26 January 2023
EMA/66726/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: dupilumab

Procedure no: EMEA/H/C/004390/II/0060

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AD	Atopic dermatitis
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BLA	Biologics License Application
BLQ	Below limit of quantitation
BMI	Body mass index
bpm	Beats per minute
BSA	Body surface area (affected by AD)
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence interval
CL	Linear clearance
Cmax	Maximum concentration
CMQ	Customized MedDRA query
CNS	Central nervous system
CRSwNP	Chronic rhinosinusitis with nasal polyps
CSR	Clinical study report
Ctrough	Trough concentration
CTD	Common Technical Document
Ctrough	Trough concentration
Ctrough,ss	Trough concentration at steady state
DFI	Dermatitis Family Index
DP	Drug product
DS	Drug substance
DTL	Drug tolerance limit
EASI	Eczema Area and Severity Index
EASI-50	50% reduction in EASI
EASI-75	75% reduction in EASI
EASI-90	90% reduction in EASI
ECG	Electrocardiogram
EMA	European Medicines Agency
EOT	End of treatment
E-R	Exposure-response
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
HLT	High-level term
HOME	Harmonising Outcome Measures for Eczema
IDQOL	Infants' Dermatology Quality of Life Index
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IgG4	Immunoglobulin G4
IL	Interleukin
IL-4Rα	Interleukin-4 receptor alpha
ISR	Incurred sample reanalysis
ISR	Injection site reaction
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation

LOCF	Last observation carried forward
LS	Least square(s)
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAb	Neutralizing antibody
nP/100 PY	Number of patients per 100 patient-years
NRS	Numeric Rating Scale
OLE	Open-label extension
PCSV	Potentially clinically significant value
PD	Pharmacodynamic
PDE4	Phosphodiesterase-4
PFS	Prefilled syringe
PK	Pharmacokinetics
POEM	Patient-Oriented Eczema Measure
PopPK	Population PK model
PT	Preferred term
QW	Once weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QOL	Quality of life
QTcB	QT corrected by Bazett's formula
QTcF	QT corrected by Fredericia's formula
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SE	Standard error
SOC	System organ class
TARC	Thymus and Activation-Regulated Chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Th2	Type 2 helper T cell
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCF	Worst-observation-carried-forward

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 8 March 2022 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from Study R668-AD-1539; this is a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 Months to <6 years with moderate-to-severe atopic dermatitis.
As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0329/2021on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0329/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0329/2021 on 25 February 2022.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Finbarr Leacy

Timetable	Actual dates
Submission date	8 March 2022
Start of procedure:	26 March 2022
CHMP Rapporteur Assessment Report	23 May 2022
PRAC Rapporteur Assessment Report	25 May 2022
CHMP Co-Rapporteur Critique	1 June 2022
Updated PRAC Rapporteur Assessment Report	2 June 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 June 2022
Request for supplementary information (RSI)	23 June 2022
CHMP Rapporteur Assessment Report	13 September 2022
PRAC Rapporteur Assessment Report	15 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	3 October 2022
Updated CHMP Rapporteur Assessment Report	6 October 2022
Request for supplementary information (RSI)	13 October 2022
CHMP Rapporteur Assessment Report	22 December 2022
PRAC Rapporteur Assessment Report	29 December 2022
PRAC members comments	4 January 2023
Updated PRAC Rapporteur Assessment Report	5 January 2023
PRAC Outcome	12 January 2023
CHMP members comments	16 January 2023
Updated CHMP Rapporteur Assessment Report	19 January 2023
Opinion	26 January 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic condition characterized by systemic immune dysregulation, altered epidermal-barrier function, and relapsing inflammatory skin lesions, variably characterised by erythema, edema, scaling, erosions/excoriations, oozing/crusting, and lichenification depending on patient age, ethnicity, and disease chronicity. The pathophysiology of AD is

complex and is influenced by genetic, immunologic, and environmental factors which lead to a dysfunctional skin barrier and dysregulation of the immune system (Bieber, 2008) (Eichenfield, 2014).

State the claimed the therapeutic indication

This submission proposes to extend the pediatric age range for the DUPIXENT indication in AD to include children ≥6 months to <6 years of age as follows:

Atopic dermatitis

Adults and adolescents

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age

Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 **months** to 11 years old who are candidates for systemic therapy.

Epidemiology

Atopic dermatitis is one of the most common skin disorders in infants and children (Mortz, 2015). In a study conducted in children 3 to 11 years old with AD, the onset of the condition occurred before the age of 6 months in 45% of children and before the age of 1 year in 60% of children with AD (Kay, 1994). A cross-sectional, international epidemiologic study showed the point prevalence of AD for children aged 6 months to <6 years ranges from 3.3% to 18.7% globally and is 10.2% in the US, 16.1% in the United Kingdom, and 7.1% in Germany (Silverberg, 2021). In a study of children aged up to 2.5 years with AD conducted in the United Kingdom (n=8530), the period prevalence rates of AD were highest at age 6 months to 18 months (25.6%) compared with 21% at 0 months to 6 months, 23.2% at 18 months to 23 months, and 19.9% at 30 months to 42 months (Wadonda-Kabondo, 2003). Disparities may exist even within industrialized nations, with urban children and black females disproportionately impacted (McKenzie, 2019).

Biologic features, Aetiology and pathogenesis

The pathophysiology of AD is influenced by genetics and environmental factors and involves a complex interplay between antigens, skin barrier defects, and immune dysregulation, in which a polarised inflammatory response induced by the marked activation of the T-helper type 2 (Th2) cell axis plays a central role (Gittler, 2012). Two cytokines, IL-4 and IL-13 are critical in the initiation and maintenance of the type 2 inflammatory pathway (Gandhi, 2016). The elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the type 2 cytokines IL-4 and IL-13 (Leung, 1999). Type 2 cytokines regulate important barrier-related functions, such as epidermal cornification and production of antimicrobial proteins. These cytokines inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensing 2 and 3 (Howell, 2007) (Guttman-Yassky, 2011a) (Guttman-Yassky, 2011b). The type 2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as TARC) and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for the Th2 cells and eosinophils, thus perpetuating the inflammatory response. Infant AD presents robust downregulations of multiple barrier-related genes in both lesional and nonlesional skin (Renert-Yuval, 2021a). The shared signature of AD across ages is type 2-skewed

and clinical severity scores significantly correlate with type 2-related markers in all pediatric age groups (Renert-Yuval, 2021a). Most mechanistic studies investigating the cellular and molecular mechanisms of disease in AD are limited to evaluating peripheral blood biomarkers given the difficulties involved with collection of skin biopsies in children. These studies have shown that, as in adults, disease activity in children correlates with several serum biomarkers (ie, CCL17, eosinophils, IgE) and a limited array of Th2/Th1 markers (Brunner, 2017) (Renert-Yuval, 2021b).

Clinical presentation, diagnosis

Clinical presentation of AD in infants (≤1 year) involves lesions that often emerge in the first few months of life, affecting the cheeks with pruritic papules and vesicles that form oozing plaques with crust. In addition, the scalp, neck, extensor extremities, and trunk may be diffusely affected by inflammatory lesions. After 1 to 2 years, lesions can still be acute; however, lichenified, chronic lesions begin to predominate with a predilection for flexural sites. In addition, hand and foot dermatitis as well as nummular plaques with oozing and crusting on the hands and wrists can appear (Nomura, 2020). Linear excoriations due to scratching are common. The background nonlesional skin is often xerotic, and there may be plate-like ichthyosis of the distal extremities, especially in older children. The cycle of itching and scratching exacerbates the cellular damage in skin lesions and facilitates secondary infections, which can be serious (Boguniewicz, 2018).

Children with AD, similar to adults with AD, are more frequently colonised with *Staphylococcus aureus* than their healthy counterparts. In addition, AD patients are at an increased risk for eczema herpeticum, a potentially life-threatening disseminated herpes simplex infection.

Atopic dermatitis has been shown to have a marked impact on the quality of life (QoL) of pediatric patients, greater than that seen in other common skin disorders like psoriasis and urticarial (Beattie, 2006). In one study nearly two-thirds of children with severe AD had moderately-to-highly impaired QoL (Ricci, 2007). In infants, the greatest impact of AD includes itching, sleep loss, mood and behavioral changes (Ramirez, 2019a) (Lewis-Jones, 2001). In children, severe pruritus is an almost universal finding in AD. Parents or caregivers of children with moderate and severe AD spend nearly 3 hours a day caring for their child's skin causing parental fatigue and irritability due to lack of sleep and/or privacy, often due to co-sleeping, and lack of leisure and family time. This, as well as treatment-related financial expenditures, and feelings of hopelessness, guilt, and depression (Tollefson, 2014) (Mancini, 2008) (Ahmed, 2013) adversely impact QoL and psychological and emotional wellbeing (Ramirez, 2019b) (Ricci, 2007) (Drucker, 2017).

Patients with AD are at risk of developing both allergic comorbidities and non-allergic conditions such as obesity, and autoimmune disease, particularly alopecia areata and gastrointestinal immune-mediated disorders (Paller, 2018). Of particular interest in younger children is the phenomenon of "Atopic March" which is characterized by a typical sequence of progression of clinical signs of atopic disease. In general, the clinical signs of AD and of food allergies predate the development of asthma and allergic rhinitis, suggesting that AD is an "entry point" for subsequent allergic disease (Spergel, 2003). Infants and young children with severe AD have a reported risk rate of around 60% for developing asthma later on in life compared to a risk of around 30% in patients with mild AD (Ricci, 2006).

Management

Currently available therapies have significant side effects, and various systemic immunosuppressive drugs are used off-label with little evidence to support their use. Similar to the adult and adolescent populations, topical treatment is the mainstay of management of AD in children.

Topical corticosteroids (TCS) of varying potency represent the cornerstone of topical treatment and some low potency TCS are approved in pediatric patients <1 year old. However, their long-term use or application to the large body-surface area is limited by the risk of local side effects (eg, skin atrophy and telangiectasia) as well as systemic adverse effects, including hypothalamic-pituitary-adrenal axis suppression and Cushing's syndrome (Hengge, 2006).

Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, are also available for use in children, mostly as second-line therapy as an alternative to or in combination with TCS. Use of these agents is typically limited to areas that are prone to skin atrophy from application of TCS, (eg, face, genitals, and flexural areas). Tacrolimus 0.03% is approved for use in ages ≥2 years, however, the more effective higher potency formation (0.1%) is not approved for use in children less than <16 years in the US or EU. Concerns of skin malignancies and increased risk of lymphomas have prompted some regulatory authorities to require a warning in the prescribing information regarding their long-term safety, including a boxed warning from the FDA.

For pediatric patients with severe disease resistant to topical therapies, systemic corticosteroids, phototherapy (UVA and UVB), and systemic immunosuppressive drugs (eg, cyclosporine,

azathioprine, mycophenolate mofetil, methotrexate) are utilized in clinical practice. A recent survey conducted in Europe found that approximately 70% of specialists recommended off-label systemic therapy for children with severe AD (Proudfoot, 2013). None of these drugs, apart from systemic corticosteroids, are approved for the treatment of AD in children. Use of systemic corticosteroids is strongly discouraged in AD due to lack of safety and efficacy data from well-designed studies, side effects associated with both short and long-term use, and risk of disease rebound following discontinuation (Boguniewicz, 2017) (Drucker, 2018).

Other systemic immunosuppressants, such as cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil, have been used off-label in infants and young children despite minimal evidence for the use of these agents in children, including limited data on efficacy, optimal dosing and monitoring, and significant potential side effects that include a wide variety of hematologic and organ toxicities and drug interactions (Lebwohl, 2019) (Flohr, 2013) (Purvis, 2019) (Anderson, 2019). These agents are nonselective, broad-acting immunosuppressive agents that can predispose patients to infection. Moreover, these agents can increase the risk of malignancy (Garritsen, 2017).

Ummet medical need

Severe AD is a serious, chronic, debilitating skin disease with substantial impact on day-to-day functioning and wellbeing of affected paediatric patients and their parents. It shares pathophysiological pathways with other atopic/allergic conditions such as asthma, allergic rhinitis, and food allergies, which are common comorbidities in patients with AD. The currently available treatments for AD in paediatric patients, including those 6 months to 6 years of age, have important limitations including unsatisfactory effectiveness and important risks and side effects. Systemic therapies are used off-label with little evidence to support their use. These limitations result in a large number of paediatric patients with severe AD whose disease cannot be safely controlled by the existing therapies. Therefore, there exists a significant unmet medical need for a treatment that is safe and effective for long term use, especially for paediatric patients with severe forms of the disease not adequately controlled by topical prescription therapies.

2.1.2. About the product

Dupilumab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) subunit

shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E (IgE). Dupilumab belongs to the pharmacological class of immunomodulators, IL inhibitors.

2.1.3. The development programme/compliance with CHMP guidance

Because AD shares pathophysiological pathways with other atopic/allergic conditions such as asthma, Chronic rhinosinusitis with nasal polyps (CRSwNP), eosinophilic esophagitis (EoE), allergic rhinitis, and food allergies, and patients with atopy often suffer from multiple comorbid conditions with varying severity, dupilumab has already received regulatory approval or is in clinical development for a number of type 2 inflammatory conditions. These have included AD in adults and pediatric patients aged ≥6 years, asthma (adult and pediatric patients ≥6 years), CRSwNP in adults, and other indications (in phase 2 or 3).

The dupilumab pediatric AD program includes the following age subsets:

• Adolescents aged ≥12 to <18 years: phase 3 completed; marketing application approved in multiple regions

• Children aged ≥6 to <12 years: phase 3 completed; marketing application approved in multiple regions

• Children and infants aged ≥6 months to <6 years: **Current submission**

2.1.4. General comments on compliance with GLP, GCP

The MAH states that the clinical studies presented in this dossier were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practice and applicable regulatory requirements.

2.2. Quality aspects

No new quality data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Justification regarding existing Drug-Device Combination

In *3.2.R Regional information* justifications have been provided regarding the use of the existing Medical Device Part of the Drug-Device Combination (DDC) 300 mg PFS, 200 mg PFS-S and 300 mg PFS-S for the AD paediatric patient population 6 months to 5 years of age.

Change assessment towards MDR Article 117 (PFS, PFS-S)

The MAH has determined that there are no changes to the design or intended purpose of the device (part), nor is there a new medical device being introduced. Therefore, a Notified Body opinion is not deemed required. The details of the MAH´s assessment is as follows:

• There is no impact on the medical device clinical use. According to clinical experts and data obtained during clinical trials and consistent with approved applications for the same marketed product, the injection sites defined for adults, adolescents, and children 6-11 years of age are also recommended for

targeted paediatric patient population (from 6 months to 5 years of age), the injection technique (lifted skinfold and an injection angle at 45°) is appropriate to deliver the drug in the subcutaneous tissue for targeted population, and the needle length combined with injection technique defined above is appropriate to avoid a potential intra-muscular injection.

• There are no changes to the medical device instructions for use related to the additional patient population.

• There is no change to the intended users who will administer the product. Healthcare professionals and lay caregivers remain the only ones to administer the injection for this paediatric population from 6 months to 5 years of age, as self-injection is not recommended for this patient population.

Table 1 below summarizes the same intended users and additional patient population for the Dupixent 200mg and 300mg pre-filled syringe presentations to be included in this variation.

Table 1 Intended users and patient populations of Dupilumab 200mg & 300mg pre-filled syringe presentations for this extension of patient population

Dupixent 200mg (1.14 mL) & 300mg (2mL) pre-filled syringe for Paediatric Patients*	
Same Intended Users	Healthcare Professionals (HCP) & Lay Caregivers
Additional patient population	*Paediatric Patients (6-months to 5 years of age)

Usability Studies

The MAH has determined that there is no need for additional Usability Studies.

The quality, safety and/or efficacy of the DDC product are not affected as the assessment results conclude the following:

• There are no changes to the medical device instructions for use related to the additional patient population.

• There are no changes to the performance requirements, nor the specifications of the medical device.

• No new or different risks in relation to the medical device use have been identified, therefore no new mitigations need to be introduced. The existing Risk Management File will be updated as part of the life cycle management activities. Hazard list is already covering this additional patient population.

With regard to the user population (healthcare professionals and lay caregivers):

Since the intended user population is unchanged versus the device currently available on the EU market, the bridging data can demonstrate the effective use of the DDC by the same intended user population (HCPs and lay caregivers).

• PFS-S presentation: The relevant data (that can be bridging data to the identical device part of the PFS-S used in adults and adolescents and children 6-11 years of age) resides in the existing Dupixent marketing authorization (refer to VV-QUAL-0555538 2.0 which is part of Module 3 P2.4 Human Factors study – 1ml and 2mL PFS-S).

• PFS presentation: The relevant data (that can be bridging data to the identical device part of the PFS used in the adult patient population) that resides in the existing Dupixent marketing authorization (refer to QUA-PD-2016-21521 2.0 which is part of Module 3 P2.4 Container Closure System – PFS – Le Trait – Cook). Moreover, published literature and instructional material which covers prefilled syringes on the

market provides guidance on how to perform subcutaneous injections with a prefilled syringe. Two links to examples are provided in the 3.2.R document.

2.2.2. Discussion on quality aspects

No new quality data have been submitted in this application which was considered acceptable by the CHMP.

The proposed change does not result in the introduction of a new medical device or a modification to the design, or aforementioned intended use/purpose of the medical device part of the Drug Device Combination (DDC). Therefore, it can be agreed that the variation application supporting the extension of the atopic dermatitis indication in the 6 months to 5 years old patient population does not require a Notified Body Opinion (NBOp) for the currently authorised DDC.

From a quality point of view, the MAH´s justifications regarding the use of the existing Medical Device Part of the DDC 300 mg PFS, 200 mg PFS-S and 300 mg PFS-S for the AD paediatric patient population 6 months to 5 years of age is accepted.

The MAH has determined that there is no need for additional usability studies. It can be agreed that the intended user population is unchanged versus the device currently available on the EU market and that the bridging data support the effective use of the DDC by the same intended user population (HCPs and lay caregivers).

2.2.3. Conclusion on the quality aspects

The available quality data do not raise concern in the indication.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

A claim for not submitting environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) because dupilumab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

2.3.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

In conclusion, the claim for ERA exemption by the MAH is justified and in conformity with the ERA guideline since the extension of marketing authorization/type II variation request concerns a monoclonal antibody consisting of naturally occurring amino acids. Dupilumab is significantly metabolized in-vivo and

is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. The antibody's structure and mode of action do not indicate any specific risk to the environment.

2.3.3. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable by the CHMP.

The extended indication does not lead to a significant increase in environmental exposure further to the use of dupilumab.

- Considering the above data, dupilumab is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study / Report Location/ Study Status	Study Population	Objective	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of patients randomized)
R668-AD-1539 Part A CSR Module 5.3.5.1 Completed	Pediatric patients (≥6 months to <6 years of age) with severe AD that cannot be adequately controlled with topical AD medications.	The primary objective for part A of the study is to characterize the safety and pharmacokinetics (PK) of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age with severe atopic dermatitis (AD).	Phase 2/3, open-label, single ascending dose, sequential cohort study. Two sequential age cohorts: Cohort 1 (patients ≥2 to <6 years) Cohort 2 (patients ≥6 months to <2 years) Two dose sub-cohorts: Sub-cohort A: 3 mg/kg Sub-cohort B: 6 mg/kg Single dose treatment period: 4 weeks Follow-up: 4 weeks (for patients not entering OLE)	Single SC doses of dupilumab 3 mg/kg or 6 mg/kg 40 children ≥6 months to <6 years of age Cohort 1A: 3 mg/kg in patients ≥2 to <6 years (n=10) Cohort 1B: 6 mg/kg in patients ≥2 to <6 years (n=10) Cohort 2A: 3 mg/kg in patients ≥6 months to <2 years (n=10) Cohort 2B: 6 mg/kg in patients ≥6 months to <2 years (n=10)
R668-AD-1539 Part B CSR Module 5.3.5.1 Completed	Pediatric patients (≥6 months to <6 years of age) with moderate-to severe AD that cannot be adequately controlled with topical AD medications.	The primary objective for part B of the study is to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with topical corticosteroids (TCS) in pediatric patients, 6 months to less than 6 years of age, with moderate-to-severe AD.	Phase 2/3, randomized, double-blind, placebo-controlled, parallel group, repeat dose study. Treatment duration: 16 weeks Follow-up: 12 weeks (for patients not entering the OLE)	SC doses of dupilumab Q4W weight-tiered fixed dose: 200 mg in patients with a baseline weight of ≥5 to <15 kg (n= 26) 300 mg in patients with a baseline weight of ≥15 to <30 kg (n= 57) Placebo Q4W: matching placebo based on baseline weight category (n = 78). 162 patients were randomized into this study

Study / Report Location/ Study Status	Study Population	Objective	Study Design and Duration	Treatment: Dose, Route of Administration, Frequency (number of patients randomized)
R668-AD-1434 Module 5.3.5.2 CSR Study Ongoing	Pediatric patients (≥6 months to <6 years of age) with moderate-to-severe AD who have previously completed a clinical study with dupilumab (R668-AD-1539 Part A or Part B).	The primary objective of the study is to assess the long-term safety of dupilumab in pediatric patients with AD.	Phase 3 open-label extension study The duration of treatment period was changed as follows: a) For patients 6 months to <12 years old at the screening visit, the treatment period will last for 5 years. b) For patients 12 to <18 years old at the screening visit: • In Poland, the treatment period will last for 5 years. • In other countries, the treatment period will last until regulatory approval in this age group in the respective geographic region. Follow-up 12 weeks	180 children aged ≥6 months to <6 years old were enrolled in the study at the time of the data cut-off date of 31 Jul 2021: 70 patients previously on placebo and 85 patients previously on SC doses of dupilumab in parent studies. • All patients from R668-AD-1539 Part A rolled over into this study under Amendment 3 and patients <6 years of age initially received weight-based dosing at 3 mg/kg QW or 6 mg/kg QW[1] • All patients from R668-AD-1539 Part A were switched to fixed dosing tiered by body weight under amendment 4 (200 mg Q4W for patients 5 kg to <15 kg, 300 mg Q4W for patients 15 kg to <30 kg, 200 mg Q2W for patients ≥30 to <60 kg, or 300 mg Q2W for patients ≥60 kg). • All patients from R668-AD-1539 Part B enrolled into this study under amendment 4 and started on the fixed dose regimens tiered by body weight. Of the 180 children aged 6 months to <6 years old: 36 children were from R668-AD-1539 Part A and 144 children were from R668-AD-1539 Part B.

AD – atopic dermatitis; OLE – open-label extension; PK – pharmacokinetics; QW – once a week; Q4W – once every 4 weeks; SC – subcutaneous.

2.4.2. Pharmacokinetics

Patients aged ≥6 months to <6 years with AD have been included in 3 dupilumab clinical studies where PK, immunogenicity and pharmacodynamic (PD) data have been collected.

As of the data cut-off date of 23 Jul 2021, the dupilumab paediatric AD clinical program in patients ≥6 months to <6 years of age consisted of study R668-AD-1539 Part A and Part B as well as study R668-AD-1434.

The purpose of this application is to seek approval for dupilumab in children aged ≥6 months to <6 years with severe AD.

The proposed indication is supported primarily by data from the randomized, placebo-controlled pivotal study R668-AD-1539 Part B, assessing efficacy and safety of dupilumab over a 16 week treatment period with concomitant topical corticosteroids (TCS) in children with moderate-to-severe AD aged ≥6 months to <6 years. Additional supportive data are included from patients aged ≥6 months to <6 years with severe AD who received a single dose of dupilumab in the PK study R668-AD-1539 Part A.

The open-label extension (OLE) study R668-AD-1434 provides long-term safety and efficacy data on the chronic use of dupilumab in children ≥6 months to <6 years of age with AD who completed previous studies R668-AD-1539 Part A and R668-AD-1539 Part B. Study R668-AD-1434 is an ongoing study which includes patients ≥6 months to <18 years of age that rolled over from different AD studies. Only data of patients in study R668-AD-1434 that rolled over from study R668-AD-1539 Part A and Part B were included in the present submission, representing the age group in focus.

SC dosing regimens that were evaluated were single dose 3 mg/kg and 6 mg/kg in study R668-AD-1539 Part A and in study R668-AD-1539 Part B weight-tiered fixed doses of 200 mg Q4W and 300 mg Q4W for children weighing ≥5 to <15 kg and ≥15 to <30 kg, respectively. Loading doses were not administered to children of this age group. In the OLE study R668-AD-1434, beginning with Amendment 4, only the weight-tired fixed dosing scheme was administered.

The proposed posology in patients ≥6 months to <6 years of age with AD is a weight-tiered dose regimen of 200 mg Q4W SC for body weight ≥5 to <15 kg and 300 mg Q4W SC for body weight ≥15 to <30 kg. No loading dose is intended in the age group of children ≥6 months to <6 years of age.

The pharmacokinetics (PK) of dupilumab have been previously characterized in adult and paediatric patients (6 years or older) with AD and is characterized as nonlinear with target-mediated disposition.

Bioanalytical methods

Overview

The bioanalytical methods used for the AD program in children ≥6 months to <6 years of age are the same used for AD patients ≥6 years to <12 years of age and included in previous applications. A summary of these methods is described in ***Table 2*** below.

Analyses included samples from the pivotal study R668-AD-1539 Part B, the pharmacokinetic study R668-AD-1539 Part A, and the OLE study R688-AD-1434.

Table 2 Summary of validation reports used in clinical studies

Validation (method) Report	Analyte	Matrix (MRD)	LLOQ Sensitivity (ng/mL)	Drug Tolerance	Accuracy (%AR)	Within-run Precision (CV%)	Between-run Precision (CV%)	Clinical Studies
REGN668-AV-13074-VA-01V1 (a)	functional dupilumab	human serum (1:50)	78	NA	96 - 105	≤9	≤9	R668-AD-1539 R668-AD-1434
REGN668-AV-13089-VA-01V3 (b)	anti-dupilumab antibodies	human serum (1:30)	9.9	164 µg/mL	NA	NA	NA	R668-AD-1539 R668-AD-1434
REGN668-AV-13112-VA-01V2 (b)	dupilumab neutralizing antibodies	human serum (1:10)	125	298 ng/mL	NA	NA	NA	R668-AD-1539 R668-AD-1434

Note: (a) Report provided in the original marketing application for AD.
(b) Report provided in the marketing application for asthma.
AD, Atopic dermatitis; %AR, %Analytical Recovery; CV, Coefficient variation LLOQ, Lower limit of quantitation; MRD, Maximum required dilution; NA, Not applicable.

Functional dupilumab

The functional dupilumab concentration assay (method validation report REGN668-AV-13074-VA-01V1) was described in the original marketing application for adult AD. The lower limit of quantitation of the method is 78 ng/mL in neat serum. A tabular summary of assay characteristics is provided in ***Table 1***.

Incurred sample reanalysis (ISR) for the functional dupilumab assay was performed for study R668-AD-1539 (Parts A and B) (***Table 2***). The ISR met acceptance criteria, indicating that the assay generated robust data in the respective study population. ISR passing rate in study R668-AD-1539 was 96.8%.

Table 3 Summary of incurred sample reanalysis conducted in clinical studies

Study (Method)	Analyte	ISR Conducted in Clinical Studies (Study Population)	Study Report Location
REGN668-AV-13074-VA-01V1 (a)	Functional dupilumab	R668-AD-1539	R668-AD-1539-BA-02V1

Note: Incurred Sample Reanalysis (ISR) criteria were that 66.7% of the reanalysis results must be within ±30% variability of the original result (EMA, 2011).
(a) Validation Report provided in the original marketing application for atopic dermatitis.

Immunogenicity

Anti-Dupilumab Antibodies (ADAs)

Assessment of ADAs in the studies R668-AD-1539 (Part A and Part B) and R688-AD-1434 for this submission was conducted using the REGN668-AV-13089-VA-01V3 assay. Previous version REGN-AV-13089-VA-01V2 of this assay has been described in the original marketing application for adult AD. Additional data were generated, and the validation report was amended to generate REGN668-AV-13089-VA-01V3. These updates were provided in the marketing application for asthma. A tabular summary of assay characteristics is provided in ***Table 3***.

The AD population cut points were used to detect ADA in clinical samples from R668-AD-1539 (Parts A and B) and R668-AD-1434 studies. These cut points were established using statistical methods recommended in appropriate guidance documents and literature (FDA, 2019) (EMA, 2011) (Mire-Sluis, 2004) (Shankar, 2008). Based on the AD population screening cut point factor, 7 out of 195 baseline serum samples from R668-AD-1539 (Parts A and B) were positive in the dupilumab ADA screening assay, resulting in an observed false positive rate of 3.6%, which is close to the target false positive rate of 5%. This indicates that true ADA positives were not missed, and the AD population cut points are appropriate for this pediatric (≥6 months to <6 years of age) AD population.

Neutralizing anti-dupilumab antibodies (NAb)

Assessment of neutralizing anti-dupilumab antibodies for this submission was conducted using the REGN668-AV-13112-VA-01V2 assay.

REGN668-AV-13112-VA-01V1 version of this assay has been described in the original marketing application for adult AD. Additional data analyses were included in the amended validation report (REGN668-AV-13112-VA-01V2) submitted in the marketing application for asthma.

Clinical studies with collection of PK and PD data

R668-AD-1539 Part A (Phase 2, Open-label, Single Ascending Dose Study)

Study Design: R668-AD-1539 Part A was a phase 2, open-label, single ascending dose, sequential cohort study investigating the PK, safety, and initial assessment of efficacy of a single dose of SC dupilumab in pediatric patients with severe AD (IGA=4).

The study enrolled patients ≥6 months to <6 years of age. Patients were enrolled into 1 of 2 age cohorts and within each age cohort, patients were enrolled into 1 of 2 dose sub-cohorts as follows:

- **Age Cohort 1** - ≥2 to <6 years (n=20):
  - Sub-Cohort 1A: 3 mg/kg (n=10)
  - Sub-Cohort 1B: 6 mg/kg (n=10)
- **Age Cohort 2** - ≥6 months to <2 years (n=20)
  - Sub-Cohort 2A: 3 mg/kg (n=10)
  - Sub-Cohort 2B: 6 mg/kg (n=10)

Thus, a total of 40 children ≥6 months to <6 years of age were included in the PK analysis for the current application and the results are summarized below.

Part A of the study consisted of a screening period, a baseline visit, and a single-dose treatment followed by a 4-week PK sampling period with samples collected for analysis of drug concentration at baseline and days 3, 8, 18, and 29.

After completing the day 29 visit, patients in study R668-AD-1539 Part A were eligible to be enrolled in the OLE study R668-AD-1434 (and 36 patients out of a total of 40 patients enrolled). For patients not entering the OLE, the follow-up period was 4 weeks.

Results (systemic exposure):

In general, dupilumab concentration-time profiles are described by target-mediated disposition and were generally characterized by a brief absorption phase after SC administration, followed by a linear elimination phase and a terminal target-mediated elimination phase.

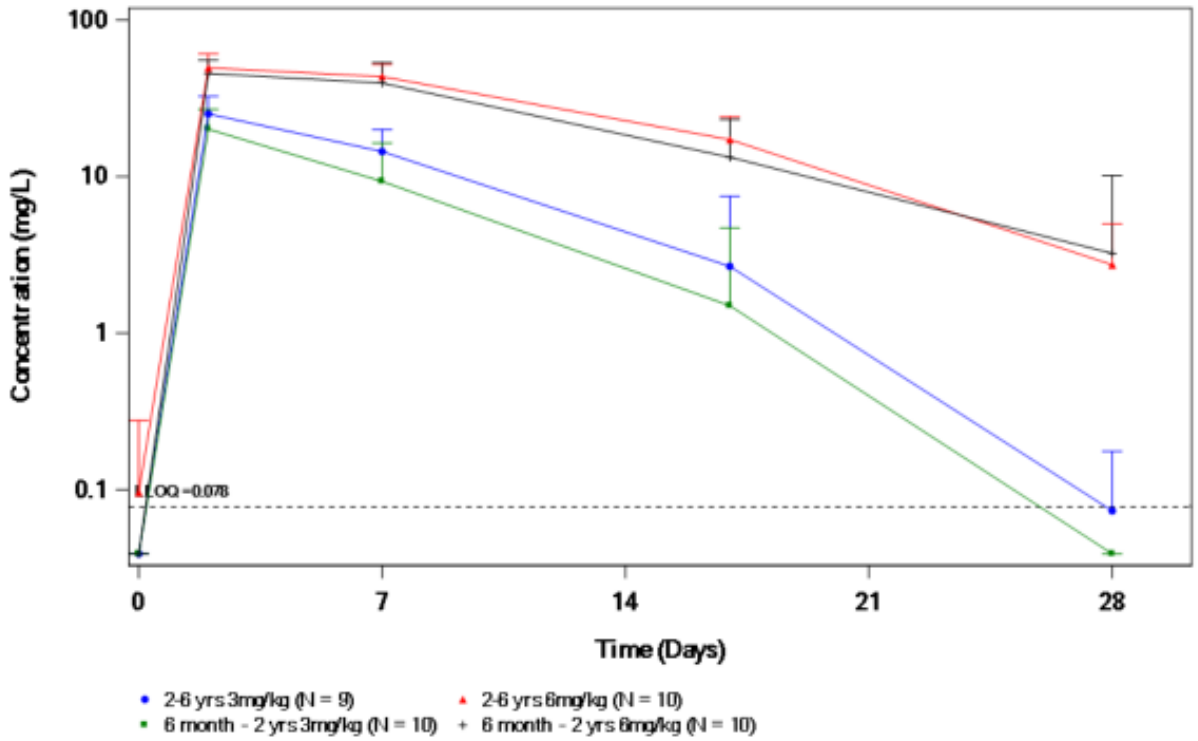
While profiles in all treatment groups demonstrated the target-mediated phase, the linear phase was more prominent for the 6 mg/kg dose cohorts and suggested that saturation of target-mediated pathway achieved in the 3 mg/kg dose cohorts may be limited in duration (***Figure 1***, ***Figure 2***).

Median body weight was higher in patients 2 to <6 years of age than in patients 6 month to <2 years of age and was comparable between dose levels within each age cohort.

Mean Cmax values were generally similar (≤25% difference) for the 2 to <6 years of age cohort compared to the 6 months to <2 years of age cohort at each dose level and median tmax was observed approximately 2 days after dosing for all cohorts, and suggest similar absorption kinetics between the age cohorts in this study. Following a single SC dose, dupilumab was measurable in serum for a longer duration in the 2 to <6 years of age cohort than in the 6 months to <2 years of age cohort at both mg/kg dose levels, suggesting higher clearance per unit body weight in children <2 years of age.

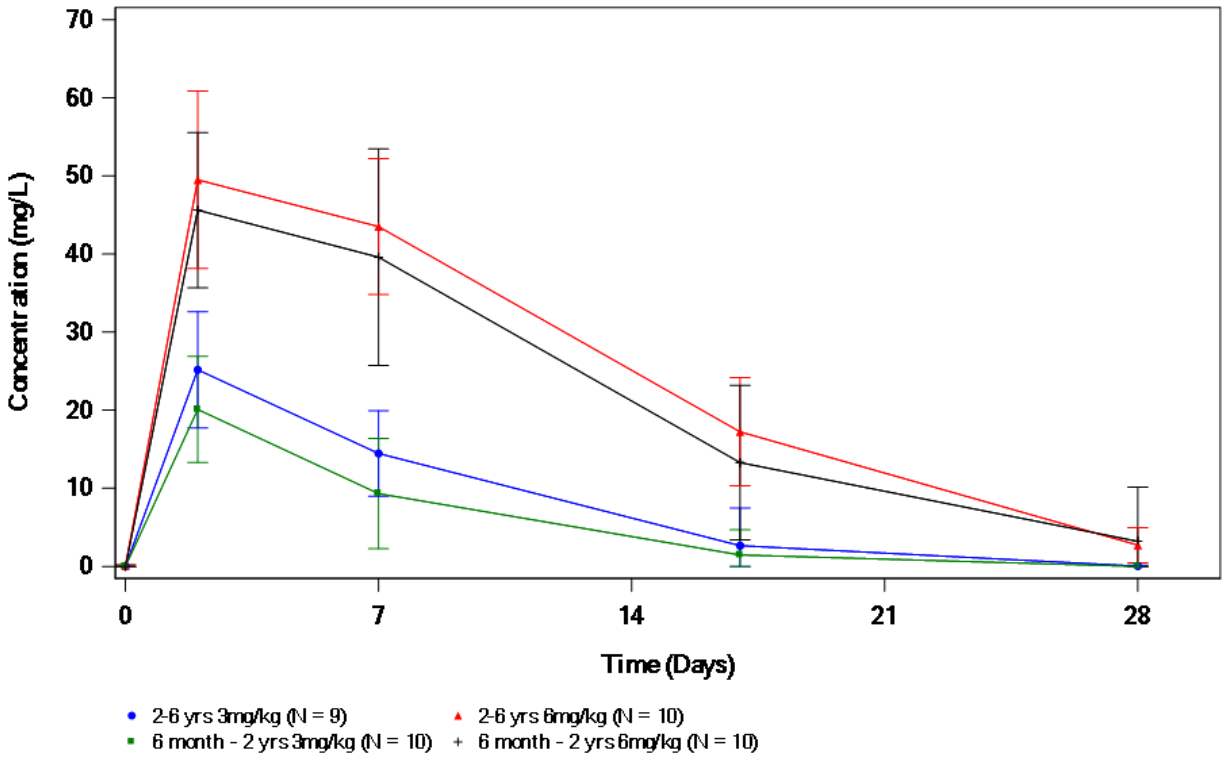
These trends towards faster body-weight normalized clearance of dupilumab in the lighter, younger age groups are consistent with the principles of allometric scaling that drug clearance scales less than proportionally with increasing body weight. Hence, use of a weight-tiered, fixed dosing scheme represents an appropriate approach to normalizing dupilumab exposure across a wide range of body weights.

Figure 1 Mean (+SD) Concentrations of Functional Dupilumab in Serum by Time and Cohort in Patients, 6 months to <6 Years of Age, with Severe Atopic Dermatitis (Study R668-AD-1539 Part A, Log-Scaled)



BLQ = Below the Limit of Quantification; LLOQ = Lower Limit of Quantification; N = Number of patients; SAP = Statistical Analysis Plan; SD = Standard Deviation; yrs = Years
Note: BLQs were set to LLOQ/2.
Early termination visit was mapped to week based on the SAP-defined visit window.
1 patient exhibited concentrations of dupilumab below the LLOQ at all time points and was excluded.

Figure 2 Mean (+SD) Concentrations of Functional Dupilumab in Serum by Time and Cohort in Patients, 6 months to <6 Years of Age, with Severe Atopic Dermatitis (Study R668-AD-1539 Part A)



BLQ = Below the Limit of Quantification; LLOQ = Lower Limit of Quantification; N = Number of patients; SD = Standard Deviation; yrs = Years
Note: BLQs were set to 0.
Value for the lower error bar was set to 0 when the value was less than 0.
Early termination visit was mapped to week based on the SAP-defined visit window.
1 patient exhibited concentrations of dupilumab below the LLOQ at all time points and was excluded.

R668-AD-1539 Part B (Phase 3, Pivotal, Randomized, Double-Blind, Placebo-Controlled Study)

Study Design: R668-AD-1539 Part B was a randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab combined with low potency TCS in patients ≥6 months to <6 years of age with moderate-to-severe AD. Patients were randomized in a 1:1 ratio, stratified by baseline body weight (≥5 to <15 kg and ≥15 to <30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America, Europe) to 1 of the following 2 treatment groups, with study treatment administered on day 1 and Q4W from week 4 to week 12:

- Dupilumab Q4W - weight-tiered fixed-dose (n=83):
  - 200 mg in patients with a baseline weight of ≥5 to <15 kg (n=26)
  - 300 mg in patients with a baseline weight of ≥15 to <30 kg (n=57)
- Placebo Q4W: matching placebo based on baseline weight category (n=78)

A total of 161 children ≥6 months to <6 years of age were included in the PK analysis for the current application and the results are summarized below.

The study consisted of 3 periods: screening, including 2 weeks of TCS standardization (up to 56 days), treatment (16 weeks) and follow-up (12 weeks). A sparse sampling scheme was utilized with samples

taken at baseline prior to the first dose, at weeks 4, 8, 12, and 16/EOT, and at week 28/EOS in case not entering the OLE.

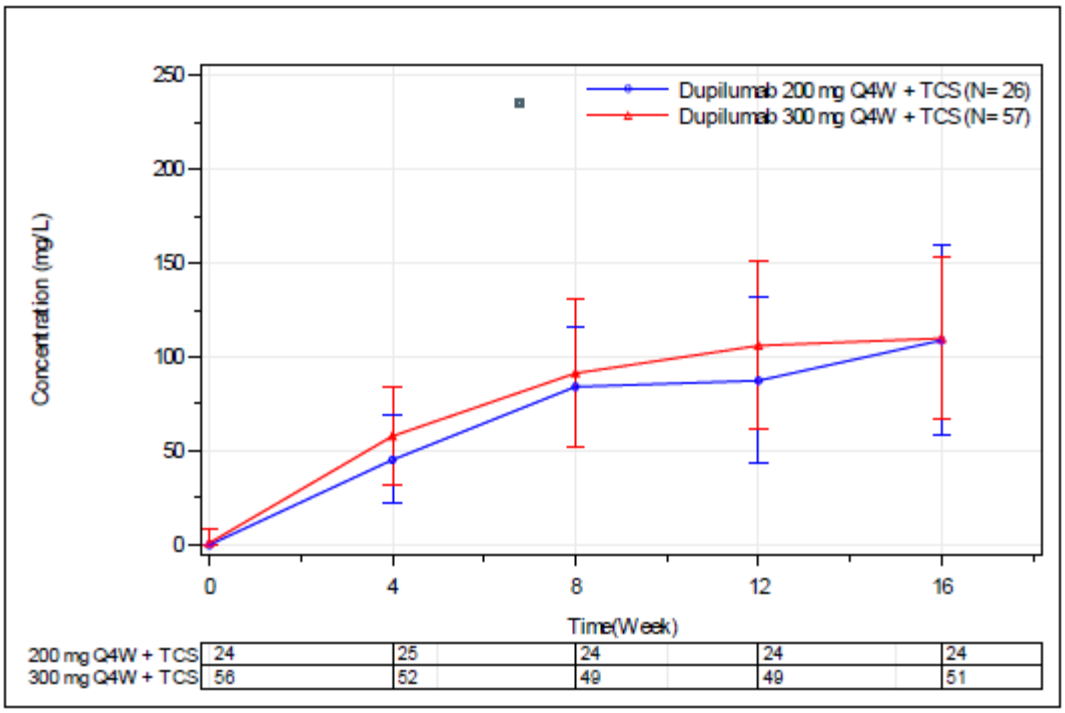
After completing the 16 weeks treatment period, 144 patients of 161 patients in study R668-AD-1539 Part B enrolled in the OLE study R668-AD-1434.

Results (systemic exposure):

Mean concentrations of dupilumab over time exhibited similar profiles in patients weighing ≥5 to <15 kg at baseline receiving dupilumab 200 mg Q4W and patients weighing ≥15 to <30 kg at baseline receiving dupilumab 300 mg Q4W, respectively (***Figure 3***). Systemic concentrations of dupilumab in the 300 mg Q4W group appeared to have reached steady-state by week 12, while the highest mean concentrations for the 200 mg Q4W group were observed at week 16. Accumulation of dupilumab C_{trough} at week 16 relative to after the initial dose at week 4 was approximately 2-fold for both dupilumab regimens.

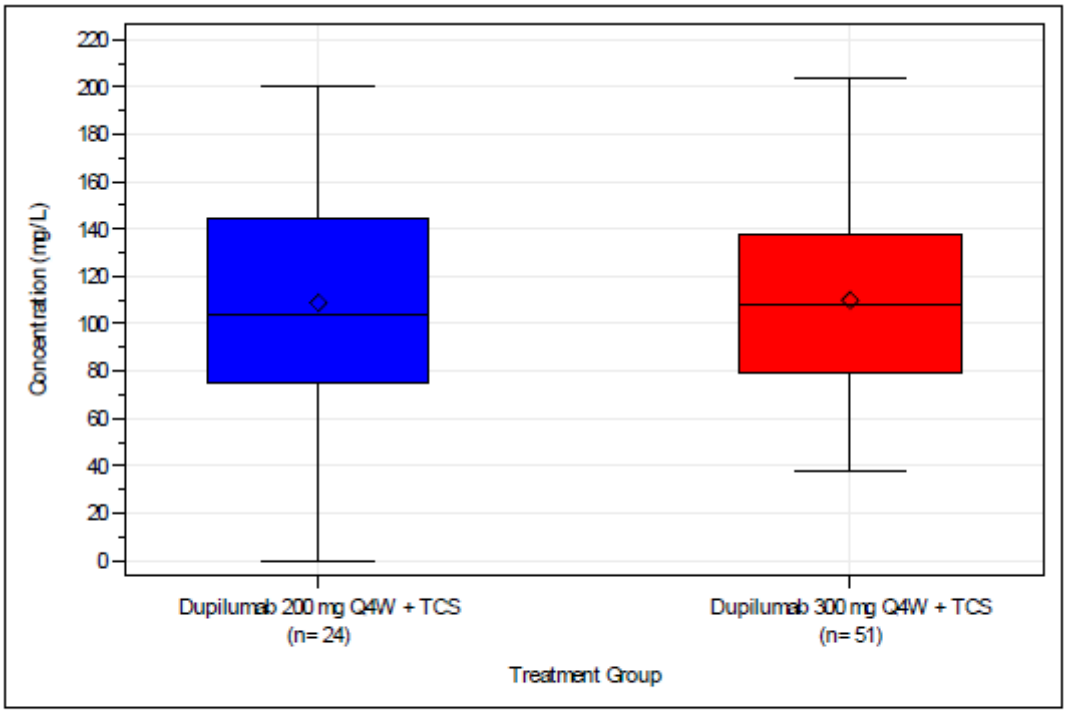
The weight-tiered dosing regimen of dupilumab evaluated in this study normalized dupilumab exposure across patients of differing body weight categories. Mean ± SD dupilumab C_{trough} at week 16 was similar between patients ≥5 to <15 kg receiving 200 mg Q4W (109 ± 50.8 mg/L) and patients ≥15 to <30 kg receiving 300 mg Q4W (110 ± 42.8 mg/L) (***Figure 4***); the distribution of C_{trough} at week 16 was also similar across the range of baseline body weights within each treatment group.

Figure 3 Mean Concentrations (±SD) of Functional Dupilumab in Serum by Nominal Time and Treatment Group in Patients ≥6 Months to <6 years of Age with Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



N = Number of patients; N is presented by nominal time point in the table below the x-axis.
Note: BLQs were set to 0. Placebo results are excluded. Numbers in the table are the number of patients at each time point.
Source: Module 5.3.5.1 R668-AD-1539 Part B Appendix 16.1.15 Clinical Pharmacology Report Figure 1

Figure 4 Concentrations of Functional Dupilumab in Serum at Week 16 by Treatment Group in Patients ≥6 Months to <6 years of Age with Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



n = Number of patients at week 16
Note: BLQs were set to 0. Placebo results are excluded. Diamond represents mean; lines of box are Q1 (lower), median (middle), and Q3 (upper); upper bar is maximum (Q3 + 1.5*IQR) and lower bar is minimum (Q1 - 1.5*IQR) with IQR = Q3 - Q1; circles are outliers above maximum or below minimum bars.
Source: Module 5.3.5.1 R668-AD-1539 Part B Appendix 16.1.15 Clinical Pharmacology Report Figure 2

R668-AD-1434 (Phase 3, Open-label, Long-term Extension Study)

Study Design: R668-AD-1434 is an ongoing, phase 3, open-label extension (OLE) study evaluating the log-term safety and efficacy of dupilumab in pediatric patients ≥6 months to <18 years old with AD who have previously completed a pediatric AD dupilumab clinical study, including parent R668-AD-1539 Part A and Part B.

The original protocol was amended to include patients ≥6 months to <6 years old with a dose regimen for this age group as a weight-based regimen of 3 mg/kg or 6 mg/kg SC QW consistent with those evaluated in R668-AD-1539 Part A; 1 patient from R668-AD-1539 Part A who reached age 6 between screening and the first dose in the OLE was initially assigned to a regimen of 300 mg Q4W per-protocol for patients of that age. Under Amendment 4, all patients in the study (ages ≥6 months to <18 years) were re-assigned to a weight-tiered SC dosing regimen regardless of age as follows:

- Patients weighing ≥60 kg: 300 mg Q2W (not applicable for the current application)
- Patients weighing ≥30 to <60 kg: 200 mg Q2W*
- Patients weighing ≥15 to <30 kg: 300 mg Q4W
- Patients weighing ≥5 to <15 kg: 200 mg Q4W

At the time of approval of Amendment 4, 36 patients ≥6 months to <6 years old from R668-AD-1539 Part A were enrolled in the OLE and switched to the weight-tiered fixed dose regimens.

Patients from Part B were only enrolled after Amendment 4 was implemented and started directly on the weight-tiered fixed dose regimens (n=144).

*A total of three patients in the age group of ≥6 months to <6 years gained weight to move to the ≥30 kg body weight category (200 mg Q2W).

Thus, a total of 180 children aged ≥6 months to <6 years old were enrolled in the study R668-AD-1434 at the time of the data cutoff date (23 Jul 2021), hereof 70 patients previously on placebo (all from R668-AD-1539 Part B) and 110 patients previously treated with dupilumab (36 patients from study R668-AD-1539 Part A and 144 patients from R668-AD-1539 Part B, respectively).

The study consists of a screening period (day -28 to day -1), a treatment period of up to 5 years, and a 12-week follow-up period. Only the portion of the data of patients ≥6 months to <6 years of age with AD enrolled from parent study R668-AD-1539 Part A and Part B are presented within this report.

A sparse sampling scheme was used with samples for PK and ADA collected at baseline prior to the first dose, and at sparse timepoints thereafter including weeks 16, 52, 76, 104, 152, 200, 260/EOT, and at week 272/EOS.

At the time of the PK/ADA data cutoff date (23 Jul 2021) 84 patients were included in the PK analysis set.

The PK analysis set includes all treated patients who received any amount of study drug (safety analysis set) and had at least one non-missing result for concentration of functional dupilumab following the first dose of study drug in the current study.

Results (systemic exposure):

Mean and distribution of trough concentrations of dupilumab at week 16 in patients who, at baseline, were ≥6 months to <6 years of age, were similar for patients receiving 200 mg Q4W (122 mg/L) or 300 mg Q4W (104 mg/L), and fell between trough concentrations in similarly aged patients receiving 3 mg/kg QW (54.6 mg/L) and patients receiving 6 mg/kg QW (240 mg/L). Once steady-state concentrations were achieved, these were maintained over the duration of the currently available data (***Table 4***).

Table 4 Summary of Concentrations of Functional Dupilumab in Serum by Time and Treatment Group in Pediatric Patients ≥6 Months to <6 years of Age with AD (Study R668-AD-1434)

	Concentrations of Functional Dupilumab in Serum (mg/L)									
	3 mg/kg QW		**6 mg/kg QW**		**200 mg Q4W**		**300 mg Q4W**		**200 mg Q2W**	
Nominal Time after First Dose (Week)	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
0	15	0.142 (0.550)	15	0.609 (2.36)	11	22.1 (35.1)	28	21.3 (30.0)	0	
16	14	54.6 (45.8)	10	240 (102)	13	122 (53.5)	40	104 (46.1)	0	
52	13	90.9 (55.5)	10	260 (84.7)	0		2	93.3 (---)	1	164 (---)
76	12	41.2 (50.5)	4	139 (98.1)	1	121 (---)	5	60.9 (66.1)	0	
104	8	66.9 (66.6)	3	248 (36.7)	2	56.6 (---)	5	96.8 (59.2)	1	71.6 (---)
152	0		0		1	25.4 (---)	7	124 (42.5)	2	83.5 (---)

n = Number of patients contributing to each timepoint; SD = Standard deviation
Note: Concentrations below the LLOQ were set to 0. Patients may have been eligible to switch treatment groups during the study. Treatment group at Week 0 was defined by the initially administered dose in Study R668-AD-1434; treatment group at all subsequent visits was defined by the last dose received prior to sample collection.

Upon CHMP's request, an updated PK analysis of study R668-AD-1434 was submitted with the data cut-off date of 10-Mar-2022, now including data of 167 patients and sufficient data at week 52. Data were consistent with the data gained from former analyses.

Population PK Analysis

An integrated PopPK model was developed to describe the concentrations of dupilumab across age groups from adults to children as young as 6 months of age with AD.

Nonlinear mixed effects modeling methodology was implemented in this analysis using NONMEM® (version 7.4.1) software (ICON Development Solutions, Ellicott City, MD). The first-order conditional estimation with interaction (FOCEI) method was utilized. Pre- and post-processing of data from each modeling step and graphical analysis of the data were performed using R (version 3.6.3 or higher).

For prior marketing applications for adult and pediatric AD patients, population PK analyses were conducted separately in healthy adults and adult patients with AD, adolescent patients with AD, and children aged ≥6 to <12 years with AD using the same base model structure. Standard 2-compartment PopPK models with parallel linear and nonlinear Michaelis-Menten (MM) elimination and transit compartments to describe absorption were previously developed to describe the pharmacokinetics of dupilumab. The final parameter estimates for each model are provided in ***Table 5*** below.

