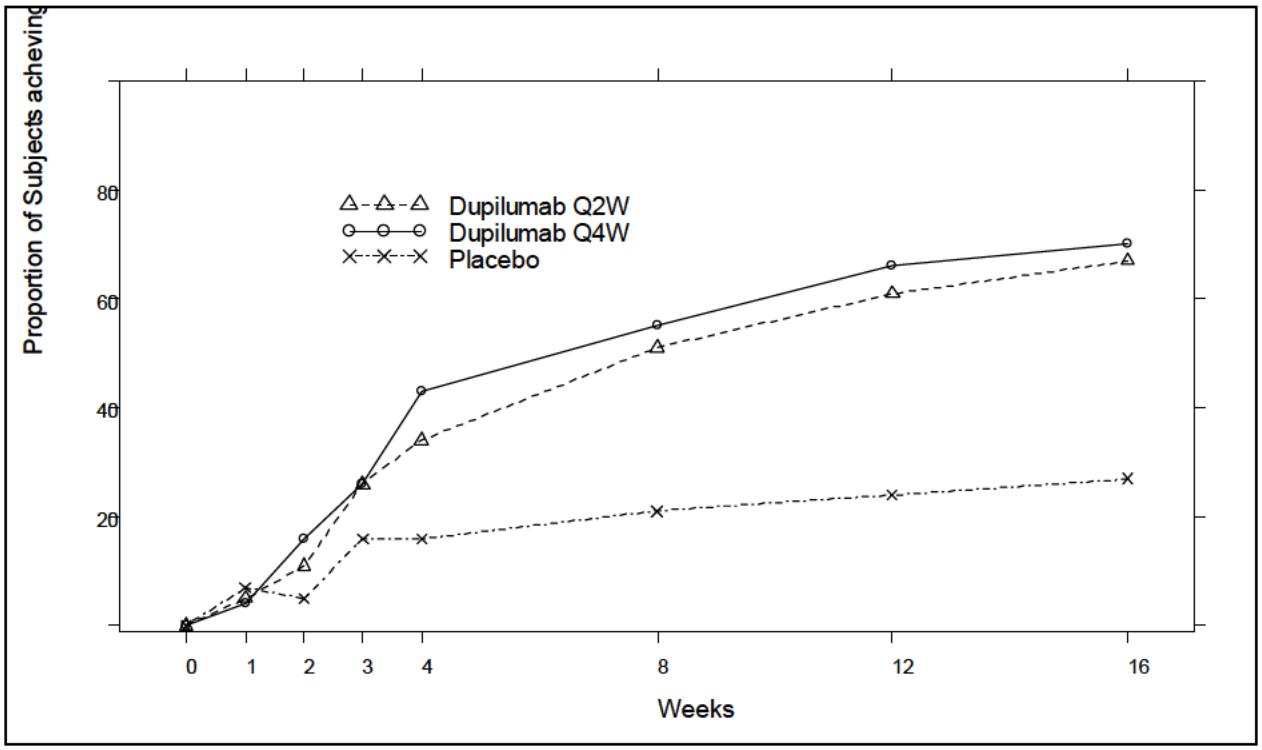
Figure 11 presents the results for IGA 0 or 1 through Week 16. It can be seen that the results for IGA 0 or 1 for the Q2W and Q4W regimens were similar through Week 16. This was also seen for the EASI 75 response through Week 16 in Figure 12.

Figure 11. Results for IGA Score of 0 or 1 Through Week 16



Source: Reviewer figures; FAS (full analysis set); Missing data were imputed using non-responder imputation (NRI).

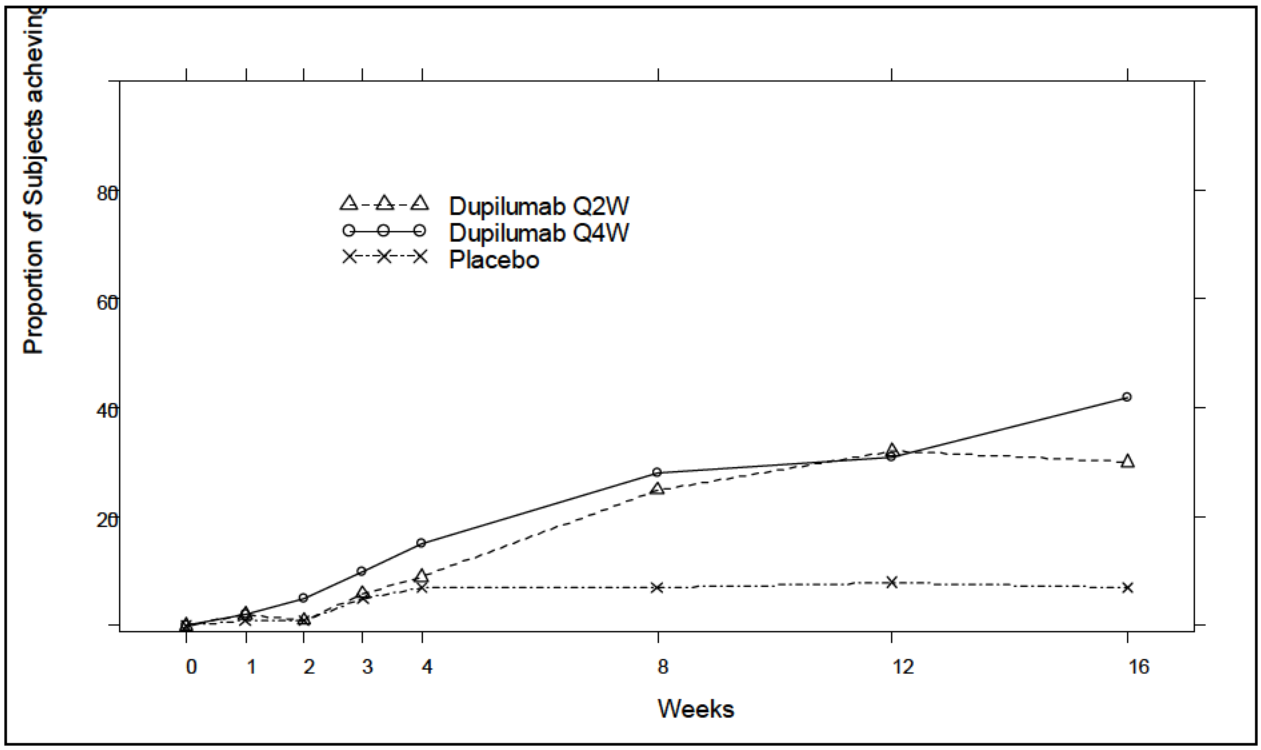
Figure 12. Results for EASI 75 Response Through Week 16



Source: Reviewer figures; FAS (full analysis set); Missing data were imputed using non-responder imputation (NRI).

The EASI 90 response over time (see Figure 13 below) also showed that the responses for the Q2W and Q4W regiments were very similar through Week 12; however, at Week 16, the Q4W regimen yielded numerically higher response than that of the Q2W.

Figure 13.Results for EASI 90 Response Through Week 16



Source: Reviewer's figure

Findings in Subgroup Populations

Table 14 presents the results for the primary efficacy endpoint of IGA score of 0 or 1 at Week 16 by sex, age, race (Asian, black, white, American Indian, Native Hawaiian/Pacific Islander, Other), and weight (<30 kg versus ≥30 kg).

Table 14. IGA Score of 0 or 1 at Week 16 by Sex, Age, and Race

Results of Primary Efficacy Endpoint	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Loading Dose	200 mg then 100 mg (<30 kg) 400 mg then 200 mg (≥30 kg) [1]	600 mg then 300 mg [2]	
IGA 0 or 1	36 (29.5%)	40 (32.8%)	14 (11.4%)
Age			
≥6 to <9	16/58 (27.6%)	21/60 (35.0%)	8/57 (14.0%)
≥9 to <12	20/64 (31.3%)	19/62 (30.6%)	6/66 (9.1%)
Sex			
Male	19/65 (29.2%)	19/57 (33.3%)	9/61(14.8%)
Female	17/57 (29.8%)	21/65 (32.3%)	5/62 (8.1%)

Results of Primary Efficacy Endpoint	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Race			
White	26/88 (29.5%)	30/89 (33.7%)	12/77 (15.6%)
Black	6/20 (30.0%)	6/19 (31.6%)	2/23 (8.7%)
Asian	4/10 (40.0%)	2/5 (40.0%)	0/13 (0%)
Other	0/4 (0%)	1/9 (%)	0/10 (0%)

Source: Reviewer Table;
[1] Same as the currently approved dose for adolescent subjects <60 kg
[2] Same as the currently approved dose for adults and adolescent subjects ≥ 60 kg

8.1.3. Additional Efficacy Analyses by Baseline Body Weight

While the SAP specified analyses for the combined Q2W versus placebo, and the combined Q4W versus placebo, the Applicant conducted an additional efficacy analysis by baseline body weight group, and reported their findings in the clinical study report (Section 8.7; page 141). It should be noted that such analysis by body weight group was not a part of the protocol-specified multiplicity adjustment plan.

(b) (4)

In the Study Report, the Applicant stated the following:

- "for patients with a baseline weight <30 kg, there were clear differences in efficacy favoring the **300 mg Q4W** + TCS dose regimen as compared to the 100 mg Q2W + TCS dose regimen for the primary endpoint of IGA 0 or 1 as well as for the stringent endpoints of EASI-75 and EASI-90", and
- "for patients with a baseline weight ≥30 kg, there were more notable differences in efficacy favoring the Q2W regimen (**200 mg Q2W + TCS**) compared to the Q4W regimen (300 mg Q4W + TCS) for the pruritus-related endpoints of ≥4- and ≥3-point reductions in pruritus NRS as well as the co-primary endpoint of EASI-75 and to a lesser extent with the primary endpoint of IGA 0 or 1."

Table 15 shows the Applicant's efficacy results by baseline weight group (<30 kg versus ≥ 30 kg).

Table 15. Efficacy Results by Baseline Weight Group (<30 kg vs. ≥30 kg)

	<30 kg			≥30 kg		
	Dupilumab 100 mg Q2W + TCS	Dupilumab 300 mg Q4W + TCS	Placebo +TCS	Dupilumab 200 mg Q2W+ TCS	Dupilumab 300 mg Q4W+ TCS	Placebo + TCS
Efficacy Results	**N=63**	**N=61**	**N=61**	**N=59**	**N=61**	**N=62**
IGA 0 or 1	13 (20.6%)	18 (29.5%)	8 (13.1%)	23 (39.0%)	22 (36.1%)	6 (9.7%)
EASI 75	38 (60.3%)	46 (75.4%)	17 (27.9%)	44 (74.6%)	39 (63.9%)	16 (25.8%)
EASI 90	16 (25.4%)	28 (45.9%)	4 (6.6%)	21 (35.6%)	23 (37.7%)	4 (8.1%)
EASI 50	50 (79.4%)	58 (95.1%)	26 (42.6%)	51 (86.4%)	53 (86.9%)	27 (43.5%)
NRS≥4	35 (55.6%)	33 (54.1%)	7 (11.7%)	35 (61.4%)	28 (47.5%)	8 (12.9%)
NRS≥3	43 (68.3%)	38 (62.3%)	11 (18.0%)	38 (66.7%)	35 (58.3%)	15 (24.2%)
% change in EASI (LS mean, SE)	-76.7 (3.04)	-84.3 (3.08)	-49.1 (3.30)	-80.4 (3.61)	-79.9 (3.57)	-48.3 (3.63)
% change in weekly average daily worst itch (LS mean, SE)	-56.1 (3.86)	-55.1 (3.94)	-27.0 (4.24)	-58.2 (4.01)	-54.3 (4.19)	-25.0 (3.95)

Source: Applicant's table 51.

As the results of the above analyses considered a baseline bodyweight threshold of 30 kg without taking into account the weight increments, we considered an additional analysis by checking the efficacy results by body weight categories in increments of 5 kg. Table 16 shows the distribution of bodyweight in 5 kg increments, which is relatively balanced across the treatment arms. Figure 14 presents the efficacy results by the body weight category of 5 kg increments

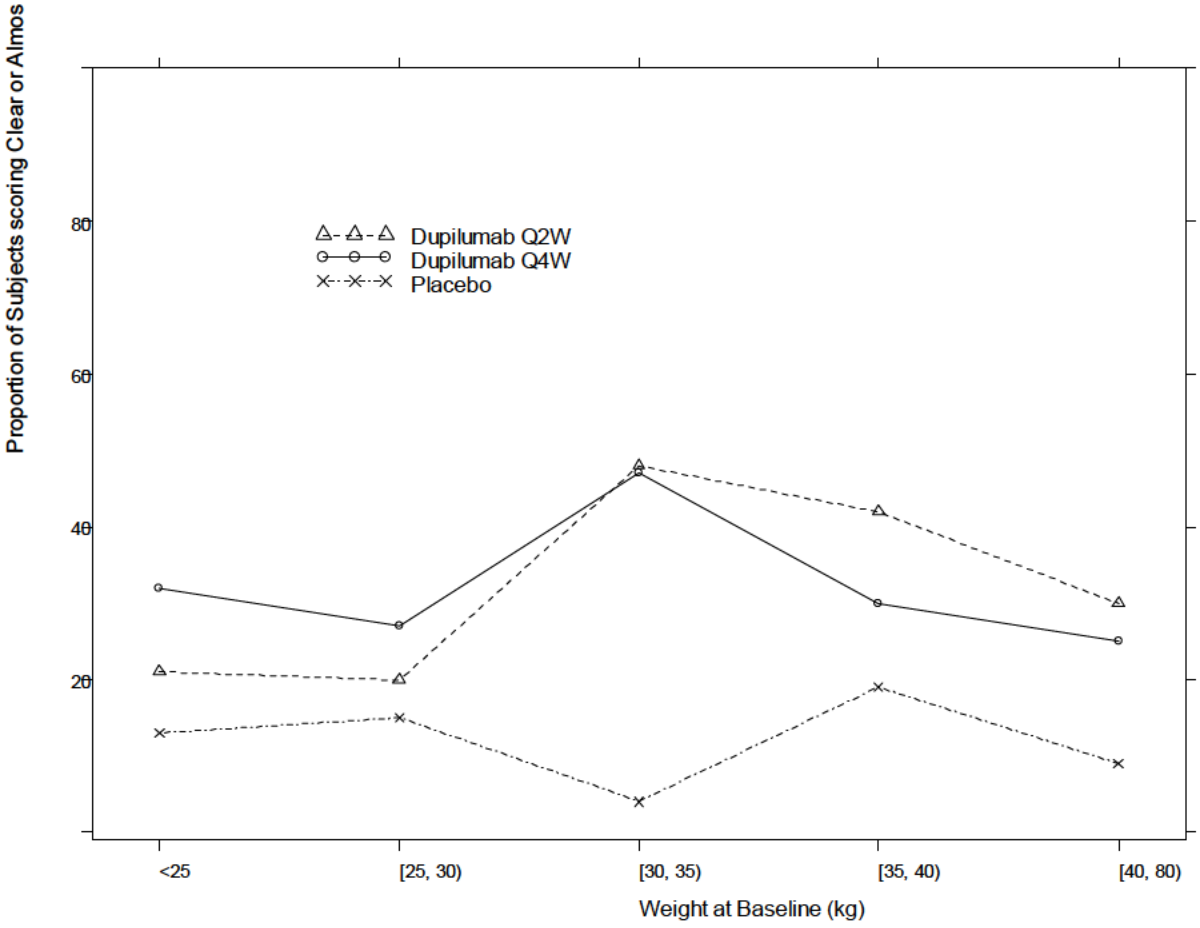
For the body weight categories, the number of subjects were generally balanced across treatment arms. Note that a total of 304 of the 367 enrolled pediatric subjects (83%) weighed <40 kg at baseline. As the number of pediatric subjects ≥ 40 kg was relatively small, the figure combined the categories ≥ 40 kg for the figure.

Table 16. Number of Enrolled Subjects for Each Baseline Weight Category (in 5kg Increments).

Baseline Body Weight (kg)	Dupilumab Q2W + TCS N=122	Dupilumab Q4W+ TCS N=122	Placebo + TCS N=123
Weight <20 kg	10	7	9
≥20 but <25 kg	23	32	31
≥25 but <30 kg	30	22	21
≥30 but <35 kg	23	30	24
≥35 but <40 kg	12	11	16
≥40 but <45 kg	12	11	11
≥45 but <50 kg	4	3	4
≥50 but <55 kg	2	2	1
≥55 kg	6	4	6

Source: Reviewer table

Figure 14. Proportion of Subjects Scoring IGA 0 or 1 at Week 16 Based on Body Weight



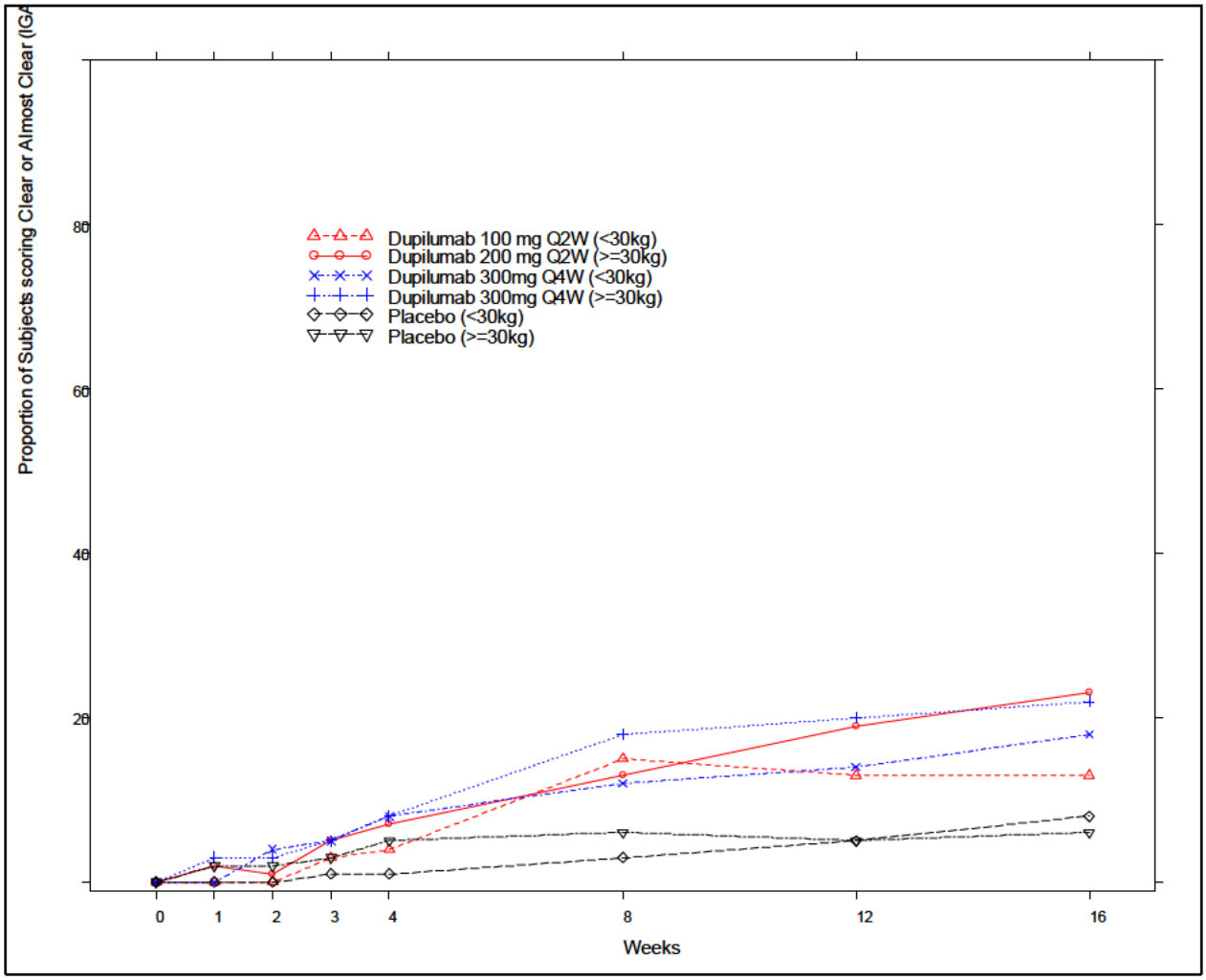
Source: Reviewer figure.
Baseline body weight of [25, 30] indicates that a subject weighed between 25 kg (inclusive) and 30 kg (exclusive).
The number of pediatric subjects ≥ 40 kg was relatively small and were combined for the figure above.

At Week 16, the figure shows the following:

- For pediatric subjects <30 kg, the proportion of subjects scoring IGA of 0 or 1 was numerically higher for those that received dupilumab **300 mg Q4W** regimen compared to those that received the 100 mg Q2W regimen.
- For the category of ≥30 but <35 kg, the response rates for the two doses (Q2w and Q4w) were similar.
- For the pediatric subjects ≥35 kg, the proportion of subjects scoring 0 or 1 was numerically higher for the dupilumab **200 mg Q2W** regimen compared to the 300 mg Q4W regimen; however it should be noted that the number of subjects in these categories was relatively small compared to the categories < 35 kg (see Table 16) and consequently, the estimate of treatment effect may be less reliable.

To explore the IGA 0 or 1 response over time by weight subgroup (<30 kg versus ≥30 kg), Figure 15 was plotted as shown below.

Figure 15. Proportion of Subjects Scoring IGA 0 or 1 Over Time From Baseline to Week 16



Source: Reviewer figure

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review will focus on the data from pivotal trial Study 1652, as this was the primary safety data. Only SAEs will be discussed from Study 1412, as the dosing regimen differed significantly from Studies 1652 and 1434 (the regimens in those studies more align with the proposed labeled dosing).

Safety data were generally not pooled, as the study designs differed for the 3 studies. Therefore, the studies will be discussed separately.

Analysis Methods

Descriptive statistics were used in the analyses of safety parameters.

For Study 1652, the Applicant separately summarized the number and proportion of subjects with TEAEs for the 16-week treatment period, the 12-week post-treatment follow-up period, and the overall study (treatment period + follow-up period).

For Studies 1434 and 1412, the Applicant summarized all TEAEs during the study.

For Study 1434, the Applicant also calculated and summarized the number of events per 100 patient-years and number of patients with at least 1 event per 100 patient-years (exposure-adjusted incidence rate) for overall TEAEs, severe TEAEs, treatment-related TEAEs, severe treatment-related TEAEs, SAEs, AEs leading to discontinuation, and Adverse Events of Special Interest (AESIs). The Applicant adjusted these calculations for the duration of the TEAE period.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database included 399 patients 6 to <12 years old. The safety analysis set (SAF) included all patients who received at least 1 dose of any study drug, and patients were analyzed as treated.

Study 1652 was the only study that exclusively enrolled children 6 to <12 years old. This study also required concomitant use of TCS as background treatment. Studies 1434 and 1412 allowed, but did not require, concomitant topical therapies e.g., TCS with or without TCIs.

See Table 17 and Table 18 below.

Study 1652 (Pivotal)

Table 17. Number of Patients ≥6 to <12 Years of Age Included in the Safety Analysis Set*

Parent Study ID Number	Number of Children Treated in the Parent Study	Number of Children Who Rolled Over to the OLE Study (R668-AD-1434)[a]	Number of Children Exposed to Dupilumab (in the Parent Study or the OLE Study)
R668-AD-1652			
≥6 to <12 years of age	362[a,b]	335	354[b]
R668-AD-1412			
≥6 to <12 years of age	37[c,d]	33	37
Total	399	368	391

*Source: Table 1 Summary of Clinical Safety

[a] The number of patients randomized and included in the full analysis set (FAS) was 367; 3 patients randomized to the dupilumab + TCS Q2W and Q4W and2 patients randomized to placebo + TCS did not receive study treatment and were not included in the safety analysis set (SAF).

[b] Eight patients in the placebo + TCS group withdrew from R668-AD-1652 and did not enter the OLE study.

[c] The number of patients randomized and included in the full analysis set (FAS) was 38; 1 patient randomized to the dupilumab 4 mg/kg QW did not receive study treatment and was not included in the SAF.

[d] One patient in the dupilumab 4 mg/kg QW withdrew from R668-AD-1412 and did not enter the OLE study. One patient in the dupilumab 2 mg/kg QW and 2 patients in the dupilumab 4 mg/kg QW group who completed R668-AD-1412 did not enter the OLE study.

