BLA Multi-Disciplinary Review and Evaluation

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<tr><td>Application Type</td><td>Efficacy Supplement - New Patient Population (SE5)</td></tr>
<tr><td>Application Number(s)</td><td>BLA 761055/S-042</td></tr>
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<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>Not Applicable</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>
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<tr><td rowspan="2">6 Months to 5 Years of Age</td><td>5 to less than 15 kg</td><td>200 mg (one 200 mg injection)</td><td>200 mg Q4W</td></tr>
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<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>Pediatrics patients with moderate-to-severe atopic dermatitis aged ≥6 months to <6 years</td></tr>
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<tr><td>Recommended Indication(s)/Population(s)</td><td>Pediatrics patients with moderate-to-severe atopic dermatitis aged ≥6 months to <6 years</td></tr>
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<tr><th>Body Weight</th><th>Initial and Subsequent Dosage</th></tr>
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DMPP = Division of Medical Policy Programs
DVP – Division of Pharmacovigilance
OPQ=Office of Pharmaceutical Quality
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

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	Signature: See DARRTS signature page			
Deputy Director for Safety	Tatiana Oussova, MD, MPH	OII/DDD	Sections: 1	**Select one:** ___ Authored _x_ Approved
	Signature: See DARRTS signature page			

Glossary

AC	advisory committee
AD	Atopic Dermatitis
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body surface area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDLQI	Children's Dermatology Life Quality Index
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IDQOL	Infants' Dermatology Quality of Life Index
IGA	Investigator's Global Assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTP	Multiplicity Testing Procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRI	non-responder imputation
NRS	numeric rating scale
OCS	Office of Computational Science
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
POEM	Patient Oriented Eczema Measure
PPS	per protocol set
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
Q4W	Every 4 weeks
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	Scoring Atopic Dermatitis
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
WCS	worst-case scenario

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 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. DUPIXENT can be used with or without topical corticosteroids.
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 6 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 months 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:

- 5 to less than 15kg: 200 mg every 4 weeks (Q4W)
- 30 to less than 60 kg: 300 mg every 4 weeks (Q4W)

With submission of this sBLA, it is recommended that postmarketing requirement (PMR) 3183-4 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 patients 6 months to less than 6 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 moderate-to-severe atopic dermatitis (AD) in children aged 6 months to less than 6 years of age, the Applicant submitted results from a single randomized, multicenter, placebo-controlled Phase 2/3 Study R668-AD-1539 Part B (1539b), that evaluated 2 weight-based dosing regimens: 200 mg Q4W or 300 mg Q4W. The treatment period was 16 weeks.

Study 1539b randomized 162 subjects (≥6 months to < 6 years of age) with moderate-to-severe AD, defined as having an Investigator's Global Assessment (IGA) score of 3, Eczema Area and Severity Index (EASI) ≥16, and Body Surface Area (BSA) ≥10% at baseline. The primary endpoint was the proportion of subjects with IGA score of 0 to 1 (on a 5-point scale) at Week 16. Secondary endpoints included the proportion of subjects with reduction of weekly average of daily worst itch score ≥4 from baseline at Week 16. Results for primary endpoint was statistically significant ($p<0.001$).

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

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 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. DUPIXENT can be used with or without topical corticosteroids.

The Applicant proposes extension of the atopic dermatitis (AD) indication to allow for the "treatment of patients aged 6 months 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 moderate-to-severe AD in children ≥6 months to < 6 years of age. The Applicant submitted the results from a single randomized, multicenter, placebo-controlled Phase 2/3 Study 1539b, that evaluated 2 weight-based dosing: 200 mg (5kg to <15kg) and 300 mg (30kg to <60 kg) administered every 4 weeks (Q4W). The treatment period was 16 weeks.

Study 1539b randomized 162 subjects (≥6 months to < 6 years of age) with moderate-to-severe AD, defined as having an Investigator's Global Assessment (IGA) score of 3, Eczema Area and Severity Index (EASI) ≥16, and Body Surface Area (BSA) ≥10% at baseline. The primary endpoint was the proportion of subjects with IGA score of 0 to 1 (on a 5-point scale) at Week 16. At Week 16, 28% of subjects on DUPIXENT+TCS achieved IGA score of 0 or 1 compared to 4% of subjects on Placebo+TCS. Results for the primary endpoint were statistically significant ($p<0.001$). The secondary endpoint was the proportion of subjects with reduction in itch measured by the Worst Scratch/Itch NRS score of ≥4-point improvement from baseline, at Week 16. At Week 16, 48% of subjects on DUPIXENT+TCS achieved Worst Scratch/Itch NRS ≥4 score compared to 9% of subjects on Placebo+TCS.

The Applicant comprehensively assessed the safety of dupilumab in subjects ≥6 months to < 6 years of age with moderate-to-severe AD. The size of the safety database, the duration of exposure, and the types and frequency of safety evaluations were adequate to characterize the safety of Dupixent in this patient population. In addition to routine safety assessments, the safety evaluations reflected what is known for

dupilumab (e.g., mechanism of action; protein product), its route of administration (subcutaneous), and the safety profile in the older children, adolescent, and adult AD populations.

The safety of DUPIXENT was assessed against the placebo in the Study 1539b in 161 pediatric subjects 6 months to 6 years of age with moderate-to-severe atopic dermatitis. The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and pediatric subjects 6 to 17 years of age with atopic dermatitis. There were no deaths or serious adverse events (SAEs) reported in pediatric subjects 6 months to 6 years of age treated with dupilumab. Common adverse reactions that occurred with a higher frequency in the dupilumab +TCS group than in the placebo +TCS group included: molluscum contagiosum (5%), rhinorrhea (5%), conjunctivitis (5%), gastroenteritis viral (4%), Covid 19 (4%), blepharitis (2%), and eosinophilia (2%). Also, treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8% of dupilumab-treated subjects and 0% in placebo-treated subjects.

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study (Study 1434) of 180 pediatric subjects treated through Week 52. The safety profile of DUPIXENT ± TCS was consistent with that seen in adults and pediatric subjects 6 to 17 years old with atopic dermatitis. In addition, hand-foot-and-mouth disease was reported in approximately 5% subjects and skin papilloma was reported in approximately 4% of subjects treated with DUPIXENT ± TCS.

This reviewer concludes that the Applicant provided substantial evidence of efficacy and safety of DUPIXENT in the treatment of pediatric patients 6 months to 6 years with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Because very few subjects aged 6 month-2 years were included in the clinical trials, the Agency will request enhanced pharmacovigilance activities to collect additional safety information in this age group . We request that for a period of 2 years from the U.S. approval date of this sBLA, the applicant submit all reported labeled and unlabeled SAEs (i.e., both 'serious and expected' or 'serious and unexpected' adverse events) with DUPIXENT (dupilumab) injection in patients aged ≥6 months to 2 years as 15-day expedited reports.

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. AD affects approximately 5 to over 20 percent of children worldwide. Although it may affect all age groups, AD is most common in children. In 60% of subjects, 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. Onset in the first six months of life appears to be associated with severe disease. The prevalence of AD in the United States in individuals 4-8 years of age has been reported as 10.63% and as 9.96% in those 9-12 years of age. For 10-30% of individuals, AD persists into the adult years. AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In infants and young children, age <2 years, atopic dermatitis typically presents with pruritic, scaly, erythematous lesions on the extensor surfaces of the body, as well as the cheeks and scalp with sparing of the diaper area. A predominant feature is oozing and crusting of vesicular lesions. In older children and adolescents, the presentation is similar to adults with less oozing and crusting. It is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, wrists, ankles. In severe cases in all age groups the AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life of the patient, as well as family members. The dysfunctional skin barrier, further compromised from scratching, may predispose subjects to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Subjects with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of subjects 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	The medical need of children (6 months to < 6 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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 subjects who are candidates for systemic therapy, including children. Its drawbacks include a potentially time intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	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 subjects. It would represent the first systemic product 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 moderate- severe AD in children ≥6 months to < 6 years of age, the Applicant submitted results from a single randomized, multicenter, placebo-controlled, Phase 2/3 Study 1539b that evaluated 2 weight-based dosing regimens every 4 weeks (Q4W). The treatment period was 16 weeks. Study 1539b randomized 162 subjects (≥6 months to <6 years of age) with moderate to severe AD, defined as having an IGA score of 3, EASI ≥16, and BSA ≥10% at baseline. The primary endpoint was the proportion of subjects with IGA score of 0 to 1 (on a 5-point scale) at Week 16. Secondary endpoints included the	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
	proportion of subjects with reduction of weekly average of daily worst itch score ≥4 from baseline at Week 16. Results for the primary efficacy endpoint was statistically significant (p<0.001).	
Risk and Risk Management	The Applicant comprehensively assessed the safety of dupilumab in subjects ≥6 months to < 6 years old with moderate- severe AD. The safety evaluations were adequate in types and frequency to identify local and systemic adverse reactions. 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). Placebo-controlled study 1539b provided the primary safety data (n= 161) 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. With the exception of hand-foot-and-mouth disease and skin papilloma, no new safety concerns were identified in children ≥6 months to <6 years of age. Because very few subjects aged 6 month-2 years were included in the clinical trials, the Agency will request enhanced pharmacovigilance activities to collect additional safety information in this age group . We request that for a period of 2 years from the U.S. approval date of this sBLA, the applicant submit all reported labeled and unlabeled SAEs (i.e., both 'serious and expected' or 'serious and unexpected' adverse events) with DUPIXENT (dupilumab) injection in patients aged ≥6 months to 2 years as 15-day expedited reports.	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. With the exception of hand-foot-and-mouth disease and skin papilloma, no new safety concerns were identified in children ≥6 months to <6 years of age. The safety profile in children ≥6 months to <6 years of age was similar to that observed in older children, adolescents and adults with AD. Dupilumab was generally well-tolerated by children ≥6 months to <6 years of age with moderate-to-severe AD.

1.4. Patient Experience Data

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

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

2 Therapeutic Context

2.1. Analysis of Condition

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 subjects, 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 infants and young children, age <2 years, atopic dermatitis typically presents with pruritic, scaly, erythematous lesions on the extensor surfaces of the body, as well as the cheeks and scalp with sparing of the diaper area. A predominant feature is oozing and crusting of vesicular lesions.[1] 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 subjects 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

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[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 February 15, 2022).

[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]

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), IL-4 receptor antagonist (dupilumab; systemic), IL-13 antagonist (tralokinumab; systemic), and JAK inhibitors (topical and systemic). 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.

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[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 February 15, 2022).
[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 subjects 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.

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.

Other topical therapies indicated for AD include the topical calcineurin inhibitors, a PDE-4 inhibitor and a JAK inhibitor. 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 subjects treated with topical calcineurin inhibitors; a causal relationship has not been established. Crisaborole ointment, 2%, a PDE-4 inhibitor, is approved for treatment of AD in pediatric patients (3 months of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD). Recently a topical JAK inhibitor, ruxolitinib, was approved for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

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[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.

Two systemic, oral JAK inhibitors are approved for the treatment of refractory moderate-severe AD: upadacitinb and abrocitinib. Upadacitinib is indicated for adolescents and adults 12 years of age and older weighing at least 40kg and abrocitinib is indicated for adults, therefore representing a somewhat different target population than for dupilumab (age ≥6 months and above). Also, the indication is restricted for patients who failed other systemic therapies including biologics and use is not recommended in combination with other immunosuppressants or biologics. While there are no approved JAK inhibitors in the age <12 years population, these products represent an alternative to having injections or systemic steroids for the treatment of moderate-severe AD. Boxed warnings for JAK inhibitors include blood clots, lymphoma and other malignancies, serious infections. Recently the boxed warnings expanded to include the risk of cardiovascular death and stroke in high-risk patients who are aged 50 and above and are current or past smokers.

Tralokinumab is an injectable IL-13 antagonist indicated for the treatment of moderate-severe atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Similar to dupilumab, common adverse events include upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. However, tralokinumab is only indicated for adults and therefore a different target population than for dupilumab.

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 ≥ 6 years of age with AD. The Applicant proposes broadening use of dupilumab to allow for the treatment of patients ≥ 6 months of age who have failed topical therapies or when those therapies are inadvisable. Specifically, the Applicant proposes dupilumab for “patients 6 months 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 subjects 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 subjects 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 subjects aged 12 and older on March 11, 2019 (S-012) and subjects aged 6 and older on May 22, 2020 (S-020) ("treatment of subjects 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 subjects with moderate-to-severe asthma aged 6 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.
- As an add-on maintenance treatment in adult subjects with inadequately controlled chronic rhinosinusitis with nasal polyposis.
- Treatment of adult and pediatric patients ages 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis.

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.

3183-4 Conduct a safety, pharmacokinetic (PK), and efficacy study in subjects 6 months to less than 6 years with 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 subjects 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 subjects 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 aged ≥6 months to > 6 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. Data from Study 1434 for subjects 6 to <12 years were submitted in S-020, under which dupilumab was licensed for treatment of AD in pediatrics aged >6 to <12 years.

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 subjects 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 Investigations (OSI)

4.1.1. Overall Assessment of Findings and Recommendations

Regeneron Pharmaceuticals, Inc. (**Regeneron**) submitted the results of a phase 2/3 study (R668-AD-1539) in support of extending the previous approval of Dupixent® (dupilumab) in treating moderate or severe atopic dermatitis (**AD**) in children, to include use in children of age under 6 years (through 6 months). Two clinical investigator (**CI**) sites were inspected on-site in auditing the phase 3 portion of the study (Part B).

No significant good clinical practice (**GCP**) violations were observed. The study appears to have been conducted in adequate compliance with GCP regulations and standards. The audited data at the two CI sites appear acceptable in support of the clinical indication for dupilumab as proposed in the sBLA.

4.1.2. Inspection Results

1. Jeffrey G. Leflein M.D.

2000 North Huron River Drive, Suite 200 Ypsilanti,
Michigan 48197-1791
Inspection dates: March 7-10, 2022

Study R668-AD-1539 Part B, Site 840539: 16 subjects were screened, 14 were enrolled, and 14 completed 16 weeks of randomized treatment. 13 subjects elected to start/continue dupilumab treatment in the OLE study; one subject (randomized to dupilumab) declined the OLE study and proceeded directly into the 12-week follow up period, to complete study Part B. Subject case records for all enrolled subjects were reviewed in detail, including verification of the major study data (IGA and EASI scores at baseline and at Week 16).

No significant deficiencies were observed. Study files and subject case records were well maintained. The inspection confirmed good compliance with the study protocol and with GCP regulations and standards. No unreported protocol deviations or adverse events (**AEs**) were discovered. Evidence of unblinding was not observed. The audited efficacy and safety data were verifiable against the data reported in the sBLA.

2. Jacek A. Zdybski, M.D.

Sienkiewicza 65/14
Ostrowiec Swietokrzyski 27-
400 POLAND
Inspection dates: March 14-18, 2022

Study R668-AD-1539 Part B, Site 616405: 19 subjects were screened, 19 were enrolled, and 19 completed 16 weeks of randomized treatment. Subject case records were reviewed in detail for all enrolled subjects, including complete verification of the major study data (IGA and EASI scores at baseline and at Week 16).

No significant deficiencies were observed. Study files and subject case records were adequately organized to facilitate review. The inspection confirmed good compliance with the study protocol and with GCP regulations and standards. No unreported protocol deviations or AEs were discovered. Evidence of unblinding was not observed. The audited efficacy and safety data were verifiable against the data reported in the sBLA.

4.2. Product Quality

4.2.1. Assessment:

This supplement contains no new CMC information.

Environmental Assessment or Claim of Categorical Exclusion
Regeneron requested categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(a).

Primary Product Quality Assessor Comment:
The categorical exclusion request from the requirement to submit an environmental assessment is acceptable.

4.2.2. Assessment conclusions:

This supplement contains no new CMC information and does qualify for categorical exclusion. Approval of this supplement is recommended.

5 Nonclinical Pharmacology/Toxicology

A Nonclinical review is not required for this efficacy supplement.

6 Clinical Pharmacology

6.1. Executive Summary

Dupilumab is a human monoclonal IgG4 interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Currently, dupilumab is approved for the treatment of AD in adult and pediatric patients aged 6 years and older, as well as for the treatment of asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP). In this BLA efficacy supplement, the Applicant seeks approval of dupilumab for the treatment of pediatric patients aged 6 months to 5 years with AD. The proposed dosing regimens are 200 mg Q4W subcutaneously (SC) for patients weighing 5 kg to less than 15 kg and 300 mg Q4W SC for patients weighing 15 kg to less than 30 kg.

The safety and effectiveness of dupilumab were assessed in a placebo-controlled phase 3 Study R668-AD-1539 Part B in pediatric subjects aged 6 months to 5 years with AD. The clinical pharmacology review evaluated pharmacokinetic (PK) data, immunogenicity, population pharmacokinetic (PopPK) and exposure-response (E-R) data obtained from Study R668-AD-1539 (Part A and Part B) as well as an ongoing, long-term extension Study R668-AD-1434.

Mean dupilumab trough concentrations were similar between pediatric subjects <15 kg receiving 200 mg Q4W and pediatric subjects ≥15 kg receiving 300 mg Q4W. Overall, mean dupilumab trough concentrations in pediatric subjects aged 6 months to 5 years were greater than or equal to approved regimens in adults, adolescents, and pediatric subjects ≥6 to <12 years of age, but lower than the previously studied dosing regimen of 300 mg QW in adults in the dupilumab development program. (b) (4) Overall, the incidence of treatment-emergent ADA was low and reported in 1.4% (1/74) of pediatric subjects with AD who received dupilumab regimens of 200 mg Q4W or 300 mg Q4W in Study R668-AD-1539 Part B. The proposed SC dosages of 200 mg Q4W for patients weighing 5 kg to less than 15 kg and 300 mg Q4W for patients weighing 15 kg to less than 30 kg with AD are acceptable based on the statistically significant improvement over placebo on the two primary efficacy endpoints (i.e., IGA score of 0 or 1 and achieving EASI-75) at Week 16 in Study R668-AD-1539 Part B and had an acceptable safety profile.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this sBLA submission and found it acceptable for approval from a clinical pharmacology standpoint, provided that a mutually satisfactory agreement can be reached between the Applicant and Agency regarding the labeling language.

6.1.2. Postmarketing Requirement and Commitments

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Dupilumab is a human monoclonal IgG4 interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Clinical pharmacokinetics of dupilumab have been previously characterized in the original BLA 761055 and supplement BLAs in healthy subjects, adult and pediatric subjects with AD aged 6 years and older, adult and pediatric subjects with asthma aged 6 years and older, and adults with CRSwNP. Relevant PK information, as described in Section 12.3 of the current dupilumab product labeling, is summarized below.

Absorption

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose followed by subsequent doses of 300 mg either weekly or Q2W, or following the administration of 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD trough concentrations at steady-state ranged from 60.3 ± 35.1 mcg/mL to 80.2 ± 35.3 mcg/mL for 300 mg administered Q2W and from 173 ± 75.9 mcg/mL to (b) (4) ± (b) (4) mcg/mL for 300 mg administered weekly. The bioavailability of dupilumab following a SC dose is similar between subjects with underlying AD, asthma, and CRSwNP, ranging between 61% and 64%.

Distribution

The estimated total volume of distribution was approximately 4.8±1.3 L.

Elimination

After the last steady-state dose of 300 mg Q2W and 300 mg QW dupilumab, the median times to non-detectable concentration (<78 ng/mL) are (b) (4) weeks, (b) (4).

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. Following a single dose of dupilumab from 75 mg to 600 mg, the systemic exposure increased by 30-fold when the dose was increased 8-fold.

(b) (4)

Immunogenicity

(b) (4) Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations (b) (4)

Clinical Pharmacokinetics in Pediatric Subjects Aged 6 Months to 5 Years with AD

In the current submission, the Applicant evaluated PK of dupilumab in pediatric subjects aged 6 months to 5 years with AD in phase 3 Study R668-AD-1539.

Mean ± SD trough dupilumab concentrations at steady-state in pediatric subjects 6 months to 5 years of age with AD following 300 mg Q4W (≥15 to <30 kg) or 200 mg Q4W (≥5 to <15 kg) was 110 ± 42.8 mg/L and 109 ± 50.8 mg/L, respectively. Based on PopPK analysis, after accounting for differences in body weight, increasing age was associated with increasing clearance in pediatric subjects from 6 months to 5 years of age. The incidence of treatment-emergent ADA was low with approximately 1.4% (1/74) of pediatric subjects with AD who received dupilumab regimens of 200 mg Q4W or 300 mg Q4W in Part B of Study R668-AD-1539. Given the low incidence of treatment-emergent ADA, the effect of immunogenicity on efficacy, safety, or PK of dupilumab in pediatric subjects aged 6 months to 5 years was not assessed.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimens of 200 mg Q4W SC for patients weighing 5 kg to less than 15 kg and 300 mg Q4W SC for patients weighing 15 kg to less than 30 kg appear to be supported by the phase 3 trial R668-AD-1539. In phase 3 trial, statistically significant improvements were demonstrated for both primary endpoints, i.e., proportion of subjects achieving IGA of 0 or 1 and EASI-75 at Week 16, in pediatric subjects treated with 200 mg Q4W or 300 mg Q4W (based on body weight) compared to those that received placebo. See Section 8 Statistical and Clinical Evaluation of this multi-discipline review for details on the efficacy results.

Therapeutic Individualization

The efficacy and safety data from Phase 3 trial R668-AD-1539 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 pediatric subjects with AD. No additional dosage adjustment based on other intrinsic or extrinsic factors is needed. See details in Section 6.3.2.

Outstanding Issues

None.

