NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	761055/S-012
Priority or Standard	Priority
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Division/Office	DDDP/ODE III
Review Completion Date	See DARRTS signature page
Established Name	DUPIXENT
Trade Name	Dupilumab
Pharmacologic Class	interleukin inhibitor
Code name	Not applicable
Applicant	Regeneron Pharmaceuticals, Inc.
Formulation(s)	Solution
Dosing Regimen	less than 60 kg: 400 mg then 200 mg every other week 60 kg or more: 600 mg then 300 mg every other week
Applicant Proposed Indication(s)/Population(s)	treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

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COA = Clinical Outcomes Assessment
DDS = Deputy Director for Safety
DMEPA = Division of Medication Error Prevention and Analysis
FOS = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
SRPM = Safety Regulatory Project Manager

Glossary

AKC	atopic keratoconjunctivitis
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
BLA	biologics license application
BSA	body surface area
CMQ	customized MedDRA query
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
E-R	exposure-response
IGA	Investigator's Global Assessment
IL	interleukin
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
OLE	open-label extension
PCSV	potentially clinically significant values
PK	pharmacokinetics
popPK	population pharmacokinetics
PPS	per protocol set
PY	patient years
QW	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
sBLA	supplemental biologics license application
SC	subcutaneous
SOC	system organ class
SS	steady-state
SU	safety update
TCS	topical corticosteroids
TCI	topical calcineurin inhibitors
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

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 (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, IL inhibitors.

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

- Treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- It can be used with or without topical corticosteroids (TCS).
- As an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Also see Section 3.1.

The supplemental biologics license application (sBLA) proposes expansion of the AD indication to allow for the "treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable." The proposed new indication would allow use of concomitant TCS, as is the case for adults. TCIs may also be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Table 1. Recommended Dosing of Dupilumab for Adolescent Patients (12 to 17 Years of Age)

Body Weight	Initial Dose	Subsequent Doses (every other week)
Less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the effectiveness of dupilumab in the treatment of moderate-to-severe AD in adolescent subjects, the Applicant submitted results from a single randomized,

multicenter, placebo-controlled phase 3 trial that evaluated two dosing frequencies: every 2 weeks (Q2W) and every 4 weeks (Q4W).

The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to-severe AD defined as having an Investigator's Global Assessment (IGA) score of at least 3 (moderate), Eczema Area and Severity Index (EASI) ≥12, and Body Surface Area (BSA) ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16.

Both dupilumab Q2W and Q4W dosing regimens were statistically superior to placebo (p-values <0.001) for the primary and secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen. The proportion of responders for the primary endpoint was 24% in the Q2W group and 18% in the Q4W group.

The Applicant provided substantial evidence of effectiveness of dupilumab for treatment of adolescent patients (12 to 17 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 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 is licensed for the following indications:

- treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without TCS.
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

The Applicant proposes expansion of the AD indication to allow for the “treatment of patients aged 12 years and older with moderate-to-severe AD 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 adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial that evaluated two dosing frequencies: every 2 weeks (Q2W) and every 4 weeks (Q4W). The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to- severe AD defined as having IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen.

The safety database was comprised of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD who had received at least one dose of dupilumab by data cut-point for the sBLA. No deaths occurred in the development program. The single subject who experienced a serious adverse event (SAE) in the primary safety group was in the placebo group (the event was appendicitis). Of the four subjects who experienced SAEs in the open-label extension (OLE) study, only one experienced an event (injection site cellulitis) where a relationship to treatment was reasonably possible. However, there was no information to implicate dupilumab itself in the occurrence of this event; it could have been related entirely to injection procedures. One subject experienced a treatment-emergent AE (TEAE) that led to permanent discontinuation of study treatment in the pivotal and OLE studies. That

subject was in the placebo group and was withdrawn due to worsening of AD. In the primary safety group, all severe TEAEs of AD occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the more frequent Q2W dosing regimen. Generally, the safety profiles between the Q4W and Q2W regimens were similar. The most-commonly reported TEAEs were upper respiratory tract infection and nasopharyngitis. 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 adult AD population. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The patterns of occurrence and course of conjunctivitis and keratitis events in dupilumab-treated adolescents were similar to what was seen in and labeled for adults with AD.

The Applicant comprehensively evaluated the safety of dupilumab in subjects 12 to17 years of age with moderate-to-severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

The medical officer concludes that the Applicant has established that the benefits of dupilumab for treatment of patients 12 to 17 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, outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. The hazard ratio for onset of AD in adolescence (12 to 17 years) has been reported as 2.04 (95% CI 1.66-2.49) compared to age of onset younger than 2 years. The prevalence of AD in individuals 13 to 17 years of age in the United States has been reported as 8.6%. • 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 adolescents, the presentation is similar to that in adults and is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, volar aspects of the wrists. 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 not only of the patient, but also of family members. The intense pruritus may disrupt sleep, which can have carryover effects of tiredness during the day. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Affected individuals may experience depression and other psychiatric associations, including impaired psychosocial functioning, social isolation, and social embarrassment. A longitudinal cohort study conducted in adolescents and adults with AD found that patients may be at increased risk for major depression, depressive disorders and anxiety disorders. Patients with AD have been found to have an increased risk of suicidal ideation and suicide attempts compared with individuals without AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• For the Applicant's target population, the only available FDA-approved systemic treatment is corticosteroids. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment. Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including adolescents. 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).	The medical need of adolescents with moderate-to-severe AD is not currently being adequately met by available therapies. Approval of dupilumab would represent an important addition to the treatment options for adolescents with moderate-to-severe AD that is not manageable by topical therapies. Approved or licensed treatment options are extremely limited for this population. In the medical officer's opinion, dupilumab would considerably advance the state of the treatment armamentarium for these patients. It would represent the first systemic product 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• To establish the effectiveness of dupilumab in the treatment of moderate-to-severe AD in adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial that evaluated two dosing every 2 weeks (Q2W) and every 4 weeks (Q4W). The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to-severe AD, defined as an IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen. The proportion of responders for the primary endpoint was 24% in the Q2W group and 18% in the Q4W group.	The medical officer concludes that the submitted evidence has met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that dupilumab is effective for treatment of the target AD population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The Applicant comprehensively evaluated the safety of dupilumab in subjects 12 to 17 years of age with moderate-to- severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD. The most-commonly reported TEAEs were upper respiratory tract infection and nasopharyngitis. Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The patterns of occurrence and course of conjunctivitis and keratitis events in dupilumab-treated adolescents were similar to what was seen in and labeled for adults with AD.	The size of the safety database and the scope of the safety analyses were sufficient to characterize the safety profile of dupilumab in the target population. The safety evaluation identified no new signals or concerns; the safety profile in adolescents was similar to that observed in adults with AD. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No serious safety concerns were identified that might require risk management beyond labeling and routine pharmacovigilance. No serious safety concerns were identified that warranted consideration of a Risk Evaluation and Mitigation Strategy. • AD occurs most commonly in children, and the safety and efficacy of dupilumab for treatment of AD in children have not been established. The Applicant has an Agreed Initial Pediatric Study Plan which covers cohorts down to 6 months of age. These required pediatric assessments are detailed in the approval letter for the original BLA submission. The study in adolescents is the first completed study of those required pediatric assessments. • Pediatric studies are waived for subjects younger than 6 months because study of these subjects would be impossible or highly impractical to conduct, since dupilumab is being developed for the treatment of moderate-to-severe AD in pediatric patients who are not adequately controlled with, or who are intolerant to TCS medications, and it would be impractical to make this determination in patients younger than 6 months of age.	Information from the ongoing OLE study, along with product labeling and routine pharmacovigilance activities should serve as adequate risk mitigation strategies.

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	Section 7.2.6
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.2.4
		□	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		[e.g., Sec 2.1 Analysis of Condition]
	□	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	[e.g., Current Treatment Options]
		□	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

Analysis of Condition

AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[1] The hazard ratio for onset of AD in adolescence (12 to 17 years) has been reported as 2.04 (95% CI 1.66-2.49) compared to age of onset younger than 2 years.[2] Shaw et al. reported the prevalence of AD in individuals 13 to 17 years of age in the United States to be 8.6%.[3] For 10 to 30% of individuals, AD persists into the adult years, and, for a smaller proportion of subjects, the disease initially presents in adulthood.[1] A population-based study found a prevalence of 3.2% for AD in adults in the United States.[4]

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 adolescents, the presentation is similar to that in adults and is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck and volar aspects of the wrists. AD may be generalized.

Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.[1,2] Comorbidities involving the eyes include atopic keratoconjunctivitis (AKC),[2] a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD.[5] Onset of AKC is typically in late adolescence or early adulthood.[5] Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep,[1] and the disruption in sleep could have carryover effects to disrupt school performance. Sleep disturbance in the AD patient may also disrupt the sleep of family members.[1] The

[1] Eichenfield LF et al., 2014, Guidelines of care for the management of atopic dermatitis Section 1. Diagnosis and assessment of atopic dermatitis, J Am Acad Dermatol, 70(2):338-51.
[2] Weston WL and W. Howe, 2019, 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 10, 2019).
[3] Shaw TE et al, 2011, Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health, J Invest Dermatol., 131:67–73.
[4] Silverberg JI and Hanifin JM, 2013, Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population–based study, J Allergy Clin Immunol, 132:1132-8.
[5] Hamrah P and Dana R. Atopic keratoconjunctivitis. Trobe J, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on February 11, 2019).

disease may also have impact on mood, and affected individuals may experience depression and also impaired psychosocial functioning, social isolation, and social embarrassment.[1,2,6] A longitudinal cohort study conducted in adolescents and adults with AD found that patients with AD may be at increased risk for major depression, depressive disorders, and anxiety disorders.[2] Patients with AD have been found to have an increased risk of suicidal ideation and suicide attempts compared with individuals without AD.[2]

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.[7]

The most common laboratory finding is an elevated IgE.[1] Approximately 80% of the AD population has elevated IgE and/or shows immediate skin test positivity to allergens. However, 20% of patients show no IgE to tested food or inhalant allergens. Some patients with severe AD have normal IgE levels. Additionally, increased allergen-specific IgE is found in 55% of the general population in the United States. Thus, this finding is nonspecific.[1]

The pathogenesis involves a complex interplay of genetic, immunological and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum, which permits the penetration of environmental allergens.[7] The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[7]

Acute AD is associated with cytokines produced by T helper 2-type cells (as well as other T-cell subsets and immune elements).[7] 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 T helper 2-type cells inflammation.[8] IL-4 has been shown to stimulate IgE production from B cells.[9] IL-13 expression correlates with disease severity and flares.[7] 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,

[6] Drucker AM et al, 2017, The burden of atopic dermatitis: summary of a report for the National Eczema Association, J Invest Dermatol, 137(1):26-30.
[7] Leung DYM, Guttman-Yassky E, 2014, Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches, J Allergy Clin Immunol, 134(4):769-79.
[8] Bao K and Reinhardt RL, 2015, The differential expression of IL-4 and IL-13 and its impact on type-2 Immunity, Cytokine, 75(1):25-37.
[9] May RD and Fung M, 2015, Strategies targeting the IL-4/IL-13 axes in disease, Cytokine, 75(1):89-116.

forming a signaling complex.[9] IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases.[9] Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4 receptor alpha (IL-4Rα) subunit.[10]

2.2. Analysis of Current Treatment Options

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

Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[11] 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.[11] Labels for systemic corticosteroids do not specify any limitations on the age of indication.

TCS represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[12] 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 AD 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.

[10] DUPIXENT package insert.
[11] Sidbury R et al, 2014, Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents, J Am Acad Dermatol, 71(2):327-49.
[12] Eichenfeld et al, Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment with topical therapies, J Am Acad Dermatol, 2014; 71(1):116-32.

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

Crisaborole ointment, 2%, a phosphodiesterase-4 inhibitor, is approved for treatment of AD in pediatric patients (2 years 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).

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including adolescents.[11] 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.[11] However, long-term risks from phototherapy treatment of AD in children have not been evaluated.[11]

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, and lotions.[12] Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease.[12] They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principle 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.[12] The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control disease.[12]

Systemic immunomodulating agents products that are used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.[11] The reported effectiveness for the products varies from “efficacious” (cyclosporine) to “inconsistent” (mycophenolate mofetil).[11] 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).

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

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dupilumab was licensed "for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable" on 03/28/2017.

On 12/20/2017, the Applicant submitted supplemental BLA (sBLA)-007 which proposed dupilumab as "an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, including those with or without an eosinophilic phenotype." That sBLA was approved by the Division of Pulmonary and Rheumatology Products on 10/19/2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant has an Agreed initial Pediatric Study Plan, with the letter of agreement dated 11/10/2015. The Agreed initial Pediatric Study Plan covers pediatric age cohorts down to 6 months.

Two of the studies that were conducted under the adolescent development program are required pediatric assessments as per the approval letter for the original BLA (approval date: 03/28/2017):

3183-2 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in subjects 12 years to less than 18 years of age with moderate to severe AD.

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 AD.

The open-label study is ongoing; the Applicant submitted analyses of data only pertaining to subjects ≥12 to <18 years in the sBLA.

The Applicant was granted Breakthrough Therapy designation of dupilumab for the treatment of moderate to severe AD in pediatric patients 12 to <18 years of age who are not adequately controlled with, or who are intolerant to topical medication on 10/14/2016.

See Section 9 of this review for additional information regarding the required pediatric assessments.

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

4.1. Office of Scientific Investigations

Study R668-AD-1526, entitled "A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis" was the pivotal study. It is considered a covered clinical study requiring financial disclosure as per 21 Code of Federal Regulations 54.2(e).

Two sites were selected for inspection. The sites were chosen primarily based on the number of enrolled subjects, positive treatment effects, reported financial disclosures, and no prior inspectional history.

David Cohen, MD, Macon, GA; Site 840033

Dr. Cohen was paid $97,849 as part of the Applicant's speaker programs. His site screened 12 subjects and enrolled 10. Inspectors found no evidence of under-reporting of adverse events (AEs). Inspectors compared all primary and secondary efficacy data points against the data listings provided by the Applicant and noted no discrepancies. The final classification of the inspection for Dr. Cohen's site was No Action Indicated.

Benjamin Lockshin, MD, Rockville, MD; Site 840016

Dr. Lockshin was paid $144,584 for "consulting services," not otherwise specified. His site screened and enrolled 16 subjects. However, one subject chose not to continue in the study and withdrew consent. The inspector found no evidence of under-reporting of AEs. The inspector compared all primary and key secondary efficacy data points against the data listings provided by the Applicant and noted no discrepancies for the primary endpoint.

However, following Office of Scientific Investigations review of the Establishment Inspection Report, the inspection was classified as voluntary action indicated for inadequate and/or inaccurate records. The voluntary action indicated classification specifically related to inspection for the key secondary endpoints (EASI raw data scores). The data discrepancies were due to transcription errors that site personnel made when entering values from the original paper source document into the electronic data capture system for three subjects. Dr. Lockshin was not issued a Form 483 (Inspectional Observations).

The medical officer concludes that the inspection findings from Dr. Lockshin's site do not affect overall subject safety or efficacy considerations.

4.2. Product Quality

In this submission, the Applicant provided no new product quality information. Therefore, section 4.2 is not applicable.

4.3. Clinical Microbiology

Section 4.3 is not applicable to this submission.

4.4. Devices and Companion Diagnostic Issues

Section 4.4 is not applicable to this submission.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In this submission, the Applicant provided no new nonclinical information. Therefore, sections 5.2, 5.3, 5.4, and 5.5 are not applicable to this review.

5.2. Referenced NDAs, BLAs, DMFs

5.3. Pharmacology

5.4. ADME/PK

5.5. Toxicology

6 Clinical Pharmacology

6.1. Executive Summary

Dupilumab (DUPIXENT) is a human immunoglobulin-G4 monoclonal antibody that inhibits IL-4 and IL-13 signaling by binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab was approved on March 28, 2017 for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without TCS. Dupilumab is administered by subcutaneous (SC) injection. The approved recommended dosing regimen is an initial dose of 600 mg, followed by 300 mg given every other week (Q2W).

In this sBLA, the Applicant has proposed to extend the currently approved age range for the AD indication to include adolescent patients ≥12 to <18 years of age. The Applicant has proposed body weight-tiered dosing regimens in adolescent AD patients:

- For adolescent AD patients weighing <60 kg: an initial dose of 400 mg (two 200 mg injections), following by 200 mg Q2W
- For adolescent patients weighing ≥60 kg: an initial dose of 600 mg (two 300 mg injections), following by 300 mg Q2W

The Applicant has submitted efficacy, safety, and pharmacokinetics (PK) data from phase 3 trial R668-AD-1526 to support the proposed indication and dosing regimens in adolescent AD patients. PK results from phase 1, phase 2, and OLE phase 3 trials (i.e., R668-AD-1607, R668-AD-1412, and R668-AD-1434, respectively) were also provided to support clinical pharmacology information of the sBLA.

6.1.1. Recommendation

From a Clinical Pharmacology standpoint, this sBLA is acceptable to support the approval of DUPIXENT (dupilumab) for the treatment of moderate-to-severe AD in adolescent patients.

6.1.2. Postmarketing Requirement and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics

In adolescents ≥12 to <18 years of age with AD who received Q2W dosing with either 200 mg (<60 kg) or 300 mg (≥60 kg) in phase 3 trial R668-AD-1526, the mean ± SD steady-state (SS) trough concentration of dupilumab was 54.5±27.0 mcg/mL.

Immunogenicity

In adolescents ≥12 to <18 years of age with AD who received Q2W dosing with either 200 mg (<60 kg) or 300 mg (≥60 kg) in phase 3 trial R668-AD-1526, the incidence for treatment emergent anti-drug antibodies (ADA) was 16% (13/81). Among the 13 ADA positive subjects, two subjects had persistent ADA. The incidence for neutralizing ADAs was 4.9%. The number of subjects was too small to draw a definitive conclusion on the clinical impact of immunogenicity, although there was no evidence of a clear correlation between ADA formation and PK or efficacy.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The efficacy and PK results in phase 3 trial R668-AD-1526 overall support the acceptability of the proposed body weight-tiered dosing regimens (200 mg/300 mg Q2W) in adolescent AD patients: for patients weighing <60 kg, an initial dose of 400 mg followed by 200 mg Q2W; for patients weighing ≥60 kg, an initial dose of 600 mg followed by 300 mg Q2W.

6.2.2.2. Therapeutic Individualization

Therapeutic individualization based on intrinsic and extrinsic factors is not necessary. Body weight has been identified a significant covariate on dupilumab PK; dupilumab

concentrations were lower in subjects with higher body weight at a given dose. At the proposed body weight-tiered dosing regimens, dupilumab concentrations were similar between subjects (<60 kg) receiving 200 mg Q2W and subjects (≥60 kg) receiving 300 mg Q2W.