Table 18. Number of Patients (≥6 to <12 Years of Age) With Dupilumab Exposure – SAF*

Safety Analysis Set	Total	Exposed to Dupilumab
Overall from 3 studies in children with AD		
Received at least 1 dose	399	391(1)
Cumulative treatment duration ≥16 weeks	NA	351
Cumulative treatment duration ≥26 weeks (6 months)		273
Cumulative treatment duration ≥ 52 weeks (1 year)	NA	101
Cumulative treatment duration ≥104 weeks (2 years)	NA	25
R668-AD-1652 – phase 3, pivotal, placebo-controlled, 16-week treatment of Dupilumab + TCS (300 mg Q4W or 100/200 mg Q2W) efficacy and safety study		
Received at least 1 dose	362	242
Cumulative treatment exposure ≥29 days (4 weeks)	361	241
Cumulative treatment exposure ≥16 weeks	258	177
R668-AD-1412 – phase 2a, open-label, 4-week treatment PK study		
Received at least 1 dose	37	37
Received the total 5 doses	37	37
Cumulative treatment exposure ≥ 4 weeks	37	37
R668-AD-1434 – phase 3, OLE, safety and efficacy study[2]		
Received at least 1 dose	368	368
Cumulative treatment exposure ≥4 weeks	368	368
Cumulative treatment exposure ≥26 weeks	227	227
Cumulative treatment exposure ≥52 weeks	38	38
Cumulative treatment exposure ≥104 weeks	25	25

Safety Analysis Set	Total	Exposed to Dupilumab
Cumulative exposure to Dupilumab (prior study and R668-AD-1434)[3]		
Received at least 1 dose	391	391
Cumulative treatment exposure ≥4 weeks	391	391
Cumulative treatment exposure ≥16 weeks	351	351
Cumulative treatment exposure ≥52 weeks	101	101
Cumulative treatment exposure ≥104 weeks	25	25

* Source: Table 7 of Clinical Overview and Post-text Table 5.2.1/2b for Study 1434 (second-step analysis)

[1] Includes all patients who received at least 1 dose of dupilumab in either the parent study or the OLE study: 354 patients from R668-AD-1652 (8 patients in the placebo group did not roll over to the OLE study, so did not receive any dupilumab dose) and 37 patients from R668-AD-1412.

[2] Under the original version of the OLE protocol, patients received 2 mg/kg QW or 4 mg/kg QW. Under protocol amendment 1 of the OLE, when patients from the pivotal Study R666-AD-1652 began to enroll into the OLE, patients received 300 mg Q4W; patients could be switched to a Q2W regimen in case of inadequate response (for patients weighing ≥60 kg, 300 mg Q2W; for patients weighing <60 kg, 200 mg Q2W).

[3] Cumulative Exposure in Prior Study and OLE R668-AD-1434 was calculated based on individual patients' treatment period in both the prior study and the OLE study. Treatment gap between the studies were not counted.

NA = not available

Study 143 (OLE)

A total of 368 patients were enrolled at the time of the second-step analysis. Of those, 217 (59.0%) had completed at least Week 26, and 39 (10.6%) had completed at least Week 52.

Table 19. Summary of Treatment Exposure to Dupilumab for Patients in the OLE - Children ≥6 to <12 Years of Age (SAF)*

Exposure Characteristics	Exposure to Dupilumab for All Patients in OLE Total (N=368)
Overall Treatment exposure (Weeks)	
n	368
Mean (SD)	35.84 (36.538)
Q1	18.21
Median	29.64
Q3	40.21
Min : Max	4.0 : 188.4
Number (%) of patients with overall treatment exposure (weeks)	
1 - <4 Weeks	0
4 - <16 Weeks	84 (22.8%)
16 - <26 Weeks	57 (15.5%)
26 - <52 Weeks	189 (51.4%)
52 - <78 Weeks	11 (3.0%)
78 - <104 Weeks	2 (0.5%)
104 - <130 Weeks	5 (1.4%)
130 - <156 Weeks	4 (1.1%)
156 - <182 Weeks	14 (3.8%)
182 - <208 Weeks	2 (0.5%)
208 - <234 Weeks	0
Number (%) of patients with overall treatment exposure (weeks) cumulatively	
≥1 Week	368 (100%)
≥4 Weeks	368 (100%)
≥16 Weeks	284 (77.2%)
≥26 Weeks	227 (61.7%)
≥52 Weeks	38 (10.3%)
≥78 Weeks	27 (7.3%)
≥104 Weeks	25 (6.8%)
≥130 Weeks	20 (5.4%)
≥156 Weeks	16 (4.3%)
≥182 Weeks	2 (0.5%)
≥208 Weeks	0

Adequacy of the safety database:

The safety database was adequate in size, extent of exposures (concentrations and duration), and the nature of the safety assessments to evaluate the safety of dupilumab in patients 6 to < 12 years with moderate-to-severe AD, under conditions of intended use.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data integrity and submission quality were adequate.

Categorization of Adverse Events

The Applicant's categorization procedures for adverse events were acceptable.

The Applicant coded AEs from the time of informed consent signature and then at each visit until the end of the study. The Applicant coded and classified all AEs according to the primary SOC, High Level Term, and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA): Version 22.0 for Study 1652, 21.1 for Study 1434, and 18.0 for Study 1412.

The Applicant coded and classified AEs according to the primary SOC, High Level Term and PT according to the current version at the time of analysis of the MedDRA for each study. All medications and treatment procedures were coded using the World Health Organization-Drug Dictionary.

To identify possible adverse drug reactions (ADRs), the Applicant applied statistical criteria to TEAE PT in Study 1652 (placebo-controlled study). These criteria were similar to that used in the adult and adolescent AD studies:

- Incidence ≥1% in either dupilumab treatment or combined group.
- Lower bound of the 95% CI for Cox hazard ratio versus placebo >1.
- Medical judgment.

The Applicant also evaluated less frequent PTs for their potential to be ADRs based on strong biological mechanism or medical judgment.

Safety monitoring was similar to what was done in the adolescent and adult AD programs, as the Applicant anticipated a similar safety profile. Safety monitoring considered:

- mechanism of action of dupilumab,
- risks associated with SC injection of monoclonal antibodies,
- complications and co-morbidities associated with AD,

- data from dupilumab clinical studies in adults, and
- general safety assessments (collection of AEs, routine laboratory assessments, physical examinations, vital signs, electrocardiograms [ECGs]).

An Independent Data Monitoring Committee or study monitoring team participated in data review for all studies.

Adverse Events of Special Interest were principally defined based on the safety profile from evaluation of dupilumab in adults. The following events were designated as AESIs in studies 1652 and 1434 and required expedited reporting (within 24 hours) by the investigator to the Applicant:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, non-metastatic squamous or basal cell carcinoma of the skin in Study 1434)
- Helminthic infections
- Suicide-related events
- Conjunctivitis (any type), keratitis, or blepharitis (only events that are either severe or serious or lasting ≥4 weeks will be reported as AESIs)

The medical officer's review of the original BLA submission provides some information regarding the designation of "suicide-related events" as an AESI. From p. 152 of that review (review dated March 27, 2017):

> The FDA requested that Suicidal Behavior (Suicidal Ideation, Suicide Attempt and Completed Suicide) be included as an AESI. The Agency made this request in the pre-BLA communication; however, the rationale was not stated in the communication.

Routine Clinical Tests

Safety assessments included collection of adverse events, clinical laboratory assessments, and ECG. The schedule of testing varied according to the study and was specified in the respective SAP for each study. Laboratory testing generally included clinical chemistry, hematology, and urinalysis evaluations.

8.2.4. Safety Results

Deaths

There were no deaths in the development program.

Serious Adverse Events

No SAEs appeared to implicate dupilumab.

Study 1652 (Pivotal)

Four subjects experienced SAEs during the treatment period:

- 2 (1.7%) in the Q4W group:
    1. *Food allergy*. A 6 y/o white female with a history of allergy to eggs, nuts, and fish, experienced a Food Allergy (verbatim: allergic hives after nuts) on Day 38, after ingesting cake that contained nuts. This event was also an AESI.
    2. *Urinary tract infection*. A 6 y/o white female experienced a Urinary tract infection on Day 40 (10 days after the most recent dose of study drug). She was hospitalized on Day 44, with discharge on Day 46. Study drug was continued on Day 57. She received all doses of study drug (last dose on Day 91).
- 2 (1.7%) in the placebo group:
    1. *Dermatitis atopic*. An 11 y/o white female experienced Dermatitis atopic (verbatim: worsening of atopic dermatitis) on Day 8.
    2. *Asthma*. A 7 y/o white female was hospitalized for Asthma (verbatim: asthma exacerbation) on Day 112 (28 days after the final dose of study drug).

Table 20. Summary of Serious TEAEs During the 16-Week Treatment Period by SOC and PT – SAF*

Primary System Organ Class Preferred Term MedDRA Version 22.0	Placebo + TCS (N=120)	Dupilumab 300mg Q4W + TCS (N=120)	Dupilumab 100mg or 200mg Q2W + TCS (N=122)	Dupilumab Combined (N=242)
Number of such events	2	2	0	2
Number of patients with at least one such event, n (%)	2 (1.7%)	2 (1.7%)	0	2 (0.8%)
Immune system disorders	0	1 (0.8%)	0	1 (0.4%)
Food allergy	0	1 (0.8%)	0	1 (0.4%)
Infections and infestations	0	1 (0.8%)	0	1 (0.4%)
Urinary tract infection	0	1 (0.8%)	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	0	0
Asthma	1 (0.8%)	0	0	0
Skin and subcutaneous tissue disorders	1 (0.8%)	0	0	0
Dermatitis atopic	1 (0.8%)	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, PT = Preferred term, PTT = Post-text table, Q2W = Once every 2 weeks, Q4W = Once every 4 weeks, SAF = Safety Analysis Set, SOC = System organ class, TCS = Topical corticosteroids, TEAE = Treatment-emergent adverse event.
Note: At each level of patient summarization, a patient is counted once if the patient-reported one or more event.
*Source: Table 60 of study report for 1652

One subject (3%) experienced an SAE during the follow-up period: A 7 y/o female experienced a Bone Contusion (contusion of the cervical spine) on Day 118.

Study 1434 (OLE)

A total of 9 subjects (2.4%) experienced a 16 SAEs, and the outcome for all events was "resolved." The two events of "Anaphylactic reaction" were also recorded as AESIs. No subjects permanently discontinued treatment due to an SAE. All SAEs resolved, and none were considered related to dupilumab.

Table 21. Summary of Incidence and Rate of Serious Treatment-Emergent Adverse Events Per 100 Patient-Years by System Organ Class and Preferred Term - Children ≥6 to <12 Years of Age (SAF)*

Primary System Organ Class Preferred Term MedDRA version 21.1	Total (N=368)	Total (N=368) nP/PY (nP/100 PY) [1]
Number of SAEs	16	
Patients with at least one SAE	9 (2.4%)	9/257.3 (3.50)
Immune system disorders	2 (0.5%)	2/270.7 (0.74)
Anaphylactic reaction	2 (0.5%)	2/270.7 (0.74)
Infections and infestations	2 (0.5%)	2/268.5 (0.74)
Impetigo	1 (0.3%)	1/269.2 (0.37)
Pneumonia	1 (0.3%)	1/272.1 (0.37)
Injury, poisoning and procedural complications	2 (0.5%)	2/271.6 (0.74)
Post procedural hemorrhage	1 (0.3%)	1/271.8 (0.37)
Upper limb fracture	1 (0.3%)	1/272.5 (0.37)
Blood and lymphatic system disorders	1 (0.3%)	1/269.5 (0.37)
Lymphadenopathy	1 (0.3%)	1/269.5 (0.37)
Congenital, familial and genetic disorders	1 (0.3%)	1/272.1 (0.37)
Cryptorchism	1 (0.3%)	1/272.1 (0.37)
Gastrointestinal disorders	1 (0.3%)	1/271.5 (0.37)
Abdominal Pain	1 (0.3%)	1/271.5 (0.37)
Investigations	1 (0.3%)	1/270.8 (0.37)
Allergy test	1 (0.3%)	1/270.8 (0.37)
Musculoskeletal and connective tissue disorders	1 (0.3%)	1/270.9 (0.37)
Arthralgia	1 (0.3%)	1/270.9 (0.37)
Nervous system disorders	1 (0.3%)	1/269.4 (0.37)
Complex regional pain syndrome	1 (0.3%)	1/269.4 (0.37)
Dizziness postural	1 (0.3%)	1/269.9 (0.37)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1/272.3 (0.37)
Asthma	1 (0.3%)	1/272.3 (0.37)
Tonsillar hypertrophy	1 (0.3%)	1/272.4 (0.37)

Patients who experienced more than 1 TEAE were counted only once in each category
Note: For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of study observation period.
[1] Total patient years were calculated as the sum of study observational period over all patients.
*Source: Table 24 of study report for 1434 (second-step analysis)
Abbreviations: MedDRA = medical dictionary for regulatory activities, nP = number of patients with events, PY = patient-years, nP/100 PY = number of patients with events per 100 patient years, TEAE = treatment- emergent adverse event, SAF = safety analysis population.

Information on some of those SAEs is provided below (limb fracture and post procedural hemorrhage are not discussed):

- *Lymphadenopathy*. An 11 y/o mixed-race female experienced swelling of left inguinal lymph nodes on Day 80, after 12 doses (2 days after the most recent dose of study

drug). She was hospitalized, and the nodes were excised on Day 82. Histopathology revealed that "the lymph node swelling may have been caused by a viral infection or atopic eczema, without any suspicion of a bacterial infection." She received intravenous antibiotics and was discharged on Day 86, with the event resolved. She resumed study treatment on Day 116.

- *Allergy Test*. A 7 y/o white female was hospitalized on Day 530 for a provocation test for a suspected food allergy of baked eggs.
- *Pneumonia*. A 7 y/o white female was diagnosed and hospitalized with pneumonia on Day 34, after 5 doses (4 days after the most recent dose of study drug). A chest x-ray showed "scare (sic) inflammatory density in the inferior area of the right lung." No culture results were provided. Treatment included intravenous antibiotics. The pneumonia was considered resolved on Day 35. Study drug was resumed on Day 57.
- A 10 y/o white male with "a possible diagnosis of Ehlers Danlos syndrome/ Marfan variant" and for whom "Loeys-Dietz syndrome had also been suggested," experienced numerous SAEs over the course of the study as follows: complex regional pain syndrome on Day 20, dizziness postural on Day 201, arthralgia on Day 551, abdominal pain on Days 786 and 791, asthma on Day 1104, and tonsillar hypertrophy on Day 1071. It does not appear that study treatment was discontinued for any of these events. The events of asthma and tonsillar hypertrophy occurred after completion of study treatment (11 and 282 days, respectively. He had received 101 doses of the study drug.
- *Anaphylactic reaction*. An 11 y/o white male, with known food allergies (cashew nuts, egg, and cow's milk), experienced the SAE and AESI of anaphylactic reaction on Day 532 at school, after a total of 76 doses of study drug (6 days after the most recent dose). A trigger for the reaction was not identified. The event was resolved on Day 533, following treatment. He experienced another anaphylactic reaction on Day 831 following an allergy test to confirm the cashew allergy. Study drug was continued according to plan.
- *Impetigo*. An 11 y/o mixed-ethnicity male who was hospitalized for impetigo on the scalp (group A Streptococcus and *Staphylococcus aureus*) on Day 10. Signs of the infection had been present on Day 1. He was treated with intravenous clindamycin, and the event was resolved on Day 21. Study drug was continued.
- *Anaphylactic reaction*. A 7 y/o Hispanic or Latino male experienced the SAE/ AESI of Anaphylactic reaction to an unknown food on Day 307, after a total of 17 doses of study drug (12 days after the most recent dose). He had known food allergies (eggs, nuts, oranges, pineapple, seafood, and dairy). He was hospitalized, and treatment included systemic steroids. He was discharged on Day 308. Per protocol, study treatment was discontinued for 4 weeks due to the steroids he received. Study treatment was resumed on Day 351.

Study 1412 (Open-label, ascending dose)

Two of 37 patients (5.4%) experienced SAEs, and both events occurred in the 4 mg/kg group (both patients had received a single dose of study drug prior to the event, which constituted the full dosing regimen for Part A of Study 1412):

- A 6 y/o white female was hospitalized for worsening of AD (study day is unclear from the narrative). Skin cultures grew *Staphylococcus aureus*. The event resolved with treatment, and she was discharged ~ 2 weeks later and completed the study.
- A 10 y/o white male was hospitalized (study day is unclear from the narrative) for painful hip and fever. He was diagnosed with bacterial arthritis. Treatment included intravenous antibiotics. He was discharged ~ 2 weeks after admission. Study drug was "temporarily withdrawn."

These SAEs would not seem likely related to dupilumab, as both occurred after only one dose. Both individuals completed the study.

Dropouts and/or Discontinuations Due to Adverse Effects

Study 1652 (Pivotal)

Four subjects experienced AEs that led to discontinuation of study treatment; none of the events were serious:

- 2 (1.6%) in the Q2W group:
    1. *Food allergy*. A 6 y/o black male experienced a food allergy (verbatim: allergic reaction to peanuts) on Day 75 after eating ice cream containing nuts. He had a history of peanut allergy. Study drug was discontinued as the subject received steroid (oral and inhalant) as treatment for the allergic reaction.
    2. *Conjunctivitis bacterial*. A 10 y/o Hispanic or Latino male experienced conjunctivitis (bacterial) on Day 73. He experienced initial symptoms (dry eye) on Day 55. He was evaluated (Day 87) and treated by an ophthalmologist. He received his final dose of study treatment on Day 72. The event was considered ongoing, but as of what date is unclear from the narrative.
- 2 (1.7%) in the placebo group:
    1. *Asthma*. A 7 y/o white male experienced asthma (verbatim term: asthma exacerbation) on Day 42. He had experienced Influenza B virus infection on Day 40. The asthma was solved on Day 44; the influenza was resolved on Day 45. Study treatment was discontinued.
    2. *Dermatitis atopic*. A 7 y/o white female experienced dermatitis atopic on Day 67, for which she ultimately received oral steroids (Day 79).

These events are not worrisome in the context of the study for the following reasons:

- A patient experienced an allergic reaction after exposure to an allergen known to him.
- Conjunctivitis is a known adverse reaction with dupilumab treatment.
- The role of influenza in contributing to the asthma exacerbation is unclear.
- A patient with moderate-to-severe AD experienced a disease flare while on placebo (with TCS).

Study 1434 (OLE)

Two patients permanently discontinued study drug due to TEAEs:

- A 7 y/o white female (placebo in parent study) experienced a flare of AD on Day 83. Treatment included oral prednisolone. She was discontinued from the study.
- A 9-year-old white female (300 mg Q4W in the parent study) experienced headache and blurred vision on Day 91. Papilledema and optic disc drusen were identified on fundoscopic examination. Study treatment was permanently discontinued.

Optic disc drusen are acellular, intra- and extracellular deposits that occur in 0.4% of children. The principal clinical significance is that they may be misdiagnosed as optic disk edema, leading to extensive workup for increased intracranial pressure (this patient was initially diagnosed with intracranial hypertension and underwent a lumbar puncture and MRI). The pathogenesis is unclear. A role for dupilumab here is unclear.[14]

Significant Adverse Events

Severe Adverse Events

Study 1652 (Pivotal)

Most severe AEs (77%) occurred in the placebo group. The only severe AE experienced by more than one subject was dermatitis atopic, and all subjects were in the placebo group. See Table 22.

[14] Chang MY and Pineles SL. Optic disk drusen in children. Survey of ophthalmology.61(2016) 745-758.

Table 22. Severe TEAEs During the 16-Week Treatment Period by SOC and PT – SAF*

Primary System Organ Class Preferred Term MedDRA Version 22.0	Placebo + TCS (N=120)	Dupilumab 300mg Q4W + TCS (N=120)	Dupilumab 100mg or 200mg Q2W + TCS (N=122)	Dupilumab Combined (N=242)
Number of events	10	0	3	3
Number of patients with at least one such event, n (%)	7 (5.8%)	0	3 (2.5%)	3 (1.2%)
Infections and infestations	4 (3.3%)	0	2 (1.6%)	2 (0.8%)
Gastroenteritis viral	0	0	1 (0.8%)	1 (0.4%)
Respiratory tract infection	0	0	1 (0.8%)	1 (0.4%)
Dermatitis infected	1 (0.8%)	0	0	0
Herpes simplex	1 (0.8%)	0	0	0
Impetigo	1 (0.8%)	0	0	0
Nasopharyngitis	1 (0.8%)	0	0	0
Rhinitis	1 (0.8%)	0	0	0
Eye disorders	0	0	1 (0.8%)	1 (0.4%)
Conjunctivitis allergic	0	0	1 (0.8%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	0	0
Rhinitis allergic	1 (0.8%)	0	0	0
Skin and subcutaneous tissue disorder	3 (2.5%)	0	0	0
Dermatitis atopic	3 (2.5%)	0	0	0

*Source: Table 58 of study report for 1652

Study 1434 (OLE)

A total of 12 patients (3.3%) had severe TEAEs. The only severe TEAEs that were reported by more than one patient were anaphylactic reaction and dermatitis atopic, each reported by 3 patients.

Adverse Events of Special Interest (AESIs) in Study 1652 (Pivotal)

AESIs were defined as:

- Systemic or extensive hypersensitivity reactions, including anaphylactic reactions
- Malignancy
- Helminthic infections
- Suicide-related events

Conjunctivitis (any type or etiology), keratitis or blepharitis (only events that are either severe or serious or lasting ≥4 weeks will be reported as AESIs)

A total of four subjects experienced four AESIs. No more than one subject in a treatment group experienced a particular AESI.

Table 23. Summary of Treatment-Emergent AESIs by AESI Category, High Level Term, and PT During the 16-Week Treatment Period – SAF*

AESI Category High Level Term Preferred Term MedDRA Version 22.0	Placebo + TCS (N=120)	Dupilumab 300mg Q4W + TCS (N=120)	Dupilumab 100mg or 200mg Q2W + TCS (N=122)	Dupilumab Combined (n=242)
Number of patients with at least one such event, n (%)	1 (0.8%)	2 (1.7%)	2 (1.6%)	4 (1.7%)
Any type of conjunctivitis or blepharitis (only events either severe or serious)	0	0	1 (0.8%)	1 (0.4%)
Conjunctival infections, irritations and inflammations	0	0	1 (0.8%)	1 (0.4%)
Conjunctivitis allergic	0	0	1 (0.8%)	1 (0.4%)
Helminthic infections	1 (0.8%)	1 (0.8%)	0	1 (0.4%)
Nematode infections	1 (0.8%)	1 (0.8%)	0	1 (0.4%)
Ascariasis	0	1 (0.8%)	0	1 (0.4%)
Enterobiasis	1 (0.8%)	0	0	0
Keratitis	0	0	1 (0.8%)	1 (0.4%)
Corneal infections, edemas and inflammations	0	0	1 (0.8%)	1 (0.4%)
Keratitis	0	0	1 (0.8%)	1 (0.4%)
Systemic or severe hypersensitivity reactions	0	1 (0.8%)	0	1 (0.4%)
Allergies to foods, food additives, drugs and other chemicals	0	1 (0.8%)	0	1 (0.4%)
Food allergy	0	1 (0.8%)	0	1 (0.4%)

*Source: Table 61 of study report for 1652

Heliminthic infections invoke immune responses that involve Th2 cytokines, including IL-4 and IL-13.[15] Because dupilumab inhibits signaling of these two cytokines, the Applicant considered Helminthic infections as AESIs. Two subjects experienced these infections:

- *Ascariasis*. A 9 y/o white female in the Q4W group developed ascariasis on Day 61. The subject was asymptomatic; the event was "accidentally" diagnosed by enzyme-linked immunosorbent assay test on allergy consultation. Past exposure to the nematode could not be excluded. (Note: No clarifying history was provided regarding the "accidental

[15] Kreider T et al. Alternatively activated macrophages in helminth infections. Current Opinion in Immunology 2007, 19:448–453.

diagnosis.") She was treated, and the event was considered resolved on Day 91. She received all planned doses of study drug.

- *Enterobiasis*. A 9 y/o white female in the placebo group developed enterobiasis on Day 84.

Conjunctivitis and keratitis are recognized adverse reactions associated with dupilumab use, and the label includes a Warning and Precaution addressing these events. Two subjects experienced events of these types:

- *Conjunctivitis allergic*. A 7 y/o white female in the Q2W group experienced conjunctivitis allergic on Day 96. She was evaluated by an ophthalmologist on Day 103, and treatment included steroid eye drops. The event was ongoing on Day 120, and the eye drops were continued until Day 218. The event was considered resolved on Day 232. She received all planned doses of study drug.
- *Keratitis*. An 8 y/o white male in the Q2W group experienced keratitis on Day 57. He was also found to have conjunctivitis. He had received a dose of study drug that same day. His presentation included itching and redness of the eyes. He was treated with artificial tears from Days 63 to 69. He was evaluated by an ophthalmologist on Day 85, and treatment included steroid eye drops. At follow-up on Day 126, the ophthalmologist determined the events to be ongoing, and the event outcome was considered "not recovered/not resolved." He received all planned doses of study drug.