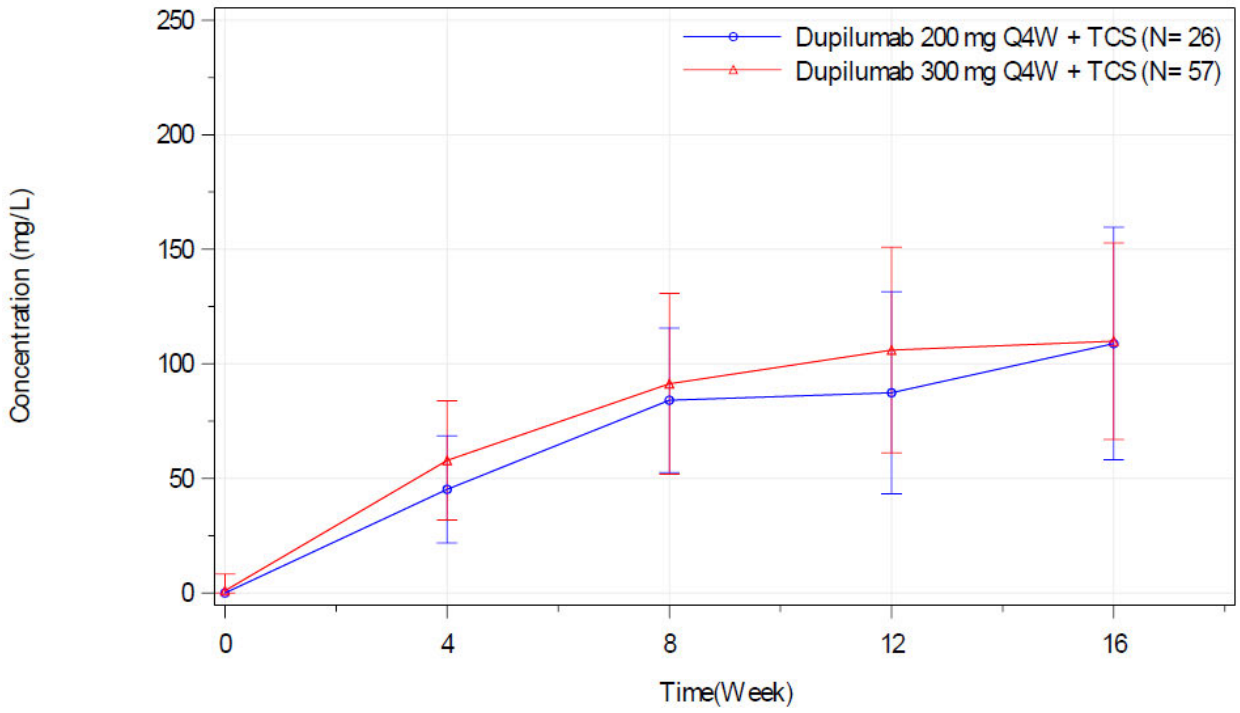
6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin 13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. The PK of dupilumab has been previously characterized in healthy subjects, adults and pediatric subjects with AD aged 6 years and older, adults and pediatric subjects with asthma aged 6 years and older, and adults with CRSwNP. Dupilumab exhibited nonlinear target-mediated PK with exposure increasing in a greater than dose proportional manner.

Mean serum dupilumab concentrations observed in Study R688-AD-1639 are presented in Figure 1 and Table 1. Mean concentrations of dupilumab over time exhibited similar profiles in subjects weighing ≥5 to <15 kg receiving dupilumab 200 mg Q4W and subjects weighing ≥15 to <30 kg receiving dupilumab 300 mg Q4W. Systemic concentrations of dupilumab in the 300 mg Q4W group appeared to have reached steady-state by week 12, while the highest mean concentrations for the 200 mg Q4W group were observed at Week 16.

Figure 1. Mean (SD) Serum Dupilumab Trough Concentrations by Treatment Group and Week in Subjects Aged 6 Months to 5 Years with Atopic Dermatitis (Study R668-AD-1539 Part B)



Note: Numbers in the table are the number of subjects at each time point.
Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Figure 1

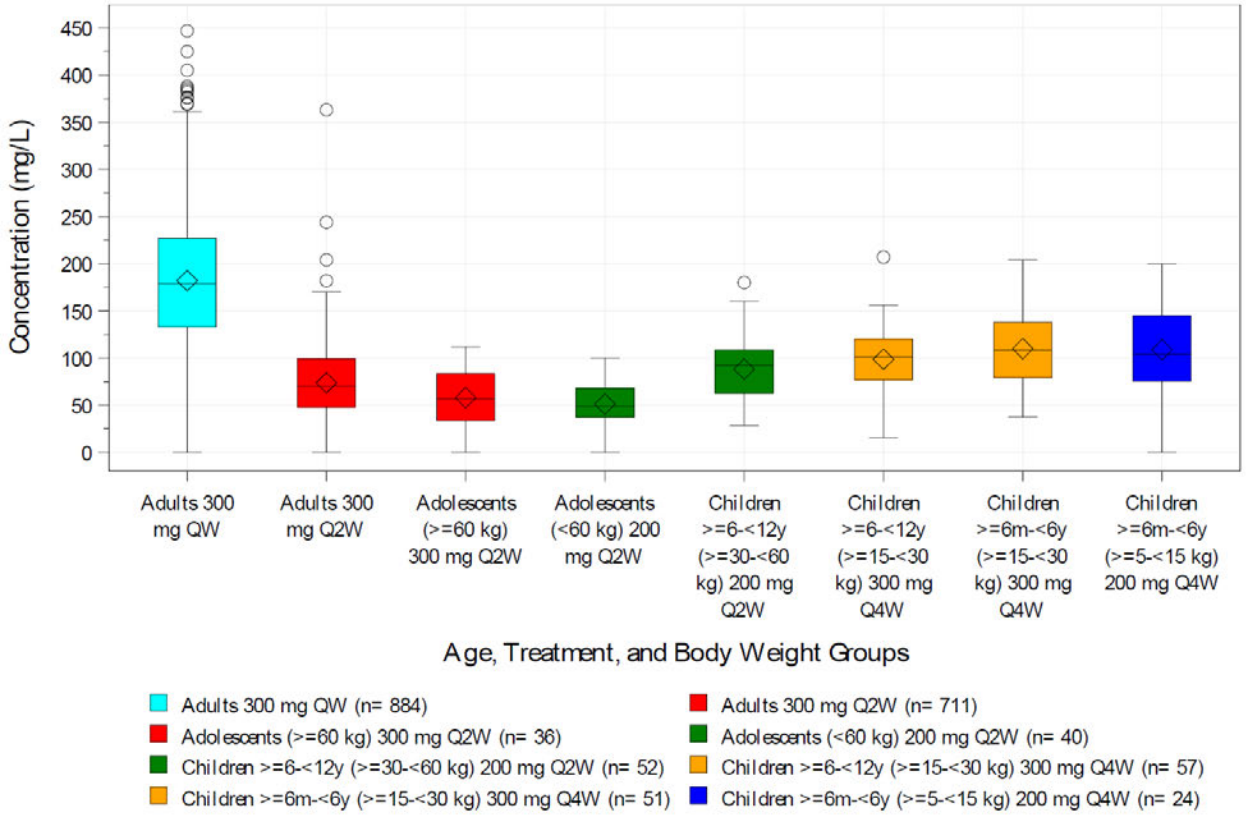
Table 1. Mean (SD) Serum Dupilumab Concentrations (mg/L) in Subjects Aged 6 Months to 5 Years with Atopic Dermatitis (Study R668-AD-1539 Part B)

Time after First Dose (Week)	Dupilumab 200 mg Q4W (N=26)		Dupilumab 300 mg Q4W (N=57)	
	n	Mean (SD)	n	Mean (SD)
0	24	0 (0)	56	0.984 (7.35)
4	25	45.2 (23.4)	52	57.9 (26.0)
8	24	84.1 (31.5)	49	91.3 (39.4)
12	24	87.4 (44.1)	49	106 (44.8)
16	24	109 (50.8)	51	110 (42.8)

Abbreviations: SD = standard deviation
Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Table 5

Mean dupilumab trough concentrations in pediatric subjects aged 6 months to 5 years following dupilumab 200 mg Q4W in subjects weighing ≥5 to <15 kg and 300 mg Q4W in subjects weighing ≥15 to <30 kg were greater than that in adult and adolescents with approved regimens, but overall dupilumab trough concentrations for pediatric subjects aged 6 months to 5 years appeared generally similar to that in pediatric subjects ≥6 to <12 years of age with approved regimens (Figure 2). In addition, mean dupilumab trough concentrations in pediatric subjects aged 6 months to 5 years were lower than the previously studied dosing regimen of 300 mg QW in adults in the dupilumab development program. (b) (4)

Figure 2. Cross-study Comparison of Dupilumab Trough Concentrations at Week 16 in Subjects with Atopic Dermatitis by Age, Treatment, and Body Weight Groups for Reference Dupilumab Regimens in the US and in Study R668-AD-1539 Part B



n= number of subjects at Week 16.
Note: Dupilumab regimen of 300 gm QW is not approved for the treatment of patients with AD. Adults, adolescents, and pediatric subjects ≥6 to <12 years received loading doses on Day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W) or 400 mg (200 mg Q2W). No loading doses were administered in pediatric subjects ≥6 months to <6 years.
Source: Adapted from Applicant's BLA 761055 S-042 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 4.

Comparison of PK in Subjects <2 Years of Age and Subjects 2 to 5 Years of Age with AD

Given PopPK analysis suggested that after accounting for differences in body weight, increasing age was associated with increasing clearance in pediatric subjects from 6 months to 5 years of age, further analysis was conducted to assess the dupilumab trough concentrations in the youngest age subgroup (i.e., <2 years of age) and compared with that in subjects 2 to 5 years of age with AD.

Overall, a total of 11 pediatric subjects aged 6 months to <2 years of age with AD were enrolled in Part B of Study R668-AD-1539. Among them, 6 pediatric subjects (weighing <15kg) received dupilumab regimen of 200 mg Q4W and the other 5 pediatric subjects received placebo. Mean

serum dupilumab concentrations at Week 16 in subjects <2 years of age and 2 to 5 years of age with AD receiving dupilumab 200 mg Q4W are presented in Table 2.

Table 2. Mean (SD) Serum Dupilumab Concentrations (mg/L) In Subjects <2 Years of Age and Subjects 2 to 5 Years of Age Receiving Dupilumab 200 mg Q4W (Study R668-AD-1539 Part B)

Week	Subjects <2 Years of Age 200 mg Q4W		Subjects 2 to 5 Years of Age 200 mg Q4W	
	n	Mean (SD)	n	Mean (SD)
16	6	120 (70.9)	18	105 (44.2)

Abbreviations: SD = standard deviation
Source: Reviewer's analysis, based on the Applicant submitted dataset "nm.xpt".

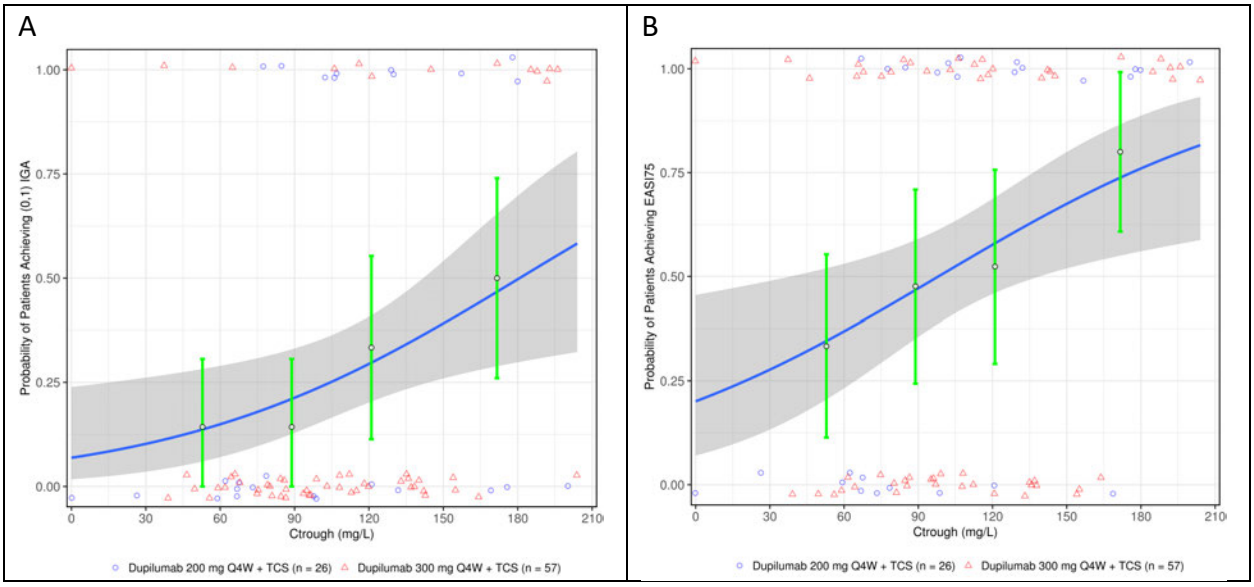
Although mean trough concentrations of dupilumab in subjects <2 years of age at Week 16 appeared higher compared to that in subjects 2 to 5 years of age treated with dupilumab 200 mg Q4W, it should be noted that cross-study comparisons indicated that mean dupilumab trough concentrations for both age subgroups were lower than the previously studied dosing regimen of 300 mg QW in adults in the dupilumab development program. Hence, the clinical safety of the 300 mg QW dose would provide additional support to the proposed dosing regimen. Since the number of subjects below the age of 2 years is small, we defer to Clinical on the adequacy of safety data in this population. See Section 8 for further information on safety.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Descriptive exposure-response (E-R) relationships for efficacy endpoints (i.e., achieving an IGA score of 0 or 1 and EASI-75 at Week 16) provide supportive evidence of effectiveness (**Figure 3**). In pediatric subjects with AD, the E-R relationships conducted using observed trough concentrations (Ctrough) of dupilumab in Part B of Study 1539 revealed increasing drug effects with increasing dupilumab trough concentration in serum.

Figure 3. Logistic Regression of Probability of Subjects Achieving an (0,1) IGA Score (Panel A) or EASI-75 (Panel B) With Dupilumab Trough Concentrations at Week 16 in Subjects ≥6 Months to 5 Years of Age with AD (Study R668-AD-1539 Part B)



Note: Among 161 pediatric subjects aged 6 months to 5 years with AD included in the E-R analysis, the percentage of subjects achieving an IGA score of 0 or 1 or a 75% reduction in EASI score was higher in quartiles of higher dupilumab concentrations. The figure shows mean Regression line - blue, confidence area around regression line - grey. 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 95% 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. The upper and lower limit is reset to 1 and 0 if the value is > 1 or < 0.
Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Figure 5, Figure 10.

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

Yes, the proposed dosing regimens of 200 mg Q4W SC for patients weighing 5 kg to less than 15 kg and 300 mg Q4W SC for patients weighing 15 kg to less than 30 kg are appropriate based on the following:

- Statistical analyses for both primary endpoints (i.e., proportion of subjects achieving IGA of 0 or 1 at Week 16 and proportion of subjects achieving EASI-75 at Week 16) demonstrated significant improvements in subjects treated with dupilumab compared to those who received placebo.
- Exposure-response findings for the primary efficacy endpoints in Part B of phase 3 Study R668-AD-1539 suggested increasing drug effects with increasing serum dupilumab trough concentrations.

- No evident E-R relationship for AESIs (broad or narrow term of conjunctivitis) at Week 16 was observed based on Part B data of Study R668-AD-1539. See Section 15.4.2 for details.
- The available safety data from the use of dupilumab in the previously studied dosage of 300 mg QW in adults provide supportive safety data. See Section 8 for statistical and clinical evaluation.

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 subjects ≥15 to <30 kg and 200 mg Q4W for subjects ≥5 kg to <15 kg. The relative higher dupilumab exposure with the proposed 300 mg Q4W and 200 mg Q4W dosing regimens compared to those seen in adolescents and adults with AD was justified based on the overall efficacy and safety analyses of phase 3 Study R668-AD-1539. A further dose adjustment is not needed.

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

No. Food-drug interactions are not applicable as dupilumab is administered by SC injection. Dupilumab has no clinically meaningful effect on exposures of substrates for major CYP enzymes as described in Section 12.3 of dupilumab product labeling.

What is the incidence of the formation of ADA and the impact of immunogenicity on dupilumab exposure?

Overall, the incidence of treatment-emergent ADA was low and reported in 1.4% (1/74) of pediatric subjects with AD who received dupilumab regimens of 200 mg Q4W or 300 mg Q4W in Part B of Study R668-AD-1539 (Table 3). This subject with treatment-emergent ADA received dupilumab 300 mg Q4W regimen and exhibited a low titer and was negative for neutralizing antibody. In addition, based on the interim analysis for the ongoing, open-label extension study R668-AD-1434, where all subjects ≥ 6 months to 5 years of age started or continued weight-tiered dupilumab regimens of 200 mg Q4W in subjects ≥5 to <15 kg or 300 mg Q4W in subjects ≥15 to <30 kg, treatment-emergent ADA responses were observed in 2 subjects (2/116, 1.7%). The 2 ADA positive subjects in study R668-AD-1434 had low titer and were both negative for neutralizing antibody. Given the limited number of ADAs observed in the study, the effect of immunogenicity on efficacy, safety or PK of dupilumab was not feasible to assess.

Table 3. Summary of ADA Status and ADA Category by Treatment Group in Subjects ≥6 Months to 5 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

ADA Status and Category	Placebo + TCS n (%)	200 mg Q4W + TCS n (%)	300 mg Q4W+ TCS n (%)
ADA Analysis Set	69 (100%)	24 (100%)	50(100%)
Negative	67 (97.1%)	24 (100%)	49 (98.0%)
Pre-existing Immunoreactivity	2 (2.9%)	0	0
Treatment-Boosted Response	0	0	0
Treatment-Emergent Response	0	0	1 (2.0%)

ADA = Anti-drug antibody; TCS = Topical corticosteroids
Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Table 6

Table 4. Summary of Treatment Boosted and Treatment Emergent ADA Category and Maximum Titer Category by Treatment Group in Subjects ≥6 Months to 5 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

		Dupilumab		
Maximum Titer Category	Placebo + TCS n (%)	200 mg Q4W + TCS n (%)	300 mg Q4W + TCS n (%)	All Active Doses n (%)
ADA Analysis Set	69 (100%)	24 (100%)	50 (100%)	74 (100%)
TE				
Persistent	0	0	0	0
Transient	0	0	0	0
Indeterminate	0	0	1 (2.0%)	1 (1.4%)
TE & TB				
Low (<1,000)	0	0	1 (2.0%)	1 (1.4%)
Moderate (1,000 to 10,000)	0	0	0	0
High (>10,000)	0	0	0	0

ADA = Anti-drug antibody; TCS = Topical corticosteroids; TE = Treatment-emergent; TB = Treatment-boosted
Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Table 7

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant provided data from 3 studies:

- R668-AD-1539a (1539a): an open-label, PK/safety Phase 2/3 study; a single ascending dose, sequential cohort study (n= 40).
- R668-AD-1539b (1539b): the pivotal, randomized, double-blind, placebo-controlled Phase 2/3 study; the primary safety data (n= 162).
- R668-AD-1434 (1434): an ongoing, open-label extension (OLE), long-term safety study (n= 180). The data cutoff date for the sBLA was July 31, 2021.

Subjects from Studies 1539a and 1539b 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 subjects who were aged ≥6 months to > 6 years at the screening visit for the OLE.

Table 5: Listing of Clinical Trials Relevant to this BLA Efficacy Supplement

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow up	No. of Subjects Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
R668-AD-1539b	Double-blind, placebo-controlled, efficacy and safety	200 mg Q4W for subjects 5 kg to <15 kg, 300 mg Q4W for subjects 15 kg to <30 kg, or placebo	•proportion of subjects with an IGA score of 0 to 1 (on a 5-point scale) at week 16 •Proportion of subjects with EASI 75 at week 16 (only in European Union [EU] and EU Reference Market Countries)	Treatment duration: 16 weeks Follow-up: 12 weeks (for subjects not entering the OLE)	162	Moderate to severe AD in subjects ≥6 months to ≤6 years of age	31; United States, Germany, United Kingdom, Poland
Studies to Support Safety							
R668-AD-1539a	open-label study, single ascending dose, sequential cohort study; safety and exploratory efficacy	Two sequential age cohorts: Cohort 1 (subjects ≥2 to <6 yrs) Cohort 2 (subjects ≥6 mo to <2 yrs) Two dose sub-cohorts: Sub-cohort A: 3 mg/kg Sub-cohort B: 6 mg/kg	•Concentration of total dupilumab in serum over time and PK parameters (summary statistics of drug concentration and PK parameters) •The incidence and severity of treatment-emergent adverse events (TEAEs) through the end of part A.	Treatment period: 4 weeks Follow-up: 4 weeks (for subjects not entering OLE)	40	Severe AD in subjects ≥6 months to ≤6 years of age	16; United States, Germany, United Kingdom

Other Studies Pertinent to the Review of Efficacy or Safety							
R668-AD-1434	Open-label extension study (OLE), efficacy and safety	• All subjects from R668-AD-1539 Part A rolled over into this study under Amendment 3 and subjects <6 years of age initially received weight-based dosing at 3 mg/kg QW or 6 mg/kg QW • All subjects from R668-AD-1539 Part A were switched to fixed dosing tiered by body weight under amendment 4 (200 mg Q4W for subjects 5 kg to <15 kg, 300 mg Q4W for subjects 15 kg to <30 kg, 200 mg Q2W for subjects ≥30 to <60 kg, or 300 mg Q2W for subjects ≥60 kg). • All subjects from R668-AD-1539 Part B enrolled into this study under amendment 4 and started on the fixed dose regimens tiered by body weight.	•Incidence and rate of treatment-emergent adverse events (TEAEs) from baseline through the last study visit.	The duration of treatment period was changed as follows: a) For subjects 6 months to <12 years old at the screening visit, the treatment period will last for 5 years. b) For subjects 12 to <18 years old at the screening visit: • In Poland, the treatment period will last for 5 years. • In other countries, the treatment period will last until regulatory approval in this age group in the respective geographic region. Follow-up 12 weeks	180 pediatrics subjects age 6 months to ≤6 years old; 36 subjects from 1539a and 144 subjects from 1539b	Moderate to severe AD in subjects ≥6 months to ≤18 years of age who have previously completed a clinical study with dupilumab	103; Canada, Czech Republic, Germany, Hungary, Poland, United Kingdom, United States

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.

Pivotal Study R668-AD-1539b was reviewed for efficacy and safety.

The Applicant provided safety data from 3 studies:

- R668-AD-1539b (1539b): randomized, double-blind, placebo-controlled Phase 2/3 study in subjects with moderate-to-severe AD; the primary safety data (n= 162).
- R668-AD-1434 (1434): ongoing Phase 3, OLE, long-term safety study (n= 180). The data cutoff date for the sBLA was July 31, 2021.
- R668-AD-1539a (1539a): open-label, PK/safety Phase 2 study; single ascending dose, sequential cohort study in severe AD (subjects ≥6 months to <6 years of age n=40).