6.2.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of dupilumab for the treatment of AD in adolescent subjects from a Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

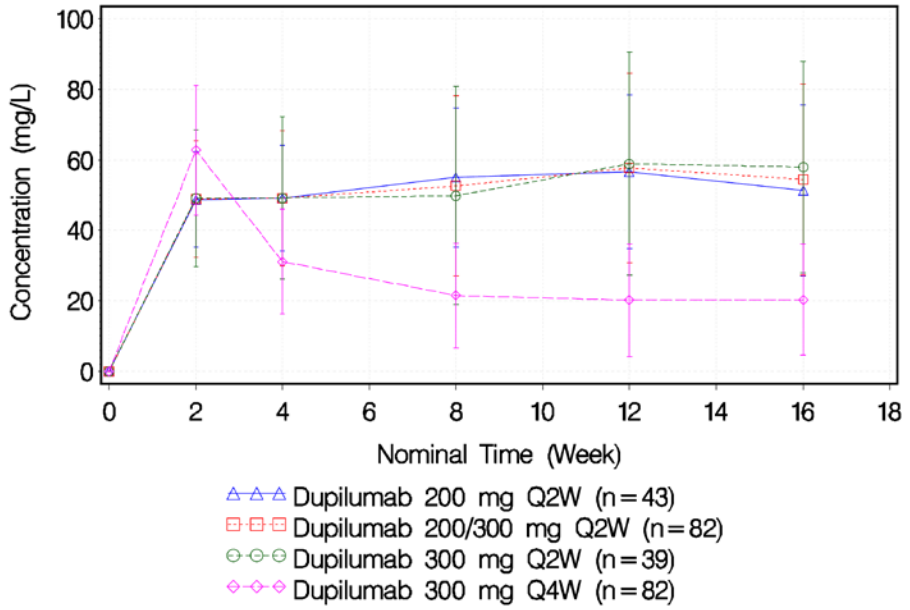
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics

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

The serum concentrations observed in study R668-AD-1526 are shown in Figure 1. The PK results showed that the SS concentrations were achieved by week 12 across the tested dosing regimens. At week 16, the mean ± SD trough concentrations of dupilumab were 54.5±27.0 mcg/mL and 19.8±15.9 mcg/mL for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively.

Figure 1. Mean ± SD Trough Serum Dupilumab Concentrations in Trial R668-AD-1526



PK samples for assessment of serum dupilumab concentrations were collected on days 1, 15, 29, 57, 85 and 197 in study R668-AD-1526. Serum dupilumab concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA). The ELISA assay has a lower limit of quantitation (LLOQ) of 0.078 mcg/mL. See Clinical Pharmacology review for the original BLA 761055 for more details regarding the performance of the PK assay.
Source: Figure 1, Summary of Clinical Pharmacology Studies

Immunogenicity

The immunogenicity incidences in phase 3 trial R668-AD-1526 are summarized in Table 2. The incidences for treatment emergent ADA were 16% (13/81) and 20.7% (17/82) for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively. The incidences for neutralizing ADAs were 4.9% and 4.9% for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively.

Table 2. Immunogenicity Incidences for Anti-Drug Antibodies (ADA) in Phase 3 Trial R668-AD-1526

		Dupilumab			
	Placebo	300 mg Q4W	200 mg/300 mg Q2W	200 mg Q2W	300 mg Q2W
Number of evaluable subjects (N)	85	82	81	42	39
Treatment-emergent ADA n (%)	3 (3.5%)	17 (20.7%)	13 (16.0%)	5 (11.9%)	8 (20.5%)
Persistent ADA n (%)	1 (1.2%)	2 (2.4%)	2 (2.5%)	1 (2.4%)	1 (2.6%)

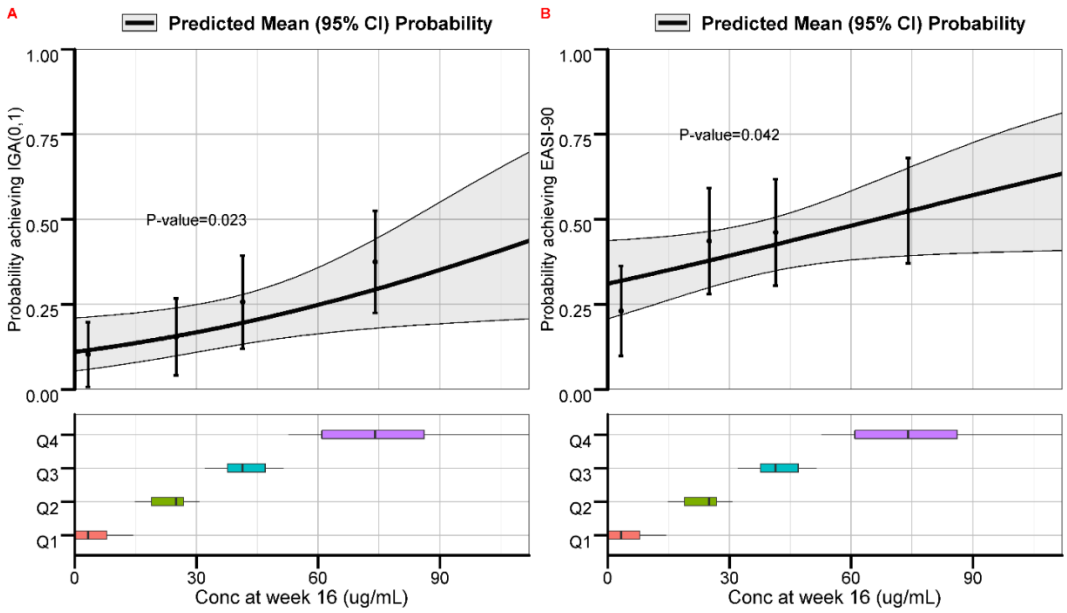
Immunogenicity samples were collected on days 1, 29, 113, and 197. Treatment emergent-ADA was defined as a negative or missing result at baseline with at least one positive postbaseline result in the ADA assay. Persistent ADA was defined as a positive result in the ADA assay detected in at least two consecutive postbaseline samples separated by at least 12-week post baseline period, with no ADA-negative results in-between, regardless of any missing sample.
Source: Table 5, Summary of Clinical of Pharmacology Studies.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

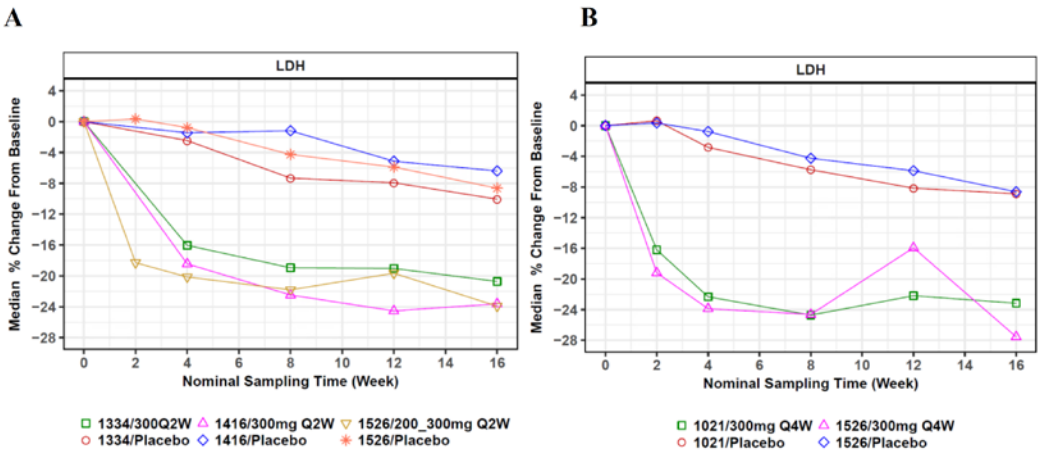
Yes, the overall efficacy data from the phase 3 trial R668-AD-1526 provide evidence that dupilumab is effective for the treatment of adolescent AD patients. See Section 7 of this multi-discipline review for details of the study design and efficacy results of the phase 3 trial. The exposure-response (E-R) relationships for efficacy provide supportive evidence of effectiveness (Figure 2). The E-R relationship revealed increasing drug effects with increasing dupilumab trough concentration in serum. The pharmacodynamic data on lactate dehydrogenase (LDH) reduction also provide supportive evidence of effectiveness (Figure 3).

Figure 2. Logistic Regression Relating Probability of Patients Achieving an (0,1) IGA Score (Panel A) or EASI-75 (Panel B) With Dupilumab Trough Concentrations at Week 16 in Adolescent Patients With Moderate-to-Severe



Among 157 adolescent patients included in the E-R analysis, the percentage of patients achieving an IGA score of 0 or 1 or a 75% reduction in EASI score was higher in quartiles of higher dupilumab concentrations. The logistic regression analysis also identified dupilumab concentration at week 16 and disease severity (baseline EASI total score) as significant covariates on both IGA (0,1) and EASI-75.
Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Reviewer's Analysis to confirm Figure 11 and Figure 12 in Applicant's Summary of Clinical Pharmacology Studies

Figure 3. Median Percentage Change From Baseline in Lactate Dehydrogenase Following Dupilumab Treatment in Adolescent and Adult Subjects With AD



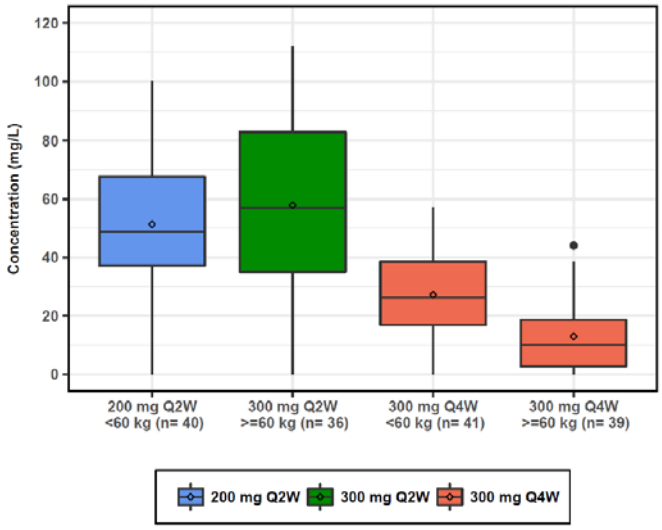
Panel A: Q2W versus placebo; Panel B, Q4W versus placebo across studies R668-AD-1021 (adults), 1334 (adults), 1416 (adults) and 1526 (adolescents). See Clinical Pharmacology review for original BLA 761055 for additional information regarding pharmacodynamic effect of dupilumab in adult AD patients.
Source: Figure 8, Applicant's Summary of Clinical Pharmacology Studies

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

Yes, the efficacy and safety data from phase 3 trial R668-AD-1526 overall support that the proposed body weight-tiered dosing regimens are appropriate for the general adolescent AD patient population. See Section 7 of this multi-discipline review for details of the study design and efficacy/safety results of the phase 3 trial. The PK and E-R relationship analysis results further supported the proposed body weight-tiered 200 mg/300 mg Q2W regimens.

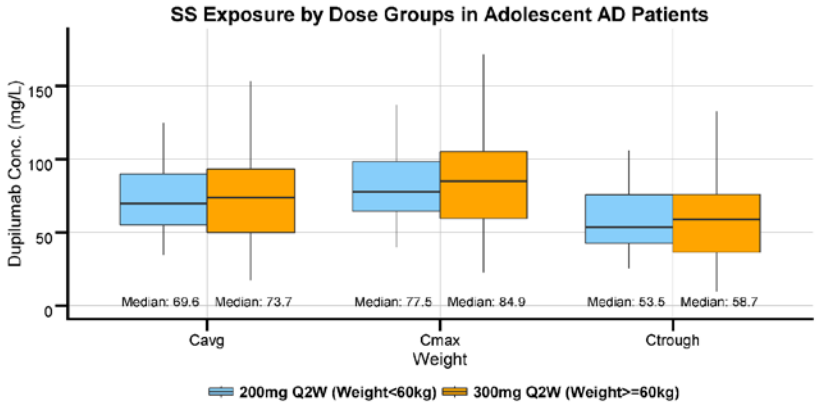
- In the phase 3 trial R668-AD-1526, adolescents <60 kg receiving 200 mg Q2W regimen and adolescents ≥60 kg receiving 300 mg Q2W regimen achieved similar dupilumab concentrations at week 16 (Figure 4). Population PK analysis results also suggest that the weight-tiered 200 mg/300 mg Q2W regimens provide similar SS exposures for average, peak and trough dupilumab concentrations between the two body weight groups (Figure 5).
- Dupilumab concentrations in adolescent AD patients receiving the 200 mg/300 mg Q2W dosing regimens were similar to the concentrations in adult AD patients receiving the approved 300 mg Q2W dosing regimen (Figure 6).
- A positive E-R relationship for efficacy was observed in adolescent AD patients treated with dupilumab (Figure 2).
- The most commonly reported AE observed in the adolescent pivotal study R668-AD-1526 was conjunctivitis. The percentage of patients developing conjunctivitis appears to be similar with increasing rank order of quartiles of dupilumab trough concentrations, indicating a lack of E-R relationship for conjunctivitis (Figure 7).

Figure 4. Concentrations of Dupilumab (mg/L) at Week 16 vs. Body Weight (kg) by Dose Group in Adolescent Patients With Moderate-to-Severe AD (R668-AD-1526)



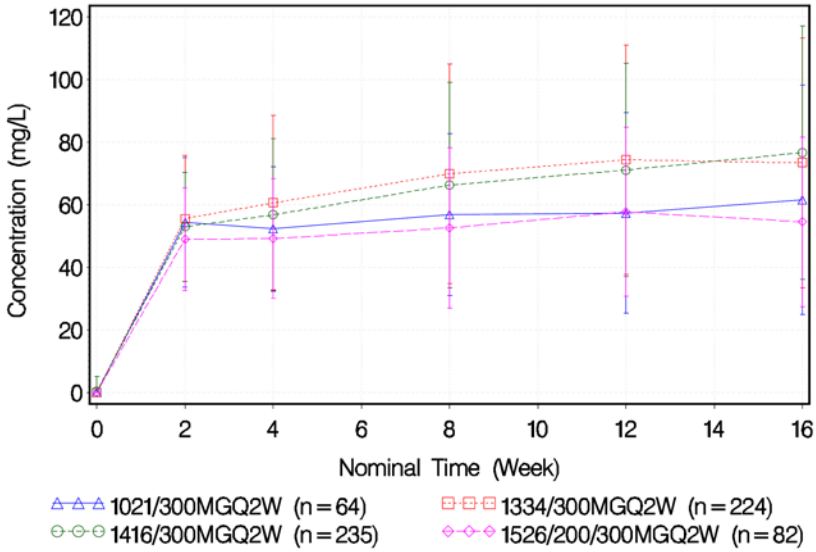
Source: Figure 7 in Applicant's Summary of Clinical Pharmacology Studies

Figure 5. Boxplot of Predicted Dupilumab Exposures at Steady-State (at 26th Dose)



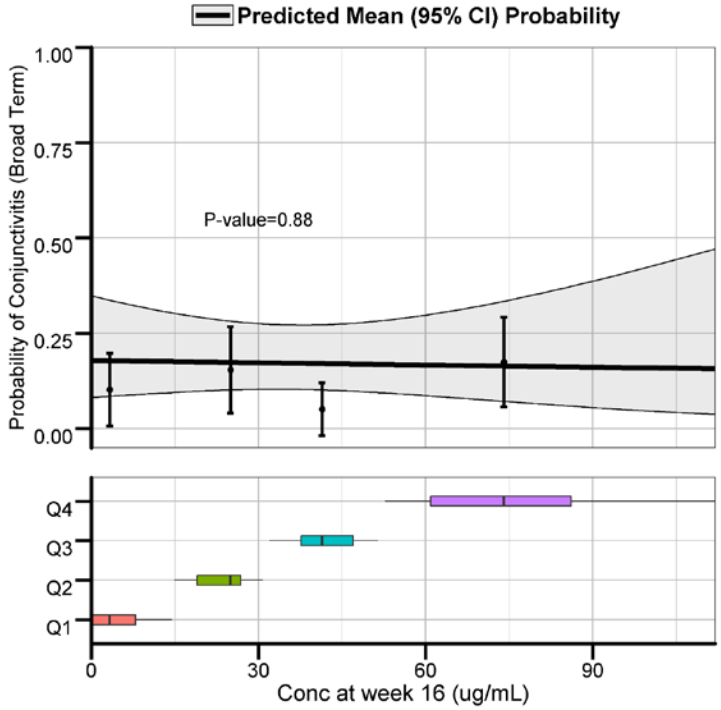
Dupilumab concentrations were predicted based on the post hoc PK parameters from 162 adolescent AD patients.
Source: Reviewer's Analysis based on Applicant's final adolescent PK model

Figure 6. Cross-Study Comparison of Mean ± SD Serum Dupilumab Concentrations in Adolescent and Adult AD patients



Adolescent AD patients received the 200 mg/300 mg Q2W dosing regimens. Adult AD patients received 300 mg Q2W dosing regimens.
Source: Figure 3, Summary of Clinical Pharmacology Studies

Figure 7. Logistic Regression Relating Probability of Developing Conjunctivitis (Broad Term) With Dupilumab Trough Concentrations at Week 16 in Adolescent Patients With Moderate-to-Severe AD



Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Reviewer's Analysis to confirm Figure 13 in Applicant's Summary of Clinical Pharmacology Studies

6.3.2.3. 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 identified body weight as a significant covariate on dupilumab PK; however, because the recommended body weight-tiered 200 mg/300 mg Q2W dosing regimens achieved similar exposure in adolescent AD patients across the two body weight groups, a further dose adjustment based on weight is not needed.