Conjunctivitis and keratitis are more broadly discussed in Section 8.2.5.

The AESI of "food allergy" was also an SAE, and this subject has been previously discussed.

AESIs in Study 1434 (OLE)

A total of 11 subjects (3.0%) experienced 15 AESIs. These events included two anaphylactic events that were reported as SAEs.

Table 24. Incidence and Rate of Adverse Events of Special Interest Per 100 Patient- Years by Adverse Events of Special Interest Category and Preferred Term - Children ≥6 to <12 Years of Age (SAF)*

AESI Category **Preferred Term** **MedDRA version 21.1**	**Total (N=368)**	**Total (N=368)** **nP/PY (nP/100PY)**
Number of AESIs n(%)	15	
Patients with at least one AESI	11 (3.0)	11/264.8 (4.15)
Anaphylactic Reaction	4 (1.1%)	4/270.3 (1.48)
Anaphylactic Reaction	4 (1.1%)	4/270.3 (1.48)
Helminthic Infections	4 (1.1%)	4/268.8 (1.49)
Enterobiasis	3 (0.8%)	3/269.0 (1.12)
Strongyloidiasis	1 (0.3%)	1/272.6 (0.37)

AESI Category Preferred Term MedDRA version 21.1	Total (N=368)	Total (N=368) nP/PY (nP/100PY)
Keratitis	3 (0.8%)	3/271.5 (1.11)
Keratitis	2 (0.5%)	2/272.0 (0.74)
Atopic keratoconjunctivitis	1 (0.3%)	1/272.2 (0.37)
Severe or Serious Conjunctivitis or Blepharitis	1 (0.3%)	1/272.2 (0.37)
Conjunctivitis bacterial	1 (0.3%)	1/272.2 (0.37)
Systemic or Severe Hypersensitivity	1 (0.3%)	1/272.0 (0.37)
Food allergy	1 (0.3%)	1/272.0 (0.37)

*Source: Table 25 of study report for 1434 (second-step analysis)

The following high-level information is presented for subjects who experienced AESIs in Study 1434 (except for two subjects who were previously discussed under SAEs):

- *Enterobiasis*. An 8-year-old white male who had a history of enterobiasis was diagnosed with enterobiasis on Day 416, after 52 doses of study treatment (55 days after his final dose).
- *Food allergy*. An 8-year-old white male with known allergy to peanuts and hazelnuts experienced food allergy (verbatim term: allergic reaction after eating ice cream with nuts) on Day 1012.
- *Enterobiasis*. A 9-year-old black female was diagnosed with enterobiasis on Day 55, after two doses of study treatment (26 days after the most recent dose). She was treated on Day 58 and continued study drug.
- *Enterobiasis*. An 11-year-old white male with a history of previous episodes of enterobiasis was diagnosed with enterobiasis on Day 90 after 6 doses of study treatment (3 days after the most recent dose). He recovered following treatment and continued study drug.
- *Conjunctival bacterial*. A 10-year-old white male experienced conjunctival bacterial on Day 118 after 5 doses (4 days after most recent dose) and atopic keratoconjunctivitis on Day 126. The conjunctivitis was resolved on Day 136, and the atopic keratoconjunctivitis was resolving. Study drug was continued.
- *Anaphylactic reaction*. A 9-year-old white male experienced an anaphylactic reaction on Day 105 after four doses (21 days after his most recent dose) while playing in long grass. He experienced Keratitis on the same day. On Day 112, 28 days after his most recent dose, he experienced a second anaphylactic reaction. Both anaphylactic reactions resolved on the day of occurrence.
- *Strongyloidiasis*. A 6-year-old black or African-American female was diagnosed with strongyloidiasis Day 62, based on the results of an “IgG blood test” performed on Day 44 after a total of three doses (1 day after most recent dose). She was given treatment, and the event was considered resolved on Day 64. She continued study drug as planned.

- *Keratitis*. A 6-year-old white male developed keratitis (verbatim term: keratitis [unknown type]) on Day 29 after one dose of study drug (28 days after the first dose). The event was resolved on Day 114 following treatment. He continued study drug as planned.
- *Anaphylactic reaction*. A 7-year-old white male experienced an anaphylactic reaction on Day 172, after five doses (59 days after his final dose). The event was believed to have been due to exposure to eggs. He had a history of numerous food allergies (peanut, tree nut, corn, coconut, strawberry, milk, egg, legumes, peas, sesame, and avocado), and drug allergies (amoxicillin, cephalexin, and azithromycin).

No new safety signals were identified with long-term exposure.

Treatment-Emergent Adverse Events and Adverse Reactions

Study 1652 (Pivotal)

TEAEs were most often reported in the Infections and Infestations SOC. The three most commonly-reported events in that SOC (in order of frequency) were nasopharyngitis, upper respiratory tract infection, and conjunctivitis.

Table 25. Summary of TEAEs Reported by ≥2% of Patients in Any Treatment Group During the 16-Week Treatment Period by Primary SOC and PT– SAF*

Primary System Organ Class Preferred Term MedDRA Version 22.0	Placebo + TCS (N=120)	Dupilumab 300mg Q4W + TCS (N=120)	Dupilumab 100mg or 200mg Q2W + TCS (N=122)	Combined (N=242)
Number of patients with at least one such event, n (%)	88 (73.3%)	78 (65.0%)	82 (67.2%)	160 (66.1%)
Infections and infestations	61 (50.8%)	52 (43.3%)	49 (40.2%)	101 (41.7%)
Nasopharyngitis	8 (6.7%)	15 (12.5%)	8 (6.6%)	23 (9.5%)
Upper respiratory tract infection	12 (10.0%)	13 (10.8%)	10 (8.2%)	23 (9.5%)
Conjunctivitis	3 (2.5%)	5 (4.2%)	7 (5.7%)	12 (5.0%)
Molluscum contagiosum	1 (0.8%)	2 (1.7%)	5 (4.1%)	7 (2.9%)
Conjunctivitis bacterial	1 (0.8%)	0	5 (4.1%)	5 (2.1%)
Furuncle	3 (2.5%)	2 (1.7%)	1 (0.8%)	3 (1.2%)
Otitis media	3 (2.5%)	2 (1.7%)	1 (0.8%)	3 (1.2%)
Pharyngitis streptococcal	3 (2.5%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Rhinitis	3 (2.5%)	3 (2.5%)	0	3 (1.2%)
Viral upper respiratory tract infection	6 (5.0%)	2 (1.7%)	1 (0.8%)	3 (1.2%)
Folliculitis	3 (2.5%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Impetigo	5 (4.2%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Influenza	4 (3.3%)	1 (0.8%)	0	1 (0.4%)
Dermatitis infected	5 (4.2%)	0	0	0

Primary System Organ Class Preferred Term MedDRA Version 22.0	Placebo + TCS (N=120)	Dupilumab 300mg Q4W + TCS (N=120)	Dupilumab 100mg or 200mg Q2W + TCS (N=122)	Combined (N=242)
Skin and subcutaneous tissue disorders	23 (19.2%)	20 (16.7%)	19 (15.6%)	39 (16.1%)
Dermatitis atopic	17 (14.2%)	8 (6.7%)	10 (8.2%)	18 (7.4%)
Urticaria	3 (2.5%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
Skin exfoliation	0	0	3 (2.5%)	3 (1.2%)
Gastrointestinal disorders	17 (14.2%)	17 (14.2%)	17 (13.9%)	34 (14.0%)
Vomiting	8 (6.7%)	6 (5.0%)	6 (4.9%)	12 (5.0%)
Diarrhea	2 (1.7%)	5 (4.2%)	3 (2.5%)	8 (3.3%)
Abdominal pain upper	5 (4.2%)	4 (3.3%)	2 (1.6%)	6 (2.5%)
Abdominal pain	3 (2.5%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
Nausea	3 (2.5%)	3 (2.5%)	1 (0.8%)	4 (1.7%)
General disorders and administration site conditions	15 (12.5%)	17 (14.2%)	17 (13.9%)	34 (14.0%)
Injection site erythema	2 (1.7%)	5 (4.2%)	7 (5.7%)	12 (5.0%)
Injection site swelling	1 (0.8%)	4 (3.3%)	6 (4.9%)	10 (4.1%)
Pyrexia	4 (3.3%)	4 (3.3%)	3 (2.5%)	7 (2.9%)
Injection site pain	3 (2.5%)	3 (2.5%)	2 (1.6%)	5 (2.1%)
Respiratory, thoracic and mediastinal disorders	31 (25.8%)	14 (11.7%)	15 (12.3%)	29 (12.0%)
Cough	9 (7.5%)	3 (2.5%)	5 (4.1%)	8 (3.3%)
Rhinitis allergic	5 (4.2%)	3 (2.5%)	4 (3.3%)	7 (2.9%)
Asthma	12 (10.0%)	2 (1.7%)	4 (3.3%)	6 (2.5%)
Oropharyngeal pain	5 (4.2%)	3 (2.5%)	0	3 (1.2%)
Eye disorders	8 (6.7%)	7 (5.8%)	15 (12.3%)	22 (9.1%)
Conjunctivitis allergic	1 (0.8%)	3 (2.5%)	5 (4.1%)	8 (3.3%)
Nervous system disorders	15 (12.5%)	8 (6.7%)	10 (8.2%)	18 (7.4%)
Headache	10 (8.3%)	6 (5.0%)	7 (5.7%)	13 (5.4%)
Immune system disorders	2 (1.7%)	3 (2.5%)	3 (2.5%)	6 (2.5%)
Food allergy	0	1 (0.8%)	3 (2.5%)	4 (1.7%)
Neoplasms benign, malignant and unspecified	1 (0.8%)	4 (3.3%)	1 (0.8%)	5 (2.1%)
Skin papilloma	0	4 (3.3%)	1 (0.8%)	5 (2.1%)

*Source: Table 57 of study report for 1652

Study 1434 (OLE)

TEAEs occurred in 219 (59.5%) patients during the study with an event per 100 patient-years of 245.73 patients per 100 patient years (nP/100 patient-years).

Table 26. Summary of Patients With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Reported in ≥2% of Patients by SOC and PT) - Children ≥6 to <12 Years of Age (SAF)*

Primary System Organ Class Preferred Term MedDRA version 21.1	Total (N=368)	Total (N=368) nP/PY (nP/100PY) [1]
Number of TEAEs	1102	
Patients with at least one TEAE	219 (59.5%)	219/89.1 (245.73)
Infections and infestations	149 (40.5%)	149/135.7 (109.77)
Nasopharyngitis	48 (13.0%)	48/213.1 (22.53)
Upper respiratory tract infection	34 (9.2%)	34/244.2 (13.92)
Conjunctivitis bacterial	10 (2.7%)	10/261.4 (3.83)
Ear infection	10 (2.7%)	10/264.5 (3.78)
Pharyngitis streptococcal	10 (2.7%)	10/269.5 (3.71)
Sinusitis	9 (2.4%)	9/267.1 (3.37)
Conjunctivitis	8 (2.2%)	8/266.6 (3.00)
Oral herpes	8 (2.2%)	8/266.3 (3.00)
Skin and subcutaneous tissue disorders	87 (23.6%)	87/211.6 (41.12)
Dermatitis atopic	58 (15.8%)	58/234.0 (24.79)
Urticaria	9 (2.4%)	9/268.4 (3.35)
Rash	8 (2.2%)	8/267.0 (3.00)
Respiratory, thoracic and mediastinal disorders	63 (17.1%)	63/212.6 (29.63)
Cough	25 (6.8%)	25/245.0 (10.20)
Oropharyngeal pain	14 (3.8%)	14/256.0 (5.47)
Rhinitis allergic	13 (3.5%)	13/264.9 (4.91)
Asthma	12 (3.3%)	12/263.8 (4.55)
Epistaxis	9 (2.4%)	9/266.9 (3.37)
Eye disorders	41 (11.1%)	41/251.5 (16.30)
Conjunctivitis allergic	24 (6.5%)	24/259.9 (9.23)
General disorders and administration site conditions	40 (10.9%)	40/241.4 (16.57)
Pyrexia	16 (4.3%)	16/257.8 (6.21)
Gastrointestinal disorders	30 (8.2%)	30/233.4 (12.85)
Vomiting	13 (3.5%)	13/256.0 (5.08)
Injury, poisoning and procedural complications[2]	26 (7.1%)	26/249.0 (10.44)
Nervous system disorders	23 (6.3%)	23/242.9 (9.47)
Headache	20 (5.4%)	20/249.4 (8.02)
Immune system disorders[3]	21 (5.7%)	21/261.4 (8.03)
Musculoskeletal and connective tissue disorders[4]	15 (4.1%)	15/252.8 (5.93)

Abbreviations: incl = including, MedDRA = medical dictionary for regulatory activities, nP = number of patients with an event, PY = patient-years, nP/100 PY = number of events per 100 patient-year, SAF = safety analysis population, SOC = system organ class
Note: Patients who experienced more than 1 TEAE were counted only once in each category. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of study observation period.
[1] Total patient years were calculated as the sum of the study observational period over all patients.
[2] Most common PTs: Contusion and Upper limb fracture (both 5 patients, 1.4%)
[3] Most common PT: Food allergy (7 patients, 1.9%)
[4] Most common PT: Arthralgia (5 patients, 1.4%)
*Source: Table 23 of study report for 1434 (second-step analysis)

Adverse Events by Body Weight

Body weight is the main covariate that affects the PK of dupilumab. The Applicant reported that:

- For subjects <30 kg: C_{trough} values at Week 16 were higher for the 300 mg Q4W regimen than for the 100 mg Q2W regimen.
- For subjects ≥30 kg: C_{trough} values at Week 16 were higher for the 200 mg Q2W regimen than for the 300 mg Q4W regimen.

In subjects <30 kg, the overall incidence of TEAEs was lower in the 300 mg Q4W group (the higher exposure group) compared to the 100 mg Q2W group: 65% versus 73%, respectively. This was primarily attributable to the lower incidence of AD-related TEAEs in the higher exposure group (i.e., the 300 mg Q4W group). The incidence of AD was 7% in the 300 mg Q4W group and 13% in the 100 mg Q2W group. The incidence of conjunctivitis events (conjunctivitis, conjunctivitis bacterial, conjunctivitis allergic) was also lower in the 300 mg Q4W group compared to the 100 mg Q2W group, the lower exposure group. Herpes infections were also less common in the higher exposure group. The Applicant suggested a possible preventative effect of the higher exposures from the 300 mg Q4W group on certain TEAEs.

In subjects ≥30 kg, the overall incidence of TEAEs was lower for the 200 mg Q2W (61%) compared to the 300 mg Q4W group (65%). The difference here was principally attributable to the lower incidence of AD-related TEAEs (AD, asthma, allergic rhinitis) in the 200 mg Q2W group. The incidence of conjunctivitis was 5% in the 300 mg Q4W group and 1.7% in the 200 mg Q2W.

The Applicant proposes that differences in the safety profiles according to weight may be a function of undertreatment with dupilumab in the lower exposure groups in each weight stratum.

Table 27. Summary of TEAEs of Interest by Regimens and Weight Strata - Study 1652*

	Baseline Weight <30 kg			Baseline Weight ≥30 kg		
	Placebo + TCS (N=60)	Dupilumab 300 mg Q4W + TCS (N=60)	Dupilumab 100 mg Q2W + TCS (N=63)	Placebo + TCS (N=60)	Dupilumab 300 mg Q4W + TCS (N=60)	Dupilumab 200 mg Q2W + TCS (N=59)
Any TEAE	43 (71.7%)	39 (65.0%)	46 (73.0%)	45 (75.0%)	39 (65.0%)	36 (61.0%)
Any severe TEAE	4 (6.7%)	0	2 (3.2%)	3 (5.0%)	0	1 (1.7%)
Infections and infestations SOC	30 (50.0%)	26 (43.3%)	28 (44.4%)	31 (51.7%)	26 (43.3%)	21 (35.6%)
Skin and subcutaneous tissue disorders SOC	10 (16.7%)	9 (15.0%)	13 (20.6%)	13 (21.7%)	11 (18.3%)	6 (10.2%)
Dermatitis atopic	7 (11.7%)	4 (6.7%)	8 (12.7%)	10 (16.7%)	4 (6.7%)	2 (3.4%)
Eye disorders	1 (1.7%)	4 (6.7%)	10 (15.9%)	7 (11.7%)	3 (5.0%)	5 (8.5%)
Conjunctivitis allergic	0	2 (3.3%)	4 (6.3%)	1 (1.7%)	1 (1.7%)	1 (1.7%)
Blepharitis	0	0	1 (1.6%)	2 (3.3%)	0	0
Eye irritation	0	1 (1.7%)	2 (3.2%)	0	1 (1.7%)	0
Respiratory, thoracic and mediastinal disorders SOC	16 (26.7%)	3 (5.0%)	10 (15.9%)	15 (25.0%)	11 (18.3%)	5 (8.5%)
Cough	5 (8.3%)	0	2 (3.2%)	4 (6.7%)	3 (5.0%)	3 (5.1%)
Rhinitis allergic	2 (3.3%)	1 (1.7%)	3 (4.8%)	3 (5.0%)	2 (3.3%)	1 (1.7%)
Asthma	7 (11.7%)	0	4 (6.3%)	5 (8.3%)	2 (3.3%)	0
Conjunctivitis cluster	2 (3.3%)	4 (6.7%)	15 (23.8%)	3 (5.0%)	5 (8.3%)	5 (8.5%)
Conjunctivitis bacterial	1 (1.7%)	0	3 (4.8%)	0	0	2 (3.4%)
Conjunctivitis	1 (1.7%)	2 (3.3%)	6 (9.5%)	2 (3.3%)	3 (5.0%)	1 (1.7%)
Conjunctivitis allergic	0	2 (3.3%)	4 (6.3%)	1 (1.7%)	1 (1.7%)	1 (1.7%)
Conjunctivitis viral	0	0	0	0	0	1 (1.7%)
Eye irritation	0	1 (1.7%)	2 (3.2%)	0	1 (1.7%)	0
Herpes simplex virus infection cluster	2 (3.3%)	0	3 (4.8%)	1 (1.7%)	1 (1.7%)	1 (1.7%)
Herpes simplex	1 (1.7%)	0	1 (1.6%)	0	1 (1.7%)	1 (1.7%)
Herpes virus infection	1 (1.7%)	0	2 (3.2%)	1 (1.7%)	0	0
Immune system disorders	2 (3.3%)	2 (3.3%)	3 (4.8%)	0	1 (1.7%)	0
Food allergy	0	1 (1.7%)	3 94.8%)	0	0	0
Keratitis cluster	0	0	1 (1.6%)	0	0	0
Keratitis	0	0	1 (1.6%)	0	0	0

*Source: Table 12 of Clinical Overview

Laboratory Findings

Study 1652 (Pivotal)

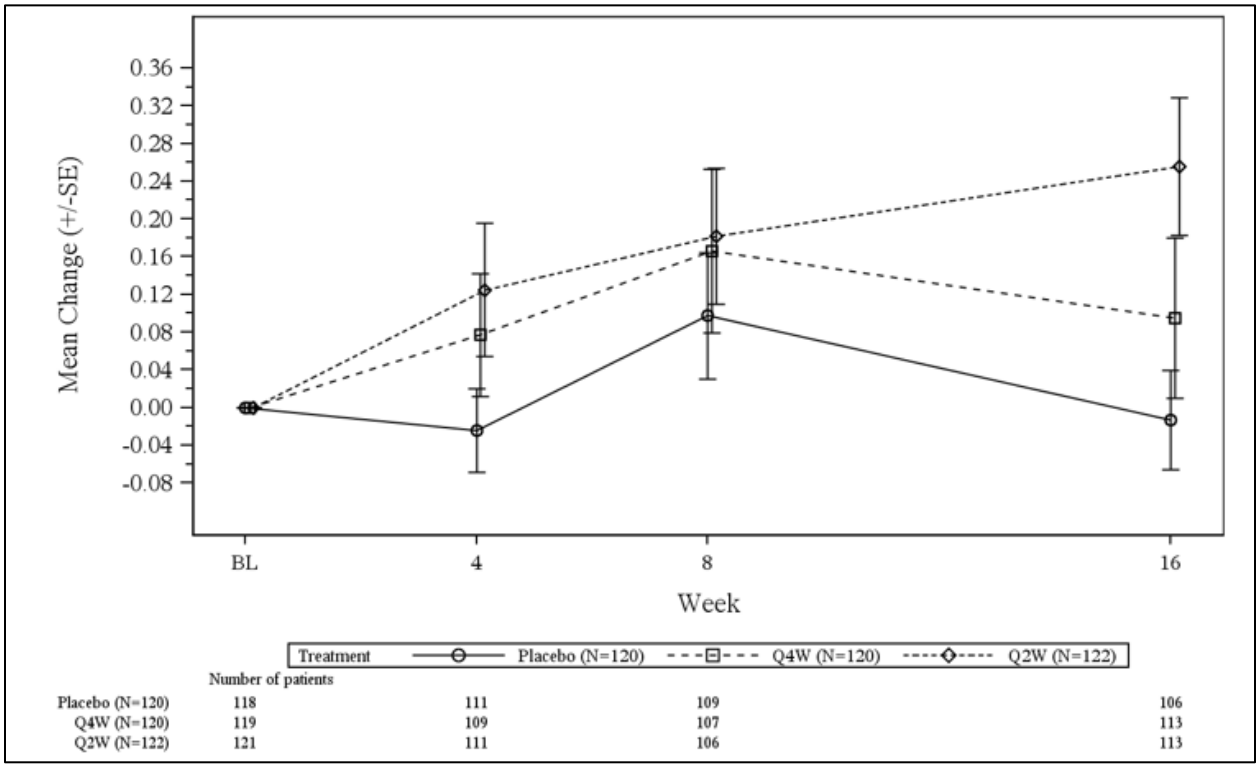
Hematology

There were no clinically-meaningful trends or differences between treatment groups in changes or shifts from baseline in any red blood cell parameter (hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, or erythrocytes) during the treatment period. Mean platelet counts remained within the normal range for all treatment groups at each study visit. However, mean platelet counts were lower relative to baseline in dupilumab groups at Weeks 4, 8, and 16. This was not noted in the placebo group. There was a single report of thrombocytopenia as a TEAE; it occurred in the Q2W group (there was also one report of thrombocytosis; it occurred in the Q4W group).

The same was generally true of white blood cells (basophils, lymphocytes, monocytes, leukocytes, and neutrophils) regarding trends or differences. Mean eosinophil counts were noted to increase from baseline in the dupilumab groups. However, at Week 8, mean counts in

all groups (i.e., including the placebo group, but to a lesser extent relative to the dupilumab groups) had increased from baseline. Mean counts peaked at Week 8 for the placebo and Q4W dupilumab groups. Increase in median counts from baseline was noted in the Q2W group.

Figure 16. Mean Change (SE) in Eosinophils (109/L) From Baseline Through Week 16 Treatment Period During the 16-Week Treatment Period – SAF*



*Source: Figure 20 from study report for 1652

There was a single report of eosinophilia as a TEAE (Q2W group). A similar trend of increase in eosinophils with dupilumab was seen in the adolescent and adult programs. The Applicant relates this eosinophil effect to the mechanism of action of dupilumab in blocking IL-4 and IL-3 activity and the resultant impact on eosinophil activity, which ultimately may lead to transient increases in circulating eosinophil counts.

Chemistry

Generally, no clinically-meaningful trends in changes or shift from baseline in any treatment group in chemistries (measures of metabolic, renal, or liver function or electrolytes or lipids) were noted. No chemistries were reported as TEAEs in the dupilumab treatment groups.

Mean lactate dehydrogenase (LDH) decreased from baseline in all treatment groups during the treatment period, but to a greater extent in the dupilumab groups compared to the placebo group. For all treatment groups, mean LDH values remained in the normal range. These

patterns were observed in the adolescent and adult AD programs. The Applicant anticipated these trends, indicating that elevated LDH levels correlate with severity and activity of AD.

Potentially clinically significant values (PCSVs) in chemistries were reported in all treatment groups and in no particular pattern.

Study 1434 (OLE)

The findings in the OLE generally did not reveal any new patterns in hematology parameters or in most white blood cell parameters relative to Study 1652. Mean eosinophil counts trended downwards in the OLE. "Eosinophil count increased" is the only eosinophil parameter that was reported as a TEAE, and there was only one report.

The findings in the OLE generally did not reveal any new patterns in chemistry parameters. Mean LDH values trended towards decrease and remained within normal limits.