The safety review focused on the data from placebo-controlled Study 1539b and an open-label extension (OLE) the Study 1434 as a primary safety database. The OLE study included subjects that rolled over from Study 1539b and Study 1539b Only serious adverse events (SAEs) will be discussed from Study 1539a, as the population and dosing regimen differed from Studies 1539b and 1434.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study Design and Endpoints

The Applicant conducted a Phase 2/3 study, which consisted of two parts:

- Part A of the study was an open-label, single-ascending dose, sequential cohort study investigating the PK, safety, and efficacy of a single dose of subcutaneous (SC) dupilumab in pediatric subjects with severe AD (children aged ≥6 months to <6 years of age).
- Part B of the study was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study with the primary objective to demonstrate efficacy of dupilumab treatment in pediatric subjects aged 6 months to <6 years with moderate-to-severe AD that could not be adequately controlled with topical AD medications.

The primary objectives of the study were:

- Part A: To characterize the safety and PK of dupilumab administered as a single dose in pediatric subjects, 6 months to less than 6 years of age, with moderate to severe AD.
- Part B: To demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with topical corticosteroid (TCS) in pediatric subjects, 6 months to less than 6 years of age, with moderate to severe AD.

<u>Part B of the study:</u>

Part B of the study consisted of the following 3 periods:

- A screening period of up to 56 days (including 2 weeks of topical corticosteroid (TCS) standardization.
- A treatment period of 16 weeks.
- A follow-up period of 12 weeks

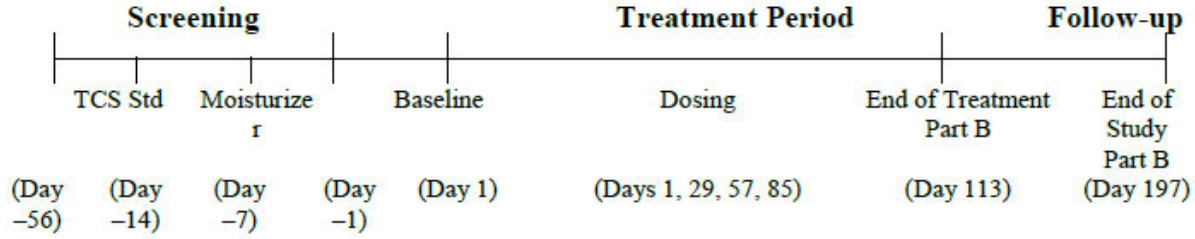
Subjects who enrolled in Part A of the study were not eligible to participate in Part B. During the screening period of Part B, systemic treatments for AD were washed out, as applicable, according to the eligibility requirements. Starting on Day -14, all subjects were required to initiate treatment with low potency TCS. Subjects were also required to apply moisturizers twice daily for at least 7 days before randomization and continue throughout the study.

Approximately 160 subjects were planned to be randomized in a 1:1 ratio, stratified by baseline body weight (≥5 to <15 kg and ≥15 to <30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America, Europe, Japan, and China), to one of the following treatment arms, with treatment administered on Day 1 and every 4 weeks (Q4W) from Week 4 to Week 12:

- Dupilumab Q4W weight-tiered fixed dose: 200 mg in subjects with a baseline weight ≥5 to <15 kg or 300 mg in subjects with a baseline weight ≥15 to <30 kg
- Placebo Q4W: matching placebo based on baseline weight category

During the treatment period, subjects could receive medium or high potency TCS, systemic corticosteroids or nonsteroidal immunosuppressants, or topical calcineurin inhibitor (TCI) as rescue treatment at the discretion of the investigator. The use of rescue treatment was only allowed after Day 14 in Part B. Subjects were to have in-clinic study visits at baseline, and Weeks 1, 2, and 4, then monthly visits through Week 16 with weekly telephone visits in between the clinic visits. Subjects who completed the treatment period were subsequently eligible to participate in an open-label extension (OLE) study (R668-AD-1434). Subjects who declined to participate in the OLE were to enter a follow-up period of 12 weeks. The study design for Part B is presented in Figure 4.

Figure 4: Study Design Diagram for Part B



Source: Protocol Amendment 4 for Trial R668-AD-1539; page 50

For enrollment in the study, subjects satisfied the following key inclusion criteria:

- Pediatric subjects aged 6 months to <6 years at the time of screening visit.
- Subjects with documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s).
- Investigator's Global Assessment (IGA) score ≥3 at screening and baseline visits.
- Eczema Area and Severity Index (EASI) score ≥16 at screening and baseline visits.
- Body surface area (BSA) involvement ≥10% at screening and baseline visits.
- Baseline worst scratch/itch score weekly average score for maximum scratch/itch intensity ≥4.
- At least 11 (of a total of 14, twice per day for 7 days) applications of a topical emollient (moisturizer) during the 7 consecutive days immediately before the baseline visit.

Investigator's Global Assessment (IGA):
IGA is a static 5-point measure of disease severity based on an overall assessment of the skin lesions.

Table 6: Investigator's Global Assessment (IGA)

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)

Source: Protocol Amendment 4 for Trial R668-AD-1539; page 121

Itch numeric rating scale (NRS):
According to the protocol, the worst itch NRS was an 11-point scale (0 to 10) in which 0 indicates no scratching/itching while 10 indicates worst scratching/itching possible. The parents/caregivers were asked to answer the question below based on what they observe and what their child tells them (if applicable): "How would you rate your child's scratching/itching at its worst in the past 24 hours?"

Itch was assessed by the parent/caregiver daily using an e-diary throughout the entire study (i.e., screening, treatment, and follow-up periods). Weekly average of daily worst scratch/itch score was calculated as the average of the available reported daily worst scratch/itch score within the week. A minimum of 4 daily scores out of the 7 days was required to calculate the baseline average score.

Eczema Area and Severity Index (EASI):
According to the protocol, the EASI score calculation is based upon the Physician's Assessment of Individual Signs [erythema (E), induration/papulation (I), excoriation (X), and lichenification (L)], where each sign is scored as 0 = Absent, 1 = Mild, 2 = Moderate, or 3 = Severe, and also upon the Area Score [based on the % (BSA) affected] where 0 = 0% BSA, 1 = 1-9% BSA, 2 = 10-29% BSA, 3 = 30-49% BSA, 4 = 50-69% BSA, 5 = 70-89% BSA, 6 = 90-100% BSA.

The protocol and SAP specified that the primary endpoint is the proportion of subjects with IGA 0 or 1 with at least 2-point improvement from baseline at Week 16.

The protocol and SAP also listed the following key secondary endpoints:

- Proportion of subjects with EASI-75 (≥75% improvement from baseline) at Week 16
- Percent change in EASI score from baseline to Week 16
- Percent change from baseline to Week 16 in weekly average of daily worst scratch/itch numeric rating scale (NRS) score

Additional secondary efficacy endpoints included the following:

- Proportion of subjects with EASI-50 at Week 16
- Proportion of subjects with EASI-90 at Week 16
- Change from baseline to Week 16 in percent BSA affected by AD
- Percent change from baseline to Week 16 in Scoring Atopic Dermatitis (SCORAD)
- Change from baseline to Week 16 in weekly average of daily worst scratch/itch NRS score
- Proportion of subjects with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline at Week 16
- Proportion of subjects with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline to Week 16

On 4/21/2017 the Agency noted that a mere change (or percent change) in Eczema Area and Severity Index and daily worst scratch/itch score might not translate to a clinically meaningful difference. Similarly, for the endpoints of change and percent change in body surface area. In addition, for secondary endpoints based on Patient Reported Outcomes (PROs), the Agency noted that instruments need to be fit-for-purpose in the context of use and a clinically meaningful threshold level for treatment response should be identified for each endpoint, along with justification for such level, as mere change from baseline may not translate to clinically meaningful treatment effect. Therefore, the review will not present results for these endpoints.

8.1.2. Statistical Methodologies

Analysis Populations:
The primary analysis population for efficacy specified in the protocol was the full analysis set (FAS) defined as all randomized subjects.

The protocol dated 10/28/2020 specified supportive analysis for the primary efficacy endpoint based on the per protocol set (PPS), defined as all subjects in the FAS, except for those with major protocol violations. However, the final version of the SAP dated 04/28/2021 removed analysis based on PPS.

Analysis Methods for the Primary and Secondary Endpoints:
The protocol/SAP-specified analysis method for the primary efficacy endpoint (i.e., IGA 0/1 at Week 16) was the Cochran-Mantel-Haenszel (CMH) test adjusted for randomization strata. The same method was specified for all binary secondary endpoints.

Multiplicity Testing Procedure (MTP):
The SAP specified a hierarchical testing procedure to control the overall Type-1 error rate at 0.05 for the primary and the secondary endpoints of dupilumab versus placebo. Each hypothesis is formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The hierarchical testing order is shown in Table 7 (all comparisons are against the placebo).

Table 7: Multiplicity Adjustment Plan

Level	Endpoints	Testing Order
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	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	2
Secondary endpoints	Percent change in EASI score from baseline to week 16	3
	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch score	4
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline	5
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline	6
	Proportion of patients with EASI-50 at week 16	7
	Proportion of patients with EASI-90 at week 16	8
	Change from baseline in percent BSA affected by AD	9
	Change from baseline to week 16 in POEM	10
	Percent change from baseline to week 16 in SCORAD	11
	Change from baseline in Patient's sleep quality NRS	12
	Change from baseline in Patient's skin pain NRS	13
	Change from baseline in DFI	14
	Change from baseline to week 16 in CDLQI	15
	Change from baseline to week 16 in IDQOL	16

Source: Sponsor's SAP for Trial R668-AD-1539 Part B (SDN 1235); page 46

Estimand Framework and Handling of Missing Data:

Table 8 presents the Estimand framework and the method of handling the missing data for the primary and key secondary endpoints.

Table 8: Estimands

Endpoints	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary/Analysis Method
• Proportion of subjects with IGA 0 or 1 with at least 2 points improvement from baseline at Week 16 • Proportion of subjects with EASI-75 at week 16	FAS	The intercurrent events are handled as follows: • Discontinuation of study intervention: Data collected after the subject discontinued treatment are included in the analyses (treatment policy strategy). • Initiation of rescue treatment: Subjects are considered as non-responders after such events (composite strategy). Missing data imputation rules: • Missing data due to withdrawn consent, Adverse Event, Lack Of Efficacy are imputed as non-responder. • Missing data due to any other reason including COVID-19 are imputed using multiple imputation (MI)	Proportion of response/ CMH test adjusted for randomization strata

Source: SAP for Trial R668-AD-1539; pages 40-42

For the multiple imputation method, the SAP specified imputing the underline continuous (e.g., EASI) or categorical variable (e.g., IGA) 40 times to generate 40 complete data sets by using the following steps:

- Step 1: The monotone missing pattern is induced by Markov Chain Monte Carlo (MCMC) method in MI procedure using seed number 12345. The monotone missing pattern means that if a subject has missing value for a variable at a visit, then the values at all subsequent visits for the same variable are all missing for the subject.
- Step 2: The missing data at subsequent visits are imputed using the regression method for the monotone pattern with seed number 54321 and adjustment for covariates including treatment groups, randomization strata (baseline weight group, baseline IGA and region), and relevant baseline variables. For the categorical variables, such as IGA, a logistic regression under monotone option is used.

Based on each imputed data, the response status (responder or non-responder) is determined for each subject. Once imputations are made, the Week 16 data (binary response) of each of the 40 complete datasets are analyzed using CMH test and results are combined from the 40 analyses using Rubin's formula. According to the SAP, "an appropriate transformation (such as

Wilson-Hilferty transformation) of CMH test statistics can be used in Rubin's formula."

The SAP specified a sensitivity analysis for the handling of missing data for the endpoints of IGA 0/1 and EASI-75 using the tipping-point analysis method. The impact from missing data on the comparisons in proportion of subjects achieving IGA 0/1 or EASI-75 at Week 16 between dupilumab and placebo groups is examined as follows.

- A sequence of analyses is performed to artificially decrease the response rate in dupilumab group and increase the response rate in placebo group with a fixed and definite set of values for data imputation.
- For each combination of increasing response rate in placebo and decreasing response rate in dupilumab, multiple imputed datasets are generated and analyzed using CMH test. The results obtained from multiple imputed datasets are combined to generate statistical inference, i.e., p-value and treatment difference between 2 treatment groups.

8.1.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

The study enrolled and randomized a total of 162 subjects (83 subjects in dupilumab and 79 subjects in placebo) in 31 study centers: 21 in the US and 10 in Europe (5 in Poland, 3 in Germany, and 2 in the United Kingdom).

This study was conducted during the COVID-19 pandemic. The sponsor decided to continue the study based on the assessment that the study could be conducted without jeopardizing participant safety, data integrity, or compliance with recent Regulatory Guidance. A COVID-19 mitigation plan was in effect during the study to give parents or caregivers the opportunity to do a telemedicine visit if they could not attend the study site, for example, due to being quarantined. No planned deviations associated with COVID-19 were needed to be implemented on the study.

Table 9 presents the disposition of subjects and shows that approximately 97% of the subjects completed the study treatment with very few subjects having discontinued the study, a higher proportion of subjects in the placebo arm discontinued the study compared to dupilumab arm.

Table 9: Subject Disposition (FAS*)

	Dupilumab +TCS N=83	Placebo + TCS N=79
Completed the study treatment, n (%)		
Yes	82 (98.8)	75 (94.9)
No	1 (1.2)	3 (3.8)
Reasons of Discontinuation, n (%)		
Adverse Event	1 (1.2)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (1.3)
Withdrawal by Subject	0 (0.0)	1 (1.3)
Other	0 (0.0)	1 (1.3)

Source: Reviewer's Analysis (same as Applicant's Analysis)

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

The demographics and baseline disease characteristics are presented in Table 10. The demographics were generally balanced across the treatment arms. The majority of enrolled subjects were male (79%), white (81%), between 2 to <6 years of age (93%) and weighted 15-<30 kg (71%). Baseline disease characteristics were also generally balanced across the 2 treatment arms. The majority of the enrolled subjects had a baseline IGA score of severe (about 77%).

Table 10: Demographics and Baseline Disease Characteristics (FAS*)

	Dupilumab + TCS N=83	Placebo + TCS N=79
Age, years		
n	83	79
Mean (SD)	3.91 (1.2)	3.78 (1.26)
Median	4.17	3.83
Range	0.8 - 5.8	0.6 - 5.9
< 2 years, n (%)	6 (7.2)	5 (6.3)
>= 2 years, n (%)	77 (92.8)	74 (93.7)
Sex, n (%)		
Male	44 (53.0)	55 (69.6)
Female	39 (47.0)	24 (30.4)
Race, n (%)		
White	58 (69.0)	53 (67.1)
Black or African American	14 (16.9)	16(20.3)
Asian	6 (7.2)	4 (5.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.3)
Not Reported	2 (2.4)	1 (1.3)
Other	3 (3.6)	4 (5.1)
Baseline Weight Group, n (%)		
5 to <15 kg	26 (31.3)	25 (31.6)
15 to <30 kg	57 (68.7)	54 (68.4)
Region, n (%)		
North America	53 (63.9%)	51 (64.6%)
Europe	30 (36.1%)	28 (35.4%)
Baseline IGA, n (%)		
Moderate (3)	20 (24.1)	17 (21.5)
Severe (4)	63 (75.9)	62 (78.5)
Baseline EASI Score		
Mean (SD)	35.1 (13.88)	33.1 (12.8)
Median	33.2	32.0
Range	16 - 72	12 - 72
Weekly Average of Daily Worst Scratch/Itch Score		
Mean (SD)	7.5 (1.32)	7.6 (1.49)
Median	7.4	7.7
Range	4 - 10	2 - 10

Source: Reviewer's Analysis (same as Applicant's Analysis)

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

8.1.4. Results for the Primary and Secondary Efficacy Endpoints

Table 11 presents the results for the primary and secondary efficacy endpoints. This review will not present results on secondary endpoints that do not translate to clinically meaningful treatment effect, as stated by the Agency comments on 4/21/2017 (see Section 8.1.1). The results show that Dupilumab + TCS was statistically superior to placebo + TCS for all primary and secondary efficacy endpoints (p-values<0.001).

Table 11: Results for the Primary and Secondary Efficacy Endpoints at Week 16 (FAS-NRI/MI [1])

Endpoint	Dupilumab + TCS N=83 n [2] (%)	Placebo + TCS N=79 n [2] (%)	Difference, % [3] (95% CI)	P-Value [4]
IGA 0 or 1	23 (27.7)	3 (3.9)	23.8 (13.27, 34.37)	< 0.001
EASI-75	44 (53.0)	8 (10.7)	42.3 (29.47,55.16)	<0.001
Worst Scratch/Itch NRS Reduction from Baseline ≥ 4	40 (48.1)	7 (8.9)	39.2 (26.18,52.27)	<0.001
Worst Scratch/Itch NRS Reduction from Baseline ≥ 3	44 (53.3)	8 (9.9)	43.3 (30.03,56.67)	<0.001
EASI-50	57 (68.7)	16 (20.0)	48.5 (35.03,62.0)	<0.001
EASI-90	21 (25.3)	2 (2.8)	22.5 (12.37,32.60)	<0.001

Source: Reviewer's Analysis (same as Applicant's Analysis)
Abbreviations: TCS = topical corticosteroids; CI = Confidence Interval
[1] Full Analysis Set (FAS) defined as all randomized subjects; missing data due to withdrawn consent, adverse event, and lack of efficacy are imputed with non-responder imputation (NRI); missing data due to any other reason including COVID-19 are imputed using multiple imputation (MI); the rates displayed are the averages over the imputed datasets.
[2] n is calculated by dividing the number of successes by the sample size and then rounding down the number of successes to the closest integer.
[3] Difference is dupilumab minus placebo; CI calculated using normal approximation.
[4] P-Value based on Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]).

As noted in Section 8.1.1, the protocol/SAP specified the tipping point analysis as a sensitivity analysis for the handling of missing data. The statistical reviewer explored sensitivity analyses for the handling of missing data using the following methods: Non-responder Imputation (NRI; missing data for both subjects on active and placebo is imputed as non-responders) and worst-case scenario (WCS, i.e., missing data for dupilumab is imputed as non-responders and missing data for placebo is imputed as responders). The results for the statistical reviewer's analysis are presented in Table 12. In all cases (including the extreme case of WCS), dupilumab was still statistically superior (p-values <0.0001) to placebo for both primary and key secondary efficacy endpoints, and therefore, the tipping point analysis was not performed.

Table 12: Sensitivity Analysis for the Primary and Key Secondary Efficacy Endpoints at Week 16 (FAS [1])

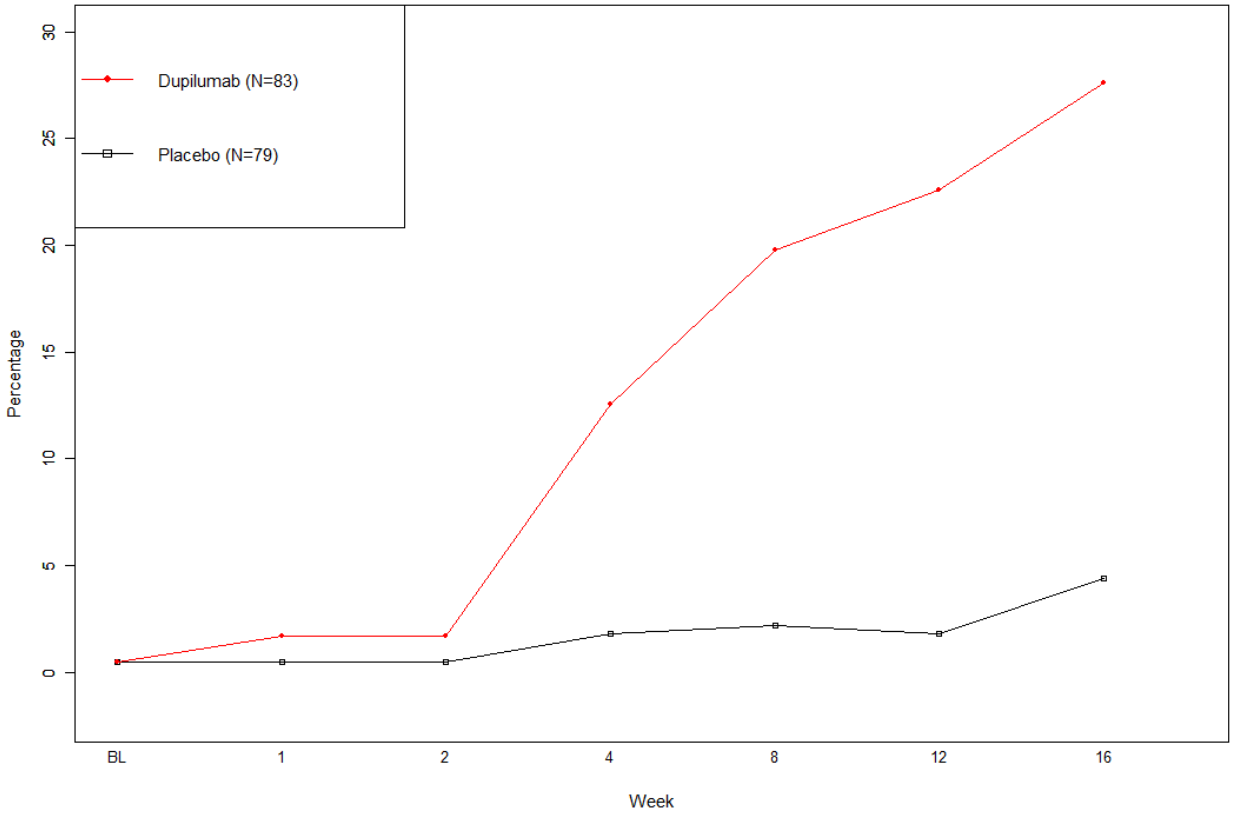
Endpoint	Dupilumab + TCS N=83 n[2] (%)	Placebo + TCS N=79 n[2] (%)	Difference, %[3] (95% CI)
IGA 0 or 1			
NRI	3 (3.8)	23 (27.7)	23.9 (13.1,34.7)
WCS	23 (27.7)	5 (6.3)	21.4 (10.0,32.4)
EASI-75			
NRI	44 (53.0)	8 (10.1)	42.9 (29.2,54.4)
WCS	44 (53.0)	10 (12.7)	40.4 (26.4,52.2)

Source: Reviewer's Analysis
Abbreviations: TCS = topical corticosteroids; CI = Confidence Interval
[1] Full Analysis Set (FAS) defined as all randomized subjects.
[2] n is calculated by dividing the number of successes by the sample size and then rounding down the number of successes to the closest integer.
[3] Difference is Dupilumab minus placebo; CI calculated using normal approximation.

8.1.5. Efficacy Over Time

Figure 5 presents the results for the proportion of subjects with success on IGA (i.e., IGA 0 or 1 with at least 2-grade improvement from baseline) through Week 16.