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

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

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 3. Listing of Clinical Trials Relevant to This sBLA

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1412	Open-label, ascending dose, sequential cohort	-For dose cohort 1: 2 mg/kg at day 1 as single dose in Part A, then weekly at day 1 to week 3 in Part B as repeat doses -For dose cohort 2: 4 mg/kg at day 1 as a single dose in Part A, then weekly at day 1 to week 3 in Part B as repeat doses	**Primary Objective:** To characterize the PK profiles of dupilumab in pediatric AD patients aged ≥6 to <18 years. **Secondary Endpoints:** -Incidence of treatment emergent adverse events (TEAEs) -Percent change from baseline in Eczema Area and Severity Index (EASI) -Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) score -Percent change from baseline in Pruritus Numerical Rating Scale (NRS) -Percentage of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 -Change from baseline in % body surface area (BSA) affected by AD	The study included Part A (including a single-dose treatment followed by an 8-week semi-dense PK sampling period), and Part B (including a 4-week repeat dose treatment period [4 weekly doses] followed by an 8-week follow-up period)	78	Pediatric subjects with moderate-to-severe AD (for adolescents aged ≥12 to <18 years at the time of baseline) or severe AD (for children aged ≥6 to <12 years at the time of baseline) that was not adequately controlled with topical medications

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1526	Randomized, double-blind, placebo controlled	-Dupilumab every 2 weeks (Q2W) treatment group: 200 mg Q2W (patients <60 kg), following an initial or 300 mg Q2W (patients ≥60 kg), following an initial loading dose of 600 mg -Dupilumab every 4 weeks (Q4W) treatment group: 300 mg Q4W, irrespective of weight, following an initial 600 mg loading dose -Placebo group	**Primary Endpoint:** -The proportion of subjects with IGA 0 or 1 at week 16 was the primary endpoint for the U.S. **Key Secondary Endpoints:** -Proportion of subjects with EASI-75 (≥75% improvement from baseline) at week 16 (this was a co-primary endpoint ex-U.S.) -Percent change in EASI score from baseline to week 16 -Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS -Proportion of subjects with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline to week 16 - Proportion of subjects with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16	16 weeks treatment/12 weeks follow-up	251	Pediatric subjects (aged ≥12 to <18 years at the time of baseline) with moderate-to-severe AD that could not be adequately controlled with topical AD medications or for whom topical treatment was medically inadvisable

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1434	Open label extension study	Based on protocol amendment 1, all subjects at the time of enrollment started on a dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at week 16 as follows: -Subjects weighing ≥60 kg: 300 mg Q2W -Subjects weighing <60 kg: 200 mg Q2W Note: Prior to amendment 1, subjects from study R668-AD-1412 received weight-based dosing regimens of 2 mg/kg or 4 mg/kg.	**Primary Endpoint:** -The incidence and rate of treatment-emergent adverse events (TEAEs) from baseline through the last study visit. **Secondary Endpoints:** -Incidence of treatment-emergent serious adverse events (SAEs) from baseline through the last study visit -Incidence of TEAEs of special interest from baseline through the last study visit -Proportion of subjects with an IGA score of 0 or 1 (clear or almost clear) at all in clinic visits postbaseline -Proportion of subjects with Eczema Area and Severity Index (EASI)-75 (≥75% reduction in EASI from baseline of parent study) response at all in-clinic visits postbaseline -Change and percent change from baseline in EASI at all in-clinic visits postbaseline -Change from baseline in body surface area (BSA) affected by AD at all in-clinic visits postbaseline -Percent change from baseline in SCORAD at all in-clinic visits postbaseline -Change from baseline in Children's Dermatology Life Quality Index (CDLQI) for patients ≥4 years of age at all in-clinic visits postbaseline in which the assessments are planned to be performed	The study will be conducted until regulatory approval of the product for the age group of the subject in his/her geographic region, and a 12-week follow-up period.	275	pediatric subjects with AD, aged ≥6 months to <18 years at the time of screening

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1607 Part A	Open-label, randomized, actual use autoinjector (AI) study	200 mg Q2W, after a loading dose of 400 mg	**Primary Endpoint:** -The number and type of validated AI device associated product technical failures (PTFs) during the treatment period divided by total number of actual injections. **Secondary Endpoints:** -Number and percentage of patients with an AI device-associated PTF -Number and type of AI device associated PTCs divided by total number of actual injections -Number and percentage of patients with an AI device-associated PTC -Number and type of AI device associated failed drug deliveries (defined as patient failure to administer the full dose at a given attempt, excluding PTF) divided by total number of actual injections -Number and percentage of patients with an AI device-associated failure to deliver dose -Number and percentage of patients with response to patient satisfaction questions with the AI device	12 weeks treatment/12 weeks follow up	85 (67 adults, and 18 adolescents)	Subjects with moderate-to-severe AD ≥12 years of age

7.1.2. 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 protocols, statistical analysis plans, clinical study reports, SAS transport datasets in Study Data Tabulation Modal, and Analysis Data Model format were in the following network path:

Original submission: \\cdsesub1\evsprod\bla761055\0300\m5\datasets\r668-ad-1526

Data and Analysis Quality

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

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The Applicant conducted a single phase 3 trial (R668-AD-1526) to support the application.

The key inclusion criteria that defined the study population were similar to those of the adult trials. The inclusion criteria included:

- Male or female subjects 12 to <18 years of age with moderate to severe AD that could not be adequately controlled with topical AD medications or for whom topical treatment was medically inadvisable (e.g., intolerance, other important side effects or safety risks). Moderate to severe AD was defined as the following:
  - IGA score ≥3 at screening and baseline
  - EASI ≥16
  - Baseline Pruritus Numeric Rating Scale (NRS) average score for maximum itch intensity ≥4
  - BSA of AD involvement ≥10%

The Sponsor's IGA scale is shown below.

Table 4. Investigator's Global Assessment Disease Severity Scale and Definitions

IGA: Disease Severity Scale and Definitions of the scoring:

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)

The EASI is shown below.

Table 5. Eczema Area and Severity Index

The definitions of the scoring signs of EASI are given below:

Erythema	**(E)**
0 – None	
1 – Mild	Faintly detectable erythema: very light pink
2 – Moderate	Dull red, clearly distinguishable
3 – Severe	Deep / dark red
Infiltration / Papulation	**(I)**
0 – None	
1 – Mild	Barely perceptible elevation
2 – Moderate	Clearly perceptible elevation but not extensive
3 – Severe	Marked and extensive elevation
Excoriations	**(Ex)**
0 – None	
1 – Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2 – Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3 – Severe	Many erosive or crusty lesions
Lichenification	**(L)**
0 – None	
1 – Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2 – Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3 – Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Scoring

Line	Area	Erythema	Infiltration	Excoriations	Lichenification	Area of Involvement	Multiplier	Score
1	Head/Neck	(_____ +	_____ +	_____ +	_____)	X _____	X 0.1	
2	Trunk	(_____ +	_____ +	_____ +	_____)	X _____	X 0.3	
3	Upper Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.2	
4	Lower Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.4	

The protocol specified the following exclusion criteria:

- Subjects treated with a systemic investigational drug before the baseline visit
- Subjects treated with a topical investigational agent within 4 weeks or within 5 half-lives, whichever was longer, before the baseline visit
- Subjects treated with TCS or TCIs within 2 weeks before the baseline visit
- Subjects that used any of the following treatments within 4 weeks before the baseline visit (immunosuppressive/immunomodulating drugs, phototherapy for AD)
- Body weight <30 kg at baseline

Using the Interactive Voice Response System/Interactive Web Response System, a total of 251 subjects were randomized to one of the following groups in a 1:1:1 ratio:

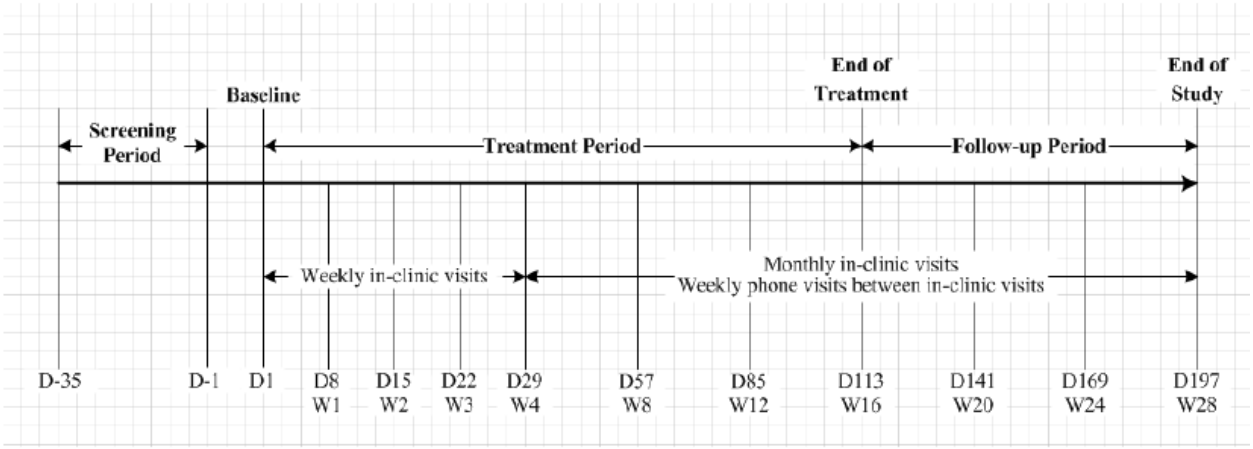
- Dupilumab every 2 weeks (Q2W) group:
  - 200 mg Q2W for subjects <60 kg (loading dose of 400 mg) or
  - 300 mg Q2W for subjects ≥60 kg (loading dose of 600 mg)
- Dupilumab every 4 weeks (Q4W) group:
  - 300 mg Q4W (loading dose of 600 mg), irrespective of weight
- Placebo
  - Subjects <60 kg will receive placebo matching 200 mg dupilumab
  - Subjects ≥60 kg will receive placebo matching 300 mg dupilumab

Note that in the phase 3 trials for the adult subjects with moderate to severe AD, dupilumab 300 mg QW and Q2W were evaluated against placebo, and based on a benefit-risk assessment, dupilumab 300 mg Q2W was approved for the indication.

The protocol specified that randomization would be stratified by baseline weight group (<60 kg and ≥60 kg) and baseline disease severity (moderate [IGA=3] versus severe [IGA=4] on the IGA).

Visits occurred weekly for the first 4 weeks, and then every 4 weeks thereafter until week 16. Follow-up visits occurred on weeks 20, 24 and 28. The following diagram is the Sponsor's study flow diagram:

Figure 8. Study Flow Diagram



D = study day; W = study week

Source: Sponsor's protocol (page 39)

Study drug was provided in prefilled glass syringes for subcutaneous administration, and the injection sites of the study drug were alternated among the different quadrants of the abdomen, upper thighs, and upper arms so that the same site was not injected for 2 consecutive weeks. In order to maintain blinding, subjects received an injection Q2W from day 1 to week 14, and placebo injections were given at the weeks dupilumab was not given. The study staff administered the first of the two injections required for the loading dose, and the subject or the caregiver administered the second injection required for the loading dose under the supervision of the clinic staff. For weeks 2 and 4, study drug was administered under the supervision of the clinic staff in-clinic, and during the weeks in which no in-clinic visit was scheduled, subjects/caregivers had the option to administer study drug outside the study site or visit the clinic to be administered by a study staff.

All enrolled subjects were required to apply moisturizers twice daily for at least 7 days before randomization and continued throughout the study. The protocol specified that to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit.

Rescue treatments, if medically necessary to control intolerable AD symptoms, were provided to subjects at the discretion of the investigator. The protocol specified that investigators were encouraged to consider rescue with topical treatment (e.g., medium/high potency TCS), and escalate to systemic medications only for subjects who did not respond adequately after at least 7 days of topical treatment. The protocol specified that TCIs were permitted for use for rescue, alone or in combination with TCS, but the use of TCIs was reserved for problem areas only. Note that the protocol specified that if rescue treatment was used, the subject was specified as a nonresponder from the time the rescue treatment was used.

As in the adult pivotal trials, the protocol-specified the primary endpoint was the proportion of subjects with IGA 0 or 1 at week 16.

The protocol-specified testing the primary and the secondary endpoints in the order shown in Table 6. Previously, in an advice letter dated 4/14/2016, the Agency stated that while EASI 75 endpoint can be considered to be clinically meaningful, a mere percent change in the EASI score might not translate to a clinically meaningful difference. Similarly, the Agency stated that a mere percent change in peak pruritus NRS might not translate to a clinically meaningful difference. In response, the Sponsor stated (SDN 826; stamp date: 5/10/2017) that "the evaluation of these endpoints is of scientific interest and may be object of publications. In addition, results of this study will support regulatory submission worldwide, and different regulatory requirements may apply in different geographical regions." Note that all endpoints in the table below except for the EASI 50, the percent change in weekly average of daily peak pruritus NRS, and the percent change in EASI score were also assessed in the adult pivotal trials and were included in the approved labeling of dupilumab 300 mg Q2W.

Table 6. Testing Hierarchy of Endpoints

	Week 16	**Dupilumab Q2W vs. Placebo**	**Dupilumab Q4W vs. Placebo**
Primary	IGA 0 or 1	1	9
Secondary	EASI 75	2	10
	Percent change in EASI score[(1)]	3	11
	Percent change in weekly average of daily peak pruritus NRS[(2)]	4	12
	Peak pruritus NRS ≥3[(3)]	5	13
	Peak pruritus NRS ≥4[(4)]	6	14
	EASI 50	7	15
	EASI 90	8	16

Source: Reviewer Table; (1), (2) The Sponsor stated that the endpoint is of scientific interest and may be object of publications. (3) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥3 from baseline to week 16; (4) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16

7.2.2. Statistical Methodologies

The primary efficacy analysis set was the full analysis set defined as all randomized subjects. The protocol specified that the per protocol set (PPS) included all subjects in the full analysis set except for those that are excluded because of major efficacy-related protocol violations. The criteria of major efficacy-related protocol deviation were the following:

- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
- Patients who received <80% of the scheduled doses during the study treatment period

For the PPS in this trial, the Sponsor excluded 11 subjects (4%), eight of whom had inadequate compliance to study drug, and three of whom violated the entry criteria.

For the analysis of the primary and the binary secondary endpoints, the protocol specified using the Cochran Mantel Haenszel test stratified by baseline disease severity (IGA 3 or 4) and baseline weight group (≤60 kg versus >60 kg). The protocol specified testing the endpoints in the hierarchical order listed in Table 6 to control the Type I error rate (two-sided, α=0.05). For the analysis of the continuous secondary endpoints, the protocol specified using analysis of covariance (ANCOVA) with baseline measurement as covariate and the treatment, baseline disease severity (IGA 3 or 4) and baseline weight group (≤60 kg versus >60 kg) as fixed factors.

For handling of missing data, the protocol specified that subjects that used rescue medication or that withdrew from the study would be considered as a nonresponder. As sensitivity analyses for handling missing data for the primary and binary secondary endpoints, the protocol specified using the last observation carried forward and using the observed data only. For continuous secondary endpoints, the protocol specified using the multiple imputation with ANCOVA as the primary imputation method, and as sensitivity analyses, the Sponsor proposed ANCOVA model with last observation carried forward, and ANCOVA model with all observed data regardless of rescue use.

7.2.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

The study randomized a total of 251 subjects. Approximately 92% of the subjects completed the study treatment at week 16, and the proportion of subjects that did not complete the study treatment was highest in the placebo group (i.e., nine out of 20 subjects that did not complete the study received placebo). The Applicant reported that six of the nine placebo subjects that did not complete 16 weeks of treatment were due to lack of efficacy. Given that the rate of missing data is low (8%) and that nine of the 20 discontinued subjects were either due to lack of efficacy or due to AEs, the impact of the imputation method on efficacy would be minimal.

Table 7. Subject Disposition

	Dupilumab		**Placebo**
	Q2W (1) N=82	Q4W N=84	N=85
Completed week 16	76 (93%)	79 (94%)	76 (89%)
Adverse events	2	0	1
Lack of efficacy	0	0	6
Protocol deviation	0	2	0
Other	4	3	2

Source: Reviewer Table (1) 200 mg for subjects <60 kg, 300 mg for subjects ≥60 kg

Table 8 presents the baseline demographics for this study. The baseline demographics were generally balanced across the treatment arms. Approximately 59% of the subjects were male, and 63% were white. The average age of the randomized subjects was about 14.5 years and the average weight at baseline was about 65 kg. According to the Applicant, 43% of the subjects were classified as being overweight (Body Mass Index ≥85% for age and gender).

Table 8. Baseline Demographics

	Dupilumab		**Placebo**
	Q2W[(1)] N=82	Q4W N=84	N=85
Sex			
Male	43 (52%)	52 (62%)	53 (62%)
Female	39 (48%)	32 (38%)	32 (38%)
Age			
Mean	14.5	14.4	14.5
SD	1.74	1.59	1.78
Range	12–17	12–17	12–17
Race			
White	54 (66%)	48 (57%)	55 (66%)
Black	7 (9%)	15 (18%)	8 (9%)
Asian	12 (14%)	13 (14%)	13 (15%)
*Other**	9 (11%)	9 (11%)	8 (10%)
Weight (kg)			
Mean	65.6	65.8	64.4
SD	24.5	20.1	21.5
Median	58.1	59.8	58.9
Range	32-174	38.2-122.60	31.0-148.2
BMI			
<85% of population	46 (56%)	47 (56%)	49 (58%)
≥85% of population	36 (44%)	37 (44%)	36 (42%)

Source: Reviewer Table (1) 200 mg for <60 kg, 300 mg for ≥60 kg

The baseline disease severity was generally balanced across the treatment arms. Approximately 46% of the subjects had IGA of 3 at baseline, and the mean EASI (SD) score at baseline was 35.5 (14.2). For the peak pruritus NRS, the average NRS score was about 7.5, and all but two randomized subjects had NRS ≥4 at baseline.

Table 9. Baseline Disease Severity

	Dupilumab		Placebo
	Q2W [(1)] N=82	Q4W N=84	N=85
IGA			
3	39 (48%)	38 (45%)	39 (46%)
4	43 (52%)	46 (55%)	46 (54%)
EASI			
Mean	35.3	35.8	35.5
SD	13.8	14.8	31.7
Median	32.5	33.5	14.0
Range	16-71	16-71	16-71
Peak pruritus NRS			
Mean	7.5	7.5	7.7
SD	1.5	1.8	1.6
Median	7.6	8.0	8
Range	4-10	2-10	4-10
NRS ≥4 at baseline	82 (100%)	83 (99%)	84 (99%)

Source: Reviewer Table (1) 200 mg for subjects <60 kg, 300 mg for subjects ≥60 kg

7.2.4. Results for the Primary and Secondary Efficacy Endpoints

Table 10 presents the results for the primary and secondary efficacy endpoints at week 16. Both dupilumab Q2W and Q4W were superior to placebo for all primary and secondary endpoints in the table below (p<0.001).

Table 10. Efficacy Results at Week 16 (Full Analysis Set)

	Dupilumab		Placebo
	Q2W[(1)] N=82	Q4W N=84	N=85
IGA 0 or 1 (primary)	20 (24%)	15 (18%)	2 (2%)
EASI 75	34 (42%)	32 (38%)	7 (8%)
Percent change in EASI score[(2)]	-65.9 (4.0)	-64.8 (4.5)	-23.6 (5.5)
Percent change in weekly average of daily peak pruritus NRS[(2)]	-47.9 (3.4)	-45.5 (3.5)	-19.0 (4.1)
Peak pruritus NRS ≥3[(3)]	40/82 (49%)	32/83 (39%)	8/85 (9%)
Peak pruritus NRS ≥4[(4)]	30/82 (37%)	22/83 (27%)	4/84 (5%)
EASI 50	50 (61%)	46 (55%)	11 (13%)
EASI 90	19 (23%)	16 (19%)	2 (2%)

Source: Reviewer Table; Full Analysis Set (FAS defined as all randomized subjects: Missing data or subjects using rescue treated as nonresponders. Analyzed using CMH test stratified by baseline IGA disease severity and baseline weight group (<60 kg versus ≥60 kg); (1) Subjects <60 kg received 200 mg Q2W; Subjects ≥60 kg received 300 mg Q2W; (2) The Sponsor stated that the endpoint is of scientific interest and may be object of publications; Least Squares (LS) mean and Standard Error (SE) from ANCOVA model with baseline as covariate and treatment, baseline IGA disease severity and baseline weight group (<60 kg versus ≥60 kg) as fixed factors; (3) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥3 from baseline to week 16; (4) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16

With only 11 subjects (4%) excluded from the PPS, the efficacy results using the PPS yielded similar results to those using the full analysis set. The analysis of the primary endpoint (IGA 0 or 1 at week 16) using the PPS were 25% (20/79), 18% (14/77), and 2% (2/84) for the dupilumab Q2W, Q4W, and placebo, respectively.