Vital Signs

No subject had abnormalities in vital signs that led to treatment discontinuation or to reporting of a SAE. No clinically-significant trends were noted in changes in vital signs in any treatment group. PCSVs. were reported in all treatment groups and in no particular pattern.

In Study 1652, the PCSV of "Respiratory rate" ">20 bpm and <= 16 bpm at baseline" was the most common PCSV vital sign event: 18.3% in the placebo group, 26.7% in the Q4W group, and 31.1% in the Q2W group.

Electrocardiograms (ECGs)

The Applicant reported no clinically-meaningful trends in mean or median changes from baseline in ECG parameters in any treatment group in Studies 1652 (pivotal) and 1434 (OLE). No ECG findings eventuated in permanent discontinuation of study treatment or in the reporting of a SAE.

ECGs were not done in Study 1434 after implementation of protocol amendment 1, supported by information from completed studies in adolescents and adults. Those studies revealed no higher incidence of abnormal ECGs in dupilumab groups relative to placebo and no TEAEs of cardiac signs and symptoms.

QT

The Applicant did not conduct a thorough QT study. Per the EOP2 meeting minutes that preceded the Phase 3 program in adults and submission of the original BLA: "Monoclonal antibodies do not need to be evaluated in a thorough QT study. Routine ECG monitoring in Phase 3 trials should be performed to capture important cardiac effects."

Immunogenicity

No subjects in the Q4W group were ADA-positive (114 ADA-negative) in Study 1652. A total of 6 subjects were ADA-positive in the Q2W group (112 ADA-negative). The only events in the skin and subcutaneous tissue disorders SOC that occurred in ADA-positive patients occurred in the Q2W group: two reports of dermatitis atopic (eight reports in ADA-negative patients) and one report of rash pruritic. There were two reports of Injection site reactions in ADA-positive patients, and both occurred in the Q2W group: Injection site erythema (12 in in ADA-negative patients) and Injection site hypoesthesia. There were no reports of events in the immune system disorders SOC in any ADA-positive patients.

The TEAEs profile did not suggest a correlation between ADA positivity and events that might suggest loss of efficacy ("dermatitis atopic") or a safety concern.

8.2.5. Analysis of Submission-Specific Safety Issues

Eye Disorders

The approved package insert includes a Warning and Precaution, entitled "Conjunctivitis and Keratitis," based on the signal for these events initially detected in the AD development program in adults.

The Applicant included conjunctivitis, blepharitis, keratitis (severe or serious or lasting ≥4 weeks) among the designated AESIs in Studies 1652 (pivotal) and 1434 (OLE).

Study 1652 (Pivotal)

The Applicant performed analyses of conjunctivitis and select other eye-related events under the following categories:

- a broad customized MedDRA query (CMQ) containing 16 terms: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, ocular hyperemia, conjunctival hyperemia, xerophthalmia and
- a narrow standardized MedDRA query (SMQ) 5 terms containing "conjunctivitis": conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic keratoconjunctivitis

Table 28 below presents results from the broad CMQ from Study 1652. Overall, events under this analysis were most frequently reported in the Q2W group. Overall incidences were similar between the placebo and Q4W groups. However, incidences of specific events were generally higher in dupilumab arms compared to placebo. See Table 28.

Table 28. Summary of Patients With Treatment-Emergent Conjunctivitis (Broad Search) During the 16-Week Treatment Period – SAF*

		Dupilumab		
Preferred Term MedDRA Version 22.0	**Placebo + TCS (N=120)**	**300mg Q4W + TCS (N=120)**	**100mg or 200mg Q2W + TCS (N=122)**	**Combined (N=242)**
Number of patients with at least one such event, n (%)	9 (7.5%)	10 (8.3%)	23 (18.9%)	33 (13.6%)
Conjunctivitis	3 (2.5%)	5 (4.2%)	7 (5.7%)	12 (5.0%)
Conjunctivitis allergic	1 (0.8%)	3 (2.5%)	5 (4.1%)	8 (3.3%)
Conjunctivitis bacterial	1 (0.8%)	0	5 (4.1%)	5 (2.1%)
Eye irritation	0	2 (1.7%)	2 (1.6%)	4 (1.7%)
Eye pruritus	1 (0.8%)	1 (0.8%)	2 (1.6%)	3 (1.2%)
Dry eye	1 (0.8%)	0	2 (1.6%)	2 (0.8%)
Blepharitis	2 (1.7%)	0	1 (0.8%)	1 (0.4%)
Conjunctivitis viral	0	0	1 (0.8%)	1 (0.4%)
Ocular hyperemia	0	0	1 (0.8%)	1 (0.4%)
Eye discharge	1 (0.8%)	0	0	0
Lacrimation increased	1 (0.8%)	0	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, Q2W = Once every 2 weeks, Q4W = Once every 4 weeks
*Source: Table 62 of study report for 1652.

The narrow SMQ is a subset of the broad CMQ. A total of 31 subjects were identified under the SMQ: placebo- 5 (4.2%), Q4W- 8 (6.7%), and Q2W- 18 (14.8%). The number of subjects per event under the SMQ is subsumed under the CMQ; see Table 28 above.

Study 1434 (OLE)

The Applicant performed broad and narrow CMQs in Study 1434. Both queries contained the same preferred terms that were included in the respective queries in Study 1652 (although the narrow query in Study 1652 was termed a "SMQ"). Under this search, the Applicant identified 51 subjects (13.9%) who experienced a conjunctivitis (or related) event.

Table 29. Number of Patients With Treatment-Emergent Conjunctivitis (Broad CMQ) by Preferred Term - Children ≥6 to <12 Years of Age (SAF)*

Preferred Term MedDRA version 2.1	**Total (N=368)**	**Total (N=368) nP/PY (Np/100PY) [1]**
Number of TEAEs	81	
Patients with at least one TEAE	51 (13.9%)	51/237.6 (21.46)
Conjunctivitis allergic	24 (6.5%)	24/259.9 (9.23)
Conjunctivitis bacterial	10 (2.7%)	10/261.4 (3.83)
Conjunctivitis	8 (2.2%)	8/266.6 (3.00)
Blepharitis	4 (1.1%)	4/271.5 (1.47)
Dry eye	4 (1.1%)	4/270.5 (1.48)
Conjunctivitis viral	3 (0.8%)	3/271.5 (1.10)
Conjunctival hyperemia	2 (0.5%)	2/271.6 (0.74)
Eye irritation	2 (0.5%)	2/271.5 (0.74)
Ocular hyperemia	2 (0.5%)	2/272.0 (0.74)

Preferred Term MedDRA version 2.1	Total (N=368)	Total (N=368) nP/PY (Np/100PY) [1]
Atopic keratoconjunctivitis	1 (0.3%)	1/272.2 (0.37)
Lacrimation increased	1 (0.3%)	1/272.2 (0.37)

*Source: Table 26 of the study report for 1434 (second-step analysis)

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

This section is not applicable to this supplement.

8.2.7. Safety Analyses by Demographic Subgroups

For the safety analyses, the Applicant defined the following subgroups by baseline factors in Study 1652:

- Age group (≥6 to <9 years, ≥9 to <12 years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino [no/yes])
- Race (white, black, Asian, other)
- Duration of AD (<5 years, ≥5 years)
- Baseline body mass index (<20, ≥20)
- Baseline weight group (<30 kg, ≥30 kg)

Table 30 presents the overall occurrence of TEAEs by subgroups. The number of subjects experiencing TEAEs appeared generally similar between treatment groups within each subgroup. However, the numbers of subjects across subgroups were generally too small to allow meaningful conclusions.

Table 30. Patients With Any TEAE in Study 1652 by Subgroups*

	Placebo		Dupilumab 300mg Q4W		Dupilumab 100mg or 200mg Q2W	
Subgroups	N	# (%) with TEAEs	N	# (%) with TEAEs	N	# (%) with TEAEs
Age group (yrs)						
≥6< 9	57	41 (71.9%)	59	40 (67.8%)	58	39 (67.2%)
≥9<12	63	47 (74.6%)	61	39 (63.9%)	64	43 (67.2%)
Gender						
Male	60	41 (68.3%)	56	37 (66.1%)	65	43 (66.2%)
Female	60	47 (78.3%)	64	42 (65.6%)	57	39 (68.4%)
Ethnicity						
Not Hispanic or Latino	107	80 (74.8%)	104	68 (65.4%)	107	74 (69.2%)
Hispanic or Latino	13	8 (61.5%)	16	11 (68.8%)	15	8 (53.3%)

	Placebo		Dupilumab 300mg Q4W		Dupilumab 100mg or 200mg Q2W	
Subgroups	**N**	**# (%) with TEAEs**	**N**	**# (%) with TEAEs**	**N**	**# (%) with TEAEs**
Race						
White	75	58 (77.3%)	87	62 (71.3%)	87	59 (67.8%)
Black	22	12 (54.5%)	19	9 (47.4%)	21	13 (61.9%)
Asian	13	10 (69.2%)	5	4 (80.0%)	10	6 (60.0%)
Other	9	8 (88.9%)	8	3 (37.5%)	2	2 (100%)
Baseline weight group						
< 30 kg	60	43 (71.7%)	60	40 (66.7%)	63	46 (73.0%)
≥ 30 kg	60	45 (75.0%)	60	39 (65.0%)	59	36 (61.0%)

*Sources: Post-text tables 7.1.1.1/3 - 7.1.1.1/7 for Study 1652

Safety Analyses by Subgroup of Moderate Disease

To support the proposed inclusion of moderate disease in the indication statement, the Applicant provided safety data for the cohort of patients from the placebo + TCS group in Study 1652 who entered the OLE Study 1434 with moderate disease (baseline IGA of 3). Analyses included comparison of this group to all patients with moderate disease, patients with severe disease, and the overall study population. The safety profile in subjects with moderate disease was similar to that of the other cohorts in all of those comparisons.

See Section 8.1.2 for baseline demographic and disease characteristics.

Table 31. Overall Summary of Treatment-Emergent Adverse Events in Patients With IGA=3 and IGA=4 at Baseline (SAF)*

	IGA=3 Patients Previously Treated with Placebo (N=35)	All IGA=3 Patients (N=94)	IGA=4 Patients Previously Treated with Placebo (N=48)	All IGA=4 Patients (N=60)	All Patients in OLE (N=368)
Patients with any TEAE	17 (48.6%)	51 (54.3%)	29 (60.4%)	39 (65.0%)	219 (59.5%)
Patients with any drug-related TEAE	3 (8.6%)	13 (13.8%)	9 (18.8%)	12 (20.0%)	52 (14.1%)
Patients with any TEAE leading to Permanent Study Drug Discontinuation	0	1 (1.1%)	1 (2.1%)	1 (1.7%)	2 (0.5%)
Patients with any TEAE by Severity					
Mild	10 (28.6%)	27 (28.7%)	9 (18.8%)	16 (26.7%)	101 (27.4%)
Moderate	6 (17.1%)	21 (22.3%)	20 (41.7%)	22 (36.7%)	106 (28.8%)
Severe	1 (2.9%)	3 (3.2%)	0	1 (1.7%)	12 (3.3%)
Patients with TEAE resulting in Death	0	0	0	0	0
Patients with any SAE	1 (2.9%)	1 (1.1%)	2 (4.2%)	2 (3.3%)	9 (2.4%)
Patients with any drug related SAE	0	0	0	0	0
Patients with SAE leading to Permanent Study Drug Discontinuation	0	0	0	0	0

Abbreviations: IGA, Investigator's Global Assessment; SAE, serious adverse event; SAF, safety analysis population; TEAE, treatment-emergent adverse event

*Source: Table 24 from Summary of Clinical Safety

Table 32 below shows the baseline atopic/allergic disease history for study subjects, according to randomized treatment group assignment. Table 33 shows the prior history of systemic treatments for AD. The atopic/allergic history and history of systemic treatments in patients ≥ 6 to < 12 years of age was generally similar to the population of adolescents with moderate-to-severe AD, evaluated under S-012, and the safety of dupilumab for treatment of adolescents with moderate AD has been established.

Table 32. Baseline Atopic/Allergic Disease History in Study 1652 – SAF*

		Dupilumab			
	Placebo + TCS (N=120)	300mg Q4W + TCS (N=120)	100mg or 200mg Q2W + TCS (N=122)	Combined (N=242)	Total (N=362)
Number (%) of Patients with current history of Atopic/Allergic Conditions					
Atopic dermatitis	120 (100%)	120 (100%)	122 (100%)	242 (100%)	362 (100%)
Food allergy	83 (69.2%)	75 (62.5%)	75 (61.5%)	150 (62.0%)	233 (64.4%)
Other allergies	81 (67.5%)	67 (55.8%)	79 (64.8%)	146 (60.3%)	227 (62.7%)
Allergic rhinitis	72 (60.0%)	73 (60.8%)	73 (59.8%)	146 (60.3%)	218 (60.2%)
Asthma	54 (45.0%)	55 (45.8%)	60 (49.2%)	115 (47.5%)	169 (46.7%)
Allergic conjunctivitis (keratoconjunctivitis)	16 (13.3%)	14 (11.7%)	14 (11.5%)	28 (11.6%)	44 (12.2%)
Hives	8 (6.7%)	14 (11.7%)	14 (11.5%)	28 (11.6%)	36 (9.9%)
Chronic rhinosinusitis	4 (3.3%)	5 (4.2%)	2 (1.6%)	7 (2.9%)	11 (3.0%)
Eosinophilic esophagitis	0	1 (0.8%)	1 (0.8%)	2 (0.8%)	2 (0.6%)
Nasal polyps	0	0	2 (1.6%)	2 (0.8%)	2 (0.6%)
Number (%) of Patients with current history of Atopic/Allergic Conditions excluding Atopic Dermatitis	111 (92.5%)	107 (89.2%)	114 (93.4%)	221 (91.3%)	332 (91.7%)

*Source: Table 7 from the study report for 1652

Table 33. Summary of Prior Use of Systemic Corticosteroid and Systemic Non-Steroidal Immunosuppressant Medications for AD for Study 1652 – SAF

		Dupilumab			
	Placebo + TCS (N=120)	300mg Q4W + TCS (N=120)	100mg or 200mg Q2W + TCS (N=122)	Combined (N=242)	Total (N=362)
Patients receiving prior systemic corticosteroids and/or systemic nonsteroidal immunosuppressants for AD, n (%)	36 (30.0%)	42 (35.0%)	40 (32.8%)	82 (33.9%)	118 (32.6%)
Patients receiving prior systemic corticosteroids	17 (14.2%)	25 (20.8%)	30 (24.6%)	55 (22.7%)	72 (19.9%)
Patients receiving prior systemic non-steroidal immunosuppressants	22 (18.3%)	23 (19.2%)	16 (13.1%)	39 (16.1%)	61 (16.9%)
Azathioprine	0	2 (1.7%)	2 (1.6%)	4 (1.7%)	4 (1.1%)
Cyclosporine	12 (10.0%)	17 (14.2%)	11 (9.0%)	28 (11.6%)	40 (11.0%)
Methotrexate	11 (9.2%)	7 (5.8%)	3 (2.5%)	10 (4.1%)	21 (5.8%)
Mycophenolate	2 (1.7%)	2 (1.7%)	1 (0.8%)	3 (1.2%)	5 (1.4%)

*Source: Table 8 from the study report for 1652

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant did not conduct any specific safety study or clinical trial.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in this development program.

Human Reproduction and Pregnancy

No pregnancies were reported in this development program.

The initial approval letter for the BLA included two pregnancy registry postmarketing requirements:

- 3183-5: A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab

during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

- 3183-6: Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a nondupilumab systemic medication or phototherapy exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The Applicant reported the status of both studies as "ongoing-on track" in the annual report submitted May 24, 2019 (Sequence 549). Three patients had been enrolled into the registry (PMR-3183-5).

Pediatrics and Assessment of Effects on Growth

The supplement that is the subject of this review pertains to a pediatric assessment. The Applicant proposes expansion of the AD indication statement to allow for use of dupilumab in patients six years of age and older. The sBLA did not include an assessment of the effects of dupilumab on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Investigators were instructed to report symptomatic overdose events in the study, and no such events were reported. The "Overdose" section of the label (Section 10) states the following:

> There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

Regarding abuse potential, the Applicant states the following (Section 5.7 of the Summary of Clinical Safety):

> The molecular structure and weight, known mechanism of action, peripheral route of administration, and metabolic pathways of dupilumab do not suggest a potential for central nervous system activity or drug dependence potential, and abuse is unlikely. Nonclinical data did not yield events raising a concern of drug dependence or abuse.

In Study 1412, the Applicant evaluated the impact of discontinuation of dupilumab during the 8-week, post-treatment follow-up period. The Applicant observed a trend towards the return of

symptoms of AD towards baseline, but not a worsening beyond baseline. Therefore, the data did not indicate a potential for a rebound effect.

Four-Month Safety Update (July 23, 2019 to November 8, 2019)

The Applicant submitted the 4-month safety update (SU) on March 24, 2020. The SU provided AE data for children ≥6 to <12 years of age from the ongoing OLE Study 1434 and covered the period July 23, 2019 (data cutoff date for the second-step analysis for the sBLA was July 22, 2019) and November 8, 2019. Study 1434 was ongoing with 318 patients ≥6 to <12 years old, as of the data cutoff date for the SU.

Disposition

The safety analysis set for the SU consisted of 352 patients observed for any length of time during the SU period. Of these, three patients had completed the study, and 31 patients (8.8%) had discontinued the study. The most common reason for discontinuing the study was "Other," with 19 patients (5.4%) discontinuing for this reason. The majority of patients (18 of 19) who discontinued due to "Other" reason, did so to either transition to commercially-available dupilumab treatment or to receive dupilumab as compassionate use when the patients reached 12 years of age. The 19th patient in this group discontinued as the patient "did not complete end of treatment follow-up visit." No patient discontinued due to an AE.

Of the 368 patients who constituted the SAF for Study 1434 at initial submission of the sBLA, 16 discontinued prior to the data cutoff for the sBLA and were not included in the SAF for the SU analysis.

See Table 34.

Table 34. Summary of Patient Disposition During the SU Period From July 23, 2019 to November 8, 2019 (Children ≥6 to <12 Years of Age) – SAF Patients Who Participated for Any Length of Time During the SU Period*

Patient Disposition	Total (N=352)
Patients in Safety Analysis Set (SAF)	352 (100%)
Patients ongoing at the end of the SU period	318 (90.3%)
Patients who completed study[1]	3 (0.9%)

Patient Disposition	Total (N=352)
Patients who discontinued from study with reason	31 (8.8%)
Adverse event	0
Physician decision	0
Lost to follow-up	2 (0.6%)
Withdrawal by patient	7 (2.0%)
Lack of efficacy	3 (0.9%)
Death	0
Other[2]	19 (5.4%)

[1] As per the protocol, patients who turned 12 years of age during the study were asked to complete an end of treatment visit and subsequently return after 12 weeks for an end of study visit for the OLE.
[2] For 18 of the 19 patients the "Other" reason was transitioning to commercially available DUPIXENT treatment or to dupilumab treatment under a compassionate use program when they reached 12 years of age (these patients did not complete the end of study visit, therefore not counted in the "completed study" category). For the remaining patient, the "Other" reason was she did not complete the end of treatment follow-up visit.
*Source: Table 1 of the Safety Update

Exposure

The mean (SD) number of injections administered to all patients (N=368) in the SAF since the beginning of the OLE study was 20.7 (±27.46). The median (range) number of injections was 13.0 (1 to 144).

The mean (SD) overall treatment exposure of all patients was 49.15 (±35.834) weeks, (median [range] was 43.86 [4 to 204.3] weeks). Durations of exposure were as follows:

- 286 (77.7%) had at least 26 weeks of treatment exposure,
- 129 (35.1%) patients had at least 52 weeks of exposure,
- 24 (6.5%) had at least 104 weeks of exposure, and
- 10 (2.7%) patients had at least 182 weeks of exposure.

Table 35. Summary of Treatment Exposure Children ≥6 to <12 Years of Age (SAF)

Exposure Characteristics	Total (N=368)
Overall Treatment exposure (Weeks)	
n	368
Mean (SD)	49.15 (35.834)
Q1	28.14
Median	43.86
Q3	53.86
Min : Max	4.0 : 204.3
Number (%) of patients with overall treatment exposure (weeks) cumulatively	
>= 1 Week	368 (100%)
>= 4 Weeks	368 (100%)
>= 16 Weeks	361 (98.1%)
>= 26 Weeks	286 (77.7%)
>= 52 Weeks	129 (35.1%)
>= 78 Weeks	28 (7.6%)
>= 104 Weeks	24 (6.5%)
>= 130 Weeks	19 (5.2%)
>= 156 Weeks	18 (4.9%)
>= 182 Weeks	10 (2.7%)
>= 208 Weeks	0

*Source: Post-text Table 5.2.1/2b-A for Safety Update

Baseline Demographics

Baseline demographics were the same as reported for the second-step analysis: white (73.1%); the percentages of male (49.2%) and female patients (50.8%) were similar; mean (SD) age of all patients was 8.6 (±1.69) years; 29.3% of patients were overweight (Body Mass Index ≥85 percentile for age and gender).

Overview of Adverse Events

In the interval since submission of the second-step analysis, 147 patients (41.8%) reported at least one TEAE. No patient was permanently discontinued due to a TEAE. No deaths were reported during the interval.

A total of six patients (1.7%) experienced an SAE:

- *Eczema herpeticum*. An 11 y/o white female was hospitalized for eczema herpeticum on Day 32 (last dose of study drug was Day 1). She received antiviral treatment, recovered, and was discharged on Day 37. Study treatment was resumed on Day 38.
- *Concussion*. An 8 y/o white female suffered a concussion from a fall on Day 403. Study treatment was not interrupted.
- *Arthropathy*. A 6 y/o white male was hospitalized for arthropathy on Day 216 after eight doses of study drug (last dose was on Day 1). Symptoms began on Day 186. He received unspecified treatment and was considered recovered on Day 218. Rheumatology workup was negative. Study treatment was resumed on Day 268; he missed three doses.

- *Pneumonia mycoplasmal*. A 9 y/o white female was diagnosed with pneumonia and hospitalized on Day 145. She had received eight doses of study drug (last dose was on Day 140). She was discharged on Day 153 and was considered to be recovered on Day 158.

Dosing of study drug was continued as planned.

- *Appendicitis perforated*. An 8 y/o black male experienced appendicitis perforated on Day 304 after 11 doses of study drug (last dose on Day 280). He underwent an appendectomy that same day and was discharged on Day 314. Study treatment was not interrupted.
- *Anaphylactic reaction*. A 6 y/o white male, with a history of peanut and soy allergies experienced an anaphylactic reaction on Day 227 after eating peanut crackers at school. This was also an AESI. He was treated, and the event was resolved on the same day. Study drug was temporarily discontinued but resumed on study Day 258.

TEAEs

TEAEs were most commonly reported in the Infections and infestations SOC 73 (20.7%), and nasopharyngitis and upper respiratory tract infection continued to be the two most commonly reported events: 19 (5.4%) and 16 (4.5%), respectively. Table 36 summarizes and compares the cumulative TEAEs until the cutoff date for the SU and until the cutoff for the sBLA.