Figure 5: Results for IGA Score 0 or 1 from baseline through Week 16 (FAS-NRI/MI*)



Source: Reviewer's figure
* Full Analysis Set (FAS) defined as all randomized subjects; missing data due to withdrawn consent, adverse event, and lack of efficacy are imputed with non-responder imputation (NRI); missing data due to any other reason including COVID-19 are imputed using multiple imputation (MI); the rates displayed are the averages over the imputed datasets.

8.1.6. Findings in Special/Subgroup Populations

8.1.6.1. Sex, Race, Age, Weight, Baseline Disease Severity and Country

Table 13 presents the results for the primary efficacy endpoint (i.e., success on the IGA at Week 16) by sex, age, baseline weight, baseline disease severity and country. In general, the results for both treatment arms are consistent across the subgroups, with some variability from the smaller subgroups (i.e., subgroup of non-White subjects, non-USA subgroups and subgroup of subjects with age <2). The sample size of these subgroup is too small to allow any meaningful conclusions.

Table 13: Proportion of Subjects Achieving IGA 0 or 1 with at Least 2-point Reduction from Baseline at Week 16 by Subgroups (FAS-NRI/MI [1])

Subgroups (n[Dupilumab], n[Placebo])		Dupilumab + TCS %	Placebo + TCS %	Difference, %[2] (95% CI)
Overall (83,79)		27.7	3.9	23.8 (13.27, 34.37)
Sex	Male (44, 55)	20.5	3.7	16.8 (3.8,29.7)
	Female (39, 24)	35.9	4.4	31.5 (14.3,48.8)
Race	White (58, 53)	34.5	5.7	28.8 (15.0,42.5)
	Black or African American (14,16)	7.1	0.3	6.8 (-7.1,20.1)
	Other (11, 10)	18.2	0.0	18.2 (-4.6,40.9)
Baseline Weight	5- <15 kg (26, 25)	38.5	4.1	34.4 (14.1,54.7)
	15-<30 kg (57, 54)	22.8	3.8	19 (6.9,31.1)
Age	< 2 years (6, 5)	33.3	20.5	13.0 (-39.2,64.9)
	>= 2 years (77, 74)	27.3	2.8	24.5 (13.9,35.1)
Country	Germany (4, 3)	50.0	0.0	50.0 (1.0,98.8)
	Poland (21, 20)	47.6	5.0	42.6 (19.2,66.0)
	United Kingdom (5, 5)	20.0	0.0	20.0 (-15.1,55.1)
	United States (53, 51)	18.9	4.1	14.8 (2.9,26.7)
Baseline IGA Score	Moderate (IGA=3) (20,17)	70.0	11.8	58.2 (32.9,83.4)
	Severe (IGA=4) (63, 62)	14.3	1.7	12.6 (3.3,21.8)

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

Abbreviations: TCS = topical corticosteroids; CI = Confidence Interval

[1] Full Analysis Set (FAS) defined as all randomized subjects; missing data due to withdrawn consent, adverse event, and lack of efficacy are imputed with non-responder imputation (NRI); missing data due to any other reason including COVID-19 are imputed using multiple imputation (MI); the rates displayed are the averages over the imputed datasets.

[2] Difference is dupilumab minus placebo. CI calculated using normal approximation.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary focus of this safety review is on the data from phase 3 study 1539b, as this was the primary safety database. Data from the long-term OLE study will be used to assess potential safety signals that may occur following long-term administration of dupilumab. However, data from this study may be difficult to interpret due to lack of a placebo arm. Safety data were generally not pooled, as the study designs differed for the 3 studies. Therefore, the studies will be discussed separately.

Descriptive statistics were used in the analyses of safety parameters.

For Study 1539b, 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 1539a, 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 subjects 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.

In addition, in Study 1539b and Study1434, adverse events were summarized for skin infections, herpes infections, injection site reactions, and COVID-19 related TEAEs.

8.2.2. Review of the Safety Database

Overall Exposure

The cumulative safety database included 201 subjects age ≥6 months to <6 years old from studies 1539 (Part A and Part B). Of these subjects, 180 subjects enrolled in an open-label (OLE) Study 1434. The safety analysis set (SAF) included all subjects who received at least 1 dose of any study drug, and subjects were analyzed as treated.

Study 1539b was the only study that exclusively enrolled subjects ≥6 months to <6 years old with moderate-to-severe atopic dermatitis and required concomitant use of TCS as background treatment. Studies 1434 and 1539a allowed, but did not require, concomitant topical therapies e.g., TCS.

The overall cumulative mean (SD) treatment duration for subjects from the parent studies and OLE study, up to the SUR data cutoff date, was 63.53 (40.67) weeks. A total of 174 subjects

were exposed for ≥24 weeks, 110 subjects had exposure for ≥48 weeks, and 90 subjects had exposure for ≥52 weeks when combining exposure from the parent and OLE studies. See Tables below.

Table 14: Overall Number of Subjects ≥6 Months to <6 Years of Age Included in the Safety Analysis Set

Previous Study ID Number	Number of Children Randomized and Treated in the Parent Study	Number of Children ≥6 Months to <6 Years Who Entered the OLE Study[a] (R668-AD-1434)[b]	Number of Children Exposed to Dupilumab (in the Parent Study or the OLE Study, R668-AD-1434)
R668-AD-1539 Part B	161	144	153
R668-AD-1539 Part A	40	36	40
Total	201	180	193

Abbreviations: OLE, open-label extension; Q4W; SAF, safety analysis set

[a] Subjects who transitioned to the OLE from a previous study and received ≥1 dose of dupilumab in the OLE.

[b] Subjects from the previous study who had reached age ≥6 years before or at the time of screening for entry in the OLE study were not included in the R668-AD-1434 third-step analysis supporting this submission.

Source: Module 5.3.5.3 R668-AD-6m to 6y M2 Table 1.1.1/1

Table 15: Summary of Total Treatment Exposure Including Parent Studies, Children ≥6 Months to <6 Years of Age

Exposure Characteristics	Total (N=180)
Number (%) of patients with overall treatment exposure (weeks) cumulatively	
≥4 weeks	180 (100%)
≥24 weeks	174 (96.7%)
≥52 weeks	90 (50.0%)
≥104 weeks	26 (14.4%)

Source: 120 day safety update, post text table 5.2.1/5c-A

Adequacy of the safety database:

The safety database was adequate in size, extent of exposures (dosage and duration), and the nature of the safety assessments to evaluate the safety of dupilumab in subjects ≥6 months to <6 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 (AEs) were acceptable.

The adverse events (AEs) were categorized as follows:

- Death
- Serious Adverse Events (SAEs)
- Adverse events that led to study drug discontinuation or withdrawal from study
- Other significant adverse events, including
    - Symptomatic Overdose of Study Drug
    - Adverse Events of Special Interest (AESI)
- Treatment Emergent Adverse Events (TEAEs) and Adverse Drug Reactions (ADRs)

Adverse Event

According to the Applicant, an AE is defined as any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug. An AE also included any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

Serious Adverse Events

An SAE was defined as any untoward medical occurrence that results in any of the following outcomes:

- Death
- Life-threatening
- Persistent or significant disability/incapacity
- Hospitalization or prolongation of hospitalization
- Congenital anomaly/birth defect
- Important medical event requiring medical or surgical intervention to prevent serious outcome

Adverse Events of Special Interest

Adverse Events of Special Interest (AESI) were principally defined based on the safety profile from evaluation of dupilumab in adults. The following events were designated as AESIs in studies 1539b and required expedited reporting (within 24 hours) by the investigator to the Applicant:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Helminthic infections
- Any severe type of conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms)

In Study 1539 Part A, the definitions used were similar. However, malignancy and suicidal behavior were included as AESI terms, and clinically symptomatic eosinophilia was not included as an AESI.

Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) were defined as those that are not present at baseline or represent the exacerbation of a pre-existing condition during the overall study period.

To identify possible adverse drug reactions (ADRs), the Applicant applied statistical criteria to TEAE preferred terms in Study 1539b (placebo-controlled study). These criteria were similar to that used in the adult and older pediatric AD studies:

- Incidence greater than or equal to 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 preferred terms for their potential to be ADRs based on pathobiological mechanism or medical judgment.

Severity of Adverse Event

The severity of AEs was graded according to the following scale:

Mild: Causes no or minimal interference with age-appropriate daily activities. No intervention needed.

Moderate: Causes more than minimal interference with age appropriate daily activities. Local or non-invasive intervention indicated.

Severe: Causes inability to perform age-appropriate daily activities. Hospitalization or invasive intervention indicated.

If a laboratory value was considered an AE, its severity was based on the degree of physiological impairment the value indicated.

The Relationship of an AE to the Study Drug
According to the Applicant, the investigators use the following definitions to assess the relationship of the AE to the use of study drug:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study Drug

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 21.1 for Study 1539 Part A and Version 23.1 for both Study 1539 Part B and Study 1434 and Version 24.1 for the 120-day safety update reporting period for Study 1434.

Safety monitoring was similar to what was done in adult AD programs as well as those used in the AD studies in older pediatric age groups, as the Applicant anticipated a similar safety profile. Safety monitoring considered:

- mechanism of action of dupilumab
- risks associated with subcutaneous injection of monoclonal antibodies
- complications and co-morbidities associated with AD
- data from dupilumab clinical studies in older children, adolescents and adults
- general safety assessments (collection of AEs, routine laboratory assessments, physical examinations, vital signs, 12-lead electrocardiogram)

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

Routine Clinical Tests

During the placebo-controlled and open label studies, the investigators performed safety assessments. The following safety assessments were performed in the placebo-controlled study 1539b:

- Hematology and clinical chemistry
- HIV, hepatitis B (HBV), and hepatitis C (HCV) at screening
- Total Serum IgE at screening
- Vital signs, weight, height
- Physical examination
- 12-lead electrocardiogram (ECG) at screening

- Screening for adverse events

The safety assessments allowed adequate characterization of safety of dupilumab.

8.2.4. Safety Results

Deaths

There were no deaths in the development program.

Serious Adverse Events

A. Study 1539b (placebo-controlled)

There were no SAEs reported in the dupilumab + TCS group during the treatment period. Four subjects reported SAEs in the placebo + TCS group (4/78; 5.1%).

Table 16: Summary of SAEs by Preferred Term in the Placebo Controlled Study 1539b

Subject	Dosing group	Serious Adverse Event	Outcome
(b) (6)	Placebo	Allergic reaction	Resolved
	Placebo	Hypersensitivity	Resolved
	Placebo	Infected dermatitis	Resolved
	Placebo	Bacteremia	Resolved

Source Reviewer's analysis, CSR: table 57, page 156

B. Study 1434 (OLE)

Cumulatively as of the SUR data cutoff date, 10 (10/180; 5.6%) subjects experienced at least 1 SAE or 4.92 nP/100 PY. One SAE (enterobiasis) was considered by the Investigator related to study drug and no subjects permanently discontinued the study drug due to an SAE.

1. **Anaphylactic reaction**: 4-year-old white male (b) (6)) with peanut allergy and dupilumab developed an AESI of Anaphylactic reaction after exposure to raw egg on study day 98, three days after the 14th dose of dupilumab. The Investigator considered the event to be severe intensity and not related to study drug. The event did not lead to study drug discontinuation.
2. **Pneumonia mycoplasmal:** A 5-year-old Hispanic or Latino ((b) (6)) with asthma developed strep throat on study day 313. On study day 318 the patient was hospitalized with pneumonia mycoplasmal (verbatim term: walking pneumonia/mycoplasma pneumonia) and was discharged on study day 321. The diagnosis was made clinically without any further laboratory investigations. The investigator considered the event to

be moderate intensity and not related to study drug. The event did not lead to study drug discontinuation.

3. **Asthma:** A 2-year-old white male ([(b) (6)]) with food allergies and asthma was hospitalized with asthma on study day 1098 (last dose of study drug was on study day 358). The subject was discharged on study day 1099 after treatment with prednisolone, salbutamol and ipratropium and the event was considered resolved. The investigator assessed the event as moderate in intensity and not related to study drug.
4. **Atopic dermatitis:** A 5-year-old white female ([(b) (6)]) with animal, dust and food allergies was hospitalized due to atopic dermatitis on study day 216 (19 days after last dose of study drug). The subject received their treatment with dupilumab 300 mg as planned on study day 224. On study day 231, the subject was discharged after completing treatment with topical emollients and medications and the event was resolved and deemed not related to study drug.
5. **Otitis media:** A 3-year-old white male ([(b) (6)]) with adenoidal hypertrophy was hospitalized on study day 186 (15 days after the most recent dose of study drug) for an SAE of otitis media, underwent an adenotonsillectomy and was treated with antibiotics. The patient was discharged on study day 188 and the event was considered to be resolved. The subject received his planned dose of dupilumab (300 mg) on study day 198. The investigator assessed the event of otitis media and reclassified as non-serious, mild in intensity and not related to study drug.
6. **Otitis media acute:** A 3-year-old white male ([(b) (6)]) developed an SAE of otitis media acute (verbatim term: acute purulent otitis media [both ears]), was hospitalized on study day 243 (48 days after the most recent dose of study drug) which resulted in an interruption of study treatment. The subject underwent bilateral tympanocentesis and bilateral ear draining and was subsequently discharged from the hospital and the SAE was considered resolved on study day 252. The subject received their next dose of dupilumab on study day 280. The investigator assessed the SAE of otitis media acute as severe in intensity and not related to study drug.
7. **Gastroenteritis viral**: A 4-year-old white male ([(b) (6)]) with food allergies was hospitalized on study day 315 (34 days after the most recent dose of study drug) due to the SAE of gastroenteritis viral and treated with intravenous fluids. On study day 316 the patient was discharged, and the event was considered resolved. No further administrations of study drug were recorded up to the data cutoff date; however, the subject remained in the study. The investigator assessed the SAE of Gastroenteritis viral as moderate in intensity and not related to study drug.
8. **Enterobiasis**: A 2-year-old Hispanic/Latino male ([(b) (6)]) with food, animal and dust allergies developed an SAE (also an AESI) of Enterobiasis (verbatim term: pinworm). The subject was diagnosed clinically and on study day 111 the subject started treatment with mebendazole for 14 days. The subject received their next dose of dupilumab on study day 112. The event of Enterobiasis was considered resolved on study day 124. The dose of study drug was not changed as a result of the event. The investigator assessed this SAE as mild in severity and related to study drug.
9. **Periorbital cellulitis:** A 4-year-old white male ([(b) (6)]) was hospitalized for an SAE of periorbital cellulitis on study day 213 (16 days after the most recent dose of study

drug) and treated with antibiotics. The subject was discharged from hospital on study day 214. The investigator assessed the SAE of periorbital cellulitis as moderate in intensity and not related to study drug.

10. **Diabetic ketoacidosis:** A 4-year-old white female ((b) (6)) was hospitalized on study day 146 (4 days after the most recent dose of study drug) with a SAE of diabetic ketoacidosis. The patient was discharged from hospital of study day 149.The investigator assessed the SAE of diabetic ketoacidosis of severe intensity and not related to study drug.

Reviewer's comment:

1. *The narratives for the SAEs of anaphylactic reaction, asthma, enterobiasis, periorbital cellulitis, diabetic ketoacidosis were reviewed. This reviewer agrees with the Investigator's assessments of these adverse events.*
2. *Regarding the SAE of mycoplasmal pneumonia, there is question whether the diagnosis is accurate due to lack of imaging and laboratory evaluation.*
3. *Regarding the SAE of AD, given that dupilumab has approximately 30% efficacy, lack of efficacy may have contributed to this AE.*
4. *Regarding the SAE of gastroenteritis viral, we cannot exclude the possibility that this AE is related to dupilumab.*

C. Study 1539a (open-label, single-ascending dose)

There were 2 subjects (2/40; 5.0%) with SAEs. Both SAEs were also categorized as adverse events of special interest (AESI). Neither were considered related to study drug. No subjects permanently discontinued the study drug due to an SAE.

- One subject (1/10; 10%) in the age ≥2 years to <6 years, 3 mg/kg cohort:
    1. **Anaphylactic reaction:** A 24-month-old male ((b) (6)) with a history of nut allergy had anaphylaxis after ingestion of seasoning containing nuts on study day 21 (3 weeks after study drug administered). The event was considered moderate intensity and unrelated to the study drug.

- One subject (1/10; 10%) in the age ≥6 months to < 2 years, 3mg/kg cohort:
    1. **Anaphylactic reaction:** A 13-month-old male ((b) (6)) ate crab stick and was hospitalized with anaphylaxis on study day 20, discharged on study day 21. The event was considered unrelated to the study drug.

Reviewer's comment: This reviewer agrees with the investigator's assessments of these SAEs.

Dropouts and/or Discontinuations Due to Adverse Effects

A. Study 1539b (placebo-controlled)

TEAEs leading to discontinuation of study drug were rare. One subject (1/78; 1.3%) in the placebo group and 1 subject (1/83; 1.2%) in the dupilumab 200 mg Q4W group had a TEAE that led to permanent discontinuation of study drug. There were no TEAEs that led to discontinuation in the dupilumab 300 mg Q4W group.

- One subject (1.2%) in the dupilumab 200mg Q4W group:
    1. **Atopic dermatitis:** A 12-month-old white male ([(b) (6)]) with AD developed an AD flare on study day 30 (same day as the second dose of study drug). Study drug was discontinued as the subject received oral corticosteroids as treatment. The event was considered resolved on study day 82. The Investigator concluded the event was moderate intensity and not related to study drug.

- One subject (1.3%) in the placebo group:
    1. **Nightmare:** A 55-month-old white male ([(b) (6)]) developed nightmares regarding blood collection on study day 29. Treatment with study drug was permanently discontinued on study day 57. On study day 85, the subject withdrew from the study. The event was designated as not related to the study drug.

Reviewer's Comment: The narratives for each of the subjects that discontinued were reviewed. This reviewer agrees with the assessment that the AE of nightmare was not treatment related. However, given that dupilumab has approximately 30% efficacy, we cannot exclude the possibility that exacerbation of AD while on dupilumab is related to study treatment.

B. Study 1434 (OLE)

One subject (1/180; 0.6%) had an adverse event that led to permanent study drug discontinuation or withdrawal.

1. **Urticaria:** A 4-year-old white male ([(b) (6)]) received a single dose of dupilumab 300 mg. On study day 1, 13 minutes after the study drug was administered, the subject experienced urticaria that led to study drug discontinuation. The investigator considered the event to be severe in intensity and related to study drug.

Reviewer's comment: The narrative of this AE was reviewed, and this reviewer agrees with the investigator's assessment.

C. Study 1539a (open-label, single-ascending dose)

There were no dropouts or discontinuations during this study related to adverse events.

Significant Adverse Events

Adverse Events of Special Interest (AESIs)

The following AEs were pre-defined as AESIs in the protocol:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Any type of severe or serious conjunctivitis or blepharitis
- Keratitis
- Clinically symptomatic eosinophilia

Reviewer's comment: The applicant reported only severe cases of conjunctivitis and blepharitis as adverse events of special interest. We do not agree with this assessment. We included in our analysis all AEs of conjunctivitis and blepharitis, irrespective of severity, as AESIs.

A. Study 1539b (placebo-controlled)

Thirty-one subjects (31/83; 37.3%) in the dupilumab + TCS group reported an AESI during the treatment period. Twenty-nine subjects (29/78; 39.7%) in the placebo + TCS group reported an AESI. There were no reported events of anaphylactic reactions, systemic hypersensitivity reactions, or helminthic infections.in either treatment group. The AESIs are discussed in greater detail in Section 8.2.4.4.

Table 17: Significant Adverse Events Including AESIs in the Placebo-Controlled Study 1539b

	Dupilumab Q4W +TCS			
	200 mg (N=26)	300 mg (N=57)	Combined 200/300mg (N=83)	Placebo + TCS (N=78)
Number of subjects with at least one such event, n(%)	7(30.8)	24(40.3)	31(37.3)	29(39.7)
Skin infections excluding herpes and varicella infections, n(%)	4(15.4)	7(12.3)	11(13.3)	21(26.9)
Herpes infections, n(%)	0	5(8.8)	5(6.0)	5(6.4)
Blepharitis, n(%)	0	2(3.6)	2(2.4)	0
Conjunctivitis, n(%)	0	6(10.5)	6(7.2)	1(1.3)
Viral keratitis, n(%)	0	1(1.8)	1(1.2)	0
Injection Site Reactions, n (%)	1(3.8)	1(1.8)	2(2.4)	2(2.6)
Covid-19 Reactions, n(%)	2(7.7)	2(3.5)	4(4.8)	1(1.3)

Source: Reviewer's analysis

B. Study 1434 (OLE)

26 subjects (26/180; 14.4%) had at least 1 AESI. None of the AESIs led to discontinuation of study drug. There were no AESIs of clinically symptomatic eosinophilia or systemic hypersensitivity reactions. The AESIs of conjunctivitis are discussed in Section 8.2.4.4

Table 18: 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 in the OLE

	Total (N=180)	Total (N=180) nP (nP/100 PY)
Subjects with at least one AESI, n (%)	26 (14.4%)	
Conjunctivitis[a], n(%)	22 (12.2%)	22/190.2 (11.57)
Anaphylactic reaction, n (%)	2 (1.1%)	2/205.6 (0.97)
Keratitis, n (%)	1 (0.6%)	1/208.3 (0.48)
Blepharitis, n (%)	1 (0.6%)	1/208.2 (0.48)
Helminthic infections, n(%)	1 (0.6%)	1/208.4 (0.48)

Abbreviations: AESI, adverse events of special interest; nP, number of subjects with events; nP/100PY, number of subjects with events per 100 patient years; SAF, safety analysis population
a: Conjunctivitis includes conjunctivitis bacterial, conjunctivitis allergic, conjunctivitis viral, dry eye, eye pruritus
Source: PTT 8.4.1.1/1c, PTT 8.4.2.2/1c-A, PTT 7.6.1.1/1c-A

1. **Anaphylactic reaction:** This AESI (subject (b) (6)) was also considered an SAE and was discussed previously. This event was not considered to be related to study drug and resolved with treatment.
2. **Keratitis:** A 4-year-old white male ((b) (6)) had an AESI of Keratitis (verbatim term: phlyctenular conjunctivitis of both eyes) on study day 126. The event resolved on study day 148.The investigator considered the event to be moderate in intensity and not related to study drug. The event was nonserious and did not lead to study drug discontinuation.
3. **Blepharitis:** A 4-year-old Asian female (b) (6)) with ongoing allergic conjunctivitis and blepharitis developed conjunctivitis (verbatim term: blepharoconjunctivitis) on study day 64. On study day 92, the event worsened to an AESI of Blepharitis (verbatim term: bilateral ulcerating blepharitis) of severe intensity. The event resolved on study day 134. The investigator considered both the TEAE of Conjunctivitis and the AESI of Blepharitis to be related to study drug. Both events were non-serious and did not lead to study drug discontinuation.
4. **Enterobiasis**: A 2-year-old Hispanic/Latino male (b) (6)) with food, animal and dust allergies developed an AESI (also a SAE) of enterobiasis (verbatim term: pinworm). The subject on study day 111 was diagnosed clinically and resolved with treatment with mebendazole for 14 days. On study day 246, the subject experienced the AESI of anaphylactic reaction (50 days after the most recent dose of study drug),treated with epinephrine with resolution of the adverse event. The source of anaphylaxis was not

reported. The investigator assessed the SAE of enterobiasis as mild in severity and related to study drug, and the AESI of anaphylactic reaction as moderate in severity and not related to the study drug.