Table 5 Population PK Parameters and Standard Errors for Primary Covariate Models of Dupilumab in Adults, Adolescents and Children ≥6 to <12 Years of Age

Parameter Name	Children [a] ≥6 to <12 years	Adolescents [b] ≥12 to <18 years	Adults [c] ≥18 years
PK Parameter			
V_2 (L)	2.18 (0.0872)	2.47 (0.0501)	2.74 (0.021)
Ke (1/day)	0.0446 (0.00152)	0.0520 (0.00188)	0.0477 (0.00078)
V_m (mg/L/day)	1.64 (fixed)	1.43 (0.0379)	1.07 (fixed)
K_{23} (1/day)	0.211 (fixed)	0.211 (fixed)	0.211 (fixed)
K_{32} (1/day)	0.310 (fixed)	0.310 (fixed)	0.310 (fixed)
Ka (1/day)	0.641 (fixed)	0.306 (fixed)	0.306 (fixed)
MTT (day)	0.105 (fixed)	0.105 (fixed)	0.105 (fixed)
K_m (mg/L)	0.01 (fixed)	0.01 (fixed)	0.01 (fixed)
F (unitless)	0.642 (fixed)	0.642 (fixed)	0.642 (fixed)
Covariates			
V_2 ~ Weight	0.849 (0.0345)	0.755 (0.0517)	0.817 (0.031)
V_2 ~ Albumin	-0.525 (0.149)	---	-0.653 (0.072)
Ke ~ BMI	---	0.357 (0.116)	0.368 (0.053)
Ke ~ ADA	---	0.193 (0.05666)	0.164 (0.029)
Ke ~ EASI	0.169 (0.0471)	0.356 (0.0523)	0.143 (0.021)
Ke ~Race (White)	---	---	-0.123 (0.018)
Omega Matrix			
$\sigma(\ln(V_2))$	0.291 (0.0204)	0.140 (0.0145)	0.206 (0.0068)
$\sigma(\ln(K_e))$	0.417 (0.0282)	0.304 (0.0242)	0.293 (0.010)
$\mathrm{Corr}(\ln(K_e), \ln(V_2))$	-0.883 (0.0212)	-0.529 (0.0902)	-0.450 (0.035)
Residual SD			
σ_{prop} (CV%)	13.1 (0.402)	9.94 (0.602)	12.5 (0.18)
σ_{add} (mg/L)	0.03 (fixed)	2.36 (0.24)	6.06 (0.23)
Derived Parameters			
CL (L/day)	0.0972	0.128	0.131
Q (L/day)	0.460	0.521	0.578
V_3 (L)	1.48	1.68	1.86

--- = Not calculated for fixed, derived, or excluded parameters; ADA = Anti-drug antibody; BMI = Body mass index; CL = Linear clearance; CV% = Coefficient of variation; EASI = Eczema Area and Severity Index; F = Bioavailability; K23/K32 = Intercompartment constants; Ka = Absorption rate constant; Ke = Linear elimination rate constant; Km = Concentration of half-maximal nonlinear clearance (Michaelis-Menten constant); MTT = Mean transit time; PK = Pharmacokinetics; SD = Standard deviation; σ = Estimate of the variance of the residual variability; σ_{add} = Additive error; σ_{prop} = Proportional error; Q = Inter-compartmental clearance; V2 = Volume of the central compartment; V3 = Volume of the peripheral compartment; Vm = Vmax = Maximum target-mediated rate of elimination

The central volume is estimated at weight of 75 kg. Central volume calculated at median weight (29.4 kg) is 0.999 L in children ≥6 to <12 years of age.

Note: Table is reproduced from report R668-PM-19142-SR-01V1.

[a] From report R668-PM-19142-SR-01V1

[b] From report R668-PM-18124-SR-01V1

[c] From report REGN668-MX-16103-CP-01V1

To create a unified model across all AD populations studied, concentration data from children aged ≥6 months to <6 years in studies R668-AD-1539 Part A and Part B were combined with data from adults, adolescents, and children ≥6 to <12 years. From the totality of these data, a single base PopPK model incorporating both body weight and maturation (age), was developed to describe the PK of dupilumab across all age groups. Overall, the the PopPK analysis included dupilumab concentration-time data from 22 clinical studies (nine phase 1, six phase 2, one phase 2/3, and six phase 3 studies). The analysis included a total of 2873 unique subjects ranging in age from 6 months to 88 years (202 healthy volunteers and 2671 patients with AD) and 20938 quantifiable PK samples. By age group, the population PK dataset included 2223 adults, 252 adolescents, 277 children ≥6 to <12 years of age, and 121 children ≥6 months to <6 years of age.

A standard two-compartment PopPK model with parallel linear and nonlinear Michaelis-Menten (MM) elimination and transit compartments to describe the SC absorption of dupilumab was utilized in each of the previous analyses. Body weight is an important predictor of dupilumab PK and a similar base model structure to the prior models was used, that included weight as a covariate. The previous models were parameterized in terms of inter-compartmental rate constants and elimination rate, whereas the current model used linear clearance (CL) and inter-compartmental clearance (Q) terms in order to implement a maturation function on CL to describe age-related changes in clearance in children ≥ 6 months to < 6 years of age. This maturation function was also incorporated into the base model. Allometric exponents for the effects of body weight on CL and Vc were estimated, instead of fixed to the standard values of 1 and 0.75, respectively, as observed data were available to characterize these relationships over a wide range of body weights.

A full PopPK model was developed including simultaneous estimation of pre-specific covariate effects. Based on statistically significant effects demonstrated in previous PopPK models, several covariates of interest were evaluated in the current integrated model in addition to the covariates of age and body weight that were incorporated in the base model. The potential effects of age on central distribution volume and Ka were also tested in the integrated model, since the current dataset includes pooled data to support testing of these effects, which would not have been possible in previous independent models developed for each age group. Following a back-elimination procedure to eliminate covariates that were not statistically significant at P <0.001, a final PopPK model was obtained. In addition to the covariate effects included in the base model of baseline body weight on linear clearance and central volume, and of age on linear clearance, the following covariates were added in the full model for evaluation: race (Black, Asian or Other race [reference: White]), ADA status (low titer level or moderate/high titer levels [reference: ADA negative/non-positive]), baseline EASI score (reference: 30) and baseline albumin (reference: 45 g/L) on linear clearance; baseline age (reference: 30 years), race (Black, Asian or Other race [reference: White]), baseline EASI score (reference: 30), and baseline albumin (reference: 45 g/L) on volume of the central compartment; and age (reference: 30 years) on Ka. Reference conditions for continuous covariates were the approximate median values in the analysis population.

After backward elimination, a final parsimonious model was identified. In addition to effects of bodyweight and age included in the base model, the final model included covariates of: Black race, Asian race, low and moderate/high ADA titer level, EASI score, and baseline albumin on CL; and age, Black race, Asian race and EASI score on Vc (see ***Table 6*** below).

Primary PK parameters were well estimated with relative standard error [RSE] <30%. IIV was modest for CL (32.5% coefficient of variation [CV]) and Vc (32.2% CV). Any age-related effects on clearance due to maturation are anticipated to be realized by approximately 6 years of age.

Table 6 Population PK Parameter Estimates for the Final Model

Parameter (Units)	Estimate	ASE	%RSE	95% CI
CL (L/day)	0.0959	0.000954	1.0	(0.0940, 0.0978)
Vc (L)	2.99	0.0389	1.3	(2.91, 3.07)
Q (L/day)	0.186	0.00950	5.1	(0.167, 0.205)
Vp (L)	1.04	0.0232	2.2	(0.995, 1.09)
Ka ($days^{-1}$)	0.341	0.00679	2.0	(0.328, 0.354)
Vmax (mg/L/day)	1.24 (FIXED)			
Km (mg/L)	2.33 (FIXED)			
F1	0.61 (FIXED)			
WT on CL (Ref: 70 kg)	0.751	0.0213	2.8	(0.710, 0.793)
WT on Vc (Ref: 70 kg)	1.25	0.0316	2.5	(1.18, 1.31)
F_{CL}	0.802	0.223	27.8	(0.365, 1.24)
β [d]	0.198			
Maturation half-life for CL (years)	1.13	0.321	28.4	(0.503, 1.76)
ALB_CL [Ref: 45g/L]	-0.787	0.0806	10.2	(-0.945, -0.629)
EASI_CL [Ref: 30]	0.149	0.0179	12	(0.114, 0.184)
ASIAN_CL [Ref: White]	0.0824	0.0196	23.8	(0.0440, 0.121)
BLACK_CL [Ref: White]	0.137	0.0271	19.7	(0.0841, 0.190)
ADA1_CL [Ref: ADA=0]	0.330	0.0312	9.4	(0.269, 0.392)
ADA23_CL [Ref: ADA=0]	1.59	0.136	8.5	(1.33, 1.86)
EASI_VC [Ref: 30]	0.0862	0.0196	22.8	(0.0477, 0.125)
ASIAN_VC [Ref: White]	0.0713	0.0219	30.7	(0.0285, 0.114)
BLACK_VC [Ref: White]	-0.0897	0.0249	27.8	(-0.138, -0.0409)
AGE_VC [Ref: 30 yr]	0.0956	0.0174	18.2	(0.0614, 0.130)
Residual Variability				
Proportional Error	16.9 [a]			(16.7, 17.2) [a]
Additive Error (mg/L)	3.73			(3.60, 3.86)
IIV (CV%)				
ETA1 – CL [b]	32.5 [a]			(31.3, 33.6) [a]
ETA2 – Vc [c]	32.2 [a]			(30.8, 33.6) [a]
OFV	134932.7			

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

[a] Transformed estimate values are provided.

[b] Shrinkage for clearance is 12.5%

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

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

Source: Module 5.3.3.5 R668-PK-21194-SR-01V1 Synopsis Table iii.

Post-hoc estimates of individual PK parameters for the pediatric patients in Study R668-AD-1539 are summarized in ***Table 7*** below.

Table 7 Summary Statistics of Individual Post-Hoc PK Parameters for AD Patients in Study R668-AD-1539 Part A and Part B

	Post-Hoc PK Parameter					
	CL (L/day)			Vc (L)		
Body Weight Group	≥5 to <15 kg	≥15 to <30 kg	All Body Weights	≥5 to <15 kg	≥15 to <30 kg	All Body Weights
N	51	70	121	51	70	121
Mean (SD)	0.024 (0.012)	0.038 (0.018)	0.032 (0.017)	0.24 (0.08)	0.47 (0.14)	0.37 (0.16)
Geometric Mean (Geometric %CV)	0.022 (49)	0.035 (40)	0.029 (52)	0.23 (35)	0.45 (29)	0.34 (48)
Median (5^{th}, 95^{th})	0.021 (0.010, 0.045)	0.036 (0.019, 0.065)	0.029 (0.014, 0.062)	0.24 (0.13, 0.36)	0.46 (0.30, 0.69)	0.35 (0.15, 0.65)

N = Number of subjects; CL = Linear clearance; Vc = Volume of the central compartment; SD = Standard deviation; CV = Coefficient of variation
Source: Module 5.3.3.5 R668-PK-21194-SR-01V1 Synopsis Table iv.

AD patients between ≥5 to <15 kg are projected to have lower mean linear clearance (0.024 L/day), than those that are between ≥15 to <30 kg (0.038 L/day). Overall, the mean linear clearance and central volume for the pediatric patients with AD in studies R668-AD-1539 Part A and Part B (CL = 0.032 L/day; Vc = 0.37 L) are lower than the estimates for a 70 kg adult subject (CL = 0.0959 L/day; Vc = 2.99 L).

The predicted C_{trough} values are tabulated following each dose up to Week 16 (end of treatment period) in the ***Table 8*** below.

Table 8 C_{trough} Exposure Predictions Over 16 Weeks for AD Patients in Study R668-AD-1539

Weeks	Model-Predicted Dupilumab C_{trough} (mg/L) in Children (≥6 months to <6 years)					
	200 mg Q4W (≥5 to <15 kg)			300 mg Q4W (≥15 to <30 kg)		
	Median	5^{th} Percentile	95^{th} Percentile	Median	5^{th} Percentile	95^{th} Percentile
4	50	29	74	51	28	77
8	81	42	133	79	39	130
12	103	47	180	95	43	168
16	117	50	216	104	45	193

C_{trough} = Dupilumab concentration at the end of each dosing interval; Q4W = Every 4 weeks
Note: The exposure predictions in Table vi are based on patient characteristics from both Part A and Part B of Study R668-AD-1539.

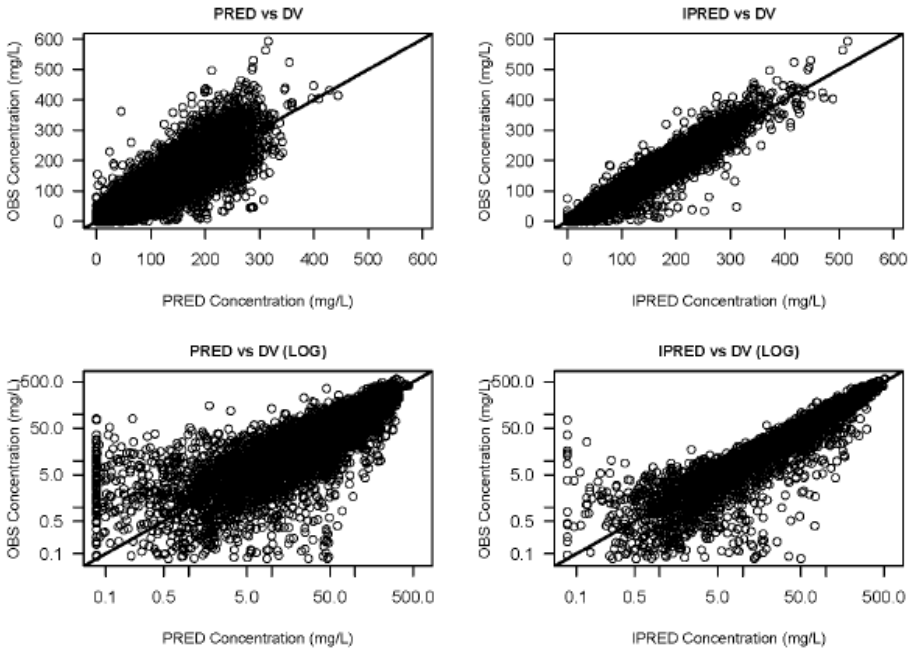
Model diagnostics

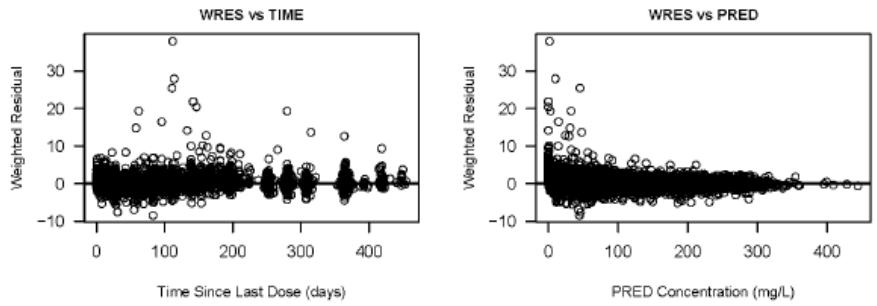
Several parameters were estimated from dense PK sampling data in adults and later fixed in the model including F1 (0.61) and nonlinear clearance parameters: Vmax (1.24 mg/L/day) and Km (2.33 mg/L). Primary PK parameters were well estimated with relative standard error [RSE] <30%. IIV was modest for CL (32.5% coefficient of variation [CV]) and Vc (32.2% CV). The model was stable with a condition number of 25, which is well below the threshold value of 1000. ETA shrinkage was low for CL (12.5%) and Vc (20.8%). The estimated exponents describing the relationships of PK parameters with body weight were 0.751 for CL and 1.25 for Vc, which are similar to the theoretical allometric scaling values of 0.75 and 1, respectively. The final model estimated the fraction of adult clearance that is present at birth to be

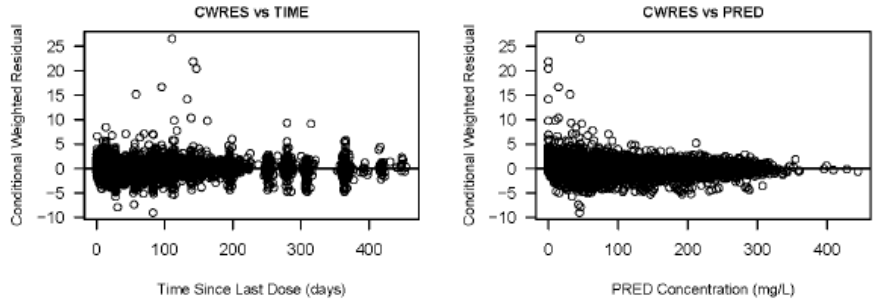
0.198 and the clearance maturation half-life estimate (95% CI) was 1.13 (0.503, 1.76) years. Pediatric clearance is anticipated to reach that of an adult by approximately 6 years of age (5 half-lives).

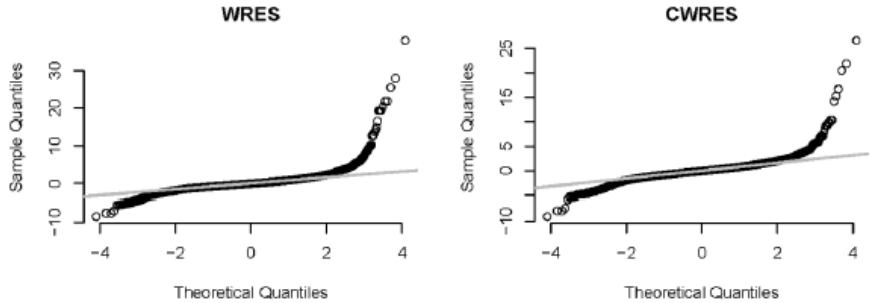
Diagnostic plots and Visual predictive check plots for the final pop PK model

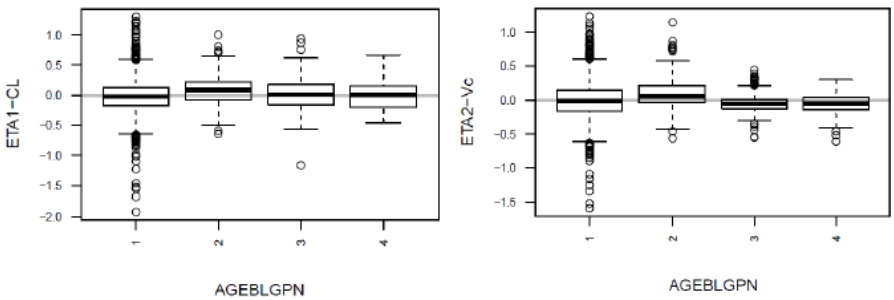
Figure 5 Final Model Diagnostic Plots

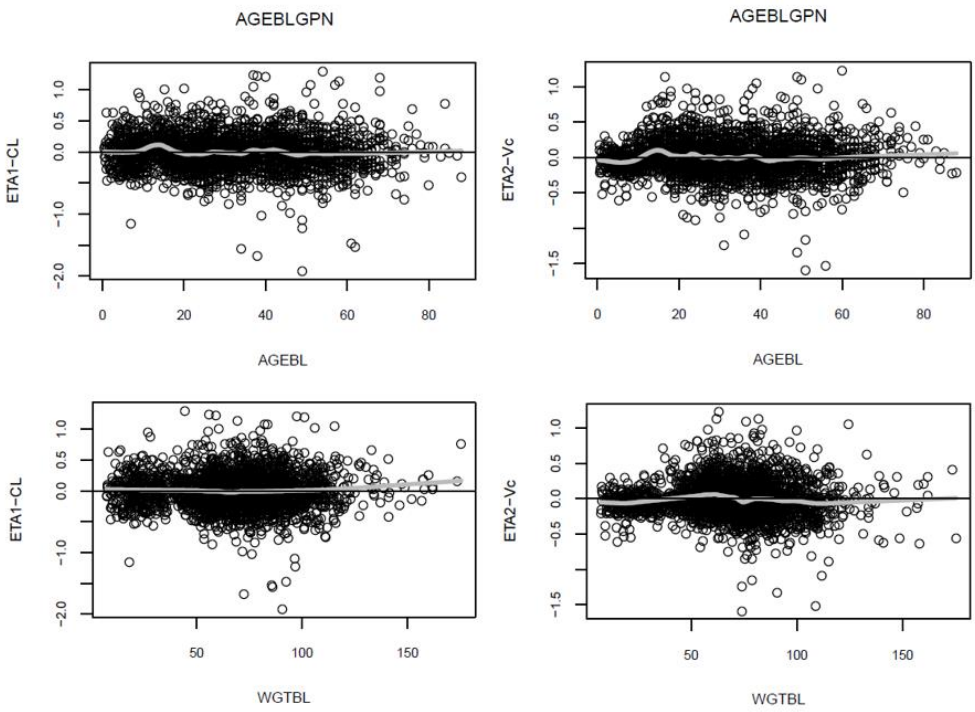



WRES vs TIME
Weighted Residual
Time Since Last Dose (days)
WRES vs PRED
Weighted Residual
PRED Concentration (mg/L)


CWRES vs TIME
Conditional Weighted Residual
Time Since Last Dose (days)
CWRES vs PRED
Conditional Weighted Residual
PRED Concentration (mg/L)


WRES
Sample Quantiles
Theoretical Quantiles
CWRES
Sample Quantiles
Theoretical Quantiles


ETA1-CL
AGEBLGPN
ETA2-Vc
AGEBLGPN



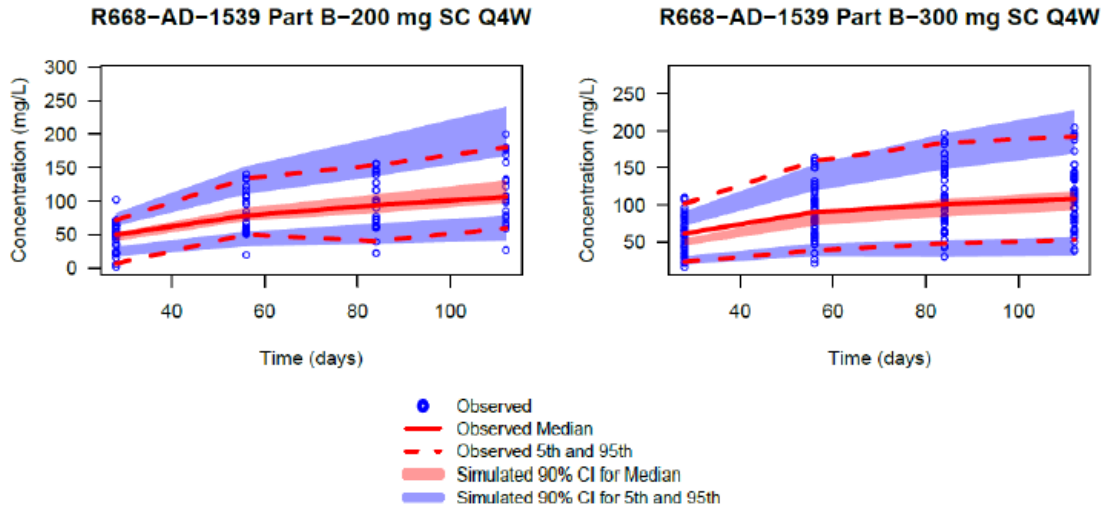
DV = Dependent variable; PRED = Population or typical individual predicted value obtained from a NONMEM model fit evaluated at eta=0; IPRED = Individual predicted value based on individual etas; WRES = Weighted residuals; CWRES = Conditional weighted residuals; OBS = Observed; CL = Linear clearance; Vc = Volume of the central compartment; AGEBLGPN = Baseline age group (1 = adults; 2 = adolescents ≥12 to <18 years of age; 3 = children ≥6 to <12 years of age; 4 = children ≥6 months to <6 years of age); AGEBL = Baseline age (years); WGTBL = Baseline body weight (kg)

Note: Concentrations below the limit of quantification were assigned a value of 0.078 mg/L (lower limit of quantification) for the concordance and goodness-of-fit plots.

A total of 25 observations in the dataset were identified as potential outliers in the final mode, but did not result differences in model parameters (eg. CL, Vc, Ka) were > 2%; therefore, the outliers were retained in the model.

VPC plots provided below indicated that the final model is able to adequately describe the data from Study R668-AD-1539 Part B, as well as all 22 studies in the dataset.

Figure 6 Visual Predictive Check Plots for the Final Model and Study R668-AD-1539 Part B



SC = Subcutaneous; Q4W = Every 4 weeks; CI = Confidence interval
Note: The VPC for Study R668-AD-1539 Part B includes concentrations only for the treatment period (16 weeks).

Exposure predictions and PK comparison across populations

In prior population PK analyses the PK of dupilumab was consistent across healthy volunteers and patients with AD, asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), suggesting a lack of effect of underlying disease on the PK of dupilumab (POH0611 and POH0668). Body weight is the primary covariate influencing the PK of dupilumab. After accounting for body weight there were no additional notable age-associated difference in the PK of dupilumab observed between adults, adolescents and children ≥6 to <12 years of age with AD or adult and adolescent patients with asthma.

The dosing regimen investigated in the pivotal study R668-AD-1539 Part B was a fixed, weight-tiered dupilumab regimen administered every 4 weeks (Q4W; 200 mg Q4W for patients with body weight of ≥5 to <15 kg at baseline, and 300 mg Q4W patients with body weight of ≥15 to <30 kg at baseline). Selection of the dose regimens in R668-AD-1539 Part B was informed by simulations from a PopPK model characterizing pharmacokinetic data for pediatric patients with AD, including children ≥6 months to <6 years old from study R668-AD-1539 Part A. The goal of dose selection for study R668-AD-1539 Part B was to achieve dupilumab steady state exposure in pediatric patients aged ≥6 months to <6 years within the range of exposures in adults, adolescents, and children ≥6 to <12 years of age where tolerability and efficacy have been demonstrated.

Dupilumab is approved in the EU for adults (300 mg Q2W) and adolescents ≥12 to <18 years of age (200 mg Q2W in patients <60 kg and 300 mg Q2W in patients ≥60 kg) with moderate-to-severe AD and children ≥6 to <12 years (300 mg Q4W in patients ≥15 to <60 kg and 300 mg Q2W in patients ≥60 kg) with severe AD. The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg to <60 kg based on physician's assessment. The 300 mg QW dose regimen in adults, the highest regimen that was studied and which demonstrated a favorable safety profile, was included as an additional reference.

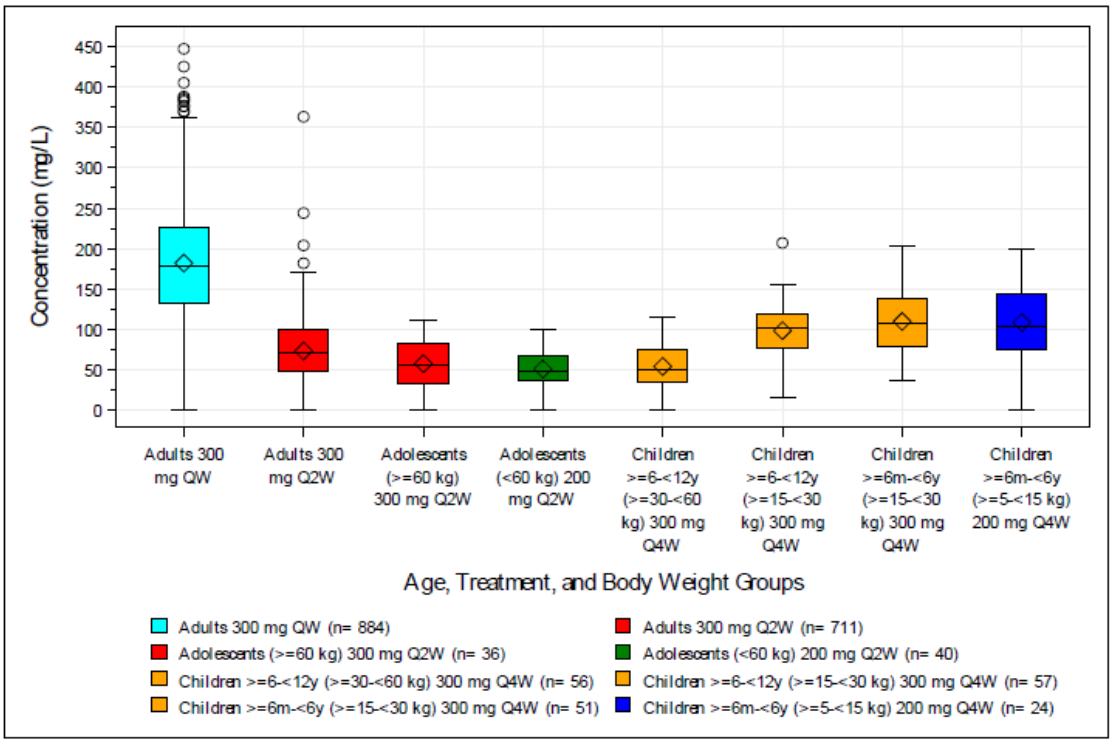
Comparisons for the PK of dupilumab in children ≥6 months to <6 years of age treated with dupilumab 200 mg Q4W in patients ≥5 to <15 kg or 300 mg Q4W in patients ≥15 to <30 kg to older populations were based on: 1) Observed concentration-time profiles of functional dupilumab and C_{trough} at week 16 in pivotal study R668-AD-1539 Part B for children ≥6 months to <6 years of age or in phase 2 and 3 studies in adults, adolescents, and children ≥6 to <12 years of age with AD; 2) Predicted exposure metrics (Cmax, AUC, and C_{trough} at steady-state) for dupilumab in adults, adolescents, children ≥6 to <12 years of age, and children ≥6 months to <6 years of age based on the integrated final population PK model.

Adult data were pooled from phase 2b dose ranging study R668-AD-1021 and phase 3 studies R668-AD-1224, R668-AD-1334, R668-AD-1416, and R668-AD-1424.

Data in adolescents and children ≥6 to <12 years of age were from phase 3 studies R668-AD-1526 and R668-AD-1652, respectively. In children ≥6 to <12 years of age weighing ≥15 to <60 kg, the approved posology in the EU of 300 mg Q4W includes a loading dose of 300 mg administered on days 1 and 15, whereas a loading dose of 600 mg was administered on day 1 in this age group in the pivotal study.

The final PopPK model was used to simulate the median and the 5th and 95th percentiles of dupilumab concentration over time in children aged ≥6 months to <6 years receiving dupilumab 200 mg Q4W (patients ≥5 to <15 kg) or 300 mg Q4W (patients ≥15 to <30 kg), as well as for the approved regimens in adults, adolescents, and children ≥6 to <12 years of age with AD, and to assess the sources of variability.
Post-hoc steady-state exposure metrics were summarized including $C_{trough,ss}$, maximum concentration (Cmax,ss), area under the curve (AUC) over a given dosing interval ($AUC_{T,ss}$), and AUC over a 4 week dosing period (AUC4weeks,ss) to allow for exposure comparisons between dosing regimens of differing intervals across age groups.
Observed C_{trough} at week 16 and PopPK model derived exposure metrics were compared for the Q4W regimens in patients ≥6 months to <6 years of age to the approved regimens in adults, adolescents, and children ≥6 to <12 years of age with AD.

Figure 7 Box-Plot of Dupilumab Trough Concentrations (ml/L) at Week 16 in Patients with Atopic Dermatitis by Age, Treatment, and Body Weight Groups for Reference Dupilumab Regimens in the EU and in Study R668-AD-1539 Part B (PK Analysis Set)



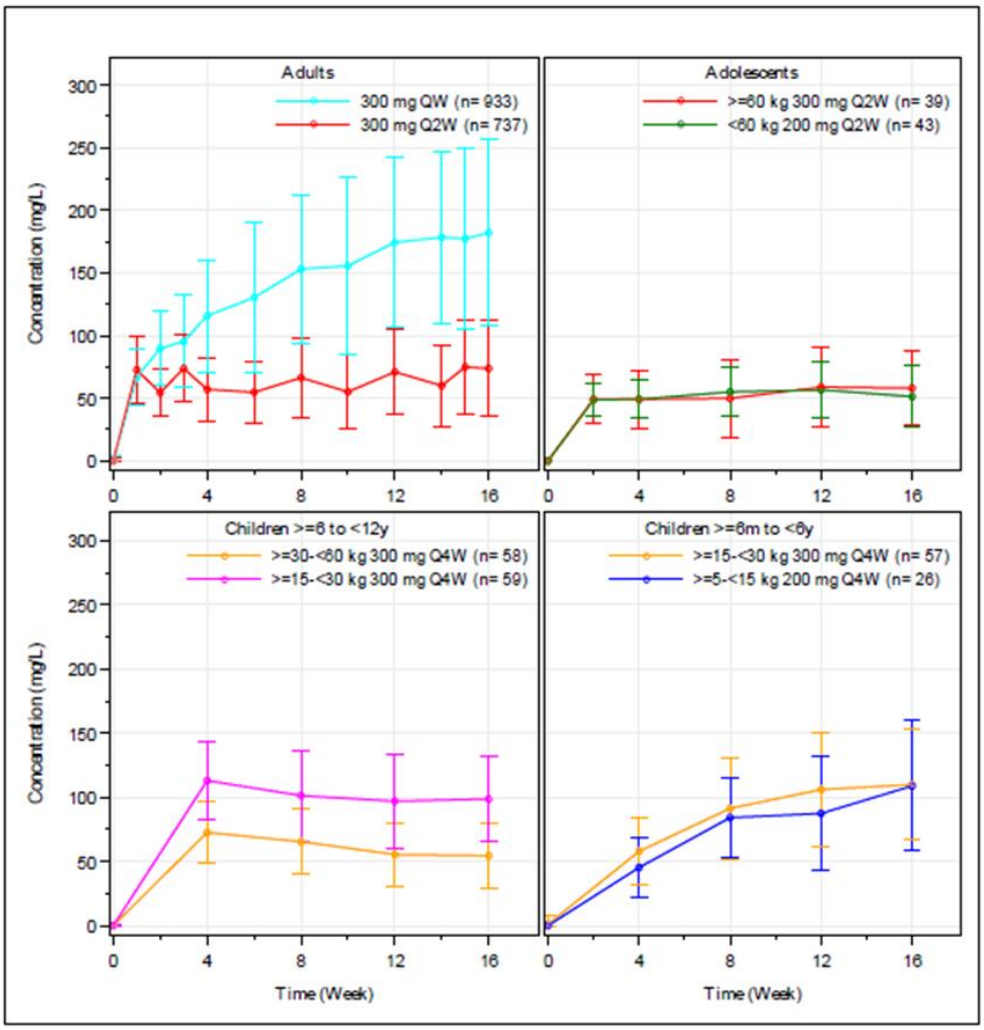
n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Concentrations at week 16 in all studies. Included studies by age group: adults (R668-AD-1021, R668-AD-1224, R668-AD-1334, R668-AD-1416, R668-AD-1424), adolescents (R668-AD-1526), children ≥6 to <12 years (AD-1652), and children ≥6 months to <6 years (AD-1539 Part B).
Dose levels supporting approved dupilumab regimens for patients with AD in the EU, 300 mg QW in adults, or studied in R668-AD-1539 Part B are shown. Adults, adolescents, and children ≥6 to <12 years received loading doses on day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W) or 400 mg (200 mg Q2W) in these studies. The approved loading dose for 300 mg Q4W in children ≥6 to <12 years is 300 mg on day 1 and 15. No loading doses were administered in children ≥6 months to <6 years.

Table 9 Summary Statistics of Individual Post-Hoc Steady-State Exposure Predictions by Treatment Group and Weight in Children ≥6 Months to <6 years of Age, Children ≥6 to <12 Years of Age, Adolescents and Adults

Population	Body Weight	Dupilumab Regimen	$C_{trough,ss}$ Median (5th, 95th)	$C_{max,ss}$ Median (5th, 95th)	$AUC_{4wk,ss}$ Median (5th, 95th)	$AUC_{\tau,ss}$ Median (5th, 95th)
Adults	Any	300 mg QW [a]	185 (80, 307)	200 (89, 328)	5333 (2370, 8741)	1303 (584, 2115)
	Any	300 mg Q2W [a]	68 (21, 126)	91 (37, 160)	2271 (842, 4048)	1128 (420, 2001)
Adolescents	≥60kg	300 mg Q2W [a]	58 (15, 109)	82 (32, 138)	2020 (743, 3487)	1009 (372, 1718)
	<60kg	200 mg Q2W [b]	54 (28, 91)	81 (44, 126)	1965 (1065, 3083)	979 (532, 1532)
Children ≥ 6 to <12 years	≥30 to <60 kg	300 mg Q4W [c]	48 (14, 94)	122 (61, 181)	2295 (992, 3790)	2295 (992, 3790)
	≥15 to <30 kg	300 mg Q4W [c]	86 (37, 153)	191 (119, 274)	3729 (2076, 5664)	3729 (2076, 5664)
Children ≥ 6 months to <6 years	≥15 to <30 kg	300 mg Q4W	104 (45, 193)	222 (144, 319)	4258 (2466, 6841)	4258 (2466, 6841)
	≥5 to <15 kg	200 mg Q4W	117 (50, 216)	219 (157, 326)	4309 (2429, 7082)	4309 (2429, 7082)

AUC = Areas under the concentration time curve (mg·day/L); τ = dosing interval; AUC4wk,ss = Area under the concentration time curve over 4 weeks at steady-state (mg·day/L); $C_{max,ss}$ = Steady-state maximum concentration (mg/L); $C_{trough,ss}$ = Steady-state minimum concentration (mg/L); QW = Every week; Q2W = Every 2 weeks; Q4W = Every 4 weeks
Note: $C_{max,ss}$ and $AUC_{\tau,ss}$ were calculated for the dosing interval ending on week 16, $C_{trough,ss}$ was reported at week 16, and $AUC4_{wk,ss}$ was calculated from weeks 12 to 16, assuming steady-state conditions by week 16.
a Loading dose of 600 mg on day 1
b Loading dose of 400 mg on day 1
c Loading dose of 300 mg on day 1 and 300 mg on day 15.
Source: Module 5.3.3.5 R668-PK-21194-SR-01V1 Synopsis Table v.

Figure 8 Mean (±SD) Concentrations of Functional Dupilumab in Serum (mg/L) vs. Time (Week) in Patients with Atopic Dermatitis by Age, Treatment, and Body Weight Group for Reference Dupilumab Regimens in the EU and in Study R668-AD-1539 Part B (PK Analysis Set)



n = Number of patients. Concentrations below the LLOQ were set to zero. Concentrations presented through week 16 for all studies. Included studies by age group: adults (R668-AD-1021, R668-AD-1224, R668-AD-1334, R668-AD-1416, R668-AD-1424), adolescents (R668-AD-1526), children ≥6 to <12 years (R668-AD-1652), and children ≥6 months to <6 years (R668-AD-1539 Part B).
Dose levels supporting approved dupilumab regimens for patients with AD in the EU, 300 mg QW in adults, or studied in R668-AD-1539 Part B are shown. Adults, adolescents, and children ≥6 to <12 years received loading doses on day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W) or 400 mg (200 mg Q2W) in these studies. The approved loading dose for 300 mg Q4W in children ≥6 to <12 years is 300 mg on day 1 and 15. No loading doses were administered in children ≥6 months to <6 years.

Absorption

Dupilumab is well absorbed after SC administration, with a reported bioavailability of 61 to 64%.

The extent of absorption (bioavailability) in children was not estimated due to lack of intravenous (IV) data, but was fixed to 61% for the target population (see population PK model)

Age was not a statistically significant covariate on absorption rate (Ka) when assessed in the full PopPK model.

The rate of absorption was estimated in children ≥6 months to <6 years of age to 0.341 (1/d).

Mean C_{max} values were generally similar (≤25% difference) for the 2 to <6 years of age cohort compared to the 6 months to <2 years of age cohort at each dose level and median t_{max} was observed

approximately 2 days after dosing for all cohorts, and suggest similar absorption kinetics between the age cohorts in study R668-AD-1539 Part A.

Distribution

Children ≥6 months to <6 years of age have a smaller body size and volume of distribution than older populations. Mean post-hoc estimates of the apparent central compartment volume of distribution (V_c) were lower for children ≥6 months to <6 years of age (0.24 L for ≥5 to <15 kg or 0.47 L for ≥15 to <30 kg) than the reference of 2.99 L in a 70 kg adult (***Table 7***).

Elimination

The PK of dupilumab is characterized as nonlinear with parallel linear and nonlinear elimination pathways (target-mediated clearance), with the target-mediated pathway expressing a high degree of nonlinearity. The time for dupilumab concentrations to decrease below the lower limit of quantitation (LLOQ; 0.078 mg/L) after cessation of dosing was determined across populations with AD using the final PopPK model. Consistent with the effects of weight and age on clearance, this duration was similar in adults or adolescents, but longer in children:

After the last steady-state dose of various dosing regimen, the median times to non-detectable concentration ranged from 9 to 13 weeks in adults and pediatric patients 12 to 17 years of age, and are approximately 1.5 times and 2.5 times longer in pediatric patients 6 to <12 years of age and pediatric patients <6 years old, respectively.

Clearance in children <6 years of age was less than would be expected from allometrically scaled values in older populations, but did not require additional adjustment to the weight-tiered dose regimens. Based on the final PopPK model, after accounting for differences in body weight, increasing age was associated with increasing clearance in children. Age-related differences in clearance observed in the younger children were accounted for by a maturation function, where linear clearance increases with age. At 6 months of age, children exhibit approximately 40% of allometrically scaled adult clearance. Clearance matures asymptotically and reaches ≥95% of allometrically scale adult clearance by approximately 6 years of age.

Age did not affect clearance of dupilumab in pediatric subjects ≥6 to <18 years of age or in adults.

Dose proportionality and time dependencies

Dose proportionality

Dupilumab, like many other monoclonal antibodies targeting endogenous receptors, is characterized by linear and nonlinear target-mediated kinetics. This nonlinear PK profile is typically observed at drug concentrations below that required to saturate the target-mediated pathway, resulting in a greater than dose proportional increase in exposure (initial adult AD marketing application). As drug concentrations increase to levels greater than those required to saturate the target-mediated pathway, the PK profile reverts to a linear and dose-proportional profile. For the regimens in R668-AD-1539 Part B, most patients exhibit exposures in the linear range throughout the treatment period.

Steady state and Accumulation

Mean dupilumab C_{trough} in patients ≥15 to <30 kg receiving dupilumab 300 mg Q4W or patients ≥5 to <15 kg received dupilumab 200 mg Q4W in study R668-AD-1539 Part B reached steady-state by week

16. Dupilumab C_{trough} at week 16 was approximately 2-fold of C_{trough} at week 4 after the first dose for both regimens (***Table 10***).

Notably, the time to achieve steady state in the ≥6 months to <6-year-old patients receiving dupilumab at a Q4W interval is most similar to that observed in adult patients receiving dupilumab 300 mg QW. This observation is consistent with the non-linear clearance of dupilumab and the exposure achieved in the ≥6 months to <6 year old patient population, compared to adults. At week 4, mean C_{trough} values in children ≥6 months to <6 years of age was lower than observed for children ≥6 to <12 years, but were similar to concentrations for the approved regimens in adults receiving 300 mg Q2W and adolescents receiving 200 mg Q2W or 300 mg Q2W. At week 8, concentrations in children ≥6 months to <6 years of age continued to increase and were similar to observations in children ≥6 to <12 years of age and higher than observed in adults and adolescents on approved dose regimens. In children ≥6 months to <6 years, systemic concentrations of dupilumab in the 300 mg Q4W group appeared to have reached steady-state by week 12, while the highest mean concentrations for the 200 mg Q4W group were observed at week 16 (***Figure 8***).

To assess the potential for continued accumulation beyond the 16 weeks of treatment evaluated in study R668-AD-1539 Part B, dupilumab C_{trough} was compared for patients that received the same regimen of dupilumab 200 or 300 mg Q4W in study R668-AD-1539 Part B and study R668-AD-1434 in the OLE. In the subset of patients with <6 weeks of treatment gap between the last dose in R668-AD-1539 Part B and the first dose in R668-AD-1434, mean±SD dupilumab C_{trough} at week 16 in the OLE (eg, after approximately 32 weeks of continuous treatment) for 300 mg Q4W (96.8±21.1 mg/L) or 200 mg Q4W (146±34.1 mg/L) were similar to C_{trough} at week 16 in R668-AD-1539 Part B for 300 mg Q4W (92.3±32.6 mg/L) or 200 mg Q4W (137±40.4 mg/L), illustrating that steady-state concentrations were achieved for both regimens after ≤16 weeks of treatment and maintained over the duration of the OLE study.

Table 10 Comparison of Dupilumab Trough Concentrations (mg/L) at Week 16 in Patients with Atopic Dermatitis by Age, Treatment, and Body Weight Groups for Reference Dupilumab Regimens in the EU and in Study R668-AD-1539 Part B (PK Analysis Set)

	300 mg QW		300 mg Q2W		200 mg Q2W		300 mg Q4W		200 mg Q4W	
Age and Body Weight Groups	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Adults	884	182 (74.2)	711	73.6 (38.4)	--		--		--	
Adolescents (≥60 kg)	--		36	57.9 (30.0)	--		--		--	
Adolescents (<60 kg)	--		--		40	51.3 (24.2)	--		--	
Children ≥6-<12y (≥30-<60 kg)	--		--		--		56	54.5 (25.6)	--	
Children ≥6-<12y (≥15-<30 kg)	--		--		--		57	98.7 (33.2)	--	
Children ≥6m-<6y (≥15-<30 kg)	--		--		--		51	110 (42.8)	--	
Children ≥6m-<6y (≥5-<15 kg)	--		--		--		--		24	109 (50.8)

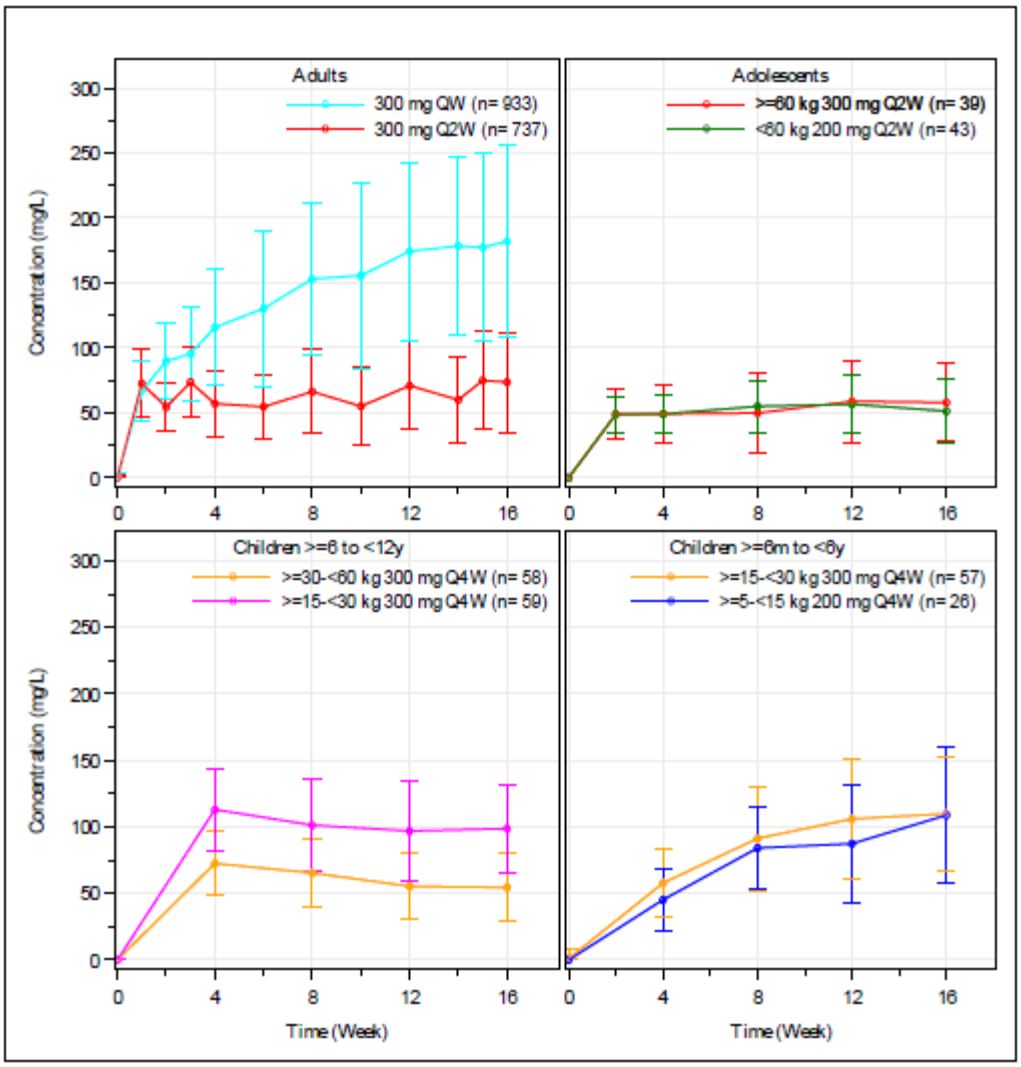
n=Number of patients contributing to each category. Concentrations below the LLOQ were set to zero. Concentrations at week 16 in all studies. Included studies by age group: adults (R668-AD-1021, R668-AD-1224, R668-AD-1334, R668-AD-1416, R668-AD-1424), adolescents (R668-AD-1526), children ≥6 to <12 years (R668-AD-1652), and children ≥6 months to <6 years (R668-AD-1539 Part B).
Dose levels supporting approved dupilumab regimens for patients with AD in the EU, 300 mg QW in adults, or studied in R668-AD-1539 Part B are shown. Adults, adolescents, and children ≥6 to <12 years received loading doses on day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W) or 400 mg (200 mg Q2W) in these studies. The approved loading dose for 300 mg Q4W in children ≥6 to <12 years is 300 mg on day 1 and 15. No loading doses were administered in children ≥6 months to <6 years.

Loading dose

In adults, adolescents, and children ≥6 to <12 years of age with AD, dupilumab is administered with a loading dose. The loading dose was intended to reduce the time required to reach effective concentrations of dupilumab. Children ≥6 months to <6 years of age have a smaller body size and volume of distribution than older populations and were expected to achieve high exposures following an initial SC injection of 200 or 300 mg dupilumab without a loading dose.

There was also interest to limit the number of injections upon initiation of treatment in this younger population. Thus, a loading dose of dupilumab was not included in the dosing regimen for children ≥6 months to <6 years of age with AD receiving dupilumab 200 mg Q4W or 300 mg Q4W in study R668-AD-1539 Part B. The inclusion or omission of a loading dose does not impact exposure at steady-state for any dose regimen, but patients may take longer to achieve steady-state without the loading dose (***Figure 9***). Nonetheless, mean concentrations of dupilumab at week 4 in children ≥6 months to <6 years of age receiving dupilumab 200 mg Q4W or 300 mg Q4W in study R668-AD-1539 Part B were similar to approved regimens administered with a loading dose in adults (300 mg Q2W with a 600 mg loading dose) and adolescents (300 mg Q2W with a 600 mg loading dose or 200 mg Q2W with a 400 mg loading dose). Rapid attainment of effective concentrations suggests that omission of a loading dose did not adversely affect evaluation of dupilumab in this patient population.

Figure 9 Mean (±SD) Concentrations of Functional Dupilumab in Serum (mg/L) vs. Time (Week) in Patients with Atopic Dermatitis by Age, Treatment, and Body Weight Group for Reference Dupilumab Regimens in the EU and in Study R668-AD-1539 Part B (PK Analysis Set)



n = Number of patients. Concentrations below the LLOQ were set to zero. Concentrations presented through week 16 for all studies. Included studies by age group: adults (R668-AD-1021, R668-AD-1224, R668-AD-1334, R668-AD-1416, R668-AD-1424), adolescents (R668-AD-1526), children ≥6 to <12 years (R668-AD-1652), and children ≥6 months to <6 years (R668-AD-1539 Part B).
Dose levels supporting approved dupilumab regimens for patients with AD in the EU, 300 mg QW in adults, or studied in R668-AD-1539 Part B are shown. Adults, adolescents, and children ≥6 to <12 years received loading doses on day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W) or 400 mg (200 mg Q2W) in these studies. The approved loading dose for 300 mg Q4W in children ≥6 to <12 years is 300 mg on day 1 and 15. No loading doses were administered in children ≥6 months to <6 years.

Special populations

From pop PK:

Summaries of subject characteristics for the combined 22 clinical studies are provided in the *Table* ***11*** and *Table* ***12*** below. A large proportion of the data is from adult studies, with the dataset providing information to characterize the PK of dupilumab in paediatric patients, including ages ≥6 months to <6 years (N=121).

Table 11 Summary of Categorical Covariates

Population	Patients with AD				Healthy Subjects	Total
	Children ≥6 months to <6 years [a]	Children ≥6 to <12 years	Adolescents ≥12 to <18 years	Adults		
N (%) Subjects	121 (4.2%)	277 (9.6%)	252 (8.8%)	2021 (70.3%)	202 (7%)	2873 (100%)
Gender						
Males	73 (60.3%)	140 (50.5%)	135 (53.6%)	1182 (58.5%)	121 (59.9%)	1651 (57.5%)
Females	48 (39.7%)	137 (49.5%)	117 (46.4%)	839 (41.5%)	81 (40.1%)	1222 (42.5%)
Patient Status						
Healthy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	202 (100%)	202 (7.0%)
AD Patient	121 (100%)	277 (100%)	252 (100%)	2021 (100%)	0 (0%)	2671 (93.0%)
Race						
White	84 (69.4%)	208 (75.1%)	176 (69.8%)	1397 (69.1%)	128 (63.4%)	1993 (69.4%)
Black	21 (17.4%)	40 (14.4%)	22 (8.7%)	155 (7.7%)	43 (21.3%)	281 (9.8%)
Asian	10 (8.3%)	15 (5.4%)	34 (13.5%)	414 (20.5%)	25 (12.4%)	498 (17.3%)
Native American	0 (0%)	0 (0%)	2 (0.8%)	6 (0.3%)	1 (0.5%)	9 (0.3%)
Pacific Islander	0 (0%)	1 (0.4%)	3 (1.2%)	4 (0.2%)	1 (0.5%)	9 (0.3%)
Other	4 (3.3%)	10 (3.6%)	13 (5.2%)	35 (1.7%)	4 (2%)	66 (2.3%)
Not Reported	2 (1.7%)	3 (1.1%)	2 (0.8%)	10 (0.5%)	0 (0%)	17 (0.6%)
ADA Status						
Negative [b]	100 (82.6%)	251 (90.6%)	190 (75.4%)	1797 (88.9%)	139 (68.8%)	2477 (86.2%)
Positive (Low Titer)	18 (14.9%)	21 (7.6%)	53 (21%)	185 (9.2%)	52 (25.7%)	329 (11.5%)
Positive (Moderate Titer)	3 (2.5%)	2 (0.7%)	6 (2.4%)	28 (1.4%)	10 (5%)	49 (1.7%)
Positive (High Titer)	0 (0%)	3 (1.1%)	3 (1.2%)	11 (0.5%)	1 (0.5%)	18 (0.6%)

N = Number; AD = Atopic dermatitis; ADA = Anti-drug antibody

Notes: Race categories "Native American" includes American Indians and Alaska Natives and "Pacific Islander" includes Native Hawaiians and other Pacific Islanders; Negative ADA status (No treatment emergent ADA) means that the subject did not exhibit ADA, pre-existing ADA levels were not treatment-boosted, or did not fall into the categories of low, moderate or high, defined as "low" > 0 to ≤ 1000, "moderate" > 1000 to ≤ 10000, and "high" >10000; Baseline IGA score is "missing" in healthy subjects.