Table 36. Summary of Treatment-Emergent Adverse Events by SOC and PT Including PTs With a Cumulative Incidence of ≥2% (Children ≥6 to <12 Years of Age) - SAF

Preferred Term	Cumulative until 08 Nov 2019 (data cutoff date for the SUR) (including raw incidence ≥2% by PT or SOC)		Cumulative until 22 Jul 2019 (data cutoff for the Second-step Analysis CSR for the sBLA) (including raw incidence ≥2%[1] by PT or SOC)	
	Total (N=368)		Total (N=368)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)[1]	nP/PY (nP/100 PY)[1]
Patients with at least 1 TEAE	261 (70.9%)	261/125.8 (207.40)	219 (59.5%)	219/89.1 (245.73)
Infections and infestations	180 (48.9%)	180/193.1 (93.20)	149 (40.5%)	149/135.7 (109.77)
Nasopharyngitis	59 (16.0%)	59/301.0 (19.60)	48 (13.0%)	48/213.1 (22.53)
Upper respiratory tract infection	44 (12.0%)	44/336.9 (13.06)	34 (9.2%)	34/244.2 (13.92)
Pharyngitis streptococcal	13 (3.5%)	13/369.3 (3.52)	10 (2.7%)	10/269.5 (3.71)
Conjunctivitis bacterial	11 (3.0%)	11/360.8 (3.05)	10 (2.7%)	10/261.4 (3.83)
Ear infection	11 (3.0%)	11/364.4 (3.02)	10 (2.7%)	10/264.5 (3.78)
Viral upper respiratory tract infection	11 (3.0%)	11/366.7 (3.00)	7 (1.9%)[1]	7/266.3 (2.63)
Conjunctivitis	10 (2.7%)	10/366.7 (2.73)	8 (2.2%)	8/266.6 (3.00)
Sinusitis	10 (2.7%)	10/367.0 (2.72)	9 (2.4%)	9/267.1 (3.37)
Herpes simplex	9 (2.4%)	9/361.2 (2.49)	7 (1.9%)[1]	7/260.9 (2.68)
Oral herpes	9 (2.4%)	9/366.6 (2.46)	8 (2.2%)	8/266.3 (3.00)
Rhinitis	9 (2.4%)	9/366.7 (2.45)	7 (1.9%)[1]	7/266.3 (2.63)
Molluscum contagiosum	8 (2.2%)	8/365.4 (2.19)	5 (1.4%)[1]	5/264.8 (1.89)
Gastroenteritis	8 (2.2%)	8/371.4 (2.15)	5 (1.4%)[1]	5/270.3 (1.85)
Skin and subcutaneous tissue disorders	113 (30.7%)	113/286.2 (39.48)	87 (23.6%)	87/211.6 (41.12)
Dermatitis atopic	69 (18.8%)	69/318.6 (21.66)	58 (15.8%)	58/234.0 (24.79)
Urticaria	14 (3.8%)	14/367.6 (3.81)	9 (2.4%)	9/268.4 (3.35)
Rash	11 (3.0%)	11/367.3 (2.99)	8 (2.2%)	8/267.0 (3.00)
Respiratory, thoracic and mediastinal disorders	78 (21.2%)	78/296.6 (26.30)	63 (17.1%)	63/212.6 (29.63)
Cough	29 (7.9%)	29/340.6 (8.52)	25 (6.8%)	25/245.0 (10.20)
Asthma	18 (4.9%)	18/362.1 (4.97)	12 (3.3%)	12/263.8 (4.55)
Oropharyngeal pain	15 (4.1%)	15/354.8 (4.23)	14 (3.8%)	14/256.0 (5.47)
Rhinitis allergic	15 (4.1%)	15/363.8 (4.12)	13 (3.5%)	13/264.9 (4.91)
Epistaxis	9 (2.4%)	9/366.8 (2.45)	9 (2.4%)	9/266.9 (3.37)
Rhinorrhoea	8 (2.2%)	8/369.6 (2.16)	5 (1.4%)[1]	5/268.5 (1.86)
Eye disorders	52 (14.1%)	52/341.1 (15.24)	41 (11.1%)	41/251.5 (16.30)
Conjunctivitis allergic	28 (7.6%)	28/355.0 (7.89)	24 (6.5%)	24/259.9 (9.23)
General disorders and administration site conditions	49 (13.3%)	49/332.0 (14.76)	40 (10.9%)	40/241.4 (16.57)
Pyrexia	22 (6.0%)	22/355.2 (6.19)	16 (4.3%)	16/257.8 (6.21)
Gastrointestinal disorders	43 (11.7%)	43/326.2 (13.18)	30 (8.2%)	30/233.4 (12.85)
Vomiting	17 (4.6%)	17/354.4 (4.80)	13 (3.5%)	13/256.0 (5.08)
Abdominal pain upper	10 (2.7%)	10/362.9 (2.76)	7 (1.9%)[1]	7/262.7 (2.66)
Abdominal pain	8 (2.2%)	8/365.0 (2.19)	6 (1.6%)[1]	6/264.2 (2.27)
Diarrhoea	8 (2.2%)	8/365.8 (2.19)	6 (1.6%)[1]	6/265.1 (2.26)
Injury, poisoning and procedural complications	34 (9.2%)	34/343.0 (9.91)	26 (7.1%)	26/249.0 (10.44)

Preferred Term	Cumulative until 08 Nov 2019 (data cutoff date for the SUR) (including raw incidence ≥2% by PT or SOC)		Cumulative until 22 Jul 2019 (data cutoff for the Second-step Analysis CSR for the sBLA) (including raw incidence ≥2%[1] by PT or SOC)	
	Total (N=368)		Total (N=368)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)[1]	nP/PY (nP/100 PY)[1]
Nervous system disorders	28 (7.6%)	28/339.2 (8.25)	23 (6.3%)	23/242.9 (9.47)
Headache	23 (6.3%)	23/346.5 (6.64)	20 (5.4%)	20/249.4 (8.02)
Immune system disorders	27 (7.3%)	27/356.6 (7.57)	21 (5.7%)	21/261.4 (8.03)
Food allergy	10 (2.7%)	10/370.3 (2.70)	7 (1.9%)[1]	7/270.4 (2.59)
Musculoskeletal and connective tissue disorders	19 (5.2%)	19/351.4 (5.41)	15 (4.1%)	15/252.8 (5.93)
Ear and labyrinth disorders	10 (2.7%)	10/370.9 (2.70)	5 (1.4%)[1]	5/270.2 (1.85)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (2.2%)	8/367.4 (2.18)	5 (1.4%)[1]	5/266.4 (1.88)
Skin papilloma	8 (2.2%)	8/367.4 (2.18)	5 (1.4%)[1]	5/266.4 (1.88)

Abbreviations: nP = number of patients, PY = patient-years
[1] For SOCs and PTs with an incidence of <2%, the incidences are presented for reference purpose
*Source: Table 7 of the Safety Update

AESIs

In the interval since submission of the second-step analysis, six patients (1.7%) reported six AESIs.

Table 37. Study R668-AD-1434: Summary of Adverse Events of Special Interest Reported During the SUR Period from July 23, 2019 to November 8, 2019 (Children ≥6 to <12 Years of Age) - SAF Patients Who Participated for Any Length of Time During the SUR Period*

Preferred term/ *Verbatim term*	Patient ID/ Age/Sex	Study day start/ Study day stop	Seriousness	Severity	Relationship to study drug[1]	Outcome	Action take with study drug
Enterobiasis/ *Enterobiasis*	(b) (6) 8/F	Day 304/ Day 306	No	Mild	Not related	Recovered/ Resolved	Dose not changed
Enterobiasis/ *Pinworm infection*	(b) (6) 7/F	Day 75/ Day 90	No	Mild	Not related	Recovered/ Resolved	Dose not changed
Keratitis/ *Right eye keratitis (unknown etiology)*	(b) (6) 8/F	Day 360/ Day 400	No	Mild	Not related	Recovered/ Resolved	Dose not changed
keratoconjunctivitis/ *Atopic keratoconjunctivitis*	(b) (6) 9/F	Day 281/	No	Mild	Related	Recovering/ Resolving	Dose not changed
Anaphylactic reaction/ *Anaphylactic reaction to possibly soy and/or peanut*	(b) (6) 8/F	Day 300/ Day 300	No	Moderate	Not related	Recovered/ Resolved	Dose not changed
Anaphylactic reaction[2]/ *Anaphylaxis*	(b) (6) 6/M	Day 227/ Day 227	Yes	Severe	Not related (see notes in Table 8)	Recovered/ Resolved	Drug interrupted

[1] The relationship of the AE to study drug as assessed by the investigator
[2] This AESI of Anaphylactic Reaction (Patient (b) (6) was assessed by the investigator to be a SAE
* Source: Table 9 of Safety Update

Conjunctivitis

The conjunctivitis broad CMQ search identified 19 patients (5.4%) in the interval since submission of the second-step analysis. The types of events are consistent with what has been observed with dupilumab use.

Table 38. Study R668-AD-1434: Number of Patients With Treatment-Emergent Broad CMQ Conjunctivitis by Preferred Term Reported During the SUR Period from July 23, 2019 to November 8, 2019 (Children ≥6 to <12 Years of Age) - SAF Patients Who Participated for Any Length of Time During the SUR Period*

Preferred Term MedDRA Version 21.1	Total (N=352)
Number of TEAEs	23
Patients with at least 1 TEAE	19 (5.4%)
Conjunctivitis allergic	7 (2.0%)
Conjunctivitis	4 (1.1%)
Eye pruritus	4 (1.1%)
Blepharitis	2 (0.6%)
Atopic keratoconjunctivitis	1 (0.3%)
Conjunctival hyperemia	1 (0.3%)
Conjunctivitis bacterial	1 (0.3%)
Conjunctivitis viral	1 (0.3%)
Ocular hyperemia	1 (0.3%)

PTs included under Conjunctivitis Broad CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperemia, conjunctival hyperemia
*Source: Table 12 of Safety Update

Conclusions

Dupilumab continued to be well-tolerated through the cut-point for the SU. The SU identified no new safety signals and raised no new safety concerns.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dupilumab is not approved for use in patients <12 years of age. However, the Applicant reviewed the Sanofi safety database and identified 736 cases involving use in patients < 12 years, three of which were serious:

- A 10-year-old male experienced vernal keratoconjunctivitis after an unspecified period of treatment for AD and with an outcome reported as “recovering/resolving.”
- An 11-year-old female was hospitalized for depression after an unspecified period of treatment and for an unspecified indication. The reporter provided no information on the patient’s past medical history or outcome.
- A 10-year-old male, who was being treated for AD, experienced a herpes virus infection and eczema herpeticum on hand. He received acyclovir and continued to receive dupilumab as planned.

A total of 733 cases were non-serious, and the “vast majority” of cases included no report of an AE. The reports were mostly of Product Use Issue and Product Prescribing Error. Reports also included Injection site reactions, atopic dermatitis and erythema.

The Applicant's review of the safety database identified no new safety concerns. Children with AD may experience depression.

Expectations on Safety in the Postmarket Setting

The data from children ≥6 to <12 years of age provided in this supplement revealed a safety profile similar to that seen in adolescents and adults. The information from off-label use in these children (discussed above) identified no new safety concerns. Therefore, based on the available safety data, the expectation is that the postmarketing safety experience for patients aged ≥6 to <12 years may be similar to the experience of adolescents and adults.

8.2.11. Integrated Assessment of Safety

The Applicant comprehensively assessed the safety of dupilumab in patients 6 to <12 years old with severe AD. The safety evaluations were adequate in types and frequency to identify local and systemic TEAEs. In addition to routine safety assessments, the safety evaluations reflected what is known about dupilumab (e.g., mechanism of action; protein product), its route of administration (SC), and its safety profile in the adolescent and adult AD populations (e.g., conjunctivitis). Pivotal Study 1652 provided the primary safety data, n= 362. Supportive safety data were provided from Study 1412 (an open-label PK study; n= 37) and the ongoing OLE, Study 1434, into which subjects from 1652 and 1412 were enrolled, n= 368. Dupilumab was well tolerated in all 3 studies. No new safety concerns were identified.

The Applicant established the safety of concomitant use of topical medications (TCS, TCIs, and phosphodiesterase 4 inhibitor) by adequately evaluating use of such products across the development program for the proposed new population. Use of dupilumab with concomitant topical therapy is likely to more reflect real-world use than use of dupilumab as monotherapy.

Dupilumab is contraindicated in patients who have known hypersensitivity to it or any of its excipients. Additionally, the label includes a Warning and Precaution entitled, "Hypersensitivity." Reactions observed in clinical trials and discussed in this section of the label include "generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions." There were no systemic hypersensitivity reactions in patients 6 to <12 years of age that implicated dupilumab. The reported systemic hypersensitivity reactions generally appeared related to exposure to known allergens in patients with food allergies.

Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo, consistent with the safety profile for dupilumab in the adolescent and adult AD populations. These events resolved with treatment and did not require discontinuation of dupilumab. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The patterns of occurrence and course of conjunctivitis and keratitis events in dupilumab-treated children were similar to what was seen in and labeled for adults with AD.

The dupilumab label includes a Warning and Precaution entitled, "Parasitic (Helminth) Infections." Unlike in the adolescent and adult programs, several cases of helminth infections were diagnosed across the development program in children 6 to <12 years of age (some of the patients had previous histories of helminth infections). However, enterobiasis is most frequently observed in children 5 to 10 years of age.[16] Similarly, ascariasis is most common in children 2 to 10 years of age.[17] Therefore, the observations of helminth infections in this development program may be a function of the age group studied and reflective of what is known regarding the occurrence of helminth infections in this age group.

Overall, dupilumab was well-tolerated in children 6 to <12 years of age, and the safety review identified no new adverse drug reactions. The safety profile was similar to that observed in adolescents and adults with moderate-to-severe AD. Therefore, based on the available safety data, the expectation is that the postmarketing safety experience for patients aged ≥6 to <12 years may be similar to the experience of adolescents and adults with AD.

Allowance for Moderate Disease in the Indication Statement

The Applicant proposes marketing of their product for treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis. The pivotal Study 1652 enrolled patients 6 to <12 years old with severe AD. To support labeling for treatment of patients 6 to <12 years old with moderate AD, the Applicant conducted safety analyses on the subset of patients from the placebo group in Study 1652 who entered the OLE Study 1434 with moderate (IGA of 3) disease (n= 35). The safety profile in subjects with moderate disease was similar to that of patients with severe disease and to the overall study population.

These safety results may have been anticipated to some extent, as the group of subjects with moderate disease was a subset of the total population for Study 1652, and generally had similar baseline demographic, disease, and medical history characteristics as the overall population. Assignment to treatment groups at baseline was random; patients in the placebo group were not assigned to that treatment based on any criteria unique to them. There was no readily apparent basis for anticipating that the safety profile of dupilumab in children with moderate AD might differ from the safety in children with severe disease.

It seems reasonable that dupilumab be made available to appropriate patients 6 to < 12 years of age who have moderate AD. Just as there are adults and adolescents with moderate AD whose disease is not adequately controlled with topical prescription therapies or for whom

[16] Leder K and Weller PF. Enterobiasis (pinworm) and trichuriasis (whipworm). Ryan ET and Edwards MS, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 26, 2020).
[17] Leder K and Weller PF. Ascariasis. Ryan ET, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on April 26, 2020).

those therapies are not advisable, there are almost certainly patients 6 to < 12 years of age with moderate AD who fall in those categories. Some of these children with moderate AD who failed or could not tolerate topicals could be relegated to off-label treatment with other systemic immunomodulating agents e.g., cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil for which the reported effectiveness varies from "efficacious" to "inconsistent" and all of which carry the potential for significant adverse effects, including boxed warnings in all of their labels.

The approved indication for patients 12 years and older is for "moderate-to-severe" AD, which seems to suggest consideration of disease severity on a continuum. In clinical practice, and in the absence of criteria, "moderate" and "severe" AD may also possibly be considered on a continuum, rather than as distinct categories defined by specific cut-points, as on an IGA scale. Additionally, clinical judgement of a need to advance to dupilumab in a patient < 12 years of age may, for some patients, rely more on a demonstration of poor response to topical therapies or a determination that such therapies are inadvisable, rather than on whether a patient meets either of those conditions and has disease that is specifically graded as "severe" by unspecified criteria.

If the indication for patients < 12 years of age is limited to severe AD, then those children would have to have failed topicals or have them found inadvisable treatments and have worse disease than what some > 12 years would have to have for those older patients to be considered dupilumab candidates. It is not clear that (or why) patients < 12 years of age should be required to have a greater disease burden than those > 12 years to be eligible to advance to dupilumab, if topical prescription therapies are not viable treatment options for either group (i.e., < or > 12 years of age). The safety data did not reveal a basis for this approach. Dupilumab is essentially the only approved systemic product currently available for such patients (systemic corticosteroids are generally not recommended).

Finally, a product for psoriasis is considered: It is noted that etanercept is indicated for "treatment of patients *4 years or older* with chronic *moderate to severe* plaque psoriasis who are candidates for systemic therapy or phototherapy" (emphasis added).

8.3.Statistical Issues

Results of the pre-specified statistical analysis for comparing each dose regimen of Q2W and Q4W were statistically superior to placebo. As randomization and analysis were stratified by weight (<30 kg and ≥30 kg), the Applicant conducted a subgroup analysis by the weight category for each dosing regimen, and the results of the analysis showed that for subjects <30 kg, the Q4W dose showed a trend for better efficacy than that of the Q2W dose; however, for the subjects ≥30kg, the Q2W dosing regimen showed better efficacy than that of the Q4W regimen.

As the original analysis only considered two bodyweight categories (<30kg and ≥30 kg), this reviewer conducted an additional analysis by considering the efficacy by body weight in 5-kg categories to get a better understanding of the efficacy results. The results of the reviewer analysis are presented in Figure 14 and appear to support the Applicant's conclusion concerning the dose selections per bodyweight.

8.4. Conclusions and Recommendations

To establish the effectiveness of dupilumab in pediatric subjects with severe AD, the Applicant submitted results from a randomized, multicenter, placebo-controlled, parallel-group, Phase 3 trial (Trial R668-AD-1652). The trial enrolled subjects ≥ 6 to <12 years of age with severe AD (i.e., IGA of 4, EASI ≥ 21, and BSA ≥15%) at baseline. The primary efficacy endpoint was the proportion of subjects achieving IGA score of 0 or 1 at Week 16.

Dupilumab was statistically superior to placebo (p-values <0.001) for the primary and secondary efficacy endpoints at Week 16. The exploratory analyses at Week 16 by baseline body weight (detailed in Section 8.1.3 of this review) provided support for this proposal as the proportion of subjects with IGA of 0 or 1 was numerically higher for those that received dupilumab **300 mg Q4W** regimen compared to those that received the 100 mg Q2W regimen for pediatric subjects <30 kg, and the results were numerically higher for the dupilumab **200 mg Q2W** regimen compared to the 300 mg Q4W regimen for pediatric subjects ≥30 kg.

To support the proposed treatment of children with moderate diseases, the Applicant provided safety data for the cohort of patients from the placebo group in Study 1652 who entered the open-label extension Study, R668-AD-1434 (1434), with moderate disease. Analyses included comparison of those data from this group to all patients with moderate disease, all patients with severe disease, and all patients in the OLE. The safety profile in subjects with moderate disease was similar to that of patients with severe disease and to the overall OLE study population.

Overall, dupilumab was well-tolerated in children 6 to <12 years of age, and the safety review identified no new adverse drug reactions. The safety profile was similar to that observed in adolescents and adults with moderate-to-severe AD. The data from children 6 to <12 years of age provided in this supplement revealed a safety profile similar to that seen in adolescents and adults. Therefore, based on the available safety data, the expectation is that the postmarketing safety experience for patients aged ≥6 to <12 years may be similar to the experience of adolescents and adults.

Recommendation on regulatory action: Approval

9 Advisory Committee Meeting and Other External Consultations

This supplement was not discussed at an Advisory Committee Meeting.

10 Pediatrics

See the body of this review.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The medical officer has reviewed labeling. Labeling negotiations were pending as this review closed.

12 Risk Evaluation and Mitigation Strategies (REMS)

The medical officer recommends product labeling and routine pharmacovigilance activities as the methods for postmarket risk evaluation and mitigation.

13 Postmarketing Requirements and Commitment

None attached to this sBLA.

14 Appendices

14.1. References

See footnotes.

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study R668-AD-1652, entitled "A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab Administered Concomitantly with Topical Corticosteroids in Patients, ≥6 Years to <12 Years of Age, with Severe Atopic Dermatitis"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 57 principal investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 20		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 20 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

14.4.1. Individual Study Summary

In the current sBLA, the Applicant submitted clinical pharmacology data from Phase 3 dupilumab clinical trial in pediatric subjects with moderate-to-severe AD (R668-AD-1652) and Phase 2 study (R668-AD-1412, only data from the relevant group was submitted). The Applicant also submitted population PK analysis report (to support the proposed dosing regimen.

14.4.2. Study R668-AD-1652

Title: A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroid in patients, ≥6 years of age to <12 years of age, with severe atopic dermatitis.

Methods: Subjects who met the inclusion criteria were randomized in a 1:1:1 ratio stratified by baseline body weight (<30 kg and ≥30 kg) and region (North America and Europe) as follows:

- Dupilumab every 2 weeks (Q2W) + TCS treatment group:
  - Subjects with baseline weight <30 kg received Q2W SC injections of 100 mg dupilumab from Week 2 to Week 14, following a loading dose of 200 mg on day 1.
  - Subjects with baseline weight ≥30 kg received Q2W SC injections of 200 mg dupilumab from Week 2 to Week 14, following a loading dose of 400 mg on day 1.
- Dupilumab every 4 weeks (Q4W) + TCS treatment group:
  - All subjects regardless of weight received Q4W SC injections of 300 mg dupilumab from Week 4 to Week 12, following a loading dose of 600 mg on day 1.
- Placebo + TCS treatment group:
  - Subjects in the <30 kg weight stratum were randomly assigned to receive, in a 1:1 ratio, either Q2W SC injections of placebo matching the 100 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).
  - Subjects in the ≥30 kg weight stratum were randomly assigned to receive, in a 1:1 ratio, either Q2W SC injections of placebo matching the 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

The study consisted of the following periods: screening of up to 9 weeks, TCS standardization period of 2 weeks, treatment period of 16 weeks, and follow-up of 12 weeks. Subjects had an option to enter the open-label extension.

PK assessment: Serum samples were collected pre-dose at Weeks 0, 4, 8, 12, 16 [end of treatment (EOT)], and then at follow-up at Weeks 24 and 48 [End of Study].

Immunogenicity assessment: Samples were collected pre-dose at Weeks 0, 4, 16 (EOT), and then at follow-up at Week 28 (End of Study).

PK Results: Systemic concentrations of dupilumab reached steady state in all treatment regimens before the primary endpoint at Week 16; the Q2W dosing regimens achieved steady state at or before Week 8 and the Q4W regimen achieved steady state at or before Week 12. Mean trough concentrations for the Q2W regimen at Week 4 were about 14% lower than that at Week 16. Mean ± SD of serum dupilumab concentration at Weeks 4 and 16 was 62.1 ± 26.8 mg/L and 72.5 ± 36.3 mg/L, respectively (Table 39). Mean trough concentrations for the Q4W regimen at Week 4 were about 21% higher than that at Week 16. Mean ± SD of serum dupilumab concentration at Weeks 4 and 16 was 92.0 ± 34.9 mg/L and 76.3 ± 37.2 mg/L, respectively (Table 39). At Week 16 (EOT), serum dupilumab concentrations between Q2W and Q4W dosing regimens were comparable (Table 39). The Applicant evaluated systemic exposure of dupilumab in two categories by body weight tier (<30 kg or ≥30 kg) (Table 40). At Week 16, mean ± SD of serum dupilumab concentration in subjects <30 kg receiving 300 mg Q4W was 53.9 ± 25.7 mg/L similar to 62.6 ± 32.3 mg/L in subjects ≥30 kg who received 100 mg Q2W (Table 40).

Immunogenicity Results: Immunogenicity of dupilumab in pediatric subjects ≥6 years to <12 years with severe AD was low. There were no ADA-positive subjects in the 300 mg Q4W group. The incidence of treatment-emergent ADA in the dupilumab 100 mg Q2W and dupilumab 200 mg Q2W groups was 4.9% (3/61 subjects) and 5.3% (3/57 subjects), respectively and that of placebo groups was 1.7%. Two subjects in the 100 mg Q2W group (3.3%) and one subject in the 200 mg Q2W group (1.8%) were neutralizing antibody-positive. The number of subjects with immunogenicity was too small to determine a clinically meaningful impact of immunogenicity on dupilumab exposure or response.