Reviewer's comment: The narratives of these AESIs were reviewed. Taking into consideration that blepharitis and keratitis are known adverse reactions of dupilumab, the relationship of these AEs to the study drug cannot be excluded.

C. Study 1539a (open-label, single-ascending dose)

There were 2 subjects (2/40; 5%) with AESIs as defined by the Applicant. Subjects (b) (6) and (b) (6) had anaphylactic reactions that were classified as SAEs and were previously discussed. There were no AESIs of blepharitis, keratitis, eosinophilia, malignancy or suicidal behavior.

8.2.4.4.1 Conjunctivitis, blepharitis and keratitis

A. Study 1539b (placebo-controlled)

The proportion of subjects with at least 1 conjunctivitis-related event during the 16-Week treatment period was higher in the dupilumab 300mg Q4W + TCS group (6/83 subjects 7.2%) than in the placebo + TCS group (1/78 subjects; 1.3%). There were no adverse events of conjunctivitis in the dupilumab 200mg Q4W +TCS group. Conjunctivitis, blepharitis and keratitis are recognized adverse events associated with dupilumab use, and the label includes a Warning and Precaution addressing these events. Two subjects experienced blepharitis in the dupilumab 300 mg Q4W group.

- Two subjects (2/57, 2.4%) in the dupilumab 300mg Q4W group:
    1. **Blepharitis:** A 53-month-old Asian female ((b) (6)) with allergic conjunctivitis developed blepharitis (verbatim term: bilateral severe ulcerating blepharitis) on study day 77, 20 days after the most recent study dose and after a total of 3 study drug doses. The subject underwent ophthalmic evaluation and treatment. The event was deemed by investigator as related to study drug and severe in intensity. The event was non-serious and did not lead to study drug discontinuation. The event was still ongoing at the end of the study when the patient transitioned into the OLE. This adverse event was also classified as a severe TEAE.
    2. **Blepharitis and keratitis viral:** A 48-month-old white male ((b) (6)) with food allergy, asthma and eczema herpeticum who developed blepharitis and keratitis viral (verbatim term: Blepharitis etiology unknown) on study day 53 (24 days after receiving dupilumab 300 mg). He underwent an ophthalmologist consultation and had subsequent resolution on day 57 after treatment with olopatadine eye drops. The diagnosis was made by an ophthalmologist; there was no mention of any lab investigations to confirm the diagnosis. The subject

completed the study drug and study per protocol. The investigator assessed both events as mild in intensity and not related to study drug.

Reviewer's comment: The narratives of these AESIs were reviewed. Taking into consideration that blepharitis and keratitis are known adverse reactions of dupilumab, the relationship of these AEs to the study drug cannot be excluded.

Table 19: Summary of Subjects with Treatment-Emergent Conjunctivitis by Preferred Term in the Placebo-Controlled Study 1539b

	Dupilumab 300 mg Q4W + TCS (N=57)		Placebo + TCS (N=78)	
Number of subjects with such events, n(%)	7	(12.3)	1	(1.3)
Blepharitis, n(%)	2	(3.5)	0	
Conjunctivitis, n(%)	4	(7.0)	0	
Conjunctivitis allergic, n(%)	1	(1.8)	0	
Eye irritation, n(%)	0		1	(1.3)

Reviewer's analysis ; CSR table 69, page 159

Reviewer's comment: This reviewer considers all blepharitis and conjunctivitis cases as possibly related to the study drug.

B. Study 1434 (OLE)

22 subjects (22/180; 12.2%) had a conjunctivitis event. One event of blepharitis was considered severe (subject (b) (6)) and was discussed previously. The remainder of events were considered mild to moderate in severity and resolved over time. None of the events were serious or led to permanent treatment discontinuation.

Table 20: Number of Subjects ≥6 Months to <6 Years of Age with Treatment-Emergent Broad CMQ Conjunctivitis by Preferred Term (Cumulative Incidence)

	Total N=180 nP (nP/N)	Total N=180 nP/PY (nP/100 PY)
Number of TEAEs	27	
Subjects with at least one TEAE	22 (12.2%)	22/190.2 (11.57)
Conjunctivitis allergic	10 (5.6%)	10/199.0 (5.02)
Conjunctivitis	5 (2.8%)	5/204.5 (2.44)
Conjunctivitis bacterial	4 (2.2%)	4/208.1 (1.92)
Blepharitis	3 (1.7%)	3/206.7 (1.45)
Conjunctivitis viral	1 (0.6%)	1/206.8 (0.48)
Dry eye	1 (0.6%)	1/207.9 (0.48)
Eye pruritus	1 (0.6%)	1/208.2 (0.48)

MedDRA version 24.1 was used for the SUR data and version 23.1 was used for the Third-step Analysis data.
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 hyperaemia, conjunctival hyperaemia.
AD, atopic dermatitis; CMQ, customized MedDRA query; CSR, Clinical Study Report; MedDRA, Medical Dictionary for Regulatory Activities; nP, number of patients; PT, preferred term; PY, patient-years; sBLA, supplemental Biologics License Application; SUR, safety update report.
Source: PTT 7.6.2.1/1c-A

Reviewer's comment: This reviewer considers all 22 cases of conjunctivitis possibly related to the study drug.

C. Study 1539a (open-label, single-ascending dose)

There were no reported treatment emergent adverse events of conjunctivitis in this study.

8.2.4.4.2 Skin infections excluding herpes and varicella infections

A. Study 1539b (placebo-controlled)

The proportion of subjects with at least 1 skin infection during the 16-week treatment period was higher in the placebo + TCS group (21/78 subjects; 26.9%) than in the dupilumab + TCS group (11/83 subjects, 13.3%). One of the adverse events in the placebo + TCS group (Cellulitis staphylococcal) was a SAE.

Table 21: Summary of Skin infections excluding herpes and varicella infections in the placebo-controlled trial Study 1539b

	dupilumab Q4W +TCS			
	200 mg (N=26)	300 mg (N=57)	Combined 200/300 mg (N=83)	Placebo + TCS (N=78)
Skin infections excluding herpes and varicella infections, (n%)	4(15.4)	7(12.3)	11(13.3)	21(26.9)
Staphylococcal skin infection[a], (n%)	0	0	0	6(7.7)
Impetigo, (n%)	1(3.8)	2(3.5)	3(3.6)	6(7.7)
Cellulitis[b], (n%)	1(3.8)	3(5.3)	4(4.8)	7(9.0)
Molluscum contagiosum, (n%)	2(7.7)	2(2.4)	4(4.8)	2(2.6)

a: staphylococcal skin infection includes staphylococcal skin infection, staphylococcal abscess

b: cellulitis includes bacterial skin infection, dermatitis infected, skin infection, cellulitis staphylococcal, superinfection
Source: Reviewer's analysis

B. Study 1434 (OLE)

A total of 27 (27/180; 15.0%; EAIR 25.87) subjects experienced a TEAE of skin infection. None of the skin infections were considered to be serious or severe and none led to discontinuation of study drug.

Table 22: Summary of Skin Infections Excluding Herpes and Varicella Skin Infections in Children Age ≥6 months to <6 Years of Age in the OLE

Preferred Term	Total N=180	Total (N=180) nP/PY (nP/100
Number of treatment-emergent skin infections	42	
Subjects with at least one treatment-emergent skin infection, n(%)	27 (15.0)	27/104.4 (25.87)
Impetigo	6 (3.3)	6/126.5 (4.74)
Skin infection	4 (2.2)	4/132.1 (3.03)
Hand-foot-and-mouth disease	3 (1.7)	3/131.4 (2.28)
Dermatitis infected	3 (1.7)	3/133.1 (2.25)
Molluscum contagiosum	3 (1.7)	3/134.5 (2.23)
Tinea capitis	2 (1.1)	2/134.3 (1.49)

Abbreviations: nP, number of subjects with an event; PY, patient-years; nP/100 PY, number of subjects with at least one event per 100 patient years; TEAE, treatment emergent adverse event; SAF, safety analysis population
Source: Reviewer's analysis; PTT 7.2.3.7/1c and 7.2.3.7/3c

During the SUR period (August 1,2021- Jan 5, 2022) there were 21 subjects with TEAEs of skin infections per table below. None were considered serious. The event of hand foot and mouth disease was considered treatment related, moderate severity and resolved at the time of the data cutoff for the SUR. Overall, the incidence of hand-foot-and mouth disease in the OLE

cumulatively until Jan 5, 2022, was 5.0% (9/180; 5.0%). There were 4 subjects (4/167; 2.4%) with TEAEs of skin papilloma reported during the SUR period. Events of skin papilloma were verrucae or warts on the hand or foot, were mild in intensity, not serious, and not considered by the investigator to be related to the study treatment. There were no adverse events of skin papilloma reported in the OLE prior to the SUR period.

Table 23: Summary of Skin Infections Excluding Herpes and Varicella Infections in Children ≥6 months to <6 years of Age During the SUR Period of the OLE

Preferred Term	Total (N=167)
Subjects with at least one treatment emergent skin infection, n(%)	21 (12.6)
Hand foot and mouth disease, n(%)	6 (3.6)
Skin papilloma, n(%)	4 (2.4)
Skin infection, n(%)	3 (1.8)
Impetigo[a], n(%)	3 (1.8)
Molluscum contagiosum, n(%)	2 (1.2)
Periorbital cellulitis, n(%)	1 (0.6)

a: Impetigo includes eczema impetiginous

Source: Reviewer's analysis

Reviewer's comment: This reviewer considers the adverse events of hand-foot-and-mouth disease and skin papilloma to be possibly related to study drug.

C. Study 1539a (open-label, single-ascending dose)

Four (4/40, 10.0%) subjects developed skin infections. 3 subjects developed impetigo and 1 subject developed folliculitis. Impetigo occurred in 1 subject in the ≥2 to <6 years old, 3mg/kg cohort and 2 in the ≥6 months to <2 years old cohort, one in the 3mg/kg cohort and one in the 6mg/kg cohort. All impetigo events were considered moderate in intensity. Folliculitis occurred in 1 subject in the ≥6 months to <2 years old, 3mg/kg cohort and was considered mild in intensity.

8.2.4.4.3 Herpes Infections

A. Study 1539b (placebo-controlled)

The proportion of subjects with at least 1 herpes virus infection during the 16-week treatment period was similar in the placebo + TCS group (5/78 subjects; 6.4%) and the dupilumab + TCS group (5/83 subjects; 6.0%). Two subjects in the dupilumab + TCS group had varicella. Both of these subjects came from Poland where varicella vaccine is not indicated in children unless they are immunocompromised.

Table 24: Herpes Infections by Preferred term in the Placebo-Controlled Trial 1539b

	dupilumab Q4W +TCS			
	200 mg (N=26)	300 mg (N=57)	Combined 200/300 mg (N=83)	Placebo + TCS (N=78)
Number of subjects with such events, n(%)	0	5(8.8)	5 (6.0)	5 (6.4)
Herpes Infections, n(%)				
Eczema herpeticum	0	1 (1.8)	1 (1.2)	1 (1.3)
Herpes simplex	0	0	0	2 (2.6)
Herpes virus infection	0	2 (3.6)	2 (2.4)	0
Oral herpes	0	2 (3.6)	2 (2.4)	2 (2.6)

Reviewer's analysis (CSR table 73, pg. 162)

One subject had a herpes infection (Herpes simplex) in the placebo + TCS group during the follow-up period. No subjects in the dupilumab + TCS group had a herpes infection during the follow-up period.

B. Study 1434 (OLE)

Nine subjects (9/180; 5.0 %) developed herpes infections. Four subjects (4/180; 2.2%) developed herpes simplex infections, 4 subjects (4/180; 2.2%) developed oral herpes, and 1 subject (1/180; 0.6%) developed herpes zoster. All TEAEs of herpes infections were mild or moderate in intensity, not serious, not considered by the investigator to be related to the study treatment and had recovered at the time of the data cutoff of the SUR period. One subject had varicella. This subject came from Poland where varicella vaccine is not indicated in children unless they are immunocompromised.

Table 25: Number of Subjects age ≥6 months to <6 years with Treatment-Emergent Herpes Infections by Preferred Term in the OLE

Preferred Term	Total N=180	Total (N=180) nP/PY (nP/100)
Number of Herpes Infections	9	
Herpes simplex	4 (2.2%)	4/204.8 (1.95)
Oral herpes	4 (2.2%)	4/208.0 (1.92)
Herpes Zoster	1 (0.6%)	1/205.8 (0.48)

Abbreviations: nP, number of subjects with an event; PY, patient-years; nP/100 PY, number of subjects with at least one event per 100 patient years; TEAE, treatment emergent adverse event; SAF, safety analysis population
Source: Reviewer's analysis; PTT 7.2.1.1/1c-A

C. Study 1539a (open-label, single-ascending dose)

There were no reports of herpes infection during this study.

8.2.4.4.4 Injection Site Reactions

A. Study 1539b (placebo-controlled)

Two (2/83; 2.4%) subjects in the dupilumab + TCS group and 2 (2/78; 2.6%) subjects in the placebo + TCS group had injection site reactions. All injections site reactions were of mild intensity and resolved.

B. Study 1434 (OLE)

A total of 4 (4/180; 2.2%) subjects experienced TEAEs of injection site reactions including injection site mass, injection site reaction. These events were mild to moderate in severity and resolved; none were serious or led to treatment discontinuation.

C. Study 1539a (open-label, single ascending dose)

One subject (1/10; 10%) in the ≥6 months to <2 years, 6mg/kg dose cohort had an injection site reaction described as erythema. This event was mild in intensity and resolved.

8.2.4.4.5 COVID-19 Related Treatment Emergent Adverse Events

A. Study 1539b (placebo-controlled)

Four subjects (4/161; 2.5%) had COVID-19 infection during the treatment period. One subject in the placebo + TCS group (1/78; 1.3%) and 3 subjects in the dupilumab + TCS group (3/83; 3.6%) had a COVID-19 related TEAE. The events were all mild or moderate in severity, were not serious and were not considered related to study drug. All TEAEs resolved over time. Study drug was temporarily discontinued for the patient in the dupilumab + TCS group with coronavirus infection due to the TEAE; in the remaining cases, study treatment was continued without interruption.

B. Study 1434 (OLE)

Seventeen subjects (17/180; 9.4 %) had a COVID-19 related TEAE during the study. The investigator deemed these events as non-serious, mild or moderate in severity, and were not considered related to study drug. The events did not lead to discontinuation or interruption of study drug. All subjects had recovered or were recovering at the time of the data cut off, with the exceptions of 1 subject with a mild TEAE of COVID-19 which had not resolved at the time of the data cutoff date, and 4 subjects with an unreported outcome (mild event). While there was a higher exposure-adjusted cumulative incidence of COVID-19 compared to the exposure-adjusted cumulative incidence of TEAEs in the ≥6 months to <6 years of age AD sBLA (9.4%

compared to 1.1%, respectively), the most recent exposure period was during a global pandemic involving the OMICRON variant of COVID-19, in an age group in which COVID vaccination was not available.

C. Study 1539a (open-label, single ascending dose)

There were no reports of COVID-19 infection during this study.

8.2.4.5 Severe TEAEs

A. Study 1539b (placebo-controlled)

There was a higher percentage of severe adverse events in the placebo +TCS group (13/78, 16.7%) than in the dupilumab Q4W +TCS group (2/83, 2.4%). There were no severe adverse events in the dupilumab 200mg Q4W group.

Two subjects in the dupilumab 300mg Q4W group had severe TEAEs:

1. **Blepharitis:** This severe TEAE was discussed previously as it was also classified as an AESI.
2. **Eosinophilia:** A 5-year-old male (b) (6)) with food allergy and allergy to dust mite developed eosinophilia on study day 28, 28 days after the first study drug dose. The subject had an absolute eosinophil count of 6.00 x 10_3/µL, increased from a screening eosinophil count of 2.73 x 10_3/µL). Subsequent measurements at an unscheduled visit at Week 8 and at the end of treatment visit (Week 16) showed counts of 6.41 x 103/µL and 7.02 x 10_3/µL. This increased eosinophil count was not associated with any clinical symptoms. This nonserious event was deemed by the investigator as severe and unrelated to study drug and did not lead to study drug discontinuation. After completion of the study, the patient transitioned into the OLE.

Reviewer's comment: The non-serious adverse event of eosinophilia was deemed by the Investigator not to be related to study drug. Taking into consideration that dupilumab has shown to increase eosinophil counts, the relationship of this AE to study drug cannot be excluded.

B. Study 1434 (OLE)

Seven subjects (7/180; 3.9%) had TEAEs that were classified as severe: blepharitis, anaphylactic reaction, urticaria, hand-foot-and-mouth disease, otitis media acute, diabetic ketoacidosis, and dermatitis atopic. The event of urticaria ((b) (6)) was considered severe, related to study drug and led to discontinuation of study drug. These events have been discussed previously.

C. Study 1539a (open-label, single-ascending dose)

One subject (1/40; 2.5%) had a TEAE that was classified as severe. The event of anaphylactic reaction was designated an AESI and was deemed not related to study drug. This event has been discussed previously.

Treatment Emergent Adverse Events and Adverse Reactions

A. Study 1539b (placebo-controlled)

The proportion of subjects who had at least 1 TEAE during the 16-week treatment period was higher in the placebo + TCS group (58/78; 74.4%) than in the dupilumab + TCS group (53/83; 63.9%). The majority of the TEAEs were mild to moderate in intensity, resolved over time, and were deemed as not related to study drug by the investigator. Common adverse reactions that occurred with a higher frequency in the dupilumab + TCS group than in the placebo + TCS group were: molluscum contagiosum (4/83; 4.8%), rhinorrhoea (4/83; 4.8%), conjunctivitis (4/83; 4.8%), gastroenteritis viral (3/83; 3.6%), Covid-19 (3/83; 3.6%), blepharitis (2/83; 2.4%), and eosinophilia (2/83; 2.4%).

Table 26: Summary of Adverse Reactions by Preferred Term with a Cumulative Incidence of ≥2% in Subjects ≥6 Months to <6 Years of Age in the Placebo-Controlled Study 1539b

	Dupilumab Q4W +TCS			
	300 mg	200 mg	Combined 200/300mg	Placebo + TCS
	(N = 57)	(N = 26)	(N = 83)	(N = 78)
Number of patients with such events, n(%)				
Dermatitis atopic, n(%)	6 (10.5)	6 (23.1)	12 (14.5)	25 (32.1)
Nasopharyngitis, n(%)	6 (10.5)	1 (3.8)	7 (8.4)	7 (9.0)
Upper respiratory tract infection[a], n(%)	3 (5.3)	2 (7.7)	5 (6.0)	14 (17.9)
Lymphadenopathy, n(%)	4 (7.0)	0	4 (4.8)	7 (9.0)
Asthma, n(%)	4 (7.0)	0	4 (4.8)	5 (6.4)
Rhinorrhoea, n(%)	3 (5.3)	1 (3.8)	4 (4.8)	2 (2.6)
Molluscum contagiosum, n(%)	2 (3.5)	2 (7.7)	4 (4.8)	2 (2.6)
Conjunctivitis, n(%)	4 (7.0)	0	4 (4.8)	0
Impetigo, n(%)	2 (3.5)	1 (3.8)	3 (3.6)	6 (7.7)
Gastroenteritis viral, n(%)	3 (5.3)	0	3 (3.6)	1 (1.3)
COVID-19[b], n(%)	1 (1.8)	2 (7.7)	3 (3.6)	1 (1.3)
Oral herpes, n(%)	2 (3.5)	0	2 (2.4)	2 (2.6)
Eosinophilia, n(%)	2 (3.5)	0	2 (2.4)	1 (1.3)
Otitis media acute, n(%)	1 (1.8)	1 (3.8)	2 (2.4)	2 (2.6)
Blepharitis, n(%)	2 (3.5)	0	2 (2.4)	0
Constipation, n(%)	0	2 (7.7)	2 (2.4)	0
Herpes virus infection, n(%)	2 (3.5)	0	2 (2.4)	0
Varicella, n(%)	0	2 (7.7)	2 (2.4)	0
Pyrexia, n(%)	1 (1.8)	0	1 (1.2)	8 (1.3)
Urticaria, n(%)	1 (1.8)	0	1 (1.2)	5 (6.4)

a: Upper respiratory tract infection includes respiratory tract infection viral and viral upper respiratory tract infection

b:Covid 19 includes coronavirus infection

Source: Reviewer's analysis

Two subjects (2/19, 10.5%) in the placebo + TCS group and 1 subject (1/19; 5.3%) in the dupilumab + TCS group reported a TEAE during the follow-up period (84 days). These events were herpes simplex and upper respiratory tract infection in the placebo + TCS group and dermatitis atopic in the dupilumab + TCS group. None of these events were severe in intensity or deemed as related to study drug by investigator.

B. Study 1434 (OLE)

139 subjects (139/180; 77.2%) experienced adverse reactions in the OLE. The most common adverse reactions include nasopharyngitis (19.4%), pyrexia (15.6%), upper respiratory tract infection (15.6%), cough (15.0%), dermatitis atopic (12.2%), COVID-19 (9.4%), rhinorrhoea (8.3%), diarrhoea (7.8%), urticaria (7.8%), food allergy (6.7%), conjunctivitis allergic (5.6%), ear infection (5.6%), vomiting (5.6%), asthma (5.0%) and hand-foot-and-mouth-disease (5.0%). During the SUR period there were 4 subjects (4/180; 2.2%) with adverse reactions of oral

herpes and 4 subjects (4/180; 2.2%) with of skin papilloma when there were no subjects with these events up to the sBLA cutoff date.

Table 27: Summary of Adverse Reactions by Preferred Term with a Cumulative Incidence of ≥2% in Subjects ≥6 Months to <6 Years of Age in the OLE through the SUR period.