[a] Study R668-AD-1539 (Part A and Part B)

[b] No Treatment-Emergent ADA

Table 12 Summary of Continuous Covariates at Baseline

Population	Patients with AD				Healthy Subjects [b]	Total
	Children ≥6 months to <6 years [a]	Children ≥6 to <12 years	Adolescents ≥12 to <18 years	Adults		
Age (years)						
N	121	277	252	2021	202	2873
Mean	3.5	8.52	15.03	38.02	34.59	31.47
SD	1.49	1.71	1.71	13.94	11.45	16.88
Median	3.75	9	14.94	36	32	30
Min	0.5	6	12	18	18	0.5
Max	5.83	11.94	17.97	88	63	88
Missing	0	0	0	0	0	0
Weight (kg)						
N	121	277	252	2021	202	2873
Mean	15.9	31.41	63.31	76.93	75.97	68.71
SD	4.83	10.05	20.1	18.76	9.87	24.61
Median	15.6	29.4	58.4	74.2	77.25	70
Min	7.4	17.7	31.7	39.8	52.1	7.4
Max	29.8	79.1	173.6	175.4	94.6	175.4
Missing	0	0	0	0	0	0
Albumin (g/L)						
N	121	277	252	2021	202	2873
Mean	45.5	46.2	46.12	44.02	43.94	44.47
SD	3.89	3.21	3.1	3.85	3.39	3.8
Median	46	46	46	44	44	45
Min	33	36	36	22	33	22
Max	53	54	53	57	53	57
Missing	0	0	0	0	0	0
EASI Score (0-72)						
N	121	277	252	2021	NA	2671
Mean	35.39	37.24	33.84	31.74	NA	32.67
SD	13.28	12.43	14.47	13.31	NA	13.45
Median	33	35.2	30.43	28.5	NA	29.8
Min	16.2	10.6	9.5	0.6	NA	0.6
Max	72	70.8	70.8	72	NA	72
Missing	0	0	0	0	202	202

N = Number of subjects; SD = Standard deviation; Min = Minimum; Max = Maximum; EASI = Eczema Area and Severity Index; NA = Not applicable

[a] Study R668-AD-1539 (Part A and Part B)

[b] Baseline EASI scores were identified as missing for healthy subjects in the dataset, and are not included in the total summary statistics.

The covariates retained in the final model, in addition to covariates in the base model (allometry and maturation effect on CL), were Black race, Asian race, low and moderate/high ADA status, EASI score, and baseline albumin on linear CL; and age, Black race, Asian race and EASI score on Vc.

Body Weight

Body weight is the primary covariate affecting the pharmacokinetics of dupilumab. The weight-tiered fixed dosing regimens were used to reduce the differences in exposure associated with weight across pediatric populations. In patients ⩾6 months to <6 years of age, dupilumab regimens of 300 mg Q4W in patients ⩾15 to <30 kg and 200 mg Q4W in patients ⩾5 to <15 kg exhibited C_{trough} at week 16 that was similar between weight groups for this age category, and similar to or higher than those observed for the approved regimens in older AD patients (***Figure 9***).

Age

When assessed in the full PopPK model, age was not a statistically significant covariate on absorption rate (Ka). After accounting for differences in body weight, increasing age was associated with increasing

clearance in children <6 years of age but did not require adjustment to the dose regimen. Incorporation of the age-related effect results in lower predicted clearance, between the ages of 6 months to 6 years (also refer to the topic *Elimination*).

In contrast, age did not affect clearance of dupilumab in pediatric subjects ≥6 to <18 years of age or in adults.

Other Covariates

The PopPK model also included covariate effects for race, baseline albumin concentration, baseline EASI score, and ADA status on dupilumab pharmacokinetics. Black or Asian race, lower albumin, higher EASI score, and low titer or moderate/high titer ADA status were associated with decreased exposure to dupilumab in patients with AD. Most of these findings, however, only resulted in small numerical differences (***Figure 10***). While ADA positive patients were associated with lower exposure to dupilumab , the immunogenicity of dupilumab in children ≥6 months to <6 years of age was low in study R668-AD-1539 Part B and no patients with moderate or high titers were observed (also refer to section Immunogenicity).

Race (Asian race/Black race)

Based on the population PK analysis, Asian and Black race were associated with lower exposure to dupilumab than White race in patients with AD. However, variability in dupilumab exposure in children ≥6 months to <6 years of age due to race was less than variability due to body weight and age and the effect of race on exposure to dupilumab resulted in only small numerical differences.

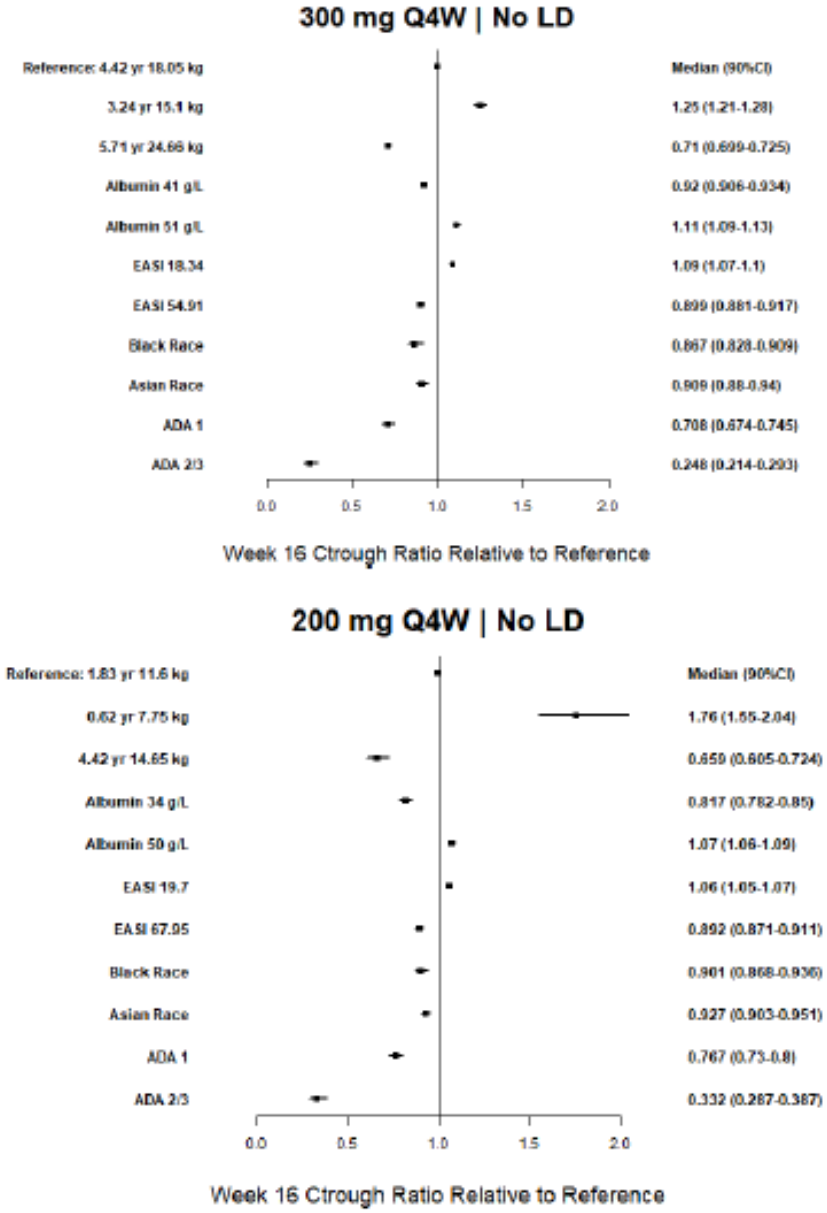
Treatment-Emergent ADA (low, moderate/high titers)

Discussed within section Immunogenicity.

Baseline Disease Activity

Based on the population PK analysis, higher EASI score at baseline was associated with decreased exposure to dupilumab in patients with AD. However, variability in dupilumab exposure in children ≥6 months to <6 years of age due to baseline EASI score was less than variability due to body weight and age and the effect of baseline disease activity on exposure to dupilumab resulted in only small numerical differences.

Figure 10 Impact of Covariates on Dupilumab C_{trough} at Week 16 in the Population PK Final Model



C_{trough} = Dupilumab concentration at the end of a dose interval; EASI = Eczema area and severity index; ADA1 = ADA positive with low titer, ADA23 = ADA positive with moderate/high titer; ADA = Anti-drug antibody; CI = Confidence interval; yr = Year. LD = loading dose

Ratios are for the test condition relative to the reference patient in each respective weight group in studies R668-AD-1539 Part A and Part B (body weight ≥ 5 to <15 kg; dupilumab 200 mg Q4W and body weight ≥15 to <30 kg; dupilumab 300 mg Q4W): 5th and 95th percentile of observed baseline age and weight relative to the median; 5th and 95th percentile of observed baseline albumin relative to reference of 45 g/L; 5th and 95th percentile of observed baseline EASI relative to reference of 30; Black race or Asian race relative to White race; ADA1 or ADA2/3 status relative to no/negative ADA status.

Source: Module 5.3.3.5 R668-PK-21194-SR-01V1 Synopsis Figure ii.

2.4.3. Pharmacodynamics

Mechanism of action

Dupilumab is a human monoclonal immunoglobulin-G4 (IgG4) antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) sub-unit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab inhibits IL-4 signaling via the Type I receptor (IL 4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine- induced responses, including the release of proinflammatory cytokines, chemokines, and IgE.

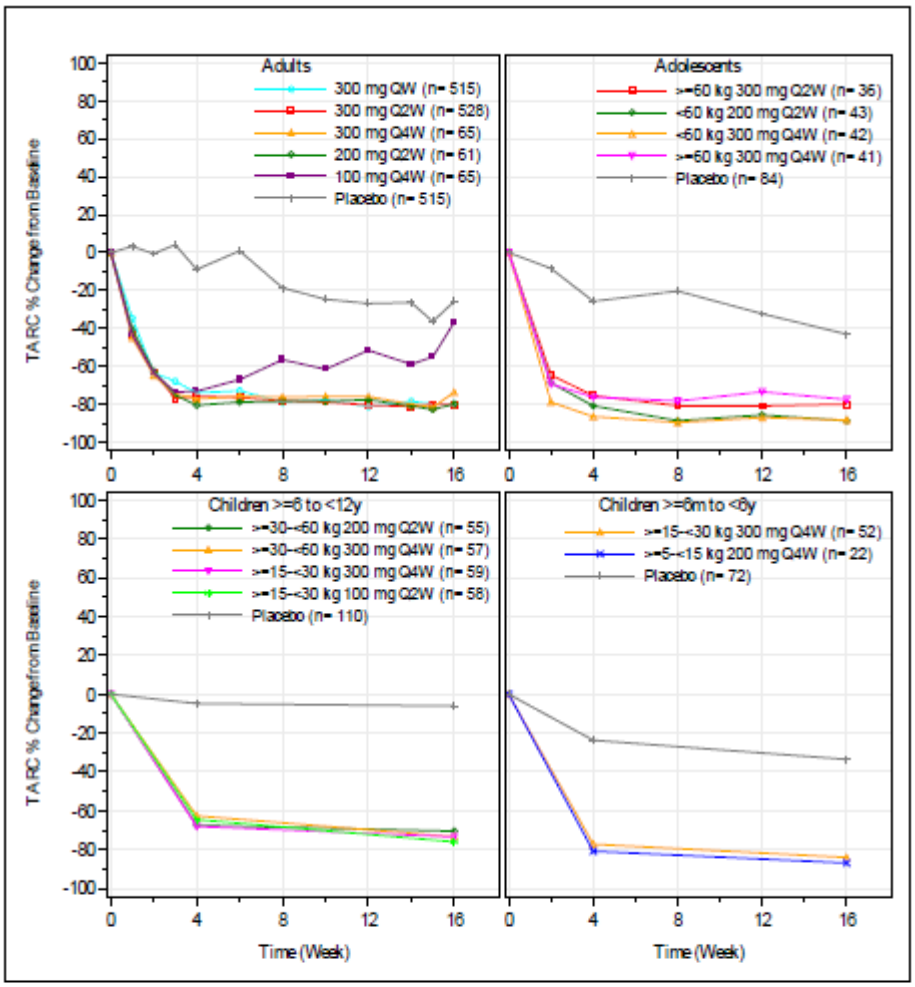
Primary and secondary pharmacology

TARC

Thymus and activation-regulated chemokine (TARC) percent change from baseline over time was analyzed as a biomarker of dupilumab pharmacodynamic activity in patients with AD.

Pharmacodynamic profiles of TARC in children ≥6 months to <6 years of age show a similar median magnitude of effect over time by dose regimen to that of dose regimens evaluated in adults, adolescents, and children ≥6 to <12 years of age (***Figure 11***). Concentrations of TARC in serum rapidly decreased, approached a nadir by week 4, and remained suppressed throughout the 16-week treatment period for all studied dose regimens except 100 mg Q4W (400 mg loading dose) evaluated in adults as part of phase 2b dose-ranging study R668-AD-1021.

Figure 11 Comparison of the Median Percentage Change from Baseline vs. Nominal Time (Week) in Thymus and Activation-Regulated Chemokine (TARC) in Patients with Atopic Dermatitis by Age and Treatment Group



n=Number of patients. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1021, R668-AD-1334, R668-AD-1416), adolescents (R668-AD-1526), children ≥6 to <12y (R668-AD-1652), and children ≥6 months to <6 years (AD-1539 Part B). Protocol planned sample time points from baseline to week 16 are shown.
A small number of patients in R668-AD-1652 with baseline weight ≥60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or ≥=30 kg receiving 100 mg Q2W (n=1) are not shown.
Adults, adolescents, and children ≥6 to <12 years received loading doses on day 1 of 600 mg (300 mg QW, Q2W, and 300 mg Q4W), 400 mg (200 mg Q2W or 100 mg Q4W), or 200 mg (100 mg Q2W). No loading doses were administered in children ≥6 months to <6 years.

Immunogenicity

As with all monoclonal antibodies, dupilumab has the potential to induce ADAs. Therefore, serum samples for immunogenicity assessment were collected from all studies, and titer levels were provided for the ADA positive samples. Samples that were positive in the ADA assay were also examined for NAb activity.

The pivotal study R668-AD-1539 Part B was the primary source for the immunogenicity assessment of dupilumab in children aged ≥6 months to <6 years with AD, as it was the largest randomized, controlled study in this population. Patients were treated for 16 weeks with the dupilumab dosing regimens proposed for use in this patient population.

Single-dose study R668-AD-1539 Part A contributed further data on the immunogenicity profile of dupilumab when administered to children aged ≥6 months to <6 years with AD.

The OLE study (R668-AD-1434) allowed additional longitudinal monitoring of ADA responses over time of patients enrolled from parental study R668-AD-1539 Part A and Part B.

The ADA status and category of each patient was classified as one of the following:

- Negative - If all samples are found to be negative in the ADA assay
- Pre-existing – if the baseline sample is positive and all post baseline ADA titers are reported as less than 4-fold the baseline titer value
- Treatment-boosted - A positive result at baseline in the ADA assay with at least 1 post baseline titer result ≥4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least 1 positive post baseline result in the ADA assay
    - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
    - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples
    - Transient - Not persistent or indeterminate, regardless of any missing samples

In addition, the maximum response titers for each patient are categorized as High/Moderate/Low:

- Low (titer <1,000)
- Moderate (1,000≤ titer ≤10,000)
- High (titer >10,000)

The anti-drug antibody (ADA) analysis set includes all treated patients who received any study drug and who had at least 1 non-missing ADA result after the first dose of the study drug.

The neutralizing antibody (NAb) analysis set includes all treated patients who received any study drug, had at least 1 non-missing ADA result following the first dose of study drug, and either tested negative at all ADA sampling times or tested positive for ADA with at least 1 non-missing Nab result after first dose of the study drug. For patients with at least 1 non-missing ADA result after the first dose of study drug and whose ADA assay results were all negative, all NAb results were imputed as negative and the patients were included as NAb negative in the NAb analysis set.

R668-AD-1539 Part A (Phase 2, Open-label, Single Ascending Dose Study)

A total of 40 patients were included in the ADA analysis set. ADA samples were collected at baseline, day 8 and day 29.

19 out of 40 (47.5%) patients developed a treatment-emergent ADA response and 1 (2.5%) patient developed a treatment-boosted ADA response following a single dose of 3 or 6 mg/kg dupilumab. The incidence of ADA to dupilumab in Part A was similar irrespective of dupilumab dose or age cohort. Positive NAb responses were observed in 11 (27.5%) patients in this study following a single dose. Most patients with a treatment-emergent or treatment-boosted ADA response exhibited low ADA titers (***Table 13***, ***Table 14*** and ***Table 15***).

Table 13 Summary of ADA Status and Category by Treatment Group in Patients 6 Months to <6 Years of Age, with Severe Atopic Dermatitis (Study R668-AD-1539 Part A)

ADA Status and Category	2 - 6 yrs 3 mg/kg N (%)	2 - 6 yrs 6 mg/kg N (%)	6 months - 2 yrs 3 mg/kg N (%)	6 months - 2 yrs 6 mg/kg N (%)	Overall N (%)
ADA Analysis Set	10 (100)	10 (100)	10 (100)	10 (100)	40 (100)
Negative*	5 (50.0)	6 (60.0)	4 (40.0)	5 (50.0)	20 (50.0)
Treatment-Boosted Response	0	0	1 (10.0)	0	1 (2.5)
Treatment-Emergent Response	5 (50.0)	4 (40.0)	5 (50.0)	5 (50.0)	19 (47.5)

ADA = Anti-drug Antibody; N = Number of Patients Contributing to Each Category.
Note: Negative* includes both negative and pre-existing responses.

Table 14 ADA Category and Maximum Titer Category od ADA Analysis Set in Patients <6 Years of Age, with Severe Atopic Dermatitis (Study R668-AD-1539 Part A)

Maximum Titer Category	2 - 6 yrs 3 mg/kg N (%)	2 - 6 yrs 6 mg/kg N (%)	6 months - 2 yrs 3 mg/kg N (%)	6 months - 2 yrs 6 mg/kg N (%)	Overall N (%)
ADA Analysis Set	10 (100)	10 (100)	10 (100)	10 (100)	40 (100)
Negative*	5 (50.0)	6 (60.0)	4 (40.0)	5 (50.0)	20 (50.0)
TB Response	0	0	1 (10.0)	0	1 (2.5)
TE Response	5 (50.0)	4 (40.0)	5 (50.0)	5 (50.0)	19 (47.5)
TE and TB Responses					
Low (<1,000)	4 (40.0)	4 (40.0)	5 (50.0)	4 (40.0)	17 (42.5)
Moderate (1,000 to 10,000)	1 (10.0)	0	1 (10.0)	1 (10.0)	3 (7.5)
High (>10,000)	0	0	0	0	0

ADA = Anti-drug Antibody; N = Number of Patients Contributing to Each Category; TB = Treatment-boosted; TE = Treatment emergent; yrs = Years
Note: Negative* includes both negative and pre-existing responses.

Table 15 Summary of ADA Status and Nab Status in Patients 6 Months to <6 Years of Age, with Severe Atopic Dermatitis (Study R668-AD-1539 Part A)

ADA Status; NAb Status	2 - 6 yrs 3 mg/kg N (%)	2 - 6 yrs 6 mg/kg N (%)	6 months - 2 yrs 3 mg/kg N (%)	6 months - 2 yrs 6 mg/kg N (%)	Overall N (%)
ADA Analysis Set	10 (100)	10 (100)	10 (100)	10 (100)	40 (100)
Negative	5 (50.0)	5 (50.0)	3 (30.0)	5 (50.0)	18 (45.0)
Pre+; NAb-	0	1 (10.0)	1 (10.0)	0	2 (5.0)
Pre+; NAb+	0	0	0	0	0
TE and TB; NAb-	0	3 (30.0)	3 (30.0)	3 (30.0)	9 (22.5)
TE and TB; NAb+	5 (50.0)	1 (10.0)	3 (30.0)	2 (20.0)	11 (27.5)

ADA = Anti-drug Antibody; N = Number of Patients Contributing to Each Category; NAb - = Negative in NAb Assay; NAb+ = Positive in NAb Assay; Pre+ = Pre-existing Immunoreactivity; TB = Treatment-boosted; TE = Treatment-emergent; yrs = Years

The rate of observed ADA response is higher in patients in the single-dose study R668-AD-1539 Part A compared to Part B (47.5 % vs. 1.4%, respectively).

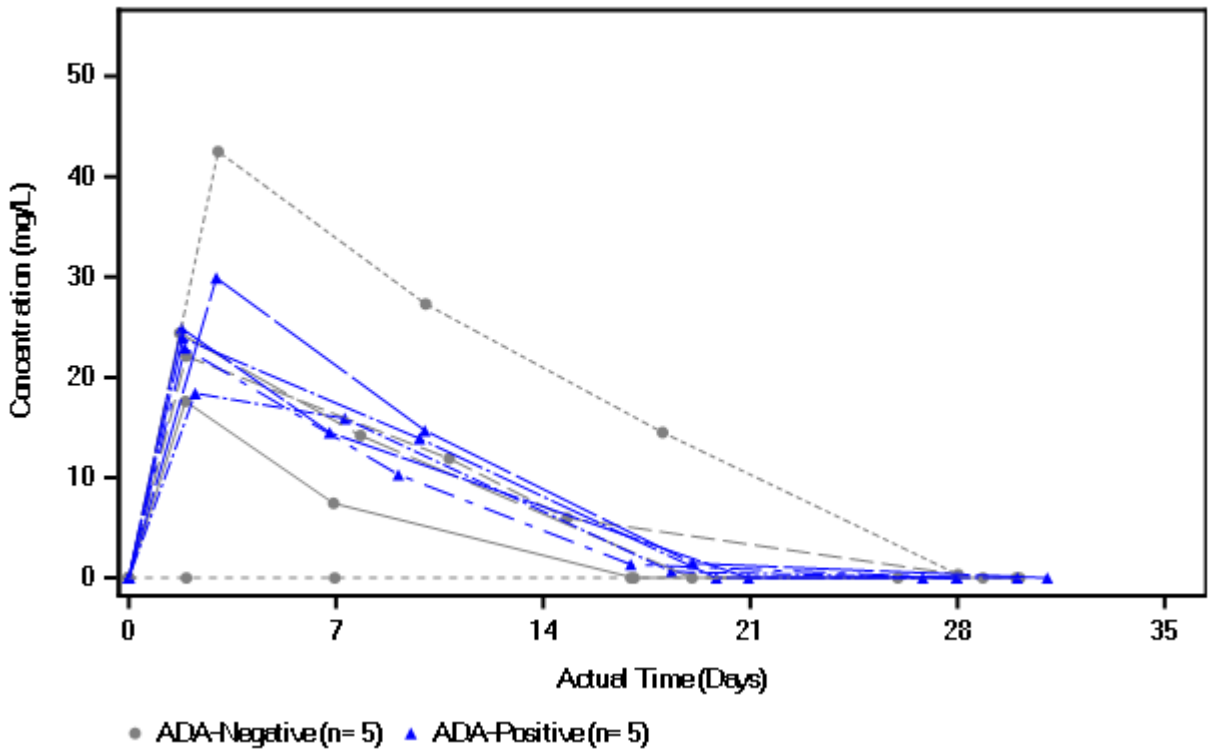
The development of high rates of ADA was previously observed in adolescents and children ≥6 to <12 years of age following administration of a single low dose of dupilumab 2 or 4 mg/kg (followed by an 8-week observation period to assess PK, followed by 4 additional weekly doses) in study R668-AD-1412 and appear to be a function of study design rather than a characteristic of the patient population. This dosing regimen invoked a significant ADA response (56,8% positive response in the ADA assay at any time), with some patients having moderate or high, and those were associated with a substantial reduction in detectable drug concentrations and a lack of notable improvement in EASI score. With continued treatment through Part B of study R668-AD-1412, and subsequently in the OLE study R668-AD-1434, a decline in ADA titers and a corresponding increase in systemic concentrations of dupilumab as well as an improvement in the EASI percent change from baseline. In conclusion from these observations, a single dose of dupilumab, +/- rechallenge after a prolonged pause, may lead to a "prime and boost" immune response to dupilumab. Nevertheless, with continued treatment, efficacy can be restored.

Lower rates of ADA were observed, in contrast, in pivotal studies with multiple doses of dupilumab over a 16-week treatment period for adolescents and children ≥6 to <12 years of age.

Impact of Anti-drug Antibodies on Dupilumab Concentrations

In study R668-AD-1539 Part A, dupilumab concentration-time profiles in ADA and/or NAb positive patients were within the range observed in ADA-negative patients (*Figure **12***).

Figure 12 Individual Concentrations of Functional Dupilumab in Serum by Actual Time and ADA Status in Patients, 2 to <6 Years of Age, with Severe Atopic Dermatitis Administered 3 mg/kg (Study R668-AD-1539 Part A)



ADA = Anti-drug Antibody; BLQ = Below the Limit of Quantitation; N = Number of Patients Contributing to Each Category
Note: BLQs were set to 0.
ADA-negative includes both negative and pre-existing responses.

R668-AD-1539 Part B (Phase 3, Pivotal, Randomized, Double-Blind, Placebo-Controlled Study)

A total of 143 patients were included in the ADA analysis set. ADA samples were collected at baseline, EOT, and EOS in case not entering the OLE.

The rate of treatment-emergent ADA responses was low in patients who received multiple doses of dupilumab 200 mg, dupilumab 300 mg, or placebo Q4W in study R668-AD-1539 Part B.

Among patients that received active drug, only 1 patient in the 300 mg dupilumab group developed a treatment-emergent ADA response (1.4%, 1/74). That patient exhibited a low titer, indeterminate response and was negative for neutralizing antibodies. No other ADA responses (e.g., treatment-boosted) were observed in this study (***Table 16***).

Figure 13 Summary of ADA Status and ADA Category by Treatment in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

		Dupilumab			
ADA Status and Category	Placebo + TCS n (%)	200 mg Q4W + TCS n (%)	300 mg Q4W + TCS n (%)	All Active Doses n (%)	Overall n (%)
ADA Analysis Set	69 (100%)	24 (100%)	50 (100%)	74 (100%)	143 (100%)
Negative	67 (97.1%)	24 (100%)	49 (98.0%)	73 (98.6%)	140 (97.9%)
Pre-existing Immunoreactivity	2 (2.9%)	0	0	0	2 (1.4%)
Treatment-Boosted Response	0	0	0	0	0
Treatment-Emergent Response	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)

ADA = Anti-drug antibody; n = Number of patients contributing to each category; Q4W = Once every 4 weeks; TCS = Topical corticosteroids
Note: See Section Module 2.7.2 Section 1.7.3 for definitions of ADA categories.
Source: Module 2.7.2 Table 6

Table 16 ADA Category and Maximum Titer Category in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

		Dupilumab			
Maximum Titer Category	Placebo + TCS n (%)	200 mg Q4W + TCS n (%)	300 mg Q4W + TCS n (%)	All Active Doses n (%)	Overall n (%)
ADA Analysis Set	69 (100%)	24 (100%)	50 (100%)	74 (100%)	143 (100%)
TE					
Persistent	0	0	0	0	0
Transient	0	0	0	0	0
Indeterminate	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)
TE & TB					
Low (<1,000)	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)
Moderate (1,000 to 10,000)	0	0	0	0	0
High (>10,000)	0	0	0	0	0

ADA = Anti-drug antibody; n = Number of patients contributing to each category; Q4W = Once every 4 weeks; TE = Treatment-emergent; TB = Treatment-boosted; TCS = Topical corticosteroids
Note: See Section Module 2.7.2 Section 1.7.3 for definitions of ADA categories.
Source: Module 2.7.2 Table 7

Impact of Anti-drug Antibodies on Dupilumab Concentrations

Due to the low frequency of treatment-emergent ADA responses, it was not feasible to assess associations between immunogenicity and concentrations of functional dupilumab in study R668-AD-1539 Part B.

R668-AD-1434 (Phase 3, Open-label, Long-term Extension Study)

A total of 151 patients were included in the ADA analysis set. ADA samples were collected at baseline and at sparse timepoints thereafter including weeks 16, 52, 76, 104, 152, 200, 260/EOT, and at week 272/EOS.

Immunogenicity status in study R668-AD-1434 was determined relative to baseline in the previous study.

Of the 161 patients who received study drug in R668-AD-1539 Part B, 144 patients ≥ 6 months to <6 years of age enrolled in the OLE study R668-AD-1434, where all patients started or continued weight-tiered dupilumab regimens of 200 mg Q4W in patients ≥5 to <15 kg or 300 mg Q4W in patients ≥15 to <30 kg. Immunogenicity of dupilumab for patients who rolled over from R668-AD-1539 Part B was consistent with the parent study. In data available as of the interim analysis, the rate of treatment-emergent ADA responses remained low for patients who received multiple doses of dupilumab 200 mg, dupilumab 300 mg, or placebo Q4W in previous study R668-AD-1539 Part B (1.7%, 2/116); the 2 ADA positive patients exhibited a low titer, indeterminate response and were negative for NAbs.

A higher rate of treatment-emergent ADA responses (57.1%, 20/35) was observed in study R668-AD-1434 for patients who entered from the study R668-AD-1539 Part A.

Samples positive for treatment-emergent ADA were detected for 19 of these patients after receiving a single dose of dupilumab 3 or 6 mg/kg in the previous study; one patient who was negative in the previous study had a transient, treatment-treatment ADA response at week 16 in study R668-AD-1434. Most ADA positive patients from study R668-AD-1539 Part A exhibited responses in the current study that were transient (37.1%, 13/35), low titer (42.9%, 15/35), and positive for NAbs (31.4%, 11/34); 3 moderate titer and 1 high titer responses were observed and all moderate/high titer responses were in patients that initially received a single dose of dupilumab 3 mg/kg which was the lowest dose evaluated in study R668-AD-1539 Part A. The single patient exhibiting a high titer response in R668-AD-1434 had a modest reduction in titer levels throughout the study. The higher rate of ADA response in patients in R668-AD-1539 Part A compared to Part B may be a function of study design.

Impact of Anti-drug Antibodies on Dupilumab Concentrations and on Concentration-Response

In study R668-AD-1434, the distribution of dupilumab concentrations for ADA positive patients ≥6 months to <6 years of age with a low maximum titer was within the range of concentrations observed in ADA negative patients. In patients with a moderate titer response, dupilumab concentrations at week 16 were lower than in patients with low titer responses or patients who were ADA negative, but were similar between these groups by week 52. In parallel, an improvement in efficacy (EASI score) was observed.

The single patient exhibiting a high titer response in R668-AD-1434 had undetectable concentrations of dupilumab throughout the study. EASI scores gradually declined in this patient over a span of 3 years, but the rate of improvement was slower than in patients with moderate titers. These data suggest that with continued dupilumab treatment a portion of patients can be treated through this moderate ADA response with restoration of efficacy.

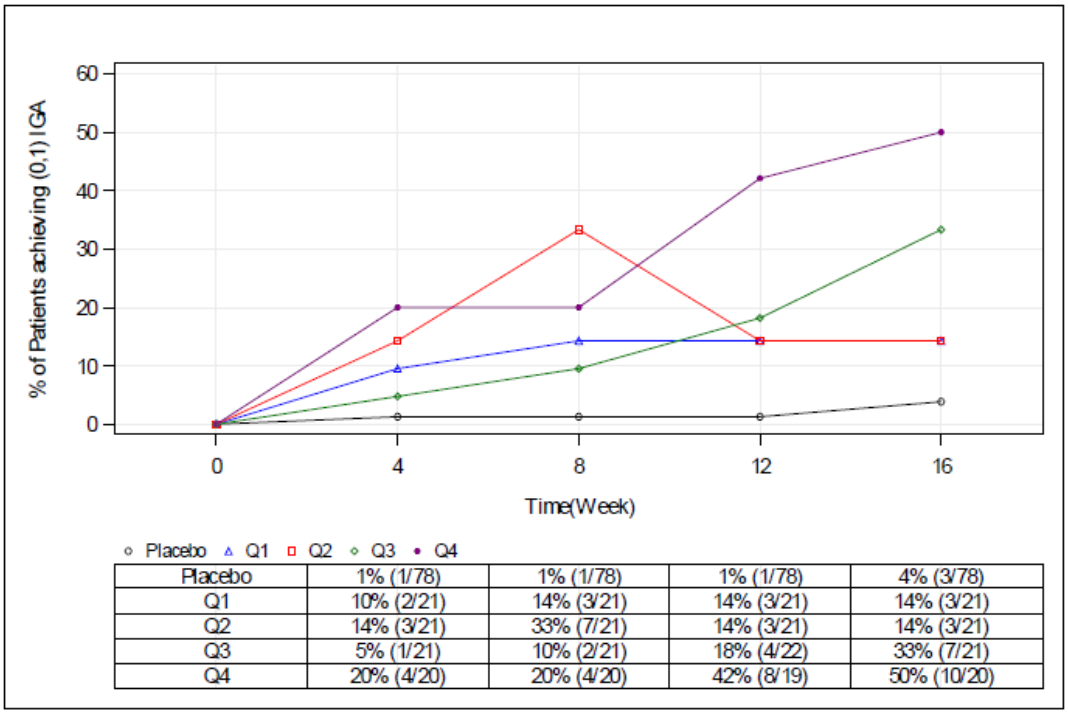
The association between exposure and ADA is consistent with PopPK calculations, at least for patients with moderate or high ADA levels, and could be due to lower drug concentrations being more immunogenic, or due to the presence of ADA increasing the clearance of drug.

In parallel to the required update for PK data of this study, the applicant further submitted an actualized analysis of the data on immunogenicity of dupilumab in children of the age group in focus for the OLE study R668-AD-1434 with a new data cut-off of 10-Mar-2022. The results of analyses were consistent with prior analyses.

2.4.4. PK/PD modelling

Drug effect increased with increasing quartile of C_{trough} of dupilumab (***Figure 14***). Logistic regression of the probability of patients achieving IGA 0 or 1 versus dupilumab C_{trough} in patients on active drug supported a positive correlation between dupilumab exposure and response as measured by IGA 0 or 1 and this trend was consistent across all age groups within the dupilumab AD program (***Figure 15***).

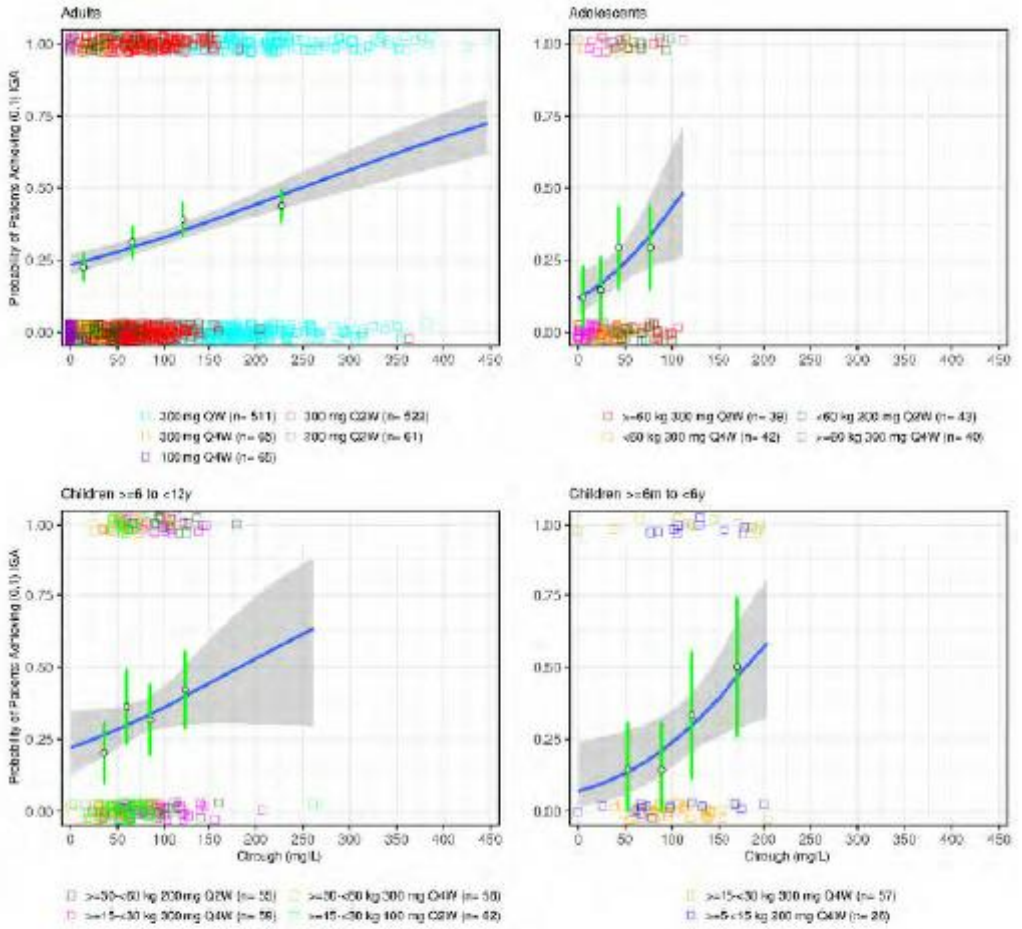
Figure 14 Percentage of Patients Achieving (0,1) IGA Score by Nominal Time and Quartile of Functional Dupilumab Trough Concentrations in Patients ≥6 Months to <6 Years of Age with Moderate-to-Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



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

IGA=Investigator's Global Assessment.
Note: BLQ concentrations set to 0 and missing concentrations imputed with a LOCF approach. Response variables were imputed according to the primary analysis method. Number in parentheses in the table is number of patients achieving (0,1) IGA / number of patients who contribute to the quartile. The quartile ranges for week 16 concentrations (mg/L): Q1 (0.0- 75.0), Q2 (75.0-103.0), Q3 (103.0-138.0), Q4 (138.0-204.0).
Source: Module 5.3.5.1 R668 AD 1539 Part B Appendix 16.1.15 Clinical Pharmacology Report Figure 4

Figure 15 Logistic Regression of the Probability of Achieving IGA 0,1 vs. Dupilumab C_{trough} (mg/L) at Week 16 in Patients with Atopic Dermatitis on Active Drug by Age and Treatment Group (PK Analysis Set)



IGA=Investigator's Global Assessment. n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1021, R668-AD-1334, R668-AD-1416), adolescents (R668-AD-1526), children ≥6 to <12y (AD-1652), and children ≥6m to <6y (AD-1539 Part B). Data were described with a mean regression line (solid line) and 95% confidence interval (grey area). Mean of response and 95% confidence upper/lower limit (green vertical lines) around the mean are presented by exposure quartile, with the vertical lines placed at the mean of the interquartile range on the x-axis. The upper and lower limit is reset to 1 and 0 if the value is > 1 or < 0.
A small number of patients in R668-AD-1652 with baseline weight ≥60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or ≥30 kg receiving 100 mg Q2W (n=1) are not shown.

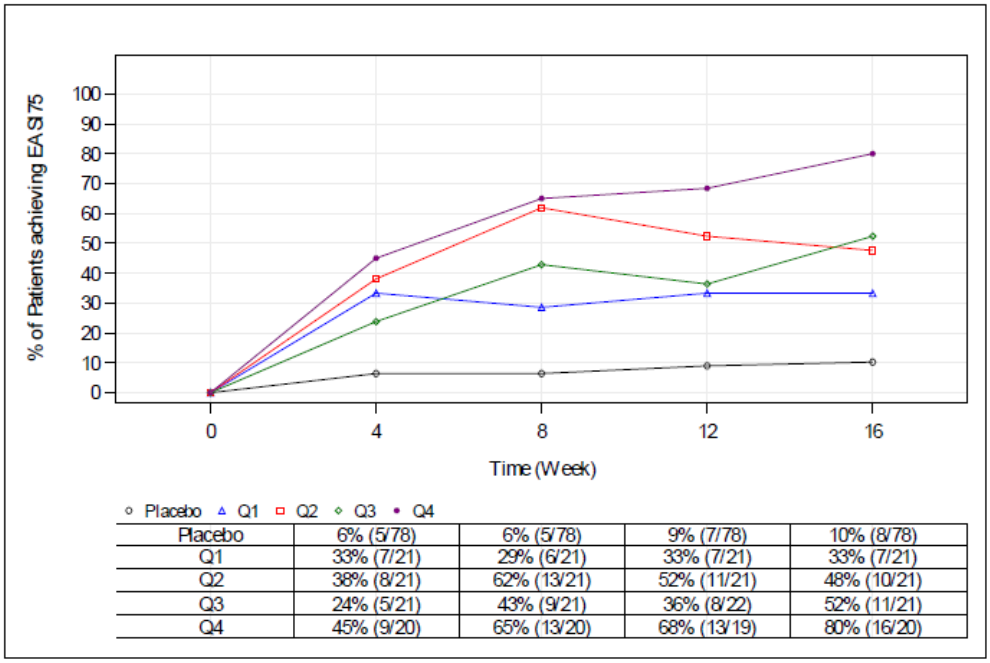
EASI

Proportion of patients with EASI-75

Proportion of patients with EASI-75 at week 16 is another key efficacy endpoint of study R688-AD-1539.

Exposure-response relationships for the proportion of patients achieving EASI-75 were similar to the proportion of patients achieving IGA 0 or 1. In an analysis of response by quartiles of dupilumab exposure over time, early separation was observed between patients on dupilumab relative to placebo with a clear rank ordering by dupilumab C_{trough} at week 16 (***Figure 16***). Logistic regression of the probability of achieving EASI-75 versus dupilumab C_{trough} at week 16 supported a positive correlation between higher dupilumab exposure and a greater probability of attaining EASI-75. In E-R analyses conducted independently for adults, adolescents, children ≥6 to <12 years of age, and children ≥6 months to <6 years with AD, positive relationships were apparent in all age groups (***Figure 17***).

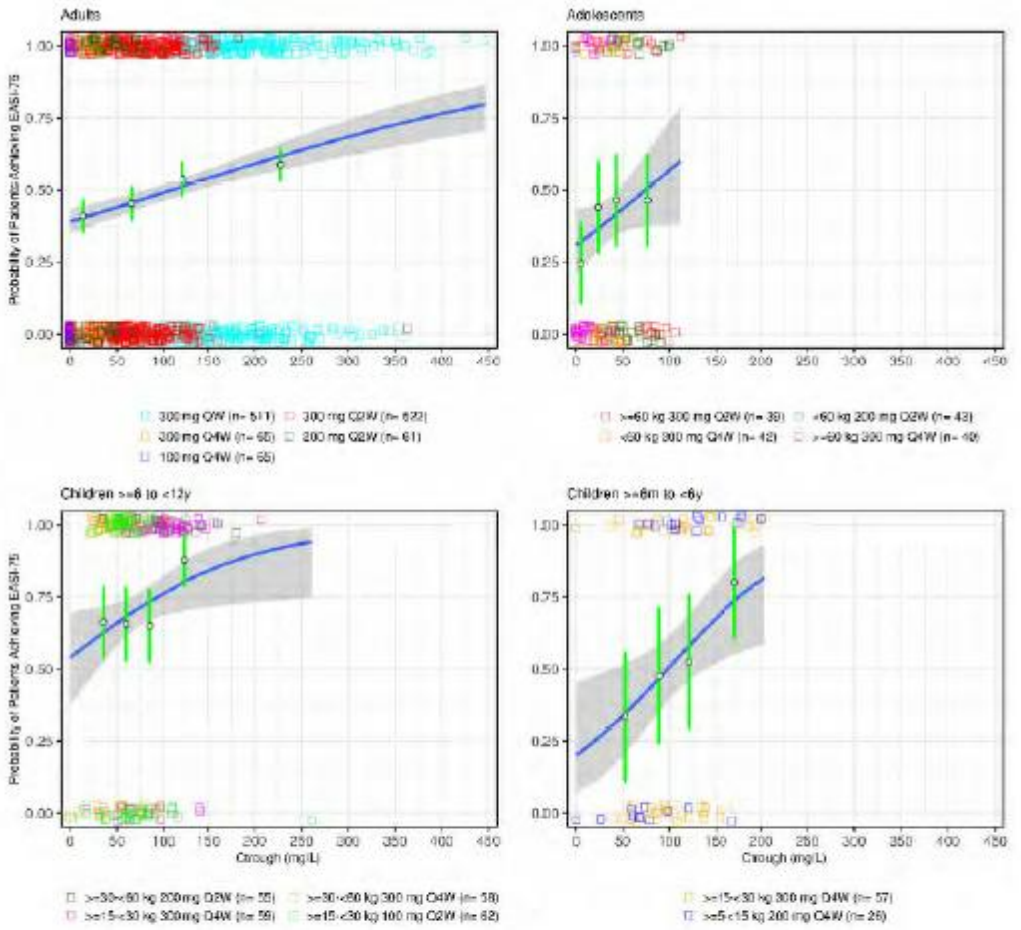
Figure 16 Percentage of Patients Achieving EASI-75 by Nominal Time and Quartile of Functional Dupilumab Trough Concentrations in Patients ≥6 Months to <6 Years of Age with Moderate-to-Severe Atopic Dermatitis (Study R668-AD-1539 Part B)



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

EASI-75 = ≥75% improvement in Eczema Area and Severity Index
Note: BLQ concentrations set to 0 and missing concentrations imputed with a LOCF approach. Response variables were imputed according to the primary analysis method. Number in parentheses in the table is number of patients achieving EASI-75 / number of patients who contribute to the quartile. The quartile ranges for week 16 concentrations (mg/L): Q1 (0.0- 75.0), Q2 (75.0-103.0), Q3 (103.0-138.0), Q4 (138.0-204.0).
Source: Module 5.3.5.1 R668 AD 1539 Part B Appendix 16.1.15 Clinical Pharmacology Report Figure 9

Figure 17 Logistic Regression of the Probability of Achieving EASI-75 vs. Dupilumab C_{trough} (mg/L) at Week 16 in Patients with Atopic Dermatitis on Active Drug by Age and Treatment Group (PK Analysis Set)

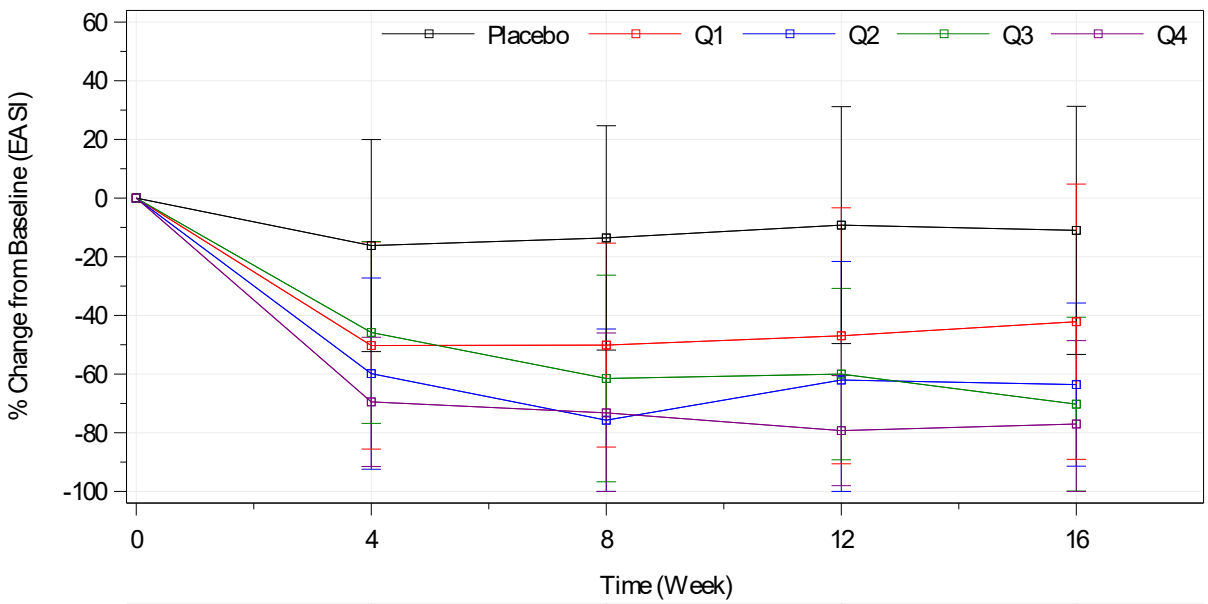


EASI-75 = ≥75% improvement in Eczema Area and Severity Index. n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1021, R668-AD-1334, R668-AD-1416), adolescents (R668-AD-1526), children ≥6 to <12y (R668-AD-1652), and children ≥6m to <6y (AD-1539 Part B). Data were described with a mean regression line (solid line) and 95% confidence interval (grey area). Mean of response and 95% confidence upper/lower limit (green vertical lines) around the mean are presented by exposure quartile, with the vertical lines placed at the mean of the interquartile range on the x-axis. The upper and lower limit is reset to 1 and 0 if the value is >1 or <0. A small number of patients in R668-AD-1652 with baseline weight ≥60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or ≥30 kg receiving 100 mg Q2W (n=1) are not shown.

Percent change from baseline

The improvement in EASI was further evaluated as a percentage change from baseline with similar results as described above (***Figure 18***).

Figure 18 Mean (±SD) EASI % Change from Baseline by Nominal Time and Quartile of Functional Dupilumab Concentrations in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

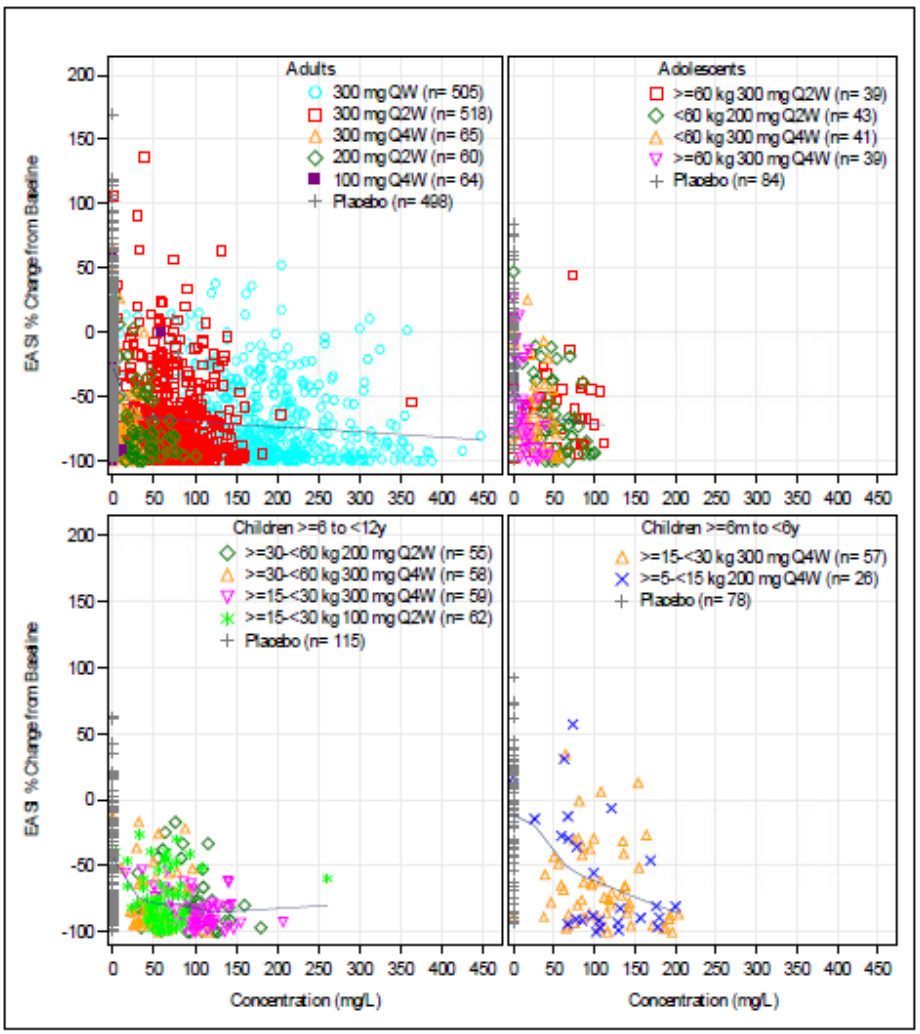


Placebo	78	78	78	78
Q1	21	21	21	21
Q2	21	21	20	21
Q3	21	21	22	21
Q4	20	20	19	20

Note: BLQ concentrations set to 0 and missing concentrations imputed with a LOCF approach. Response variables were imputed according to the primary analysis method. Number in parentheses in the table is the number of patients who contribute to the quartile. The quartile ranges for Week 16 concentrations (mg/L): Q1(0.0 - 75.0), Q2 (75.0-103.0), Q3 (103.0-138.0), Q4 (138.0-204.0). Y-axis minimum was set to -100%.

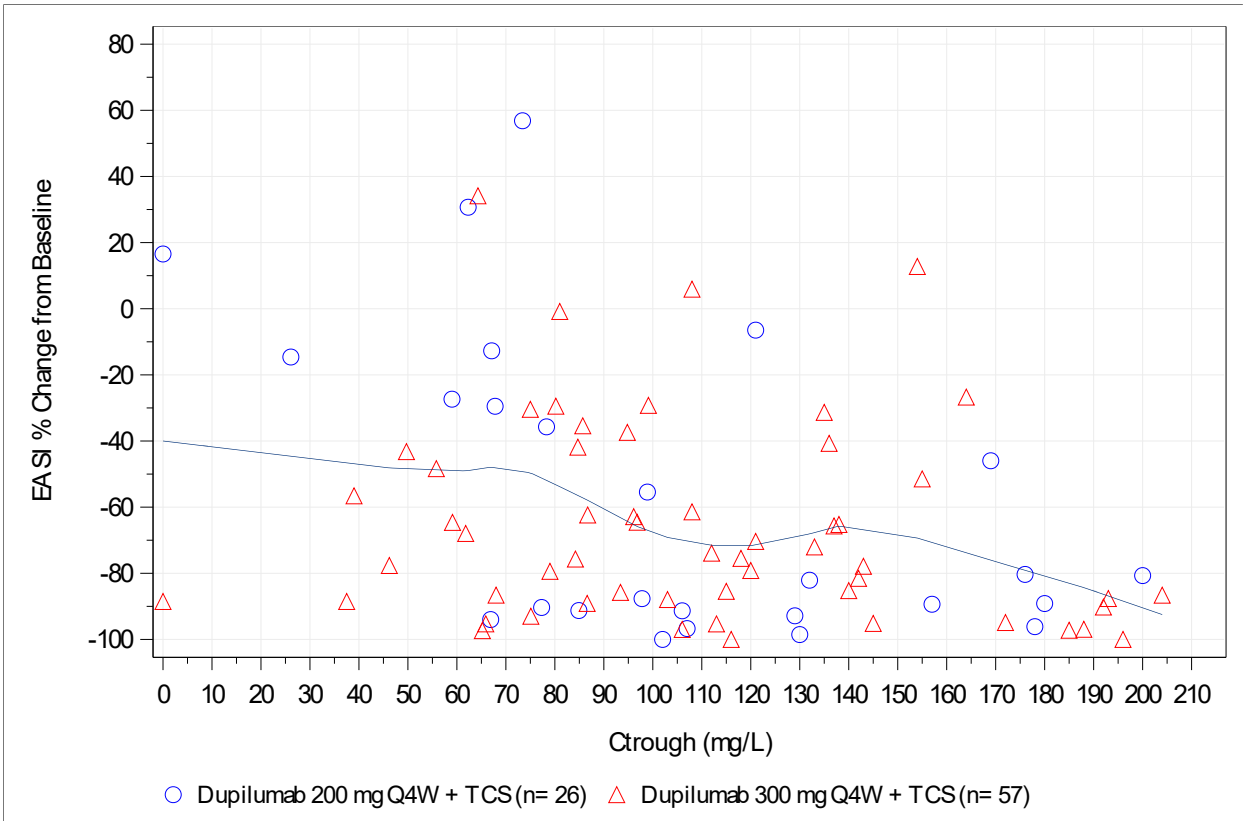
A steep decline in EASI percent change from baseline is observed in adults, adolescents, and children ≥6 to <12 years of age at concentrations up to ~30 mg/L, with more modest rate of continued improvements as concentrations continue to increase. This evidence of a nonlinear, saturable relationships with efficacy was less apparent in children ≥6 months to <6 years of age. Dupilumab concentrations observed at week 16 in children ≥6 months to <6 years were generally higher with improvements in EASI percent change from baseline similar to or better than those observed in adults, adolescents, and children ≥6 to <12 years on the highest end of the exposure range trendline Limited data are available to inform steady-state E-R relationships at lower concentrations in this age group. The apparent differences in shape of the E-R relationship for dupilumab with EASI (percent change from baseline) in children 6 months to <6 years of age relative to older populations may be due to the limited data informing this relationship at low dupilumab exposure in study R668-AD-1539 Part B (***Figure 19***, ***Figure 20***).