Table 39.Summary of Serum Dupilumab Concentration by Time and Treatment Group

	Concentrations of Functional Dupilumab in Serum (mg/L)									
	Placebo (N=120)		300 mg Q4W (N=119)		100 or 200 mg Q2W (N=122)		200 mg Q2W (N=59)		100 mg Q2W (N=63)	
Time (Weeks)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
0	119	0 (0)	119	0.00875 (0.0651)	121	0.00123 (0.0135)	58	0.00257 (0.0196)	63	0 (0)
4	120	0 (0)	118	92.0 (34.9)	119	62.1 (26.8)	58	74.4 (26.6)	61	50.4 (21.5)
8	115	0 (0)	115	82.3 (35.7)	116	69.3 (32.2)	55	86.9 (33.8)	61	53.4 (20.4)
12	110	0.901 (9.44)	111	75.0 (37.8)	110	69.8 (30.7)	52	86.4 (32.8)	58	55.0 (19.1)
16	116	0 (0)	114	76.3 (37.2)	117	72.5 (36.3)	56	84.5 (36.2)	61	61.5 (33.1)
24	3	0 (0)	4	0 (0)	4	2.83 (3.63)	3	3.78 (3.80)	1	0 (---)
28	1	0 (---)	1	0 (---)	1	0 (---)	1	0 (---)	0	

N = Number of patients; n = Number of samples per time point; SD = Standard deviation; ET = Early termination; EOS = End of study

Source: Table 5 in Clinical pharmacology report R668-AD-1652-CP-01V1

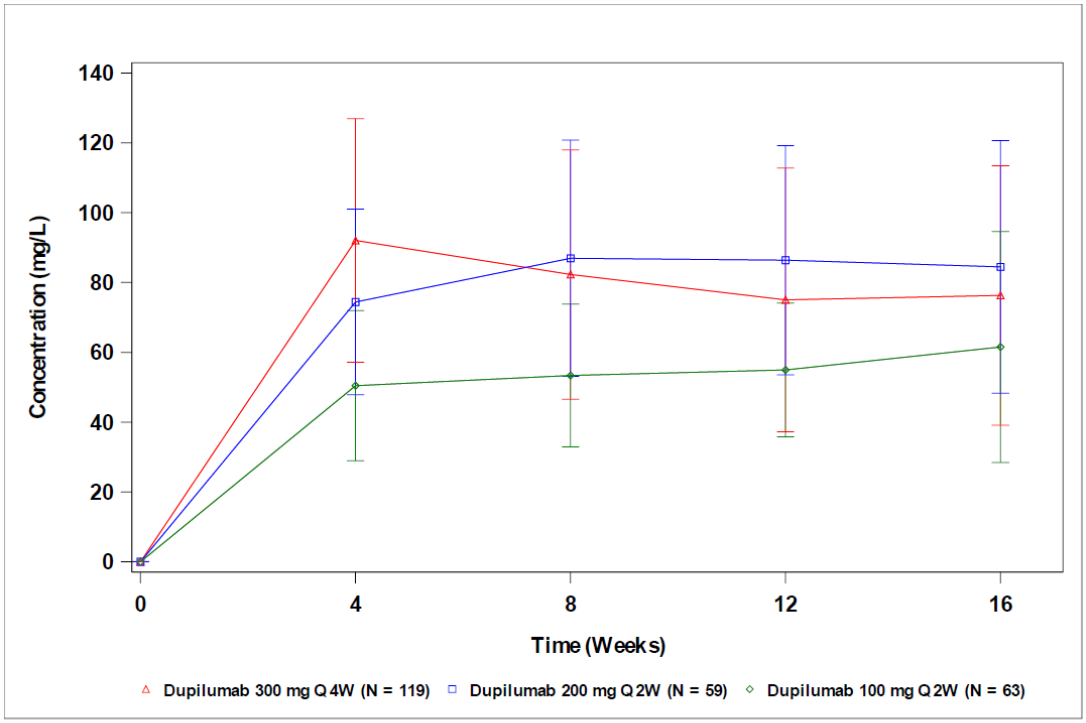
Table 40.Summary of Serum Dupilumab Concentration at Week 16 by Body Weight Stratum

	Concentrations of Functional Dupilumab in Serum (mg/L)									
	Placebo (N=116)		300 mg Q4W (N=114)		100 or 200 mg Q2W (N=117)		200 mg Q2W (N=56)		100 mg Q2W (N=61)	
Body Weight Category (Mean)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
<30 kg (23.9)	57	0 (0)	57	98.7 (33.2)	61	61.5 (33.1)	1	0 (---)	60	62.6 (32.3)
>=30 kg (39.3)	59	0 (0)	57	53.9 (25.7)	56	84.5 (36.2)	55	86.0 (34.6)	1	0 (---)

N = Number of patients contributing to each category, n = Number of samples per category; SD = Standard deviation, ET = Early termination, EOS = End of study

Source: Table 6 in Clinical pharmacology report R668-AD-1652-CP-01V1

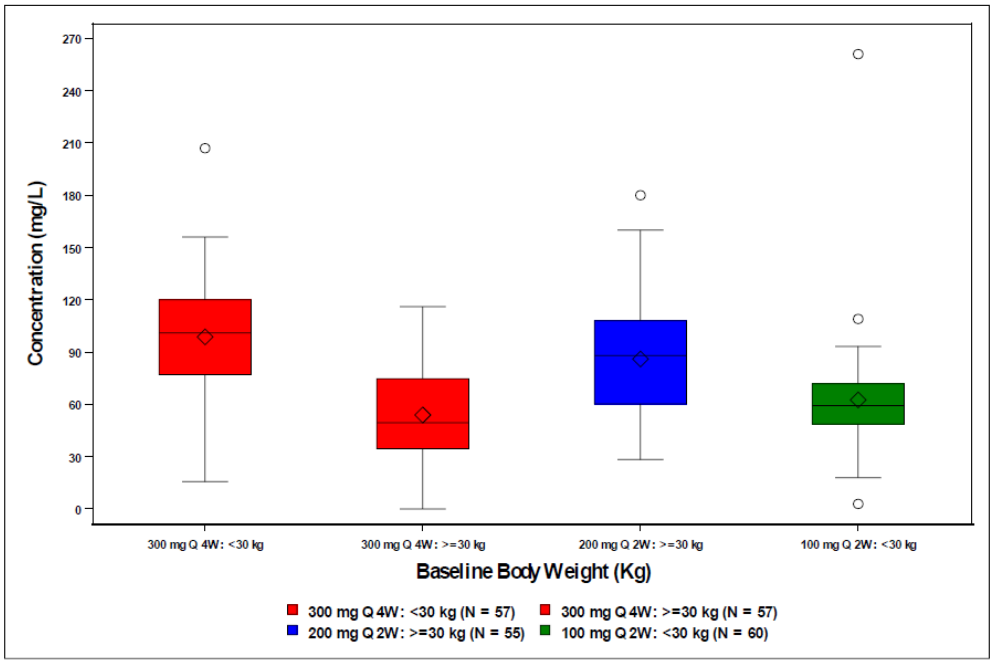
Figure 17. Mean (±SD) Concentration of Serum Dupilumab by Time and Treatment Group



N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were set to 0.

Source: Figure 1 in Clinical pharmacology report R668-AD-1652-CP-01V1

Figure 18. Serum Dupilumab Concentrations at Week 16 by Subject's Body Weight Category and Treatment Group



Note: Concentrations below the LLOQ were set to 0.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); 2 Subjects with a baseline body weight greater than 30 Kg and less than 30 Kg and assigned to 100 Q2W and 200 Q2W respectively were excluded from analysis.
Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR],with IQR = Q3 - Q1.

Source: Figure 3 in Clinical pharmacology report R668-AD-1652-CP-01V1

Table 41. ADA Category and Maximum Titer Category

Maximum Titer Category	Placebo n (%)	Dupilumab				All Active Doses n (%)	Overall n (%)
		300 mg Q4W n (%)	100 or 200 mg Q2W n (%)	200 mg Q2W n (%)	100 mg Q2W n (%)		
ADA Analysis Set	116 (100%)	114 (100%)	118 (100%)	57 (100%)	61 (100%)	232 (100%)	348 (100%)
Negative*	114 (98.3%)	114 (100%)	112 (94.9%)	54 (94.7%)	58 (95.1%)	226 (97.4%)	340 (97.7%)
Treatment-Boosted Response	0	0	0	0	0	0	0
Treatment-Emergent Response	2 (1.7%)	0	6 (5.1%)	3 (5.3%)	3 (4.9%)	6 (2.6%)	8 (2.3%)
TE & TB							
Low (<1,000)	2 (1.7%)	0	6 (5.1%)	3 (5.3%)	3 (4.9%)	6 (2.6%)	8 (2.3%)
Moderate (1,000 to 10,000)	0	0	0	0	0	0	0
High (>10,000)	0	0	0	0	0	0	0

n = Number of patients contributing to each category; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre+) responses.

Source: Table 9 in Clinical pharmacology report R668-AD-1652-CP-01V1

Table 42. Summary of ADA Status and NAb Status

ADA Status; NAb Status	Placebo	Dupilumab			
		300 mg Q4W	100 or 200 mg Q2W	200 mg Q2W	100 mg Q2W
	n (%)				
NAb Analysis Set	116 (100%)	114 (100%)	118 (100%)	57 (100%)	61 (100%)
Pre+; NAb-	3 (2.6%)	4 (3.5%)	2 (1.7%)	1 (1.8%)	1 (1.6%)
Pre+; NAb+	0	0	0	0	0
TE & TB; NAb-	2 (1.7%)	0	3 (2.5%)	2 (3.5%)	1 (1.6%)
TE & TB; NAb+	0	0	3 (2.5%)	1 (1.8%)	2 (3.3%)

N = Number of patients contributing to each category; Pre+ = Pre-existing immunoreactivity; TE = Treatment-emergent; TB = Treatment-boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay

Source: Table 10 in Clinical pharmacology report R668-AD-1652-CP-01V1

14.4.3. Population PK Analysis

Population PK Analysis in Children

The goal of the population PK (popPK) analysis (R668-PM-19142-SR-01V1) in children ≥6 to <12 years of age was to develop a popPK model using a structural model originally built using adult data to assess sources of variability (intrinsic and extrinsic covariates) of dupilumab with severe AD in children. Additionally, the aim was to simulate and compare predicted exposure for children with severe AD to previously predicted exposure in adolescents and adults with moderate-to-severe AD.

The popPK model included 239 children ≥6 to <12 years of age with severe AD who were on active dupilumab treatment from Study R668-AD-1652: 1) dupilumab every 2 weeks (Q2W): 100 mg for patients <30 kg (n = 62) or 200 mg for patients ≥30 kg (n = 58); 2) dupilumab every 4-weeks (Q4W): 300 mg (n = 119).

The PK of dupilumab were characterized with a two-compartment model with parallel linear and nonlinear Michaelis-Menten elimination and transit compartments used to describe the absorption of dupilumab (Figure 17). Same model structure had been applied to the previous popPK models in adult and adolescent AD patients (reports R668-MX-16103-CP-01V2 and R668-PM-18124-SR-01V1). Population PK of dupilumab were characterized by nonlinear mixed-effects modeling using Monolix version 2019R1 (Lixoft). Parameter estimates of final model with significant covariates were provided in Table 39. Shrinkage was 27.9% and 35.9% for empirical Bayes estimates of elimination rate and V2(central compartment volume), respectively. There were small and inconsequential numeric differences in popPK parameters between the adolescent and adult models. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 18 and Figure 19). As it is well established that weight is an important and statistically significant covariate of volume of distribution for dupilumab, weight was included as a covariate on central volume of distribution in all models including the primary base model. The effect of disease activity (EASI score) and ADA on dupilumab exposure is not considered clinically relevant. Body weight demonstrates as a statistically significant and clinically relevant covariate on dupilumab exposure. Weight- tiered dosing regimen with a cut-

off values of 30 kg and 60 kg were applied in the clinical trial. Bootstrap confidence intervals, visual predictive check, and sensitivity analyses were used to validate the results.

Based on a cross-study and cross-age groups PK comparison, at the recommended dosing regiments, the drug exposure in children ≥6 to <12 years of age appears higher than those in adolescents and adults. To assist the PK comparison across the age/body-weight bands and the identification of source of exposure variability, the agency recommended that the Applicant update the popPK model with the pooled dataset from children ≥6 to <12 years of age, adolescents, and adults.

Population PK Analysis with Pooled Data in Children, Adolescents and Adults

To assist the PK comparison across the age/body-weight bands and the identification of source of exposure variability, the previously developed population PK model in AD patients was updated using data pooled across age groups (children ≥6 to <12 years of age, adolescents and adults) to further justify the proposed dosing regimen for children ≥6 to <12 years of age.

The previously developed AD population PK model for dupilumab was updated using a total of 23272 dupilumab concentration records obtained from 2497 subjects from 15 phase 1 through 3 studies in adults (original BLA submission, 2016), the Phase 3 study in adolescent patients (sBLA for AD adolescents, 2018), and data from the current submission, the Phase 3 study (R668-AD-1652) and Phase 2a study (R668-AD-1412) in children aged ≥6 to <12 years of age (sBLA for AD children ≥6 to <12 years of age).

Population PK of dupilumab were characterized by nonlinear mixed-effects modeling using Monolix version 2019R1 (Lixoft). The model-building strategy was based on a previously developed model (Figure 17) in adults, adolescents, and children aged ≥6 to <12 years (R668-PM-18124-SR-01V1, R668-MX-16103-CP-01V2, R668-PM-19142-SR-01V1). There were no changes in the structural model and interindividual variability terms were included on ke (elimination rate constant), V2, Vm (maximum target-mediated rate of elimination), ka (absorption rate constant), and MTT (mean transit time).

No signs of model misspecification were identified in the goodness-of-fit plots (Figure 20 and Figure 21). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of dupilumab in all treatment groups (Figure 22). As it is well established that body weight is an important and statistically significant covariate of volume of distribution for dupilumab, body weight was included as a covariate on central volume of distribution in all models. Age was re-tested as a covariate, and it was found to be statistically significant for Vm and Ka; however, its covariate effect is considered not clinical meaningful.

Based on the developed final popPK model with pooled data in children, adolescents and adults, individual PK parameter estimates were used to predict steady-state dupilumab exposure $C_{troughSS}$ (trough concentration at steady state) , AUC_{SS} (area under the concentration-time curve at steady state), and C_{maxSS} (peak concentration at steady state) to allow PK

comparison between dosing regimens in children aged ≥6 to <12 years to the approved dosing regimens in adolescents and adults. The exposure metrics were summarized by age, weight, and treatment categories (Table 41).

This simulation indicated the dupilumab exposure (C_{trough}, C_{max}, and AUC) with dosing regimen 300 mg Q4W in children <30 kg and ≥6 to <12 years of age is higher than those predicted in adolescents (200/300 mg Q2W) and adults (300 mg Q2W), whereas, the dupilumab exposure with dosing regimen 100 mg Q2W in children<30 kg and ≥6 to <12 years of age is more comparable to the exposure predicted in adolescents (200/300 mg Q2W) and adults (300 mg Q2W). In order to address this drug exposure discrepancy, the agency requested the Applicant to provide justifications for the proposed dosing regimen for children <30 kg and ≥6 to <12 years of age based on exposure-response relationships and comparisons among children, adolescents and adults for efficacy and safety.

Table 43 Parameter Estimates of the Final PopPK Model in Children

Parameter Name	Children ≥6 to <12 Years of Age		Adolescents ≥12 to <18 years		Adults ≥18 years	
	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)	Population Estimate (SE)	Bootstrap Median (2.5th, 97.5th percentiles)
PK parameter						
V_2 (L)	2.18 (0.0872)	2.15 (1.98, 2.36)	2.47 (0.0501)	2.45 (2.34, 2.56)	2.74 (0.021)	2.72 (2.67, 2.78)
k_e (1/d)	0.0446 (0.00152)	0.0448 (0.0411, 0.0485)	0.0520 (0.00188)	0.0504 (0.0338, 0.0560)	0.0477 (0.00078)	0.0477 (0.0457, 0.0498)
V_m (mg/L/d)	1.64 (fixed)	---	1.43 (0.0379)	1.43 (1.25, 1.61)	1.07 (fixed)	---
K_m (mg/L)	0.01 (fixed)	---	0.01 (fixed)	---	0.01 (fixed)	---
k_{23} (1/d)	0.211 (fixed)	---	0.211 (fixed)	---	0.211 (fixed)	---
k_{32} (1/d)	0.310 (fixed)	---	0.310 (fixed)	---	0.310 (fixed)	---
k_a (1/d)	0.641 (fixed)	---	0.306 (fixed)	---	0.306 (fixed)	---
MTT (d)	0.105 (fixed)	---	0.105 (fixed)	---	0.105 (fixed)	---
F (unitless)	0.642 (fixed)	---	0.642 (fixed)	---	0.642 (fixed)	---
Covariates						
V_2 ~ weight	0.849 (0.0345)	0.773 (0.671, 0.865)	0.755 (0.0517)	0.722 (0.579, 0.845)	0.817 (0.031)	0.805 (0.740, 0.891)
V_2 ~ albumin	-0.525 (0.149)	-0.632 (-0.960, -0.216)	---	---	-0.653 (0.072)	-0.679 (-0.829, -0.536)
k_e ~ BMI	---	---	0.357 (0.116)	0.367 (0.0244, 0.809)	0.368 (0.053)	0.378 (0.225, 0.521)
k_e ~ ADA	---	---	0.193 (0.0566)	0.196 (0.0634, 0.325)	0.164 (0.029)	0.168 (0.103, 0.248)
k_e ~ EASI	0.169 (0.0471)	0.156 (0.0265, 0.262)	0.356 (0.0523)	0.350 (0.237, 0.481)	0.143 (0.021)	0.147 (0.104, 0.198)
k_e ~ race (white)	---	---	---	---	-0.123 (0.018)	-0.116 (-0.168, -0.0749)
Omega Matrix						
σ ($\ln(V_2)$)	0.291 (0.0204)	0.258 (0.119, 0.325)	0.140 (0.0145)	0.140 (0.105, 0.172)	0.206 (0.0068)	0.213 (0.198, 0.231)
σ ($\ln(k_e)$)	0.417 (0.0282)	0.375 (0.182, 0.506)	0.304 (0.0242)	0.309 (0.245, 0.351)	0.293 (0.010)	0.306 (0.280, 0.332)
Corr($\ln(k_e)$,$\ln(V_2)$)	-0.883 (0.0212)	---	-0.529 (0.0902)	---	-0.450 (0.035)	---
Residual SD						
σ prop. (CV%)	13.1 (0.402)	13.5 (12.0, 14.8)	9.94 (0.602)	10.1 (7.19, 12.2)	12.5 (0.18)	12.3 (11.7, 13.2)
σ add. (mg/L)	0.03 (fixed)	---	2.36 (0.24)	2.33 (1.56, 3.81)	6.06 (0.23)	6.04 (4.85, 7.03)
Derived Parameters						
CL (L/d)	0.0972	---	0.128	---	0.131	---
Q (L/d)	0.460	---	0.521	---	0.578	---
V_3 (L)	1.48	---	1.68	---	1.86	---

BMI = Body mass index; EASI = Eczema Area and Severity Index; --- = Not calculated for fixed, derived, or excluded parameters
Note: The central volume was calculated at weight of 75 kg. Bootstrap correlation coefficients are not provided as PsN software summarizes covariances.

Source: Table 10, Population PK report R668-PM-19142-SR-01V1

Table 44. Parameter Estimates of the Final PopPK Model With Pooled Data

Fixed Effects		**se_sa**	**rse(%)**
VM_pop	1.14	0.0125	1.1
beta_VM_tAGE	-0.0806	0.0197	24.5
KM_pop	0.01		
KE_pop	0.0507	0.000667	1.31
beta_KE_HML_1	0.211	0.0189	8.97
beta_KE_RACEW_1	-0.115	0.0133	11.6
beta_KE_tBMI	0.182	0.036	19.8
V2_pop	2.6	0.0157	0.605
beta_V2_tALB	-0.535	0.0488	9.12
beta_V2_tWT	0.837	0.0156	1.87
KA_pop	0.433	0.0264	6.1
beta_KA_age18_1	-0.255	0.0644	25.3
K23_pop	0.211		
K32_pop	0.31		
MTT_pop	0.127	0.00906	7.13
F_pop	0.642		
Standard Deviation of the Random Effects			
omega_VM	0.268	0.00851	3.18
omega_KE	0.334	0.00757	2.27
omega_V2	0.227	0.00482	2.13
omega_KA	0.451	0.0188	4.18
omega_MTT	0.738	0.056	7.58
Correlations			
corr_V2_KE	-0.589	0.0192	3.26
Error Model Parameters			
a	0.03		
b	0.16	0.00106	0.665

	min	max	max/min
Eigen values	0.059	2.1	37

Source: Table 2. PK Memorandum (dated March 26th, 2020)

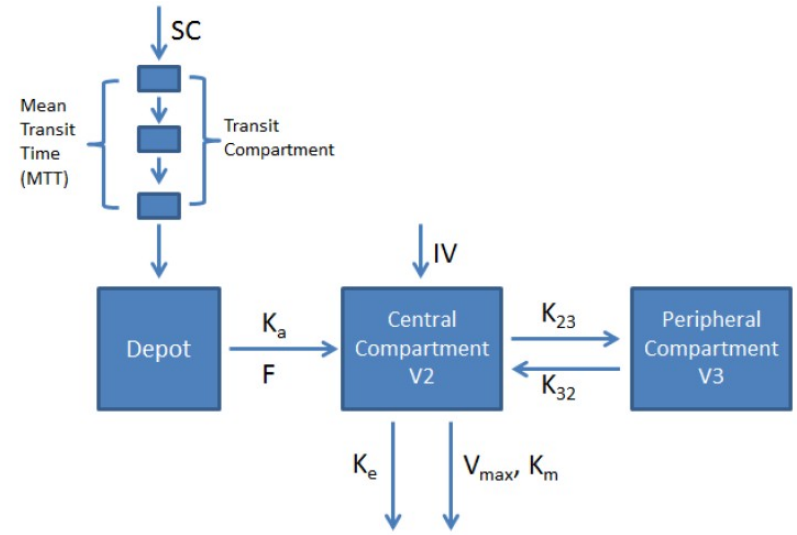
Table 45. Individual Predicted Exposure of Dupilumab in Children, Adolescents, and Adults at Steady-State by Treatment, Age and Weight Categories

Variable / Age Group			Treatment																			
			100 mg Q2W SC				200 mg Q2W SC				300 mg Q2W SC				300 mg Q4W SC				300 mg QW SC			
			Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95	Mean	P5	P50	P95
CtroughSS (mg/L)	6-11 yo	1) <30 kg	59.6	28.3	59.0	93.3									79.8	40.1	77.5	128				
		2) >=30 kg					89.1	36.7	83.4	140					44.4	10.8	41.1	78.5				
	12-17 yo	3) <60 kg					54.9	26.5	52.6	84.9					23.3	3.74	21.5	43.6				
		4) >=60 kg									56.7	17.7	55.0	102	9.47	0.000784	6.68	26.6				
	Adults	5) All weights									69.6	24.7	67.0	122					181	85.1	175	295
CmaxSS (mg/L)	6-11 yo	1) <30 kg	86.8	48.6	86.6	125									175	111	175	241				
		2) >=30 kg					126	62.3	124	184					110	54.5	111	157				
	12-17 yo	3) <60 kg					82.4	46.6	80.2	119					71.8	45.2	70.1	106				
		4) >=60 kg									85.5	42.7	80.5	133	43.4	20.9	41.8	69.6				
	Adults	5) All weights									94.5	42.4	91.9	153					197	96.7	191	314
Monthly AUC (mg.day/L)	6-11 yo	1) <30 kg	2092	1112	2075	3084									3529	2117	3499	5076				
		2) >=30 kg					3075	1388	2935	4601					2139	876	2039	3276				
	12-17 yo	3) <60 kg					1965	1024	1892	2905					1310	606	1275	2005				
		4) >=60 kg									2037	882	1912	3309	718	251	638	1349				
	Adults	5) All weights									2353	975	2277	3935					5350	2573	5183	8596
Weight (kg)	6-11 yo	1) <30 kg	24.0	18.6	24.0	29.2									24.0	18.6	24.0	29.2				
		2) >=30 kg					39.2	30.5	36.2	58.5					39.2	30.5	36.2	58.5				
	12-17 yo	3) <60 kg					49.2	35.4	51.3	58.3					49.2	35.4	51.3	58.3				
		4) >=60 kg									80.4	60.0	75.4	117	80.4	60.0	75.4	117				
	Adults	5) All weights									76.5	52.0	74.6	108					76.5	52.0	74.6	108

Note: The steady-state AUC is calculated per week.

Source: Table 4. PK Memorandum (dated March 26th, 2020)

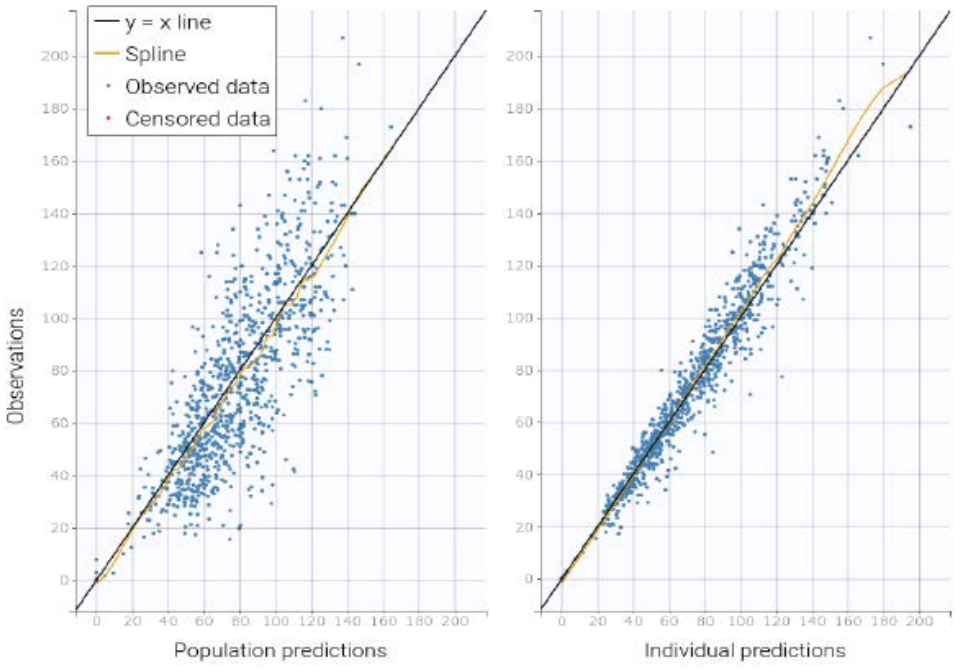
Figure 19. Structural Representation of Dupilumab PopPK Model With Parallel Linear and Michaelis-Menten Elimination



F = Bioavailability; K_a = Absorption rate constant; MTT = Mean transit time; V_2 = Central compartment volume; V_3 = Peripheral compartment volume; k_{23}, k_{32} = Inter-compartmental rate constants; K_e = Elimination rate constant; V_m = Maximum target-mediated rate of elimination; K_m = Michaelis-Menten constant.