	Cumulative until 05 Jan 2022 (data cutoff date for the SUR)	
	Total (N=180)	
Preferred Term	nP (nP/N)	nP/PY (nP/100 PY)
Number of TEAEs	874	
Subjects with at least 1 TEAE, n(%)	139 (77.2%)	139/69.4 (200.27)
Nasopharyngitis	35 (19.4%)	35/168.4 (20.78)
Pyrexia	28 (15.6%)	28/172.8 (16.20)
Upper respiratory tract infection	28 (15.6%)	28/178.1 (15.72)
Cough	27 (15.0%)	27/185.1 (14.59)
Dermatitis atopic	22 (12.2%)	22/184.6 (11.91)
COVID-19	17 (9.4%)	17/204.2 (8.32)
Rhinorrhoea	15 (8.3%)	15/195.5 (7.67)
Urticaria	14 (7.8%)	14/191.5 (7.31)
Diarrhoea	14 (7.8%)	14/197.7 (7.08)
Food allergy	12 (6.7%)	12/195.6 (6.13)
Conjunctivitis allergic	10 (5.6%)	10/199.0 (5.02)
Vomiting	10 (5.6%)	10/198.0 (5.05)
Ear infection	10 (5.6%)	10/192.7 (5.19)
Asthma	9 (5.0%)	9/199.5 (4.51)
Hand-foot-and-mouth disease	9 (5.0%)	9/200.4 (4.49)
Rash	8 (4.4%)	8/193.3 (4.14)
Impetigo	8 (4.4%)	8/195.8 (4.09)
Skin infection	7 (3.9%)	7/201.9 (3.47)
Viral upper respiratory tract infection	7 (3.9%)	7/203.3 (3.44)
Hypersensitivity	6 (3.3%)	6/201.1 (2.98)
Epistaxis	6 (3.3%)	6/205.1 (2.93)
Pharyngitis streptococcal	6 (3.3%)	6/200.0 (3.00)
Conjunctivitis	5 (2.8%)	5/204.5 (2.44)
Molluscum contagiosum	5 (2.8%)	5/204.8 (2.44)
Rhinitis	5 (2.8%)	5/203.0 (2.46)
Nasal congestion	5 (2.8%)	5/204.5 (2.44)
Sinusitis	5 (2.8%)	5/202.1 (2.47)
Headache	5 (2.8%)	5/202.9 (2.46)
Bronchitis	4 (2.2%)	4/207.4 (1.93)
Conjunctivitis bacterial	4 (2.2%)	4/208.1 (1.92)
Croup infectious	4 (2.2%)	4/208.1 (1.92)
Gastroenteritis	4 (2.2%)	4/204.4 (1.96)
Herpes simplex	4 (2.2%)	4/204.8 (1.95)
Hordeolum	4 (2.2%)	4/204.3 (1.96)
Oral herpes	4 (2.2%)	4/208.0 (1.92)
Otitis media	4 (2.2%)	4/208.3 (1.92)
Rhinitis allergic	4 (2.2%)	4/206.0 (1.94)
Seasonal allergy	4 (2.2%)	4/205.4 (1.95)

Headache	5 (2.8%)	5/202.9 (2.46)
Skin papilloma	4 (2.2%)	4/207.4 (1.93)

MedDRA version 24.1 was used for the SUR data and version 23.1 was used for the Third-step Analysis data.
AD, atopic dermatitis; MedDRA, Medical Dictionary for Regulatory Activities; nP, number of patients; PY, patient years; sBLA, supplemental Biologics License Application; SUR, safety update report; TEAE, treatment-emergent adverse event.
Source: Reviewer's analysis; 120-day safety update report, table 10, page 19

C. Study 1539a (open-label, single-ascending dose)

Nineteen subjects (19/40, 47.5%) developed at least one TEAE during the treatment period. There was a trend towards a higher incidence of TEAEs in the ≥6 months to <2 years age group. Most TEAEs were mild to moderate in intensity, unrelated to study drug, and resolved. 2 serious TEAEs (anaphylactic reaction) were classified as not related to study drug. No other serious events were reported. No events of herpes infection, conjunctivitis, blepharitis, keratitis, hypersensitivity reactions were reported.

Table 28: Summary of TEAEs in the open-label, single-ascending dose Study 1539a by Preferred Term

		≥6 months to <2 years old			≥2 to <6 years old		
	Total	3 mg/kg	6 mg/kg	Combined	3 mg/kg	6 mg/kg	Combined
Preferred Term	**(N=40)**	**(N=10)**	**(N=10)**	**(N=20)**	**(N=10)**	**(N=10)**	**(N=20)**
Subjects with at least one TEAE, n(%)	19 (47.5)	7 (70.0)	7 (70.0)	14 (70.0)	3 (30.0)	2 (20.0)	5 (25.0)
Nasopharyngitis	5 (12.5%)	1 (10.0)	2 (20.0)	3 (15.0)	1 (10.0)	1 (10.0)	2 (10.0)
Impetigo	3 (7.5%)	1 (10.0)	1 (10.0)	2 (10.0)	1 (10.0)	0	1 (5.0)
Anaphylactic reaction	2 (5.0%)	1 (10.0)	0	1 (5.0)	1 (10.0)	0	1 (5.0)
Pyrexia	2 (5.0%)	1 (10.0)	0	1 (5.0)	1 (10.0)	0	1 (5.0)
Dermatitis atopic	2 (5.0%)	0	1 (10.0)	1 (5.0)	1 (10.0)	0	1 (5.0)
Cough	2 (5.0%)	0	1 (10.0)	1 (5.0)	0	1 (10.0)	1 (5.0)
Urticaria	2 (5.0%)	1 (10.0)	1 (10.0)	2 (10.0)	0	0	0
Upper respiratory tract infection	2 (5.0%)	1 (10.0%)	1 (10.0)	2 (10.0)	0	0	0
Diarrhoea	2 (5.0%)	1 (10.0%	1 (10.0)	2 (10.0)	0	0	0
Injection site erythema	1 (2.5%)	0	1 (10.0)	1 (5.0)	0	0	0
Folliculitis	1 (2.5%)	1 (10.0%	0	1 (5.0)	0	0	0
Constipation	1 (2.5%)	1 (10.0)	0	1 (5.0)	0	0	0
Thrombocytosis	1 (2.5%)	0	1 (10.0)	1 (5.0)	0	0	0
Joint swelling	1 (2.5%)	1 (10.0%)	0	1 (5.0)	0	0	0
Lacrimation increased	1 (2.5%)	0	1 (10.0)	1 (5.0)	0	0	0
Skin abrasion	1 (2.5%)	0	0	0	0	1 (10.0)	1 (5.0)

MedDRA (Version 21.1) dictionary applied.
TEAE, treatment-emergent adverse event.
Source: Reviewer's analysis and PTT 7.2.1.1

Subjects aged ≥6 months to <2 years

Fourteen subjects (14/20, 70.0%) experienced TEAEs. In both the 3 mg/kg and 6 mg/kg dose cohorts (7/10, 70.0%) experienced at least 1 TEAE. The most common TEAEs were nasopharyngitis (3/20,15.0%), upper respiratory tract infection (2/20, 10.0%), impetigo (2/20, 10.0%), urticaria (1/20, 10.0%), and diarrhoea (2/20, 10.0%). Notable TEAEs included 1 event of anaphylactic reaction (in subject (b) (6)) which was deemed unrelated to study drug and has been discussed previously.

Subjects aged ≥2 years to < 6 years

Five subjects (5/20; 25.0%) experienced TEAEs. In the 3 mg/kg dose cohort, 3 subjects (3/10, 30.0%) experienced at least 1 TEAE, and in the 6 mg/kg dose cohort, 2 subjects (2/10, 20.0) experienced at least 1 TEAE. The most frequent TEAE reported was nasopharyngitis (2/20, 10.0%) Notable TEAEs included a serious adverse event of anaphylactic reaction (in subject (b) (6)) was deemed unrelated to study drug. No events of injection site reactions were reported.

Laboratory Findings

A. Study 1539 (placebo-controlled)

There were no clinically meaningful trends or differences in mean or median changes from baseline for any red blood cell parameter (i.e., hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, or erythrocytes) or platelets.

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in 8% of dupilumab-treated subjects (7/83; 8.4%) and 0% in placebo-treated subjects. Mean (SD) eosinophil counts at baseline were similar across both treatment groups. The greatest increase occurred in the dupilumab 200 mg Q4W +TCS at Week 4 with a decline towards baseline at Week 16. There was an increase in eosinophil counts in the dupilumab 300 mg Q4W + TCS group at Week 4 and Week 16, and as assessed by the mean change from baseline, with the greatest increase being seen at Week 4. There was a trend towards declining to baseline at Week 16 in the dupilumab 200 mg Q4W +TCS and placebo +TCS groups but not in the Dupilumab 300 mg Q4W +TCS group.

Figure 6: Subjects with Treatment-Emergent Eosinophilia (≥5,000 cells/mcL) in the Dupilumab Treatment Group During the Placebo-Controlled Study 1539b

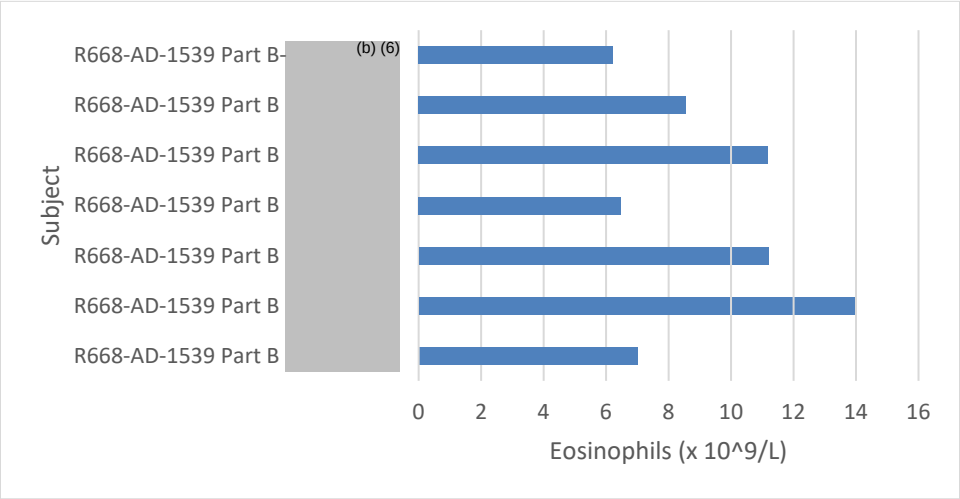
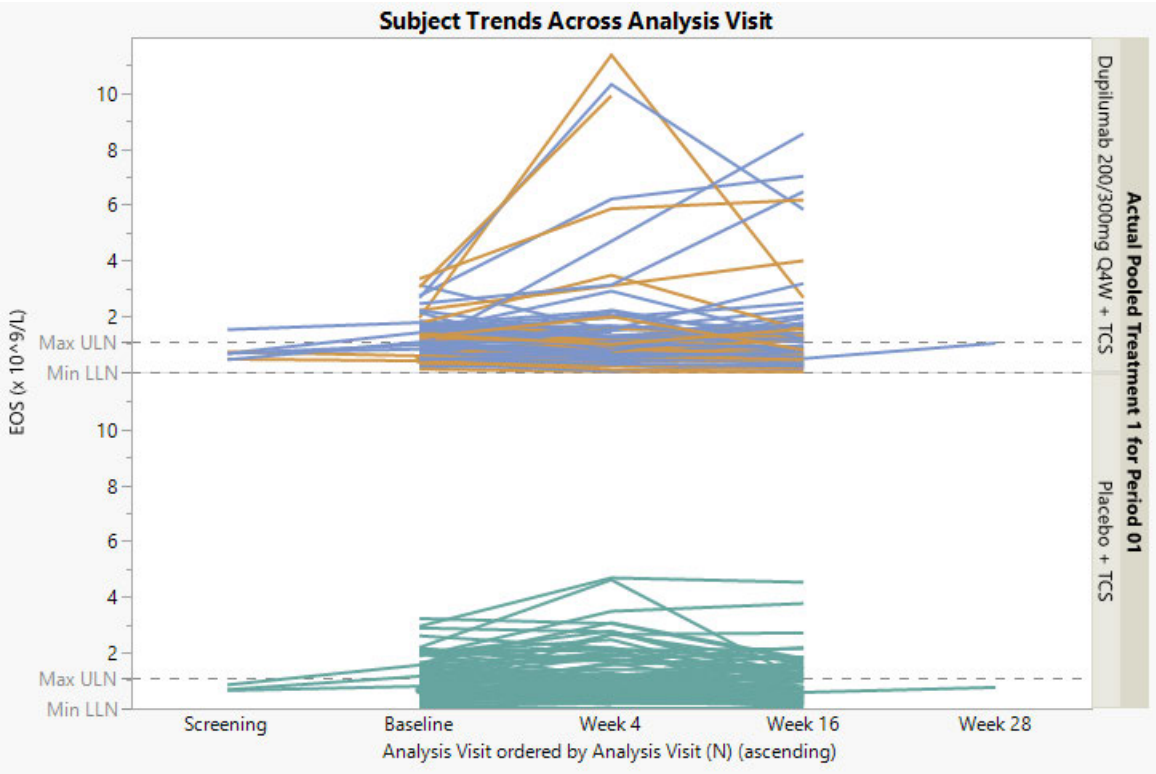
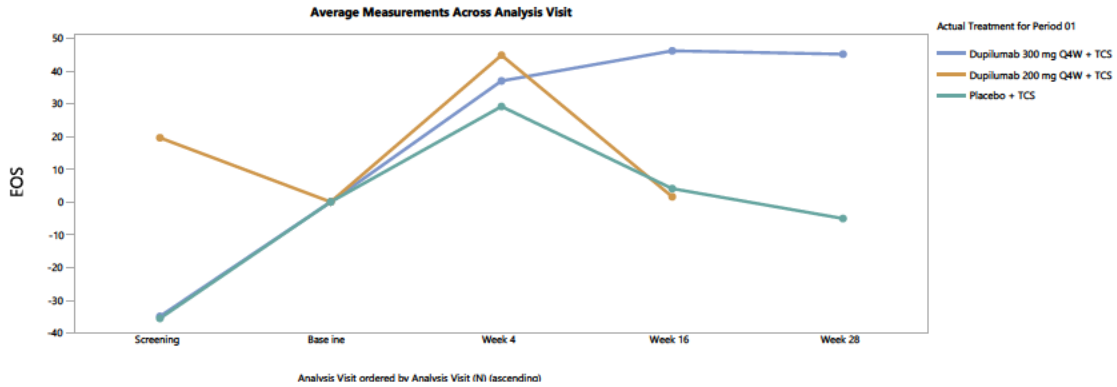


Figure 7: Observed Eosinophils(x 10^9/L) Counts from Baseline through Week 16



Source: Reviewer's analysis

Figure 8: Percent Change from Baseline for Eosinophils (x 10^9/L) From Baseline through Week 16



Source: Reviewer's analysis

Two subjects (2/83; 2.4%) in the dupilumab + TCS group had a TEAE of eosinophilia, 1 (1/83; 1.2%) had a TEAE of neutropenia and 1 subject (1/83; 1.2%) had a TEAE of white blood cell count increased. None of these events were serious and none led to discontinuation of study treatment. The TEAE of neutropenia was not resolved by the end of treatment. No additional information was provided regarding the adverse events of neutropenia or white blood cell count increased.

1. **Eosinophilia:** This TEAE has been discussed previously. A 5-year-old male ((b) (6)) with food allergy and allergy to dust mite developed eosinophilia on study day 28, 28 days after the first study drug dose. The subject had an absolute eosinophil count of 6.00 x 10_3/µL, increased from a screening eosinophil count of 2.73 x 103/µL). Subsequent measurements at an unscheduled visit at Week 8 and at the end of treatment visit (Week 16) showed counts of 6.41 x 103/µL and 7.02 x 103/µL. This increased eosinophil count was not associated with any clinical symptoms. This nonserious event was deemed by the investigator as severe and unrelated to study drug and did not lead to study drug discontinuation. After completion of the study, the patient transitioned into the OLE.

2. **Eosinophilia:** A 4-year-old white male ((b) (6)) developed eosinophilia of moderate intensity. No narrative was provided regarding this AE.

Time	Eosinophil count:
Screening visit:	2.66 x 10^3/uL
Visit 7 (week 4):	9.17 x 10^3/uL
Unscheduled visit week8:	9.86 x 10^3/uL
Unscheduled visit week 10:	11.2 x 10^3/uL
Unscheduled visit week 13:	11.03 x 10^3/uL
Visit 19 (week 16):	5.83 x 10^3/uL

There was a discrepancy between the number of subjects with elevated eosinophil counts and the adverse events of eosinophilia as reported by the Applicant. This discrepancy is attributed to, per the Applicant, the decision of the Investigator whether to report an abnormal laboratory finding as an AE.

No clinically meaningful trend towards an increase or decrease in mean or median values over time was seen in either treatment group for the majority of chemistry parameters (metabolic, electrolyte, renal function, liver function, and lipid parameters). No AEs related to clinical chemistry were reported.

B. Study 1434 (OLE)

There were no clinically meaningful changes in mean and median hematology parameters. There were no meaningful changes in leukocytes, lymphocytes, monocytes, basophils and neutrophils during the course of treatment.

One subject had an eosinophil count >5000 per microliter (1/180; 0.6%). Five subjects had elevated eosinophil counts above normal range that did not resolve. No TEAEs were reported for eosinophilia in any of these subjects. No subject had a TEAE related to neutrophil counts.

C. Study 1539a (open-label, single-ascending dose)

There were no clinically meaningful changes in mean and median hematology or clinical chemistry parameters over the first 4 weeks of the study. Shifts from normal at baseline to high at week 4 were reported for all 4 subjects aged ≥2 years to <6 years in the 3 mg/kg dose cohort who had normal baseline value and 1 of 2 subjects aged ≥6 months to <2 years in the 6 mg/kg dose cohort who had a normal baseline value.

Vital Signs

A. Study 1539b (placebo-controlled)

No abnormal vital sign values were reported as TEAEs. No subject had abnormalities in vital signs that led to treatment discontinuation or to reporting of a SAE.

B. Study 1434 (OLE)

There were no clinically meaningful trends in mean or median vital sign values over time (systolic blood pressure, diastolic blood pressure, respiratory rate and for temperature). There was a trend for a decrease in heart rate over time. The mean heart rate decreased from 102.6 beats/min at baseline to 99.3 beats/min at week 52 and 94.5 beats/min at week 104. The Applicant proposes that this is expected as heart rate tends to decrease with age in pediatric patients, especially in this very young age group. Mean and median body weight increased from baseline to week 52. The applicant proposes this is expected in this growing pediatric population. There were no TEAEs regarding vital signs reported.

C. Study 1539a (open-label, single-ascending dose)

There were no clinically meaningful changes in vital signs (blood pressure, pulse rate, respiratory rate, weight, or temperature) over the course of the study. No abnormal vital sign values were reported as TEAEs.

Electrocardiograms (ECGs)

A. Study 1539b (placebo-controlled)

There were no clinically meaningful trends in mean or median changes from baseline in electrocardiogram parameters (ECG mean heart rate, PR interval, QRS interval, QT interval, QTcB, QTcF, or RR interval) in either treatment group. No patient had an ECG abnormality that was reported as a TEAE. In the cohort of subjects with QTcF prolongations, there were no adverse events of ventricular arrythmia or syncope.

B. Study 1434 (OLE)

There were no clinically meaningful trends in mean or median changes from baseline in electrocardiogram (ECG) parameters in any treatment group. No patient had an ECG abnormality that was reported as a TEAE. In the cohort of patients with QTcF prolongations, there were no adverse events of ventricular arrythmia or syncope.

C. Study 1539a (open-label, single-ascending dose)

There were no clinically meaningful changes in electrocardiogram parameters over the course of the study.

8.2.5. Safety Analyses by Demographic Subgroups

For the safety analyses, the Applicant defined the following subgroups by baseline factors in Study 1539b:

- Age group (≥6 months to <2 years, ≤2 to <6 years)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino [no/yes])
- Race (White, Black or African American, Other)
- Baseline weight group (5- <15kg, 15-<30 kg)
- Baseline BMI group (Not overweight, Overweight)
- Duration of AD (<3 years, ≥3 years)
- Severity of AD (IGA 4)
- History of food allergies (no/yes)

Due to the small number of subjects in each treatment group and small numbers of adverse events, definitive conclusions are difficult to make within the subgroups of age, sex, race, baseline weight, duration of AD, severity of AD or history of food allergy.

Table 29: Demographic Subgroups in Subjects Aged 6 Months to <2 Years in the placebo-controlled trial Study 1539b

	dupilumab Q4W +TCS							
	200 mg (N=26)		300 mg (N=57)		Combined 200/300mg (N=83)		Placebo + TCS (N=78)	
Age								
6 months - < 2 years	6	(23.1)	0		6	(7.2)	4	(5.1)
≤2 - <6 years	20	(76.9)	57	(100.0)	77	(92.8)	74	(94.9)
Sex								
F	16	(61.5)	23	(40.4)	39	(47.0)	24	(30.8)
M	10	(38.5)	34	(59.6)	44	(53.0)	54	(69.2)
Ethnicity								
Hispanic or Latino	4	(15.4)	7	(12.3)	11	(13.3)	8	(10.3)
Not Hispanic or Latino	22	(84.6)	50	(87.7)	72	(86.7)	70	(89.7)
Race								
White	17	(65.4)	41	(71.9)	58	(69.9)	52	(66.7)
Black or African American	4	(15.4)	10	(17.5)	14	(16.9)	16	(20.5)
Asian	3	(11.5)	3	(5.3)	6	(7.2)	4	(5.1)
Native Hawaiian or other Pacific Islander	0		0		0		1	(1.3)
Other	1	(3.8)	2	(3.5)	3	(3.6)	4	(5.1)
Not reported	1	(3.8)	1	(1.8)	2	(2.4)	1	(1.3)
Baseline weight group								
5- <15kg	26	(100.0)	0		26	(31.3)	24	(30.8)
15-<30 kg	0		57	(100.0)	57	(68.7)	54	(69.2)

Baseline BMI group								
Not Overweight	22	(84.6)	37	(64.9)	59	(71.1)	66	(84.6)
Overweight	4	(15.4)	19	(33.3)	23	(27.7)	11	(14.1)
Duration of AD								
<3 years	20	(76.9)	9	(15.8)	29	(34.9)	27	(34.6)
≥3 years	6	(23.1)	48	(84.2)	54	(65.1)	51	(65.4)
Severity of AD								
Moderate (IGA=3)	8	(30.8)	12	(21.1)	20	(24.1)	17	(21.8)
Severe (IGA=4)	18	(69.2)	45	(78.9)	63	(75.9)	61	(78.2)
History of food allergies								
Yes	17	(65.4)	42	(73.7)	59	(71.1)	56	(71.8)
No	9	(34.6)	15	(26.3)	24	(28.9)	22	(28.2)

Source: Reviewer's analysis, Post text table Table 4.1.1/5 Subgroups Relevant for Safety Analysis (Safety Analysis Set) pg. 48

8.2.5.1. **Age 6 months to 2 years**

A. Study 1539b (placebo-controlled)

The proportion of subjects aged 6 months to <2 years who had at least 1 adverse reaction during the 16-week treatment period was comparable between the placebo + TCS group (3/4; 75.0%) and the dupilumab + TCS group (4/6; 66.7%). Most common adverse reactions were upper respiratory infection and dermatitis atopic. One subject in the dupilumab + TCS group had a TEAE (dermatitis atopic) that led to discontinuation of study drug. All TEAEs were mild to moderate in intensity. No SAEs were reported in this age group.