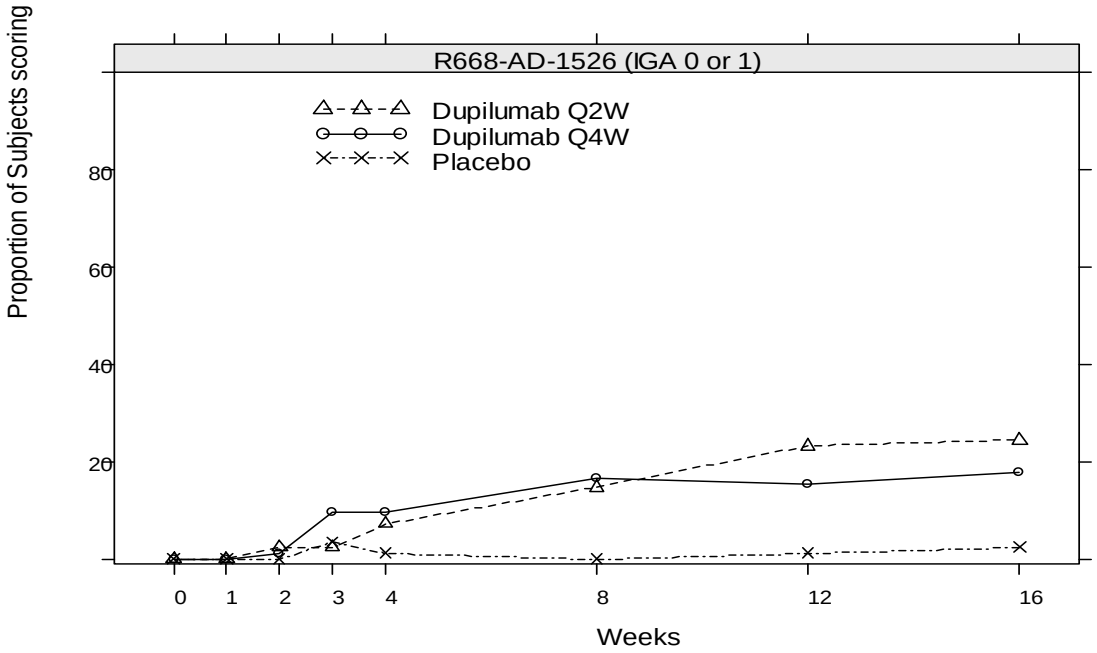
7.2.5. Patient Reported Outcomes (PROs)

The protocols specified secondary efficacy endpoints based on an 11-point NRS. The results are presented in the table above.

7.2.6. Efficacy Over Time

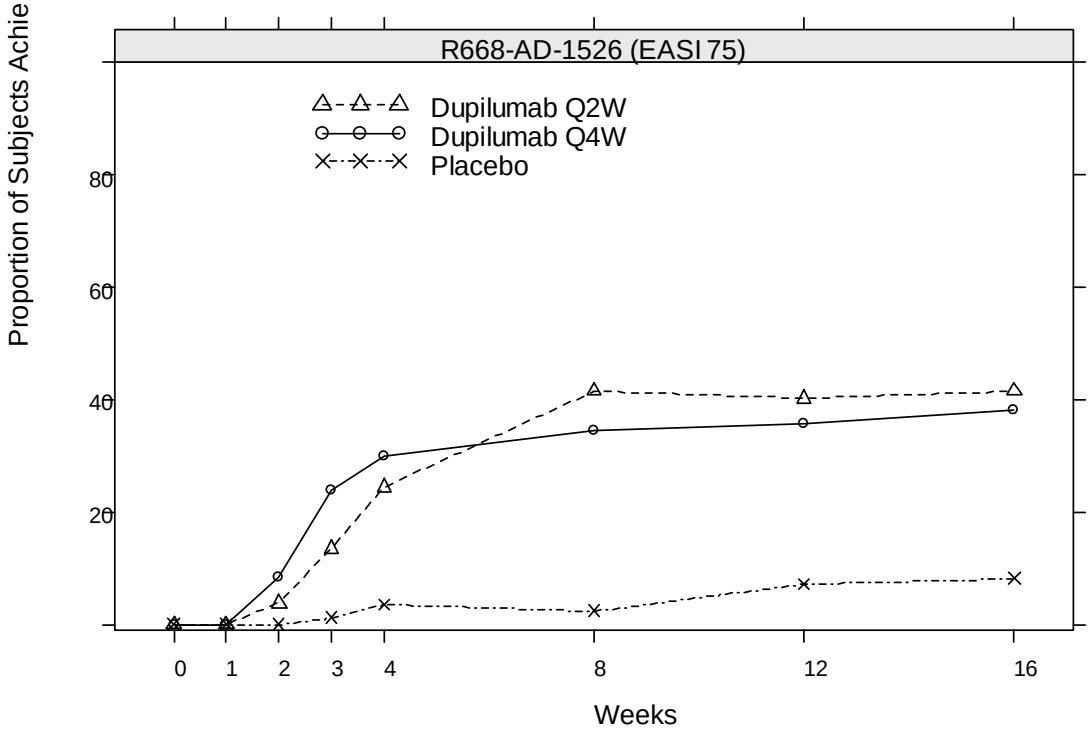
Figure 9 presents the results for IGA 0 or 1 through week 16. Figure 10 presents the results for EASI 75 through week 16.

Figure 9. Results for IGA of 0 or 1 Through Week 16



Source: reviewer figures; Full Analysis Set (FAS) defined as all randomized subjects; Missing data and subjects that used rescue were imputed using nonresponders.

Figure 10. Results for EASI 75 Through Week 16



Source: reviewer figures; Full Analysis Set (FAS) defined as all randomized subjects; Missing data and subjects that used rescue were imputed using nonresponders.

7.2.7. Findings in Special/Subgroup Populations

7.2.7.1. Sex, Race, Age, Weight, Baseline Disease Severity

Table 11 presents the results for the primary efficacy endpoint of IGA score of 0 or 1 at week 16 by sex, age (<15 versus ≥15 to <17 years), race (white, black or African American, Asian, other), weight (<60 kg versus ≥60 kg), and baseline IGA severity. As the number of subjects is small for the subgroups, it would be difficult to draw any meaningful conclusions.

Table 11. Proportion of Subjects With IGA 0 or 1 at Week 16 by Age, Sex, Race, Weight, and by Baseline IGA Severity

	Dupilumab		Placebo
IGA 0 or 1 at week 16	Q2W (1) N=82	Q4W N=84	N=85
Age			
<15	12/43 (28%)	7/45 (16%)	0/41 (0%)
≥15 to <17	8/39 (21%)	8/39 (21%)	2/44 (5%)
Sex			
Male	13/43 (30%)	8/52 (15%)	2/53 (4%)
Female	7/39 (18%)	7/32 (22%)	0/32 (0%)
Race			
White	13/54 (24%)	11/55 (20%)	1/48 (2%)
Black	4/7 (57%)	2/8 (25%)	1/15 (7%)
Asian	2/12 (17%)	2/13 (15%)	0/13 (0%)
Other	1/7 (14%)	0/8 (0%)	0/6 (0%)
Weight			
<60 kg	13/43 (30%)	7/42 (17%)	1/43 (2%)
≥60 kg	7/39 (18%)	8/42 (19%)	1/42 (2%)
Baseline IGA			
3	12/39 (31%)	13/38 (34%)	1/39 (3%)
4	8/43 (19%)	2/46 (4%)	1/46 (2%)

Source: Reviewer table; (1) subjects <60 kg received 200 mg Q2W; subjects ≥60 kg received 300 mg Q2W.

7.2.7.2. Rescue Medication

The protocol specified that investigators were encouraged to consider rescue initially with topical treatment (e.g., medium/high potency TCS), and to escalate to systemic medications only for subjects who did not respond adequately after at least 7 days of topical treatment. Note that the protocol specified that if rescue treatment was used, the subject was specified as a nonresponder from the time the rescue treatment was used.

Table 12 shows that the proportion of subjects who used at least one rescue medications. Rescue medication use was higher in the placebo group (59%) compared to the dupilumab Q2W (21%) and Q4W (33%) group. The most common use of rescue medication was corticosteroids.

Table 12. Proportion of Subjects With Rescue Medication Use

	Dupilumab		Placebo
	Q2W (1) N=82	Q4W N=83	N=85
≥1 Rescue	17 (21%)	27 (33%)	50 (59%)
Corticosteroids	14 (17%)	26 (31%)	47 (55%)
Other dermatological preparations	3 (4%)	1 (1%)	7 (8%)
Corticosteroids for systemic use	2 (2%)	0	5 (6%)
Immunosuppressants	0	0	3 (4%)

Source: Reviewer Table; Safety Analysis Set

7.3. Review of Safety

Safety Review Approach

The Applicant provided safety data from adolescents exposed to dupilumab in four studies. These constituted the adolescent development program for AD. The number of subjects presented below reflects only the adolescents, in those studies that also enrolled other age groups:

- Study R668-AD-1526 (1526): Phase 3, randomized, double-blind, placebo-controlled, pivotal study; 16-week dosing period; n=165
- Study R668-AD-1607 (1607): Phase 1, open-label, prefilled pen (also known as the autoinjector) study; 12-week dosing period; adolescents in Part A n=18
- Study R668-AD-1412 (1412): Phase 2a, open-label, PK study; single dose followed by 4-week repeat dose treatment; adolescents n=40
- Study R668-AD-1434 (1434): Phase 3, ongoing, OLE, long-term safety study; adolescents n=275 (as of the cutoff for the sBLA; April 21, 2018)

Study 1526 was the only one that exclusively enrolled adolescents. Also, study 1526 was the only monotherapy study; the other three studies allowed concomitant topical therapies e.g., TCS, TCI.

Subjects from studies 1526, 1607, and 1412 could be “rolled over” into study 1434, a long-term treatment study into which all pediatric subjects (irrespective of age) may ultimately be enrolled.

Study 1526 provided for the primary safety data. The safety review will focus on the primary safety data (study 1526) and the supportive safety data from the OLE (study 1434). Only SAEs will be discussed from studies 1412 and 1607. The supplement did not include pooled data for an integrated safety assessment, due to the differing designs of the four studies.

Across the development program, the Applicant analyzed the safety data according to three periods, with each period being defined differently for each study:

- Treatment period
- Follow-up period
- Overall study (consisted of the treatment period and the follow-up periods).

Study 1526 (pivotal)

See Section 7.2.1 for discussion of the study design. The treatment period was 16 weeks; the follow-up period was 12 weeks.

Study 1434 (OLE)

This study enrolls pediatric subjects (≥6 months to <18 years at screening) with moderate-to-severe AD and who had completed a prior dupilumab clinical study across the pediatric development program. The OLE treatment period for a particular pediatric age group (≥6 months to ≤6 years, 6 years to <12 years, and 12 years to <18 years) will continue up to the time when dupilumab is approved for treatment of AD for the age group of the subject in his/her geographic region, or until the company decides not to continue development of dupilumab for treatment of AD in that particular age group and/or overall pediatric population. In addition, if adequate efficacy and safety is demonstrated in future development in a particular age group with AD, the company may then transition subjects from the OLE in this age group in certain geographic regions to some other mechanism to continue to receive drug up to the time of approval. The primary endpoint is the incidence and rate of TEAEs from baseline through the last study visit.

Under the original protocol, subjects ≥12 years to <18 years old received weight-based dosing of 2 mg/kg once weekly (QW) or 4 mg/kg QW, which was the dosing regimen from the parent study (PK), 1412. Protocol Amendment 1 modified the dosing to a fixed-dose regimen of 300 mg Q4W, which was one of the regimens in the parent study (pivotal), 1526. Further, the amendment allowed for up-titration to 200 mg Q2W for subjects <60 kg or 300 mg Q2W for those ≥60 kg, in the face of an inadequate clinical response, defined as failure to achieve an IGA score of 0 or 1 (disease severity of “almost clear,” or “clear”) for at least 16 weeks from the date of initiation of treatment with the 300 mg Q4W regimen.

Safety procedures in this study include the assessment of vital signs, body weight and height, physical examination, laboratory testing (hematology, serum chemistry, urinalysis, and pregnancy testing), ophthalmology examination for subjects who experience adverse events of special interest (AESI) related to eye disorders (any type of conjunctivitis or blepharitis [severe or serious or lasting ≥4 weeks]).

Pharmacokinetic and antibody procedures involve the measurement of dupilumab concentrations and collection of serum samples for ADA assessment.

7.3.2. Review of the Safety Database

Overall Exposure

The Applicant defined the safety analysis set as subjects who received at least one dose of study treatment. Subjects were analyzed according to treatment received.

Table 13. Number of Adolescent Subjects Included in the Safety Analysis Set*

Parent Study ID Number	Number of Adolescents Treated in the Parent Study	Number of Adolescents Patients Who Rolled Over to the OLE Study (R668-AD-1434)	Number of Adolescents Exposed to Dupilumab (in the Parent Study or the OLE Study, R668-AD-1434)
R668-AD-1526	250[a]	201	234[b]
R668-AD-1412			
≥12 to <18 years of age	40	33	40
≥6 to <12 years of age[c]	3[c]	3	3
R668-AD-1607 Part A	18	11	18
R668-AD-1607 Part B[d]	27	27	27
Total	338	275	322

*Source: Table 1 of the Summary of Clinical Safety
a The number of subjects randomized and included in the full analysis set (FAS) was 251; one subject randomized to the dupilumab 300 mg Q4W group did not receive study treatment and was not included in the safety analysis set (SAF).
b 16 subjects in the placebo group withdrew from R668-AD-1526 and did not enter the OLE study
c Subjects who were enrolled as children in parent study and reached adolescence (12 years of age) before or at the time of screening for entry in the OLE study by the time of the data cut for this application
d Data from study R668-AD-1607 Part B (300 mg PFP portion, not complete as of data cutoff for this application) are not discussed in this application, however, the 27 adolescents from Part B who entered the OLE study R668-AD-1434 are included in the OLE analysis dataset (not complete as of data cutoff for this application).

A total of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD had received at least one dose of dupilumab by data cut-point for the sBLA (April 21, 2018), with durations of exposure as follows:

- 246 (76.4%) subjects had completed at least 16 weeks of treatment
- 35 (10.9%) subjects had completed at least 52 weeks of treatment
- 27 (8.4%) subjects had completed at least 104 weeks of treatment

Table 14 below presents a summary of study drug administration and duration of treatment in the adolescent program.

Table 14. Summary of Study Drug Administration (Cumulative) and Duration of Treatment in Adolescent Subjects From All Studies—SAF

	Dupilumab					
Exposure Characteristics	**2 mg/kg QW (N = 21)**	**4 mg/kg QW (N = 22)**	**300 mg Q4W (N = 284)**	**200 mg Q2W (N = 99)**	**300 mg Q2W (N = 89)**	**All Combined [3] (N = 322)**
Number of treated patients [1]	21	22	284	99	89	322
Number of study doses administered						
Mean (SD)	74.4 (39.53)	73.0 (34.61)	5.0 (4.12)	8.5 (4.88)	8.0 (5.30)	19.1 (27.00)
Q1	56.0	58.0	1.0	5.0	3.0	6.0
Median	93.0	81.0	4.0	9.0	9.0	11.0
Q3	108.0	100.0	9.0	9.0	11.0	15.0
Min-Max	5:109	1:109	1:18	1:23	1:22	1:113
Number of doses administered, cumulative, n (%)						
≥1	21 (100%)	22 (100%)	284(100%)	99 (100%)	89 (100%)	322 (100%)
≥4	21 (100%)	21 (95.5%)	148 (52.1%)	83 (83.8%)	66 (74.2%)	282 (87.6%)
≥8	17 (81.0%)	19 (86.4%)	80 (28.2%)	68 (68.7%)	49 (55.1%)	233 (72.4%)
≥12	17 (81.0%)	19 (86.4%)	25 (8.8%)	17 (17.2%)	20 (22.5%)	144 (44.7%)
≥16	17 (81.0%)	19 (86.4%)	1 (0.4%)	10 (10.1%)	9 (10.1%)	80 (24.8%)
≥24	17 (81.0%)	18 (81.8%)	0	0	0	36 (11.2%)
≥48	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥52	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥76	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥100	8 (38.1%)	6 (27.3%)	0	0	0	17 (5.3%)
≥124	0	0	0	0	0	0
≥148	0	0	0	0	0	0

Exposure Characteristics	Dupilumab					
	2 mg/kg QW (N = 21)	4 mg/kg QW (N = 22)	300 mg Q4W (N = 284)	200 mg Q2W (N = 99)	300 mg Q2W (N = 89)	All Combined [3] (N = 322)
Summary of treatment duration [2] (weeks)						
n	21	22	284	99	89	322
Mean (SD)	75.4 (39.91)	75.4 (35.74)	14.4 (9.52)	16.0 (9.34)	15.4 (10.03)	32.0 (28.73)
Q1	57.1	58.0	4.1	10.0	7.6	16.0
Median	93.3	90.6	15.9	15.9	15.9	24.0
Q3	108.7	101.3	20.1	18.0	20.1	36.3
Min-Max	5:109	1:109	2:52	2:44	2:42	1:125
Treatment duration [2] (weeks) cumulative, n (%)						
≥1 week	21 (100%)	22 (100%)	284 (100%)	99 (100%)	89 (100%)	322 (100%)
≥4 weeks	21 (100%)	21 (95.5%)	271 (95.4%)	94 (94.9%)	75 (84.3%)	320 (99.4%)
≥8 weeks	17 (81.0%)	19 (86.4%)	193 (68.0%)	80 (80.8%)	65 (73.0%)	295 (91.6%)
≥12 weeks	17 (81.0%)	19 (86.4%)	168 (59.2%)	71 (71.7%)	55 (61.8%)	272 (84.5%)
≥16 weeks	17 (81.0%)	19 (86.4%)	137 (48.2%)	47 (47.5%)	44 (49.4%)	246 (76.4%)
≥26 weeks	17 (81.0%)	18 (81.8%)	34 (12.0%)	13 (13.1%)	16 (18.0%)	141 (43.8%)
≥39 weeks	16 (76.2%)	18 (81.8%)	4 (1.4%)	5 (5.1%)	2 (2.2%)	73 (22.7%)
≥52 weeks	16 (76.2%)	18 (81.8%)	1 (0.4%)	0	0	35 (10.9%) [4]
≥78 weeks	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥104 weeks	7 (33.3%)	4 (18.2%)	0	0	0	27 (8.4%)
≥130 weeks	0	0	0	0	0	0

*Source: Table 5 of the Summary of Clinical Safety
[1] Including a total of four studies: R668-AD-1526, R668-AD-1412, R668-AD-1607 (Part A), and R668-AD-1434.
[2] Treatment duration is calculated as sum of treatment duration to dupilumab for each dose regimen in each individual study.
[3] Subjects received at least one dupilumab dose in one of the studies were included in this column and counted only once. The duration of treatment exposure to dupilumab dose for a patient who entered study R668-AD-1434 was calculated as the sum of duration of treatment exposure to dupilumab in the previous study plus duration of treatment exposure to dupilumab in the OLE study. The 322 subjects include all subjects who received at least one dose of dupilumab in either the parent study or the OLE study: 234 patients from R668-AD-1526 (16 subjects in the placebo group did not rollover to the OLE study), 43 subjects from R668-AD-1412 (40 adolescent subjects and three subjects who turned 12 years of age at the time rolling over to the OLE study), 18 adolescent subjects from Part A of R668-AD-1607 and 27 adolescent subjects from Part B of R668-AD-1607.
[4] These are 34 subjects from parent study R668-AD-1412 and one subject from parent study R668-AD-1526 who all rolled over in OLE study R668-AD-1434.
Abbreviations: OLE, open-label extension; Q1, first quartile; Q3, third quartile; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; SD, standard deviation.

Study 1526 (pivotal)

Because the weight-based dosing resulted in similar systemic exposures across the span of adolescents, the Applicant pooled the data from the 200 mg Q2W and 300 mg Q2W treatment groups.

Treatment exposures were generally similar across treatment groups.