Figure 19 Scatter Plot EASI Percent Change from Baseline vs. Dupilumab C_{trough} (mg/L) at Week 16 in Patients with Atopic Dermatitis by Age and Treatment Group (PK Analysis Set)



EASI= Eczema Area and Severity Index. n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1021, R668-AD-1334, R668-AD-1416), adolescents (R668-AD-1526), children >=6 to <12y (R668-AD-1652), and children >=6m to <6y (AD-1539 Part B). Data were described with a LOESS with smooth line 0.5 (solid line).
A small number of patients in R668-AD-1652 with baseline weight >=60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or >=30 kg receiving 100 mg Q2W (n=1) are not shown.

Figure 20 Scatter Plot EASI % Change from Baseline and Dupilumab Trough Concentrations at Week 16 by Treatment Group in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis on Active Drug (Study R668-AD-1539 Part B)



n = Number of patients at Week 16
Note: BLQ concentrations set to 0 and missing concentrations imputed with a LOCF approach. Response variables were imputed according to the primary analysis method. Black line represents a Loess (smooth: 0.5).

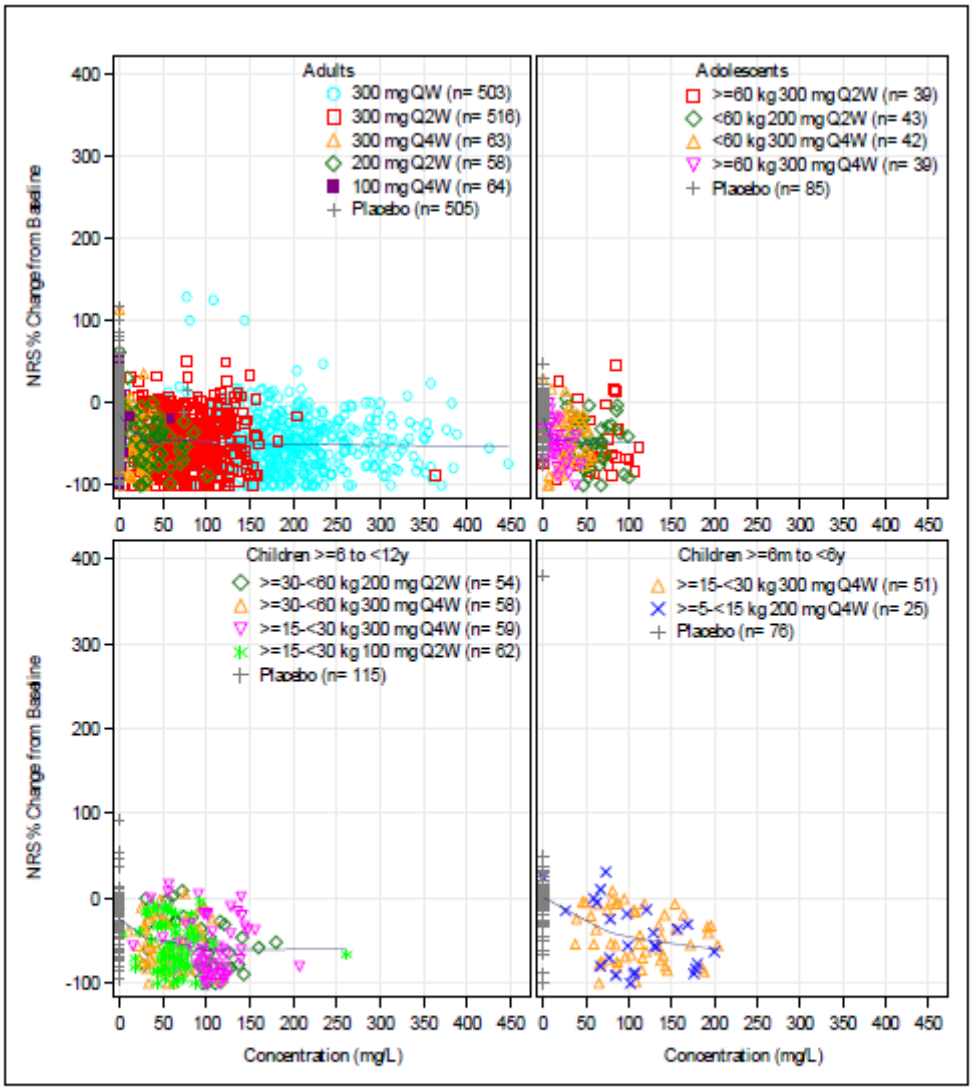
Exposure-Response for Weekly Average of Daily Worst Scratch/Itch NRS

Positive correlations between dupilumab concentrations versus weekly average of daily worst scratch/itch NRS percent change from baseline at week 16 were observed for adults, adolescents, children ≥6 to <12 years of age, and children ≥6 months to <6 years of age (***Figure 21***). These relationships were generally described by a rapid improvement at lower concentrations and a plateauing of improvement at higher dupilumab concentrations. In children ≥6 months to <6 years of age, the weekly average of daily worst scratch/itch score improved with increasing dupilumab concentrations for patients below approximately 100 mg/L, while a shallower slope in the relationship was observed at higher concentrations.

As with other E-R relationships for efficacy endpoints in these children, characterization of the full E-R relationship is limited by the sparsity of patients with dupilumab C_{trough} at week 16 <50 mg/L.

Daily worst scratch/itch was a patient report measurement in adults, adolescents, and children ≥6 to <12 years of age, and was a caregiver reported measure in children ≥6 months to <6 years of age. The differing nature of this instrument in the youngest children limits the inferences that can be made by direct comparison of these relationships across age groups.

Figure 21 Scatter Plot Weekly Average of Daily Worst Scratch/Itch NRS Percent Change from Baseline vs. Dupilumab C_{trough} (mg/L) at Week 16 in Patients with Atopic Dermatitis by Age and Treatment Group (PK Analysis Set)



NRS=Numerical Rating Scale. n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1021, R668-AD-1334, R668-AD-1416), adolescents (R668-AD-1526), children >=6 to <12y (R668-AD-1652), and children >=6m to <6y (AD-1539 Part B). Pruritus was reported by patients for adults, adolescents, children >=6 to <12y, and caregivers for children >=6m to <6y. Data were described with a LOESS with smooth line 0.5 (solid line).
A small number of patients in R668-AD-1652 with baseline weight >=60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or >=30 kg receiving 100 mg Q2W (n=1) are not shown.

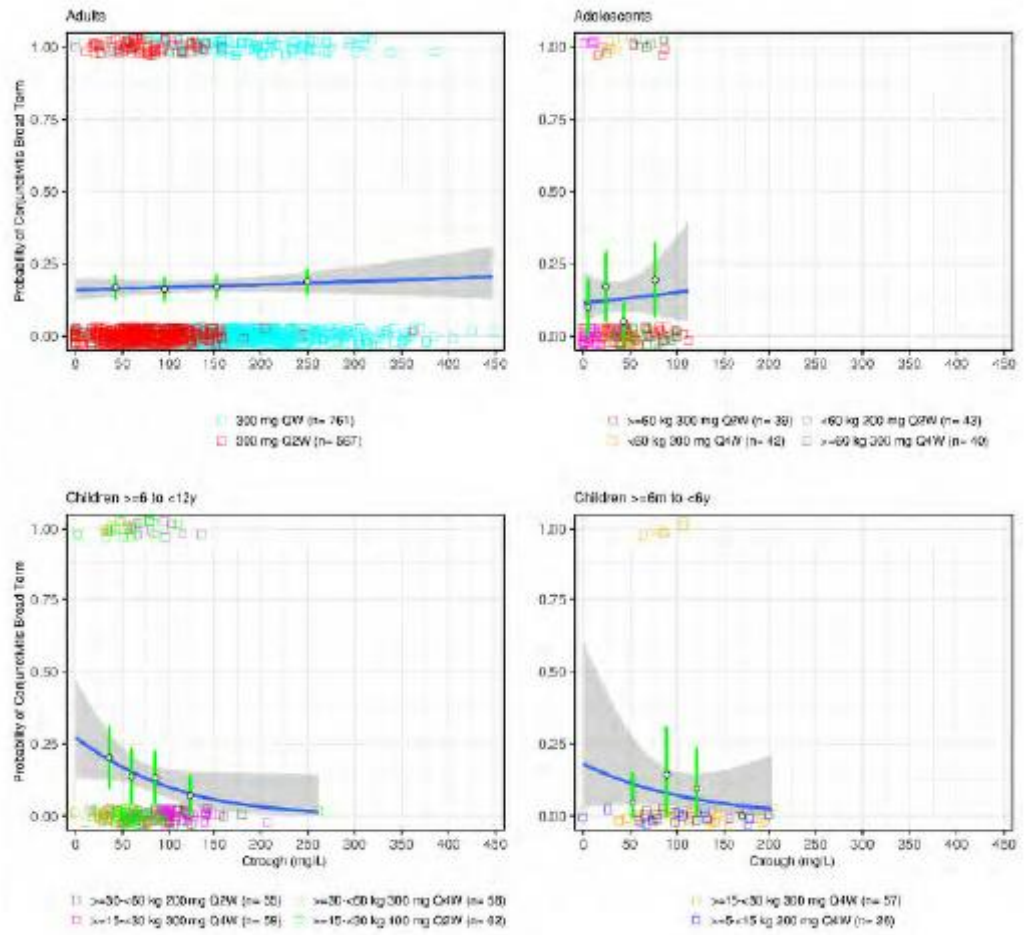
Exposure-response analyses with respect to safety

Higher rates of conjunctivitis have been reported in patients with AD treated with dupilumab than patients receiving placebo, and the relationship between exposure to dupilumab and the probability of developing conjunctivitis was previously evaluated in adults, adolescents, and children ≥6 to <12 years of age with AD.

Logistic regression relating probability of patients developing conjunctivitis (broad term) with dupilumab C_{trough} at week 16 showed no positive correlation between dupilumab exposure and the probability of developing conjunctivitis (broad CMQ term) in study R668-AD-1539 Part B (***Figure 22***). The E-R relationships for conjunctivitis in adults, adolescents, children 6 to 11 years of age and children <6 years

of age were either flat or showed an inverse E-R relationship, indicating no positive relationship of developing conjunctivitis with increasing week 16 dupilumab C_{trough}.

Figure 22 Logistic Regression of the Probability of Developing Conjunctivitis (Broad Term) vs. Dupilumab C_{trough} (mg/L) at Week 16 by Age and Treatment Group in Patients with Atopic Dermatitis on Active Drug (PK Analysis Set)



n=Number of patients at week 16. Concentrations below the LLOQ were set to zero. Included studies by age group: adults (R668-AD-1334, R668-AD-1416, R668-AD-1224), adolescents (R668-AD-1526), children ≥6 to <12 years (R668AD-1652), and children ≥6 months to <6 years (R668-AD-1539 Part B). Mean linear regression (solid line) and 95% confidence interval (grey area). Mean of response and 95% confidence upper/lower limit (green vertical lines) around the mean are presented by exposure quartile in patients on active drug, with the vertical lines placed at the mean of the interquartile range on the x-axis. The upper and lower limit is reset to 1 and 0 if the value is >1 or <0. A small number of patients in R668-AD-1652 with baseline weight ≥60 kg (n=5), <30 kg receiving 200 mg Q2W (n=1), or ≥30 kg receiving 100 mg Q2W (n=1) are not shown.

2.4.5. Discussion on clinical pharmacology

Bioanalytical methods

The method applied for the detection of functional dupilumab corresponds to the method used in the initial marketing authorisation application for AD and this method has been accurately validated (REGN668-AV-13074-VA01V1). Incurred sample reanalysis performed for both parts of study R668-AD-1539 confirmed that the assay also produced robust and reproducible results in the younger paediatric AD population ≥6 months to <6 years of age.

Methods applied for the detection of anti-dupilumab antibodies and neutralising antibodies also correspond to the methods already utilized and described in previous EU applications for dupilumab.

Pharmacokinetics

The MAH seeks a change in the target indication to include children aged ≥6 months to <6 years with severe AD.

The package on clinical pharmacology regarding children of this age group with severe AD comprises 3 dupilumab clinical studies where PK and pharmacodynamic (PD) data have been collected. A phase 3 pivotal study (R668-AD-1539 Part B) was conducted with patients of this age group and the results of two further studies, R668-AD-1539 Part A (Phase 2 PK) and R668-AD-1434 (OLE), providing further supporting data.

In the single-dose PK-study R668-AD-1539 Part A, dupilumab SC dosing regimens of 3 mg/kg and 6 mg/kg were evaluated, whereas in the pivotal study R668-AD-1539 Part B SC dosing regimens of 200 mg Q4W and 300 mg Q4W for children weighing ≥5 to <15 kg and ≥15 to <30 kg, respectively, were assessed. In contrast to the older age groups, neither loading doses of dupilumab were administered to children of this age group, nor a more intense dosing interval was used.

Open-label extension (OLE) study R668-AD-1434 is an ongoing study which includes patients ≥6 months to <18 years of age that rolled over from different AD studies, including patients of study R668-AD-1539 Part A and Part B. This study provided further data on long-term use of dupilumab.

At the time of the PK/ADA data cutoff date (23 Jul 2021) 84 patients were included in the PK analysis set of the OLE study R668-AD-1434 with only a few data on the 200 mg Q4W and 300 mg Q4W regimes at the later time points (week 56 and thereafter). An updated PK analysis of study R668-AD-1434 was submitted with the data cut-off date of 10-Mar-2022, now including data of 167 patients and sufficient data at week 52. Data were consistent with the data gained from former analyses.

Dupilumab concentration-time profiles are described by target-mediated disposition and were generally characterized by a brief absorption phase after SC administration, followed by a linear elimination phase and a terminal target-mediated elimination phase. The linear phase was more prominent for the 6 mg/kg dose cohorts of study R668-AD-1539 Part A and suggested that saturation of target-mediated pathway achieved in the 3 mg/kg dose cohorts may be limited in duration. Dupilumab was measurable in serum for a longer duration in the 2 to <6 years of age cohort than in the 6 months to <2 years of age cohort at both mg/kg dose levels, suggesting higher clearance per unit body weight in children <2 years of age.

Mean concentrations of dupilumab over time exhibited similar profiles in patients receiving weight-tired dupilumab 200 mg Q4W and 300 mg Q4W respectively. Systemic concentrations of dupilumab in the 300 mg Q4W group appeared to have reached steady-state by week 12, while the highest mean concentrations for the 200 mg Q4W group were observed at week 16. Accumulation of dupilumab C_{trough} at week 16 relative to after the initial dose at week 4 was approximately 2-fold for both dupilumab regimens.

The weight-tiered dosing regimen of dupilumab evaluated in this study (R668-AD—1539 Part B) normalized dupilumab exposure across patients of differing body weight categories (≥5 to <15 kg and ≥15 to <30 kg, respectively). Mean ± SD dupilumab C_{trough} at week 16 was similar between patients ≥5 to <15 kg receiving 200 mg Q4W (109 ± 50.8 mg/L) and patients ≥15 to <30 kg receiving 300 mg Q4W (110 ± 42.8 mg/L). This information has been added in section 5.2 of the SmPC.

The extent of absorption (Bioavailability, F) was not estimated in children ≥6 months to <12 years population due to the lack of intravenous (IV) data. The absorption rate Ka was estimated based on PK data.

Mean post-hoc estimates of the apparent central compartment volume of distribution (Vc) were lower for children ≥6 months to <6 years of age (0.24 L for ≥5 to <15 kg or 0.47 L for ≥15 to <30 kg) than the reference of 2.99 L in a 70 kg adult.

The PK of dupilumab is characterized as nonlinear with parallel linear and nonlinear elimination pathways (target-mediated clearance).

Clearance in children <6 years of age was less than would be expected from allometrically scaled values in older populations. Based on the final PopPK model, after accounting for differences in body weight, increasing age was associated with increasing clearance in children. After the last steady-state dose of various dosing regimen, the median times to non-detectable concentration ranged from 9 to 13 weeks in adults and paediatric patients 12 to 17 years of age, and are approximately 1.5 times and 2.5 times longer in paediatric patients 6 to <12 years of age and paediatric patients <6 years old, respectively. This information has been adequately reflected in SmPC section 5.2.

Mean post-hoc estimates of the clearance were 0.024 L/d for children weighing ≥5 to <15 kg and 0.038 L/d for children weighing ≥15 to <30 kg, respectively, with a reference value of 0.0959 L/d in a 70 kg adult.

Mean dupilumab C_{trough} in patients ≥15 to <30 kg receiving dupilumab 300 mg Q4W or patients ≥5 to <15 kg received dupilumab 200 mg Q4W in study R668-AD-1539 Part B reached steady-state by week 16. Dupilumab C_{trough} at week 16 was approximately 2-fold of C_{trough} at week 4 after the first dose for both regimens.

In contrast to adults, adolescents, and children ≥6 to <12 years of age with AD, no loading dose of dupilumab was included in the dosing regimen for children ≥6 months to <6 years of age. Mean concentrations of dupilumab at week 4 were similar to approved regimens administered with a loading dose in adults and adolescents. The rapid attainment of effective concentrations suggests that omission of a loading dose did not adversely affect evaluation of dupilumab in this patient population.

Population PK

PopPK analysis was conducted by the use of standard software (NONMEM) in combination with R for pre- and post-processing of data, which is endorsed.

An integrated PopPK model was developed to describe the concentrations of dupilumab across age groups from adults to children as young as 6 months of age with AD. Therefore, concentration data from children aged ≥6 months to <6 years in studies R668-AD-1539 Part A and Part B were combined with data from adults, adolescents, and children ≥6 to <12 years. From the totality of these data, a single base PopPK model incorporating both body weight and maturation (age), was developed to describe the PK of dupilumab across all age groups.
Overall, the PopPK analysis included dupilumab concentration-time data from 22 clinical studies (nine phase 1, six phase 2, one phase 2/3, and six phase 3 studies). The analysis included a total of 2873 unique subjects ranging in age from 6 months to 88 years (202 healthy volunteers and 2671 patients with AD) and 20938 quantifiable PK samples. By age group, the population PK dataset included 2223 adults, 252 adolescents, 277 children ≥6 to <12 years of age, and 121 children ≥6 months to <6 years of age.

The base model was identified in an iterative procedure (Run1-Run18), starting with using data from adult and successively adding data from paediatric subgroups. This is in general agreed, however, several fixing of parameters, including those describing absorption needed to be fixed during the base model selection process. After the inclusion of all age groups, IIV was included on Ka, but resulted in a high shrinkage value because most subjects, especially the paediatric subgroups, did not have informative data in the absorption phase. In consequence, IIV was only estimated on CL and Vc.

Covariates of interest to be tested have been selected based on statistically significant effects demonstrated in previous PopPK models, in addition to the covariates of age (maturation on CL) and body weight (estimated allometry on CL and V) that were incorporated in the base model. The potential effects

of age on central distribution volume and Ka were also tested in the integrated model, however, other parameters such as F, accounting for absorption, have been fixed in advance to values mainly based on adult data. There was no prior forward inclusion step to the stepwise backward elimination step during covariate selection for the integrated model.

The overall model structure is endorsed and in line with findings based on previous pop PK. The change in parameterizing from rate-based to parameterization in terms of CL and V is appreciated in light of the need of incorporating the maturation effect on CL. The assumption of a fix lower bioavailability (61% vs 64%; although comparable) and a lower ka (0.341 vs 0.641 1/day) in the youngest age group is not expected. Indeed, it is assumed that absorption is at least as well as observed in older age groups, with an expected increased absorption rate for mAbs in infants and young children compared to adults (Temrikar et al, 2020).

The estimated exponents (95% CI) describing the relationships of PK parameters with body weight were 0.751 (0.710, 0.793) for CL and 1.25 (1.128, 1.31) for Vc. As these values are in the range of the theoretical allometric scaling values of 0.75 and 1, respectively, the use of the estimated allometry is supported.

The final model estimated the fraction of adult clearance that is present at birth to be 0.198 and the clearance maturation half-life estimate (95% CI) was 1.13 (0.503, 1.76) years. Paediatric clearance is anticipated to reach that of an adult by approximately 6 years (~2.5-8.5 years) of age (5 half-lives).

Thus, to ensure PK comparability, the MAH was asked to provide an external validation of PK data collected from the paediatric subgroup 6 months to 6 years by use of the previous model that was used to describe PK data from 6-12 years of age, re-parameterized (CL,V), allometric scaling and maturation effect included.

Observed PK in the age group 6 month to 2 years of age and 2 years of age to 6 years of age were compared with model-based exposure predictions (VPC plots stratified by respective weight bands correlating with both age groups). The requested VPC plots stratified by age groups indicate an adequate description of data by the pop PK model.

The predictive performance of the final model was evaluated through VPC plots for Study R668-AD-1539 Part B, stratified by dose, and additional VPC plots stratified by study and dose level. The VPC plots provided indicate that overall, the final model can explain dupilumab concentration data, over the 16-week treatment period including young children (≥6 months to <6 years of age) with AD in Study R668-AD-1539 Part B following multiple dose administration.

PK comparison across populations

It is agreed that observed as well as model-predicted exposures were comparable for all age groups following weight-based tiered dosing regimens of dupilumab. Exposure following 300 mg Q4W and 200 mg Q4W assuming the proposed weight bands of ≥15 kg to 30 kg and ≥5 kg to 15 kg, respectively, is up to 2-fold higher at steady state compared to children aged between 6-12 years. Nevertheless, the exposure range expected is not exceeding the observed range observed during the clinical development.

Pharmacodynamics

Pharmacodynamic profiles of TARC in children ≥6 months to <6 years of age show a similar effect over time (rapid decrease) compared to adults, adolescents, and children ≥6 to <12 years of age.

Immunogenicity

Immunogenicity of dupilumab in children aged 6 months to <6 years with moderate-to-severe AD receiving dupilumab 200 mg Q4W or 300 mg Q4W regimens was low, with minimal impact of immunogenicity on dupilumab exposure in these patients.

In pivotal study R668-AD-1539 Part B, only one patient developed a low-titer treatment-emergent ADA response. Thus, it was not feasible to assess associations between immunogenicity and concentrations of functional dupilumab in this study population.

The rate of observed ADA response was higher in patients in the single-dose study R668-AD-1539 Part A compared to Part B (47.5 % vs. 1.4%, respectively) with most patients exhibiting low ADA titers. The development of high rates of ADA was previously observed in adolescents and children ≥6 to <12 years of age following administration single low dose administration of dupilumab (followed by additional doses after a 8-week observation period) in study R668-AD-1412 and appear to be a function of study design - akin a "prime and boost" regimen. Dupilumab concentration-time profiles in ADA and/or NAb positive patients were within the range observed in ADA-negative patients.

The rate of treatment-emergent ADA responses remained low in OLE study R668-AD-1434 for patients who received multiple doses of dupilumab or placebo Q4W in previous study R668-AD-1539 Part B (1.7%, 2/116); both patients had low titer, indeterminate response and were negative for NAbs.

A higher rate of treatment-emergent ADA responses (57.1%, 20/35) was observed in the OLE study R668-AD-1434 for patients who entered from the study R668-AD-1539 Part A. Most responses in the current study were transient (37.1%, 13/35), low titer (42.9%, 15/35), and positive for NAbs (31.4%, 11/34); 3 moderate titer and 1 high titer responses were observed.

In the longitudinal assessment, dupilumab concentrations of patients with a moderate titer response at week 16 were lower than in patients with low titer responses or patients who were ADA negative, but were similar between the groups by week 52. In parallel, an improvement in efficacy (EASI score) was observed.

The single patient that exhibited a high titer response and had undetectable concentrations of dupilumab throughout the study. EASI scores improved gradually, but the rate of improvement was slower in that patient than in patients with moderate titers. Overall, these data suggest that with continued treatment a portion of patients can be treated through a moderate (or high) ADA response with restoration of efficacy.

In parallel to the required update for PK data of this study, the MAH further submitted an actualized analysis of the data on immunogenicity of dupilumab in children of the age group in focus for the OLE study R668-AD-1434 with a new data cut-off of 10-Mar-2022. The results of these analyses were consistent with prior analyses.

Exposure-Response

Positive concentration-response relationships were observed between higher dupilumab C_{trough} at week 16 and increases in the proportion of patients achieving IGA (0,1), increases in the proportion of patients with EASI-75 which both were key efficacy endpoints study R668-AD-1539 Part B, and this was consistent across all age groups within the dupilumab AD program. Positive exposure-response relationships were moreover observed for improvement in EASI percent change from baseline and improvement in weekly average of daily worst scratch/itch NRS change from baseline.

Due the sparsity of patients with dupilumab C_{trough} at week 16 <50 mg/L, the characterization of the full E-R relationship is limited.

No positive relationship between dupilumab C_{trough} at week 16 and the probability of developing conjunctivitis (broad or narrow CMQ terms) was observed, suggesting that higher exposures to dupilumab were not associated with a greater risk of developing conjunctivitis.

2.4.6. Conclusions on clinical pharmacology

The MAH provided a comprehensive package on clinical pharmacology to support the dosing regimen in children ≥6 months to <6 years of age with severe AD. The proposed posology in this patient group is tiered by body weight with patients ≥5 to <15 kg receiving 200 mg Q4W and with patients ≥15 to <30 kg receiving 300 mg Q4W. No loading dose is intended in the age group. This posology is considered acceptable by the CHMP.

No relationship with respect to safety (probability of developing conjunctivitis (broad or narrow CMQ terms) can be found. Due the sparsity of patients with lower (<50 mg/L) dupilumab C_{trough} at week 16, the characterization of the full E-R relationships with regard to safety and efficacy is limited (see sections 2.5 Clinical efficacy and 2.6 Clinical Safety).

2.5. Clinical efficacy

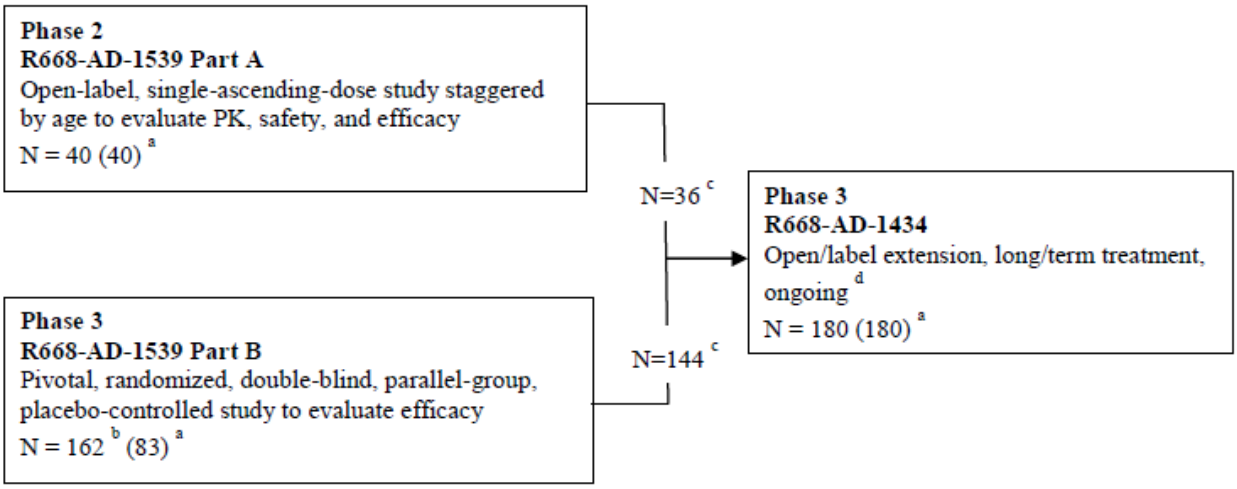
The clinical data package includes 3 studies: Phase 3 Study R668-AD 1539-Part B (completed), Phase 2 Study R668-AD 1539-Part A (completed) and the open-label extension (OLE) study R668-AD-1434 (ongoing). The final CSR will be submitted by the MAH around Q4-2026. Efficacy data supporting this application come from pivotal, placebo-controlled, **phase 3 study R668-AD-1539 Part B**. Supportive data come from Part A and the OLE study (see ***Figure 23***).

For study **R668-AD 1539-Part B**, the CSR is based upon a database lock when all patients had completed the end of treatment visit and is considered the final CSR (16 September 2021).

For study **R668-AD-1539 Part A**, the CSR to support this submission is based on a database lock date of when all patients completed Part A (09 September 2019).

For the ongoing **OLE study, R668-AD-1434**, a third-step analysis is based on a data cut-off date of 31 July 2021 and focuses on the population of children ≥6 months to <6 years of age with AD studied in the dupilumab program to support this application.

Figure 23 Dupilumab Studies in the Paediatric Patients ≥6 Months to <6 Years of Age Atopic Dermatitis Program



AD=atopic dermatitis; FAS=full analysis set; PK=pharmacokinetics; SAF=safety analysis set
Note: Arrows represent roll-over of patients into the OLE study R668-AD-1434. All studies are included in this dossier.
[a] Number in parentheses is the number of patients exposed to dupilumab, ie, included in the SAF.
[b] The number of patients included in the FAS was 162; 1 patient did not receive study treatment and was not included in the SAF and PKAS.
[c] The number of patients who progressed into R668-AD-1434.
[d] Study R668-AD-1434 includes patients ≥6 months to <18 years of age. The number of patients (180) listed included all patients ≥6 months to <6 years of age from the 2 prior studies as of data cut-off for this submission (31 Jul 2021.), including 36 of the 40 patients from R668-AD-1539 Part A and 144 of the 162 patients from R668-AD-1539 Part B. Study R668-AD-1539 Part A was open-label and study R668-AD-1539 Part B has been locked and unblinded.
Source: Module 5.3.5.1 R668-AD-1539 Part B, Module 5.3.5.2 R668-AD-1434 Third-step Analysis, and Module 5.3.5.1 R668-AD-1539 Part A.

An overview of clinical efficacy studies is presented below:

Table 17 Overview of Clinical Efficacy Studies for Dupilumab in the Treatment of Children ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis

Study/Phase/ Data Cut-off Date /Study Status[a]	Efficacy Objectives	Study Design and Duration	Treatment: Dose Regimen/Route of Administration	Children (≥6 months to <6 years of age) Planned/ Enrolled
R668-AD-1539 Part B/Phase 3/ NA/ Completed	The primary objective of this study was to demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in pediatric patients ≥6 months to <6 years of age with moderate-to-severe AD. Key efficacy results are summarized in Table 4	Randomized (1:1), double-blind, placebo-controlled, parallel-group 16-week treatment duration in combination with low potency TCS 12-week follow-up See Section 2.1	Dupilumab Q4W + TCS treatment group: 200 mg SC Q4W (patients ≥5 to <15 kg) or 300 mg SC (patients ≥15 to <30 kg) Placebo + TCS group: matching placebo based on weight category	160/162
R668-AD-1539 Part A/Phase 2/ NA/ Completed	Secondary objectives included evaluation of the efficacy of a single dose of dupilumab in patients ≥6 months to <6 years of age with severe AD. Key efficacy results are summarized in Table 6.	Open-label, single ascending dose, sequential cohort Single-dose treatment followed by a 4-week PK sampling period and 4-week follow-up See Section 2.2	Dupilumab SC single dose, 3 mg/kg for cohort 1A (≥2 to <6 years old) and cohort 2A (≥6 months to <2 years old), and 6 mg/kg for cohort 1B (≥2 to <6 years old) and cohort 2B (≥6 months to <2 years old)	40/40
R668-AD-1434/ Phase 3/ 31 Jul 2021/ Ongoing	Secondary objectives included assessment of long-term efficacy in pediatric patients. Key efficacy results for patients ≥6 months to <6 years of age are summarized in Table 7.	Open-label treatment with dupilumab for a planned treatment duration of 5 years. The study is ongoing at time of data cut-off date (31 Jul 2021). See Section 2.3	Under the protocol amendment 3, patients were dosed with dupilumab SC 3 mg/kg QW or 6 mg/kg QW. From amendment 4 onwards, patients were dosed with dupilumab 200 mg SC Q4W (patients ≥5 to <15 kg) or 300 mg SC Q4W (patients ≥15 to <30 kg) or 200 mg SC Q2W (≥30 to <60 kg)	NA [b]/180 [c]

Abbreviations: AD=atopic dermatitis; NA=not applicable; OLE=open-label extension; PK=pharmacokinetics, QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous; TCS=topical corticosteroids.
[a] Study status is based on the time of the data cut-off date for the studies in this submission.
[b] The number of patients ≥6 months to <6 years of age planned was not defined in the protocol.
[c] 30 patients ≥6 months to <6 years of age completed at least 52 weeks of the treatment period in OLE study.
Source: Module 5.3.5.1 R668-AD-1539 Part B, Module 5.3.5.1 R668-AD-1539 Part A, Module 5.3.5.2 R668-AD-1434 Third-step Analysis

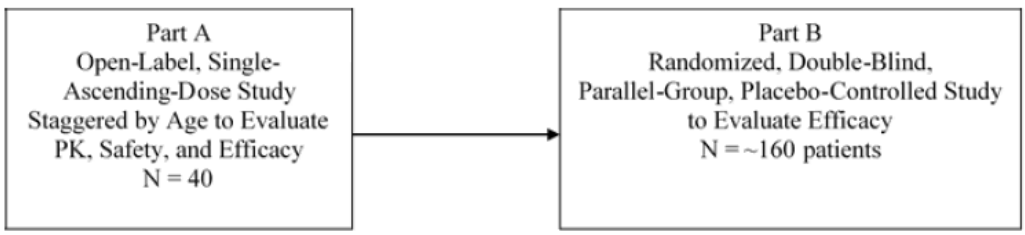
2.5.1. Main study

Study R668-AD-1539, A Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in Patients Aged ≥6 Months to <6 Years with Moderate-to-Severe Atopic Dermatitis

Methods

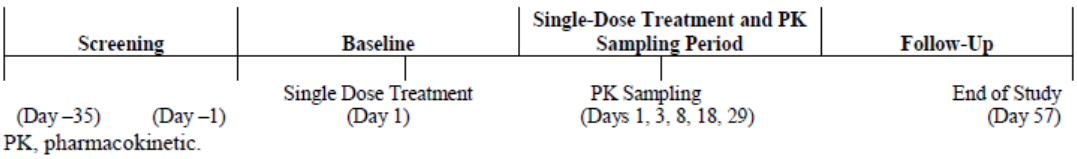
Study design

Study R668-AD-1539 was a two-part, Phase2/3 study investigating the PK, efficacy and safety of dupilumab in paediatric patients aged ≥6 months to <6 years with moderate-to-severe AD, see Figure below:



Part A was an open-label, single ascending dose, sequential cohort study investigating the PK, safety, and initial assessment of efficacy of a single dose of SC dupilumab in pediatric patients with severe AD and enrolled 40 patients. Efficacy was assessed as secondary objective. This study part included two age cohorts; age cohort 1 (20 patients ≥2 to <6 years old) and age cohort 2 (20 patients ≥6 months to <2 years old) that subdivided in 2 dose cohorts (cohort A: 3 mg/kg bw or cohort B: 6 mg/kg bw). The treatment sequence was 1A, 1B, 2A, 2B. Safety reviews were interposed before dosing of the next cohort. The dose of Part B was determined based on results from Part A. The study design for Part A is displayed in *Figure* ***24***.

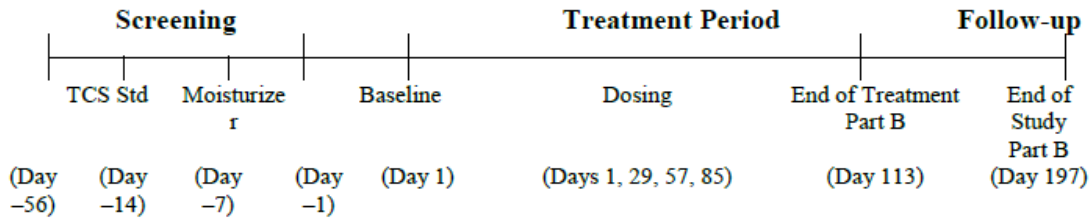
Figure 24 Study Flow Diagram – Part A



PK, pharmacokinetic.

Part B was a randomized, double-blind, parallel-group, placebo-controlled study in which SC dupilumab was administered concomitantly with low potency TCS for 16 weeks to pediatric patients 6 months to <6 years of age with moderate-to- severe AD using a fixed dose regimen, tiered by body weight: 200 mg Q4W for patients ≥5 to <15 kg, 300 mg Q4W for patients ≥15 to <30 kg. The study population of patients with moderate AD was capped at 40 patients. Patient were randomized 1:1 and stratified by baseline body weight (≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America, Europe, Japan, and China). The study design for Part B is displayed in *Figure* ***25***.

Figure 25 Study Flow Diagram for Part B



TCS Std: topical corticosteroid standardization
Note: The length of the screening period was not fixed but was not to exceed 56 days (including TCS standardization). The length of the TCS standardization period was fixed at 14 days. Moisturizers were to be applied at least twice daily during the 7 consecutive days prior to randomization (not including day of randomization) and were to be used throughout the study. At least 11 of the 14 total applications of moisturizers prior to randomization had to be applied for the patient to remain eligible for the study.

Study participants

Main Inclusion criteria:

- Male or female ≥6 months to <6 years of age at the screening visit
- Diagnosis of AD according to the American Academy of Dermatology consensus criteria at the screening visit
- Patients with documented recent history (within 6 months before the screening visit) of inadequate response to topical AD medication(s)
    - Patients who are unable to achieve and/or maintain remission and low disease activity (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of medium

to higher potency TCS (±TCI as appropriate), applied for at least 28 days of use, or for the maximum duration recommended by the product prescribing information, whichever is shorter, will meet the definition of inadequate response for the purpose of this study.

- Patients with documented systemic treatment for AD in the past 6 months are also considered as inadequate responders to topical treatments and are potentially eligible for treatment with dupilumab after appropriate washout.

- IGA/EASI score and BSA involvement at screening and baseline visits: NOTE: The target population with respect to disease severity differs for part A (severe AD) and part B (moderate-to-severe AD). Therefore, disease severity criteria are specified separately for part A and part B in inclusion criterion 4 to 6 below:
    - part A: IGA = 4
    - part B: IGA ≥3
    - part A: EASI ≥21
    - part B: EASI ≥16
    - part A: ≥15%
    - part B: ≥10%
- Baseline worst scratch/itch score weekly average score for maximum scratch/itch intensity ≥4 (**for part B of the study only**)
- At least 11 (of a total of 14) applications of a topical emollient (moisturizer) during the 7 consecutive days immediately before the baseline visit (not including the day of randomization) (**for part B of the study only**).
- At least 11 (of a total of 14) daily applications of low potency TCS during the 2-week TCS standardization period (beginning on day -14) leading up to the baseline visit (**for part B of the study only**).

Main Exclusion criteria:

- Prior treatment with dupilumab.
- History of important side effects of low potency topical corticosteroids (**only applicable for part B of the study**).
- Treatment with a topical investigational drug within 2 weeks or within 5 half-lives (if known), whichever is longer, or treatment with a systemic investigational drug prior to the baseline visit.
- Treatment with a TCI within 2 weeks prior to the baseline visit (**only applicable for part B of the study**)
- Having used any of the following treatments within 4 weeks, or within a period equal to 5 times the half-life of the drug, before the baseline visit, whichever is longer: Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
- Phototherapy for AD
- Treatment with biologics
- Treatment with crisaborole within 2 weeks prior to the baseline visit **(only applicable for part B of the study)**

- Treatment with a live (attenuated) vaccine within 4 weeks before the baseline visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment.
- Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit) (**for part B of the study only**).

Treatments

Investigational product

Dupilumab was administered subcutaneously throughout Study R668-AD-1539, alternating among

the different quadrants of the abdomen, upper thighs, and upper arms so that the same site is not injected for 2 consecutive administrations. All study interventions were provided centrally by the sponsor.

Part A

- 5 mL vial containing 2.5 mL of 150 mg/mL, 3 mg/kg or 6 mg/kg single dose.

Part B:

- Dupilumab 175 mg/mL PFS, 200 mg (1.14 mL of a 175 mg/mL solution) or
- Dupilumab 150 mg/mL PFS, 300 mg (2.0 mL of a 150 mg/mL solution) or
- Matching Placebo (same formulation without protein)
- Dose regimens: For patients ≥5 to <15 kg: 200 mg (1.14 mL) Q4W, for patients ≥15 to <30 kg: 300 mg (2.0 mL) Q4W

Concomitant Therapy

Background treatment was administered only in Part B. All patients applied moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization until week 28 (EOS).

Rescue treatment for worsening of AD could be provided to study patients based on adjudication performed through a prespecified algorithm and at the discretion of the investigator.

Objectives and Outcomes/endpoints

R668-AD-1539 Part B

Objectives	Endpoints/variables
Primary	
• To demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in pediatric patients, 6 months to less than 6 years of age, with moderate-to-severe AD	Primary endpoint was defined for the US and US reference market countries: • Proportion of patients with an Investigator's Global Assessment (IGA) score of 0 to 1 (on a 5-point scale) at week 16 Co-primary endpoints were defined for the EU and EU Reference Market Countries only: • Proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at week 16 • Proportion of patients with an IGA score of either 0 or 1 (on a 5-point scale) at week 16
Secondary	
• To assess the safety and immunogenicity of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS in patients 6 months to less than 6 years of age with moderate-to-severe AD	The following safety endpoints were assessed: • Incidence of SAEs through week 16 • Incidence of skin infection TEAEs (excluding herpetic infections) through week 16 The following endpoint to evaluate immunogenicity was defined: • Immunogenicity variables included anti-drug antibody status (ADA) status, titer, neutralizing antibody (NAb) status, and time-point/visit In addition, the following secondary efficacy endpoints were assessed: Key secondary efficacy endpoints: • Proportion of patients with EASI-75 at week 16 (not applicable for EU or EU Reference Market Countries) • Percent change in EASI score from baseline to week 16 • Percent change from baseline to week 16 in weekly average of daily worst scratch/itch Numeric Rating Scale (NRS) score

R668-AD-1539 Part A

Objectives	Endpoints
Primary	
• To characterize the safety and PK of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age, with severe AD	• Concentration of functional dupilumab in serum over time and PK parameters (summary statistics of drug concentration and PK parameters) • The incidence and severity of TEAEs to week 4
Secondary	
• To evaluate the efficacy and immunogenicity of a single dose of dupilumab in patients 6 months to less than 6 years of age with severe AD	• The incidence of SAEs and severe TEAEs to week 4 • Percent change in EASI score from baseline to week 4 • Percent change in SCORAD score from baseline to week 4 • Proportion of patients with an IGA score of either 0 or 1 (on a 5-point scale) at week 4 • Immunogenicity variables include anti-drug antibody status (positive or negative) and titer

AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; PK, pharmacokinetic; SAE, serious adverse event; SCORAD, SCORing Atopic Dermatitis; TEAE, treatment-emergent adverse event.

Sample size

Overall 160 patients were planned to be randomised in a 1:1 ratio allocation to dupilumab versus placebo. The sample size was powered for the co-primary endpoints rate of patients with IGA score of 0 to 1 at week 16 and rate of patients with an EASI-75 at week 16 tested with Cochran-Mantel-Haenszel test.

Assuming 2-sided 5% significance level, the study can fulfil the following power considerations, based on Fisher's exact test:

• 88% power to detect a difference of 21.4% between the dupilumab and placebo groups in the percentage of patients who achieve an IGA score of 0 to 1 at week 16, assuming 32.8% and 11.4% for the dupilumab and placebo groups, respectively.

• 99% power to detect a difference of 42.9% in the percentage of patients who achieve an EASI-75 response at week 16, assuming 69.7% and 26.8% for the dupilumab and placebo groups, respectively.

The assumptions used for the above power calculations were based on results from patients in the R668-AD-1652 study (phase 3 combination study for patients ≥6 to <12 years of age with severe AD). The tiered fixed-dose regimen (200 mg Q4W in patients ≥5-<15 kg, 300 mg Q4W in patients ≥15-<30 kg) is expected to provide exposure comparable to that seen with 300 mg Q4W in patients ≥6 to <12 years of age or 300 mg Q2W in adult patients. Further justification for the sample size comes from the results from the R668-AD-1224 study (a phase 3 combination [with TCS] study for adult patients with moderate-to-severe AD). In this study, the proportions of patients who achieved an IGA score of 0 to 1 at week 16 were 38.7% and 12.4% for dupilumab and placebo, respectively. The proportions of patients who

achieved an EASI-75 response at week 16 were 23.3% and 68.9% for dupilumab and placebo, respectively.

The study will have a power of 96% on both the co-primary endpoints based on the results from the R668-AD-1224 study. Additional support for the sample size comes from the R668-AD-1526 study (a phase 3 study for adolescent patients with moderate-to-severe AD).

Randomisation

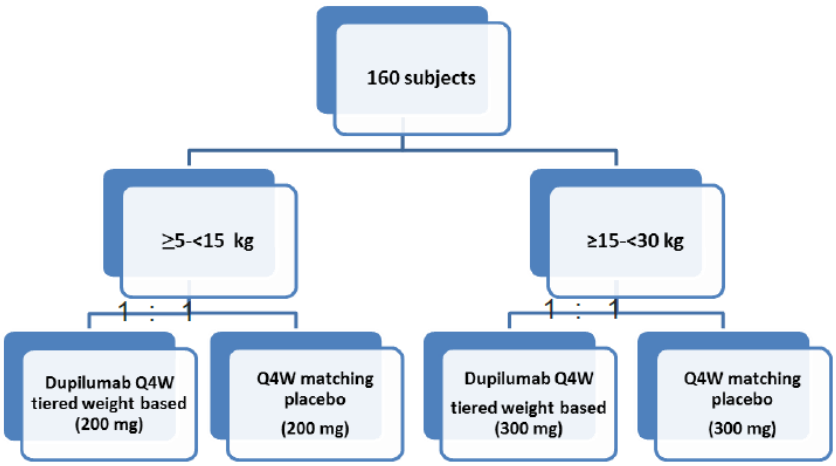
R668-AD-1539 Part B

Patients were planned to be randomized in a 1:1 ratio stratified by baseline body weight (≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America, Europe, Japan, and China). The number of patients with moderate AD (IGA=3) was planned to be capped at approximately 40. Approximately 160 patients were planned to be randomized to 1 of the following 2 treatment regimens:

- Dupilumab every 4 weeks (Q4W; a weight-tiered regimen):
  - For patients with baseline weight ≥5 to <15 kg: 200 mg Q4W
  - For patients with baseline weight ≥15 to <30 kg: 300 mg Q4W
- Placebo Q4W: matching placebo based on baseline weight category

*Figure **26*** shows the randomization scheme for part B of the study.

Figure 26 Randomisation Scheme (Part B)



Randomization was planned to be conducted according to a central randomization scheme provided by an IWRS (Interactive Web Response system) to the designated study pharmacist (or qualified designee).

Blinding (masking)

R668-AD-1539 Part B

Part B of the study was to be blinded to all individuals until the prespecified unmasking to conduct the primary analyses, except for IDMC members and for emergency unblinding. Blinded study drug kits coded with a medication numbering system were used. In order to maintain the blind, lists linking these codes

with product lot numbers were not accessible to individuals involved in study conduct. Anti-drug antibody and drug concentration results should not be communicated to the sites, and the sponsor's operational team should not have access to results associated with patient identification until after the final database lock.

Statistical methods

Analysis Populations

The full analysis set (FAS) was defined as all randomized patients. Efficacy analyses were based on the treatment allocated at randomization (as randomized). All efficacy variables were evaluated in the FAS, which was the primary analysis set.

The safety analysis set (SAF) was defined as all randomized patients who received at least one dose of study drug and were analyzed as treated. Patients were considered as treated with dupilumab if ≥ 1 dose of dupilumab was administered regardless of the allocated treatment. In addition, nonrandomized but treated patients were defined not to be part of the safety population (SAF); however, their safety data were presented separately. Randomized patients for whom it was unclear whether they took the study drug were defined to be included in the safety population as randomized. Treatment compliance/administration and all clinical safety variables were summarized based on the SAF.

Additionally a PK analysis set (FAS with ≥ 1 dose of IMP and ≥ 1 PK measurement), an ADA analysis set (AAS; all patients with ADA measurements; analysed as treated) and a NAb analysis set (NAS; all patients with NAb measurements; analysed as treated) were defined.

Primary Estimands

	Estimands			
Endpoint Category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis Method**
Co-primary (Proportion)	• Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16 • Proportion of patients with EASI-75 at week 16	FAS	The intercurrent events will be handled as follows: • Discontinuation of study intervention: Data collected after the patient discontinued treatment will be included in the analyses (treatment policy strategy). • Initiation of rescue treatment: Patients will be considered as non-responders after such events (composite strategy).	Proportion of response/ CMH test adjusted by randomization strata

Primary Analysis

The Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata (baseline weight group: ≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), and region/country (North America,

Europe)) was to be used for the analysis of percentage of patients with IGA 0 or 1 at week 16. Similar procedures were to be used for percentage of patients with EASI-75 at week 16.

Handling of missing data

For the co-primary endpoints missing values due to withdrawn consent, AE and lack of efficacy were planned to be imputed as non-responder. Missing values due to any other reason including COVID-19 were planned to be imputed using multiple imputation (MI). All non-missing data were used for MI and are planned to be imputed using regression method for a monotone pattern and adjustment for covariates including treatment groups, randomization strata (baseline weight group, baseline IGA

and region), and relevant baseline variables. The missing values are planned to be imputed 40 times. The corresponding results are planned to be combined by Rubin`s formula.

Supplementary Analyses for Primary Endpoints

Sensitivity analyses on co-primary efficacy endpoints were to be performed using a tipping-point analyses. To assess the robustness of primary analysis results, a delta-adjusting pattern-mixture approach for tipping point analysis (2013, Ratitch) under MNAR (missing not at random) assumption, was conducted for the co-primary endpoints.

Secondary Estimands

	Estimands			
Endpoint Category	**Endpoints**	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary/Analysis Method**
Key Secondary (Continuous)	• Percent change in EASI score from baseline to week 16 • Percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score	FAS	The intercurrent events will be handled as follows: • Discontinuation of study intervention: Data collected after the patient discontinued treatment will be included in the analyses (treatment policy strategy). • Initiation of rescue treatment: data after rescue treatment will be assigned by postbaseline worst-observation- carried-forward (WOCF) (hypothetical strategy). If there is no post-baseline assessment, the baseline value will be used (hypothetical strategy).	Mean Change from baseline/ ANCOVA model with treatment and randomization strata as covariates

Secondary Analysis

The secondary binary efficacy endpoints were to be analysed using the same approaches used for the analysis of the primary endpoints described above (Cochran-Mantel-Haenszel (CMH) test adjusted by randomization strata).

The continuous endpoints (e.g. EASI, worst scratch/itch NRS score) were to be analysed using analysis of covariance (ANCOVA) model with treatment, randomization strata (baseline weight group: ≥5-<15 kg and ≥15-<30 kg), baseline disease severity (IGA=3 and 4), region/country (North America, Europe)) and relevant baseline value included in the model as the primary analysis method.

Handling of missing data

For the (key-) secondary endpoints missing values due to withdrawn consent, AE and LOE were planned to be imputed by post-baseline WOCF (worst observation carried forward). Thereby the missing data was imputed by post-baseline WOCF if there was at least one non-missing post-baseline value or by baseline value if there was no post-baseline value.

Missing values due to any other reason including COVID-19 was planned to be imputed using multiple imputation (MI) comparable to the methods described above for efficacy endpoints.

Multiplicity

A hierarchical procedure was used to control the overall Type-1 error rate at 0.05 (2-sided). The hierarchical testing order is shown in below table (all comparisons are with the placebo). Both co-primary endpoints needed to have a significant result before secondary endpoints could be tested.