Table 30: Adverse Reactions in Subjects Aged 6 Months to <2 Years By Preferred Term in the placebo-controlled trial Study 1539b

	Dupilumab 200 mg Q4W + TCS (N=6)	**Placebo + TCS (N=4)**
Number of subjects with such events, n(%)	4(66.7)	3(75.0)
Number of adverse reactions	11	9
Upper respiratory tract infection[a] , n(%)	3(50.0)	2(50.0)
Dermatitis atopic, n(%)	2(33.3)	1(25.0)
Injection site erythema, n(%)	1(16.7)	0
COVID-19, n(%)	1(16.7)	0
Impetigo, n(%)	1(16.7)	0
White blood cell count increased, n(%)	1(16.7)	0
Rhinorrhoea, n(%)	1(16.7)	0
Nail dystrophy, n(%)	1(16.7)	0

[a]Upper respiratory tract infection includes nasopharyngitis, respiratory tract infection viral, viral upper respiratory tract infection
Source: Reviewer's analysis

B. Study 1434 (OLE)

Approximately 79% of subjects (15/19; 78.9%) aged 6 months to 2 years had at least 1 TEAE during the study. The events were all mild to moderate in intensity and none led to permanent discontinuation of study drug. None of the subjects aged <2 years had SAEs and no deaths were reported.

The most common adverse reactions reported are upper respiratory tract infection (11/19; 57.9%), nasopharyngitis (7/19; 36.8%), food allergy (7/19; 36.8%), dermatitis atopic (6/19; 31.6%), and rhinitis (6/19; 31.6%). No further information was provided regarding these adverse reactions.

Table 31: Summary of Adverse Reactions by Preferred Term Reported in ≥2 Subjects Aged 6 months to <2 Years in the OLE

	Total (N=19)
Number of adverse reactions	188
Subjects with at least one adverse reaction, n(%)	15 (78.9)
Upper respiratory tract infection[a]	11(57.9)
Nasopharyngitis	7 (36.8)
Food allergy[b]	7 (36.8)
Dermatitis atopic	6 (31.6)
Rhinitis[c]	6 (31.6)
Urticaria	5 (26.3)
Cough	4 (21.1)
Rash	3 (15.8)
Diarrhoea[d]	3 (15.8)
Pyrexia	3 (15.8)
Pruritus	2 (10.5)
Ear infection	2 (10.5)
Rhinitis allergic	2 (10.5)
Gastroenteritis	2 (10.5)

Abbreviations: SAF, safety analysis population; TEAE, treatment-emergent adverse event
Source: Reviewer's analysis and PTT 7.2.1.1/2c
a: Upper respiratory tract infection includes Viral upper respiratory tract infection
b: food allergy includes milk allergy
c: Rhinitis includes rhinitis allergic, nasal congestion and rhinorrhoea
d: diarrhoea includes diarrhoea infectious
Source: Reviewer's analysis, PTT 7.2.1.1/2c

During the SUR period, a total of 15 (15/180; 8.8%) subjects aged ≥6 months to <2 years reported at least 1 TEAE, with no subjects in this age group reporting an SAE or AE leading to permanent discontinuation of study drug. All subjects in this age group experienced TEAEs which were mild or moderate in intensity, and all events recovered/resolved or were recovering/resolving except for 1 subject with a TEAE of chalazion (moderate intensity) which had not recovered by the end of the reporting period.

C. Study 1539a (open label, single-ascending dose)

Fourteen subjects (14/20, 70.0%) aged ≥6 months to <2 years experienced TEAEs. In both the 3 mg/kg and 6 mg/kg dose cohorts (7/10, 70.0%) experienced at least 1 TEAE. These TEAEs were discussed previously.

8.2.5.2. Subjects with Severe AD (IGA = 4)

A. Study 1539b (placebo-controlled)

A total of 124 subjects with an IGA=4 (severe AD) received treatment. The proportion of subjects with severe AD who had at least 1 adverse reaction during the 16-Week treatment period was higher in the placebo + TCS group (45/61; 73.8%) than in the dupilumab + TCS group (42/63; 66.7%). However, in the dupilumab +TCS group there was a higher incidence of nasopharyngitis (6/63; 9.5%), molluscum contagiosum (4/63; 6.3%), dental carries (4/63; 6.3%), conjunctivitis (3/63; 4.8%), gastroenteritis viral (3/63; 4.8%) and eosinophilia (2/63; 3.2%). Adverse reactions of conjunctivitis and eosinophilia are known adverse events with dupilumab. The majority of the TEAEs in patients with severe AD were mild to moderate in intensity. One subject (1/61; 1.6%) in the placebo + TCS group and 1 subject (1/63; 1.6%) in the dupilumab + TCS group had a TEAE that led to permanent discontinuation of study drug Three subjects (3/61; 4.9%) in this sub-population reported SAEs in the placebo + TCS group; there were no SAEs in the dupilumab + TCS group.

Table 32: Summary of Adverse Reactions Reported by ≥2 Subjects with IGA=4 (Severe AD) in any Treatment Group by Preferred Term in the Placebo-Controlled Trial 1539b

	Dupilumab 200/300mg Q4W + TCS (N=63)	Placebo + TCS (N=61)
Number of subjects with at least one such event, n (%)	42 (66.7)	45 (73.8)
Dermatitis atopic	10 (15.9)	16 (26.2)
Upper respiratory tract infection	5 (7.9)	5 (8.2)
Nasopharyngitis	6 (9.5)	2 (3.3)
Molluscum contagiosum	4 (6.3)	2 (3.3)
Dental caries	4 (6.3)	0
Conjunctivitis	3 (4.8)	0
Gastroenteritis viral	3 (4.8)	0
Asthma	3 (4.8)	5 (8.2)
Lymphadenopathy	3 (4.8)	5 (8.2)
Impetigo	2 (3.2)	5 (8.2)
Eosinophilia	2 (3.2)	0
Pyrexia	1 (1.6)	7 (11.5)
Urticaria	1 (1.6)	3 (4.9)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; SOC=system organ class; TCS=topical corticosteroids; TEAE=treatment-emergent adverse event.

MedDRA (Version 23.1) coding dictionary applied.

Source: Reviewer's analysis, PTT 7.2.1.4/9

B. Study 1434 (OLE)

A total of 50 subjects were enrolled with severe AD (IGA=4) at baseline. 33 subjects (33/50; 66.0%) had at least 1 TEAE in the study. Most of the events were considered unrelated to study drug by the investigator. 17 subjects (17/50; 34.0%) had severe TEAEs. No subject experienced a TEAE that led to permanent study drug discontinuation and no subject experienced an SAE or an AESI in this population.

The most common adverse reactions were upper respiratory tract infection (11/50; 22.0), nasopharyngitis (6/50; 12.0%), pyrexia (8/50; 16.0%), cough (6/50; 12.0%), urticaria (6/50; 12.0%) and asthma (5/50; 10.0%). In this population, 4 subjects (4/50; 8.0%) reported conjunctivitis. Overall, adverse reactions of skin infections occurred in 18/50 (36.0%) subjects. None of the skin infections were considered to be SAEs, of severe intensity, or led to discontinuation of study drug.

Table 33: Summary of TEAEs Reported by ≥2 Subjects with IGA=4 (Severe AD) in any Treatment Group by Preferred Term in the OLE Study 1434

	Total (N=50)
Number of TEAEs	259
Subjects with at least one TEAE, n(%)	33 (66.0)
Upper respiratory tract infection	11 (22.0)
Pyrexia	8 (16.0)
Nasopharyngitis	6 (12.0)
Urticaria	6 (12.0)
Cough	6 (12.0)
Asthma	5 (10.0)
Conjunctivitis[a]	4 (8.0)
Impetigo	4 (8.0)
Dermatitis atopic	4 (8.0)
Rhinitis[b]	4 (8.0)
Food allergy	3 (6.0)
Diarrhoea	3 (6.0)
Vomiting	3 (6.0)
Croup infectious	3 (6.0)
Dermatitis infected	3 (6.0)
Ear infection	3 (6.0)
Hand-foot-and-mouth disease	3 (6.0)
Headache	3 (6.0)
Hypersensitivity	2 (4.0)
Blepharitis	2 (4.0)
Influenza	2 (4.0)
Molluscum contagiosum	2 (4.0)
Rhinitis	2 (4.0)
Sinusitis	2 (4.0)
Tinea capitis	2 (4.0)
Rash	2 (4.0)
Urinary tract infection	2 (4.0)

Abbreviations: IGA, Investigator's Global Assessment; SAF, safety analysis population; TEAE, treatment-emergent adverse event
a: Conjunctivitis includes conjunctivitis allergic
b: Rhinitis includes rhinorrhoea
Source: Reviewer's analysis, PTT 12.2.5/2c

C. Study 1539a (open label, single-ascending dose)

All subjects had an IGA score of 4 and were diagnosed with severe AD at baseline. The TEAEs have been discussed previously.

8.2.6. Specific Safety Studies/Clinical Trials

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

8.2.7. 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 non-dupilumab 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 25, 2021 (Sequence 1329). 117 subjects 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 subjects six months 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.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

DUPIXENT (dupilumab) is approved in the United States for the indication of moderate-to-severe atopic dermatitis in patients 6 years and older. Since the original approval in 2017, there are no newly identified safety signals.

Expectations on Safety in the Postmarket Setting

There are no safety concerns that are expected to change the favorable risk/benefit assessment or lead to increased risk with administration of DUPIXENT in the post market setting.

8.2.9. Integrated Assessment of Safety

As the Applicant conducted one placebo-controlled study for this efficacy supplement, there was no integrated assessment of safety.

8.3. Statistical Issues

The results of the analysis for the primary and key secondary efficacy endpoints at Week 16, success of the IGA and EASI 75, respectively, were statistically superior to placebo ($p<0.001$).

Thus, supporting the efficacy claim of dupilumab in moderate to severe atopic dermatitis (AD) in patients aged ≥6 months to <6 years. The proportion of subjects who did not complete the trial was very small (1 on dupilumab and 3 on the placebo), and consequently the impact of handling missing data on the efficacy results is negligible. The results of subgroup analysis were consistent across subgroup classification by age, race, sex and baseline disease severity; however, it should be noted that number of subjects in some subgroup classifications are small to draw a meaningful conclusion about subgroup. There were no major statistical issues affecting the overall conclusions.

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-1539b). The trial enrolled subjects ≥6 months to >6 years with moderate-severe AD (IGA of 3-4, Eczema Area and Severity Index (EASI) ≥16, and Body Surface Area (BSA) ≥10%) 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 for the primary endpoint at Week 16.

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

Because very few subjects aged 6 month-2 years were included in the clinical trials, DDD requested the consultation from Division of Pharmacovigilance (DPV) to provide recommendation on additional safety data collection post approval. DPV recommended that under the Reporting Requirements section of the sBLA action letter for dupilumab, the following be included:

"We request that for a period of 2 years from the U.S. approval date of this sBLA, the Applicant submit all reported labeled and unlabeled SAEs (i.e., both 'serious and expected' or 'serious and unexpected' adverse events) with DUPIXENT (dupilumab) injection in patients aged ≥6 months to 2 years as 15-day expedited reports, and we request that you provide detailed analyses of these SAEs in the periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.800(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should include an assessment of the interval and cumulative adverse event reports for all labeled and unlabeled SAEs in patients ≥6 months to 2 years of age in your post-market safety database; reports from IND, non-IND, and NDA studies; and the medical literature. The summary should include the report narrative or the manufacturer control number if submitted to MedWatch."

DDD agreed with the proposal recommended by DPV.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labelling negotiations are ongoing at the time of this review.

12 Risk Evaluation and Mitigation Strategies (REMS)

The labeling and enhanced pharmacovigilance activities (discussed in section **10 Pediatrics** of this review) as the methods for post market risk evaluation and mitigation.

13 Postmarketing Requirements and Commitment

None attached to this sBLA.

14 Appendices

14.1. References

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 February 15, 2022).

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6. May RD, Fung M. Strategies targeting the IL-4/IL-13 axes in disease. Cytokine 2015;75:89-116.

7. DUPIXENT package insert.

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10. Yaghmaie P et al. Mental health comorbidity in subjects with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.

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Invest Dermatol (2017) 137, 26-30.

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.

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14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study R668-AD-1539 entitled "A Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in Patients Aged ≥6 months to < 6 years of age with Moderate to Severe Atopic Dermatitis"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 19		
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): 19		
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: 19 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: Sanofi and Regeneron		
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. OCP Appendices (Technical documents supporting OCP recommendations)

14.3.1. Population PK analysis

The Applicant conducted population pharmacokinetic (PopPK) analysis to:

- Characterize the PopPK of dupilumab in pediatric subjects ≥6 months to <6 years of age with AD using a structural model built using pediatric and adult data;
- Assess if covariates, which have been found to be statistically significant in pediatric subjects ≥6 to <18 years of age and adults, are also assess statistical significance in pooled data across age groups including pediatric subjects ≥6 months to <6 years of age;
- Simulate and compare predicted exposure for pediatric subjects ≥6 months to <6 years of age with AD to predicted exposure for pediatric subjects ≥6 to <12 years of age, adolescents and adults with AD.

Informed by previous modeling of dupilumab PK, an integrated PopPK model was developed to understand the PK of dupilumab in children ≥6 months to <6 years of age with AD relative to AD subjects ≥6 years of age to adult. Briefly, data from a total of 121 pediatric subjects ≥6 months to <6 years of age with AD in Study R668-AD-1539 were pooled with data from pediatric subjects ≥6 to <18 years of age and adults for this PopPK analysis. The PopPK analysis included a total of 2873 unique subjects (2223 adults, 252 adolescents aged ≥12 to <18 years, 277 pediatric subjects aged ≥6 to <12 years and 121 pediatric subjects aged ≥6 months to <6 years) from 22 clinical studies (nine Phase 1, six Phase 2, one Phase 2/3, and six Phase 3 studies) in healthy subjects and adult and pediatric subjects with AD). The integrated PopPK model consisted of two-compartment disposition, linear absorption following SC administration, direct IV administration into the central compartment, parallel linear and nonlinear (Michaelis-Menten) elimination and a first-order maturation function to characterize changes in linear clearance that occur with growth and development in the pediatric AD subjects ≥6 months to <6 years of age.

Summaries of categorical and continuous covariates for the combined 22 studies, stratified by patient population and age group are provided in Table 34 and Table 35.

Table 34. Summary of Categorical Covariates in Healthy Subjects and Subjects with AD Stratified by Age Group

Population	Patients with AD				Healthy Subjects	Total
	Children ≥6 months to <6 years [a]	Children ≥6 to <12 years	Adolescents ≥12 to <18 years	Adults		
Number of Subjects (%)	121 (4.2%)	277 (9.6%)	252 (8.8%)	2021 (70.3%)	202 (7%)	2873 (100%)
Sex						
Males	73 (60.3%)	140 (50.5%)	135 (53.6%)	1182 (58.5%)	121 (59.9%)	1651 (57.5%)
Females	48 (39.7%)	137 (49.5%)	117 (46.4%)	839 (41.5%)	81 (40.1%)	1222 (42.5%)
Patient Status						
Healthy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	202 (100%)	202 (7.0%)
Patient (AD)	121 (100%)	277 (100%)	252 (100%)	2021 (100%)	0 (0%)	2671 (93.0%)
Race						
White	84 (69.4%)	208 (75.1%)	176 (69.8%)	1397 (69.1%)	128 (63.4%)	1993 (69.4%)
Black	21 (17.4%)	40 (14.4%)	22 (8.7%)	155 (7.7%)	43 (21.3%)	281 (9.8%)
Asian	10 (8.3%)	15 (5.4%)	34 (13.5%)	414 (20.5%)	25 (12.4%)	498 (17.3%)
Native American	0 (0%)	0 (0%)	2 (0.8%)	6 (0.3%)	1 (0.5%)	9 (0.3%)
Pacific Islander	0 (0%)	1 (0.4%)	3 (1.2%)	4 (0.2%)	1 (0.5%)	9 (0.3%)
Other	4 (3.3%)	10 (3.6%)	13 (5.2%)	35 (1.7%)	4 (2%)	66 (2.3%)
Not Reported	2 (1.7%)	3 (1.1%)	2 (0.8%)	10 (0.5%)	0 (0%)	17 (0.6%)
ADA Status						
No Treatment-Emergent ADA	100 (82.6%)	251 (90.6%)	190 (75.4%)	1797 (88.9%)	139 (68.8%)	2477 (86.2%)
Positive ADA: Low Titer	18 (14.9%)	21 (7.6%)	53 (21%)	185 (9.2%)	52 (25.7%)	329 (11.5%)
Positive ADA: Moderate Titer	3 (2.5%)	2 (0.7%)	6 (2.4%)	28 (1.4%)	10 (5%)	49 (1.7%)
Positive ADA: High Titer	0 (0%)	3 (1.1%)	3 (1.2%)	11 (0.5%)	1 (0.5%)	18 (0.6%)

AD = Atopic dermatitis; ADA = Anti-drug antibody
Notes: Race categories "Native American" includes American Indians and Alaska Natives and "Pacific Islander" includes Native Hawaiians and other Pacific Islanders; ADA titer levels corresponding to "No treatment emergent" means that the subject did not exhibit ADA or pre-existing ADA levels were not treatment-boosted. Positive ADA was categorized as Low Titer (> 0 to ≤ 1000), Moderate Titer (> 1000 to ≤ 10000) or High Titer (>10000).
[a] Study R668-AD-1539 Part A and Part B

Table 35. Summary of Continuous Covariates at Baseline in Healthy Subjects and Subjects with AD Stratified by Age Group

Population	Patients with AD				Healthy Subjects [b]	Total
	Children ≥6 months to <6 years [a]	Children ≥6 to <12 years	Adolescents ≥12 to <18 years	Adults		
Number of Subjects	121	277	252	2021	202	2873
Age (years)						
N	121	277	252	2021	202	2873
Mean (SD)	3.5 (1.49)	8.52 (1.71)	15.03 (1.71)	38.02 (13.94)	34.59 (11.45)	31.47 (16.88)
Median (Min, Max)	3.75 (0.5, 5.83)	9 (6, 11.94)	14.94 (12, 17.97)	36 (18, 88)	32 (18, 63)	30 (0.5, 88)
Missing	0	0	0	0	0	0
Weight (kg)						
N	121	277	252	2021	202	2873
Mean (SD)	15.9 (4.83)	31.41 (10.05)	63.31 (20.1)	76.93 (18.76)	75.97 (9.87)	68.71 (24.61)
Median (Min, Max)	15.6 (7.4, 29.8)	29.4 (17.7, 79.1)	58.4 (31.7, 173.6)	74.2 (39.8, 175.4)	77.25 (52.1, 94.6)	70 (7.4, 175.4)
Missing	0	0	0	0	0	0
Albumin (g/L)						
N	121	277	252	2021	202	2873
Mean (SD)	45.5 (3.89)	46.2 (3.21)	46.12 (3.10)	44.02 (3.85)	43.94 (3.39)	44.47 (3.80)
Median (Min, Max)	46 (33, 53)	46 (36, 54)	46 (36, 53)	44 (22, 57)	44 (33, 53)	45 (22, 57)
Missing	0	0	0	0	0	0
EASI Score (0-72)						
N	121	277	252	2021	NA	2671
Mean (SD)	35.39 (13.28)	37.24 (12.43)	33.84 (14.47)	31.74 (13.31)	NA	32.67 (13.45)
Median (Min, Max)	33 (16.2, 72)	35.2 (10.6, 70.8)	30.43 (9.5, 70.8)	28.5 (0.6, 72)	NA	29.8 (0.6, 72)
Missing	0	0	0	0	202	202

AD = Atopic dermatitis; N = Number of subjects; SD = Standard deviation; Min = Minimum; Max = Maximum; EASI = Eczema Area and Severity Index; NA = Not applicable
[a] Study R668-AD-1539 Part A and Part B
[b] Baseline EASI scores were identified as missing for healthy subjects in the dataset, and are not included in the total summary statistics.

The parameter estimates for the final PopPK model with the pooled dataset (22 studies) are presented in the following table.