Table 15. Summary of Study Drug Administration and Treatment Exposure in Study R668-AD-1526–SAF*

		Dupilumab		
	Placebo (N=85)	300 mg Q4W (N=83)	200 mg or 300 mg Q2W (N=82)	Combined (N=165)
Number of study drug doses administered				
Mean (SD)	8.5 (1.48)	8.7 (1.34)	8.7 (1.06)	8.7 (1.20)
Median	9.0	9.0	9.0	9.0
Minimum : Maximum	2 : 9	2 : 9	4 : 9	2 : 9
Overall treatment exposure (days)				
Mean (SD)	105.9 (21.49)	108.5 (18.66)	108.9 (15.49)	108.7 (17.11)
Median	112.0	112.0	112.0	112.0
Minimum : Maximum	14 : 146	14 : 119	42 : 154	14 : 154

*Source: Table 2 of Summary of Clinical Safety
Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; SD, standard deviation.

Study 1434 (OLE)

A total of 69 subjects enrolled in the OLE study had received placebo in their parent study. At data cutoff for the sBLA, 275 adolescent subjects were enrolled, and their exposures were as follows:

- 152 subjects had been exposed to dupilumab for 16 weeks
- 34 subjects had been exposed for ≥52 weeks
- 22 subjects had been exposed for ≥104 weeks

Table 16. Summary of Treatment Exposure to Dupilumab for Subjects in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

Exposure Characteristics	Exposure to Dupilumab for All Patients in OLE Total (N=275)
Overall Treatment exposure (Weeks)	
n	275
Mean (SD)	26.44 (30.366)
Q1	8.00
Median	16.57
Q3	28.00
Min : Max	4.0 : 120.1
Number (%) of patients with overall treatment exposure (weeks) cumulatively	
≥1 Week	275 (100%)
≥4 Weeks	275 (100%)
≥16 Weeks	152 (55.3%)
≥26 Weeks	80 (29.1%)
≥52 Weeks	34 (12.4%)
≥78 Weeks	29 (10.5%)
≥ 104 Weeks	22 (8.0%)
≥ 130 Weeks	0
Number (%) of patients with treatment exposure with Q4W (weeks) cumulatively	
≥1 Week	268 (97.5%)
≥4 Weeks	250 (90.9%)
≥16 Weeks	80 (29.1%)
≥ 26 Weeks	11 (4.0%)
≥52 Weeks	0
≥78 Weeks	0
Number (%) of patients with treatment exposure with Q2W (weeks) cumulatively	
≥1 Week	126 (45.8%)
≥4 Weeks	103 (37.5%)
≥16 Weeks	36 (13.1%)
≥ 26 Weeks	8 (2.9%)
≥52 Weeks	0
≥78 Weeks	0

*Source: Table 24 of study report for 1434
Abbreviations: Min, minimum; Max, maximum; SD, standard deviation; Q1, quartile 1; Q3, quartile 3

Relevant Characteristics of the Safety Population

See Section 7.2.3 for tables of baseline demographic and disease characteristics for this study.

Baseline demographic and disease characteristics were generally similar across treatment arms. Most subjects (84.9%) had their AD diagnosed before the age of 5 years, and the mean (SD) duration of disease was 12.2 (3.20) years. Most subjects had a history or allergic rhinitis (65.6%), food allergy (60.8%), and/or asthma (53.6%). A higher proportion of subjects (24.8%) in the dupilumab combined group had a history of allergic conjunctivitis compared to the placebo group (18.8%).

All subjects had received at least one prior medication. By therapeutic class, the most commonly used prior medications were dermatological preparations of corticosteroids (96.0%), antihistamines for systemic use (76.8%), drugs for obstructive airway disease (52.8%), and emollients and protectives (49.6%).

In this study, 95% of subjects reported an inadequate response to topicals, 28% had received systemic corticosteroids for AD treatment, and 21% had received systemic nonsteroidal immunosuppressants: azathioprine (1%), cyclosporine (13%), methotrexate (10%), and mycophenolate (1%).

Table 17 suggests that some subjects had a history of treatment with both systemic corticosteroids and systemic nonsteroidal immunosuppressants. Most subjects (67%) who took cyclosporine took it for more than 3 months and, a poor response was the most common reason for discontinuing cyclosporine (54%). All of this suggests a population with refractory disease at baseline.

Table 17. Summary of Prior Use of Systemic Corticosteroid and Systemic Non-Steroidal Immunosuppressant Medications for AD in Study 1526–SAF*

		Dupilumab			
	Placebo (N=85)	300 mg Q4W (N=83)	200 mg or 300 mg Q2W (N=82)	Combined (N=165)	Total (N=250)
Patients receiving prior systemic corticosteroids and/or systemic non-steroidal immunosuppressants, n (%)	33 (38.8%)	38 (45.8%)	35 (42.7%)	73 (44.2%)	106 (42.4%)
Patients receiving prior systemic corticosteroids	21 (24.7%)	27 (32.5%)	21 (25.6%)	48 (29.1%)	69 (27.6%)
Patients receiving prior systemic non-steroidal immunosuppressants	17 (20.0%)	15 (18.1%)	20 (24.4%)	35 (21.2%)	52 (20.8%)
Azathioprine	1 (1.2%)	1 (1.2%)	0	1 (0.6%)	2 (0.8%)
Cyclosporine	12 (14.1%)	6 (7.2%)	14 (17.1%)	20 (12.1%)	32 (12.8%)
Methotrexate	6 (7.1%)	10 (12.0%)	10 (12.2%)	20 (12.1%)	26 (10.4%)
Mycophenolate	0	1 (1.2%)	2 (2.4%)	3 (1.8%)	3 (1.2%)

*Source: Table 11 of the study report for 1526

Adequacy of Safety Database

The safety database was adequate in size and extent of exposures (concentrations and duration) to assess the safety of dupilumab in subjects 12 to <18 years with moderate-to-severe AD, under conditions of intended use.

7.3.3. 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 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 system organ class (SOC), high-level term, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Version 20.1 was used for studies 1526 and 1434.

For study 1526, 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 study 1434, the Applicant summarized all TEAEs during the study period. The Applicant also calculated and summarized the number of events per 100 subject-years and number of subjects with at least one event per 100 subject-years (exposure-adjusted incidence rate [EAIR]) for overall TEAEs, severe TEAEs, treatment-related TEAEs, severe treatment-related TEAEs, SAEs, AEs leading to discontinuation, and AESIs. These calculations were adjusted for the duration of the TEAE period.

AESIs

AESIs were mostly defined based on the safety profile from evaluation of dupilumab in adults. The following events were designated as AESIs in studies 1526 and 1434 and required expedited reporting (within 24 hours) by the investigator to the Applicant:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, nonmetastatic squamous or basal cell carcinoma of the skin)
- Helminthic infections
- Suicide-related events
- Any type of conjunctivitis or blepharitis (severe or serious)
- Keratitis

The medical officer's review of the original BLA submission provides some information regarding the designation of "suicide-related events" as an AESI. From p. 152 of that review (review dated 03/27/2017):

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

Routine Clinical Tests

The schedule of testing varied according to the study and was specified in the respective statistical analysis plan for each study. Laboratory testing generally included clinical chemistry, hematology, and urinalysis evaluations.

7.3.4. Safety Results

Deaths

No deaths occurred in the adolescent AD program.

Serious Adverse Events

Study 1526 (pivotal)

One SAE was reported in this study, and it occurred in a subject in the placebo group during the treatment period:

- A 13-year-old male experienced appendicitis.

Study 1434 (OLE)

A total of four SAEs occurred in adolescents through the cutoff point (1.5%; 2.9 patients per 100 patient years [nP/100 PY]). Information pertaining to these SAEs is presented below:

- *Injection Site Cellulitis*. A 16-year-old black female experienced pain and swelling at the injection site (abdomen) on day 35 (5 days after second dose of study drug). Pain and swelling worsened eventuating in presentation to the emergency department, and she was hospitalized the same day. Treatment included intravenous antibiotics. She recovered and continued in the study as planned.
- *Ankle fracture*. A 12-year-old white female fractured her ankle in a tobogganing accident.
- *Patent ductus arteriosus*. A 17-year-old white female was hospitalized for a closure procedure (initial procedure done in childhood was unsuccessful).

- *Food allergy*. A 17-year-old white male with a history of allergy to eggs experienced an "acute allergic reaction" after ingesting mayonnaise (contained eggs). He was treated in the emergency department and continued in the study as planned.

SAEs in studies 1412 and 1607 part A

In study 1412, two subjects experienced two SAEs each:

- A 17-year-old male experienced "dermatitis infected" and "palpitations." He was taking salbutamol for asthma. One day after receiving one dose of dupilumab (2 mg/kg) he experienced palpitations ≤120 seconds. He experienced several episodes over the subsequent 2 to 3 days, with resolution (without treatment) after approximately 4 days. Study treatment was not interrupted. This subject was also hospitalized after the fifth dose of dupilumab for "infected AD." He was treated and recovered. He had completed study treatment at the time of this event.
- A 13-year-old white female experienced "dermatitis infected" and "Staphylococcal skin infection" 7 weeks after one injection of dupilumab (4 mg/kg). She was hospitalized and treated with oral antibiotics; the event resolved. No action was taken with study drug.

In study 1607 Part A, two subjects experienced SAEs; both subjects were older than 18 years of age, and high-level details are presented below:

- A 60-year-old male experienced lymphadenopathy. He had a history of "swollen lymph nodes." He was hospitalized for a severe disease flare accompanied by fever, chills, and "sweats." Evaluation revealed widespread lymphadenopathy. The narrative indicates that he was "worked up" for lymphoma. Lymph node biopsies revealed "no morphologic evidence of lymphoma." Ultimately, the lymphadenopathy "regressed."
- A 63-year-old male experienced sepsis. History included obesity, type 2 diabetes mellitus, and prostate cancer. On the day of his 3rd study treatment, he experienced symptoms considered to be suggestive of "blood infection" and was hospitalized. He was treated with intravenous antibiotics and also underwent several investigations while hospitalized. The narrative is somewhat complex and convoluted. Ultimately, however, he recovered from the event.

Dropouts and/or Discontinuations Due to Adverse Effects

Study 1526 (pivotal)

One subject (1.2%) experienced a TEAE that led to permanent discontinuation of study treatment: a 17-year-old black male in the placebo group was withdrawn from treatment on day 19 due to worsening of AD.

Study 1434 (OLE)

No AEs led to permanent discontinuation or withdrawal of study treatment in this study.

Significant Adverse Events

Severe TEAEs in study 1526 (pivotal)

A total of six subjects reported eight severe TEAEs during the treatment period. A subject was only counted once if the subject experienced the event more than once.

The only severe AE that was reported by more than one subject during the treatment period was “Dermatitis atopic.” Two subjects reported this event (1.2%), both of whom were in the dupilumab Q4W group. The remaining five events and the treatment group in which they occurred were:

- Biliary colic in the 300 mg Q4W
- Food allergy; jaw fracture in the 200 mg or 300 mg Q2W
- Lymphadenitis; appendicitis in the placebo group

One severe event was reported during the follow-up period: “Dermatitis atopic” in the dupilumab Q4W group.

It may be noteworthy that all of the severe TEAEs of AD reported over the course of the study occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the Q2W dosing frequency.

Severe TEAEs in study 1434 (OLE)

A total of seven subjects (2.5%) experienced TEAEs that were reported as severe: AD exacerbation or worsening (two subjects; 0.7%), and one subject each (0.4%) experienced severe diarrhea, bone fracture, pain in extremity, patent ductus arteriosus, and allergic conjunctivitis (the case of conjunctivitis is discussed below with the AESIs).

AESIs in study 1526 (pivotal)

Three AESIs were reported during the treatment period, all of which occurred in dupilumab treatment groups:

- *Keratitis*. A 12-year-old white female (Q4W group; stratum <60 kg) experienced “bilateral viral keratoconjunctivitis” on day 12, which was 11 days after her baseline dose of 300 mg received on day 1. She was evaluated by an ophthalmologist and prescribed tobramycin-dexamethasone eye drops. Dosing of study treatment was not interrupted. She was considered to have recovered from the event on day 67 and received her final dose of study treatment on day 99. The investigator graded the event as “mild.” She was reported to have a history of allergic keratoconjunctivitis.

- *Suicidal behavior*. A 15-year-old Asian male (300 mg Q2W) experienced "suicidal ideation–passive" (verbatim term) on day 26. His most recent dose of dupilumab had been on day 13. On day 26, he reported daily thoughts of suicide, without accompanying plans for commission of the act. He had a history of depression and of a suicide attempt, prior to entry into the study. He had been on fluoxetine but had been off of it since the last 3 months prior to this episode. A diagnosis of depression with passive suicidal ideation was made. The subject was restarted on fluoxetine in the context of a comprehensive management plan for his depression. Study treatment was not altered, and he received his last dose on day 97.
- *Food allergy*. A 15-year-old white male (200 mg Q2W) experienced an "allergic reaction to food" on day 30, 17 days after his last dose of dupilumab. He had a history of allergy to dairy, eggs, and peanuts. He experienced "anaphylaxis" after consumption of cheese-flavored chips. Treatment in the emergency department included intramuscular epinephrine, oral diphenhydramine, and intravenous methylprednisolone. The event resolved the same day. Study drug was discontinued as the subject had received methylprednisolone which was a prohibited medication.

AESIs in study 1434 (OLE)

Three AESIs were reported in the OLE study:

- *Food allergy*. This 17-year-old subject has been previously discussed (see discussion of SAEs).
- *Depression*. A 17-year-old white female with a history of depression with suicidal ideation began experiencing depression with suicidal thoughts on day 443 (after 55 doses of study drug). The episode was triggered by her AD (conclusion of investigator). She also had a etonogestrel contraceptive implant, and "depressed mood" is labeled in the Warnings and Precautions section of the label. She was treated with antidepressants, and the event ultimately resolved. She continued in the study as planned.
- *Conjunctivitis allergic*. A 13-year-old white female with a history of allergic conjunctivitis began experiencing itching, burning, and several other eye symptoms on day 31. She also had periorbital and eyelid eczematous lesions. An ophthalmologist diagnosed bilateral AKC; she was treated accordingly. The investigator recorded the event as being "severe" and related to study drug. She was treated and continued in the study as planned.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs in study 1526 (pivotal)

TEAEs were most often reported in the Infections and Infestations SOC, and the two most commonly-reported events in that SOC were Upper respiratory tract infection and Nasopharyngitis. Conjunctivitis was the third most commonly-reported event in this SOC, and it occurred at higher incidences in the dupilumab groups: placebo-1.2%,

Q4W-3.6%, and Q2W-4.9%. The incidences of Conjunctivitis were similar between dupilumab groups, but slightly higher in the Q2W compared to Q4W. “Dermatitis atopic” occurred at the highest frequency in the placebo group (24.7%) and at similar incidences in the Q4W and Q2W groups (18.1% and 18.3%, respectively). Injection site reactions of various types were generally more common in the Q2W group. Generally, there was no evidence of a dose-response in the occurrence of TEAEs.

TEAEs that occurred in ≥2.0% in a dupilumab group and at a higher incidence than placebo are presented in Table 18. Presentation of events by “≥2%” is reasonable, as the report of a single event in any treatment group made for an incidence of “1.2%.”

Table 18. Treatment-Emergent Adverse Events That Occurred in ≥2.0% in a Dupilumab Group and at a Higher Incidence Than Placebo*

System Organ Class Preferred Term	Placebo (n=85)	Dupilumab	
		300 mg Q4W (n=83)	200 mg or 300 mg Q2W (n=82)
Infections and infestations	37 (43.5%)	38 (45.8%)	34 (41.5%)
Conjunctivitis	1 (1.2%)	3 (3.6%)	4 (4.9%)
Pharyngeal streptococcal	0	4 (4.8%)	2 (2.4%)
Viral upper respiratory tract infection	1 (1.2%)	3 (3.6%)	2 (2.4%)
Herpes simplex	1 (1.2%)	4 (4.8%)	0
Conjunctivitis viral	0	2 (2.4%)	1 (1.2%)
Gastroenteritis viral	1 (1.2%)	0	3 (3.7%)
Bronchitis	0	0	2 (2.4%)
Conjunctivitis bacterial	0	2 (2.4%)	0
Sinusitis bacterial	0	0	2 (2.4%)
Urinary tract infection viral	0	2 (2.4%)	0
Skin and subcutaneous disorders	26 (30.6%)	20 (24.1%)	22 (26.8%)
Rash	0	2 (2.4%)	1 (1.2%)
General disorders and administration site conditions	6 (7.1%)	9 (10.8%)	10 (12.2%)
Injection site pain	1 (1.2%)	1 (1.2%)	3 (3.7%)
Injection site swelling	1 (1.2%)	1 (1.2%)	3 (3.7%)
Malaise	0	3 (3.6%)	0
Fatigue	0	0	2 (2.4%)
Injection site erythema	1 (1.2%)	0	2 (2.4%)
Injection site warmth	0	0	2 (2.4%)
Respiratory, thoracic and mediastinal disorders	13 (15.3%)	9 (10.8%)	6 (7.3%)
Oropharyngeal pain	1 (1.2%)	3 (3.6%)	2 (2.4%)
Gastrointestinal disorders	4 (4.7%)	7 (8.4%)	6 (7.3%)
Nausea	1 (1.2%)	2 (2.4%)	2 (2.4%)
Abdominal pain upper	1 (1.2%)	1 (1.2%)	2 (2.4%)
Eye disorders	7 (8.2%)	6 (7.2%)	6 (7.3%)
Conjunctivitis allergic	3 (3.5%)	4 (4.8%)	3 (3.7%)
Injury, poisoning and procedural complications	2 (2.4%)	3 (3.6%)	9 (11.0%)
Ligament sprain	0	0	2 (2.4%)
Procedural pain	0	0	2 (2.4%)

*Source: Table 57 of study report for 1526

TEAEs in study 1434 (OLE)

In the OLE study, 149 subjects (54.2%) reported TEAEs making for an EAIR of 283.1 nP/100 PY. Similar to study 1526, TEAEs were most often reported in the infections and infestations SOC, and the two most commonly-reported events were nasopharyngitis (13.8%; 17.8 nP/100 PY) and upper respiratory tract infection (8.0%; 33.3 nP/100 PY) (although the order of frequency of these two TEAEs was reversed in study 1526).