Level	Endpoints	Testing Order
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	1
Co-primary endpoint for EMA and EMA Reference Market Countries only, key secondary for US	Proportion of patients with EASI-75 (>=75% improvement from baseline) at week 16	2
Secondary endpoints	Percent change in EASI score from baseline to week 16	3
	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch score	4
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 from baseline	5
	Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3 from baseline	6
	Proportion of patients with EASI-50 at week 16	7
	Proportion of patients with EASI-90 at week 16	8
	Change from baseline in percent BSA affected by AD	9
	Change from baseline to week 16 in POEM	10
	Percent change from baseline to week 16 in SCORAD	11
	Change from baseline in Patient's sleep quality NRS	12
	Change from baseline in Patient's skin pain NRS	13
	Change from baseline in DFI	14
	Change from baseline to week 16 in CDLQI	15
	Change from baseline to week 16 in IDQOL	16

Subgroup Analyses

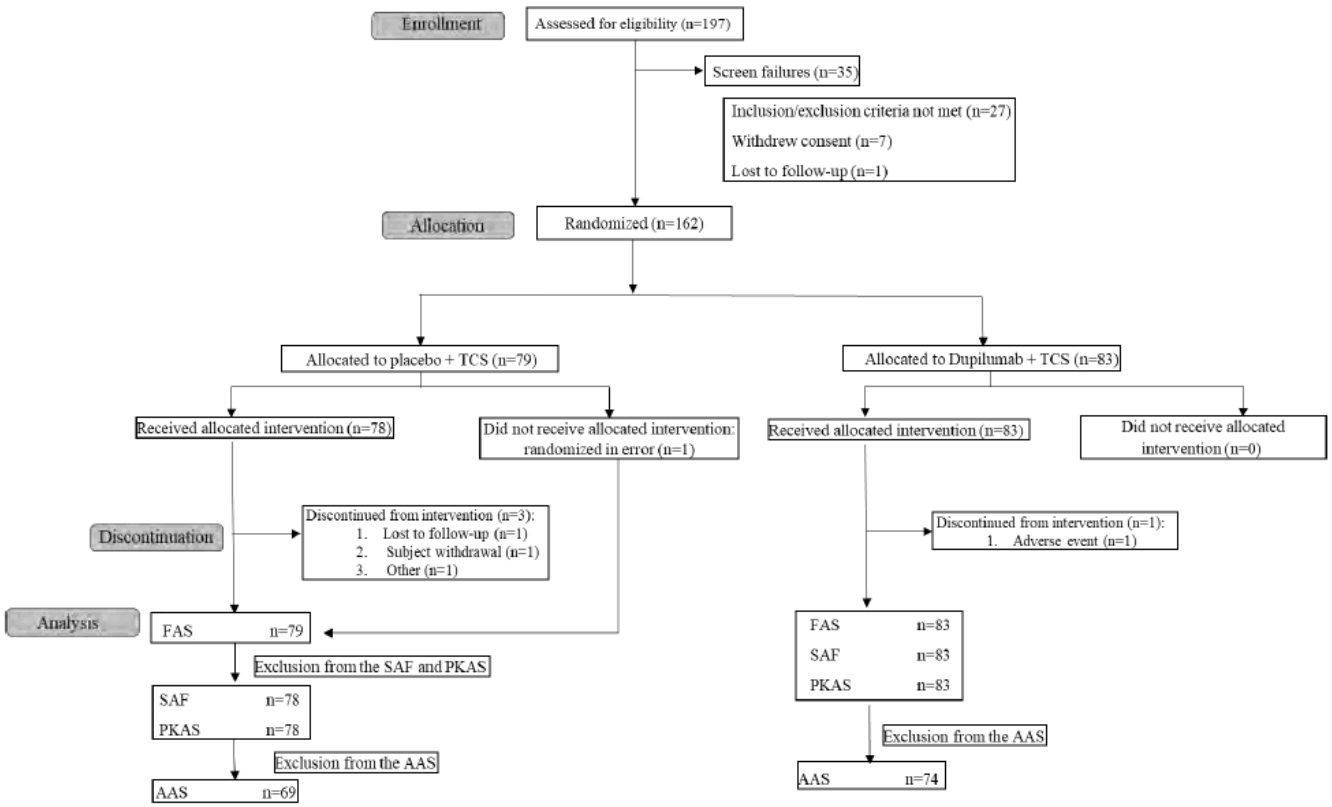
Subgroup analyses of the primary/co-primary and key secondary efficacy endpoints in the moderate-to-severe population (FAS) were to be performed by sex, race, age of onset of AD, family history of atopic disease, baseline body weight group, baseline BMI group, region, AD severity by baseline IGA score, AD severity by baseline EASI score, baseline worst scratch/itch NRS score, BSA involvement in AD at baseline, previous use of systemic immunosuppressants, history of asthma, history of allergic rhinitis, and history of food allergies.

Results

Efficacy results are first presented for Study R668-AD Part B. Results of Part A are presented in Section Supportive Studies.

Participant flow

Figure 27 Participant Disposition – Part B



AAS=anti-drug antibody analysis set; FAS=full analysis set; PKAS=pharmacokinetic analysis set; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids
Source: PTT 1.1.1/3, PTT 3.1.1/1

Primary Reasons for premature study and treatment discontinuation are displayed in *Table **18*** and *Table **19***.

Table 18 Primary Reason for Premature Discontinuation from the Study – Part B (All Randomised)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Transition into another study, n (%)			
Yes	75 (94.9%)	81 (97.6%)	156 (96.3%)
R668-AD-1434	75 (94.9%)	81 (97.6%)	156 (96.3%)
No	4 (5.1%)	2 (2.4%)	6 (3.7%)
Completed Week 28 (End of Study), n (%)	1 (1.3%)	1 (1.2%)	2 (1.2%)
Ongoing, n (%)	0	1 (1.2%)	1 (0.6%)
Discontinuation from study with reason, n (%)	3 (3.8%)	0	3 (1.9%)
Noncompliance with protocol by the subject	0	0	0
Adverse event	0	0	0
Lack of Efficacy	0	0	0
Decision by the Investigator / Sponsor	0	0	0
Withdrawal of consent by the Subject	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	1 (1.3%)	0	1 (0.6%)
Death	0	0	0
Other	1 (1.3%)	0	1 (0.6%)
Patient randomized in error.	1 (1.3%)	0	1 (0.6%)
Completed Week 16, n (%)	76 (96.2%)	83 (100%)	159 (98.1%)
Discontinuation through Week 16 with reason, n (%)	3 (3.8%)	0	3 (1.9%)
Noncompliance with protocol by the subject	0	0	0
Adverse event	0	0	0
Lack of Efficacy	0	0	0
Decision by the Investigator / Sponsor	0	0	0
Withdrawal of consent by the Subject	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	1 (1.3%)	0	1 (0.6%)
Death	0	0	0
Other	1 (1.3%)	0	1 (0.6%)
Patient randomized in error.	1 (1.3%)	0	1 (0.6%)
Entered Follow-up Period, n (%)	19 (24.1%)	19 (22.9%)	38 (23.5%)
Transitioned to OLE, n (%) [2]	18 (22.8%)	17 (20.5%)	35 (21.6%)
Completed F/u period and did not transition to OLE, n (%)	1 (1.3%)	1 (1.2%)	2 (1.2%)
Ongoing, n (%) [1]	0	1 (1.2%)	1 (0.6%)
Discontinuation from Study with reason, n (%)	0	0	0

Abbreviations: Q4W=once every 4 weeks; TCS=topical corticosteroids.
[1] This patient was ongoing as at the primary data cutoff and was subsequently reported to be lost to follow-up (see Section 1.1 for details).
[2] These participants first entered the follow-up period and then transitioned to the OLE.
The percentage is based on the number of randomized patients in each treatment group as denominator
No subjects discontinued study due to COVID-19.
Source: PTT 1.1.2/1

Table 19 Primary Reason for Premature Discontinuation from the Study Treatment - Part B (All Randomised)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Received study medication, n (%)	78 (98.7%)	83 (100%)	161 (99.4%)
Patient randomized but not treated, n (%)	1 (1.3%)	0	1 (0.6%)
Completed the study treatment, n (%)			
Yes	75 (94.9%)	82 (98.8%)	157 (96.9%)
No	3 (3.8%)	1 (1.2%)	4 (2.5%)
Adverse event	0	1 (1.2%)	1 (0.6%)
Withdrawal of consent by the Subject	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	1 (1.3%)	0	1 (0.6%)
Other	1 (1.3%)	0	1 (0.6%)
Subject started systemic corticosteroid and had to withdraw study IP	1 (1.3%)	0	1 (0.6%)

Abbreviations: Q4W=every 4 weeks; TCS=topical corticosteroids.
The percentage is based on the number of randomized patients in each treatment group as denominator.
No subjects discontinued study treatment due to COVID-19.
Source: PTT 1.1.2/2

Recruitment

Study Initiation Date: 30 Jun 2020 (first participant first screening visit)

Cut-off date for Clinical Study Report: 09 Jul 2021

Final database lock: 16 Sep 2021

Conduct of the study

Protocol deviations

There were no unblinding events during Part B of the study.

In Part B, 12/83 (14.5%) subjects of the DUP+TCS group and 8/79 (10.1%) of the PBO+TCS group had at least one major protocol deviation, overall more patients assigned to the PBO+TCS group had one (97.5% vs. 94.0%), see ***Table 20***. In both groups, the most common important protocol deviation was receiving an excluded concomitant medication (5/79, 6.3% in the PBO+TCS group vs. (6/83, 7.2% in the DUP+TCS group).

Table 20 Summary of Protocol Deviations – Part B (All Randomised Patients)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of Protocol Deviations	455	509
Patients with Any Protocol Deviation, n(%)	77 (97.5%)	78 (94.0%)
Number of Protocol Deviations due to COVID-19 Pandemic	1	10
Patients with Any Protocol Deviation due to COVID-19 Pandemic, n(%)	1 (1.3%)	4 (4.8%)
Number of Important Protocol Deviations	8	12
Patients with Any Important Protocol Deviation by Categories, n(%)	7 (8.9%)	11 (13.3%)
Received an excluded concomitant treatment	5 (6.3%)	6 (7.2%)
Entered study even though entry criteria were not satisfied	1 (1.3%)	4 (4.8%)
Procedure not performed	1 (1.3%)	1 (1.2%)
Inadequate informed consent administration	0	1 (1.2%)

Abbreviations: Q4W=every 4 weeks; PD=protocol deviation; TCS=topical corticosteroids.
The percentage is based on the number of randomized patients in each treatment group as denominator.
All COVID-19 related PDs were minor PDs. One participant had 5 PDs of 'procedure not performed' (TCS dispensation not performed at 2 visits, TCS accountability not performed and vital signs not collected at 2 visits), 1 participant had 2 PDs of 'procedure not performed' (TCS dispensation not performed, TCS accountability not performed) and 1 PD of 'visit performed out of window'. Another participant had a PD of 'visit performed out of window' and 2 participants had PDs of 'visit not performed' (information from datasets).
The case of inadequate informed consent was for a participant who turned 4 years old at the EOT visit and therefore should have signed the assent form. However, the assent form was not signed prior to rolling over to the OLE study. The participant was consented to the Main ICF at V1 (information from datasets).
Among the participants who received excluded concomitant treatment, 1 received a concomitant live (attenuated) vaccination of MMR vaccine, and 2 received vaccinations of and MMR and Varicella vaccine (Post-text Listing 2.4.2/1).
Source: PTT 2.1.1/1

Changes to the conduct of the study

Changes in the conduct of the study that were implemented by protocol amendments after initiation of Part B. Overall, 4 protocol amendments were implemented.

Amendment	Purpose
4	The number of patients with moderate AD (IGA=3) were capped at approximately 40 in order to meet the European Union (EU) regulatory requirement (as per commitment in the approved Pediatric Investigational Plan) to enroll approximately 120 patients with severe AD (IGA=4).
3	• A weight-tiered fixed-dose regimen was chosen for part B. • Randomization stratification in part B was changed from by age group and region to by body weight, baseline disease severity, and region/country. • The target population with respect to disease severity was changed from severe AD to moderate-to-severe AD for part B. • Introduction of 2-week TCS standardization period to Part B. • Use of medium potency steroids was changed to low potency steroids. • Added other (exploratory) objectives to assess effects of dupilumab on blood and skin biomarkers and to study its mechanism of action. • Clarified patient eligibility for the open-label extension (OLE) study. • Updated planned sample size to 160 patients (80 patients per group) from 240 and revised power calculations. • Added assessment of neutralizing antibodies (NAbs). • Added exclusion criterion #27 for patients with body weight <5 kg or ⩾30 kg at baseline (part B only): A weekly average worst scratch/itch score ⩾4 at baseline (part B).

	• Further described analyses that may be performed, including multiple imputation method. Added hierarchical procedure to be used for part B to control overall Type-1 error rate. • Clarified/updated list of adverse events of special interest (AESIs). • Specified a new key secondary endpoint for pruritus and added other secondary endpoints for worst scratch/itch NRS, skin pain NRS, and sleep quality NRS scores, and improvement in worst scratch/itch NRS score ⩾4 and ⩾3.
2	• Increased the follow-up period for patients who decline or are not eligible for a subsequent OLE study, from 4 weeks to 8 weeks. • Added the following exclusion criterion: "Treatment with crisaborole within 2 weeks prior to the baseline visit." • Added 1 medication to the list of prohibited agents: Treatment with crisaborole (only for part B). • Changed conditions for potential entry into the OLE (R668-AD-1434) so that all patients in part B will be able to roll over into the OLE at the end of the treatment period. • Added an Ophthalmological Examination section. • The list of AESIs has been revised across the dupilumab program in AD.
1 (UK)	Changed conditions for potential entry into the OLE (R668-AD-1434) so that all patients in Part B will be able to roll over into the OLE at the end of the treatment period.

Baseline data

Demographics of participants included in Part B are displayed in *Table **21*** and *Table **22***.

Table 21 Summary of Demographics for the Overall Population – Part B (FAS)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Age (years) descriptive			
n	79	83	162
Mean (SD)	3.78 (1.262)	3.91 (1.225)	3.84 (1.241)
Median	3.83	4.17	4.04
Q1 : Q3	2.92 : 4.75	3.08 : 4.83	3.08 : 4.75
Min : Max	0.6 : 5.9	0.8 : 5.8	0.6 : 5.9
Age group (years), n (%)			
6 months to <2 years	5 (6.3%)	6 (7.2%)	11 (6.8%)
≥2 years and <6 years	74 (93.7%)	77 (92.8%)	151 (93.2%)
Sex n (%)			
Male	55 (69.6%)	44 (53.0%)	99 (61.1%)
Female	24 (30.4%)	39 (47.0%)	63 (38.9%)
Ethnicity n (%)			
Not Hispanic or Latino	70 (88.6%)	72 (86.7%)	142 (87.7%)
Hispanic or Latino	9 (11.4%)	11 (13.3%)	20 (12.3%)
Race n (%)			
White	53 (67.1%)	58 (69.9%)	111 (68.5%)
Black or African American	16 (20.3%)	14 (16.9%)	30 (18.5%)
Asian	4 (5.1%)	6 (7.2%)	10 (6.2%)
Native Hawaiian or Other Pacific Islander	1 (1.3%)	0	1 (0.6%)
Not Reported	1 (1.3%)	2 (2.4%)	3 (1.9%)
Other	4 (5.1%)	3 (3.6%)	7 (4.3%)
Height (cm) descriptive			
n	78	82	160
Mean (SD)	100.6 (10.70)	99.9 (12.29)	100.2 (11.51)
Median	101.1	101.6	101.2
Q1 : Q3	95.0 : 108.5	94.9 : 108.5	95.0 : 108.5
Weight (kg) descriptive			
n	79	83	162
Mean (SD)	16.66 (3.629)	17.08 (4.407)	16.88 (4.039)
Median	16.50	16.90	16.50
Q1 : Q3	14.20 : 19.20	13.90 : 19.40	14.20 : 19.20
Min : Max	7.5 : 27.3	8.1 : 29.8	7.5 : 29.8
Baseline weight group n (%)			
5 to <15 kg	25 (31.6%)	26 (31.3%)	51 (31.5%)
15 to <30 kg	54 (68.4%)	57 (68.7%)	111 (68.5%)
BMI (kg/m2)			
n	78	82	160
Mean (SD)	16.2 (1.88)	17.0 (5.55)	16.6 (4.19)
Median	16.0	16.3	16.0
Q1 : Q3	15.0 : 16.6	15.0 : 17.7	15.0 : 17.4
Baseline BMI group[1] n (%)			
Not Overweight	66 (83.5%)	59 (71.1%)	125 (77.2%)
Overweight	12 (15.2%)	23 (27.7%)	35 (21.6%)
Missing	1 (1.3%)	1 (1.2%)	2 (1.2%)
Country n (%)			
Germany	3 (3.8%)	4 (4.8%)	7 (4.3%)
Poland	20 (25.3%)	21 (25.3%)	41 (25.3%)
United Kingdom	5 (6.3%)	5 (6.0%)	10 (6.2%)
United States	51 (64.6%)	53 (63.9%)	104 (64.2%)
Region n (%)			
North America	51 (64.6%)	53 (63.9%)	104 (64.2%)
Europe	28 (35.4%)	30 (36.1%)	58 (35.8%)

Abbreviations: BMI=body mass index; FAS=full analysis set; Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
[1] For ≥2 years, BMI is calculated using weight/height^2. For <2 years, BMI is calculated as weight/length. Overweight: ≥85 percentile of BMI for ≥2 years based on age and gender, ≥ 95 percentile of weight based on length (height), age and gender for <2 years, based on CDC (Centers for Disease Control and Prevention) chart. Not overweight: not meeting the criteria of overweight.
Source: PTT 4.1.1/1

Table 22 Demographics for Participants with Severe AD (Baseline IGA=4)

	Placebo + TCS (N=62)	Dupilumab 200/300mg Q4W + TCS (N=63)	Total (N=125)
Age (years) descriptive			
n	62	63	125
Mean (SD)	3.9 (1.20)	3.9 (1.30)	3.9 (1.25)
Median	4.0	4.2	4.1
Q1 : Q3	2.9 : 4.8	3.1 : 4.9	3.1 : 4.8
Min : Max	1 : 6	1 : 6	1 : 6
Age group (years), n (%)			
6 months - <2 years	3 (4.8%)	6 (9.5%)	9 (7.2%)
≥2 years and <6 years	59 (95.2%)	57 (90.5%)	116 (92.8%)
Sex n (%)			
Male	42 (67.7%)	37 (58.7%)	79 (63.2%)
Female	20 (32.3%)	26 (41.3%)	46 (36.8%)
Ethnicity n (%)			
Not Hispanic or Latino	56 (90.3%)	52 (82.5%)	108 (86.4%)
Hispanic or Latino	6 (9.7%)	11 (17.5%)	17 (13.6%)
Race n (%)			
White	38 (61.3%)	43 (68.3%)	81 (64.8%)
Black or African American	15 (24.2%)	12 (19.0%)	27 (21.6%)
Other	9 (14.5%)	8 (12.7%)	17 (13.6%)
Height (cm) descriptive			
n	61	63	124
Mean (SD)	101.2 (10.22)	99.8 (12.70)	100.5 (11.52)
Median	101.0	102.0	101.6
Q1 : Q3	95.3 : 108.8	95.9 : 108.5	95.4 : 108.7
Weight (kg) descriptive			
n	62	63	125
Mean (SD)	17.01 (3.659)	17.18 (4.546)	17.10 (4.114)
Median	16.50	17.00	16.50
Q1 : Q3	14.80 : 19.20	14.60 : 19.40	14.60 : 19.40
Min : Max	9.4 : 27.3	8.1 : 29.8	8.1 : 29.8
Baseline weight group n (%)			
5 - <15 kg	18 (29.0%)	18 (28.6%)	36 (28.8%)
15 - <30 kg	44 (71.0%)	45 (71.4%)	89 (71.2%)
BMI (kg/m2)			
n	61	63	124
Mean (SD)	16.3 (1.97)	17.2 (6.27)	16.8 (4.68)
Median	16.0	16.2	16.0
Q1 : Q3	15.1 : 16.6	14.8 : 18.1	15.0 : 17.5
Baseline BMI group[1] n (%)			
Not Overweight	50 (80.6%)	45 (71.4%)	95 (76.0%)
Overweight	11 (17.7%)	18 (28.6%)	29 (23.2%)
Missing	1 (1.6%)	0	1 (0.8%)
Country n (%)			
Germany	2 (3.2%)	4 (6.3%)	6 (4.8%)
Poland	15 (24.2%)	15 (23.8%)	30 (24.0%)
United Kingdom	5 (8.1%)	4 (6.3%)	9 (7.2%)
United States	40 (64.5%)	40 (63.5%)	80 (64.0%)
Region n (%)			
North America	40 (64.5%)	40 (63.5%)	80 (64.0%)
Europe	22 (35.5%)	23 (36.5%)	45 (36.0%)

Abbreviations: BMI=body mass index; FAS=full analysis set; Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
[1] For ≥2 years, BMI is calculated using weight/height^2. For <2 years, BMI is calculated as weight/length. Overweight: ≥85 percentile of BMI for ≥2 years based on age and gender, ≥ 95 percentile of weight based on length (height), age and gender for <2 years, based on CDC (Centers for Disease Control and Prevention) chart. Not overweight: not meeting the criteria of overweight.
Source: PTT 4.1.2/25

Baseline Disease Characteristics

Baseline disease characteristics are displayed in *Table **23*** and *Table **24***.

Table 23 Summary of Baseline Disease Characteristics of the Overall population - Part B (FAS)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Age at disease onset group, n (%)			
<6 months	57 (72.2%)	50 (60.2%)	107 (66.0%)
≥6 months	22 (27.8%)	33 (39.8%)	55 (34.0%)
Number of patients with duration of atopic dermatitis (years), n (%)			
<3 years	28 (35.4%)	29 (34.9%)	57 (35.2%)
≥3 years	51 (64.6%)	54 (65.1%)	105 (64.8%)
Duration of atopic dermatitis (years)			
Mean (SD)	3.4 (1.30)	3.4 (1.33)	3.4 (1.31)
Median	3.4	3.6	3.5
Q1:Q3	2.7:4.4	2.3:4.4	2.6:4.4
Min:Max	0:6	0:6	0:6
Weekly average of daily worst scratch/itch score (range: NRS 0-10)			
Mean (SD)	7.6 (1.49)	7.5 (1.32)	7.6 (1.40)
Median	7.7	7.4	7.6
Q1:Q3	6.8:8.7	6.6:8.3	6.7:8.5
Min:Max	2:10	4:10	2:10
≥7, n(%)	57 (72.2%)	54 (65.1%)	111 (68.5%)
<7, n(%)	22 (27.8%)	29 (34.9%)	51 (31.5%)
Baseline IGA (range: 0-4)			
IGA=3	17 (21.5%)	20 (24.1%)	37 (22.8%)
IGA=4	62 (78.5%)	63 (75.9%)	125 (77.2%)
Baseline EASI Score (range: 0-72)			
Mean (SD)	33.1 (12.18)	35.1 (13.88)	34.1 (13.08)
Median	32.0	33.2	32.8
Q1:Q3	24.0:38.0	23.4:44.6	23.8:40.4
Min:Max	12:72	16:72	12:72
≥25, n (%)	58 (73.4%)	59 (71.1%)	117 (72.2%)
<25, n (%)	21 (26.6%)	24 (28.9%)	45 (27.8%)
SCORing Atopic Dermatitis (SCORAD) score (range: 0-103)			
Mean (SD)	72.2 (11.44)	72.7 (12.95)	72.4 (12.20)
Median	72.1	73.6	72.2
Q1:Q3	65.0:79.0	61.9:81.4	64.0:80.5
Min:Max	41:98	47:98	41:98

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
BSA of atopic dermatitis			
Mean (SD)	57.4 (20.91)	59.3 (22.51)	58.4 (21.70)
Median	54.5	56.0	55.3
Q1:Q3	41.0:74.0	42.0:78.0	41.0:76.0
Min:Max	14:100	19:100	14:100
Caregiver Global Impression of Disease, n (%)			
Moderate	10 (12.7%)	12 (14.5%)	22 (13.6%)
Severe	42 (53.2%)	43 (51.8%)	85 (52.5%)
Very severe	27 (34.2%)	28 (33.7%)	55 (34.0%)
Patient Oriented Eczema Measure (POEM) (range: 0-28)			
Mean (SD)	23.3 (4.04)	23.1 (4.49)	23.2 (4.26)
Median	24.0	24.0	24.0
Q1:Q3	21.0:27.0	20.0:27.0	20.0:27.0
Min:Max	9:28	9:28	9:28
Children's Dermatology Life Quality Index (CDLQI) (range: 0-30)			
Total Score			
n	38	48	86
Mean (SD)	17.7 (6.25)	17.5 (5.43)	17.6 (5.77)
Median	17.5	18.0	18.0
Q1:Q3	11.0:23.0	13.0:21.5	13.0:22.0
Min: Max	5:28	7:29	5:29
Infants' Dermatitis Quality of Life Index (IDQOL) (range: 0-30)			
Total Score			
n	41	35	76
Mean (SD)	17.1 (5.37)	17.4 (5.41)	17.2 (5.35)
Median	17.0	17.0	17.0
Q1:Q3	14.0:20.0	13.0:21.0	13.5:21.0
Min:Max	5:28	7:29	5:29
Global Individual Signs Score (GISS) (range: 0-12)			
n	79	83	162
Mean (SD)	9.6 (1.76)	9.7 (1.79)	9.7 (1.77)
Median	10.0	10.0	10.0
Q1:Q3	8.0:11.0	8.0:11.0	8.0:11.0
Min:Max	6:12	5:12	5:12
Dermatitis Family Impact Questionnaire (DFI) (range: 0-30)			
n	79	83	162
Mean (SD)	17.6 (7.24)	17.2 (5.99)	17.4 (6.61)
Median	19.0	17.0	18.0
Q1:Q3	12.0:23.0	13.0:21.0	13.0:22.0
Min:Max	3:29	5:30	3:30
Weekly average of daily skin pain score (range: NRS 0-10)			
n	78	81	159
Mean (SD)	7.2 (1.84)	6.8 (1.76)	7.0 (1.80)
Median	7.6	6.8	7.1
Q1:Q3	5.8:8.7	5.9:7.9	5.9:8.3
Min:Max	2:10	1:10	1:10

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Weekly average of daily patient's sleep quality score [1] (range: NRS 0-10)			
n	79	81	160
Mean (SD)	4.6 (2.09)	4.9 (1.90)	4.8 (2.00)
Median	4.7	5.0	4.8
Q1:Q3	3.4:6.0	3.6:6.1	3.5:6.1
Min:Max	0:9	0:9	0:9
Weekly average of daily caregiver's sleep quality score [1] (range: NRS 0-10)			
n	79	81	160
Mean (SD)	4.7 (2.06)	5.1 (1.91)	4.9 (1.99)
Median	5.0	5.2	5.0
Q1:Q3	3.3:6.1	3.8:6.6	3.6:6.2
Min:Max	0:9	0:9	0:9

Abbreviations: BSA=body surface area; EASI= Eczema Area and Severity Index; FAS=full analysis set; IGA=Investigator Global Assessment; Max=maximum; Min=minimum; NRS=numerical rating scale; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation; TCS=topical corticosteroids.
Note: AD duration=baseline age - AD onset age; if AD onset age is missing but AD onset category is available,¬ AD duration=baseline age - lowest age within the selected onset category (e.g. 6 months for 'Between the age of 6 months and less than 6 years old').
The Dermatitis Family Impact Questionnaire (DFI) is referred to as the Dermatitis Family Index (DFI) in the post-text Tables.
[1]: Higher scores represent better quality of sleep.
Source: PTT 4.2.1/1

Table 24 Baseline Disease Characteristics for Participants with Severe AD (Baseline IGA=4)

	Placebo + TCS (N=62)	Dupilumab 200/300mg Q4W + TCS (N=63)	Total (N=125)
Age at disease onset group, n (%)			
<6 months	44 (71.0%)	36 (57.1%)	80 (64.0%)
>=6 months	18 (29.0%)	27 (42.9%)	45 (36.0%)
Duration of atopic dermatitis (years)			
n	62	63	125
Mean (SD)	3.5 (1.27)	3.3 (1.44)	3.4 (1.35)
Median	3.3	3.6	3.6
Q1 : Q3	2.8 : 4.5	2.1 : 4.5	2.6 : 4.5
Min : Max	0 : 6	0 : 6	0 : 6
Number of patients with duration of atopic dermatitis (years),n (%)			
<3 years	22 (35.5%)	23 (36.5%)	45 (36.0%)
≥3 years	40 (64.5%)	40 (63.5%)	80 (64.0%)
Weekly average of daily worst scratch/itch score (range: NRS 0-10)			
n	62	63	125
Mean (SD)	7.6 (1.56)	7.6 (1.41)	7.6 (1.48)
Median	7.7	7.4	7.6
Q1 : Q3	6.8 : 8.6	6.6 : 8.5	6.6 : 8.5
Min : Max	2 : 10	4 : 10	2 : 10

	Placebo + TCS (N=62)	Dupilumab 200/300mg Q4W + TCS (N=63)	Total (N=125)
≥7, n(%)	45 (72.6%)	40 (63.5%)	85 (68.0%)
<7, n(%)	17 (27.4%)	23 (36.5%)	40 (32.0%)
Baseline EASI score (range: 0-72)			
n	62	63	125
Mean (SD)	35.4 (12.04)	38.8 (13.66)	37.1 (12.94)
Median	33.6	36.0	34.7
Q1 : Q3	28.5 : 39.1	29.5 : 45.7	29.2 : 44.6
Min : Max	12 : 72	18 : 72	12 : 72
>=25, n(%)	52 (83.9%)	54 (85.7%)	106 (84.8%)
<25, n(%)	10 (16.1%)	9 (14.3%)	19 (15.2%)
SCORing Atopic Dermatitis (SCORAD) score (range: 0-103)			
n	62	63	125
Mean (SD)	74.8 (10.81)	76.7 (11.49)	75.8 (11.16)
Median	74.0	76.8	75.1
Q1 : Q3	67.6 : 81.4	69.2 : 83.2	68.8 : 81.9
Min : Max	50 : 98	50 : 98	50 : 98
BSA of atopic dermatitis			
n	62	63	125
Mean (SD)	58.9 (21.37)	63.1 (21.10)	61.0 (21.25)
Median	57.0	63.0	60.0
Q1 : Q3	42.0 : 77.0	47.0 : 80.0	44.5 : 79.0
Min : Max	14 : 100	19 : 100	14 : 100
Caregiver Global Impression of Disease, n (%)			
Moderate	9 (14.5%)	7 (11.1%)	16 (12.8%)
Severe	31 (50.0%)	31 (49.2%)	62 (49.6%)
Very severe	22 (35.5%)	25 (39.7%)	47 (37.6%)
Patient Oriented Eczema Measure (POEM) (range: 0-28)			
n	62	63	125
Mean (SD)	23.4 (3.97)	23.7 (3.93)	23.6 (3.93)
Median	24.0	24.0	24.0
Q1 : Q3	21.0 : 27.0	20.0 : 28.0	21.0 : 27.0
Min : Max	9 : 28	14 : 28	9 : 28
Children's Dermatology Life Quality Index (CDLQI) (range: 0-30) Total Score			
n	32	38	70
Mean (SD)	17.8 (6.42)	17.5 (5.54)	17.6 (5.92)
Median	18.0	18.5	18.0
Q1 : Q3	11.0 : 23.0	14.0 : 21.0	12.0 : 23.0
Min : Max	5 : 28	7 : 29	5 : 29
Infants' Dermatitis Quality of Life Index (IDQOL) (range: 0-30) Total Score			
n	30	25	55
Mean (SD)	17.4 (5.44)	18.4 (5.07)	17.8 (5.25)
Median	17.0	19.0	17.0
Q1 : Q3	14.0 : 21.0	14.0 : 22.0	14.0 : 22.0
Min : Max	5 : 28	10 : 29	5 : 29

	Placebo + TCS (N=62)	Dupilumab 200/300mg Q4W + TCS (N=63)	Total (N=125)
Global Individual Signs Score (GISS) (range: 0-12)			
n	62	63	125
Mean (SD)	10.1 (1.51)	10.3 (1.47)	10.2 (1.49)
Median	10.0	10.0	10.0
Q1 : Q3	9.0 : 12.0	9.0 : 12.0	9.0 : 12.0
Min : Max	7 : 12	7 : 12	7 : 12
Dermatitis Family Impact Questionnaire (DFI) (range: 0-30)			
n	62	63	125
Mean (SD)	17.4 (7.51)	17.6 (6.02)	17.5 (6.78)
Median	19.0	18.0	18.0
Q1 : Q3	10.0 : 23.0	13.0 : 21.0	13.0 : 22.0
Min : Max	3 : 29	5 : 30	3 : 30
Weekly average of daily skin pain score (range: NRS 0-10)			
n	61	62	123
Mean (SD)	7.1 (1.91)	6.9 (1.88)	7.0 (1.89)
Median	7.6	6.7	7.1
Q1 : Q3	5.9 : 8.5	5.9 : 7.9	5.9 : 8.3
Min : Max	2 : 10	1 : 10	1 : 10
Weekly average of daily patient's sleep quality score [1] (range: NRS 0-10)			
n	62	62	124
Mean (SD)	4.7 (2.03)	4.9 (1.98)	4.8 (2.00)
Median	4.7	5.1	4.9
Q1 : Q3	3.4 : 6.0	3.5 : 6.3	3.5 : 6.1
Min : Max	0 : 9	0 : 9	0 : 9
Weekly average of daily caregiver's sleep quality score [1] (range: NRS 0-10)			
n	62	62	124
Mean (SD)	4.8 (1.99)	5.1 (2.01)	4.9 (2.00)
Median	5.0	5.3	5.0
Q1 : Q3	3.3 : 6.1	3.8 : 6.7	3.6 : 6.3
Min : Max	0 : 9	0 : 9	0 : 9

Abbreviations: BSA=body surface area; EASI= Eczema Area and Severity Index; FAS=full analysis set; IGA=Investigator Global Assessment; Max=maximum; Min=minimum; NRS=numerical rating scale; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SCORAD=SCORing Atopic Dermatitis; SD=standard deviation; TCS=topical corticosteroids.
Note: AD duration=baseline age - AD onset age; if AD onset age is missing but AD onset category is available,¬ AD duration=baseline age - lowest age within the selected onset category (e.g. 6 months for 'Between the age of 6 months and less than 6 years old').
The Dermatitis Family Impact Questionnaire (DFI) is referred to as the Dermatitis Family Index (DFI) in the post-text Tables.
[1]: Higher scores represent better quality of sleep.
Source: PTT 4.2.2/25

Medical History and Concurrent Illnesses

A summary of disease history is provided in *Table* ***25***.

Table 25 Summary of Prior Atopic/Allergic Disease History – Part B (SAF)

	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Number (%) of Patients with current history of Atopic/Allergic Conditions			
Atopic dermatitis	78 (100%)	83 (100%)	161 (100%)
Food allergy	55 (70.5%)	55 (66.3%)	110 (68.3%)
Other allergies	42 (53.8%)	43 (51.8%)	85 (52.8%)
Allergic rhinitis	36 (46.2%)	35 (42.2%)	71 (44.1%)
Asthma	21 (26.9%)	20 (24.1%)	41 (25.5%)
Hives	15 (19.2%)	14 (16.9%)	29 (18.0%)
Allergic conjunctivitis (keratoconjunctivitis)	3 (3.8%)	4 (4.8%)	7 (4.3%)
Eosinophilic esophagitis	1 (1.3%)	2 (2.4%)	3 (1.9%)
Chronic rhinosinusitis	2 (2.6%)	1 (1.2%)	3 (1.9%)
Number (%) of Patients with current history of Atopic/Allergic Conditions excluding Atopic Dermatitis	65 (83.3%)	66 (79.5%)	131 (81.4%)
Number (%) of Patients with family history of Atopic/Allergic Conditions			
Atopic dermatitis	50 (64.1%)	52 (62.7%)	102 (63.4%)
Allergic rhinitis	36 (46.2%)	42 (50.6%)	78 (48.4%)
Asthma	35 (44.9%)	37 (44.6%)	72 (44.7%)
Other allergies	27 (34.6%)	34 (41.0%)	61 (37.9%)
Food allergy	24 (30.8%)	25 (30.1%)	49 (30.4%)
Allergic conjunctivitis (keratoconjunctivitis)	9 (11.5%)	11 (13.3%)	20 (12.4%)
Hives	8 (10.3%)	11 (13.3%)	19 (11.8%)
Chronic rhinosinusitis	4 (5.1%)	5 (6.0%)	9 (5.6%)
Nasal polyps	3 (3.8%)	4 (4.8%)	7 (4.3%)
Eosinophilic esophagitis	0	1 (1.2%)	1 (0.6%)

Abbreviations: AD=atopic dermatitis; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
Source: PTT 4.3.1/2

Prior Medications and Procedures

There were no meaningful differences between the treatment groups in the use of prior medications or procedures, see *Table **26***.

Table 26 Summary of Prior Systemic Corticosteroids and/or Systemic Nonsteroidal Immunosuppressants for Atopic Dermatitis – Part B (SAF)

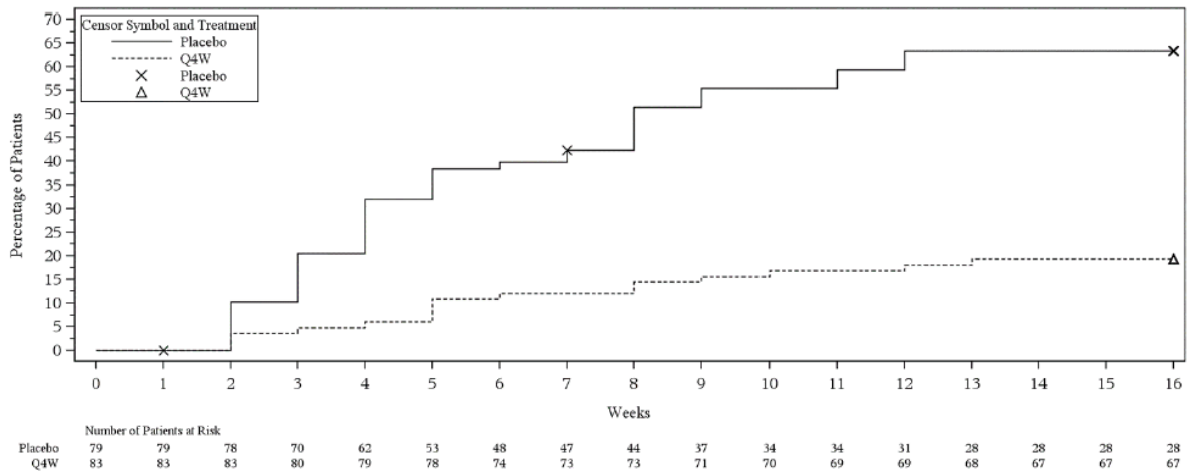
	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Patients receiving prior systemic corticosteroids and/or systemic nonsteroidal immunosuppressants for AD, n (%)	22 (28.2%)	24 (28.9%)	46 (28.6%)
Patients receiving prior systemic corticosteroids	14 (17.9%)	16 (19.3%)	30 (18.6%)
Patients receiving prior systemic non-steroidal immunosuppressants	12 (15.4%)	13 (15.7%)	25 (15.5%)
Azathioprine	1 (1.3%)	0	1 (0.6%)
Cyclosporine	7 (9.0%)	10 (12.0%)	17 (10.6%)
Methotrexate	7 (9.0%)	4 (4.8%)	11 (6.8%)
Mycophenolate	1 (1.3%)	1 (1.2%)	2 (1.2%)

Abbreviations: AD=atopic dermatitis; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
Data summarized were collected from the concomitant medications for AD CRF.
Source: PTT 4.4.5/2

Rescue Medications

The first use of rescue medication is displayed in ***Figure 28***, Kaplan Meier Curve.

Figure 28 Kaplan Meier Curves of Time to First Rescue Treatment Use During the 16-week Treatment Period in Study R668-AD-1539 Part B (FAS)



Abbreviations: FAS=full analysis set; Q4W=every 4 weeks.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 4.4.1/1

Treatment Compliance

The mean injection compliance with study treatment was approximately 99% in each treatment group and was similar across the 2 treatment groups (*Table **27***).

Table 27 Compliance with Study Treatment in Study R668-AD-1539 Part B (SAF)

Exposure Characteristics	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Injection Compliance			
n	78	83	161
Mean (SD)	99.36 (3.977)	99.70 (2.744)	99.53 (3.391)
Q1	100.00	100.00	100.00
Median	100.00	100.00	100.00
Q3	100.00	100.00	100.00
Min: Max	75.0: 100.0	75.0: 100.0	75.0: 100.0
Injection Compliance, n(%)			
≥80%	76 (97.4%)	82 (98.8%)	158 (98.1%)
< 80%	2 (2.6%)	1 (1.2%)	3 (1.9%)

Abbreviations: Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SAF=safety analysis set; SD=standard deviation; TCS=topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 5.1.1/1

All patients were to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization and were to continue to apply moisturizers throughout the study. The mean background treatment compliance was high and similar across the 2 treatment groups with a mean compliance of approximately 80% in each treatment group (*Table **28***).

Table 28 Compliance with Background Emollient Treatment in Study R668-AD-1539 Part B (FAS)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)
Compliance (%)		
n	79	83
Mean (SD)	78.3 (24.43)	80.9 (20.36)
Median	87.5	89.3
Min: Max	10: 99	7: 99

Abbreviations: FAS=full analysis set; Max=maximum; Min=minimum; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
The compliance rate for the background treatment used within 7 days before the baseline visit through end of study is defined as the (number of days background treatment used during the period) / (number of days within the period)x100%.
Note: Only emollients are included in this summary.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 4.4.4/2

Numbers analysed

A summary of Study analysis sets is provided in *Table **29***. One participant in the placebo +TCS treatment group was excluded from the safety analysis set (SAF) and the pharmacokinetic analysis set (PKAS) as this participant was randomized in error and did not receive study treatment (hence not included in SAF) and did not have blood samples taken for assessment of dupilumab levels in blood (hence not included in PKAS).The anti-drug antibody analysis set (AAS) included 143 participants, 69 in the placebo +TCS treatment group and 74 in the dupilumab +TCS treatment group.

Table 29 Summary of Study Analysis Sets – Part B (All Randomised Participants)

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
All Randomized Patients	79	83	162
Patients Included in the Safety Analysis Set (SAF), n (%)	78 (98.7%)	83 (100.0%)	161 (99.4%)
Patients Excluded from Safety Analysis Set (Not Treated), n (%)	1 (1.3%)	0	1 (0.6%)
Other: patient randomized in error.	1 (1.3%)	0	1 (0.6%)
Patients Entered follow-up period, n(%) [1][2]	19 (24.4%)	19 (22.9%)	38 (23.6%)
Patients Included in the Full Analysis Set (FAS), n(%)	79 (100%)	83 (100%)	162 (100%)
Patients Excluded from FAS, n(%)	0	0	0
Patients Included in the Pharmacokinetic Analysis Set (PKAS), n (%)	78 (98.7%)	83 (100%)	161 (99.4%)
Patients Included in the ADA Analysis Set (AAS), n (%)	69 (87.3%)	74 (89.2%)	143 (88.3%)

Abbreviations: AAS=anti-drug antibody analysis set; ADA=anti-drug antibody; FAS=full analysis set; PKAS=pharmacokinetic analysis set; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
The percentage is based on the number of randomized patients in each treatment group as denominator.
[1] For patients who did not have week 16 visit¬Day 113 or last visit day was used whichever comes first.
[2] n (%) based on SAF population.
Source: PTT 3.1.1/1

Outcomes and estimation

Co-Primary Efficacy Endpoints

A summary of efficacy results is provided in ***Table 30*** and the proportion of patients with IGA 0/1 from Baseline to Week 16 in *Figure* ***29*** below. The primary efficacy analyses were based on the full analysis set (FAS), which included all randomized patients.

Table 30 Summary of Key Efficacy Results for R668-AD-1539 Part B (FAS)

Endpoint	Placebo + TCS (N=79)	Dupilumab 200/300 mg Q4W+ TCS (N=83)	Treatment Difference (95% CI) P-value[1]
Primary/Co-primary Endpoint(s)			
Proportion of patients with IGA 0 or 1 at Week 16, n (%)	3 (3.9)	23 (27.7)	23.8 (13.27, 34.37) <0.0001
Proportion of patients achieving EASI-75 at Week 16, n (%)[2]	8 (10.7)	44 (53.0)	42.3 (29.47, 55.16) <0.0001
Key Secondary Endpoints			
Percent change from baseline in EASI score at Week 16, LS mean (SE)	-19.6 (5.13)	-70.0 (4.85)	-50.4 (-62.38, -38.40) <0.0001
Percent change from baseline in worst scratch/itch NRS at Week 16, LS mean (SE)	-2.2 (5.22)	-49.4 (5.03)	-47.1 (-59.47, -34.79) <0.0001
Other Secondary Endpoints			
Proportion of patients with improvement (reduction) of worst scratch/itch NRS ≥4 from baseline at Week 16, n (%)	7 (8.9)	40 (48.1)	39.2 (26.18, 52.27) <0.0001

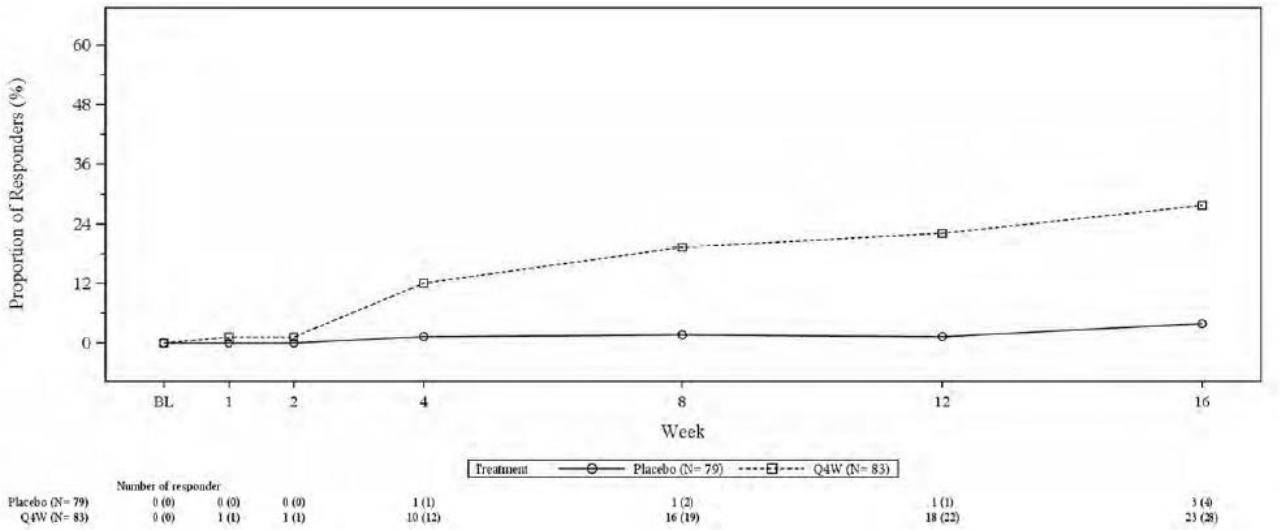
Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; EASI-75=75% reduction in EASI; FAS=full analysis set; IGA=Investigator's Global Assessment; LS=least square; NRS=numeric rating scale; Q4W=every 4 weeks; SE=standard error; TCS=topical corticosteroids

[1] Categorical endpoints: difference is dupilumab minus placebo. CI calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]). The stratum (region=EU, baseline weight<15 kg, IGA=3) was combined with the stratum (region=EU, baseline weight ≥15 kg, IGA=3) as the former had only 2 patients. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of IGA score due to other reasons including COVID-19 were imputed by multiple imputation (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40. Continuous endpoints: the CI with p-value is based on treatment difference (dupilumab group vs. placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.

[2] Co-primary endpoint in the European Union and European Union reference market countries and key secondary endpoint in United States and United States reference market countries.

Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Tables 6.1.1.1/1, 6.1.2.1/1, 6.2.1.1/1, 6.2.2.1/1, and 6.2.4.1/1.

Figure 29 Proportion of Patients with IGA 0 or 1 from Baseline to Week 16 in Study R668-AD-1539 Part B (FAS)



Abbreviations: BL=baseline; FAS=full analysis set; IGA=Investigator Global Assessment; Q4W=every 4 weeks;
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of IGA score due to other reasons including COVID-19 were imputed by multiple imputation, and the response status was then derived.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.1.1.1/1

In sensitivity analysis using all observed values regardless of rescue treatment use, with patients with missing values (those that dropped out early from the study) counted as non-responders (***Table 31***) and in last observation carried forward (LOCF) sensitivity analysis with values after first rescue treatment use set to missing and then using LOCF method to impute the missing data (***Table 32***), the results were consistent with the primary analysis and showed the proportion of patients with IGA 0 or 1 at week 16 was higher in the dupilumab + TCS group than in the placebo + TCS group

Table 31 Sensitivity Analysis of Proportion of Patients with IGA 0 or 1 at Week 16 in Study R668-AD-1539, All Observed Values Regardless of Rescue Treatment Use – Part B (FAS)

Treatment	Patients with IGA 0 or 1 n(%)	95% CI	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	25 (30.1)	(20.53, 41.18)	25.1(14.07, 36.05)	<0.0001
Placebo + TCS (N=79)	4 (5.1)	(1.40, 12.46)		

Abbreviations: CI=confidence interval; FAS=full analysis set; IGA=Investigator Global Assessment; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: Patients with missing score at each visit were considered as a non-responder.
[1] Difference is dupilumab minus placebo. CI = Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5- <15 kg vs ≥15- <30 kg]. The stratum (region = EU, baseline weight<15 kg, IGA=3) is combined with the stratum (region = EU, baseline weight ≥15 kg, IGA=3) as the former has only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.1.3/3

Table 32 Sensitivity Analysis of Proportion of Patients with IGA 0 or 1 at Week 16 in Study R668-AD-1539, LOCF – Part B (FAS)

Treatment	Patients with IGA 0 or 1 n(%)	95% CI	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	23 (27.7)	(18.45, 38.62)	23.9(13.40, 34.42)	<0.0001
Placebo + TCS (N=79)	3 (3.8)	(0.79, 10.70)		

Abbreviations: CI=confidence interval; FAS=full analysis set; IGA=Investigator Global Assessment; LOCF=Last observation carried forward; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing, then LOCF method was used to impute the missing data to determine patient's status (responder yes or no) at each visit.
[1] Difference is dupilumab minus placebo. CI = Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]. The stratum (region = EU, baseline weight<15 kg, IGA=3) is combined with the stratum (region = EU, baseline weight >= 15 kg, IGA=3) as the former has only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.1.3/2

Proportion of Patients with EASI-75

The proportion of patients in the FAS achieving EASI-75 (≥75% improvement from baseline) at week 16 was higher in the dupilumab + TCS group (44/83; 53.0%) than in the placebo + TCS group (8/79; 10.7%) (*Table **33***). The difference was statistically significant (p<0.0001).

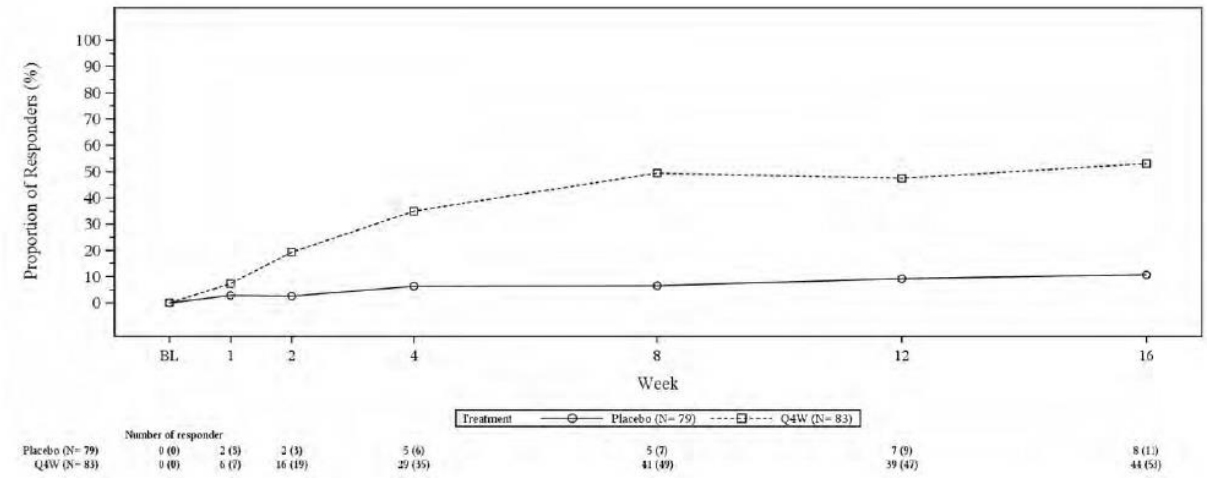
Table 33 Primary Analysis of Proportion of Patients Achieving EASI-75 (≥75% improvement from baseline) at week 16 in Study R668-AD-1539 - Part B (FAS)

Treatment	Patients with EASI-75 at Week 16 n(%)	95% CI [1]	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	44 (53.0)	(41.74, 64.07)	42.3 (29.47, 55.16)	<0.0001
Placebo + TCS (N=79)	8 (10.7)	(3.65, 17.74)		

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of EASI score due to other reasons including COVID-19 were imputed by (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] Difference is dupilumab minus placebo. CI calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]). The stratum (region=EU, baseline weight<15 kg, IGA=3) was combined with the stratum (region=EU, baseline weight ≥15 kg, IGA=3) as the former had only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.2.1/1

As shown in *Figure **30***, when compared to the placebo + TCS group, a greater proportion of patients in the DUP+TCS treatment group achieved EASI-75 by as early as week 2 (nominal p=0.0022 at week 2) and this treatment group difference was sustained throughout the remainder of the 16-week treatment period (nominal p<0.0001 at all subsequent measurements through week 16).

Figure 30 Proportion of Patients Achieving EASI-75 (≥75% improvement from baseline) to week 16 in Study R668-AD-1539 - Part B (FAS)



Abbreviations: BL=baseline; EASI=Eczema Area and Severity Index; FAS=full analysis set; Q4W=every 4 weeks.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of EASI score due to other reasons including COVID-19 were imputed by multiple imputation, and the response status was then derived.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.1.1.2/1

Rescue treatment use had minimal impact on the study results. In sensitivity analysis using all observed values regardless of rescue treatment use, with patients with missing values (those that dropped out early from the study) counted as non-responders (*Table **34***) and in LOCF sensitivity analysis with values after first rescue treatment use set to missing and then using LOCF method to impute the missing data (*Table **35***), the results were consistent with the primary analysis and showed the proportion of patients achieving EASI-75 (≥75% improvement from baseline) at week 16 was higher in the dupilumab + TCS group than in the placebo + TCS group.

Table 34 Sensitivity Analysis of Proportion of Patients Achieving EASI-75 (≥75% improvement from baseline) at week 16 in Study R668-AD-1539, All Observed Values Regardless of Rescue Treatment Use – Part B (FAS)

Treatment	Patients with EASI-75 n(%)	95% CI	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	53 (63.9)	(52.57, 74.12)	47.4(34.22, 60.58)	<0.0001
Placebo + TCS (N=79)	13 (16.5)	(9.06, 26.49)		

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: Patients with missing score at each visit were considered as a non-responder.
[1] Difference is dupilumab minus placebo. CI = Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]. The stratum (region = EU, baseline weight<15 kg, IGA=3) is combined with the stratum (region = EU, baseline weight ≥15 kg, IGA=3) as the former has only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.2.3/3

Table 35 Sensitivity Analysis of Proportion of Patients Achieving EASI-75 (≥75% improvement from baseline) at week 16 in Study R668-AD-1539, LOCF – Part B (FAS)

Treatment	Patients with EASI-75 n(%)	95% CI	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	47 (56.6)	(45.29, 67.47)	45.2(32.48, 57.99)	<0.0001
Placebo + TCS (N=79)	9 (11.4)	(5.34, 20.53)		

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; LOCF=last observation carried forward; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing, then LOCF method was used to impute the missing data to determine patient's status (responder yes or no) at each visit.
[1] Difference is dupilumab minus placebo. C.I. = Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]. The stratum (region = EU, baseline weight<15 kg, IGA=3) is combined with the stratum (region = EU, baseline weight ≥ 15 kg, IGA=3) as the former has only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.2.3/2

Efficacy Analysis in Patients with Severe AD

A prespecified sub-population analysis was performed for patients with severe AD (IGA 4) in study R668-AD-1539 Part B. A similar approach for statistical analysis as that used in the overall population was used for this sub-population analysis. Endpoints in this sub-population were not included in the statistical testing hierarchy and, therefore, nominal p-values are provided. A summary of the results for the co-primary and the secondary endpoints for patients with severe AD at baseline is provided in *Table **36***.