Table 36. Final PopPK Model

Parameter (Units)	Estimate	ASE	%RSE	95% CI
CL (L/day)	0.0959	0.000954	1.0	(0.0940, 0.0978)
Vc (L)	2.99	0.0389	1.3	(2.91, 3.07)
Q (L/day)	0.186	0.00950	5.1	(0.167, 0.205)
Vp (L)	1.04	0.0232	2.2	(0.995, 1.09)
Ka ($days^{-1}$)	0.341	0.00679	2.0	(0.328, 0.354)
Vmax (mg/L/day)	1.24 (FIXED)			
Km (mg/L)	2.33 (FIXED)			
F1	0.61 (FIXED)			
WT on CL (Ref: 70 kg)	0.751	0.0213	2.8	(0.710, 0.793)
WT on Vc (Ref: 70 kg)	1.25	0.0316	2.5	(1.18, 1.31)
F_{CL}	0.802	0.223	27.8	(0.365, 1.24)
β [d]	0.198			

Maturation half-life for CL (years)	1.13	0.321	28.4	(0.503, 1.76)
ALB_CL [REF: 45g/L]	-0.787	0.0806	10.2	(-0.945, -0.629)
EASI_CL [REF: 30]	0.149	0.0179	12.0	(0.114, 0.184)
ASIAN_CL [REF: White]	0.0824	0.0196	23.8	(0.0440, 0.121)
BLACK_CL [REF: White]	0.137	0.0271	19.7	(0.0841, 0.190)
ADA1_CL [REF: ADA=0]	0.330	0.0312	9.4	(0.269, 0.392)
ADA23_CL [REF: ADA=0]	1.59	0.136	8.5	(1.33, 1.86)
EASI_VC [REF: 30]	0.0862	0.0196	22.8	(0.0477, 0.125)
ASIAN_VC [REF: White]	0.0713	0.0219	30.7	(0.0285, 0.114)
BLACK_VC [REF: White]	-0.0897	0.0249	27.8	(-0.138, -0.0409)
AGE_VC [REF: 30 yr]	0.0956	0.0174	18.2	(0.0614, 0.130)
Residual Variability				
Proportional Error (%)	16.9 [a]			(16.7, 17.2) [a]
Additive Error (mg/L)	3.73			(3.60, 3.86)
IIV (CV%)				
ETA1 – CL [b]	32.5 [a]			(31.3, 33.6) [a]
ETA2 – Vc [c]	32.2 [a]			(30.8, 33.6) [a]
OFV	134932.7			

ASE = Asymptotic standard error; %RSE = Percent relative standard error; 95% CI = 95 Percent confidence interval; CL = Linear clearance; Vc = Volume of the central compartment; Ka = First-order absorption rate constant; Q = Inter-compartmental clearance; Vp = Volume of the peripheral compartment; WT = Weight; CV = Coefficient of variation; IIV = Inter-individual variability; OFV = Objective function value; F_{CL} = Parameter in the maturation function that defines the estimated fraction of adult CL that is present at birth (β); β = Derived parameter ($1-F_{CL}$); ALB = Baseline albumin; REF = Reference; EASI = Eczema Area and Severity Index score (0-72); ADA1 = ADA positive with low titer; ADA23 = ADA positive with moderate/high titer; ADA = Anti-drug antibody; Yr = Years

[a] Transformed estimate values are provided.

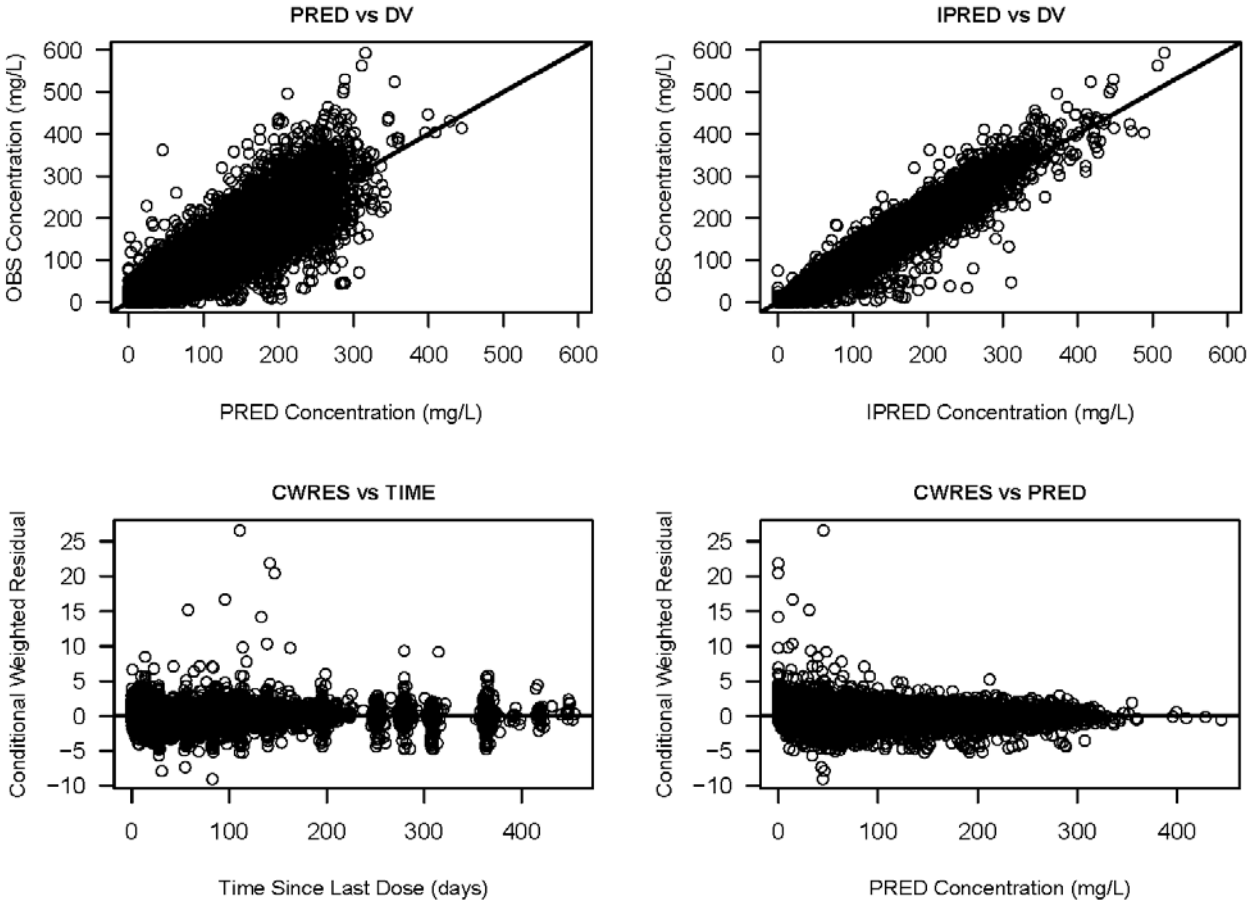
[b] Shrinkage for clearance is 12.5%

[c] Shrinkage for volume of the central compartment is 20.8%

[d] Derived parameter: estimated fraction of adult clearance present at birth is $\beta = [1 - F_{CL}] = 0.198$

Source: Applicant 's PopPK Report R668-PK-21194-SR-01V1, Table 15.

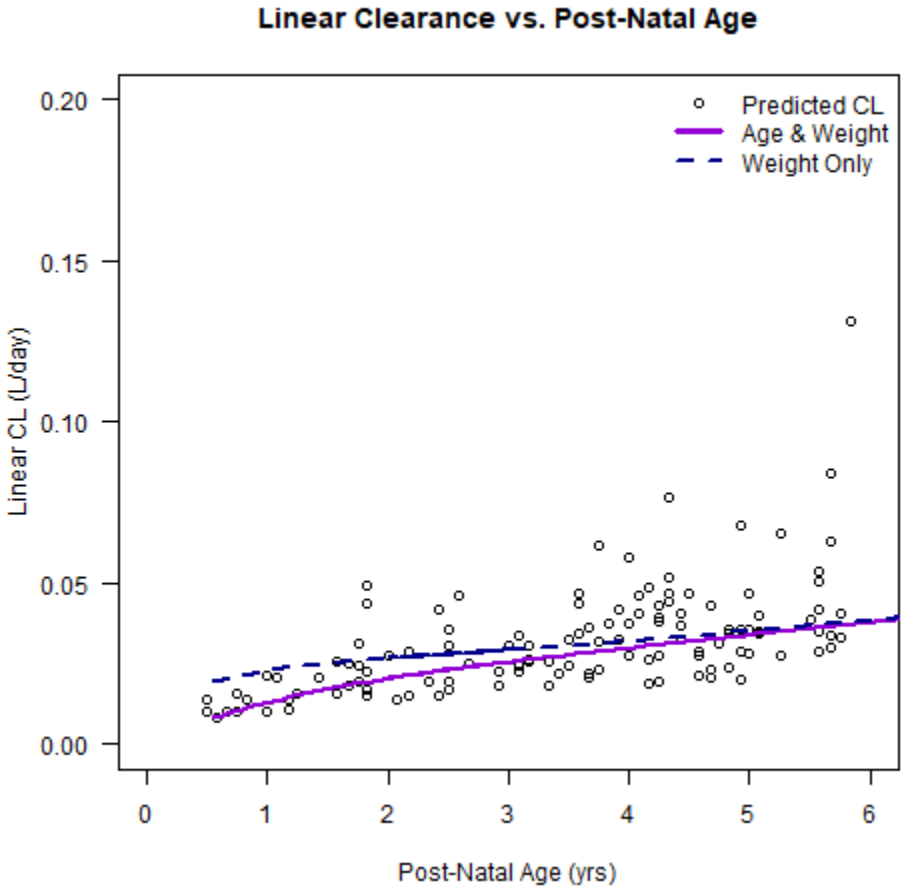
Figure 9. Goodness-of-fit Plots for the Final Model



Source: Adapted from Applicant 's PopPK Report R668-PK-21194-SR-01V1, Figure 6.

Reviewer's Comments: *The Applicant's population PK analyses is acceptable for describing dupilumab PK in pediatric subjects with AD aged 6 months to <6 years. Across the studied populations, body weight has been identified as a significant covariate on linear clearance and central distribution volume in the final integrated PopPK model. While age is not a factor influencing PK in subjects over the age of 6 years, pediatric subjects between the ages of ≥6 months to <6 years undergo a maturation process that impacts dupilumab clearance. Consequently, dupilumab clearance is influenced by both age and body weight in this subgroup of pediatric subjects and clearance matures with age and is estimated to reach final maturation by approximately 6 years (***Figure 10***). It should be noted that limited number of pediatric subjects <2 years of age was included in the PopPK analysis. In addition, the ability to predict exposure in pediatric subjects <2 years old might be limited due to maturation process as well as limited number of subjects evaluated for this sub-age group.*

Figure 10. Relationship of Linear Clearance with Age in Pediatric Subjects Predicted by Combined Effects of Body Weight and Age in the Population PK Model



Source: Applicant 's PopPK Report R668-PK-21194-SR-01V1, Figure 14.

Based on PopPK analysis and simulations, after the last steady-state dose of dupilumab, the predicted median time to a non-detectable concentration (0.078 mg/L) was 23 weeks and 32 weeks, respectively, for pediatric subjects with body weight ≥15 to <30 kg receiving dupilumab 300 mg Q4W and pediatric subjects with body weight ≥5 to <15 kg receiving dupilumab 200 mg Q4W (Table 37).

Table 37. Predicted Median Time to LLOQ Following Final Dose in Subjects with AD

Age Group	Weight Group	Dosing Regimen	Median Time to Washout (Weeks)
Adult			
≥18 years	-	300 mg QW | 600 mg LD	14
≥18 years	-	300 mg Q2W | 600 mg LD	11
Adolescent			
≥12 to <18 years	≥60 kg	300 mg Q2W | 600 mg LD	10
≥12 to <18 years	<60 kg	200 mg Q2W | 400 mg LD	11
Children			
≥6 to <12 years	[30-60) kg	200 mg Q2W | 400 mg LD - Day 1	14
≥6 to <12 years	[30-60) kg	300 mg Q4W | 300 mg Day 1/15	14
≥6 to <12 years	[15-30) kg	300 mg Q4W | 600 mg LD - Day 1	19
≥6 to <12 years	[15-30) kg	300 mg Q4W | 300 mg Day 1/15	19
≥6 months to <6 years	[15-30) kg	300 mg Q4W | No LD	23
≥6 months to <6 years	[5-15) kg	200 mg Q4W | No LD	32

LLOQ = Lower limit of quantification; AD = Atopic dermatitis; Q4W = Every 4 weeks; Q2W = Every 2 weeks; QW = Once weekly; LD = Loading dose
Note: Doses were simulated for a 16-week treatment period. Median time to washout was calculated from the last dose administration to the median concentration at LLOQ (0.078 mg/L) (eg, for Q4W dosing, the time to washout was calculated from week 12 to LLOQ).
Source: Applicant 's PopPK Report R668-PK-21194-SR-01V1, Table 20.

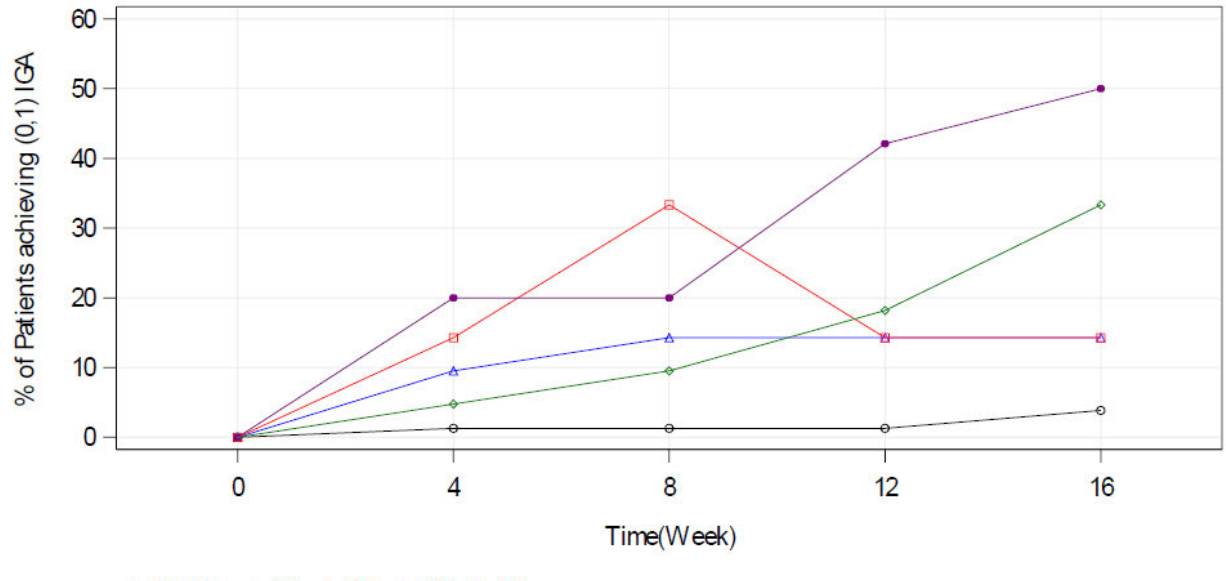
14.3.2. Exposure-Response Analyses

The Applicant conducted descriptive E-R analyses using observed through concentrations (Ctrough) of dupilumab in Part B of Study R668-AD-1539. The key efficacy endpoints were evaluated, with a focus on the two primary clinical efficacy endpoints of the proportion of subjects achieving an IGA score of 0 or 1 and EASI-75 at Week 16. The E-R analysis for safety was conducted for AESI only (broad and narrow term of conjunctivitis), since in previous studies of dupilumab in older subjects with AD, subjects receiving dupilumab had reported TEAEs of conjunctivitis at higher rates than subjects receiving placebo.

The E-R relationships for achieving an IGA score of 0 or 1 at Week 16 are shown in **Figure 3** (Panel A: logistic regression of probability of subjects achieving IGA of 0 or 1) and Figure 11 (percentage of subjects achieving IGA of 0 or 1) The E-R relationship for achieving ESAI-75 at Week 16 are shown in **Figure 3** (Panel B: logistic regression of probability of subjects achieving ESAI-75) and Figure 12 (percentage of subjects achieving ESAI-75). Overall, the E-R findings suggested increasing drug effects with increasing dupilumab trough concentration in serum. Of note, this trend is consistent with the E-R relationships observed in older pediatric subjects (6 to 17 years) and adults with AD.

The E-R analysis for AESI (broad and narrow term of conjunctivitis) did not identify a relationship between dupilumab Ctrough and AESI at Week 16 (Figure 13). However, this analysis might be limited due to overall low number of AESIs included.

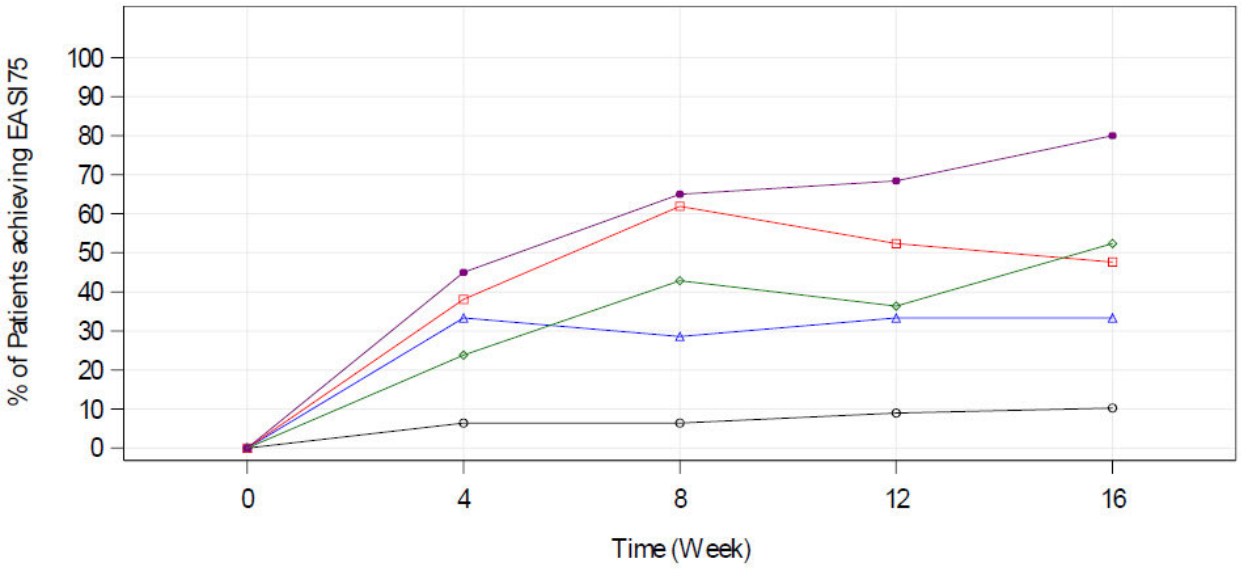
Figure 11. Percentage of Subjects Achieving (0,1) IGA Score by Nominal Time and Quartile of Dupilumab Concentrations in Subjects ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



Placebo	1% (1/78)	1% (1/78)	1% (1/78)	4% (3/78)
Q1	10% (2/21)	14% (3/21)	14% (3/21)	14% (3/21)
Q2	14% (3/21)	33% (7/21)	14% (3/21)	14% (3/21)
Q3	5% (1/21)	10% (2/21)	18% (4/22)	33% (7/21)
Q4	20% (4/20)	20% (4/20)	42% (8/19)	50% (10/20)

Source: Clinical Pharmacology Report R668-AD-1539-CP-02V1, Figure 4.

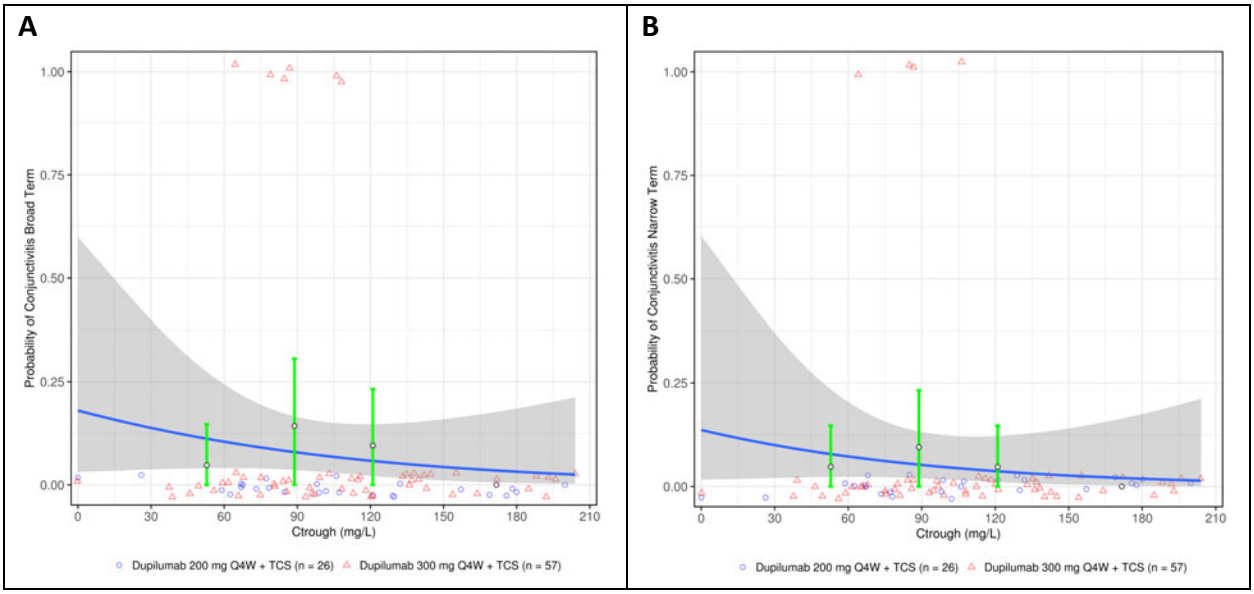
Figure 12. Percentage of Subjects Achieving EASI-75 by Nominal Time and Quartile of Dupilumab Concentrations in Subjects ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



Placebo	6% (5/78)	6% (5/78)	9% (7/78)	10% (8/78)
Q1	33% (7/21)	29% (6/21)	33% (7/21)	33% (7/21)
Q2	38% (8/21)	62% (13/21)	52% (11/21)	48% (10/21)
Q3	24% (5/21)	43% (9/21)	36% (8/22)	52% (11/21)
Q4	45% (9/20)	65% (13/20)	68% (13/19)	80% (16/20)

Source: Clinical Pharmacology Report R668-AD-1539-CP-02V1, Figure 9.

Figure 13. Logistic Regression Relating Probability of Subjects Developing Conjunctivitis (Broad Term in Panel A and Narrow Term in Panel B) with Concentrations of Dupilumab in Serum at Week 16 as a Predictor in Subjects ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



Source: Adapted from Clinical Pharmacology Report R668-AD-1539-CP-02V1, Figures 14 and 15.

14.3.3. Bioanalytical Method Report

The bioanalytical methods used for analyzing samples from pediatric subjects ≥6 months to <6 years of age with AD to determine dupilumab concentrations in serum are the same as those previously submitted and reviewed in the original marketing application for AD and bioanalytical methods to assess the immunogenicity are the same as those previously submitted and reviewed in the marketing application for asthma. Please refer to the clinical pharmacology review by Dr. Jie Wang during the original application (DARRTS date 12/19/2016) for the treatment of moderate to severe atopic dermatitis and supplement BLA S07 reviewed by Dr. Dipak Pisal (DARRTS date 10/19/2018) for the treatment of moderate to severe asthma.

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/

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LAURA L JOHNSON on behalf of MOHAMED A ALOSH
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Laura Lee Johnson signing on behalf of Mohamed Alosh.

SANGEETA J JAIN
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