Table 19**. Summary of Subjects With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Reported in ≥2% of Subjects by SOC) in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)***

System Organ Class Preferred Term	Total (N=275) (nP/100PY)	Total (N=275) (nP/PY)
Number of TEAEs	700	700 (493.915)
Patients with at least one TEAE	149 (54.2%)	149/52.6 (283.051)
Infections and infestations	100 (36.4%)	100/79.6 (125.684)
Nasopharyngitis	38 (13.8%)	38/114.2 (33.262)
Upper respiratory tract infection	22 (8.0%)	22/131.3 (16.759)
Influenza	13 (4.7%)	13/136.8 (9.506)
Oral herpes	11 (4.0%)	11/130.3 (8.445)
Tonsillitis	7 (2.5%)	7/134.9 (5.190)
Pharyngitis	6 (2.2%)	6/138.1 (4.344)
Skin and subcutaneous tissue disorders	57 (20.7%)	57/112.3 (50.742)
Dermatitis atopic	39 (14.2%)	39/122.9 (31.738)
Acne	7 (2.5%)	7/135.0 (5.185)
Gastrointestinal disorders	31 (11.3%)	31/115.0 (26.954)
Diarrhoea	8 (2.9%)	8/129.7 (6.170)
Vomiting	8 (2.9%)	8/132.7 (6.028)
Abdominal pain upper	6 (2.2%)	6/137.8 (4.353)
Respiratory, thoracic and mediastinal disorders	23 (8.4%)	23/116.1 (19.806)
Oropharyngeal pain	12 (4.4%)	12/131.2 (9.148)
Cough	7 (2.5%)	7/134.5 (5.205)
Nervous system disorders	21 (7.6%)	21/123.4 (17.022)
Headache	16 (5.8%)	16/126.0 (12.702)
Injury, poisoning and procedural complications [1]	20 (7.3%)	20/123.8 (16.149)
General disorders and administration site conditions	18 (6.5%)	18/124.2 (14.495)
Pyrexia	6 (2.2%)	6/134.4 (4.464)
Eye disorders	13 (4.7%)	13/135.3 (9.607)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Musculoskeletal and connective tissue disorders [2]	10 (3.6%)	10/134.3 (7.449)
Psychiatric disorders [3]	9 (3.3%)	9/135.1 (6.661)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) [4]	6 (2.2%)	6/135.3 (4.435)

*Source: Table 27 of study report for 1434; Subjects who experienced more than one TEAE were counted only once in each category. For subjects with event, number of patient years is calculated up to date of the first event; for subjects without event, it corresponds to the length of study observation period.

Laboratory Findings

Study 1526 (pivotal)

Hematology

There were no clinically-meaningful trends or differences between treatment groups in changes or shifts from baseline in any red blood cell parameter during the treatment period. Mean platelet counts remained within the normal range for all treatment groups at each study visit.

The same was generally true of white blood cells (basophils, monocytes, leukocytes, and neutrophils). Regarding eosinophils, mean counts were noted to increase from baseline in the dupilumab groups, peaking at week 8, then trending back towards baseline. A similar trend was seen in the adult program. In the placebo group, mean counts showed a progressive decrease from baseline. The Applicant relates this eosinophil effect to the mechanism of action of dupilumab in blocking IL-4 and IL-3 activity and the resultant impact on eosinophil activity, which ultimately may lead to transient increases in circulating eosinophil counts.

Table 20. Mean and Median Changes From Baseline in Eosinophils–SAF*

		Change from Baseline ($x10^9$/L)							
Treatment	**Visit**	**n**	**Mean**	**SD**	**Min**	**Q1**	**Median**	**Q3**	**Max**
Placebo (N=85)	Week 4	78	-0.080	0.4206	-1.76	-0.280	-0.075	0.130	1.29
	Week 8	76	-0.086	0.4924	-2.42	-0.240	0.010	0.140	1.03
	Week 16	72	-0.092	0.5284	-2.09	-0.275	-0.105	0.125	1.45
	Week 28	2	-0.105	0.0778	-0.16	-0.160	-0.105	-0.050	-0.05
Dupilumab 300 mg Q4W (N=83)	Week 4	79	0.027	0.5248	-1.03	-0.270	-0.050	0.120	2.23
	Week 8	78	0.177	0.7203	-1.11	-0.230	0.000	0.440	2.88
	Week 16	78	-0.094	0.5368	-1.16	-0.420	-0.125	0.080	2.23
	Week 28	3	-0.140	0.1400	-0.30	-0.300	-0.080	-0.040	-0.04
Dupilumab 200 mg or 300 mg Q2W (N=82)	Week 4	81	0.035	0.6412	-1.53	-0.190	-0.030	0.190	4.17
	Week 8	76	0.189	0.8246	-1.57	-0.145	0.025	0.430	3.84
	Week 16	74	0.027	0.8075	-1.97	-0.300	-0.040	0.270	5.23
	Week 28	4	-0.233	0.5160	-1.00	-0.535	-0.005	0.070	0.08
Dupilumab Combined (N=165)	Week 4	160	0.031	0.5848	-1.53	-0.215	-0.040	0.175	4.17
	Week 8	154	0.183	0.7710	-1.57	-0.190	0.015	0.440	3.84
	Week 16	152	-0.035	0.6825	-1.97	-0.310	-0.075	0.200	5.23
	Week 28	7	-0.193	0.3769	-1.00	-0.300	-0.070	0.060	0.08

*Source: Table 62 of study report for 1526.

No subject had relevant hematology test abnormalities that led to treatment discontinuation or to reporting of a SAE. One subject in the dupilumab Q4W group did have a TEAE reported as “Eosinophil count increased.”

Chemistry

Generally, no clinically-meaningful trends in changes or shift from baseline in any treatment group in chemistries (measures of metabolic, renal, liver or liver function or electrolytes or lipids) were noted. No subject had abnormalities in these parameters that led to treatment discontinuation or to reporting of a SAE. However, the following chemistries were reported as TEAEs:

- "Blood creatine phosphokinase increased":
  - Two subjects in the Q4W group (2.4%) and one subject each in the placebo and Q2W groups (1.2% each)
- "Transaminases increased": one subject each in the placebo and Q2W groups (1.2% each)
- "Liver function test increased": one subject in the placebo group (1.2%).

Mean LDH decreased from baseline in all treatment groups during the treatment period, but to a greater extent in the dupilumab groups compared to the placebo group. For all treatment groups, mean LDH values remained in the normal range. These patterns were observed in the adult AD program. The Applicant anticipated these trends, indicating that LDH levels correlate with severity and activity of AD.

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

Study 1434 (OLE)

The findings in the OLE generally did not reveal any new patterns in hematology parameters or in most white blood cell parameters relative to study 1526. Mean eosinophil counts trended downwards in the OLE. The Applicant theorizes that this may possibly have been due to subjects previous dupilumab exposure. "Eosinophil count increased" is the only parameter that was reported as a TEAE, and there was only one report.

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

Vital Signs

No subject had abnormalities in vital signs that led to treatment discontinuation or to reporting of a SAE. No clinically-significant trends were noted in changes in vital signs in any treatment group. PCSVs were reported in all treatment groups and in no particular pattern. In study 1526, the PCSV of "Respiratory rate" ">20 bpm and <=20 bpm at baseline" was the only PCSV vital sign event that occurred at a higher incidence in the Q2W group (7.3%), compared to the Q4W and placebo groups (4.8% and 1.2%, respectively). In studies 1526 and 1434, the most common PCSV was diastolic

hypertension (>=95th percentile for gender, age and height; baseline <95th percentile and increase from baseline >=10 mmHg). In study 1526, this was reported at similar incidences in the placebo and Q2W groups, 20.0% and 20.7%, respectively (12.0% in the Q4W group). This PCSV was reported in 6.9% of subjects in the OLE study.

Electrocardiograms

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

QT

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

Immunogenicity

The TEAEs profile did not suggest a correlation between ADA positivity and events that might suggest loss of efficacy ("Dermatitis atopic") or in injection site reactions. In study 1526:

- "Dermatitis atopic" was reported in ADA-positive subjects as follows:
  - Q4W 17.6% (in ADA-negative: 20.0%)
  - Q2W 15.4% (in ADA-negative: 19.1%).
- Injection site reactions were reported in ADA-positive subjects as follows:
  - Q4W 11.8% (in ADA-negative: 10.8%)
  - Q2W 7.7% (in ADA-negative: 13.2%).

Also, see Section 6.2.1 of this review.

7.3.5. Analysis of Submission-Specific Safety Issues

Conjunctivitis

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

The Applicant included “Any type of conjunctivitis or blepharitis (severe or serious)” and “Keratitis” among the designated AESIs in studies 1526 (pivotal) and 1434 (OLE). Table 21 below presents all of events of this type that were reported in study 1526.

Conjunctivitis events were more common in the dupilumab groups compared to placebo in study 1526. The OLE did not reveal any difference in the types of eye-related events; the same types of conjunctivitis events were reported in that study. Eye-related findings in studies 1526 and 1434 were similar to those observed in dupilumab-treated subjects in the adult studies in the AD population.

Table 21. Conjunctivitis Events During the Treatment Period in Study 1526 (Pivotal)*

System Organ Class Preferred Term	Placebo (n=85)	Dupilumab	
		300 mg Q4W (n=83)	200 mg or 300 mg Q2W (n=82)
Infections and infestations	37 (43.5%)	38 (45.8%)	34 (41.5%)
Conjunctivitis	1 (1.2%)	3 (3.6%)	4 (4.9%)
Conjunctivitis viral	0	2 (2.4%)	1 (1.2%)
Conjunctivitis bacterial	0	2 (2.4%)	0
Viral keratitis	0	1 (1.2%)	0
Eye disorders	7 (8.2%)	6 (7.2%)	6 (7.3%)
Conjunctivitis allergic	3 (3.5%)	4 (4.8%)	3 (3.7%)

*Sources: Table 8 of the Summary of Clinical Safety and Post text table 7.2.1.1/1 of the study report for 1526

In the OLE, the Applicant further evaluated conjunctivitis by performing a narrow customized MedDRA query (CMQ) containing five terms that included the term “Conjunctivitis.” Additionally, the Applicant conducted a broader CMQ containing 16 terms. This is similar to the approach that the Applicant took in the analysis of the data in the adult program once the signal had been identified. The terms included in each CMQ are listed with the respective tables below.

Summary of narrow CMQ search for conjunctivitis; study 1434 (OLE)

Under this search, 12 subjects (4.4%) reported a conjunctivitis event. The event was graded as severe for one subject (discussed above in Section 7.3.4). However, none of the events was serious, and none resulted in discontinuation of treatment.

Table 22. Number of Subjects With Treatment-Emergent Conjunctivitis by (Narrow CMQ) by Preferred Term in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

	Total (N=275)	Total(N=275) nP/PY (nP/100 PY))
Number of TEAEs	22	
Patients with at least one TEAE	12 (4.4%)	12/131.2 (9.149)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	1 (0.4%)	1/141.5 (0.707)

*Source: Table 31 of the study report for 1434
Search terms for Narrow CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis
Subjects who experienced more than one TEAE were counted only once in each category
Abbreviations: CMQ, customized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; nP, number patients with events; TEAE, treatment emergent adverse event

Summary of broad CMQ search for conjunctivitis; study 1434 (OLE)

Under this search, the Applicant identified 16 subjects (5.8%) who experienced a conjunctivitis event.

Table 23. Number of Subjects With Treatment-Emergent Conjunctivitis (Broad CMQ) by Preferred Term in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

Preferred Term MedDRA version 20.1	Total (N=275)	Total (N=275) nP/PY (nP/100 PY)
Number of TEAEs	27	
Patients with at least one TEAE	16 (5.8%)	16/130.7 (12.240)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	5 (1.8%)	5/135.8 (3.681)
Dry eye	3 (1.1%)	3/141.3 (2.124)
Conjunctivitis bacterial	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	1 (0.4%)	1/141.5 (0.707)
Eye pruritus	1 (0.4%)	1/141.5 (0.707)
Ocular hyperaemia	1 (0.4%)	1/141.5 (0.707)

*Source: Table 30 of study report for 1434
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
Subjects who experienced more than one TEAE were counted only once in each category
Abbreviations: CMQ, customized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; nP, number of patients with events; TEAE, treatment emergent adverse event.

Conclusion

The pattern of occurrence of conjunctivitis events in adolescents was similar to that seen in the adult program.

7.3.6. Safety Analyses by Demographic Subgroups

Table 24 presents the overall occurrence of TEAEs by subgroups. The number of subjects experiencing TEAEs was generally similar between treatment groups within each subgroup.

Table 24. Number of Subjects With TEAEs in Study 1526 by Subgroups*

	Placebo		Dupilumab			
			300 mg Q4W		200 mg or 300 mg Q2W	
	N (%)	# (%) with TEAEs	N (%)	# (%) with TEAEs	N (%)	# (%) with TEAEs
Age Group (yrs)						
≥12<15	41 (48.2%)	28 (68.3%)	45 (54.2%)	30 (66.7%)	43 (52.4%)	34 (79.1%)
≥15<18	44 (51.8%)	31 (70.5%)	38 (45.8%)	24 (63.2%)	39 (47.6%)	26 (66.7%)
Gender						
Male	53 (62.4%)	37 (69.8%)	51 (61.4%)	32 (62.7%)	43 (52.4%)	29 (67.4%)
Female	32 (37.6%)	22 (68.8%)	32 (38.6%)	22 (68.8%)	39 (47.6%)	31 (79.5%)
Ethnicity						
Not Hispanic or Latino	72 (84.7%)	50 (69.4%)	63 (75.9%)	41 (65.1%)	69 (84.1%)	50 (72.5%)
Hispanic or Latino	13 (15.3%)	9 (69.2%)	20 (24.1%)	13 (65.0%)	13 (15.9%)	10 (76.9%)
Race						
White	48 (56.5%)	34 (70.8%)	55 (66.3%)	37 (67.3%)	54 (65.9%)	40 (74.1%)
Black	15 (17.6%)	8 (53.3%)	8 (9.6%)	4 (50.0%)	7 (8.5%)	4 (57.1%)
Asian	13 (15.3%)	10 (76.9%)	13 (15.7%)	9 (69.2%)	12 (14.6%)	10 83.3%)
Other	6 (7.1%)	5 (83.3%)	7 (8.4%)	4 (57.1%)	7 (8.5%)	4 (57.1%)
Not reported or missing	3 (3.5%)	—	0	—	2 (2.4%)	—
Baseline weight group						
<60 kg	43 (50.6%)	31 (72.1%)	42 (50.6%)	27 (64.3%)	43 (52.4%)	35 (81.4%)
≥60 kg	42 (49.4%)	28 (66.7%)	41 (49.4%)	27 (65.9%)	39 (47.6%)	25 (64.1%)

*Sources: Post-text tables 7.2.1.1/2, 7.2.1.1/3, 7.2.1.1/4, 7.2.1.1/5, 7.2.1.1/6, 7.2.1.1/7 for study 1526

7.3.7. Specific Safety Studies/Clinical Trials

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

7.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in the adolescent program. Six subjects (2.2%) reported seven events in the "Neoplasms benign, malignant and unspecified (including cysts and polyps)" SOC in the OLE study (1434): skin papilloma (5), hemangioma (1), and melanocytic nevus (1). No events were reported in this SOC in the pivotal study 1526.

Pediatrics and Assessment of Effects on Growth

The Applicant proposes a pediatric indication in the supplement that is the subject of this review. Therefore, this sBLA review pertains to a pediatric assessment. The sBLA did not include an assessment of the effects 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 approved package insert advises the following in Section 10 ("OVERDOSE"):

> 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 molecule 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.

The data (clinical and nonclinical) do not indicate a potential for addiction, abuse, or physical dependency with use of dupilumab.

In the phase 2a PK study, R668-AD-1412, the Applicant evaluated the impact of discontinuation of dupilumab on efficacy parameters. The Applicant observed a trend towards the return of signs and symptoms of AD towards baseline, but not a worsening beyond baseline. Therefore, the data did not indicate a potential for a rebound effect.

Four-Month Safety Update

The four-month safety update (SU) provided updates on the AE data from study 1434 (OLE), the only ongoing study in the adolescent program. The SU covered the period from 04/22/2018 (04/21/2018 was the data cut-point for the sBLA) through 08/15/2018. An additional 25 subjects were included in safety analysis set for the SU relative to the 275 subjects in the safety analysis set in the submission of the supplement, making for a cumulative disposition of 300 subjects by cut-point for the SU. Study 1434 is currently ongoing with 270 subjects at data cut-point for the SU.

Table 25. Study R668-AD-1434: Summary of Subject Disposition–Cumulative Until 15 August 2018, and 21 April 2018 (Adolescents ≥12 to <18 Years of Age)–SAF

	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR)	Cumulative until 21 Apr 2018 (data cutoff for the First-step Analysis for the sBLA)
	Total (N=300)	Total (N=275)
Patients in Safety Analysis Set (SAF)	300 (100%)	275 (100%)
Patients who completed study	5 (1.7%)[1]	1 (0.4%)[2]
Patients ongoing	270 (90.0%)	270 (98.2%)
Patients who discontinued from study with reason	25 (8.3%)	4 (1.5%)
Adverse Event	1 (0.3%)	0
Physician Decision	4 (1.3%)	1 (0.4%)
Lost to Follow-up	1 (0.3%)	1 (0.4%)
Withdrawal by Patient	9 (3.0%)	2 (0.7%)
Lack of Efficacy	8 (2.7%)	0
Death	0	0
Other	2 (0.7%)	0
Patients who completed ≥ Week 16	273 (91.0%)	142 (51.6%)
Patients who completed ≥ Week 24	200 (66.7%)	83 (30.2%)
Patients who completed ≥ Week 26	174 (58.0%)	69 (25.1%)
Patients who completed ≥ Week 52	34 (11.3%)	34 (12.4%)
Patients who completed ≥ Week 78	34 (11.3%)	34 (12.4%)
Patients who completed ≥ Week 104	34 (11.3%)	32 (11.6%)
Patients who completed ≥ Week 156	0	0
Patients who completed ≥ Week 208	0	0
Patients who completed ≥ Week 260	0	0

*Source: Table 2of the Safety Update
[1]Per the protocol, subjects who turned 18 years of age during the study were asked to complete an end of treatment visit for the OLE and subsequently transitioned to commercial dupilumab.

No deaths were reported during the interval.

One subject experienced an SAE:

- *Herpes simplex*. A 13-year-old white female developed perioral vesicles with throat pain on day 864 (after 82 doses of study treatment and 79 days after last dose) with progression to periocular distribution at some point (unstated). She was hospitalized on day 870, where ophthalmological examination documented acute keratoconjunctivitis. She improved rapidly with oral and topical antiviral treatment and eye drops. She was discharged on an unspecified day and continued in the study as planned. Verbatim term: Disseminated Herpes Simplex.

One subject experienced a TEAE that resulted in permanent discontinuation of study treatment:

- *Dermatitis atopic*. A 16-year-old Asian female enrolled with AD graded as moderate: IGA of 3, EASI of 24.6; BSA was 31%. By day 113, her best recorded responses were IGA 3. EASI 15.8. and BSA 22%. On day 176 (7 days after most recent dose), “worsening AD” was recorded. Her IGA remained 3, EASI was 22, and BSA was 36%. She was withdrawn from the study.

Three subjects experienced AESIs:

- *Conjunctivitis viral*. A 15-year-old Asian male was diagnosed with viral conjunctivitis on day 135. He was treated and recovered. Study treatment was interrupted for approximately 2 weeks. He resumed treatment and continued in the study as planned.
- *Suicidal ideation*. A 12-year-old white male with a history of anxiety and insomnia began experiencing suicidal thoughts on day 240 (after 16 doses of study treatment and 15 days after last dose). The event resolved the following day. The investigator related the event to the AD. The subject was also taking sertraline and continued in the study as planned.
- *AKC.* A 14-year-old white male began experiencing eye symptoms on day 213. He was evaluated by an ophthalmologist on an unspecified day and was treated with eye drops. The investigator graded the event as “mild.” He recovered and continued in the study as planned.

In the SU, the most-commonly reported TEAEs continued to be Nasopharyngitis and Upper respiratory tract infection.

Conjunctivitis

Under the narrow CMQ, 25 (8.3%) of subjects reported an event compared with 12 subjects (4.4%) in the original supplement submission.