Table 36 Summary of Key Efficacy Results for Patients with Baseline IGA=4 in R668-AD-1539 – Part B (FAS, Baseline IGA=4)

Endpoint	Placebo + TCS (N=62)	Dupilumab 200/300 mg Q4W+ TCS (N=63)	Treatment Difference (95% CI) P-value[1]
Primary/Co-primary Endpoint(s)			
Proportion of Patients with IGA 0 or 1 at Week 16, n (%)	1 (1.7)	9 (14.3)	12.6 (3.28, 21.82) 0.0194
Proportion of Patients achieving EASI-75 at Week 16, n (%)[2]	4 (7.2)	29 (46.0)	38.9 (24.79, 52.92) <0.0001
Key Secondary Endpoints			
Percent change from baseline in EASI score at Week 16, LS mean (SE)	-10.3 (5.16)	-55.4 (5.01)	-45.1 (-59.21, -30.97) <0.0001
Percent change from baseline in worst scratch/itch NRS at Week 16, LS mean (SE)	0.5 (5.40)	-41.8 (5.35)	-42.3 (-57.18, -27.38) <0.0001
Other Secondary Endpoints			
Proportion of patients with improvement (reduction) of worst scratch/itch NRS ≥4 from baseline at Week 16, n (%)	5 (8.8)	27 (42.3)	33.5 (19.01, 47.97) 0.0002

Abbreviations: EASI=Eczema Area and Severity Index; EASI-75=75% reduction in EASI; FAS=full analysis set; IGA=Investigator's Global Assessment; LS=least square; NRS=numeric rating scale; Q4W=every 4 weeks; SE=standard error; TCS=topical corticosteroids.

Note: Subpopulation analysis of patients with IGA=4 at baseline was prespecified in the SAP but was not included in the testing hierarchy, therefore nominal p-values were provided.

[1] Categorical endpoints: difference is dupilumab minus placebo. C.I = Confidence interval calculated using normal approximation. P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]). The stratum (region=EU, baseline weight<15 kg, IGA=3) was combined with the stratum (region=EU, baseline weight ≥15 kg, IGA=3) as the former had only 2 patients. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of IGA score due to other reasons including COVID-19 were imputed by multiple imputation (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
Continuous endpoints: the confidence interval (CI) with p-value is based on treatment difference (dupilumab group vs. placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by MI. All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.

[2] Co-primary endpoint in the European Union and European Union reference market countries and key secondary endpoint in the United States and United States reference market countries.

Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Tables 6.1.1.2/13, 6.1.2.2/13, 6.2.1.2/13, 6.2.2.2/13, and 6.2.4.2/13.

Key Secondary Efficacy Endpoints

Percent Change in EASI Score from Baseline to Week 16

Results of the Primary analysis of the Percent Change from baseline in EASI score at Week 16 are presented in *Table **37***. The least squares (LS) mean percent change (reduction indicates improvement) from baseline to week 16 in EASI score was greater in the dupilumab + TCS (−70.0%) group than in the placebo + TCS group (−19.6%). The LS mean difference in the percent change from baseline to week 16 in EASI score was statistically significant between the dupilumab + TCS group and the placebo + TCS group (p<0.0001).

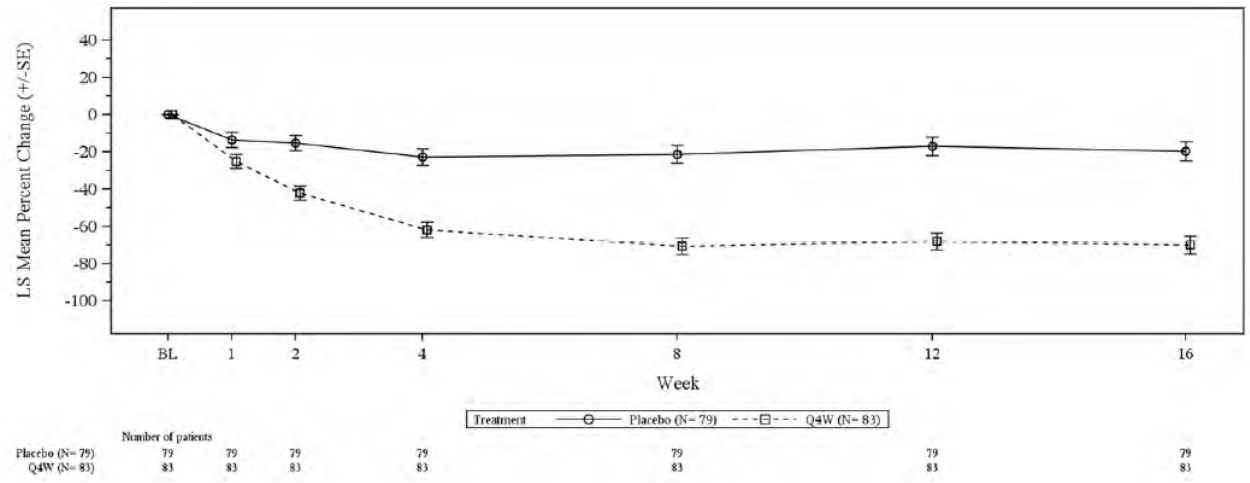
Table 37 Primary Analysis of Percent Change from Baseline in EASI Score at Week 16 in Study R668-AD-1539 – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value[1]	LS Mean Difference (95% CI)[1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-70.0 (4.85)	(-79.5, -60.5)	-63.1 (36.05)	35.13 (13.885)	67/16	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-50.4 (-62.38, -38.40)
Placebo + TCS (N=79)	-19.6 (5.13)	(-29.7, -9.6)	-11.4 (42.24)	33.07 (12.176)	28/51			

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; LS=least squares; Q4W=every 4 weeks; SE=standard error; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] The CI with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.1.1/1

The temporal variation of the LS mean percent change from baseline in EASI score in both treatment groups is displayed in *Figure **31***.

Figure 31 Percent Change from Baseline in EASI Score from Baseline to Week 16 in Study R668-AD-1539 – Part B (FAS)



Abbreviations: BL=baseline; EASI=Eczema Area and Severity Index; FAS=full analysis set; LS=least squares; Q4W=every 4 weeks; SE=standard error.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for MI.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.2.1.1/1

Sensitivity analysis were performed to isolate the treatment effect of dupilumab independent of rescue treatment. *Table **38*** shows the analysis using all observed values regardless of rescue treatment use. In *Table **39***, results of LOCF sensitivity analysis are presented with values after first rescue treatment use set to missing and then using LOCF method to impute the missing data.

Table 38 Sensitivity Analysis of Percent Change from Baseline in EASI Score to Week 16 in Study R668-AD-1539, All Observed Values Regardless of Rescue Treatment Use – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI)[1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-74.5 (3.96)	(-82.3 , -66.7)	-72.4 (26.85)	35.13 (13.885)	83	Dupilumab 200/ 300mg Q4W + TCS vs Placebo + TCS	<0.0001	-32.3 (-42.19, -22.41)
Placebo + TCS (N=79)	-42.2 (4.20)	(-50.5 , -33.9)	-39.5 (35.64)	33.22 (12.160)	76			

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; LS=least squares; Q4W=every 4 weeks; SE=standard error; SD=standard deviation; TCS=topical corticosteroids.
[1] The CI with p-value is based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.1.1/5

Table 39 Sensitivity Analysis of Percent Change from Baseline in EASI Score to Week 16 in Study R668-AD-1539, LOCF – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-74.1 (4.20)	(-82.3, -65.8)	-70.0 (28.14)	35.13 (13.885)	67/16	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-46.1 (-56.55, -35.72)
Placebo + TCS (N=79)	-27.9 (4.43)	(-36.7, -19.2)	-23.3 (38.74)	33.33 (12.023)	28/50			

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; LOCF=last observation carried forward; LS=least squares; Q4W=every 4 weeks; SE=standard error; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing, then LOCF method was used to impute the missing data at each visit.
[1] The CI with p-value is based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.1.1/4

Percent Change in EASI Score from Baseline to Week 16 in Patients with Severe AD

Table 40 Analysis of Percent Change from Baseline in EASI Score at Week 16 for Patients with IGA = 4 – Part B (FAS, Baseline IGA=4)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value[1]	LS Mean Difference (95% CI)[1]
Dupilumab 200/300mg Q4W + TCS (N=63)	-55.4 (5.01)	(-65.2, -45.6)	-56.0 (37.88)	38.82 (13.665)	47/16	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-45.1 (-59.21, -30.97)
Placebo + TCS (N=62)	-10.3 (5.16)	(-20.4, -0.2)	-9.7 (40.63)	35.44 (12.039)	22/40			

Abbreviations: CI=confidence interval; EASI=Eczema Area and Severity Index; FAS=full analysis set; IGA=Investigator Global Assessment; LS=least squares; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, AE, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] The CI with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: PTT 6.2.1.2/13

Percent Change from Baseline to Week 16 in Weekly Average of Worst Scratch/Itch NRS Score from Baseline to Week 16

The mean weekly average of the daily worst scratch/itch NRS score at baseline was similar in both treatment groups (*Table **41***). The LS mean percent change (reduction indicates improvement) from baseline to week 16 in the weekly average of daily worst scratch/itch NRS score was greater in the DUP+TCS (−49.4%) group than in the PBO+TCS group (−2.2%). The LS mean difference in the percent change from baseline to week 16 in the weekly average of daily worst scratch/itch NRS score was statistically significant (p<0.0001).

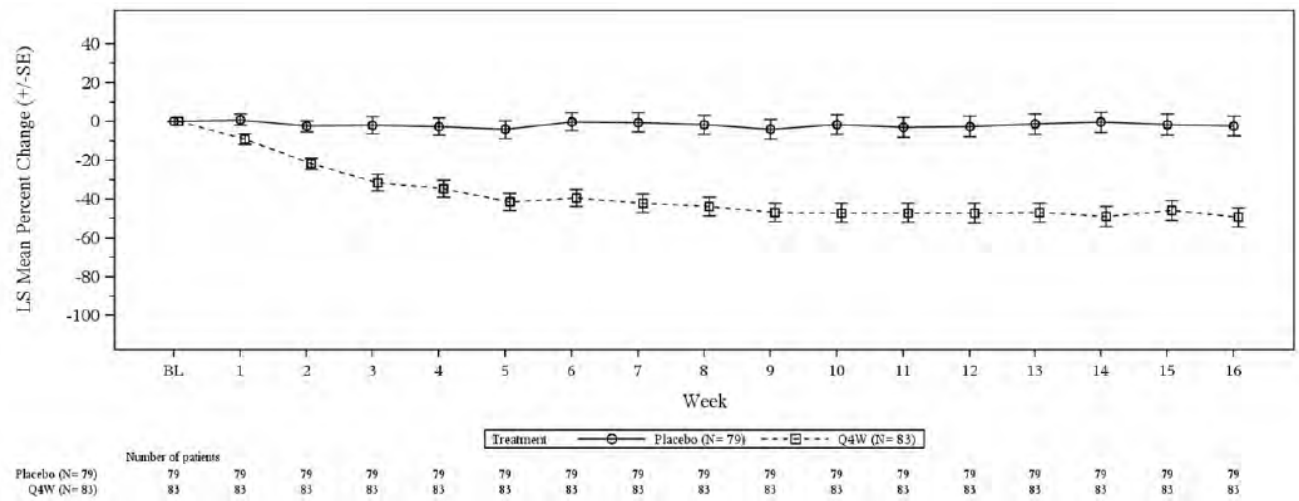
Table 41 Primary Analysis of Percent Change from Baseline in Weekly Average of Daily Worst Scratch/Itch NRS Score at Week 16 in Study R668-AD-1539 – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-49.4 (5.03)	(-59.2 , -39.5)	-46.4 (32.26)	7.51 (1.322)	60/23	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-47.1 (-59.47, -34.79)
Placebo + TCS (N=79)	-2.2 (5.22)	(-12.5 , 8.0)	-0.1 (50.62)	7.63 (1.489)	26/53			

Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; NRS=numeric rating scale; Q4W=every 4 weeks; SE=standard error; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for multiple imputation MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] The CI with p-value was based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group ≥[≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.2.1/1

A greater LS mean percent change from baseline in weekly average of daily worst scratch/itch NRS score was observed in the DUP+TCS group by as early as week 1 (nominal p=0.0039 at week 1). The treatment group difference was sustained throughout the remainder of the 16-week treatment period (nominal p<0.0001 at all subsequent measurements through week 16).

Figure 32 Percent Change from Baseline in Weekly Average of Daily Worst Scratch/Itch NRS Score from Baseline to Week 16 in Study R668-AD-1539 – Part B (FAS)



Abbreviations: BL=baseline; FAS=full analysis set; LS=least squares; NRS=numeric rating scale; Q4W=every 4 weeks; SE=standard error.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for MI.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.2.2.1/1

In sensitivity analysis using all observed values regardless of rescue treatment use (*Table **42***) and in LOCF sensitivity analysis with values after first rescue treatment use set to missing and then using LOCF method to impute the missing data (*Table **43***), the results showed the LS mean percent change (reduction indicates improvement) from baseline to week 16 in the weekly average of daily worst scratch/itch NRS score was greater in the dupilumab + TCS group than in the placebo + TCS group.

Table 42 Sensitivity Analysis of Percent Change from Baseline in Weekly Average of Daily Worst Scratch/Itch NRS Score to Week 16 in Study R668-AD-1539, All Observed Values Regardless of Rescue Treatment Use – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-56.0 (3.72)	(-63.4 , -48.7)	-53.5 (28.70)	7.55 (1.313)	73	Dupilumab 200/ 300mg Q4W + TCS vs Placebo + TCS	<0.0001	-30.7 (-40.14, -21.18)
Placebo + TCS (N=79)	-25.4 (4.03)	(-33.3 , -17.4)	-23.1 (26.64)	7.77 (1.294)	64			

Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; NRS=numeric rating scale; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
[1] The CI with p-value is based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to < 15 kg vs ≥15 to < 30 kg]) as fixed factors.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.2.1/5

Table 43 Sensitivity Analysis of Percent Change from Baseline in Weekly Average of Daily Worst Scratch/Itch NRS Score to Week 16 in Study R668-AD-1539, LOCF – Part B (FAS)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200/300mg Q4W + TCS (N=83)	-53.4 (4.94)	(-63.2, -43.7)	-50.6 (29.97)	7.51 (1.322)	60/23	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-42.4 (-54.66, -30.19)
Placebo + TCS (N=79)	-11.0 (5.12)	(-21.1, -0.9)	-9.4 (52.21)	7.65 (1.492)	26/52			

Abbreviations: CI=confidence interval; FAS=full analysis set; LS=least squares; NRS=numeric rating scale; Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing, then LOCF method was used to impute the missing data at each visit.
[1] The CI with p-value is based on treatment difference (dupilumab group vs placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.2.1/4

Percent Change from Baseline to Week 16 in Weekly Average of Worst Scratch/Itch NRS Score from Baseline to Week 16 in Patients with Severe AD

Table 44 Analysis of Percent Change from Baseline in Weekly Average of Daily Worst Scratch/Itch NRS Score at Week 16 for Patients with IGA = 4 – Part B (FAS, Baseline IGA=4)

Treatment	LS Mean %Change (SE)	LS Mean %Change 95% CI	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value[1]	LS Mean Difference (95% CI)[1]
Dupilumab 200/300mg Q4W + TCS (N=63)	-41.8 (5.35)	(-52.3 , -31.3)	-41.5 (33.27)	7.57 (1.411)	42/21	Dupilumab 200/300mg Q4W + TCS vs Placebo + TCS	<0.0001	-42.3 (-57.18, -27.38)
Placebo + TCS (N=62)	0.5 (5.40)	(-10.1 , 11.0)	0.1 (54.10)	7.64 (1.562)	22/40			

Abbreviations: CI=confidence interval; FAS=full analysis set; IGA=Investigator Global Assessment; LS=least squares, Q4W=every 4 weeks; SD=standard deviation; TCS=topical corticosteroids.
Note: Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were imputed by worst-observation-carried-forward (WOCF) or baseline value if there was no postbaseline value. Patients with missing values due to other reasons including COVID-19 were imputed by multiple imputation (MI). All non-missing data before imputation of WOCF were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] The CI with p-value was based on treatment difference (dupilumab group vs. placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (region [North America vs Europe] and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]) as fixed factors.
Source: PTT 6.2.2.2/13

Other secondary endpoints

Proportion of Patients with Improvement (Reduction) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥4 from Baseline at Week 16

The proportion of patients achieving a reduction of ≥4 points from baseline in the weekly average of daily worst scratch/itch NRS score at week 16 was higher in the DUP+TCS group (40/83; 48.1%) than in the PBO + TCS group (7/78; 8.9%) (*Table **45***). The comparison was statistically significant (p<0.0001).

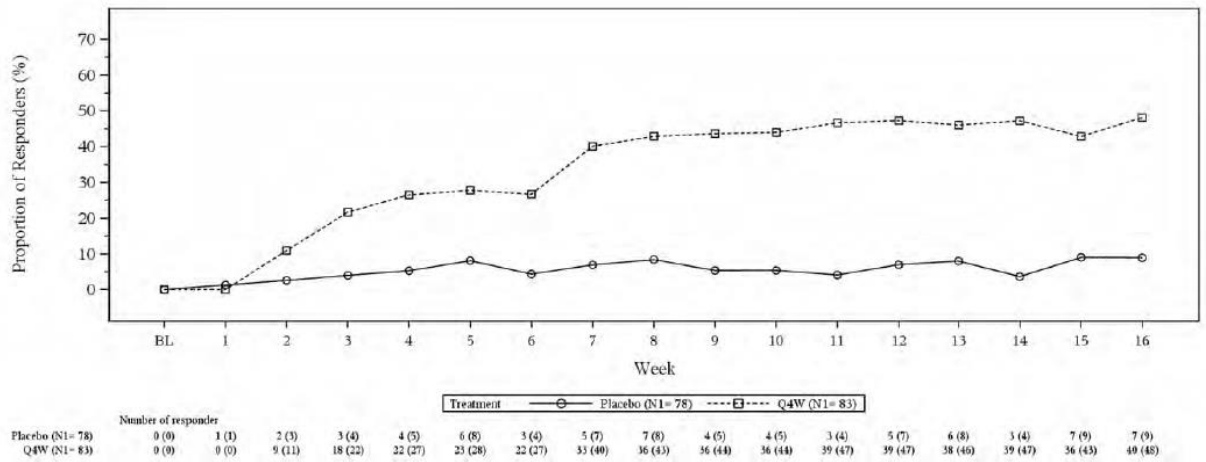
Table 45 Primary Analysis of Proportion of Patients with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥4 points at Week 16 in Study R668-AD-1539– Part B (FAS)

Treatment	Patients achieving NRS Reduction from Baseline ≥4 at Week 16 n/N1(%)	95% CI [1]	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	40/83 (48.1)	(37.05, 59.15)	39.2 (26.18, 52.27)	<0.0001
Placebo + TCS (N=79)	7/78 (8.9)	(2.25, 15.51)		

Abbreviations: CI=confidence interval; FAS=full analysis set; IGA=Investigator Global Assessment; NRS=numeric rating scale; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: N1 stands for number of patients with baseline NRS score ≥4. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of NRS score due to other reasons including COVID-19 were imputed by multiple imputation (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers are 12345 and 54321 with imputation size 40.
[1] Difference is dupilumab minus placebo. CI calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]). The stratum (region=EU, baseline weight<15 kg, IGA=3) was combined with the stratum (region=EU, baseline weight ≥15 kg, IGA=3) as the former had only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.4.1/1

A greater proportion of patients in the DUP+TCS treatment group achieved a reduction of ≥4 points from baseline in weekly average of daily worst scratch/itch NRS score by as early as week 2. The treatment group difference was sustained throughout the remainder of the 16-week treatment period (nominal p<0.01 at all subsequent measurements through week 16.

Figure 33 Proportion of Patients with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥4 Points from Baseline to Week 16 in Study R668-AD-1539– Part B (FAS)



Abbreviations: BL=baseline; FAS=full analysis set; NRS=numeric rating scale; Q4W=every 4 weeks.
Note: N1 stands for number of patients with baseline NRS score ≥4. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of NRS score due to other reasons including COVID-19 were imputed by multiple imputation, and the response status was then derived.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.2.4.1/1

Proportion of Patients with Improvement (Reduction) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥3 from Baseline at Week 16

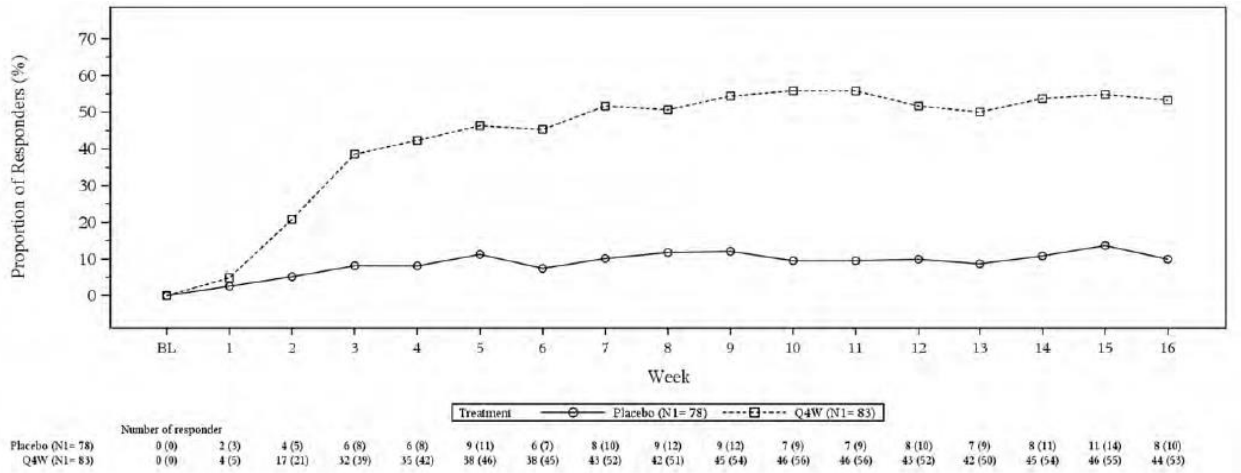
The proportion of patients in the FAS achieving a reduction of ≥3 points from baseline in the weekly average of daily worst scratch/itch NRS score at week 16 was higher in the DUP+TCS (44/83; 53.3%) group than in the PBO+TCS group (8/78; 9.9%) (*Table **46***). The comparison was statistically significant (p<0.0001).

Table 46 Primary Analysis of Proportion of Patients with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥3 Points at Week 16 in Study R668-AD-1539– Part B (FAS)

Treatment	Patients achieving NRS Reduction from Baseline ≥3 at Week 16 n/N1(%)	95% CI [1]	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200/300mg Q4W + TCS (N=83)	44/83 (53.3)	(42.29, 64.22)	43.3 (30.03, 56.67)	<0.0001
Placebo + TCS (N=79)	8/78 (9.9)	(2.59, 17.22)		

Abbreviations: CI=confidence interval; FAS=full analysis set; NRS=numeric rating scale; Q4W=every 4 weeks; TCS=topical corticosteroids.
Note: N1 stands for number of patients with baseline NRS score ≥3. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of NRS score due to other reasons including COVID-19 are imputed by multiple imputation (MI), and the response status was then derived. All non-missing data were used for MI. In MI, the seed numbers were 12345 and 54321 with imputation size 40.
[1] Difference is dupilumab minus placebo. CI calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel (CMH) test stratified by region [North America vs Europe], baseline disease severity [IGA = 3 vs 4], and baseline weight group [≥5 to <15 kg vs ≥15 to <30 kg]). The stratum (region=EU, baseline weight <15 kg, IGA=3) was combined with the stratum (region=EU, baseline weight ≥15 kg, IGA=3) as the former had only 2 patients.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.3.1/1

Figure 34 Proportion of Patients with Improvement (Reduction from Baseline) of Weekly Average of Daily Worst Scratch/Itch NRS Score ≥3 Points from Baseline to Week 16 in Study R668-AD-1539– Part B (FAS)



Abbreviations: BL=baseline; FAS=full analysis set; NRS=numeric rating scale; Q4W=every 4 weeks.
Note: N1 stands for number of patients with baseline NRS score ≥3. Values after first rescue treatment used were set to missing. Patients with missing values at week 16 due to rescue treatment, withdrawn consent, adverse event, and lack of efficacy were considered as non-responders. Patients with missing values of NRS score due to other reasons including COVID-19 were imputed by multiple imputation, and the response status was then derived.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 6.2.3.1/1

Other secondary endpoints in patients with Severe AD

Table 47 Efficacy Results for Patients with IGA=4 - Part B (FAS, Baseline IGA=4)

	Endpoints	Placebo (N=62)	Dupilumab (N=63)	Treatment Difference (95% CI) P-value[1]
Primary Endpoint	Proportion of patients with IGA score of 0 or 1 at Week 16, n (%)	1 (1.7)	9 (14.3)	12.6 (3.28, 21.82) 0.0194
Co-primary Endpoint[2]	Proportion of patients achieving EASI-75 at Week 16, n (%)	4 (7.2)	29 (46.0)	38.9 (24.79, 52.92) <0.0001
Secondary Endpoints	Percent change from baseline in EASI score at Week 16, LS mean (SE)	-10.3 (5.16)	-55.4 (5.01)	-45.1 (-59.21, -30.97) <0.0001
	Percent change from baseline in worst scratch/itch NRS at Week 16, LS mean (SE)	0.5 (5.40)	-41.8 (5.35)	-42.3 (-57.18, -27.38) <0.0001
	Proportion of patients with improvement (reduction) of worst scratch/itch NRS ≥4 from baseline at Week 16, n (%)	5 (8.8)	27 (42.3)	33.5 (19.01, 47.97) 0.0002
	Proportion of patients with improvement (reduction) of worst scratch/itch NRS ≥3 from baseline at Week 16, n (%)	6 (9.5)	29 (45.4)	35.9 (21.02, 50.84) <0.0001
	Proportion of patients with EASI-50 at Week 16, n(%)	12 (19.2)	38 (60.3)	41.1 (25.32, 56.85) <0.0001
	Proportion of patients with EASI-90 at Week 16, n(%)	0 (0.4)	10 (15.9)	15.5 (6.24, 24.78) 0.0043
	Change from baseline in percent BSA affected by AD at Week 16, LS mean (SE)	-7.6 (2.98)	-29.4 (2.94)	-21.8 (-30.03, -13.58) <0.0001
	Change from baseline in POEM at Week 16, LS mean (SE)	-2.5 (0.95)	-10.6 (0.93)	-8.1 (-10.70, -5.48) <0.0001

Ancillary analyses

Subgroup analyses

Efficacy analysis by weight

A summary of the results for the co-primary endpoints and the key secondary endpoints by weight subgroup in study R668-AD-1539 Part B is provided in ***Table 48***.

Table 48 p Values for Efficacy Results by Weight Subgroup in R668-AD-1539– Part B (FAS) for the primary and key secondary endpoints

Endpoints	≥5 to <15 kg			P value	≥15 to <30 kg			P value
	Placebo (N=25)	Dupilumab 200mg Q4W (N=26)	Treatment Difference (95% CI)		Placebo (N=54)	Dupilumab 300mg Q4W (N=57)	Treatment Difference (95% CI) P-value[1]	
Proportion of patients with IGA score of 0 or 1 at Week 16, n (%)	1 (4.1)	10 (38.5)	34.4 (14.07, 54.65)	0.0068	2 (3.8)	13 (22.8)	19.0 (6.96, 31.06)	0.0077
Proportion of patients achieving EASI-75 at Week 16, n (%)	2 (9.0)	15 (57.7)	48.7 (26.37, 71.01)	0.0009	6 (11.5)	29 (50.9)	39.4 (23.81, 54.98)	<0.0001
Percent change from baseline in EASI score at Week 16, LS mean (SE)	-14.6 (8.77)	-57.3 (8.20)	-42.7 (-66.24, -19.21)	0.0004	-10.1 (5.29)	-65.5 (5.13)	-55.4 (-69.86, -40.89)	<0.0001
Percent change from baseline in worst scratch/itch NRS at Week 16, LS mean (SE)	11.5 (10.60)	-44.0 (10.27)	-55.5 (-84.40, -26.54)	0.0002	-5.6 (3.98)	-47.3 (3.89)	-41.7 (-52.62, -30.78)	<0.0001

Efficacy Results in the Subgroup of Patients who Rolled Over from R668-AD-1539 Part A and Received Weight-Based Weekly Dosing (N=35)

The results of longer-term efficacy data of the 35 patients who rolled over from Part A to the ongoing OLE study are presented in *Table **49***. In study R668-AD-1539 Part A, patients had received a weight-based dosing (3 mg/kg QW or 6 mg/kg QW) and were then switched to the fixed dose regimen of 200 or 300 mg Q4W based on their weight at baseline.

Table 49 Summary of Key Efficacy Results for Children ≥6 Months to <6 Years of Age While on Weight-Based Dosing (3mg/kg QW or 6 mg/kg QW) in Study R668-AD-1434 – (SAF – Patients Who Rolled Over from 1539 Part A – Under Amendment 3)

	Total (N=35)					
	Baseline of OLE	Week 4	Week 16	Week 28	Week 52	Week 104
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	0/34	2/34 (5.9%)	6/31 (19.4%)	8/29 (27.6%)	11/25 (44.0%)	7/14 (50.0%)
Proportion of patients achieving EASI-75 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	1/35 (2.9%)	11/34 (32.4%)	16/31 (51.6%)	20/29 (69.0%)	21/24 (87.5%)	12/14 (85.7%)
Proportion of patients achieving EASI-50 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	11/35 (31.4%)	24/34 (70.6%)	22/31 (71.0%)	23/29 (79.3%)	21/24 (87.5%)	13/14 (92.9%)
Proportion of patients achieving EASI-90 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	0/35	3/34 (8.8%)	8/31 (25.8%)	14/29 (48.3%)	14/24 (58.3%)	11/14 (78.6%)
Mean % change in EASI score from baseline of R668-AD-1539 Part A (SD)	-27.0 (32.45)	-53.5 (36.98)	-65.5 (33.15)	-74.1 (30.51)	-85.8 (21.59)	-90.3 (14.59)
Median % change in EASI score from baseline of OLE (Q1-Q3) [1]	--	-44.7 (-69.50, -5.30)	-68.0 (-86.53, -26.62)	-77.9 (-88.89; -36.69)	-92.4 (-98.65, -76.44)	-92.72 (-97.25; -88.42)
Mean % change in BSA involved from baseline of R668-AD-1539 Part A (SD)	-11.2 (17.66)	-25.6 (26.31)	-32.3 (25.35)	-37.3 (23.78)	-44.3 (20.54)	-50.6 (19.37)

[1] The median percent change was used because the distribution for percent change in EASI score from baseline of the OLE study was skewed and not normally distributed. Hence, the median was a better indicator of central tendency.
Note: n stands for the number of patients who were responder. N1 stands for number of patients with observed data at the visit. The efficacy analysis does not include the period when these patients switched to the fixed dose of 200/300 mg Q4W under amendment 4.
Abbreviations: BSA=body surface area; EASI=eczema area and severity index; EASI-50=50% reduction in EASI; EASI-75=75% reduction in EASI; EASI-90=90% reduction in EASI; IGA=Investigator's Global Assessment; OLE=open-label extension; Q1=quartile 1; Q3=quartile 3; QW=once a week; Q4W=every 4 weeks; SAF=safety analysis set; SD=standard deviation.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Tables 6.7.1.1/1c, 6.7.5.1/1c, 6.7.10.1/1c, 6.7.11.7/1c, 6.7.7.1/1c, 6.7.6.1/1c, and 6.7.13.2/1c.

Efficacy Analysis in Patients with ≥6 Months to <2 Years of Age

R668-AD-1539 Part B

A descriptive analysis of efficacy results for the primary and key secondary endpoints in patients ≥6 months to <2 years of age in R668-AD-1539 Part B is provided in *Table **50***.

Table 50 Efficacy Results for Children ≥6 Months to <2 Years in R668-AD-1539– Part B (FAS, Age ≥6 Months to <2 Years)

	Endpoints	Placebo (N=5)	Dupilumab (N=6)
Primary Endpoint	**Proportion of patients with IGA score of 0 or 1 at Week 16, n (%)**	1 (20.5)	2 (33.3)
Co-primary Endpoint[1]	**Proportion of patients achieving EASI-75 at Week 16, n (%)**	1 (25.0)	4 (66.7)
Key Secondary Endpoints	**Percent change from baseline in EASI score at Week 16, LS mean (SE)**	-30.0 (35.63)	-64.6 (42.12)
	Percent change from baseline in worst scratch/itch NRS at Week 16, LS mean (SE)	-5.5 (11.84)	-52.4 (39.82)

Abbreviations: EASI=Eczema Area and Severity Index; FAS=full analysis set; IGA=Investigator Global Assessment; LS=least squares; NRS=Numeric rating scale; SE=standard error.
[1]Co-primary endpoint for EU and EU reference market countries only, key secondary endpoint for US and US reference market countries.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.1.1.2/1, 6.1.2.2/1, 6.2.1.2/1, and 6.2.2.2/1.

Efficacy data relevant for dose recommendation

For children ≥6 months to <6 years of age weighing ≥5 to <15 kg the proposed dose regimen is 200 mg Q4W and for children weighing ≥15 to <30 kg the proposed dose regimen is 300 mg Q4W. The efficacy data from the pivotal, phase 3 study (R668-AD-1539 Part B) show that weight-tiered dupilumab 200/300 mg Q4W resulted in statistically significant improvements in signs, symptoms, and QOL in children ≥6 months to <6 years of age with moderate-to-severe AD, including in the subgroup of severe AD patients.

Patients in the placebo + TCS arm were more likely to require rescue therapies; sensitivity analyses demonstrate nominally significant efficacy with dupilumab over placebo control when considering all observed values regardless of rescue treatment use, as well as LOCF sensitivity analysis with values after first rescue treatment use set to missing and then using LOCF method to impute the missing data. Consistency of the dupilumab + TCS treatment effect was observed among all the subgroups with the proposed dose regimen. Furthermore, the efficacy data in children ≥6 months to <6 years of age were generally consistent with efficacy data for children ≥6 to <12 years of age, adolescents, and adults.

A rapid onset of effect was seen for outcome measures evaluating pruritus as well as signs of AD providing validation that a loading dose was not needed in this age group. For percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score and EASI score, a nominally statistically significant difference between the dupilumab 200/300 mg Q4W and placebo arm was seen as early as week 2. A similar rapid improvement was seen in the proportion of patients with improvement (reduction) of weekly average of daily worst scratch/itch NRS score ≥4 from baseline, with a nominally statistically significant difference between the dupilumab 200/300 mg Q4W and the placebo groups seen as early as week 3. Positive concentration-response relationships were observed, with higher dupilumab C_{trough} at week 16 leading to increases in the proportion of patients achieving IGA 0/1, increases in the proportion of patients with EASI-75, improvement in EASI percent change from baseline, and improvement in weekly average of daily worst scratch/itch NRS percent change from baseline for children ≥6 months to <6 years of age in the pivotal study. Efficacy data in patients with severe AD in the pivotal phase 3 study (R668-AD-1539 Part B) show a consistent pattern of nominally significant improvements in signs, symptoms, and QOL with a weight-tiered dupilumab 200/300 mg Q4W regimen.

Overall, clinical efficacy data support the proposed posology in patients ≥6 months to <6 years of age with AD: for patients with body weight ≥5 to <15 kg the proposed dose regimen is 200 mg Q4W and for patients with body weight ≥15 to <30 kg the proposed dose regimen is 300 mg Q4W, both administered without a loading dose.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

<table>
<tr><td colspan="3"><u>Title:</u> Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in Patients Aged ≥6 Months to <6 Years with Moderate-to-Severe Atopic Dermatitis</td></tr>
<tr><td>Study identifier</td><td colspan="2">R668-AD-1539 – Part B</td></tr>
<tr><td rowspan="2">Design</td><td colspan="2">This study was a randomized, double-blind, parallel-group, placebo-controlled study in which dupilumab was administered concomitantly with low potency topical corticosteroids (TCS) for 16 weeks to pediatric patients 6 months to <6 years of age with moderate-to- severe AD.</td></tr>
<tr><td>Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>16 weeks
8 weeks</td></tr>
<tr><td>Hypothesis</td><td colspan="2">Superiority:</td></tr>
<tr><td rowspan="2">Treatments groups</td><td>Dupilumab 200 mg or 300 mg Q4W + topical corticosteroids (TCS)</td><td>Dupilumab Q4W weight-tiered fixed dose: 200 mg in patients with a baseline weight of ≥5 to <15 kg or 300 mg in patients with baseline weight of ≥15 to <30 kg</td></tr>
<tr><td>Matching Placebo + topical corticosteroids (TCS)</td><td>Placebo Q4W: matching placebo based on baseline weight category</td></tr>
</table>

Endpoints and definitions	Primary endpoint	IGA score of 0 to 1 at week 16	The primary endpoint is the proportion of patients with an IGA score of 0 to 1 (on a 5-point scale) at week 16.
	Co-primary endpoint	EASI – 75 at week 16	Proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at week 16
	Secondary endpoint	Change in EASI score to week 16	Percent change in EASI score from baseline to week 16
		Change in NRS Score to week 16	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch Numeric Rating Scale (NRS) score
		NRS reduction ≥4 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily worst scratch/itch NRS score ≥4 from baseline at week 16
		NRS reduction ≥3 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily worst scratch/itch NRS score ≥3 from baseline at week 16
		EASI-50 score at week 16	Proportion of patients with EASI-50 at week 16
		EASI-90 score at week 16	Proportion of patients with EASI-90 at week 16
		POEM change at week 16	Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)
		Change in BSA affected by AD	Change from baseline to week 16 in percent body surface area (BSA) affected by AD
		Change in SCORAD at week 16	Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
		Sleep quality NRS change at week 16	Change from baseline to week 16 in sleep quality NRS
		Skin pain NRS change at week 16	Change from baseline to week 16 in skin pain NRS
		DFI change at week 16	Change from baseline to week 16 in Dermatitis Family Impact Questionnaire (DFI)

		CDLQI change at week 16	Change from baseline to week 16 in health related quality of life, as measured by children's Dermatology Life Quality Index (CDLQI) (patients ≥4 years of age)
		IDQOL change at week 16	Change from baseline to week 16 in health related quality of life, Infants Dermatology Quality of Life Index (IDQOL) (patients <4 years of age)
Database lock	16 September 2021		

Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	ITT population was used for primary and secondary analyses reported below

Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 200 mg or 300 mg Q4W + TCS**	**Placebo + TCS**
	Number of subjects	83	79
	IGA 0 or 1 at week 16 (n(%))	23(27.7)	3(3.9)
	95% CI (%)	(18.45, 38.62)	(-0.42, 8.21)
	Easi-75 at week 16 (n(%))	44(53.0)	8(10.7)
	95% CI (%)	(41.74, 64.07)	(3.65, 17.74)

Effect estimate per comparison			
	Co-primary endpoint IGA 0 or 1 at week 16	Comparison groups	Dupilumab 200 mg or 300 mg Q4W + TCS versus placebo + TCS
		Difference in %	23.8
		P-value	<0.0001
	Co-Primary endpoint Easi-75 at week 16	Difference in %	42.3
		P-value	<0.0001

Analysis description	Secondary Analysis

Analysis population and time point description	ITT population was used for primary and secondary analyses reported below		
Descriptive statistics and estimate variability	Treatment group	Dupilumab 200 mg or 300 mg Q4W	Placebo
	Number of subjects	83	79
	Change in EASI score to week 16, (LS Mean % Change (SE))	-70.0 (4.85)	-19.6 (5.13)
	95% CI (%)	(-79.5, -60.5)	(-29.7, -9.6)
	Change in NRS Score to week 16 (LS Mean % Change (SE))	-49.4 (5.03)	-2.2 (5.22)
	95% CI (%)	(-59.2, -39.5)	(-12.5, 8.0)
	NRS reduction ≥4 at week 16 n/N1(%)	40 (48.1)	7 (8.9)
	95% CI (%)	(37.05, 59.15)	(2.25, 15.51)
	NRS reduction ≥3 at week 16 n/N1(%)	44 (53.3)	8 (9.9)
	95% CI (%)	(42.29, 64.22)	(2.59, 17.22)
	EASI-50 score at week 16 n(%)	57 (68.7)	16 (20.2%)
	95% CI (%)	(57.56, 78.41)	(11.09, 29.23)
	EASI-90 score at week 16 n (%)	21 (25.3)	2 (2.8)
	95% CI (%)	(16.39, 36.04)	(-1.02, 6.66)
	Change in BSA affected by AD (LS Mean % Change (SE))	-35.00 (2.815)	-10.74 (2.926)
	95% CI (%)	(-40.52, -29.49)	(-16.47, -5.00)
	POEM change at week 16 (LS Mean % Change (SE))	-12.9 (0.89)	-3.8 (0.92)
	95% CI (%)	(-14.6, -11.1)	(-5.6, -2.0)

	Change in SCORAD at week 16 (LS Mean % Change (SE))	-54.7 (3.39)	-16.2 (3.54)	
	95% CI (%)	(-61.3, -48.0)	(-23.2, -9.3)	
	Sleep quality NRS change at week 16 (LS Mean % Change (SE))	2.04 (0.251)	0.34 (0.256)	
	95% CI (%)	(1.55, 2.53)	(-0.17, 0.84)	
	Skin pain NRS change at week 16 (LS Mean % Change (SE))	-3.93 (0.295)	0.62 (0.302)	
	95% CI (%)	(-4.51, -3.35)	(-1.21, -0.02)	
	DFI change at week 16 (LS Mean % Change (SE))	-10.48 (0.806)	-2.68 (0.839)	
	95% CI (%)	(-12.06, -8.90)	(-4.32, -1.04)	
	CDLQI change at week 16 (LS Mean % Change (SE))	-10.0 (1.56)	-2.5 (1.66)	
	95% CI (%)	(-13.1, -7.0)	(-5.8, 0.7)	
	IDQOL change at week 16 (LS Mean % Change (SE))	-10.91 (1.159)	-1.95 (1.078)	
	95% CI (%)	(-13.18, -8.64)	(-4.07, 0.16)	

Effect estimate per comparison		**Comparison groups**	**Dupilumab 200 mg or 300 mg Q4W + TCS versus placebo + TCS**
	Secondary endpoint Change in EASI score to week 16	Least means square (SE)	-50.4
		P-value	<0.0001
	Secondary endpoint Change in NRS Score to week 16	Least means square (SE)	-47.1
		P-value	<0.0001
	NRS reduction ≥4 at week 16	Difference in %	39.2
		P-value	<0.0001

	NRS reduction ≥3 at week 16	Difference in %	43.3
		P-value	<0.0001
	EASI-50 score at week 16 n(%)	Difference in %	48.5
		P-value	<0.0001
	EASI-90 score at week 16	Difference in %	22.5
		P-value	<0.0001
	Change in BSA affected by AD	Least means square (SE)	-24.3
		P-value	<0.0001
	POEM change at week 16	Least means square (SE)	-9.1
		P-value	<0.0001
	Change in SCORAD at week 16	Least means square (SE)	-38.4
		P-value	<0.0001
	Sleep quality NRS change at week 16	Least means square (SE)	1.7
		P-value	<0.0001
	Skin pain NRS change at week 16	Least means square (SE)	-3.3
		P-value	<0.0001
	DFI change at week 16	Least means square (SE)	-7.8
		P-value	<0.0001
	CDLQI change at week 16	Least means square (SE)	-7.5

		P-value	<0.0001
	IDQOL change at week 16	Difference in %	-9.0
		P-value	<0.0001

Summary of Efficacy for trial R668-AD-1539 Part B – Pre-Specified Severe AD Analysis

Title: Phase 2/3 Study Investigating the Pharmacokinetics, Safety, and Efficacy of Dupilumab in Patients Aged ≥6 Months to <6 Years with Moderate-to-Severe Atopic Dermatitis			
Study identifier	R668-AD-1539 – Part B		
Design	This study was a randomized, double-blind, parallel-group, placebo-controlled study in which dupilumab was administered concomitantly with low potency topical corticosteroids (TCS) for 16 weeks to pediatric patients 6 months to <6 years of age with moderate-to- severe AD.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16 weeks 8 weeks	
Hypothesis	Superiority:		
Treatments groups	Dupilumab 200 mg or 300 mg Q4W + topical corticosteroids (TCS)		Dupilumab Q4W weight-tiered fixed dose: 200 mg in patients with a baseline weight of ≥5 to <15 kg or 300 mg in patients with baseline weight of ≥15 to <30 kg
	Matching Placebo + topical corticosteroids (TCS)		Placebo Q4W: matching placebo based on baseline weight category
Endpoints and definitions	Primary endpoint	IGA score of 0 to 1 at week 16	The primary endpoint is the proportion of patients with an IGA score of 0 to 1 (on a 5-point scale) at week 16.
	Co-primary endpoint	EASI – 75 at week 16	Proportion of patients with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at week 16
	Secondary endpoint	Change in EASI score to week 16	Percent change in EASI score from baseline to week 16
		Change in NRS Score to week 16	Percent change from baseline to week 16 in weekly average of daily worst scratch/itch Numeric Rating Scale (NRS) score
		NRS reduction ≥4 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily worst scratch/itch NRS score ≥4 from baseline at week 16
		NRS reduction ≥3 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily worst scratch/itch NRS score ≥3 from baseline at week 16
		EASI-50 score at week 16	Proportion of patients with EASI-50 at week 16

		EASI-90 score at week 16	Proportion of patients with EASI-90 at week 16
		POEM change at week 16	Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)
		Change in BSA affected by AD	Change from baseline to week 16 in percent body surface area (BSA) affected by AD
		Change in SCORAD at week 16	Percent change from baseline to week 16 in SCORing Atopic Dermatitis (SCORAD)
		Sleep quality NRS change at week 16	Change from baseline to week 16 in sleep quality NRS
		Skin pain NRS change at week 16	Change from baseline to week 16 in skin pain NRS
		DFI change at week 16	Change from baseline to week 16 in Dermatitis Family Impact Questionnaire (DFI)
		CDLQI change at week 16	Change from baseline to week 16 in health related quality of life, as measured by children's Dermatology Life Quality Index (CDLQI) (patients ≥4 years of age)
		IDQOL change at week 16	Change from baseline to week 16 in health related quality of life, Infants Dermatology Quality of Life Index (IDQOL) (patients <4 years of age)

Database lock	16 September 2021
Results and Analysis	

Analysis description	Pre-specified Severe AD Analysis			
Analysis population and time point description	The severe AD population (Baseline IGA=4) was used for the pre-specified analyses reported below			
Descriptive statistics and estimate variability	**Treatment group**	**Dupilumab 200 mg or 300 mg Q4W + TCS**	**Placebo + TCS**	
	Number of subjects	63	62	

	IGA 0 or 1 at week 16 (n(%))	9(14.3)	1(1.7)	
	95% CI (%)	(6.75, 25.39)	(-1.62, 5.09)	
	Easi-75 at week 16 (n(%))	29(46.0)	4(7.2)	
	95% CI (%)	(33.39, 59.06)	(0.36, 13.99)	

Effect estimate per comparison	Co-primary endpoint IGA 0 or 1 at week 16	Comparison groups	Dupilumab 200 mg or 300 mg Q4W + TCS versus placebo + TCS
		Difference in %	12.6
		P-value	0.0194
	Co-Primary endpoint Easi-75 at week 16	Difference in %	38.9
		P-value	<0.0001
Analysis description	Secondary Pre-specified Severe AD Analysis		
Analysis population and time point description	The severe AD population (Baseline IGA=4) was used for the pre-specified analyses reported below		

Descriptive statistics and estimate variability	Treatment group	Dupilumab 200 mg or 300 mg Q4W	Placebo
	Number of subjects	63	62
	Change in EASI score to week 16, (LS Mean % Change (SE))	-55.4 (5.01)	-10.3 (5.16)
	95% CI (%)	(-65.2, -45.6)	(-20.4, -0.2)
	Change in NRS Score to week 16 (LS Mean % Change (SE))	-41.8 (5.35)	0.5 (5.40)
	95% CI (%)	(-52.3, -31.3)	(-10.1, 11.0)

NRS reduction ≥4 at week 16 n/N1(%)	27 (42.3)	5 (8.8)
95% CI (%)	(29.81, 54.80)	(1.49, 16.14)
NRS reduction ≥3 at week 16 n/N1(%)	29 (45.4)	6 (9.5)
95% CI (%)	(32.78, 58.01)	(1.71, 17.22)
EASI-50 score at week 16 n(%)	38 (60.3)	12(19.2)
95% CI (%)	(47.20, 72.43)	(9.10, 29.37)
EASI-90 score at week 16 n (%)	10 (15.9)	0 (0.4)
95% CI (%)	(7.88, 27.26)	(-1.79, 2.52)
Change in BSA affected by AD (LS Mean % Change (SE))	-29.4 (2.94)	-7.6 (2.98)
95% CI (%)	(-35.18, -23.67)	(-13.47 , -1.78)
POEM change at week 16 (LS Mean % Change (SE))	-10.6 (0.93)	-2.5 (0.95)
95% CI (%)	(-12.41, -8.76)	(-4.36, -0.63)
Change in SCORAD at week 16 (LS Mean % Change (SE))	-44.6(3.40)	-11.1 (3.47)
95% CI (%)	(-51.2, -37.9)	(-18.0, -4.3)

	Sleep quality NRS change at week 16 (LS Mean % Change (SE))	1.7 (0.25)	0.2 (0.25)	
	95% CI (%)	(1.24 , 2.22)	(-0.25, 0.71)	
	Skin pain NRS change at week 16 (LS Mean % Change (SE))	-3.4 (0.29)	-0.34 (0.29)	
	95% CI (%)	(-4.02, -2.87)	(-0.91, 0.23)	
	DFI change at week 16 (LS Mean % Change (SE))	-9.1 (0.83)	-2.1 (0.84)	
	95% CI (%)	(-10.75, -7.51)	(-3.71, -0.41)	
	CDLQI change at week 16 (LS Mean % Change (SE))	-9.1 (1.09)	-2.6 (1.18)	
	95% CI (%)	(-11.26, -7.01)	(-4.87, -0.25)	
	IDQOL change at week 16 (LS Mean % Change (SE))	-9.1 (1.26)	-0.6 (1.14)	
	95% CI (%)	(-11.53, -6.57)	(-2.79, 1.68)	
Effect estimate per comparison		**Comparison groups**	**Dupilumab 200 mg or 300 mg Q4W + TCS versus placebo + TCS**	
	Secondary endpoint Change in EASI score to week 16	Least means square (SE)	-45.1	

		P-value	<0.0001
	Secondary endpoint Change in NRS Score to week 16	Least means square (SE)	-43.3
		P-value	<0.0001
	NRS reduction ≥4 at week 16	Difference in %	33.5
		P-value	0.0002
	NRS reduction ≥3 at week 16	Difference in %	35.9
		P-value	<0.0001
	EASI-50 score at week 16 n(%)	Difference in %	41.1
		P-value	<0.0001
	EASI-90 score at week 16	Difference in %	15.5
		P-value	0.0043
	Change in BSA affected by AD	Least means square (SE)	-21.8
		P-value	<0.0001
	POEM change at week 16	Least means square (SE)	-8.1
		P-value	<0.0001
	Change in SCORAD at week 16	Least means square (SE)	-33.4
		P-value	<0.0001

	Sleep quality NRS change at week 16	Least means square (SE)	1.5
		P-value	<0.0001
	Skin pain NRS change at week 16	Least means square (SE)	-3.1
		P-value	<0.0001
	DFI change at week 16	Least means square (SE)	-7.1
		P-value	<0.0001
	CDLQI change at week 16	Least means square (SE)	-6.6
		P-value	<0.0001
	IDQOL change at week 16	Difference in %	-8.5
		P-value	<0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant provided a comparison of efficacy data across the studies included in the AD clinical development program. Results are presented in *Table **51*** (Baseline Disease Characteristics), *Table **52*** (Co-primary and Key secondary endpoints) and *Table **53*** (Sensitivity analyses). As outlined by the applicant, there are differences in study designs that need to be taken into consideration:

• **R668-AD-1652** – **children ≥6 to <12 years** – enrolled patients with severe AD only, whereas R668-AD-1539 Part B enrolled patients with moderate-to-severe AD. Additionally in R668-AD-1652, dupilumab was administered in combination with medium potency TCS, while in R668-AD-1539 Part B dupilumab was administered in combination with low-potency TCS.

• **R668-AD-1526** – **adolescents** – dupilumab was administered as monotherapy, whereas in R668-AD-1539 Part B dupilumab was administered in combination with low-potency TCS.

• **Pooled SOLO – adults** – dupilumab was administered as monotherapy in the SOLO 1 and SOLO 2 studies, whereas in R668-AD-1539 Part B dupilumab was administered in combination with low-potency TCS. Although there were additional adult studies where dupilumab was evaluated in combination with medium-potency TCS (eg, R668-AD-1224), the SOLO studies were thought to provide a better basis for comparison as the monotherapy setting is closer to low-potency TCS used in R668-AD-1539 Part B than studies in combination with medium-potency TCS.

In studies in children ≥6 to <12 years, adolescents, and adults a loading dose of dupilumab was administered on day 1, whereas in R668-AD-1539 Part B no loading dose was used, in order to limit the number of injections in this younger population. Furthermore, assessment of pruritus was reported by caregivers in children ≥6 months to <6 years and reported by patients in the other age groups.

The following approved dosing regimens, which have been shown to provide comparable trough concentrations of dupilumab at steady-state, were used as the basis for comparisons of efficacy data across the dupilumab program:

- R668-AD-1652 – children ≥6 to <12 years – dupilumab 300 mg Q4W
- R668-AD-1526 – adolescents – dupilumab 200/300 mg Q2W
- Pooled SOLO – adults – dupilumab 300 mg Q2W

Table 51 Comparison of Baseline Disease Characteristics in the Dupilumab Program between Children, Adolescents, and Adults

	Children ≥6 months to <6 years		Children ≥6 to <12 years		Adolescents		Adults	
	R668-AD-1539 Part B Study (Phase 3)		R668-AD-1652 Study (Phase 3)		R668-AD-1526 Study (Phase 3)		Pooled SOLO[1] (Phase 3)	
	Placebo + TCS	Dupilumab 200/300 mg Q4W + TCS	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Placebo + TCS	Dupilumab 200/300 mg Q2W + TCS	Placebo	Dupilumab 300 mg Q2W
N (FAS)	79	83	123	122	85	82	460	457
EASI (0-72), mean (SD)	33.1 (12.18)	35.1 (13.88)	39.0 (12.01)	37.4 (12.45)	35.5 (13.97)	35.3 (13.84)	34.0 (14.38)	32.4 (13.32)
IGA (0-4), n (%)								
3	17 (21.5)	20 (24.1)	0	1 (0.8)	39 (45.9)	39 (47.6)	234 (50.9)	234 (51.2)
4	62 (78.5)	63 (75.9)	123 (100)	121 (99.2)	46 (54.1)	43 (52.4)	225 (48.9)	223 (48.8)
Worst scratch/itch NRS (0-10)[2], mean (SD)	7.6 (1.49)	7.5 (1.32)	7.7 (1.54)	7.8 (1.58)	7.7 (1.62)	7.5 (1.52)	7.4 (1.81)	7.4 (1.76)
BSA involvement (%), mean (SD)	57.4 (20.91)	59.3 (22.51)	60.2 (21.46)	54.8 (21.58)	56.4 (24.13)	56.0 (21.40)	55.8 (23.25)	53.7 (22.21)
SCORAD (0-103), mean (SD)	72.2 (11.44)	72.7 (12.95)	72.9 (12.01)	75.6 (11.71)	70.4 (13.25)	70.6 (13.89)	68.8 (14.45)	67.1 (13.71)
CDLQI/DLQI [3]	17.7 (6.25)	17.5 (5.43)	14.6 (7.41)	16.2 (7.85)	13.1 (6.72)	13.0 (6.21)	15.1 (7.47)	14.7 (7.25)

CI=confidence interval
[1] Including pivotal studies SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416 in adults
[2] Peak Pruritus NRS for adolescent and adult data.
[3] CDLQI in pediatric patients 4 to 18 years, DLQI in adults
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 4.2.1/1 for children ≥6 months to <6 years data; children ≥6 to <12 years AD marketing application Module 5.3.5.1 R668-AD-1652 Post-text Table 4.2.1/1 for children ≥6 to <12 years data; Adolescent AD marketing application Module 5.3.5.1 R668-AD-1526 Post-text Table 4.2.1/1 for adolescent data; and initial AD marketing application Module 5.3.5.3 Pool 1 Table 4.2.1/1 for adult data.