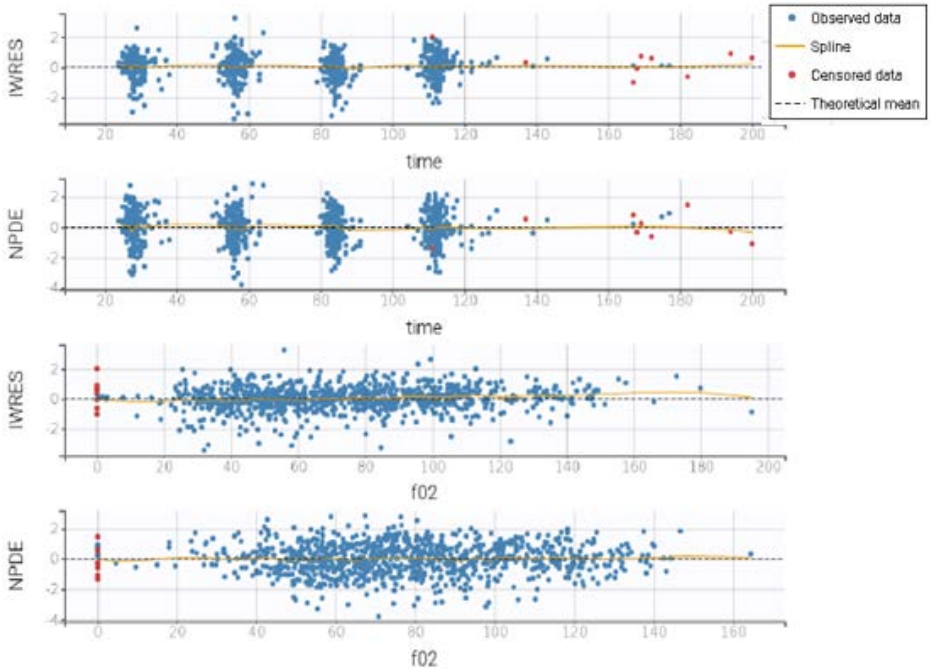
Source: Figure 1, Population PK report R668-PM-19142-SR-01V1

Figure 20. Observed vs. Population and Individual Predicted Concentrations for Final PopPK Model in Children



Source: Figure 15, Population PK report R668-PM-19142-SR-01V

Figure 21. Scatter Plots of Residuals for Final PopPK Model in Children



Notes: IWRES - individual weighted residuals; NPDE - normalized prediction distribution error; f02 – population predicted concentration of dupilumab; time is expressed in days.
Source: Figure 16, Population PK report R668-PM-19142-SR-01V1

Figure 22. Observed vs. Population and Individual Predicted Concentrations for Final PopPK Model With Pooled Data

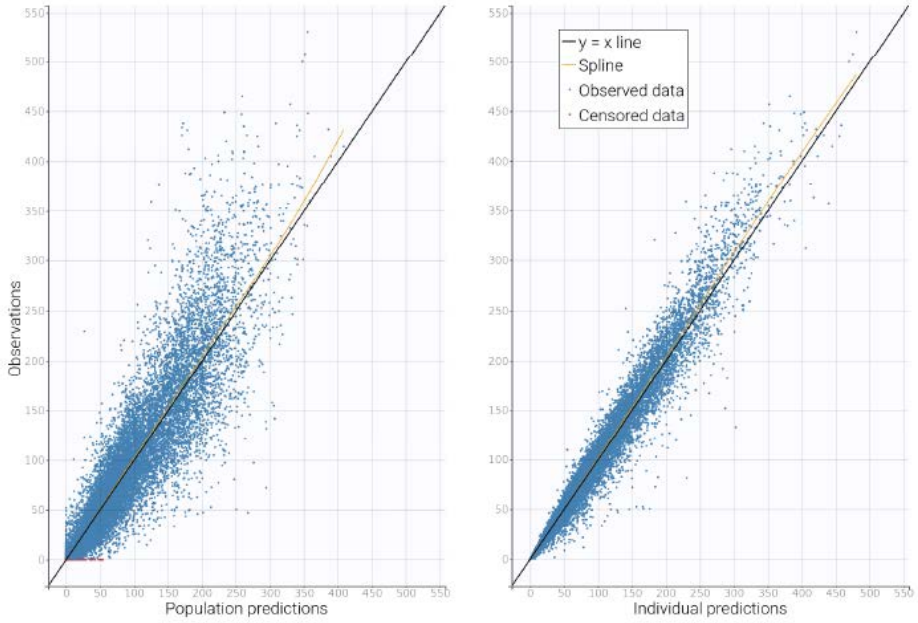
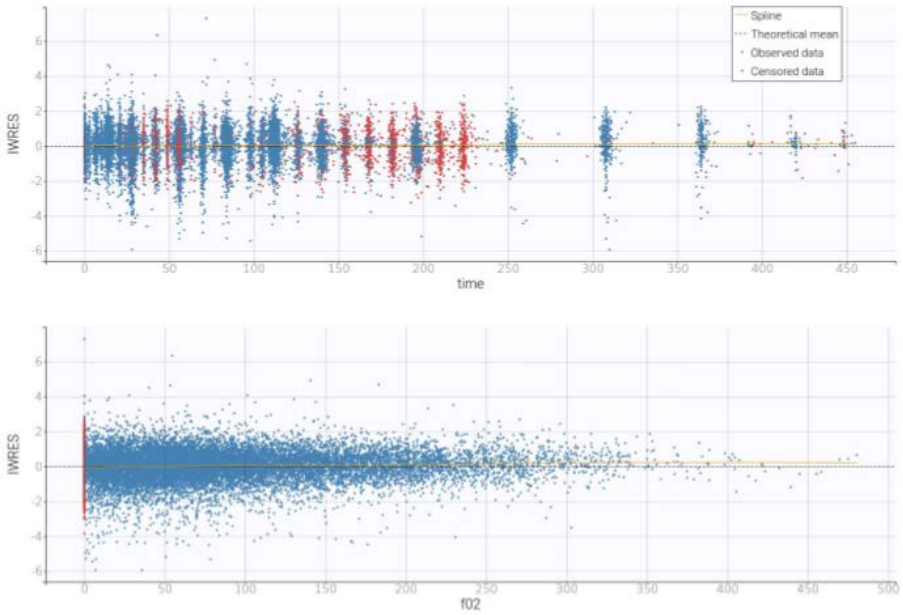
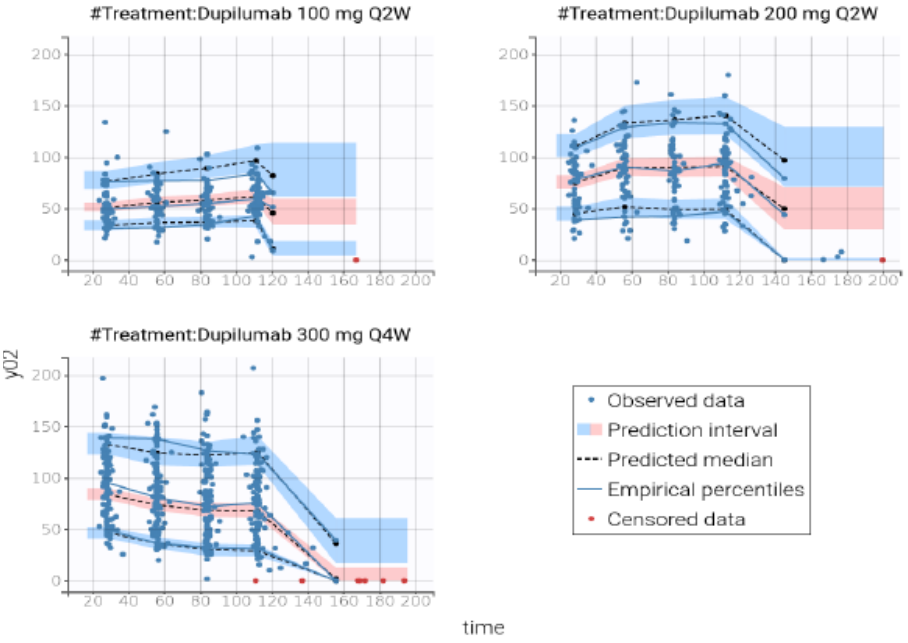


Figure 23. Scatter Plots of Residuals for Final PopPK Model With Pooled Data



Note: Time is expressed in days. f02 is individual predicted concentration of dupilumab.

Figure 24. Visual Predictive Checks for Final PopPK Model With Pooled Data by Treatment vs. Actual Day



Source: Figures A1, A2 and 19, PK Memorandum (dated March 26th, 2020)

14.4.4. Dose/Exposure Response Relationships

Dose/Exposure Responses in Children (Phase 3 Study R668-AD-1652)

In Study R668-AD-1652, the efficacy data demonstrated that both the weight-tiered Q2W dupilumab dosing regimen (100 mg +TCS in patients <30 kg and 200 mg + TCS in patients ≥30 kg) and the non-weight-tiered Q4W regimen (300 mg + TCS in all patients irrespective of body weight) resulted in statistically significant, clinically meaningful improvements in signs, symptoms, and quality of life in children ≥6 to <12 years of age with severe AD in all pre-specified endpoints, including intensity and extent of signs (measured by IGA, EASI, and SCORing Atopic Dermatitis) (Table 46).

Exposure-response analyses including the percentage of patients achieving IGA 0 or 1, percent change in EASI from baseline, and the proportion of patients achieving EASI-50, EASI-75, and EASI-90 at Week 16 were conducted. The exposure-response analysis of the relationship between quartile of dupilumab C_{trough} with the primary efficacy endpoint, percentage of patients achieving IGA 0 or 1, showed a trend of increasing drug effect with increasing quartile of C_{trough} of dupilumab over time (Figure 25). Similar E-R relationships were observed for other efficacy endpoints including percent of patients achieving EASI-75 (co-primary efficacy endpoint), and EASI percent change from baseline (Figure 26). Logistic regression on binary response variables such as the primary and co-primary endpoints of IGA 0 or 1 (Figure 27) and

EASI-75 (Figure 28) also demonstrated positive exposure-response relationships, showing increasing effects with increasing steady-state C_{trough} of dupilumab.

Dupilumab was well tolerated in children aged ≥6 to <12 years in the pivotal Phase 3 study (R668-AD-1652). The safety profile in this pediatric population was comparable to that previously observed in adult and adolescent patients with AD for whom the drug is already approved. No new ADRs were identified in this patient population of children; only the known ADRs of Injection Site Reactions (ISRs) and conjunctivitis occurred more frequently in the dupilumab groups than in the placebo group.

Exposure-safety relationship was evaluated in children ≥6 to <12 years of age from Study R668-D-1652. Safety endpoint was conjunctivitis, the most commonly reported adverse drug reaction, and the evaluated exposure metric was observed dupilumab concentration at Week 16. Logistic regression relating probability of patients developing conjunctivitis (broad term) with dupilumab C_{trough} at Week 16 showed a slight trend for an inverse E-R relationship with the highest probability of developing conjunctivitis observed at lower drug concentrations and the lowest probability at higher drug concentrations (Figure 29).

Dose/Exposure Response Comparison in Patients with AD Across Age Groups

Dose/Exposure Efficacy Comparison in Patients with AD Across Age Groups

The simulation based on the updated popPK PK model with the pooled data across age groups indicated the dupilumab exposure (C_{trough}, C_{max}, and AUC) with the recommended dosing regimen of 300 mg Q4W in children <30 kg and ≥6 to <12 years of age is higher than those predicted in adolescents (200/300 mg Q2W) and adults (300 mg Q2W), whereas the dupilumab exposure with dosing regimen of 100 mg Q2W in children <30 kg and ≥6 to <12 years of age is more comparable to the exposure predicted in adolescents (200/300 mg Q2W) and adults (300 mg Q2W). In order to address this drug exposure discrepancy, the agency requested the Applicant to provide justifications for the dose selection for children <30 kg and ≥6 to <12 years of age based on exposure-response relationships and comparisons among children, adolescents, and adults for efficacy and safety.

A cross-study comparison was conducted across phase 3 studies in children ≥6 to <12 years of age, adolescents and adults. The studies and dosing regimens included in this comparison were:

- Phase 3 study (R668-AD-1652) in children ≥6 to <12 years old in the weight subgroup <30 kg: the 300 mg q4w dose (following a 600 mg loading dose) and the 100 mg q2w dose (following a 200 mg loading dose)
- Phase 3 study (R668-AD-1224; CHRONOS) in adults receiving 300 mg q2w (following a 600 mg loading dose)

- Phase 3 study (R668-AD-1526) in adolescents receiving 200/300 mg q2w (following a loading dose of 400 mg/600 mg respectively). Patients <60 kg were administered 200 mg q2w; patients ≥60 kg were administered 300 mg q2w.

A comparison on the primary and key secondary efficacy endpoints across studies was demonstrated in Table 47. In children ≥6 to <12 years of age, the 300 mg Q4W dosing regimen was numerically superior to 100 mg Q2W dosing regimen for the primary and key secondary lesional endpoints. The placebo adjusted effect for 300 mg Q4W dose in children were either comparable or numerically superior to that seen with approved dosing regimen in adolescents and adults. However, placebo adjusted effects for the 100 mg Q2W dosing regimen were substantially lower on the lesional endpoints.

In addition, exposure-response analyses were conducted on binary efficacy endpoints IGA 0 or1 and EASI-75 using logistic regression employing a non-linear E_{max} function to characterize the sensitive region of the respective E-R relationship, as well as the plateau. The logistic function converts the binary categorical measure into the probability (continuous variable bound from 0-1) of reporting the categorical response. The goal of these E-R analyses was to see where the mean C_{trough} of each regimen in children, and approved regimens in adults and adolescents, fall on the E-R relationships with respect to the plateau (maximal response). As shown in Figure 30 and Figure 31, the E-R relationships of probability of achieving IGA 0 or 1 response and EASI-75 versus C_{trough} at Week16 by age groups demonstrated that the mean C_{trough} exposure achieved by the proposed 300 mg Q4W regimen in children < 30 kg lies closer to the plateau of the respective E-R relationship compared to the 100 mg Q2W regimen which achieved lower mean C_{trough} at steady-state.

Dose/Exposure Safety Comparison in Patients with AD Across Age Groups

A safety profile comparison (TEAE) was conducted in children ≥6 to <12 years of age (<30 kg), the adolescents and adults (Table 48). In children ≥6 to < 12 years of age who weighed <30 kg, there was a trend towards a slightly higher number of TEAEs in the 100 mg Q2W dosing regimen as compared to 300 mg Q4W dosing regimen, driven by a higher incidence of conjunctivitis events in the 100 mg Q2W arm. The overall TEAE profile was comparable between the 300 mg Q4W dosing regimen and the approved dosing regimens in adolescents and adults. The 100 mg Q2W dosing regimen in children was associated with a higher incidence of conjunctivitis events as compared to those seen in adolescents and adults at approved doses.

Logistic regression relating probability of children aged ≥6 to <12 years developing conjunctivitis with observed dupilumab C_{trough} at Week 16 (Figure 32) showed a slight trend for an inverse E-R relationship with the highest probability of developing conjunctivitis observed at lower drug concentrations and the lowest probability at higher drug concentrations. This observation is consistent with the safety findings showing the 100 mg Q2W dosing regimen (lower C_{trough} exposure) had a higher incidence of conjunctivitis events. The E-R relationships on

conjunctivitis in adolescents and adults were flat indicating no relationship of developing conjunctivitis with Week 16 C_{trough}.

Based on the efficacy, safety and E-R analyses, the proposed dosing regimen of 300 mg Q4W for children ≥ 6 to <12 years of age who weigh <30 kg is justified to be an effective and safe optimal dosing regimen.

Table 46. Overview of Co-Primary and Key Secondary Efficacy Endpoints of Pivotal Study R668-AD-1652

Level	Efficacy Endpoints at Week 16	Placebo + TCS	Dupilumab +TCS [2,3]					
			300 mg Q4W			100/200 mg Q2W		
		N=123		N=122	Difference vs. Placebo % or LS Mean (95% CI)[2]		N=122	Difference vs. Placebo % or LS Mean (95% CI)[2]
Primary	Proportion of patients with IGA 0 or 1 on a 5-point scale), n (%)	14 (11.4%)	7	40 (32.8%)	21.4% (11.36, 31.45)*	1	36 (29.5%)	18.1% (8.28, 27.97)**
Co-primary[1]	Proportion of patients with EASI-75 (≥75% improvement from baseline), n (%)	33 (26.8%)	8	85 (69.7%)	42.8% (31.54, 54.15)*	2	82 (67.2%)	40.4% (28.95, 51.82)*
Secondary	Percent change from baseline in EASI, LS mean percent change (SE)	-48.6 (2.46)	9	-82.1 (2.37)	-33.4 (-40.06, -26.82)*	3	-78.4 (2.35)	-29.8 (-36.33, -23.24)*
	Proportion of patients with EASI-50 (≥50% improvement from baseline), n (%)	53 (43.1%)	10	111 (91.0%)	47.9% (37.77, 58.01)*	4	101 (82.8%)	39.7% (28.68, 50.72)*
	Percent change from baseline in weekly average of daily worst itch score, LS mean percent change (SE)	-25.9 (2.90)	11	-54.6 (2.89)	-28.6 (-36.47, -20.82)*	5	-57.0 (2.77)	-31.0 (-38.76, -23.26)*
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4, n (%)	15 (12.3%)	12	61 (50.8%)	38.5% (27.86, 49.21)*	6	70 (58.3%)	46.0% (35.47, 56.61)*
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3, n (%)	26 (21.1%)	15	73 (60.3%)	39.2% (27.88, 50.51)*	13	81 (67.5%)	46.4% (35.30, 57.42)*
	Proportion of patients with EASI-90 (≥90% improvement from baseline), n (%)	9 (7.3%)	16	51 (41.8%)	34.5% (24.60, 44.37)*	14	37 (30.3%)	23.0% (13.65, 32.38)*
	Change from baseline in POEM, LS mean change (SE)	-5.3 (0.69)	20	-13.6 (0.65)	-8.3 (-10.13, -6.43)*	17	-13.4 (0.65)	-8.1 (-9.96, -6.31)*
	Change from baseline in CDLQI, LS mean change (SE)	-6.4 (0.51)	21	-10.6 (0.47)	-4.2 (-5.57, -2.89)*	18	-10.7 (0.46)	-4.3 (-5.62, -2.99)*
	Percent change from baseline in SCORAD, LS mean percent change (SE)	-29.8 (2.26)	22	-62.4 (2.13)	-32.6 (-38.57, -26.59*	19	-60.2 (2.11)	-30.4 (-36.30, -24.48)*

[1] Coprimary endpoint for EU and EU reference market countries only, key secondary endpoint for US and US reference market countries.
[2] P -value vs placebo. For the primary analyses using the FAS, each hypothesis was formally tested only if the preceding one was significant at the 2-sided 0.05 significance level. * P-value <0.0001; ** P-value =0.004
[3] Numbers in shaded columns specify the hierarchical testing order for the primary analysis using the FAS.
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LS mean, least squares mean; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids.

Source: Table 2, Module 5.2.5.

Table 47.Efficacy Endpoints Results at Week 16 in R668- AD-1652 (Children 6 to <12 Years of Age), CHRONOS R668-AD-1224 (Adult Patients With Baseline IGA 4) and R668-AD-1526 (12 to <18 Years of Age AD Patients With Baseline IGA 4)

	6 to <12 years (R668-AD-1652) <30kg			Adult (Study R668-AD-1224) IGA=4 at baseline		12 to <18 years of age (Study R668-AD-1526) IGA=4 at baseline	
	Placebo	Dupilumab 100 mg q2w	Dupilumab 300 mg q4w	Placebo	Dupilumab 300 mg Q2w	Placebo	Dupilumab 200/300 mg q2w
N (FAS)	61	63	61	147	53	46	43
IGA 0-1 (%) at week 16 n/N (%) Difference vs. placebo (95% CI)	8/61 (13.1%)	13/63 (20.6%) 7.5% (-5.58%, 20.62%)	18/61 (29.5%) 16.4% (2.15%, 30.63%)	8/147 (5.4%)	15/53 (28.3%) 22.9% (7.24%, 37.86%)	1/46 (2.2%)	8/43 (18.6%) 16.4% (4.06%, 28.80)
EASI75 (%) at week 16 n/N (%) Difference vs. placebo (95% CI)	17/61 (27.9%)	38/63 (60.3%) 32.4% (15.94%, 48.96%)	46/61 (75.4%) 47.5% (31.94%, 63.14%)	25/147 (17.0%)	36/53 (67.9%) 50.9% (36.12%, 64.23%)	3/46 (6.5%)	17/43 (39.5%) 33.0% (16.75%, 49.28%)
% change in EASI from baseline to week 16 LSM(SE) Difference vs. placebo (95% CI)	-49.1 (3.30)	-76.7 (3.04) -27.6 (-36.26, -18.95)	-84.3 (3.08) -35.1 (-43.96, -26.34)	-44.4 (3.12)	-79.9 (4.58) -35.5 (-45.75, -25.24)"	-23.4 (6.87)	-61.3 (5.04) -37.9 (-54.43, -21.33)
%Change Peak Pruritus NRS from baseline to week 16 LSM(SE) Difference vs. placebo (95% CI)	-27.0 (4.24)	-56.1 (3.86) -29.0 (-40.19, -17.88)	-55.1 (3.94) -28.1 (-39.24, -16.89)	-30.8 (3.07)	-57.6 (4.54) -26.9 (-37.66, -16.09)	-17.3 (6.79)	-50.0 (4.79) -32.7 (-49.17, -16.22)
Peak Pruritus NRS improvement ≥ 4 at week 16 n/N (%) Difference vs. placebo (95% CI)	7/60 (11.7)	35/63 (55.6%) 43.9% (29.17%, 58.60%)	33/61 (54.1%) 42.4% (27.52%, 57.34%)	26/142 (18.3%)	29/51 (56.9%) 38.6% (23.01%, 53.01%)	3/46 (6.5%)	19/43 (44.2%) 37.7% (21.20%, 54.13%)

Post-text table for 2.7.3: Table P1.1/1, Table P1.2/1, Table P1.6/1; Post-text table for AD-1652 CSR: Table 12.1.1/1, Table 12.1.1/2, Table 12.1.2/1, Table 12.1.2/2, Table 12.1.2/3; Post-hoc tables: Table 21.6.2.18.3/7b, Table 21.6.2.7.3/7b, Table 19.6.2.2.3/1a, Table 19.6.2.1.3/1a

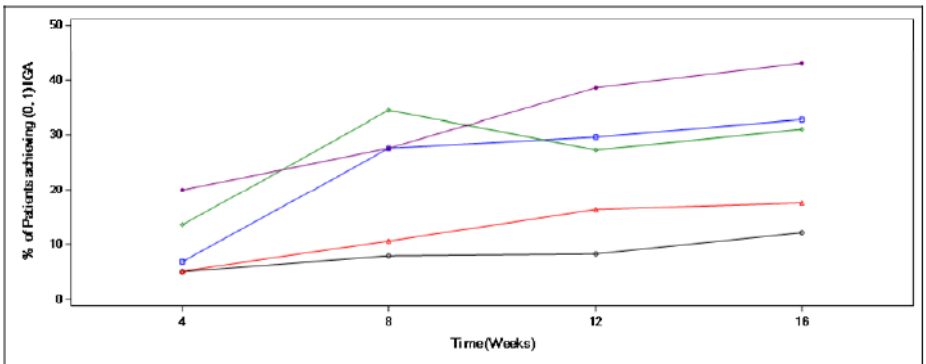
Source: Table 1, Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