Table 26. Study R668-AD-1434: Number of Subjects With Treatment-Emergent Narrow CMQ Conjunctivitis by Preferred Term (Cumulative Incidence) (Adolescents ≥12 to <18 Years of Age)–SAF*

Preferred Term MedDRA version 21.1	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR) Total (N=300)		Cumulative until 21 Apr 2018 (data cutoff date for the First-Step Analysis CSR for the sBLA) Total (N=275)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)	nP/PY (nP/100 PY)
Number of TEAEs	40		22	
Patients with at least 1 TEAE	25 (8.3%)	25/211.9 (11.797)	12 (4.4%)	12/131.2 (9.149)
Conjunctivitis allergic	14 (4.7%)	14/219.6 (6.374)	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	9 (3.0%)	9/220.0 (4.090)	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	3 (1.0%)	3/224.6 (1.336)	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	2 (0.7%)	2/227.5 (0.879)	1 (0.4%)	1/141.5 (0.707)
Atopic keratoconjunctivitis	1 (0.3%)	1/227.9 (0.439)	0	0

*Source: Table 9 of the Safety Update
PTs included under Conjunctivitis Narrow CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis.

Under the broad CMQ, 29 (9.7%) of subjects reported an event compared with 16 subjects (5.8) in the original supplement submission.

Table 27. Study R668-AD-1434: Number of Subjects With Treatment-Emergent Broad CMQ Conjunctivitis by Preferred Term (Cumulative Incidence) (Adolescents ≥12 to <18 Years of Age)–SAF*

Preferred Term	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR) Total (N=300)		Cumulative until 21 Apr 2018 (data cutoff date for the First-Step Analysis CSR for the sBLA) Total (N=275)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)	nP/PY (nP/100 PY)
Number of TEAEs	47		27	
Patients with at least 1 TEAE	29 (9.7%)	29/210.2 (13.793)	16 (5.8%)	16/130.7 (12.240)
Conjunctivitis allergic	14 (4.7%)	14/219.6 (6.374)	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	9 (3.0%)	9/220.0 (4.090)	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	3 (1.0%)	3/224.6 (1.336)	2 (0.7%)	2/138.8 (1.441)
Dry eye	3 (1.0%)	3/226.7 (1.323)	3 (1.1%)	3/141.3 (2.124)
Ocular hyperaemia	3 (1.0%)	3/227.3 (1.320)	1 (0.4%)	1/141.5 (0.707)
Conjunctivitis viral	2 (0.7%)	2/227.5 (0.879)	1 (0.4%)	1/141.5 (0.707)
Atopic keratoconjunctivitis	1 (0.3%)	1/227.9 (0.439)	0	0
Eye pruritus	1 (0.3%)	1/227.6 (0.439)	1 (0.4%)	1/141.5 (0.707)

*Source: Table 11 of the Safety Update
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.

The Applicant reported the following outcomes for the 47 events identified under the broad analysis:

- 41 (87.2%) were resolved or resolving,
- 4 (8.5%) did not resolve by SU data cutoff,
- 1 (2.1%) had an unknown outcome, and
- 1 (2.1%) had a missing outcome.

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

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dupilumab is not currently approved for treatment of AD in patients <18 years of age.

Expectations on Safety in the Postmarket Setting

The data from adolescents provided in this supplement revealed a safety profile similar to that seen in adults. Therefore, based on the available safety data, the expectation is that the postmarketing experience for adolescents may be similar to adults.

7.3.10. Integrated Assessment of Safety

The sBLA did not include pooled data for an integrated safety assessment, due to the differing designs of the four studies that constituted the adolescent AD program. The safety database was comprised of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD who had received at least one dose of dupilumab by data cut-point for the sBLA. The safety review of the application focused on the placebo-controlled data from the pivotal study, 1526 (primary safety data) and the data from the OLE study, 1434 (supportive safety data).

No deaths occurred in the development program, and the incidence of SAEs was low. The single subject who experienced an SAE (appendicitis) in the primary safety group (study 1526), was in the placebo group. Of the four subjects who experienced SAEs in the OLE study (1434), only one experienced an event (injection site cellulitis) where a relationship to treatment was reasonably a consideration. However, there was no information to implicate dupilumab itself in the occurrence of this event; it could have been related entirely to injection procedures. The subject recovered fully and completed the study as planned.

Only one subject experienced a TEAE that led to permanent discontinuation of study treatment in studies 1526 and 1434. That subject was in the placebo group and was withdrawn from treatment due to worsening of AD. In the primary safety group (study 1526), all of the severe TEAEs of AD reported over the course of the study occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the more frequent Q2W dosing regimen. Generally, the safety profiles between the Q4W and Q2W regimens were similar.

In studies 1526 and 1434, TEAEs were most-commonly reported in the Infections and infestations SOC. The two most frequently-reported events in that SOC in both studies were Upper respiratory tract infection and Nasopharyngitis, both of which are common illnesses in the general population.

Laboratory, vital signs and ECG findings were generally unremarkable or consistent with previous experience with dupilumab (eosinophils) or the disease state (LDH in AD). The safety profile did not suggest a correlation between ADA positivity and events that might suggest loss of efficacy (“Dermatitis atopic”) or in injection site reactions.

Conjunctivitis and Keratitis

“Conjunctivitis and Keratitis” is a Warning and Precautions sub-section in the approved dupilumab package insert, and it was driven by a signal identified in the AD program in adults. In the adolescent program, the Applicant included conjunctivitis and keratitis events among the AESIs, events that required expedited reporting. Additionally, and similar to what was done in the adult program, the Applicant performed CMQs in the OLE study to further evaluate this known signal.

Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo in study 1526. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The incidences of conjunctivitis events under the narrow and broad CMQ analyses were higher in the OLE relative to the pivotal study. No eye disorders were recorded as SAEs. One case of “mild” keratitis was reported in a dupilumab-treated subject in study 1526 (pivotal). The subject was treated and recovered, and dupilumab dosing was not interrupted; the subject completed study treatment. One case of allergic conjunctivitis that occurred in study 1434 (OLE) was graded as “severe.” The subject was treated and continued dupilumab as planned. The experiences of these two subjects are consistent with those described in the label for adults, wherein subjects who experienced conjunctivitis or keratitis recovered or were recovering during dupilumab treatment. Based on review of placebo-controlled data (pivotal study 1526) and long-term data (study 1434), the patterns of occurrence and course of conjunctivitis and keratitis events in adolescents were similar to what was seen in the adult program.

The Applicant adequately evaluated the risk of eye disorders in adolescents. Additionally, the Applicant has adequate measures in place for continued assessment of these events in pediatric subjects in the ongoing, long-term study 1434. This study will ultimately enroll subjects down to 6 months of age, and the protocol specifies procedures for referral to an ophthalmologist and, per the protocol, preferably one with pediatric expertise or cornea and external eye disease subspecialty expertise.

Hypersensitivity

"Hypersensitivity" is labeled in the Warning and Precautions section of the approved package insert, based on the safety data from the AD program in adults. Labeled reactions noted in the adult program included generalized urticaria and serum sickness or serum sickness-like reactions. No systemic hypersensitivity reactions were reported in the adolescent program.

Concomitant Use of Topicals

Study 1526 was the only monotherapy study in the adolescent development program. The other three studies allowed concomitant topical therapies e.g., TCS, TCI. The safety profile of dupilumab when administered as monotherapy was similar to that when it was administered with concomitant topical therapy. Thus, the development program supports the labeling for use of dupilumab "with or without topical corticosteroids" and for the allowance of use of concomitant TCIs ("for problem areas only, such as the face, neck, intertriginous and genital areas") in adolescents.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting the overall conclusion. The amount of missing data was relatively small (approximately 8%) at the primary timepoint, week 16. The results for the primary and secondary efficacy endpoints in Table 10 for both dupilumab dosing regimens (Q2W and Q4W) were statistically significant (p-values <0.001). Approximately 59% of the subjects were male, and 63% were white. The average age was about 14.5 years with an average weight of 65 kg. Due to the limited sample size, it was difficult to draw any meaningful conclusions in the efficacy analysis by subgroups (age, sex, race, weight, baseline disease severity).

7.4.2. Conclusions and Recommendations

To establish the effectiveness of dupilumab in the treatment of moderate to severe AD in adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial. The trial randomized 251 adolescent subjects (12 to <17 years of age) with moderate to severe AD defined as having IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with

at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16.

The Applicant comprehensively evaluated the safety of dupilumab in 322 subjects 12 to 17 years of age with moderate-to-severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. The safety evaluation identified no new signals or concerns, and the safety profile in adolescents was similar to that observed in adults with AD. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

Results from the ongoing long-term study (1434) will continue to inform the safety of use of dupilumab in adolescents with moderate to severe AD. Information from this study along with product labeling and routine pharmacovigilance activities should serve as adequate risk mitigation strategies.

The submitted safety data support approval of the sBLA and the proposed expansion of the indication to allow for the “treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.” The data further support labeling for allowance of use of concomitant TCS and TCI.

8 Advisory Committee Meeting and Other External Consultations

This application was not discussed at an Advisory Committee Meeting.

9 Pediatrics

The approval letter for the original BLA (03/28/2017) details the following outstanding required pediatric assessments:

3183-1 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 6 years to less than 12 years of age with severe AD.

Final Protocol Submission: 03/18

Study Completion: 06/19

Final Report Submission: 09/19

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 AD.

Final Protocol Submission: 04/18

Study Completion: 12/22

Final Report Submission: 03/23

3183-4 Conduct a safety, PK, and efficacy study in subjects 6 months to less than 6 years with severe AD.

Final Protocol Submission: 01/18

Study Completion: 08/21

Final Report Submission: 11/21

The Applicant provided the status of the outstanding pediatric assessments in the Annual Report submitted 05/25/2018 as Sequence 0264:

- The study in subjects 6 years to less than 12 years of age with severe AD (3183-1) is ongoing and "on track."
- The safety, PK, and efficacy study in subjects 6 months to less than 6 years with severe AD (3183-4) is enrolling. However, "the clinical trial authorization was slower than anticipated as several queries were received from the health authorities, all of which were successfully clarified and resolved. The study enrollment is also proving to be slower than anticipated."

The 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 AD (3183-3) is also ongoing. The Applicant provided data from this study for the adolescent population in this supplement (study 1434).

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

10 Labeling Recommendations

10.1. Prescribing Information

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

10.2. Patient Labeling

11 Risk Evaluation and Mitigation Strategies (REMS)

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

12 Postmarketing Requirements and Commitments

See Section 10.

13 Appendices

13.1. References

See footnotes in Section 2.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study R668-AD-1526 ("A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 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: 45		
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): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

In this submission, the Applicant provided no new nonclinical information. Therefore, section 13.3 is not applicable to this review.

13.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

13.4.1. Individual Study Summary

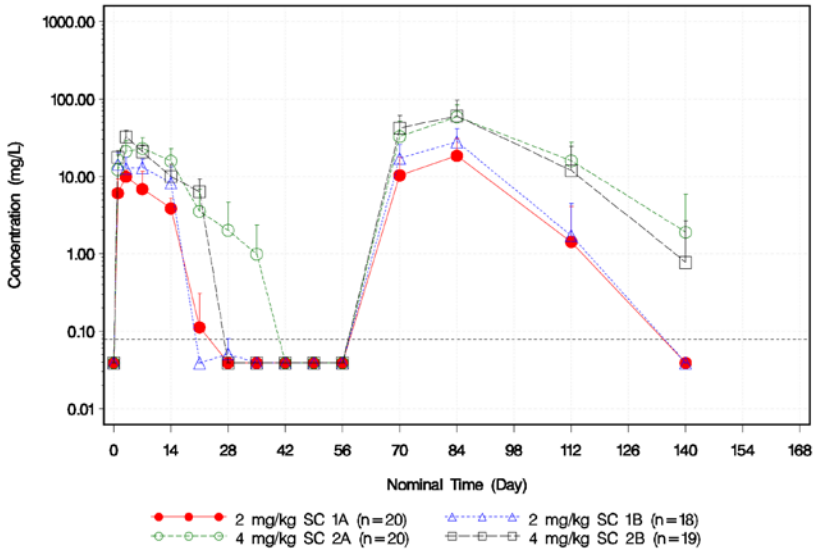
In the current sBLA, the Applicant submitted clinical pharmacology data from four dupilumab clinical trials in adolescent patients with moderate-to-severe AD: R668-AD-1526, R668-AD-1412, R668-AD-1434 and R668-AD-1607. The PK and immunogenicity data for phase 3 study R668-AD-1526 are summarized in Section 6 of this review. Note that it was decided internally that study R668-AD-1607 supporting the approval of the autoinjector presentation will be reviewed in a separate sBLA. This section provides individual study summary for phase 2a study R668-AD-1412 and the OLE phase 3 study R668-AD-1434.

13.4.1.1. Study R668-AD-1412

Study R668-AD-1412 was a phase 2a ascending dose, sequential cohort study of single dose and repeat doses of SC dupilumab in pediatric AD patients ≥6 to <18 years of age. Pediatric AD patients were administered with single dose in Part A followed by four repeated weekly doses of 2 mg/kg (Cohort 1) or 4 mg/kg (Cohort 2) in Part B.

The concentration-time profiles for dupilumab in serum are shown in Figure 11. The maximal concentrations were observed on day 2 through day 8 following a single SC administration. The PK results suggest concentration dependent elimination, consistent with target-mediated drug disposition.

Figure 11. Mean ± SD Serum Dupilumab Concentrations-Time Profiles in Study R668-AD-1412



1A and 2A, adolescents ≥12 to <18 years of age; 1Band 2B, children ≥6 to <12 years of age
Source: Figure 2, PK report for CSR R668-AD-1412

13.4.1.2. Study R668-AD-1434

This summary for study R668-AD-1434 is based on Applicant's individual study summary provided in Section 2.2.4 of the Summary of Clinical Pharmacology Studies.

Study R668-AD-1434 was an ongoing, phase 3, OLE study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in pediatric patients with AD who have previously completed a clinical study with dupilumab (i.e., Studies R668-AD-1412, R668-AD-1526, and R668-AD-1607). Pediatric patients who had previously enrolled in prior dupilumab pediatric AD studies were given dupilumab 2 mg/kg QW, 4 mg/kg QW, 300 mg Q4W, or 200/300 Q2W, delivered by PFS. Only results from adolescent patients ≥12 years to <18 years of age were reported in this sBLA.

Patients aged ≥6 years to <18 years were started on a dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at week 16 to either 300 mg Q2W (for patients weighing ≥60 kg) or 200 mg Q2W (for patients weighing <60 kg). It should be noted that in the original protocol, patients received weight-based dosing of 2 mg/kg or 4 mg/kg; a fixed dose regimen of 300 mg Q4W was implemented with amendment 1.

Patients who rolled over from R668-AD-1412 received weight-based dosing (2 mg/kg QW or 4 mg/kg QW) for a significant duration (median duration of treatment exposure was around 89 weeks), before being switched to a fixed dose (300 mg Q4W). On the

other hand, patients who rolled over from R668-AD-1526 and R668-AD-1607 received a fixed dose from the time they enrolled into the study.

For patients entering from study R668-AD-1412, PK data were summarized through week 48, during which all patients were maintained on either 2 or 4 mg/kg QW. Individual PK and ADA data were presented for as long as week 104. For patients entering from R668-AD-1607 and R668-AD-1526, both summary and individual level data were presented through week 16. Samples for drug concentration assessments for the patients ≥12 years to <18 years were collected on days 1, 113, 365, 533, 729, 1065, 1401, and 1821. Samples for ADA analysis were collected at baseline, and weeks 4, 12, 24, 36, and 48 for patients recruited from parent study R668-AD-1412 and for patients recruited from R668-AD-1607 and R668-AD-1526, samples were collected at baseline and week 16.

PK Results

At the time of the data cut-off for this report, a total of 275 patients aged ≥12 to <18 years from parent studies were included in the study. Adolescent patients receiving a 2 mg/kg QW regimen achieved mean SS trough concentration at week 48 of 73 mcg/mL versus 161 mcg/mL for the 4 mg/kg QW regimen. The mean concentration of dupilumab at week 16 in adolescent patients from parent studies R668-AD-1526 and R668-AD-1607 who received 300 mg Q4W in R668-AD-1434 was 15.9 mcg/mL. In those adolescent patients who were up-titrated to 200 mg/300 mg Q2W due to inadequate response, mean trough concentrations at week 16 was approximately 45 mcg/L.

Immunogenicity Results

The overall incidence of treatment-emergent ADA in R668-AD-1434 was 26.5% and the responses were mostly transient and of low titer. The overall incidence of persistent ADA was 5.9%. Three (2.2%) high titer responses were observed (2 of the patients from study R668-AD-1412 who initially received a 2 mg/kg QW dose and one from study R668-AD-1526). Three (2.2%) moderate responses were observed in patients who received a 4 mg/kg QW regimen from parent study R668-AD-1412. The distribution of dupilumab concentrations for ADA positive patients was generally in the range of concentrations of ADA negative patients with the exception of a few patients with high or moderate ADA titers.

13.4.2.Population PK Analysis

The goal of population PK (popPK) analysis was to develop a popPK model to assess sources of variability (intrinsic and extrinsic covariates) of dupilumab in adolescent subjects with AD. The popPK model included 162 adolescent patients ≥12 years to <18 years of age with moderate to severe AD who were on active dupilumab treatment from

study R668-AD-1526. Among them 43 patients received dupilumab 200 mg Q2W, 37 received dupilumab 300 mg Q2W, and 82 received 300 mg Q4W.

The PK of dupilumab was characterized with a two-compartment model with parallel linear and nonlinear Michaelis-Menten elimination and transit compartments used to describe the absorption of dupilumab (Figure 12). Same model structure had been applied to the previous popPK model in adult AD patients. Population PK of dupilumab were characterized by nonlinear mixed-effects modeling using Monolix version 2018R1 (Lixoft). Parameter estimates of final model with significant covariates were provided in Table 28. Shrinkage was 25.3% and 54.3% for empirical bayes estimates of elimination rate and V2, respectively. There were small and inconsequential numeric differences in popPK parameters between adolescent and adult models. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 13 and Figure 14).

Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of dupilumab in all treatment groups (Figure 15). The final popPK model included statistically significant effects of body weight on apparent volume of distribution and body mass index, ADA and EASI on apparent elimination rate. The covariate coefficients for ADA, body mass index, EASI score, and body weight were similar to those in the adult model (Table 28). The effect of disease activity (EASI score) and ADA on dupilumab exposure is not clinically relevant. Body weight was a statistically significant and clinically relevant covariate on dupilumab exposure. Weight-tiered dosing regimen with a cut-off value of 60 kg was applied in the clinical trial.