Table 52 Comparison between Children, Adolescents, and Adults Data on Primary and Key Secondary Efficacy Endpoints

	Children ≥6 months to <6 years			Children ≥6 to <12 years			Adolescents			Adults		
	R668-AD-1539 Part B Study (Phase 3)			R668-AD-1652 Study (Phase 3)			R668-AD-1526 Study (Phase 3)			Pooled SOLO[1] (Phase 3)		
	Placebo + TCS	Dupilumab 200/300 mg Q4W + TCS	Difference vs Placebo (95% CI)	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Difference vs Placebo (95% CI)	Placebo	Dupilumab 200/300 mg Q2W + TCS	Difference vs Placebo (95% CI)	Placebo	Dupilumab 300 mg Q2W	Difference vs Placebo (95% CI)
N (FAS)	79	83		123	122		85	82		460	457	
Patients achieving IGA 0 or 1 at week 16, %	3.9	27.7	23.8 (13.27, 34.37)	11.4	32.8	21.4 (11.36, 31.45)	2.4	24.4	22.0 (12.20, 31.87)	9.3	37.0	27.6 (22.47, 32.80)
Patients achieving EASI-75 at week 16, %	10.7	53.0	42.3 (29.47, 55.16)	26.8	69.7	42.8 (31.54, 54.15)	8.2	41.5	33.2 (21.07, 45.39)	13.3	47.7	34.4 (28.91, 39.97)
% Change in EASI from baseline to week 16, LS mean (SE)	-19.6 (5.13)	-70.0 (4.85)	-50.4 (-62.38, -38.40)	-48.6 (2.46)	-82.1 (2.37)	-33.4 (-40.06, -26.82)	-23.6 (5.49)	-65.9 (3.99)	-42.3 (-55.60, -29.04)	-34.3 (2.25)	-70.0 (1.81)	-35.7 (-41.28, -30.16)
% Change in weekly average of daily worst scratch/itch NRS from baseline to week 16, LS mean (SE)[2]	-2.2 (5.22)	-49.4 (5.03)	-47.1 (-59.47, -34.79)	-25.9 (2.90)	-54.6 (2.89)	-28.6 (-36.47, -20.82)	-19.0 (4.09)	-47.9 (3.43)	-29.0 (-39.54, -18.38)	-20.5 (1.92)	-47.4 (1.71)	-26.8 (-31.69, -21.99)

CI=confidence interval; LS=least squares; NRS=numeric rating scale; Q2W=every 2weeks; Q4W=every 4 weeks; SE=standard error
[1] Including pivotal studies SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416 in adults
[2] Peak Pruritus NRS for adolescent and adult data.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Tables 6.1.1.1/1, 6.1.2.1/1, 6.2.1.1/1, and 6.2.2.1/1 for children ≥6 months to <6 years data; children ≥6 to <12 years AD marketing application Module 5.3.5.1 R668-AD-1652 Post-text Tables 6.1.1.1/1, 6.1.2.1/1, 6.2.1.1/1, and 6.2.2.1/1 for children ≥6 to <12 years data; adolescent AD marketing application Module 5.3.5.1 R668-AD-1526 Post-text Tables 6.1.1.1/1, 6.1.2.1/1, 6.2.1.1/1, and 6.2.2.1/1 for adolescent data; and initial AD marketing application Module 5.3.5.3 Pool 1 Tables 6.1.1.1/1, 6.2.1.1/1, 6.2.3.1/1, and 6.2.9.1/1 for adult data.

Table 53 Comparison between Children, Adolescents, and Adults Data on Primary and Key Secondary Efficacy Endpoints – Sensitivity Analysis with All Observed Values Regardless of Rescue Treatment Use for Continuous Variables

	Children ≥6 months to <6 years			Children ≥6 to <12 years			Adolescents			Adults		
	R668-AD-1539 Part B Study (Phase 3)			R668-AD-1652 Study (Phase 3)[1]			R668-AD-1526 Study (Phase 3) [1]			Pooled SOLO[2] (Phase 3)		
	Placebo + TCS	Dupilumab 200/300 mg Q4W + TCS	Difference vs Placebo (95% CI)	Placebo + TCS	Dupilumab 300 mg Q4W + TCS	Difference vs Placebo (95% CI)	Placebo + TCS	Dupilumab 200/300 mg Q2W + TCS	Difference vs Placebo (95% CI)	Placebo	Dupilumab 300 mg Q2W	Difference vs Placebo (95% CI)
N (FAS)	79	83		123	122		85	82		460	457	
% Change in EASI from baseline to week 16, LS mean (SE)	-42.2 (4.20)	-74.5 (3.96)	-32.3 (-42.19, -22.41)	-45.3 (2.60)	-81.8 (2.55)	-36.5 (-43.48, -29.47)	-31.3 (3.54)	-66.2 (3.56)	-34.9 (-44.76, -25.11)	-36.8 (1.61)	-71.8 (1.59)	-35.0 (-39.26, -30.75)
% Change in weekly average of daily worst scratch/itch NRS from baseline to week 16, LS mean (SE)[3]	-25.4 (4.03)	-56.0 (3.72)	-30.7 (-40.14, -21.18)	-24.8 (2.84)	-54.5 (2.90)	-29.7 (-37.51, -21.92)	-20.9 (3.24)	-48.1 (3.27)	-27.3 (-36.29, -18.24)	-25.0 (1.56)	-49.4 (1.54)	-24.4 (-28.54, -20.28)

CI=confidence interval; LS=least squares; NRS=numeric rating scale; Q2W=every 2weeks; Q4W=every 4 weeks; SE=standard error
[1] In studies R668-AD-1652 and R668-AD-1526 missing data was imputed by multiple imputation method, while in R668-AD-1539 Part B and the pooled SOLO analysis there was no imputation of missing data.
[2] Including pivotal studies SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416 in adults
[3] Peak Pruritus NRS for adolescent and adult data.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 6.2.1.1/5 and 6.2.2.1/5 for children ≥6 months to <6 years data; children ≥6 to <12 years AD marketing application Module 5.3.5.1 R668-AD-1652 Post-text Tables 6.2.1.1/3 and 6.2.2.1/3 for children ≥6 to <12 years data; adolescent AD marketing application Module 5.3.5.1 R668-AD-1526 Post-text Tables 6.2.1.1/2 and 6.2.2.1/2 for adolescent data; and initial AD marketing application Module 5.3.5.3 Pool 1 Tables 6.2.3.1/6 and 6.2.9.1/6 for adult data

Supportive studies

R668-AD-1539 Part A

Efficacy analyses were performed using the safety analysis set (SAF), which included all patients who received any study drug. Overall, 39/40 patients completed the study and were included in the final analysis of R668-AD-1539 Part A. A trend towards numerically higher effect was seen with the 6 mg/kg dose as compared to 3 mg/kg dose, especially at week 4, see *Table **54***. See also pharmacological section.

Table 54 Summary of Key Efficacy Results for R668-AD-1539 – Part A – SAF

	≥2 to <6 years old				≥6 months to <2 years old			
	3 mg/kg (N=10)		6 mg/kg (N=10)		3 mg/kg (N=10)		6 mg/kg (N=10)	
	Week 3	Week 4	Week 3	Week 4	Week 3	Week 4	Week 3	Week 4
Mean % change in EASI score from baseline (SD)	-44.6 (36.77)	-26.6 (47.37)	-49.7 (29.05)	-48.7 (28.89)	-42.7 (33.13)	-22.4 (42.52)	-38.8 (24.98)	-43.2 (35.55)
Mean % change in pruritis NRS from baseline (SD)	-22.9 (29.90)	-16.7 (32.48)	-44.7 (17.48)	-22.0 (34.46)	-11.1 (57.54)	4.1 (84.21)	-18.2 (26.39)	-26.7 (35.48)
Mean % change in SCORAD score from baseline (SD)	-33.0 (32.09)	-18.6 (26.18)	-34.7 (23.18)	-31.9 (17.45)	-32.9 (23.76)	-22.4 (26.44)	-25.2 (17.18)	-28.1 (27.84)
Mean % change in % BSA from baseline (SD)	-34.5 (33.6)	-15.9 (25.48)	-40.8 (25.72)	-30.3 (23.60)	-22.1 (31.57)	-5.2 (16.94)	-40.3 (21.21)	-24.9 (16.62)
Number and proportion of patients achieving IGA 0 or 1, n (%)	0	1 (10.0%)	0	0	0	1 (10.0%)	0	1 (10.0%)
Proportion of patients with an EASI-50, n (%)	5 (50.0%)	3 (30.0%)	5 (50.0%)	4 (40.0%)	5 (50.0%)	2 (20.0%)	4 (40.0%)	4 (40.0%)

Abbreviations: BSA=body surface area; EASI=Eczema area and severity index; EASI-50=50% reduction in EASI; IGA=Investigator's global assessment; NRS=numeric rating scale; SAF=safety analysis set, SCORAD=SCORing atopic dermatitis; SD=standard deviation.
Source: Module 5.3.5.1 R668-AD-1539 Part A Post-text Tables 6.1.1.1, 6.1.2.1, 6.2.1.1, 6.3.1.1, 6.4.1.1, 6.5.1.1

R668-AD-1434 – Phase 3, 104-Week Treatment, Open-Label Extension Study (ongoing)

Efficacy results for the overall study population (N=180 children ≥6 months to <6 years of age), include data from children who rolled over from R668-AD-1539 Part A and R668-AD-1539 Part B. A summary of the results is displayed in *Table **55***.

Numbers analysed

At the time of the third-step analysis, of the 180 children ≥6 months to <6 years of age enrolled in the study, 122 patients had completed at least 16 weeks in the OLE, 68 patients had completed at least 26 weeks, 30 patients had completed at least 52 weeks, and 29 patients had completed at least 104 weeks of treatment period.

Study design

Study R668-AD-1434 is a phase 3, ongoing OLE study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in pediatric patients with AD who had previously completed a clinical study with dupilumab in patients with AD.

The study consisted of a screening period (day -28 to day -1), a treatment period of up 5 years for patients ≥6 months to <6 years of age, and a 12-week follow-up period.

Objectives

The primary objective of the OLE study was to assess the long-term safety of dupilumab in pediatric patients with AD. Long-term efficacy was evaluated as a secondary objective.

Outcomes

Efficacy assessments included EASI, IGA of AD severity, SCORAD, BSA involvement with AD, CDLQI, and IDQOL.

Study participants

The patient population consists of pediatric patients ≥6 months to <18 years of age with AD who participated in a prior clinical study of dupilumab in AD. The majority of these patients entered the OLE from the pivotal study (R668-AD-1539 Part B) and received a weight-tiered fixed-dose regimen of dupilumab.

Study treatment

Starting from R668-AD-1434 amendment 4, the dose regimen for children ≥6 months to <6 years old was changed from weight-based dosing (3 mg/kg QW or 6 mg/kg QW) to a fixed dose regimen, tiered by body weight irrespective of age (5 kg to <15 kg: 200 mg Q4W, 15 kg to <30 kg: 300 mg Q4W). The use of topical medication for AD (including TCS and TCIs) was permitted during the study. It was recommended that investigators should select the potency based on the age of the patient, severity of disease and affected region, and that use be consistent with local guidelines.

The treatment duration of an individual patient in the OLE study was determined by enrollment date (which varied across patients) and the data cut-off date for the study (which was the same across all patients, 31 Jul 2021).

Table 55 Summary of Key Efficacy Parameters for Overall Study Population in Study R668-AD-1434 - Children ≥6 Months to <6 Years of Age – (SAF)

	Total (N=180)					
	Baseline of OLE	**Week 4**	**Week 16**	**Week 28**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	23/179 (12.8%)	36/172 (20.9%)	41/123 (33.3%)	22/55 (40.0%)	13/30 (43.3%)	14/27 (51.9%)
Proportion of patients achieving EASI-75 relative to baseline of previous study, n/N1 (%)	53/180 (29.4%)	98/172 (57.0%)	89/123 (72.4%)	43/55 (78.2%)	26/29 (89.7%)	25/27 (92.6%)
Proportion of patients achieving EASI-50 relative to baseline of previous study, n/N1 (%)	103/180 (57.2%)	143/172 (83.1%)	108/123 (87.8%)	49/55 (89.1%)	26/29 (89.7%)	26/27 (96.3%)
Proportion of patients achieving EASI-90 relative to baseline of previous study, n/N1 (%)	26/180 (14.4%)	54/172 (31.4%)	54/123 (43.9%)	31/55 (56.4%)	17/29 (58.6%)	20/27 (74.1%)
Mean % change in EASI score from baseline of previous study (SD)	-50.3 (35.68)	-71.0 (28.07)	-79.8 (23.95)	-82.1 (25.03)	-86.4 (19.78)	-91.0 (11.18)
Median % change from baseline of OLE in EASI score (Q1-Q3)	--	-40.5 (-71.32, -12.25)	-64.5 (-88.04, -27.89)	-80.8 (-93.94, -55.02)	-89.8 (-96.69, -76.47)	-89.0 (-94.16, -83.33)
Mean % change in BSA involved from baseline of previous study (SD)	-26.3 (23.72)	-37.2 (23.72)	-42.8 (22.91)	-41.8 (23.16)	-45.6 (20.03)	-51.2 (17.76)

Note: n stands for the number of patients who were responder. N1 stands for number of patients with observed data at the visit.
Abbreviations: BSA=body surface area; EASI=eczema area and severity index; EASI-50=50% reduction in EASI; EASI-75=75% reduction in EASI; EASI-90=90% reduction in EASI; IGA=Investigator's Global Assessment; OLE=open-label extension; Q1=quartile 1; Q3=quartile 3; SAF=safety analysis set; SD=standard deviation.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Tables 6.1.1.1/1c, 6.2.1.1/1c, 6.2.6.1/1c, 6.2.7.1/1c, 6.2.3.1/1c, 6.2.2.1/1c, and 6.3.2.2/1c.

Table 56 Summary of Key Efficacy Results for Children ≥6 Months to <6 Years of Age While on Weight-Based Dosing (3 mg/kg QW or 6 mg/kg QW) in Study R668-AD-1434 – (SAF – Patients Who Rolled Over from 1539 Part A – Under Amendment 3)

	Total (N=35)					
	Baseline of OLE	**Week 4**	**Week 16**	**Week 28**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	0/34	2/34 (5.9%)	6/31 (19.4%)	8/29 (27.6%)	11/25 (44.0%)	7/14 (50.0%)
Proportion of patients achieving EASI-75 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	1/35 (2.9%)	11/34 (32.4%)	16/31 (51.6%)	20/29 (69.0%)	21/24 (87.5%)	12/14 (85.7%)
Proportion of patients achieving EASI-50 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	11/35 (31.4%)	24/34 (70.6%)	22/31 (71.0%)	23/29 (79.3%)	21/24 (87.5%)	13/14 (92.9%)
Proportion of patients achieving EASI-90 relative to baseline of R668-AD-1539 Part A, n/N1 (%)	0/35	3/34 (8.8%)	8/31 (25.8%)	14/29 (48.3%)	14/24 (58.3%)	11/14 (78.6%)
Mean % change in EASI score from baseline of R668-AD-1539 Part A (SD)	-27.0 (32.45)	-53.5 (36.98)	-65.5 (33.15)	-74.1 (30.51)	-85.8 (21.59)	-90.3 (14.59)
Median % change in EASI score from baseline of OLE (Q1-Q3) [1]	--	-44.7 (-69.50, -5.30)	-68.0 (-86.53, -26.62)	-77.9 (-88.89; -36.69)	-92.4 (-98.65, -76.44)	-92.72 (-97.25; -88.42)
Mean % change in BSA involved from baseline of R668-AD-1539 Part A (SD)	-11.2 (17.66)	-25.6 (26.31)	-32.3 (25.35)	-37.3 (23.78)	-44.3 (20.54)	-50.6 (19.37)

[1] The median percent change was used because the distribution for percent change in EASI score from baseline of the OLE study was skewed and not normally distributed. Hence, the median was a better indicator of central tendency.
Note: n stands for the number of patients who were responder. N1 stands for number of patients with observed data at the visit. The efficacy analysis does not include the period when these patients switched to the fixed dose of 200/300 mg Q4W under amendment 4.
Abbreviations: BSA=body surface area; EASI=eczema area and severity index; EASI-50=50% reduction in EASI; EASI-75=75% reduction in EASI; EASI-90=90% reduction in EASI; IGA=Investigator's Global Assessment; OLE=open-label extension; Q1=quartile 1; Q3=quartile 3; QW=once a week; Q4W=every 4 weeks; SAF=safety analysis set; SD=standard deviation.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Tables 6.7.1.1/1c, 6.7.5.1/1c, 6.7.10.1/1c, 6.7.11.7/1c, 6.7.7.1/1c, 6.7.6.1/1c, and 6.7.13.2/1c.

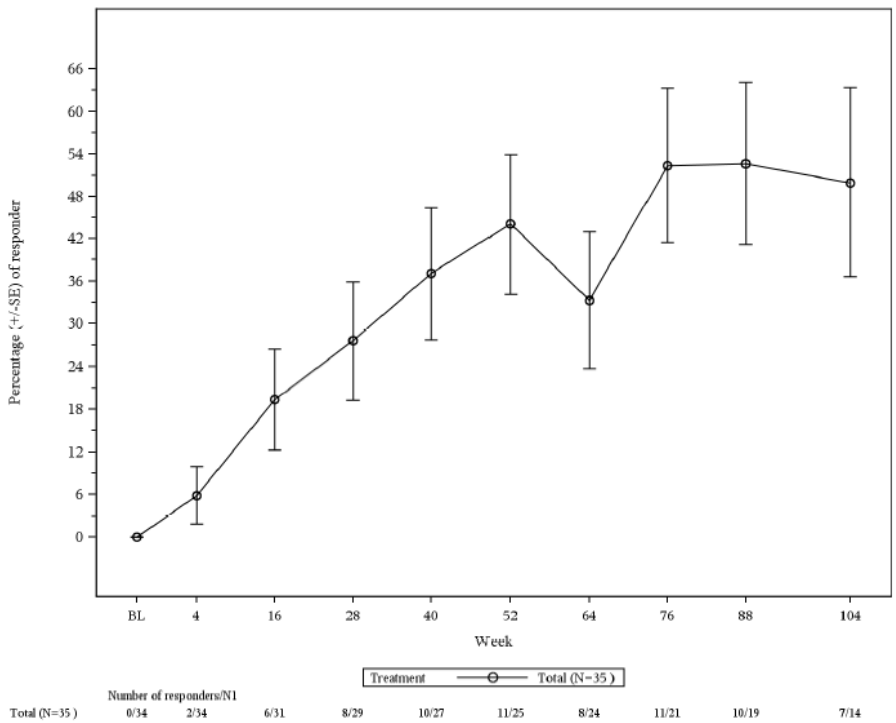
Table 57 Key Efficacy Parameters for Patients with Severe AD (IGA=4 at Baseline) in Study R668-AD-1434 – Children ≥6 Months to <6 Years of Age – (SAF, Patients with IGA=4 at Baseline)

	Total (N=50)					
	Baseline of OLE	**Week 4**	**Week 16**	**Week 28**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	0/50	0/48	8/35 (22.9%)	6/21 (28.6%)	4/15 (26.7%)	6/14 (42.9%)
Proportion of patients achieving EASI-75 relative to baseline of previous study, n/N1 (%)	0/50	12/48 (25.0%)	18/35 (51.4%)	14/21 (66.7%)	13/15 (86.7%)	14/14 (100%)
Proportion of patients achieving EASI-50 relative to baseline of previous study, n/N1 (%)	2/50 (4.0%)	24/48 (50.0%)	26/35 (74.3%)	17/21 (81.0%)	13/15 (86.7%)	14/14 (100%)
Proportion of patients achieving EASI-90 relative to baseline of previous study, n/N1 (%)	0/50	4/48 (8.3%)	11/35 (31.4%)	9/21 (42.9%)	7/15 (46.7%)	10/14 (71.4%)
Mean % change in EASI score from baseline of previous study (SD)	-8.9 (21.85)	-45.6 (34.75)	-67.8 (32.21)	-72.8 (32.23)	-84.7 (18.53)	-92.5 (5.80)
Mean % change in BSA involved from baseline of previous study (SD)	-6.0 (18.47)	-23.4 (27.24)	-36.1 (23.88)	-38.6 (26.76)	-51.7 (21.51)	-56.8 (15.56)

Note: n stands for the number of patients who were responder. N1 stands for number of patients with observed data at the visit.
Abbreviations: AD=atopic dermatitis; BSA=body surface area; EASI=eczema area and severity index; EASI-50=50% reduction in EASI; EASI-75=75% reduction in EASI; EASI-90=90% reduction in EASI; IGA=Investigator's Global Assessment; OLE=open label extension; SAF=safety analysis set; SD=standard deviation.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Tables 12.2.4/10c, 12.2.4/11c, 12.2.4/16c, 12.2.4/17c, 12.2.4/12c, and 12.2.4/13c.

Proportion of Patients Achieving an IGA Score of 0 or 1 at Each Visit in R668-AD-1434

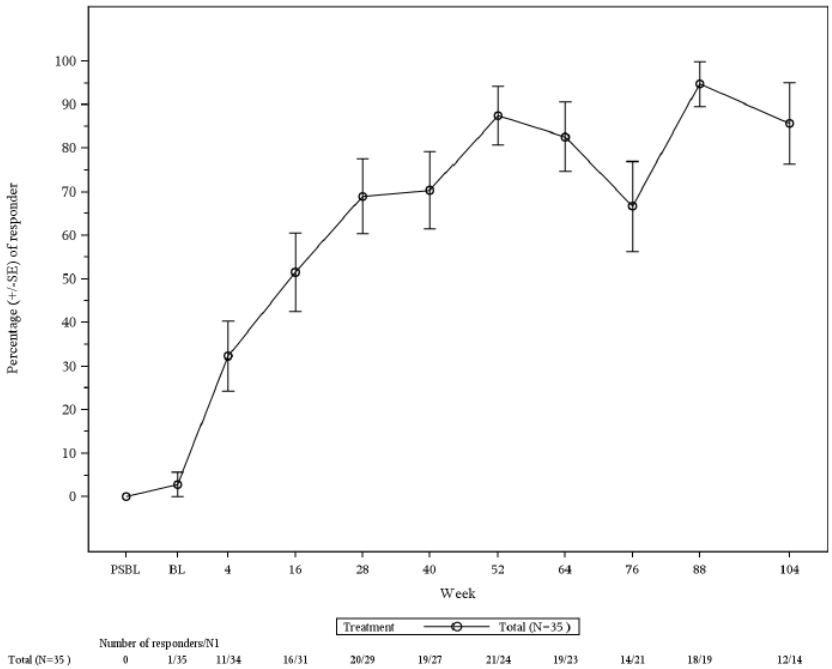
Figure 35 Proportion (±SE) of Patients Achieving IGA Score of 0 or 1 by Visit – Children ≥6 Months to <6 Years of Age (SAF – Patients Who Rolled Over from 1539 Part A – Under R668-AD-1434 Protocol Amendment 3)



Abbreviations: BL=baseline of OLE; IGA=Investigator's Global Assessment; N=number of patients; OLE=open-label extension; SAF=safety analysis set, SE=standard error.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Figure 6.7.1.1/1c

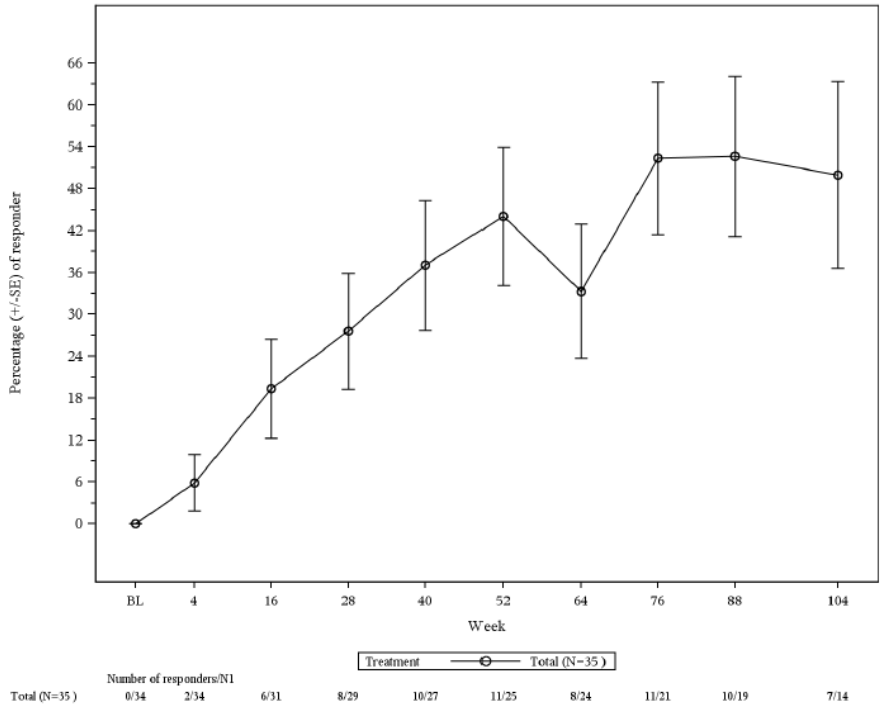
Proportion of Patients Achieving EASI-75 Response Relative to the Baseline of R668-AD-1539 Part A at Each Visit in R668-AD-1434

Figure 36 Proportion (±SE) of Patients Achieving EASI-75 Relative to the Baseline of R668-AD-1539 Part A by Visit – Children ≥6 Months to <6 Years of Age (SAF – Patients Who Rolled Over from 1539 Part A – Under R668-AD-1434 Protocol Amendment 3)



Abbreviations: BL=baseline of OLE; EASI=eczema area and severity index; N=number of patients; OLE=open-label extension; PBSL=previous study baseline, SAF=safety analysis set; SE=standard error.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Figure 6.7.2.1/1c

Figure 37 Proportion (±SE) of Patients Achieving IGA Score of 0 or 1 by Visit – Children ≥6 Months to <6 Years of Age (SAF – Patients Who Rolled Over from 1539 Part A – Under R668-AD-1434 Protocol Amendment 3)



Abbreviations: BL=baseline of OLE; IGA=Investigator's Global Assessment; N=number of patients; OLE=open-label extension; SAF=safety analysis set, SE=standard error.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Figure 6.7.1.1/1c

R668-AD-1434

Table 58 Key Efficacy Parameters for Children ≥6 Months to <2 Years of Age (SAF, Children ≥6 Months to <2 Years of Age)

	Total (N=19)					
	Baseline of OLE	**Week 4**	**Week 16**	**Week 28**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	2/19 (10.5%)	3/18 (16.7%)	6/15 (40.0%)	3/11 (27.3%)	5/10 (50.0%)	3/8 (37.5%)
Proportion of patients achieving EASI-75 relative to baseline of previous study, n/N1 (%)	5/19 (26.3%)	7/18 (38.9%)	8/15 (53.3%)	8/11 (72.7%)	8/10 (80.0%)	7/8 (87.5%)
Proportion of patients achieving EASI-50 relative to baseline of previous study, n/N1 (%)	7/19 (36.8%)	11/18 (61.1%)	10/15 (66.7%)	8/11 (72.7%)	8/10 (80.0%)	8/8 (100%)
Proportion of patients achieving EASI-90 relative to baseline of previous study, n/N1 (%)	2/19 (10.5%)	5/18 (27.8%)	6/15 (40.0%)	5/11 (45.5%)	6/10 (60.0%)	6/8 (75.0%)
Mean % change in EASI score from baseline of previous study (SD)	-35.3 (42.37)	-49.8 (44.97)	-65.6 (38.51)	-70.2 (40.24)	-81.8 (29.10)	-91.51 (8.19)

Note: n stands for the number of patients who were responder. N1 stands for number of patients with observed data at the visit.
Abbreviations: EASI, eczema area and severity index; IGA, Investigator's Global Assessment; SAF, safety analysis set; SD, standard deviation.
Source: PTT 6.1.1.1/2c, 6.2.1.1/2c, 6.2.6.1/2c, 6.2.7.1/2c, and 6.2.3.1/2c.

Assessment of Efficacy Parameters Following Treatment Discontinuation

As per protocol, dupilumab was discontinued in patients who achieved a sustained remission defined as achieving and maintaining an IGA score of 0/1 for at least 12 consecutive weeks after 40 weeks of treatment. In patients who had achieved sustained remission, AD disease activity was monitored after discontinuation of dupilumab. In case these patients had a relapse of disease defined as IGA score ≥2,

dupilumab was re-initiated at the same dose regimen they were receiving previously. *Table **59*** provides efficacy data following treatment discontinuation. 30/180 (16.7%) patients completed week 52, 18/30 (60%) had a sustained remission and 14 of these re-initiated dupilumab treatment after 12 weeks (median).

Table 59 Summary of Sustained Remission Defined by IGA 0 or 1 for ≥12 Weeks - Children ≥6 Months to <6 Years of Age (SAF)

	Total (N=180)
Number of Patient who completed Week 52	30 (16.7%)
Number of Patient with Sustained Remission [1]	18/30 (60.0%)
Number of Patient re-initiated study drug after first sustained remission [2]	14/18 (77.8%)
Time to re-initiation of study drug after first sustained remission (weeks) [3]	
n	14
Mean (SD)	17.9 (16.50)
Q1	12.0
Median	12.0
Q3	12.0
Min : Max	8 : 64

[1] Percentages were calculated based on number of patients who completed week 52.
[2] Percentages were calculated based on number of patients who completed week 52 and with sustained remission.
[3] A patient had re-initiation of study drug at unscheduled visit, hence time to re-initiation of study drug cannot be determined.
Note: Patients who had sustained remission of the disease, as defined by maintenance of an Investigator's Global Assessment (IGA) score of 0 or 1 continuously for a 12-week period, after week 40 were discontinued from study drug (for example, a patient who has an IGA score of 0 or 1 through week 40 to week 52, inclusive, was discontinued from the study drug at week 52; similarly, a patient who has an IGA score of 0 or 1 through week 52 to week 64, inclusive, was discontinued from study drug at week 64, and so on)
Abbreviations: IGA=Investigator's Global Assessment; Max=maximum; Min=minimum; SAF=safety analysis set; SD=standard deviation; Q1=quartile 1; Q3=quartile 3.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Post-text Table 6.1.4.2/1c

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This application for extension of indication is supported by 3 clinical studies: the pivotal completed phase 3 study R668-AD 1539-Part B, and two supportive studies R668-AD 1539-Part A (completed Phase 2) and R668-AD-1434 (ongoing open-label extension study, OLE). The studies target patients aged ≥6 months to ≤6 years with moderate-to severe AD whose disease was not adequately controlled with topical treatment (note: In Part A only patients with severe AD were enrolled and in Part B, the patient number with moderate disease was capped at ~40). The claimed indication is "Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy".

A paediatric investigation plan was submitted in 2013 and approved in 2014 followed by 7 modifications. A waiver was granted for the paediatric population from birth to less than 6 months.

The integral parts of the main study R668-AD-1539 were conducted sequentially.

Part A was a phase 2, open-label, single ascending dose, sequential cohort study investigating the pharmacokinetics, safety, and initial assessment of efficacy of a single dose of SC dupilumab (DUP) in 40

paediatric patients with severe AD. Part A was initiated to establish the dose regimen for the subsequent pivotal study Part B; patients were dosed with dupilumab 3 mg or 6 mg per kg bodyweight. All received concomitant low to medium TCS/TCI. The study design included 2 age cohorts: Cohort 1 (≥2 to <6 years) and cohort 2 (≥6 months to <2 years) which were subdivided in 2 dose cohorts, i.e. sub-cohort A (3 mg/kg) and sub-cohort B (6 mg/kg).

Part B was a phase 3, randomised, double-blind, placebo (PBO)-controlled, pivotal study in paediatric patients ≥6 months to <6 years of age with moderate-to-severe AD whose disease was not adequately controlled with topical medication investigating the efficacy of 200/300 mg dupilumab Q4W in combination with low potency TCS after 16 weeks of treatment. Patients were randomised in a 1:1 ration to the 200/300 mg Q4W+TCS or placebo+TCS treatment group.

Patients who had completed the treatment period of study parts A and/or B were eligible for participation in the **OLE study R668-AD-1434**, i.e. at week 4 or 16. The OLE study is investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in paediatric patients with AD aged ≥6 months to <18 years who had previously completed a clinical study with dupilumab. Patients declining this participation were followed-up for either 4 weeks (Part A) or 12 weeks (Part B).

The overall design of Study R668-AD 1539 was conducted in accordance with the agreed PIP and considered adequate by the CHMP. The selected study population in Part A is relevant for the applied indication. The study population in Part B comprises patients with moderate or severe AD, whereas the claimed indication is restricted to severe AD. At the CHMP request, further analyses were conducted by the MAH and discussed below.

The co-primary endpoint of the pivotal Study Part B was the Proportion of patients with IGA 0 or 1 at week 16 and the Proportion of patients with EASI-75 at week 16. The key secondary endpoints were the Percent change in EASI score from baseline to week 16 and the Percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score. Efficacy assessments included the analyses of IGA, EASI, daily worst scratch/itch NRS score, and BSA involvement with AD. As to the primary endpoints both the IGA and EASI scales are established outcome measures and correlation with disease severity and activity. The worst itch (WI-)NRS scale as patient-reported outcome is a valid and fit-for-purpose tool to measure itch severity, thus, this is an accepted key secondary efficacy endpoint. The co-primary and key secondary endpoints, including standard efficacy variables like the EASI-75 and IGA 0 or 1 which represent a sufficient degree of improvement, are considered adequate and in line with the objectives of this study. The chosen study objectives and endpoints are considered relevant to support the claimed indication. Topical treatment with TCS and moisturizers was standardised before randomisation. The choice of the background treatment is reasonable to address the considerable disease burden of patients, especially of those assigned to the PBO arm. As these young patients might experience a greater toxicity from percutaneous absorption of TCS with higher potency due to their increased surface to volume ratio and/or metabolic differences the use of low-potency TCS is endorsed.

In Part A, the primary endpoints were the concentration of functional dupilumab in serum over time and PK parameters and the incidence and severity of TEAEs to week 4. The secondary endpoints were related to safety, efficacy and immunogenicity.

Overall, 197 patients were eligible, 162 thereof were randomised in both treatment groups (n=83 in the DUP+TCS group, n=79 in the PBO+TCS group). The compliance with the study treatments was excellent in both treatment groups. The proportions of patients completing Week 16 were 83/83 (100%) the DUP+TCS group and 76/79 (96.2%) in the PBO+TCS group.

The sample sizes are considered acceptable and are in line with PDCO requirements. R668-AD-1539 Part B was adequately powered for the primary efficacy analysis for the indication moderate-to-severe AD. Overall, the study R668-AD-1539 Part B was not planned to assess the efficacy of dupilumap in patients

with severe AD. The analyses in the severe population were not included in the hierarchical testing strategy (but 16 endpoints were controlled for multiplicity in the FAS) and there is no type 1 error control for the tests on the severe population which leads to uncertainty of the results from a statistical point of view. The MAH was requested to provide additional evidence of biological plausibility and reproducibility of the observed effects and to provide a comparison of efficacy data in patients with severe AD in different age groups (<6, 6-12, adolescents and adults) and discuss them, giving explanation to possible differences. From a statistical perspective, in general, to support a new indication the efficacy analysis should have the relevant population as the primary population in the statistical analysis plan and therefore assessed with type 1 error control, especially in such a feasible population. From a clinical perspective however, the totality of evidence from the clinical program is considered adequate to support the nominally statistically significant difference between the dupilumab and placebo arms reported for the severe AD population. In addition, the moderate-to-severe multiplicity-controlled endpoints, at time of final analysis, was made up of 75% of patients (125/162) with severe disease at baseline thus the efficacy results in the overall population was represented in majority by the severe patients. In addition, the current approved indication for patients 6 years-11 years old in the EU is 'severe AD', maintaining continuity across paediatric age groups which is endorsed by the CHMP at this time point.

Demographic factors 'age group' and 'weight' are considered unbalanced as the minority of study participants was ≥6 months to <2 years old. A minority of study participants was ≥6 months to <2 years old, i.e. 5/11 (6.3%) in the PBO + TCS group and 6/11 (7.2%) in the DUP+TCS group, and the majority ≥2 years and <6 years (74/79, 93.7% in the PCO+TCS group and 77/83, 92.8% in the DUP+TCS group) resulting in a mean age of 3.9 years in both treatment groups. As to the weight groups: at baseline, 51/162 (31.5%) weighed ≥5 to <15 kg and 111/162 (68.5%) ≥15 to <30 kg group. Other demographic factors were relatively consistent in the overall study population. As requested, the MAH discussed the imbalances based on subgroup analyses and literature review (see below).

Efficacy data and additional analyses

In part B, the proportion of patients achieving IGA scores of 0 or 1 (23/83, 27.7% vs. 3/79, 3.9%, p<0.0001) and EASI-75 (44/83, 53.0% vs. 8/79, 10.7%, p<0.0001) at Week 16 was numerically higher in the DUP+TCS group compared with the PBO+TCS group. In patients with severe AD (IGA 4 at baseline), who achieved IGA scores of 0 or 1 at Week 16, the proportion was also larger in the verum group, (9/63, 14.3% vs. 1/62. 1.7%), and the proportion of patients achieving EASI-75 at Week 16 wad larger in the DUP+TCS group compared with the PBO+TCS group (29/63, 46.0% vs. 4/62, 7.8%). The comparison of the efficacy results in the overall vs. the severe subgroup population showed that the more favourable results related to IGA 0/1 and EASI-90 at week 16 were driven by the treatment response of the patients with moderate disease at Baseline. The results of the requested sensitivity analyses for the co-primary endpoints in the severe population however support the results of the primary analyses. Sensitivity analyses for the key secondary endpoints partly showed differences in the effect size but supported the direction of the effect.

The remaining results were comparable in both subgroups suggesting a consistent treatment effect in the target population. Results from the OLE study confirmed a beneficial effect as increasing patient numbers achieved IGA 0/1 and EASI-90 over time. The results of the Co-primary endpoints are statistically significant and considered clinically relevant and thus, superiority of dupilumab over placebo is demonstrated in patients with (moderate-to-) severe AD.

Results of the key secondary endpoints substantiate the efficacy of dupilumab in the investigated population of patients with moderate-to-severe AD as shown by decline of EASI score which was considerably more pronounced in the DUP+TCS group (-70; mean %Change -63.1 vs. -19.6; mean %change -11.4) with a statistically significant LS mean difference in the percent change from baseline to

week 16 between both treatment groups at Week 16 i.e., -50.4 (-62.38, -38.40). This is interpreted as clinically relevant treatment effect. Another key secondary endpoint was the Percent Change from Baseline to Week 16 in Weekly Average of Worst Scratch/Itch NRS Score from Baseline to Week 16. Decreases in daily worst scratch/itch NRS score were more significant in the verum group (−49.4% vs. −2.2%, LS mean difference -47.1) and considered clinically meaningful. Similar results were observed as to the improvement of weekly average of daily worst scratch/itch NRS score ≥4 or ≥3 from Baseline at Week 16 (≥4 points: 48.1% vs. 8.9%, p<0.0001; ≥3 points: 53.3% vs. 9.9%, p<0.0001). As pruritus is a cardinal symptom of AD with a high impact on life quality, these results substantiate the clinical benefit of dupilumab in the target population. The results of the key secondary endpoints in the subpopulation with severe AD were significant and are considered clinically relevant. These results have been added in section 5.1 of the SmPC.

The analysis of further EASI endpoints, i.e. the proportion of patients in the FAS achieving EASI-50 and -90, or endpoints assessing AD severity as Change from baseline to week 16 in SCORAD/Percent BSA affected by AD, showed that treatment with dupilumab combined with TCS improved AD symptoms far more effectively than placebo and TCS. This is also reflected by results regarding observer- or patient-reported assessments related to treatment effects on sleep quality, skin pain, POEM and others.

The subgroup analyses performed for the most relevant endpoints confirm the superiority of dupilumab over placebo in both weight groups and genders. Regarding both weight subgroups, results differ minimally among each other and compared with the overall results, e.g. the proportion of patients with IGA score 0/1 and EASI-75 at week 16 was higher in patients weighing ≥5 to <15 kg (38.5% vs. 22.8% and 57.7% vs. 50.9%) probably due to a higher exposure. Principally, the results are consistent with those of the overall study population.

As to the age, a trend towards higher clinical benefit caused by dupilumab treatment is observed in the younger patients in the pivotal and the open-label extension study.

The effect of treatment discontinuation on efficacy was analysed in 30 patients who had rolled over from study R668-AD-1539 into Study R668-AD-1434 and who had completed week 52. The majority of patients (14/18, 77.8%) re-initiated dupilumab treatment due to relapse (IGA score ≥2) after an initial sustained remission defined as achieving and maintaining an IGA score of 0/1 for at least 12 consecutive weeks after 40 weeks of treatment. Overall, the data are too limited to draw any robust conclusions; however, results from the older patient population were similar suggesting the need for continuous treatment with dupilumab.

Efficacy results were compared across the paediatric and adult population. Study R668-AD-1652 had enrolled children ≥6 to <12 years with severe AD who received dupilumab in combination with medium potency TCS. Study R668-AD-1526 enrolled an adolescent population with moderate-to-severe AD where dupilumab was administered as monotherapy. Pooled SOLO studies investigated the efficacy of dupilumab monotherapy in adults. Thus, the data allow an orienting evaluation of cross-study efficacy results. The FAS analysis sets were of similar sizes in the paediatric populations; within the adolescent and adult population the ratio of patients with moderate or severe disease was more balanced than in the youngest study population. At baseline, mean EASI, worst scratch/itch NRS score, SCORAD and BSA involvement were balanced across all studies, IGA scores varied dependent of disease severity. Considering the variations in study designs, the systematic comparison of all relevant efficacy parameters provides evidence that dupilumab provides clinical benefit to a similar extent also in the age group ≥6 months to ≤6 years.

In Part A, only one single dose was administered, results should be construed as supplementary information, however, indicate some clinical benefit after Week 3.

In OLE study R668-AD-1434, overall 180 patients ≥6 months to <6 years of age were enrolled, 30 of these received dupilumab until week 52 and 27 until week 104. The majority applied concomitantly TCS with variable potency (146/180, 81%).

Patients enrolled in parent study R668-AD-1539 Part A had a measurable therapeutic benefit throughout the open-label extension study R668-AD-1434. Results of the primary and (key) secondary endpoints show steady improvement of AD related symptoms that are considered clinically meaningful even in the uncontrolled setting. At the CHMP request, the MAH performed additional efficacy analyses based on an updated data cut off of OLE study R688-AD-1434 (10-Mar-2022). There was a consistent trend towards incremental efficacy consistently across all endpoints between week 16 and week 52. This was displayed with updated data in the FAS, across the two age and weight sub-groups. Key efficacy outcomes by previous treatment (placebo/dupilumab) were also reported with an updated data cut off, again consistent with efficacy trends.

2.5.3. Conclusions on the clinical efficacy

The co-primary endpoints were met and considered statically and clinically relevant. The superiority of dupilumab+TCS over placebo+TCS in the indication "Dupixent is indicated for the treatment of severe atopic dermatitis in children 6 months to 11 years old who are candidates for systemic therapy" was demonstrated for the target population (severe AD).

The final results of the OLE study R668-AD-1434 will be submitted by the MAH to provide additional long term efficacy data.

2.6. Clinical safety

Introduction

The safety evaluation plan comprises different safety analysis sets. The safety analysis set (SAF) for the individual studies described in the clinical summary included all patients who received at least 1 dose of study drug. Patients were analyzed as they were treated. For ADA analyses sets, see Immunogenicity section below. The safety data have not been pooled except for patient accountability and exposure.

Patient exposure

Patient disposition

A summary of the sample sizes per study (SAF) is presented in *Table* ***60***. The safety analysis set (SAF) for the individual studies described in this summary included all patients who received at least 1 dose of study drug. Patients were analyzed as they were treated.

Table 60 Sample Size by Study Number – SAF – (All Enrolled Patients)

Study Identifier	Number of Patients Enrolled	Not Randomized	Randomized	Randomized but not Treated	Treatment Group	SAF
R668-AD-1539 Part B	162	0	162	1	TOTAL	161
	79	0	79	1	Placebo + TCS	78
	83	0	83	0	Dupilumab 200/300 mg Q4W + TCS	83
R668-AD-1434 [1]	180	NA	NA	NA	TOTAL	180
R668-AD-1539 Part A	40	NA	NA	NA	TOTAL	40
					Dupilumab 3 mg/kg	20
					Dupilumab 6 mg/kg	20

Abbreviations: NA, not applicable; OLE, open label extension; Q4W, every 4 weeks; SAF, safety analysis set.
[1] Study R668-AD-1434 includes patients ≥6 months to <18 years of age. The number of patients listed in the table includes all patients from the studies R668-AD-1539 Parts A and B (and therefore aged ≥6 months to <6 years) as of data cutoff for this submission (31 Jul 2021), including 36 of the 40 patients from R668-AD-1539 Part A and 144 of 161 patients from R668-AD-1539 Part B who entered the OLE.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 5, Module 5.3.5.2 R668-AD-1434 Third-step Analysis Table 5, and Module 5.3.5.1 R668-AD-1539 Part A Table 3.

R668-AD-1539 Part B

Patient disposition in study R668-AD-1539 Part B is presented in *Table **61***.

Table 61 Summary of Patient Disposition in Study R668-AD-1539– Part B – All Randomised Patients

	Placebo + TCS (N=79)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=162)
Received study medication, n (%)	78 (98.7%)	83 (100%)	161 (99.4%)
Patient randomized but not treated, n (%)	1 (1.3%)	0	1 (0.6%)
Completed the study treatment, n (%)			
Yes	75 (94.9%)	82 (98.8%)	157 (96.9%)
No	3 (3.8%)	1 (1.2%)	4 (2.5%)
Adverse event	0	1 (1.2%)	1 (0.6%)
Withdrawal of consent by the Subject	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	1 (1.3%)	0	1 (0.6%)
Other	1 (1.3%)	0	1 (0.6%)
Subject started systemic corticosteroid and had to withdraw study IP	1 (1.3%)	0	1 (0.6%)
Transition into another study, n (%)			
Yes	75 (94.9%)	81 (97.6%)	156 (96.3%)
R668-AD-1434	75 (94.9%)	81 (97.6%)	156 (96.3%)
No	4 (5.1%)	2 (2.4%)	6 (3.7%)
Completed Week 28 (End of Study), n (%)	1 (1.3%)	1 (1.2%)	2 (1.2%)
Ongoing, n (%)	0	1 (1.2%)	1 (0.6%)
Discontinuation from study with reason, n (%)	3 (3.8%)	0	3 (1.9%)
Noncompliance with protocol by the subject	0	0	0
Adverse event	0	0	0
Lack of Efficacy	0	0	0
Decision by the Investigator / Sponsor	0	0	0
Withdrawal of consent by the Subject	1 (1.3%)	0	1 (0.6%)
Lost to follow-up	1 (1.3%)	0	1 (0.6%)
Death	0	0	0
Other	1 (1.3%)	0	1 (0.6%)
Patient randomized in error	1 (1.3%)	0	1 (0.6%)

Abbreviations: Q4W=every 4 weeks; TCS=topical corticosteroids.
The percentage is based on the number of randomized patients in each treatment group as denominator.
No subjects discontinued study treatment due to COVID-19.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 3 and Table 4

Study R668-AD-1539 Part A

Patient disposition in study R668-AD-1539 Part B is presented in *Table **62***.

Table 62 Summary of Patient Disposition – Part A (Enrolled Patients)

	≥2 to <6 years old			≥6 months to <2 years old			
	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	Total (N=40)
Patients enrolled	10 (100%)	10 (100%)	20 (100%)	10 (100%)	10 (100%)	20 (100%)	40 (100%)
Safety analysis set	10 (100%)	10 (100%)	20 (100%)	10 (100%)	10 (100%)	20 (100%)	40 (100%)
Patients who completed Part A	10 (100%)	10 (100%)	20 (100%)	9 (90.0%)	10 (100%)	19 (95.0%)	39 (97.5%)
Number of patients who discontinued from the study, n (%)	0	0	0	1 (10.0%)	0	1 (5.0%)	1 (2.5%)
Reason for premature discontinuation							
Adverse event	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0
Lack of efficacy	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0	0
Physician decision	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0
Withdrawal by subject	0	0	0	1 (10.0%)	0	1 (5.0%)	1 (2.5%)
Other	0	0	0	0	0	0	0
Completed week 4, n (%)	10 (100%)	10 (100%)	20 (100%)	10 (100%)	10 (100%)	20 (100%)	40 (100%)
Patients who continued in open label extension study (R668-AD-1434)	10 (100%)	10 (100%)	20 (100%)	9 (90.0%)	9 (90.0%)	18 (90.0%)	38 (95.0%)

Percentages are based on the number of enrolled patients.
Source: PTT 1.1.1

Study R668-AD-1434

The disposition of participants in the OLE study is displayed below:

Table 63 Summary of Patient Accountability and Study Disposition - Children ≥6 Months to <6 Years of Age (SAF)

	Total (N=180)
Patients Screened	180
From Previous Study Number	
R668-AD-1539	36 (20.0%)
R668-AD-1539 PART B	144 (80.0%)
Patients Enrolled[1]	180 (100%)
Patients Screen Failed[1]	0
Patients in Safety Analysis Set (SAF)	180 (100%)
Patients who completed study	0
Patients ongoing	167 (92.8%)
Patients who did not complete study	13 (7.2%)
Adverse Event	1 (0.6%)
Physician Decision	0
Withdrawal by Subject	10 (5.6%)
Lack of Efficacy	1 (0.6%)
Lost to Follow-up	1 (0.6%)

	Total (N=180)
Death	0
Other	0
Patients who completed >= Week 16	122 (67.8%)
Patients who completed >= Week 24	74 (41.1%)
Patients who completed >= Week 26	68 (37.8%)
Patients who completed >= Week 52	30 (16.7%)
Patients who completed >= Week 78	30 (16.7%)
Patients who completed >= Week 104	29 (16.1%)
Patients who completed >= Week 156	15 (8.3%)
Patients who completed >= Week 208	0
Patients who completed >= Week 260	0

[1] Percentages are based on the number of screened patients
[2] Refers to discontinuation from the study, not study treatment
Abbreviation: SAF, safety analysis set
Source: Summarized from PTT 1.1.1/3c and PTT 1.1.2/1c

In total, 13/180 (7.2%) patients had discontinued from the OLE study R668-AD-1434 at the time of data cutoff. The primary reasons for discontinuation were as follows

- Withdrawal by subject: 10/180 (5.6%) patients
- Adverse event: 1/180 (0.6%) patients
- Lack of efficacy: 1/180 (0.6%) patients
- Lost to follow-up: 1/180 (0.6%) patients.

Patient exposure

Exposure data were pooled for the studies included in this submission and are presented by treatment duration and dupilumab dose administration in *Table **64*** of the clinical summary including all patients who received at least 1 dose of dupilumab in R668-AD-1539 Part A, R668-AD-1539 Part B, or R668-AD-1434.