Table 48. Key Safety Results Comparing the Treatment Emergent Adverse Events in Children (6 to <12 Years of Age), CHRONOS R668-AD-1224 (Adult Patients With Baseline IGA 4) and Adolescents (12 to <18 Years of Age With Baseline IGA 4 at Week 16)

	≥6 to <12 years of age (R668-AD-1652) <30kg			Adult (Study R668-AD-1224) IGA=4 at baseline		Adolescent (Study R668-AD-1526) IGA=4 at baseline	
Number of patients with event	Placebo	100 mg q2w	Dupilumab 300 mg q4w	Placebo	Dupilumab 300 mg Q2w	Placebo	Dupilumab 200/300 mg q2w
N (SAF)	60	63	60	147	54	46	43
TEAE	43 (71.7%)	46 (73.0%)	39 (65.0%)	105 (71.4%)	40 (74.1%)	34 (73.9%)	35 (81.4%)
TE SAEs	0	0	2 (3.3%)	3 (2.0%)	2 (3.7%)	1 (2.2%)	0
Any TEAE Leading to Permanent Treatment Discontinuation	2 (3.3%)	1 (1.6%)	0	10 (6.8%)	1 (1.9%)	(2.2%)	0
TEAEs in Injection Site Reactions HLT	4 (6.7%)	5 (7.9%)	6 (10.0%)	6 (4.1%)	5 (9.3%)	3 (6.5%)	2 (4.7%)
TEAEs in Conjunctivitis cluster[1]	2 (3.3%)	15(23.8%)	4 (6.7%)	13 (8.8%)	5 (9.3%)	1 (2.2%)	7 (16.3%)
TEAEs in Herpes simplex virus infection cluster [2]	2 (3.3%)	3 (4.8%)	0	1 (0.7%)	0	1 (2.2%)	0
TEAEs in Keratitis cluster [3]	0	1 (1.6%)	0	0	4 (7.4%)	0	0

Source: Table 2, Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

Figure 25. Percent of Patients Achieving IGA 0 or 1 Over Time by Quartile of Functional Dupilumab Concentrations in Pivotal Study R668- AD-1652

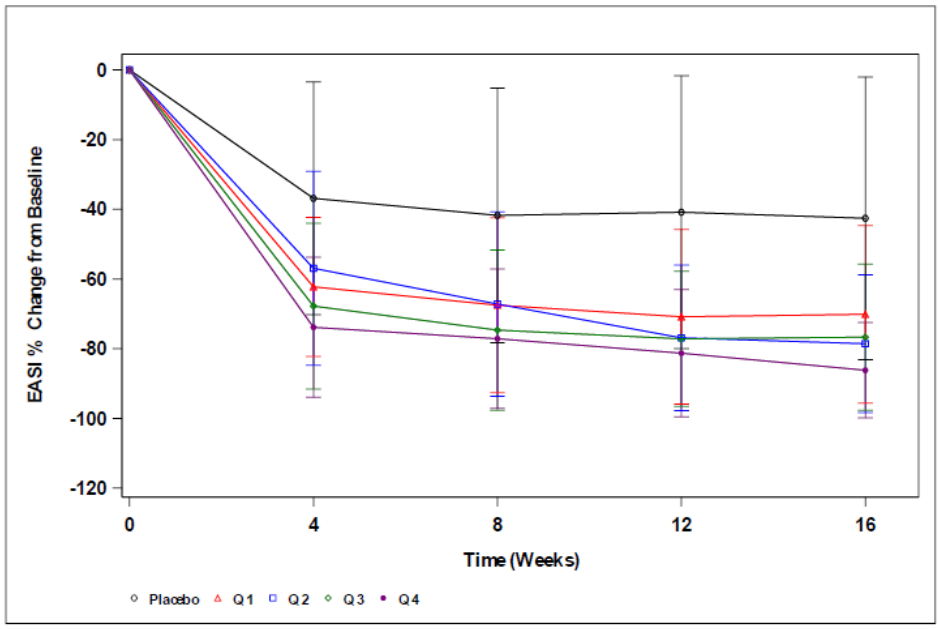


Placebo	5% (6/120)	8% (9/115)	8% (9/110)	12% (14/116)
Q1	5% (3/59)	11% (6/57)	16% (9/55)	18% (10/57)
Q2	7% (4/59)	28% (16/58)	30% (16/54)	33% (19/58)
Q3	14% (8/59)	34% (20/58)	27% (15/55)	31% (18/58)
Q4	20% (12/60)	28% (16/58)	39% (22/57)	43% (25/58)

Note: Concentrations below the LLOQ were set to 0. The quartile ranges for week 16 concentrations (mg/L): Q1 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261)
Missing data were imputed as non-responders.
Data up to week 16 are used; number in parentheses in the table is number of patients achieving IGA 0 or 1/ number of patients who contribute to the quartile.

Source: Figure 8., Module 5.3.5.1 R668-AD-1652 Primary Analysis Appendix 5 Clinical Pharmacology Report

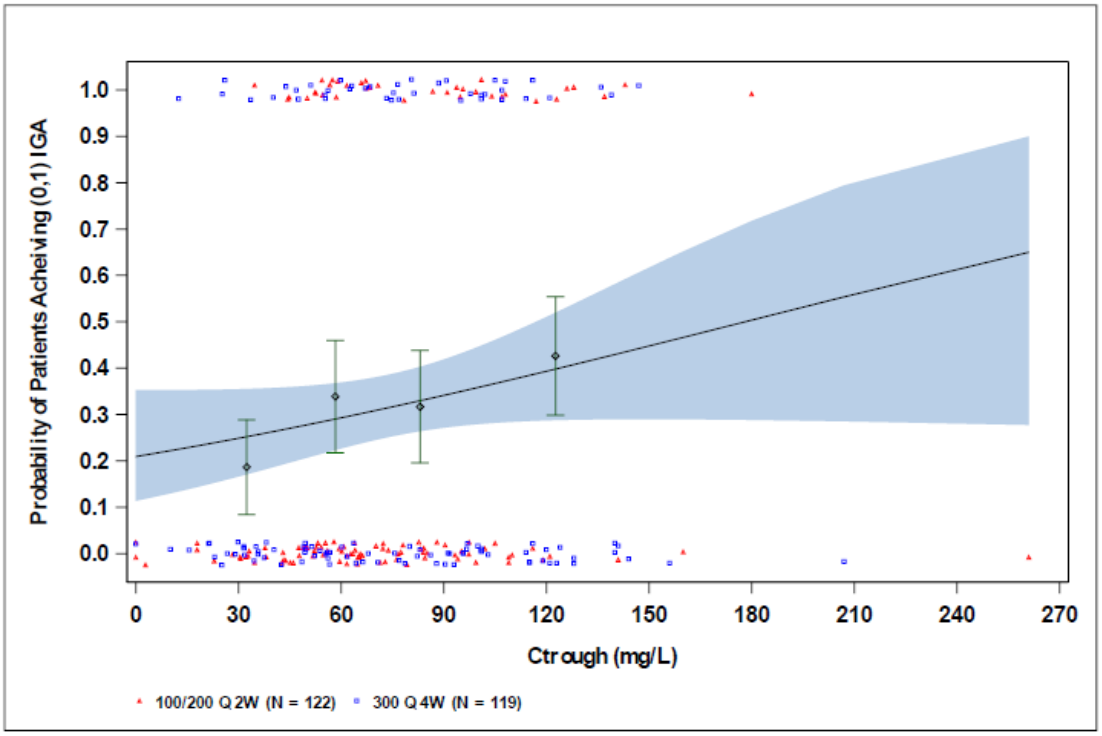
Figure 26. Mean (±SD) EASI Percent Change From Baseline Over Time by Quartile of Functional Dupilumab Concentration in Pivotal Study R668- AD-1652



Note: Concentrations below the LLOQ were set to 0. LOCF Imputation was used.
Concentrations below the LLOQ were set to 0. The quartile ranges for week 16 concentrations (mg/L): Q1 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261).

Source: Figure 10., Module 5.3.5.1 R668-AD-1652 Primary Analysis Appendix 5 Clinical Pharmacology Report

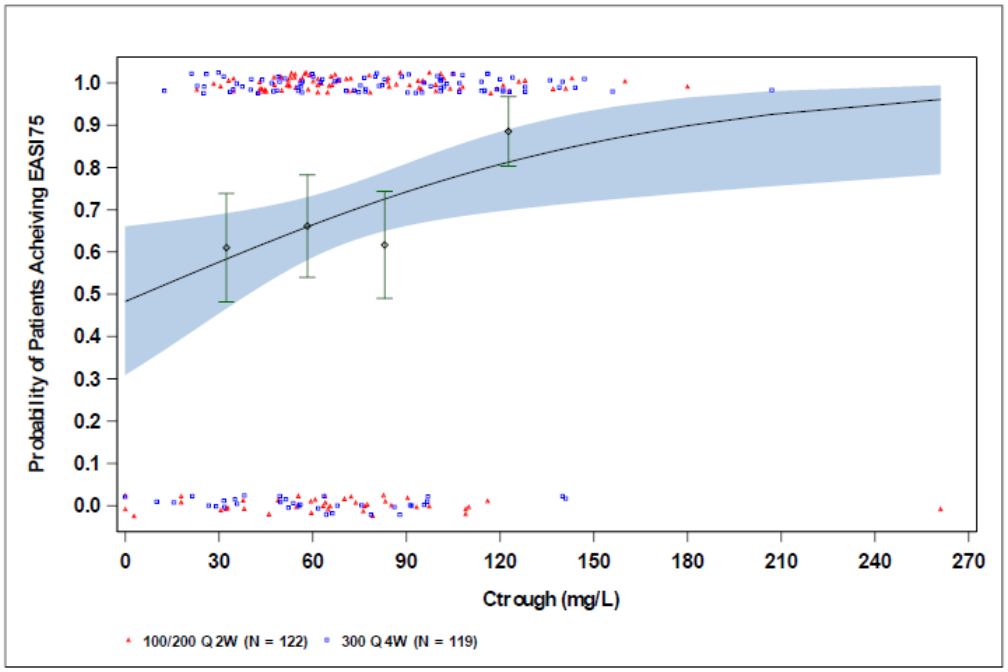
Figure 27. Logistic Regression Relating Probability of Patients Achieving IGA 0 or 1 With Dupilumab Trough Concentrations at Week 16 in Pivotal Study R668- AD-1652



Mean Regression line - black, confidence area around regression line - blue. Non-responders (0) and responders (1) individual concentration values are jittered and represented at the bottom and top of the figure respectively. The p-value (p=0.0467) represents the statistical significance of the inclination of the regression line. Means of response and confidence intervals (green vertical lines) around the means are presented in the figures by exposure quartiles, these vertical lines are placed at the means of interquartile ranges of an exposure on the x-axis.

Source: Figure 15, Module 5.3.5.1 R668 AD 1652 Primary Analysis Appendix 5 CP Clinical Pharmacology Report

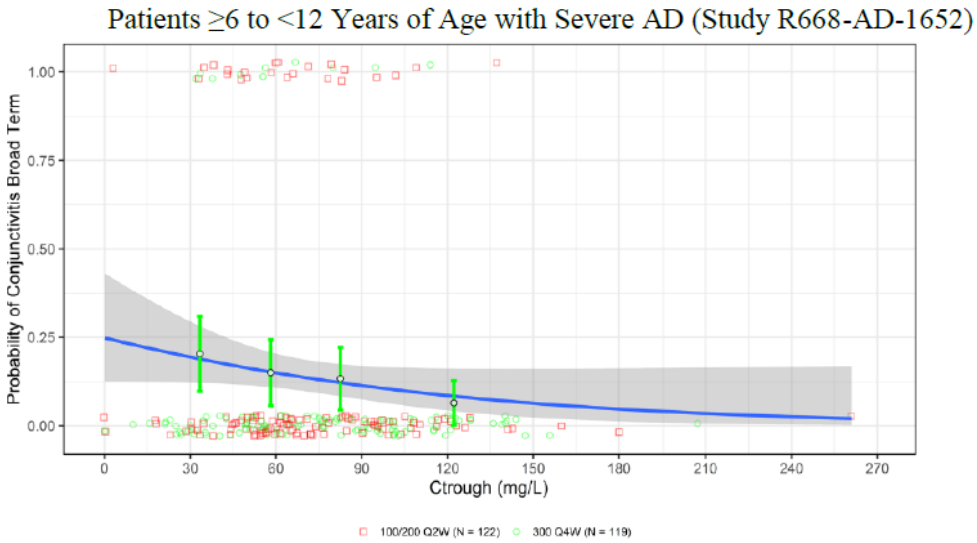
Figure 28. Logistic Regression Relating Probability of Patients Achieving EASI-75 With Dupilumab Trough Concentrations at Week 16 in Pivotal Study R668- AD-1652



Concentrations are imputed using LOCF rule when the efficacy endpoint is available and concentration is missing at planned PK visit. Mean Regression line - black, confidence area around regression line - blue. Non-responders (0) and responders (1) individual concentration values are jittered and represented at the bottom and top of the figure respectively. The p-value (p=0.004) represents the statistical significance of the inclination of the regression line. Means of response and confidence intervals (green vertical lines) around the means are presented in the figures by exposure quartiles, these vertical lines are placed at the means of interquartile ranges of an exposure on the x-axis.

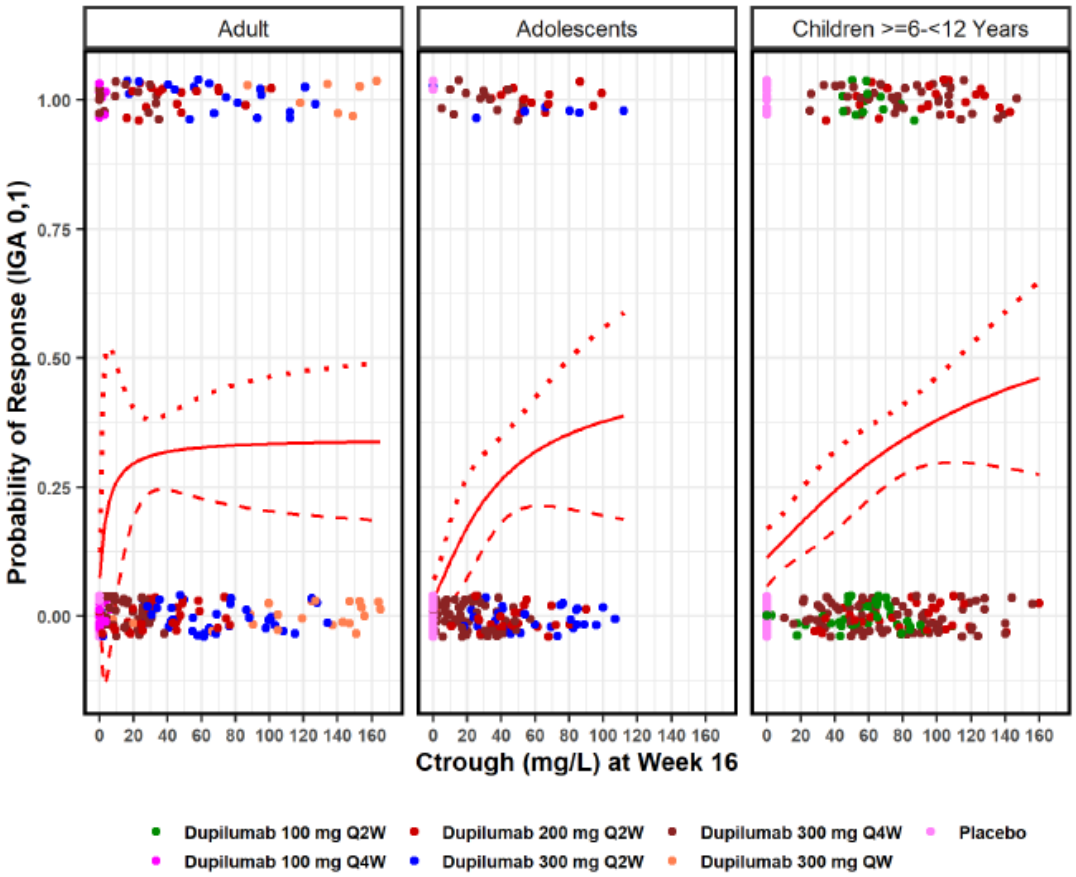
Source: Figure 15, Module 5.3.5.1 R668 AD 1652 Primary Analysis Appendix 5 CP Clinical Pharmacology Report

Figure 29. Logistic Regression Relating Probability of Patients Developing Conjunctivitis (Broad Term) With Dupilumab Trough Concentrations at Week 16



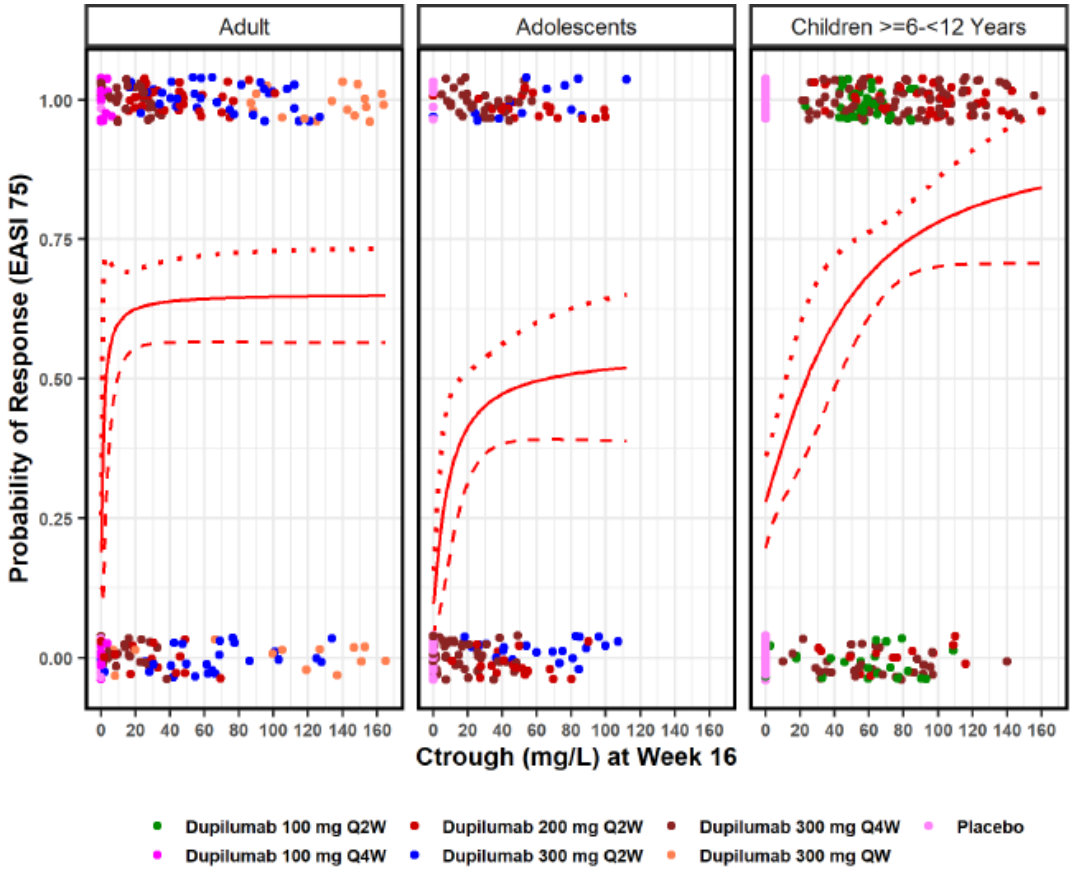
Source: Figure 10, Module 2.7.2

Figure 30. Probability of Response (IGA 0-1) vs. C_{trough} (mg/L) at Week 16 in Adults, Adolescents and Children (≥6 to <12 Years)



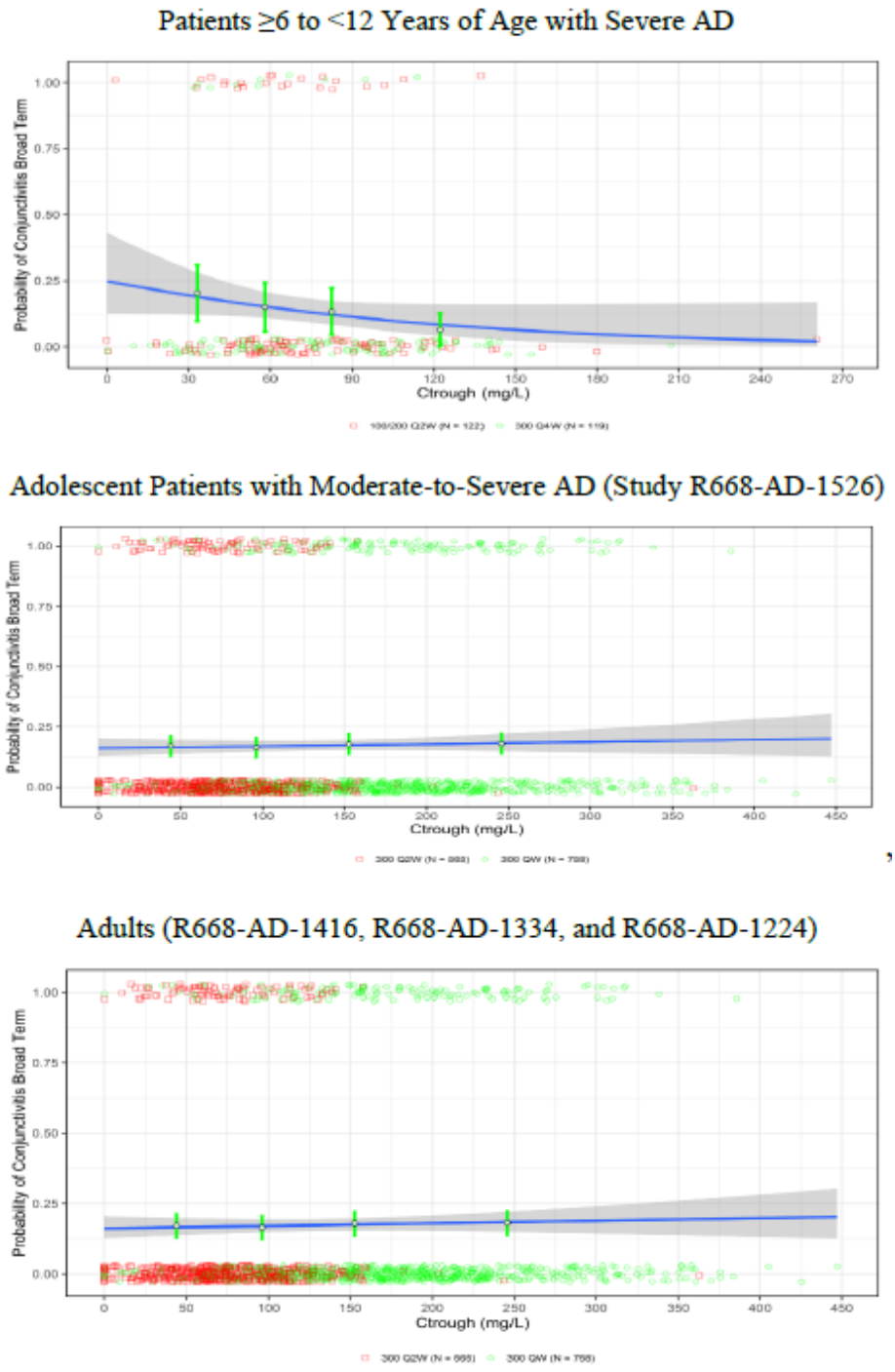
Source: Figure 1., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

Figure 31. Probability of Response (EASI -75) vs. C_{trough} (mg/L) at Week 16 in Adults, Adolescents and Children (≥6 to <12 Years)



Source: Figure 2., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

Figure 32. Logistic Regression Relating Probability of Patients Developing Conjunctivitis With Dupilumab Trough Concentrations at Week 16 in Adults, Adolescents and Children (≥6 to <12 Years)



Source: Figure 5., Response to Agency Request for Information – Integrated Population PK Analysis, 1.11.3. Clinical Information Amendment (dated April 10th, 2020)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MATTHEW E WHITE
05/22/2020 09:41:56 AM

LUKE Y OH
05/22/2020 12:25:07 PM

CHINMAY SHUKLA
05/22/2020 12:27:39 PM

DA ZHANG
05/22/2020 12:28:49 PM

JIANG LIU
05/22/2020 01:02:07 PM

CARIN J KIM
05/22/2020 01:16:24 PM

MOHAMED A ALOSH
05/22/2020 01:46:49 PM

BRENDA CARR
05/22/2020 01:50:29 PM

SNEZANA TRAJKOVIC
05/22/2020 01:53:00 PM

TATIANA OUSSOVA
05/22/2020 03:05:03 PM