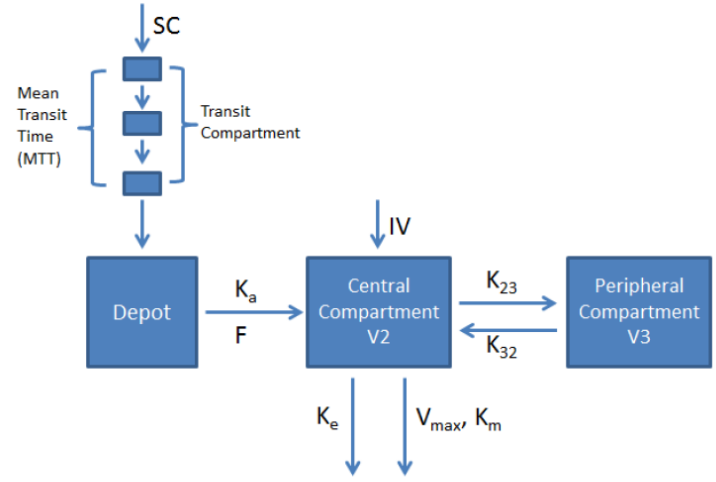
The dupilumab concentration-time profile in 1-year treatment period with the recommended weight-tiered Q2W dosing regimen was predicted based on the post hoc PK parameters in 162 adolescent AD patients from study R668-AD-2526 (Figure 16). The central tendency and variability of dupilumab concentrations were comparable between the two dosing regimens (200 mg Q2W and 300 mg Q2W). In addition, average, trough and maximum concentration at SS (the 26th dose) with the recommended dosing regimen were calculated. The distributions of C_{avg}, C_{trough}, and C_{max} achieved by the two dosing regimens were similar. The difference in median point estimate is within 10%. The SS C_{trough} of dupilumab achieved by the recommended dosing regimen (200/300 mg Q2W) in adolescent AD patients appears to be slightly lower (within 25%) than that in adult AD patients (300 mg Q2W), which is partly due to the difference in body weights between adolescent and adult patients.

Table 28. Parameter Estimates of the Final Model

Parameter Name	Adolescent Covariate Model		Adult Covariate Model	
	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)
PK parameter				
V_2 (L)	2.47 (0.0501)	2.45 (2.34, 2.56)	2.74 (0.021)	2.72 (2.67, 2.78)
k_e (1/d)	0.0520 (0.00188)	0.0504 (0.0338, 0.0560)	0.0477 (0.00078)	0.0477 (0.0457, 0.0498)
V_m (mg/L/d)	1.43 (0.0379)	1.43 (1.25, 1.61)	1.07 (fixed)	---
k_{23} (1/d)	0.211 (fixed)	---	0.211 (fixed)	---
k_{32} (1/d)	0.310 (fixed)	---	0.310 (fixed)	---
k_a (1/d)	0.306 (fixed)	---	0.306 (fixed)	---
MTT (d)	0.105 (fixed)	---	0.105 (fixed)	---
K_m (mg/L)	0.01 (fixed)	---	0.01 (fixed)	---
F (unitless)	0.642 (fixed)	---	0.642 (fixed)	---
Covariates				
V_2 ~ weight	0.755 (0.0517)	0.722 (0.579, 0.845)	0.817 (0.031)	0.805 (0.740, 0.891)
V_2 ~ albumin	---	---	-0.653 (0.072)	-0.679 (-0.829, -0.536)
k_e ~ BMI	0.357 (0.116)	0.367 (0.0244, 0.809)	0.368 (0.053)	0.378 (0.225, 0.521)
k_e ~ ADA	0.193 (0.0566)	0.196 (0.0634, 0.325)	0.164 (0.029)	0.168 (0.103, 0.248)
k_e ~ EASI	0.356 (0.0523)	0.350 (0.237, 0.481)	0.143 (0.021)	0.147 (0.104, 0.198)
k_e ~ race (white)	---	---	-0.123 (0.018)	-0.116 (-0.168, -0.0749)
Omega Matrix				
$\sigma(\eta(V_2))^a$	0.304 (0.0242)	0.309 (0.105, 0.172)	0.206 (0.0068)	0.213 (0.198, 0.231)
$\sigma(\eta(k_e))$	0.140 (0.0145)	0.140 (0.245, 0.351)	0.293 (0.010)	0.306 (0.280, 0.332)
Corr (k_e,V_2)	-0.529 (0.0902)	-0.563	-0.450 (0.035)	-0.502
Residual SD				
σ prop. (CV%)	9.94 (0.602)	10.1 (7.19, 12.2)	12.5 (0.18)	12.3 (0.117, 0.132)
σ add. (mg/L)	2.36 (0.24)	2.33 (1.56, 3.81)	6.06 (0.23)	6.04 (4.85, 7.03)
Derived Parameters[b]				
CL (L/d)	0.128	---	0.131	---
Q (L/d)	0.521	---	0.578	---
V_3 (L)	1.68	---	1.86	---

Source: Table 10, Population PK report

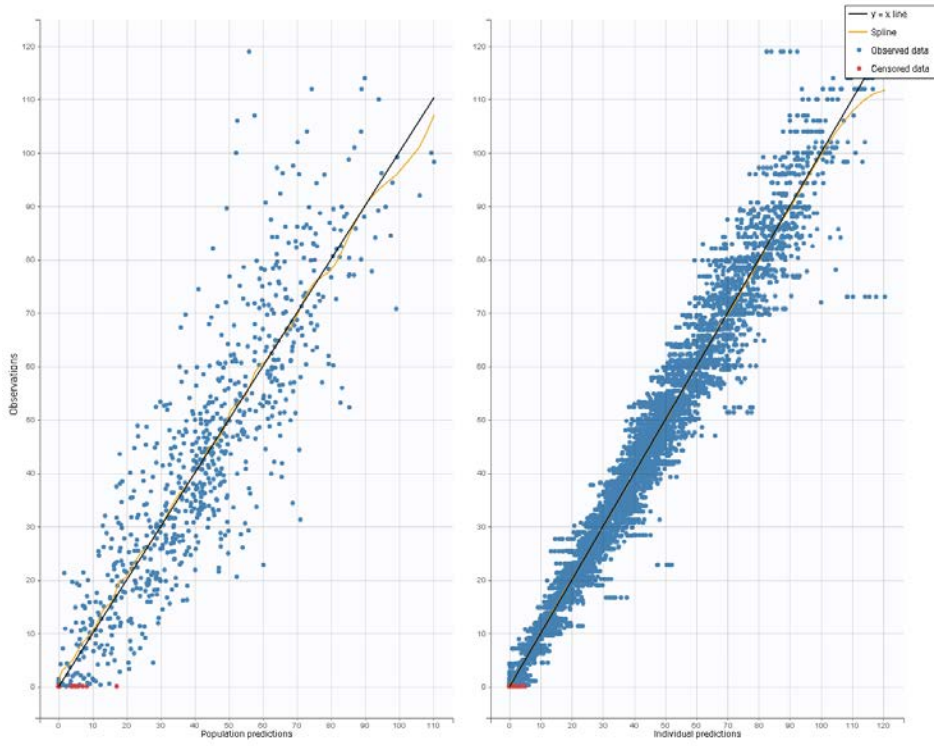
Figure 12. Structural Representation of Model With Parallel Michaelis-Menten and Linear Elimination of Dupilumab



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

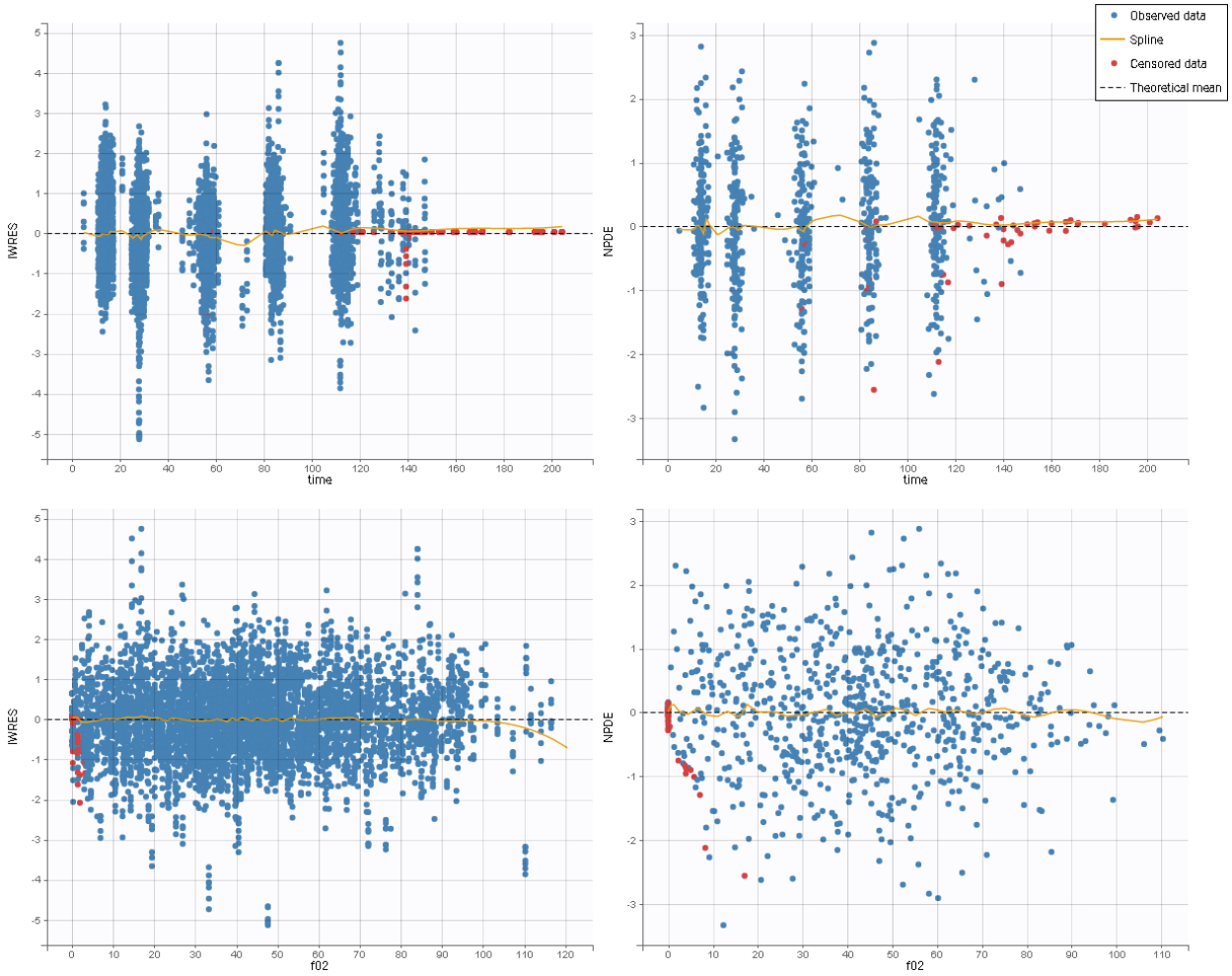
Source: Figure 2, Population PK report

Figure 13. Observed vs. Population and Individual Predicted Concentrations for Final Adolescent Model



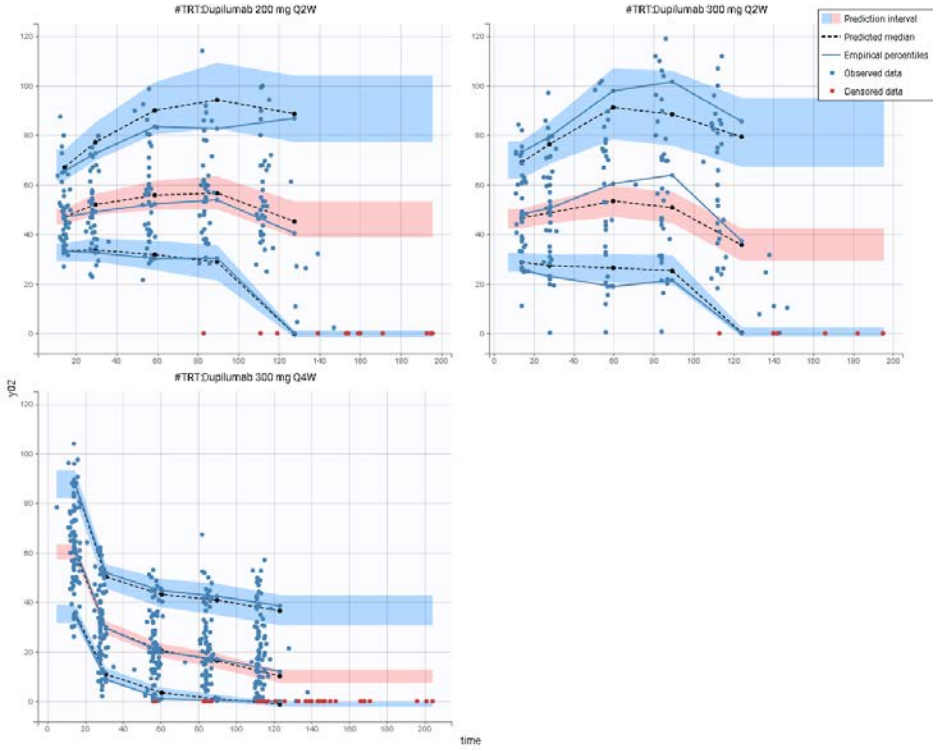
Source: Reviewer's analysis to confirm Figure 11 in Applicant's Population PK report

Figure 14. Scatter Plots of Residuals for Final Adolescent Model



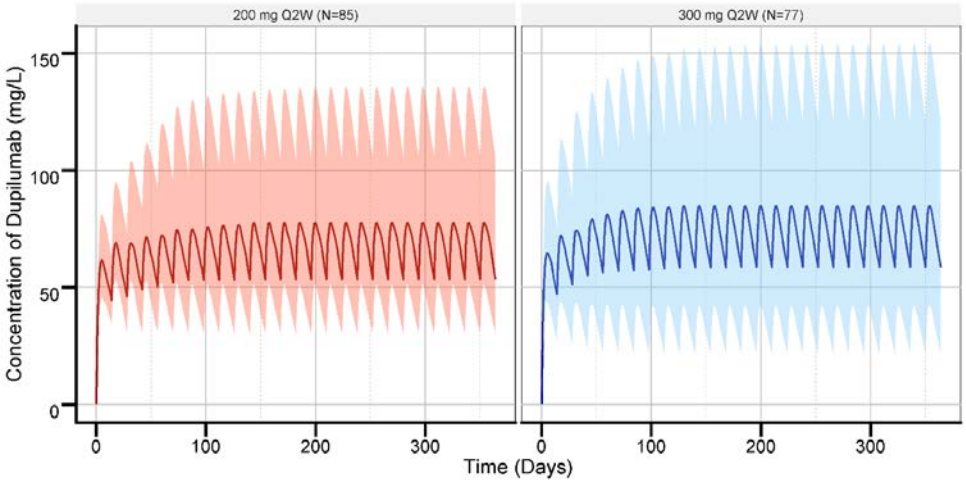
Source: Reviewer's analysis to confirm Figure 12 in Applicant's Population PK report

Figure 15. Visual Predictive Checks for Final Adolescent Model by Treatment vs. Actual Day



Source: Reviewer's analysis to confirm Figure 16 in Applicant's Population PK report

Figure 16. Predicted Dupilumab Concentration-Time Profile Based on Weight-Tiered Q2W Dosing Regimen



Dupilumab concentration was predicted based on post hoc PK parameters from 162 adolescent AD patients.
Solid line: Median. Colored bands: 5th and 95th percentile
Source: Reviewer's analysis based on final adolescent PK model

13.4.3.Dose/Exposure Response Relationships

In study R668-AD-1526, following the initial dosing both dose regimens (200 mg/300 mg Q2W and 300 mg Q4W) showed statistically significant improvement over placebo on both primary and secondary efficacy endpoints. The efficacy responses achieved with the weight-tiered Q2W regimen (adolescents <60 kg receiving 200 mg Q2W and adolescents ≥60 kg receiving 300 mg) were numerically higher to those with the 300 mg Q4W for the majority of efficacy endpoints (Table 29). Within the Q2W dosing regimen, the efficacy responses were observed to be lower in 300 mg Q2W group compared to 200 mg Q2W group despite similar observed dupilumab exposure (Table 30). However, this exploratory comparison is limited by small sample size and could be confounded by unknown baseline predictors.

Exposure-efficacy analyses were conducted in adolescents with moderate-to-severe AD receiving 200 mg Q2W (N=40), 300 mg Q2W (N=36) and 300 mg Q4W (N=81) from study R668-AD-1526. Efficacy endpoints include the co-primary endpoints, percentage of patients achieving an IGA score of 0 or 1 (IGA (0,1)) and reduction of 75% in EASI score from baseline (EASI-75), and the evaluated exposure metric was observed dupilumab concentration at week 16. Among 157 adolescent patients included in the analysis, the percentage of patients achieving an IGA score of 0 or 1 or a 75% reduction in EASI score is higher in quartiles of higher dupilumab concentration. Week 16 dupilumab concentration appears to be positively associated with both the co-primary efficacy endpoints. The final logistic regression model also identified dupilumab concentration at week 16 and disease severity (baseline EASI total score) as significant covariates on both IGA (0,1) and EASI-75 (Figure 2).

Exposure-safety relationship was also evaluated in 157 adolescent patients from study R668-AD-1526. Safety endpoint was conjunctivitis, the most commonly reported adverse drug reaction, and the evaluated exposure metric was observed dupilumab concentration at week 16. Percentage of patients developing conjunctivitis appears to be similar with increasing rank order of quartiles of dupilumab trough concentrations. No evident ER relationship for the probability of developing conjunctivitis was identified in the logistic regression analysis (Figure 7).

Table 29. Overview of Co-Primary and Key Secondary Efficacy Endpoints of Pivotal Study R668-AD-1526

	Placebo	Dupilumab	
	N=85	300 mg Q4W N=84	200/300 mg Q2W N=82
Co-Primary Efficacy Endpoints			
Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16			
n (%)[1]	2 (2.4)	15 (17.9)**	20 (24.4)*
Difference vs. placebo (95% CI)		15.5 (6.70, 24.31)	22.0 (12.20, 31.87)
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16			
n (%)[1]	7 (8.2)	32 (38.1)*	34 (41.5)*
Difference vs. placebo (95% CI)		29.9 (17.94, 41.78)	33.2 (21.07, 45.39)
Key Secondary Efficacy Endpoints			
Percent change in EASI score from baseline to week 16			
LS mean (SE)[2]	-23.6 (5.49)	-64.8 (4.51)*	-65.9 (3.99)*
Difference vs. placebo (95% CI)		-41.2 (-54.44, -28.02)	-42.3 (-55.60, -29.04)
Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS			
LS mean (SE)[2]	-19.0 (4.09)	-45.5 (3.54)*	-47.9 (3.43)*
Difference vs. placebo (95% CI)		-26.5 (-37.45, -15.63)	-29.0 (-39.54, -18.38)
Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline to week 16			
n/N1[3] (%)[1]	8/85 (9.4)	32/83 (38.6)*	40/82 (48.8)*
Difference vs. placebo (95% CI)		29.1 (16.97, 41.32)	39.4 (26.90, 51.84)
Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16			
n/N1[4] (%)[1]	4/84 (4.8)	22/83 (26.5)*	30/82 (36.6)*
Difference vs. placebo (95% CI)		21.7 (11.21, 32.28)	31.8 (20.45, 43.20)

LS = least square; SE = standard error; CI = confidence interval
Source: Table 2, Clinical Overview

Table 30. Overview of Efficacy Endpoints by Treatment and Weight Groups (Study R668-AD-1526)

	200 mg Q2W (<60 kg) (n=40)	300 mg Q2W (>=60 kg) (n=36)	300 mg Q4W (<60 kg) (n=41)	300 mg Q4W (>=60 kg) (n=40)
Proportion of patients with IGA 0 to 1 at week 16	13 (32.5%)	7 (19.4%)	7 (17.1%)	8 (20%)
Proportion of patients with EASI-75 at week 16	20 (50.0%)	13 (36.1%)	18 (43.9%)	14 (35.0%)

Source: Reviewer's analysis based on dataset "adpcef.xpt"

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