Table 64 Summary of Study Drug Administration (Cumulative) and Duration of Treatment in Children Aged ≥6 Months to <6 Years from All Studies (Pooled) – SAF

	Dupilumab				
Exposure Characteristics	**3 mg/kg single dose or 3 mg/kg QW (N=20)**	**6 mg/kg single dose or 6 mg/kg QW (N=20)**	**200/300 mg Q2W (N=8)**	**200/300 mg Q4W (N=179)**	**All Combined [3] (N=193)**
Number of treated patients [1]	20	20	8	179	193
Summary of number of study drug injections administered					
Mean (SD)	69.4 (45.28)	49.7 (38.10)	16.4 (20.21)	7.3 (4.83)	19.8 (32.37)
Q1	28.5	13.0	4.0	5.0	5.0
Median	81.0	46.0	7.5	7.0	7.0
Q3	106.0	74.0	23.0	9.0	11.0
Min : Max	1 : 139	1 : 116	1 : 61	1 : 50	1 : 145
Number of study drug administered cumulative, n(%)					
>=1	20 (100%)	20 (100%)	8 (100%)	179 (100%)	193 (100%)
>=4	17 (85.0%)	18 (90.0%)	6 (75.0%)	157 (87.7%)	170 (88.1%)
>=8	16 (80.0%)	17 (85.0%)	4 (50.0%)	73 (40.8%)	92 (47.7%)
>=12	16 (80.0%)	16 (80.0%)	3 (37.5%)	17 (9.5%)	43 (22.3%)
>=16	16 (80.0%)	14 (70.0%)	3 (37.5%)	6 (3.4%)	33 (17.1%)
>=24	15 (75.0%)	14 (70.0%)	2 (25.0%)	2 (1.1%)	32 (16.6%)
>=48	14 (70.0%)	10 (50.0%)	1 (12.5%)	1 (0.6%)	28 (14.5%)
>=52	14 (70.0%)	9 (45.0%)	1 (12.5%)	0	28 (14.5%)
>=76	11 (55.0%)	5 (25.0%)	0	0	20 (10.4%)
>=100	6 (30.0%)	3 (15.0%)	0	0	10 (5.2%)
>=124	2 (10.0%)	0	0	0	6 (3.1%)
>=148	0	0	0	0	0
Summary of treatment duration [2] (Weeks)					
Mean (SD)	73.7 (47.12)	52.1 (38.28)	35.0 (41.19)	29.5 (16.77)	41.8 (40.65)
Q1	36.2	18.1	9.0	20.0	20.0
Median	86.6	48.5	18.2	27.9	28.1
Q3	110.9	78.9	50.6	36.3	43.7
Min : Max	1 : 141	1 : 119	2 : 122	4 : 113	1 : 183

Exposure Characteristics	Dupilumab				
	3 mg/kg single dose or 3 mg/kg QW (N=20)	6 mg/kg single dose or 6 mg/kg QW (N=20)	200/300 mg Q2W (N=8)	200/300 mg Q4W (N=179)	All Combined [3] (N=193)
Summary of treatment duration [2] (Weeks)					
Treatment duration [2] (Weeks) cumulative, n(%)					
>=1 week	20 (100%)	20 (100%)	8 (100%)	179 (100%)	193 (100%)
>=4 weeks	17 (85.0%)	18 (90.0%)	7 (87.5%)	179 (100%)	189 (97.9%)
>=8 weeks	16 (80.0%)	17 (85.0%)	6 (75.0%)	170 (95.0%)	181 (93.8%)
>=12 weeks	16 (80.0%)	17 (85.0%)	6 (75.0%)	164 (91.6%)	175 (90.7%)
>=16 weeks	16 (80.0%)	15 (75.0%)	5 (62.5%)	153 (85.5%)	164 (85.0%)
>=26 weeks	15 (75.0%)	14 (70.0%)	3 (37.5%)	94 (52.5%)	109 (56.5%)
>=52 weeks	15 (75.0%)	10 (50.0%)	2 (25.0%)	8 (4.5%)	31 (16.1%)
>=78 weeks	12 (60.0%)	5 (25.0%)	1 (12.5%)	4 (2.2%)	26 (13.5%)
>=104 weeks	7 (35.0%)	3 (15.0%)	1 (12.5%)	2 (1.1%)	22 (11.4%)
>=130 weeks	1 (5.0%)	0	0	0	16 (8.3%)
Treatment duration [2] (Weeks) by category, n(%)					
<1 week	0	0	0	0	0
1-<4 weeks	3 (15.0%)	2 (10.0%)	1 (12.5%)	0	4 (2.1%)
4-<8 weeks	1 (5.0%)	1 (5.0%)	1 (12.5%)	9 (5.0%)	8 (4.1%)
8-<12 weeks	0	0	0	6 (3.4%)	6 (3.1%)
12-<16 weeks	0	2 (10.0%)	1 (12.5%)	11 (6.1%)	11 (5.7%)
16-<26 weeks	1 (5.0%)	1 (5.0%)	2 (25.0%)	59 (33.0%)	55 (28.5%)
26-<52 weeks	0	4 (20.0%)	1 (12.5%)	86 (48.0%)	78 (40.4%)
52-<78 weeks	3 (15.0%)	5 (25.0%)	1 (12.5%)	4 (2.2%)	5 (2.6%)
78-<104 weeks	5 (25.0%)	2 (10.0%)	0	2 (1.1%)	4 (2.1%)
104-<130 weeks	6 (30.0%)	3 (15.0%)	1 (12.5%)	2 (1.1%)	6 (3.1%)
>=130 weeks	1 (5.0%)	0	0	0	16 (8.3%)

[1] Includes the studies R668-AD-1539 Part A, R668-AD-1539 Part B, and R668-AD-1434. The 193 patients include all patients who received at least 1 dose of dupilumab in R668-AD-1539 Part A, R668-AD-1539 Part B or the OLE study: 153/161 patients from R668-AD-1539 Part B (8 patients in the placebo + TCS group did not rollover to the OLE study) and 40 patients from R668-AD-1539 Part A.
[2] Treatment duration is calculated as sum of treatment exposure to dupilumab for each dose regimen in each individual study.
[3] Patients who received at least 1 dupilumab dose in 1 of the studies were included in this column and counted only once. The duration of treatment exposure to dupilumab for a patient who entered study R668-AD-1434 OLE was calculated as the sum of the duration of treatment exposure to dupilumab in the previous study plus the duration of treatment exposure to dupilumab in the OLE study.
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; TCS, topical corticosteroid.
Source: Module 5.3.5.3 R668-AD-6m to 6y Table 5.2.1/1 and Table 5.2.2/1

R668-AD-1539, Part B

The exposure in study R668-AD-1539 Part B is presented in *Table **65*** (clin. summary) and *Table **66***.

Table 65 Summary of Study Drug Administration and Treatment Exposure in Study R668-AD-1539 – Part B – SAF

Exposure Characteristics	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Summary of number of study drug doses administered			
Mean (SD)	3.9 (0.37)	4.0 (0.27)	3.9 (0.32)
Median	4.0	4.0	4.0
Min: Max	2: 4	2: 4	2: 4
Number of study drug doses administered, n(%)			
1	0	0	0
2	2 (2.6%)	1 (1.2%)	3 (1.9%)
3	3 (3.8%)	2 (2.4%)	5 (3.1%)
4	73 (93.6%)	80 (96.4%)	153 (95.0%)
Summary of treatment duration (Days) [1]			
Mean (SD)	110.7 (9.81)	112.1 (7.84)	111.4 (8.85)
Median	112.0	112.0	112.0
Min: Max	56: 126	57: 134	56: 134

Abbreviations: Max=maximum; Min=minimum; Q4W=every 4 weeks; SAF=safety analysis set; SD=standard deviation; TCS=topical corticosteroids.
[1] Treatment duration = date of last study injection - date of first study drug injection + 28 for Q4W patients
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Table 5.2.1/1 and 5.2.1/2.

Table 66 Treatment Exposure and Duration – Part B (SAF)

Exposure Characteristics	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Summary of treatment duration (Days) [1]			
n	78	83	161
Mean (SD)	110.7 (9.81)	112.1 (7.84)	111.4 (8.85)
Q1	111.0	111.0	111.0
Median	112.0	112.0	112.0
Q3	113.0	113.0	113.0
Min: Max	56: 126	57: 134	56: 134
Treatment duration (Days) by category, n (%)			
1 - 27 Days	0	0	0
28 - 55 Days	0	0	0
56 - 83 Days	2 (2.6%)	1 (1.2%)	3 (1.9%)
84 - 111 Days	21 (26.9%)	20 (24.1%)	41 (25.5%)
≥ 112 Days	55 (70.5%)	62 (74.7%)	117 (72.7%)
Treatment duration (Days) cumulative, n (%)			
≥28 Days	78 (100%)	83 (100%)	161 (100%)
≥56 Days	78 (100%)	83 (100%)	161 (100%)
≥84 Days	76 (97.4%)	82 (98.8%)	158 (98.1%)
≥112 Days	55 (70.5%)	62 (74.7%)	117 (72.7%)
Summary of patients with observation period during the study [2]			
n	78	83	161
Mean (SD)	115.3 (14.32)	117.1 (12.82)	116.2 (13.55)
Q1	113.0	113.0	113.0
Median	113.0	113.0	113.0
Q3	115.0	115.0	115.0
Min: Max	50: 198	109: 197	50: 198
Patients with observation period during the study (Days) by category, n(%)			
1 - 7 Days	0	0	0
8 - 14 Days	0	0	0
15 - 21 Days	0	0	0
22 - 28 Days	0	0	0
29 - 56 Days	1 (1.3%)	0	1 (0.6%)
57 - 84 Days	0	0	0
85 - 112 Days	15 (19.2%)	13 (15.7%)	28 (17.4%)
113 - 140 Days	59 (75.6%)	65 (78.3%)	124 (77.0%)
141 - 168 Days	2 (2.6%)	4 (4.8%)	6 (3.7%)
169 - 196 Days	0	0	0
≥197 Days	1 (1.3%)	1 (1.2%)	2 (1.2%)

Exposure Characteristics	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)	Total (N=161)
Patients with observation period duration during the study cumulative, n(%)			
< 8 Days	0	0	0
≥8 Days	78 (100%)	83 (100%)	161 (100%)
≥15 Days	78 (100%)	83 (100%)	161 (100%)
≥ 22 Days	78 (100%)	83 (100%)	161 (100%)
≥ 29 Days	78 (100%)	83 (100%)	161 (100%)
≥ 57 Days	77 (98.7%)	83 (100%)	160 (99.4%)
≥ 85 Days	77 (98.7%)	83 (100%)	160 (99.4%)
≥113 Days	62 (79.5%)	70 (84.3%)	132 (82.0%)
≥ 141 Days	3 (3.8%)	5 (6.0%)	8 (5.0%)
≥ 169 Days	1 (1.3%)	1 (1.2%)	2 (1.2%)
≥ 197 Days	1 (1.3%)	1 (1.2%)	2 (1.2%)

Abbreviations: Max=maximum; Min=minimum; Q1=quartile 1; Q3=quartile 3; Q4W=every 4 weeks; SAF=safety analysis set; SD=standard deviation; TCS=topical corticosteroids.
[1] Treatment duration = date of last study injection - date of first study drug injection + 28.
[2] Observation period = date of the last visit - date of the first study drug injection + 1.
Source: PTT 5.2.1/2

R668-AD-1539, Part A

The age-specific observation periods are presented below:

Table 67 Duration of Observation Period (Safety Analysis Set)

	≥2 to <6 years old			≥6 months to <2 years old			
Exposure Characteristics	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	Total (N=40)
Summary of patients with observation period during the study							
n	10	10	20	10	10	20	40
Mean (SD)	31.7 (6.62)	30.4 (2.76)	31.1 (4.98)	34.8 (15.01)	30.9 (4.56)	32.9 (10.98)	32.0 (8.46)
Q1	29.0	28.0	28.5	27.0	29.0	28.0	28.0
Median	30.0	30.5	30.0	29.0	29.0	29.0	29.0
Q3	31.0	32.0	32.0	32.0	32.0	32.0	32.0
Min : Max	27 : 50	27 : 35	27 : 50	23 : 67	25 : 41	23 : 67	23 : 67
Patients with observation period during the study (days) by category, n(%)							
≥3 days	0	0	0	0	0	0	0
≥8 days	0	0	0	0	0	0	0
≥18 days	2 (20.0%)	3 (30.0%)	5 (25.0%)	4 (40.0%)	2 (20.0%)	6 (30.0%)	11 (27.5%)
≥29 days	7 (70.0%)	7 (70.0%)	14 (70.0%)	4 (40.0%)	8 (80.0%)	12 (60.0%)	26 (65.0%)
≥43 days	1 (10.0%)	0	1 (5.0%)	0	0	0	1 (2.5%)
≥57 days	0	0	0	2 (20.0%)	0	2 (10.0%)	2 (5.0%)

Observation period categories were mutually exclusive.
Source: PTT 5.1.1

R668-AD-1434

*Table **68*** below summarises the treatment sequence for all patients included in the OLE, as the administered dose regimens differed in both parts A and B of parent study R668-AD-1539 due to different study designs and protocol amendments.

Table 68 Summary of Actual Treatment Sequence Received for ALL Patients in the OLE - Children ≥6 Months to <6 Years of Age (SAF)

Actual Treatment Sequence	Total (N=180)
Dupilumab 3 mg/kg QW	7
Dupilumab 3 mg/kg QW->200 or 300 mg Q4W	10
Dupilumab 6 mg/kg QW	3
Dupilumab 6 mg/kg QW->200 or 300 mg Q4W	13
Dupilumab 6 mg/kg QW->200 or 300 mg Q4W->200 or 300 mg Q2W	2
Dupilumab 200 or 300 mg Q4W	139
Dupilumab 200 or 300 mg Q4W->200 or 300 mg Q2W	4
Dupilumab 200 or 300 mg Q2W	2

Abbreviations: OLE, open-label extension; SAF, safety analysis population; QW, once a week; Q2W, every 2 weeks; Q4W, every 4 weeks
Source: PTT 1.1.1/1c

Adverse events

The MAH provided adverse event analyses for all included patients with moderate-to-severe AD and a so-called subgroup analysis for those patients who had severe AD at baseline. Safety results and the corresponding assessment of patients with severe AD (claimed indication) are presented together in the respective sections for pivotal study R668-AD-1539 Part B and OLE study R668-AD-1434 to provide a better comparability of the data. In supportive study R668-AD-1539 Part A, all patients had severe AD on enrollment.

Overview of adverse events

R668-AD-1539 Part B (moderate-to-severe AD)

An overview of adverse events is provided in *Table* ***69***.

The proportion of patients who had at least 1 TEAE during the 16-week treatment period was higher in the PBO + TCS group (58/78; 74.4%) than in the DUP + TCS group (53/83; 63.9%).

Table 69 Overall Summary of Treatment-Emergent Adverse Events During the 16-Week Treatment Period in Study R668-AD-1539 Part B – SAF

	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Any TEAE	58 (74.4%)	53 (63.9%)
Any drug related TEAE	5 (6.4%)	9 (10.8%)
Any TEAE leading to discontinuation of study drug permanently	1 (1.3%)	1 (1.2%)
Maximum intensity for any TEAE, n(%)		
MILD	22 (28.2%)	30 (36.1%)
MODERATE	26 (33.3%)	21 (25.3%)
SEVERE	10 (12.8%)	2 (2.4%)
Any death	0	0
Any TE SAE	4 (5.1%)	0
Any drug related TE SAE	0	0

Any TE SAE leading to Discontinuation of study drug permanently	0	0

Abbreviations: Q4W=every 4 weeks; SAE=serious adverse event; SAF=safety analysis set; TCS=topical corticosteroids; TE=treatment-emergent; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 62

R668-AD-1539 Part B (severe AD)

A summary of TEAEs in patients with severe AD is presented in *Table **70***. 45/61 (73.8%) in the PBO+TCS group experiences any TEAE, slightly more compared with the DUP+TCS group 42/63 (66.7%). Most TEAEs were mild-to-moderate in intensity and balanced between the treatment groups. TESAEs were reported in the PCO+TCS group in 3/61 (4.9%) patients, none occurred in the verum group.

Table 70 Overall Summary of TEAEs in Patients with Severe AD (IGA=4) During the 16-Week Treatment Period in Study R668-AD-1539 Part B (SAF)

	Placebo + TCS (N=61)	**Dupilumab 200/300mg Q4W + TCS (N=63)**
Any TEAE	45 (73.8%)	42 (66.7%)
Any drug related TEAE	5 (8.2%)	8 (12.7%)
Any TEAE leading to discontinuation of study drug permanently	1 (1.6%)	1 (1.6%)
Maximum intensity for any TEAE, n(%)		
MILD	19 (31.1%)	21 (33.3%)
MODERATE	19 (31.1%)	19 (30.2%)
SEVERE	7 (11.5%)	2 (3.2%)
Any death	0	0
Any TE SAE	3 (4.9%)	0
Any drug related TE SAE	0	0
Any TE SAE leading to Discontinuation of study drug permanently	0	0

Abbreviations: Q4W=every 4 weeks; SAE=serious adverse event; SAF=safety analysis set; TCS=topical corticosteroids; TE=treatment-emergent; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 74

R668-AD-1539 Part A (severe AD)

In patients aged ≥2 years to <6 years, 5/20 patients (25.0%) experienced a TEAE in the 4-week treatment period, with a similar incidence between the 2 dose groups: 3/10 (30%) and 2/10 (20%) in patients receiving the 3 mg/kg and 6 mg/kg dupilumab dose, respectively. None of these events

were severe in intensity or assessed by the investigator as being related to study drug. There was 1 serious TEAE (Anaphylactic reaction) which was unrelated to study drug.

In patients aged ≥6 months to <2 years, 14/20 patients (70.0%) experienced a TEAE (*Table **71***). The incidence was the same in the 2 dose groups (7/10 [70%]) indicating no dose response relationship. One patient (5.0%) had a TEAE that was severe in intensity (anaphylactic reaction), and 2 patients (10.0%) had events (1 event per patient) related to the study drug (PT: injection site erythema and PT: diarrhea). All but 3 events in 2 patients (PT: dermatitis atopic, PT: impetigo, and PT: thrombocytosis) were transient and had resolved or were resolving at the time of the data cutoff date. There was one serious TEAE (PT: anaphylactic reaction), which was considered by the investigator to be unrelated to study drug and for which a clear alternative cause was present.

Table 71 Summary of Adverse Events to Week 4 – Part A (Safety Analysis Set)

	≥2 to <6 years old			≥6 months to <2 years old			
	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)	Total (N=40)
Number of TEAEs	5	3	8	11	11	22	30
Number of TEAEs related to study drug	0	0	0	0	2	2	2
Number of serious TEAEs	1	0	1	1	0	1	2
Number of TEAEs resulting in death	0	0	0	0	0	0	0
Number of severe TEAEs	0	0	0	1	0	1	1
Patients with no TEAEs	7 (70.0%)	8 (80.0%)	15 (75.0%)	3 (30.0%)	3 (30.0%)	6 (30.0%)	21 (52.5%)
Patients with at least one TEAE	3 (30.0%)	2 (20.0%)	5 (25.0%)	7 (70.0%)	7 (70.0%)	14 (70.0%)	19 (47.5%)
Patients with TEAEs related to study drug	0	0	0	0	2 (20.0%)	2 (10.0%)	2 (5.0%)
Patients with serious TEAEs	1 (10.0%)	0	1 (5.0%)	1 (10.0%)	0	1 (5.0%)	2 (5.0%)
Patients with TEAEs resulting in study drug discontinuation permanently	0	0	0	0	0	0	0
Patients with TEAEs resulting in study drug discontinuation temporarily	0	0	0	0	0	0	0
Patients with TEAEs resulting in death	0	0	0	0	0	0	0
Patients with severe TEAEs	0	0	0	1 (10.0%)	0	1 (5.0%)	1 (2.5%)

TEAE, treatment-emergent adverse event.
Source: PTT 7.1.1

R668-AD-1434 (moderate-to-severe AD)

A total of 109/180 (60.6%) patients had at least 1 TEAE during the study, see *Table **72***. The majority of the events were mild to moderate in intensity, deemed unrelated to the study drug by the investigator, and resolved over time. One patient permanently discontinued the study drug due to a TEAE (Urticaria). There were 2 (2/180; 1.1%) patients who experienced an SAE during the study (Anaphylactic reaction and Pneumonia mycoplasmal). Neither of the SAEs was deemed related to dupilumab and no patient permanently discontinued study drug due to SAEs.

Table 72 Overall Summary of Treatment-Emergent Adverse Events in Study R668-AD-1434 – Children ≥6 Months to <6 Years of Age (SAF)

	Total (N=180)
Patients with any TEAE	109 (60.6%)
Patients with any drug related TEAE	15 (8.3%)
Patients with any TEAE leading to Permanent Study Drug Discontinuation	1 (0.6%)
Patients with any TEAE with Maximum Intensity	
MILD	50 (27.8%)
MODERATE	56 (31.1%)
SEVERE	3 (1.7%)
Patients with TEAE resulting in Death	0
Patients with any Serious TEAE	2 (1.1%)
Patients with any drug related Serious TEAE	0
Patients with Serious TEAE leading to Permanent Study Drug Discontinuation	0

Abbreviations: SAE=serious adverse event; SAF=safety analysis set; TEAE=treatment-emergent adverse event.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Table 26

R668-AD-1434 (severe AD)

33/50 (66.0%) had at least 1 TEAE in the study, see *Table **73***, and for 10% of patients the TEAEs were deemed drug-related. No severe TEAE were reported.

Table 73 Overall Summary of Treatment-Emergent Adverse Events in Patients with Severe AD (IGA=4) at Baseline - Study R668-AD-1434 (SAF)

	Total (N=50)
Patients with any TEAE	33 (66.0%)
Patients with any drug related TEAE	5 (10.0%)
Patients with any TEAE leading to Permanent Study Drug Discontinuation	0
Patients with any TEAE with Maximum Intensity	
MILD	10 (20.0%)
MODERATE	23 (46.0%)
Patients with TEAE resulting in Death	0
Patients with any Serious TEAE	0
Patients with any drug related Serious TEAE	0
Patients with Serious TEAE leading to Permanent Study Drug Discontinuation	0

Abbreviations: IGA, Investigator's Global Assessment; SAE, serious adverse event; SAF, safety analysis population; TEAE, treatment-emergent adverse event
Source: Module 5.3.5.2 R668 AD 1434 Third-step Analysis Table 37

Treatment-emergent adverse events

R668-AD-1539 Part B (moderate-to-severe AD)

Treatment-emergent Adverse Events (TEAEs) are displayed in *Table **74***. A higher proportion of patients in the PBO + TCS group reported TEAEs during the 16-week treatment period than in the dupilumab + TCS groups.

Table 74 Summary of TEAEs Reported by ≥3% of Patients in any Treatment Group by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1539 Part B – SAF

Primary System Organ Class Preferred Term	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of patients with at least one such event, n (%)	58 (74.4%)	53 (63.9%)
Infections and infestations	40 (51.3%)	35 (42.2%)
Nasopharyngitis	7 (9.0%)	7 (8.4%)
Upper respiratory tract infection	6 (7.7%)	5 (6.0%)
Molluscum contagiosum	2 (2.6%)	4 (4.8%)
Conjunctivitis	0	3 (3.6%)
Gastroenteritis viral	0	3 (3.6%)
Impetigo	6 (7.7%)	3 (3.6%)
Respiratory tract infection viral	3 (3.8%)	0
Staphylococcal skin infection	3 (3.8%)	0
Skin and subcutaneous tissue disorders	28 (35.9%)	17 (20.5%)
Dermatitis atopic	25 (32.1%)	11 (13.3%)
Urticaria	4 (5.1%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	15 (19.2%)	9 (10.8%)
Rhinorrhea	1 (1.3%)	4 (4.8%)
Asthma	5 (6.4%)	3 (3.6%)
Cough	5 (6.4%)	0
Gastrointestinal disorders	6 (7.7%)	8 (9.6%)
Dental caries	0	4 (4.8%)
Blood and lymphatic system disorders	7 (9.0%)	6 (7.2%)
Lymphadenopathy	6 (7.7%)	3 (3.6%)
General disorders and administration site conditions	9 (11.5%)	5 (6.0%)
Pyrexia	7 (9.0%)	1 (1.2%)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; SOC=system organ class; TCS=topical corticosteroids; TEAE=treatment-emergent adverse event.
MedDRA (Version 23.1) coding dictionary applied.
At each level of patient summarization, a patient is counted once if the patient reported one or more events
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 64

R668-AD-1539 Part B (severe AD)

The subgroup with severe AD, a higher proportion of patients in the PBO + TCS group reported TEAEs during the 16-week treatment period than in the dupilumab + TCS groups. TEAEs that occurred with a higher frequency in the verum group were Nasopharyngitis (9.5% vs. 3.3%), Molluscum contagiosum (6.3% vs. 3.3%), Conjunctivitis (4.8% vs. 0), Gastroenteritis viral (4.8% vs. 0), and Dental caries (6.3% vs. 0).

R668-AD-1539 Part A (severe AD)

In patients aged ≥2 years to <6 years (N=20), 3 patients (30.0%) experienced at least 1 TEAE in the 3 mg/kg dose cohort, and 2 patients (20.0%) experienced at least 1 TEAE in the 6 mg/kg dose cohort (*Table **75***).

Table 75 Summary of Treatment-Emergent Adverse Events in Patients ≥2 to <6 years old by System Organ Class and Preferred Term to Week 4 - R668-AD-1539 Part A (Safety Analysis Set)

Primary System Organ Class Preferred Term	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)
Patients with at least one TEAE	3 (30.0%)	2 (20.0%)	5 (25.0%)
Infections and infestations	2 (20.0%)	1 (10.0%)	3 (15.0%)
Nasopharyngitis	1 (10.0%)	1 (10.0%)	2 (10.0%)
Impetigo	1 (10.0%)	0	1 (5.0%)
Skin and subcutaneous tissue disorders	1 (10.0%)	0	1 (5.0%)
Dermatitis atopic	1 (10.0%)	0	1 (5.0%)
General disorders and administration site conditions	1 (10.0%)	0	1 (5.0%)
Pyrexia	1 (10.0%)	0	1 (5.0%)
Immune system disorders	1 (10.0%)	0	1 (5.0%)
Anaphylactic reaction	1 (10.0%)	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	0	1 (10.0%)	1 (5.0%)
Cough	0	1 (10.0%)	1 (5.0%)
Injury, poisoning and procedural complications	0	1 (10.0%)	1 (5.0%)
Skin abrasion	0	1 (10.0%)	1 (5.0%)

MedDRA (Version 21.1) dictionary applied.
Abbreviations: TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part A Post-text Table 7.2.1.1

In patients aged ≥6 months to <2 years, in both the 3 mg/kg and 6 mg/kg dose cohorts, 7/10 patients (70.0%) experienced at least 1 TEAE (*Table **76***).

Table 76 Summary of Treatment-Emergent Adverse Events in Patients ≥6 months to <2 years by System Organ Class and Preferred Term to Week 4 - R668-AD-1539 Part A (Safety Analysis Set)

Primary System Organ Class Preferred Term	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)
Patients with at least one TEAE	7 (70.0%)	7 (70.0%)	14 (70.0%)
Infections and infestations	3 (30.0%)	4 (40.0%)	7 (35.0%)
Nasopharyngitis	1 (10.0%)	2 (20.0%)	3 (15.0%)
Impetigo	1 (10.0%)	1 (10.0%)	2 (10.0%)
Upper respiratory tract infection	1 (10.0%)	1 (10.0%)	2 (10.0%)
Folliculitis	1 (10.0%)	0	1 (5.0%)
Gastrointestinal disorders	3 (30.0%)	1 (10.0%)	4 (20.0%)
Diarrhoea	1 (10.0%)	1 (10.0%)	2 (10.0%)
Constipation	1 (10.0%)	0	1 (5.0%)
Teething	1 (10.0%)	0	1 (5.0%)
Skin and subcutaneous tissue disorders	1 (10.0%)	2 (20.0%)	3 (15.0%)
Dermatitis atopic	0	1 (10.0%)	1 (5.0%)
Urticaria	1 (10.0%)	1 (10.0%)	2 (10.0%)
Primary System Organ Class Preferred Term	**3 mg/kg (N=10)**	**6 mg/kg (N=10)**	**Combined (N=20)**
General disorders and administration site conditions	1 (10.0%)	1 (10.0%)	2 (10.0%)
Pyrexia	1 (10.0%)	0	1 (5.0%)
Injection site erythema	0	1 (10.0%)	1 (5.0%)
Immune system disorders	1 (10.0%)	0	1 (5.0%)
Anaphylactic reaction	1 (10.0%)	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	0	1 (10.0%)	1 (5.0%)
Cough	0	1 (10.0%)	1 (5.0%)
Blood and lymphatic system disorders	0	1 (10.0%)	1 (5.0%)
Thrombocytosis	0	1 (10.0%)	1 (5.0%)
Eye disorders	0	1 (10.0%)	1 (5.0%)
Lacrimation increased	0	1 (10.0%)	1 (5.0%)
Musculoskeletal and connective tissue disorders	1 (10.0%)	0	1 (5.0%)
Joint swelling	1 (10.0%)	0	1 (5.0%)

MedDRA (Version 21.1) dictionary applied.
Abbreviations: TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part A Post-text Table 7.2.1.1

R668-AD-1434 (moderate-to-severe AD)

In the OLE study R668-AD-1434, TEAEs occurred in 109/180 (60.6%) patients with an exposure-adjusted incidence rate (EAIR) of 228.66 per 100 patient years (nP/100PY) (*Table **77***).

Table 77 Summary of TEAEs Reported by ≥2% of Patients by SOC and PT Study R668-AD-1434 – Children ≥6 Months to <6 Years of Age (SAF)

Primary System Organ Class Preferred Term	Total (N=180)	Total (N=180) nP/PY (nP/100 PY)
Number of TEAEs	566	
Patients with at least one TEAE	109 (60.6%)	109/47.7 (228.66)
Infections and infestations	75 (41.7%)	75/68.3 (109.77)
Nasopharyngitis	23 (12.8%)	23/109.0 (21.09)
Upper respiratory tract infection	21 (11.7%)	21/116.5 (18.02)
Ear infection	7 (3.9%)	7/124.6 (5.62)
Impetigo	6 (3.3%)	6/126.5 (4.74)
Conjunctivitis	5 (2.8%)	5/134.6 (3.71)
Pharyngitis streptococcal	5 (2.8%)	5/129.7 (3.85)
Sinusitis	4 (2.2%)	4/132.4 (3.02)
Skin infection	4 (2.2%)	4/132.1 (3.03)
Viral upper respiratory tract infection	4 (2.2%)	4/133.8 (2.99)
Respiratory, thoracic and mediastinal disorders	36 (20.0%)	36/106.7 (33.75)
Cough	15 (8.3%)	15/122.9 (12.21)
Rhinorrhoea	11 (6.1%)	11/129.3 (8.51)
Asthma	6 (3.3%)	6/131.6 (4.56)
Epistaxis	4 (2.2%)	4/135.5 (2.95)
Skin and subcutaneous tissue disorders	29 (16.1%)	29/100.7 (28.80)
Urticaria	13 (7.2%)	13/124.7 (10.42)
Dermatitis atopic	12 (6.7%)	12/119.8 (10.02)
Rash	6 (3.3%)	6/124.6 (4.81)
General disorders and administration site conditions	27 (15.0%)	27/100.3 (26.92)
Pyrexia	21 (11.7%)	21/111.0 (18.91)
Eye disorders	23 (12.8%)	23/115.7 (19.89)
Conjunctivitis allergic	7 (3.9%)	7/130.6 (5.36)
Immune system disorders	18 (10.0%)	18/113.6 (15.84)
Food allergy	9 (5.0%)	9/128.5 (7.00)
Hypersensitivity	5 (2.8%)	5/131.6 (3.80)
Seasonal allergy	4 (2.2%)	4/135.4 (2.95)
Gastrointestinal disorders	14 (7.8%)	14/123.9 (11.30)
Diarrhoea	7 (3.9%)	7/129.6 (5.40)
Vomiting	7 (3.9%)	7/129.8 (5.39)

Note: Patients who experienced more than 1 TEAE were counted only once in each category. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of study observation period.
Abbreviations: nP, number of patients with an event; PY, patient-years; nP/100 PY, number of patients with at least one event per 100 patient-year; SAF, safety analysis population; SOC, system organ class.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Table 27

R668-AD-1434 (severe AD)

TEAEs occurred in 33/50 (66.0%) patients with severe AD, see ***Table 73***. The most common TEAEs were Upper respiratory tract infection (22.0%), Nasopharyngitis (12.0%), Pyrexia (16.0%), Cough (12.0%), Urticaria (12.0%) and Asthma (10.0%).

Severity of Treatment-Emergent Adverse Events

R668-AD-1539 Part B (moderate-to-severe AD)

A higher proportion of patients in the placebo + TCS group experienced severe TEAEs than in the dupilumab + TCS group (12.8% vs. 2.4%). Severe TEAEs are displayed in *Table **78***.

Table 78 Summary of Treatment-Emergent Adverse Events by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1539 Part B – SAF

Primary System Organ Class Preferred Term	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of such events	13	2
Number of patients with at least one such event, n (%)	10 (12.8%)	2 (2.4%)
Blood and lymphatic system disorders	0	1 (1.2%)
Eosinophilia	0	1 (1.2%)
Eye disorders	0	1 (1.2%)
Blepharitis	0	1 (1.2%)
Infections and infestations	4 (5.1%)	0
Cellulitis staphylococcal	1 (1.3%)	0
Dermatitis infected	1 (1.3%)	0
Staphylococcal bacteraemia	1 (1.3%)	0
Staphylococcal skin infection	1 (1.3%)	0
Injury, poisoning and procedural complications	1 (1.3%)	0
Head injury	1 (1.3%)	0
Skin and subcutaneous tissue disorders	7 (9.0%)	0
Dermatitis atopic	6 (7.7%)	0
Pruritus	1 (1.3%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; SOC=system organ class; TCS=topical corticosteroids; TEAE=treatment-emergent adverse event.
MedDRA (Version 23.1) coding dictionary applied.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 65

Part A (severe AD)

In patients aged ≥2 years to <6 years, no TEAEs of severe intensity were reported.

In patients aged ≥6 months to <2 years, 1 severe TEAE (PT Anaphylactic reaction) was reported in the 3 mg/kg dose cohort. Anaphylactic reaction was defined as an AESI, see assessment below.

Study R668-AD-1434 (moderate-to-severe AD)

In the OLE study R668-AD-1434, 3 patients (3/180; 1.7%) had TEAEs that were classified as severe: Blepharitis (1 event), Anaphylactic reaction (1 event), and Urticaria (1 event). All events resolved under supportive treatment.

Treatment-Emergent Treatment-Related Adverse Events

R668-AD-1539 Part B (moderate-to-severe AD)

The proportion of patients who had at least 1 treatment-related TEAE was higher in the dupilumab + TCS group than in the placebo + TCS group (10.8% vs. 6.4%), see *Table **79***.

Table 79 Summary of Treatment-Emergent Treatment-Related Adverse Events by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1539 Part B – SAF

Primary System Organ Class Preferred Term	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of such events	7	10
Number of patients with at least one such event, n (%)	5 (6.4%)	9 (10.8%)
Infections and infestations	2 (2.6%)	4 (4.8%)
Conjunctivitis	0	3 (3.6%)
Herpes virus infection	0	1 (1.2%)
Impetigo	1 (1.3%)	0
Respiratory syncytial virus infection	1 (1.3%)	0
Staphylococcal infection	1 (1.3%)	0
General disorders and administration site conditions	2 (2.6%)	2 (2.4%)
Injection site erythema	0	1 (1.2%)
Injection site swelling	0	1 (1.2%)
Injection site oedema	1 (1.3%)	0
Injection site urticaria	1 (1.3%)	0
Skin and subcutaneous tissue disorders	2 (2.6%)	2 (2.4%)
Erythema	0	1 (1.2%)
Hair growth abnormal	0	1 (1.2%)
Dermatitis atopic	2 (2.6%)	0
Blood and lymphatic system disorders	0	1 (1.2%)
Eosinophilia	0	1 (1.2%)
Eye disorders	0	1 (1.2%)
Blepharitis	0	1 (1.2%)

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

R668-AD-1539 Part A (severe AD)

In patients aged ≥6 months to <2 years, in the 6 mg/kg dose cohort, there were 2 patients with TEAEs considered to be related to the study drug: 1 patient with Diarrhea, and 1 patient with Injection site erythema. Both events were mild in intensity and resolved.

R668-AD-1434 (moderate-to-severe AD)

In the OLE study R668-AD-1434, a total of 15 (15/180; 8.3%) patients experienced a TEAE considered by the investigator to be related to study drug. The most common related TEAEs were: Conjunctivitis, which was reported in 3 patients, and Blepharitis, Conjunctivitis allergic, and Urticaria, which were each reported in 2 patients. All other TEAEs considered to be related to study drug occurred in no more than 1 patient each.

Deaths

There were no deaths in the AD program in patients aged ≥6 months to <6 years.

Treatment-Emergent Serious Adverse Events

R668-AD-1539 Part B (moderate-to-severe AD)

Four patients (4/78; 5.1%) reported SAEs during the 16-week treatment period in the PBO + TCS group; there were no SAEs in the dupilumab + TCS group (***Table 80***). In the placebo + TCS group, 1 patient had 1 SAE of Dermatitis atopic and 1 SAE of Dermatitis infected, 1 patient had an SAE of Hypersensitivity, 1 patient had an SAE of Staphylococcal bacteremia and 1 patient had an SAE of Cellulitis staphylococcal (*Table* ***80***). None of the SAEs were considered related to study medication and none led to study drug discontinuation.

Table 80 Summary of Serious TEAEs during the 16-Week Treatment Period by SOC and PT - Part B (SAF)

Primary System Organ Class Preferred Term	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of such events	5	0
Number of patients with at least one such event, n (%)	4 (5.1%)	0
Immune system disorders	1 (1.3%)	0
Hypersensitivity	1 (1.3%)	0
Infections and infestations	3 (3.8%)	0
Cellulitis staphylococcal	1 (1.3%)	0
Dermatitis infected	1 (1.3%)	0
Staphylococcal bacteraemia	1 (1.3%)	0
Skin and subcutaneous tissue disorders	1 (1.3%)	0
Dermatitis atopic	1 (1.3%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; SOC=system organ class; TCS=topical corticosteroids; TEAE=treatment-emergent adver event.
MedDRA (Version 23.1) coding dictionary applied.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Source: PTT 8.2.1.2/1

R668-AD-1539 Part B (severe AD)

No SAEs were reported in the DUP + TCS group. 3/61 patients (4.9%) with severe AD at baseline reported 4 SAEs during the 16-week treatment period in the PBO + TCS group.

R668-AD-1539 Part A (severe AD)

In patients aged ≥2 years to <6 years, an SAE of Anaphylactic reaction of moderate intensity was reported in 1 patient in the 3 mg/kg cohort.

In patients aged ≥6 months to <2 years, an SAE of Anaphylactic reaction of severe intensity was reported in 1 patient in the 3 mg/kg cohort. Both of the SAEs were defined as an AESI.

R668-AD-1434 (moderate-to-severe AD)

In study R668-AD-1434, 2 patients (2/180; 1.1%) experienced an SAE (Anaphylactic reaction and Pneumonia mycoplasmal). Neither of the reported SAEs lead to permanent treatment discontinuation and neither were considered to be related to dupilumab. Both SAEs resolved over time with treatment.

R668-AD-1434 (severe AD)

No SAEs were reported in patients with severe AD.

Other significant events

Adverse Events of Special Interest

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

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

R668-AD-1539 Part B (moderate-to-severe AD)

One patient reported 1 AESI of non-serious, severe, bilateral, ulcerating blepharitis (DUP+PBO group) 20 days after the third dose of study drug that was considered related to study treatment. The AESI improved under supportive treatment and the study drug was continued until the end of the study.

No AESIs were reported in the follow-up period.

Table 81 Summary of Treatment-Emergent AESIs by AESI Category, High Level Term, and PT during the 16-Week Treatment Period - Part B (SAF)

AESI category High Level Term Preferred Term	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Number of patients with at least one such event, n (%)	0	1 (1.2%)
Any severe type of conjunctivitis or blepharitis	0	1 (1.2%)
Lid, lash and lacrimal infections, irritations and inflammations	0	1 (1.2%)
Blepharitis	0	1 (1.2%)

Abbreviations: AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
MedDRA (Version 23.1) coding dictionary applied.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Source: PTT 8.4.1.1/2

Conjunctivitis

The proportion of patients with at least 1 conjunctivitis-related event during the 16-week treatment period was higher in the dupilumab + TCS group using narrow (4.8% vs. 0) and broad (7.2% vs. 1.3%) customized MedDRA query (CMQ).

Injection Site Reactions

Injection site reaction events were rarely reported, of mild intensity and frequencies were balanced across the treatment groups (DUP+ TCS 2.4% vs. 2.6% in the PBO +TCS).

R668-AD-1539 Part A (severe AD)

There were 2 patients with an AESI of serious anaphylactic food reaction, both unrelated to the study drug.

R668-AD-1434 (moderate-to-severe AD)

3 AESIs were reported in 3 patients (1.7%). A serious, severe Anaphylactic reaction of food allergy that was considered unrelated to dupilumab, one dupilumab-related severe blepharitis and subsequent blepharoconjunctivitis (ongoing AESI of patient 840525501, see above), and an unrelated moderate keratitis. None of the AESIs led to discontinuation of dupilumab. All events resolved over time with treatment.

Table 82 Incidence and Rate of Adverse Events of Special Interest per 100 Patient-Years by Adverse Events of Special Interest Category and Preferred Term - Children ≥6 to <12 Years of Age (SAF)

Adverse Events of Special Interest Category Preferred Term	Total (N=180)	Total (N=180) nP (nP/100 PY)
Number of AESIs n (%)	3	
Patients with at least one AESI	3 (1.7)	3/134.2 (2.24)
Anaphylactic reaction	1 (0.6%)	1/134.4 (0.74)
Anaphylactic reaction	1 (0.6%)	1/134.4 (0.74)
Keratitis	1 (0.6%)	1/137.1 (0.73)
Keratitis	1 (0.6%)	1/137.1 (0.73)
Any severe type of conjunctivitis or blepharitis	1 (0.6%)	1/136.9 (0.73)
Blepharitis	1 (0.6%)	1/136.9 (0.73)

Abbreviations: AESI, adverse events of special interest; nP, number of patients with events; nP/100PY, number patients with events per 100 patient years; SAF, safety analysis population
Source: PTT 8.4.1.2/1c and PTT 8.4.2.2/1c

Conjunctivitis

Using the narrow search, 7.2% of the patients had a conjunctivitis events in the OLE study, using the conjunctivitis broad CMQ 8.9%. None of the events were serious or led to treatment discontinuation. Most of the events were reported as recovered/resolved during the study period after treatment.

Injection Site Reactions

The incidence of Injection site reactions was very low during the OLE study (2.2%, EAIR 3.05), no severe or serious reaction was observed.

Adverse drug reactions

The applicant's review of all TEAEs did not identify any new ADRs in the population of children with AD aged ≥6 months to <6 years as compared to the older children (≥6 years to <12 years), adolescent, and adult AD patient populations who received dupilumab treatment. There were no TEAEs in which the lower bound of the 95% confidence interval for the Cox hazard ratio in dupilumab + TCS versus placebo + TCS was greater than 1, and a medical review did not identify any ADRs based on an evaluation of less-frequent PTs.

Discontinuation due to adverse events

Adverse Events Leading to Permanent Study Drug Discontinuation

R668-AD-1539 Part B (moderate-to-severe AD)

In ***Table 83***, all AEs leading to permanent study drug discontinuation are listed. Overall, 4 patients assigned to the placebo group experienced SAEs, all of them were considered unrelated and resolved during the course of the study. Non-serious TEAE occurred in 2 patients of either treatment group that resulted in permanent study drug discontinuation; both mild and moderate, respectively, and were also considered unrelated to the study drug.

Table 83 Serious Adverse Events and Adverse Events Leading to Permanent Study Drug Discontinuation Reported in Study R668-AD-1539 Part B

Treatment	Patient ID	Preferred Term	Verbatim Term	Serious	Severity	Relationship to Study Drug	Action Taken with IP	Outcome
Serious Adverse Events								
Placebo	840518503	Staphylococcal bacteremia	Staph aureus bacteremia	Yes	Severe	Not related	No action taken	Resolved
Placebo	840508504	Hypersensitivity	Allergic reaction [unknown]	Yes	Mild	Not related	No action taken	Resolved
Placebo	840519504	Cellulitis staphylococcal	Cellulitis methicillin-resistant staphylococcus aureus infection	Yes	Severe	Not related	No action taken	Resolved
Placebo	826603505	Dermatitis atopic Dermatitis infected	Worsening of flare of atopic dermatitis Infected atopic dermatitis	Yes	Severe	Not related	No action taken	Resolved
Adverse Events Leading to Permanent Study Drug Discontinuation								
Dupilumab + TCS	840503502	Dermatitis atopic	Atopic dermatitis flare	No	Moderate	Not related	Discontinued	Resolved
Placebo	276208504	Nightmares	Nightmares regarding blood collection	No	Mild	Not related	Discontinued	Ongoing

Abbreviations: AE, adverse events; SAE, serious adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part B Listings 2.7.2 and 2.7.3

R668-AD-1539 Part A (severe AD)

Not applicable.

R668-AD-1434 (moderate-to-severe AD)

One patient had one non-serious, severe and dupilumab-related TEAE of urticaria that led to permanent study drug discontinuation or withdrawal.

Laboratory findings

Mean/Median Changes from Baseline

Red Blood Cells and Platelets

All studies

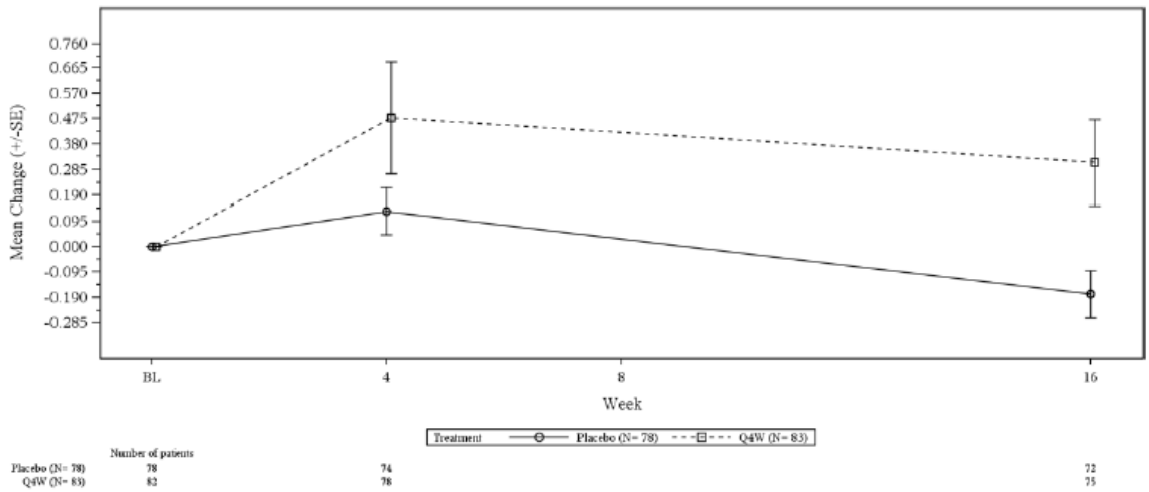
During the treatment period of study R668-AD-1539 Part B, Part A and R668-AD-1434, there were no clinically meaningful trends or differences in mean or median changes from baseline for any red blood cell (RBC) parameter or platelets.

White Blood Cells

R668-AD-1539 Part B

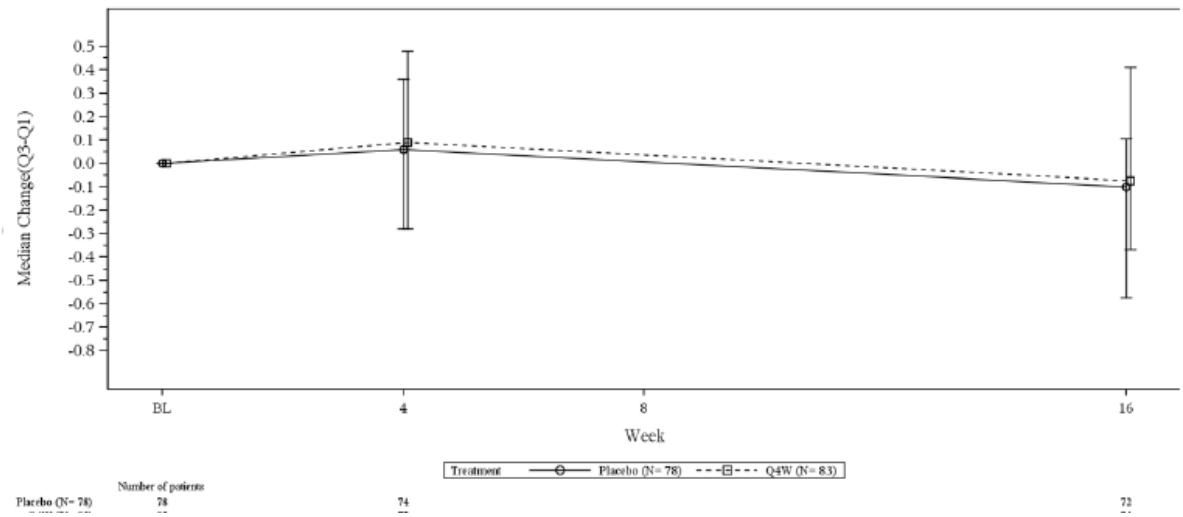
There were no clinically meaningful trends or differences between treatment groups in mean or median changes from baseline in most white blood cell (WBC) parameters during the treatment period. Mean (SD) eosinophil counts at baseline were similar across both treatment groups. There was an increase in eosinophil counts in the dupilumab + TCS group at week 4 and week 16 as assessed by the mean change from baseline, with the a peak at week 4 (see *Figure* ***38***). This increase was not seen in the median values indicating that the mean change was driven by a small subset of patients (*Figure* ***39***).

Figure 38 Mean Change (SE) in Eosinophils (109 /L) from Baseline Through Week 16 Treatment Period in Study R668-AD-1539 Part B - SAF



Q4W = dupilumab 200/300 mg + TCS every 4 weeks; SAF = Safety Analysis Set; SE = Standard error; TCS=topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 9.1.1/2

Figure 39 Median Change (SE) in Eosinophils (109 /L) from Baseline Through Week 16 Treatment Period in Study R668-AD-1539 Part B - SAF

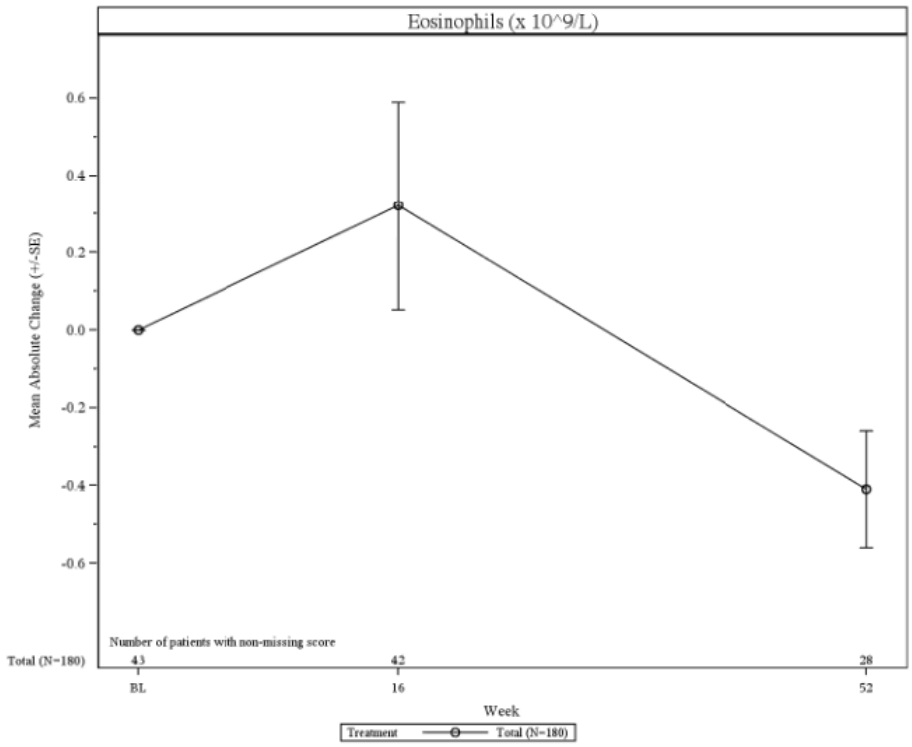


In study R668-AD-1539 Part A, there was a trend towards modest increases in mean eosinophil counts from baseline to week 4.

R668-AD-1434

There was no meaningful change from baseline in WBC during the treatment period. See *Figure **40*** for changes in mean eosinophil counts. The mean change from baseline was 0.32 (1.56) ×109/L at week 16 and - 0.41 (0.71) ×109/L at week 52. This pattern of an increase at week 16 was not seen with median change from baseline, suggesting it was driven by a few outlier patients.

Figure 40 Mean Absolute Change (±SE) in Eosinophils by Visit - Children ≥6 Months to <6 Years of Age (SAF)



Potentially Clinically Significant Values

Red Blood Cells and Platelets

R668-AD-1539 Part B

The proportion of patients with at least 1 treatment-emergent PCSV during the treatment period was low and comparable in both treatment groups for RBCs and platelets (PBO+TCS 6.5% vs. DUP+TCS 3.7%). A greater proportion of patients in the dupilumab + TCS group than the placebo + TCS group had

treatment-emergent PCSVs for WBCs. Details are shown in *Table **84***.

Table 84 Summary of Patients with at Least One Treatment-Emergent PCSV During 16-Week Treatment Period – Red Blood Cells and Platelets – Part B (SAF)

Parameter (unit) Treatment-emergent PCSV Category	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Patients with at least 1 treatment-emergent PCSV	5/77 (6.5%)	3/82 (3.7%)
Hemoglobin (g/L)		
<100 g/L and ≥100 g/L at baseline or any decrease ≥20 g/L (≥2 - <6 years) or <90 g/L and ≥90 g/L at baseline or any decrease ≥20 g/L (6 - 23 months)	3/77 (3.9%)	2/81 (2.5%)
Hematocrit (RATIO)		
< 0.32 and ≥0.32 at baseline (≥2 - <6 years) or < 0.29 and ≥0.29 at baseline (6 - 23 months)	0/77	0/82
>0.47 and ≤0.47 at baseline (≥2 - <6 years) or >0.42 and ≤0.42 at baseline (6 - 23 months)	2/77 (2.6%)	0/82
Platelets (10^9/L)		
<100 Giga/L and ≥100 Giga/L at baseline	0/77	0/82
>700 Giga/L and ≤700 Giga/L at baseline	0/77	1/82 (1.2%)

Abbreviations: PCSV=potentially clinically significant value; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
A patient who had 2 or more post-baseline PCSV for the same test was counted only once and by the worst PCSV.
% was calculated using the number of patients with PCSV over the number of patients assessed.
Source: PTT 9.1.3.1/1A

R668-AD-Part A

In study R668-AD-1539 Part A, PCSVs were not defined. 1 patient was however observed with an unrelated non-serious AE of moderate thrombocytosis that started on study day 1. Platelet counts were high throughout the period: 390 ×109/L at screening, 609 ×109/L on day 1, 568 ×109/L on day 10, and 481 ×109/L on day 29 (normal range 213-363×109/L).

R668-AD-1434

Overall, 1 (2.4%) patient had 1 treatment-emergent PCSV for RBCs and platelets at week 52 (baseline 367 ×109/L, week 52 744 ×109/L), however, platelet counts had returned to the normal range (197 to 382 ×109/L) at an unscheduled visit 165 days later (367 ×109/L) and remained within normal range at week 104 (364 ×109/L). Platelet counts were flagged as high at the last laboratory assessment on study day 901 (334 ×109/L; normal range 175-311 ×109/L). No TEAEs related to platelet counts were reported for the patient.

White Blood Cells

R668-AD-Part B

As shown in *Table **85***, a greater proportion of patients in the dupilumab + TCS group than the placebo + TCS group had treatment-emergent PCSVs for WBCs. This difference was mainly driven by the eosinophil PCSVs: 13 patients in the dupilumab + TCS group had a treatment-emergent increase in eosinophil count that was classified as a PCSV, compared with 9 patients (15.9% vs. 11.7%) in the placebo + TCS group.

Two patients (2/83; 2.4%) in the dupilumab + TCS group had a TEAE of eosinophilia, 1 patient (1/83; 1.2%) had a TEAE of neutropenia, and 1 patient (1/83; 1.2%) had a TEAE of WBC increased. None of these events were serious and none led to discontinuation of study treatment. The TEAEs of eosinophilia were only laboratory abnormalities, were not associated with any clinical symptoms, and did not results in study drug interruption or discontinuation. The eosinophilia and WBC increased events had resolved by the end of treatment. The TEAE of neutropenia was not resolved by the end of treatment. None of these events were associated with clinical symptoms.

Table 85 Summary of Patients with at Least One Treatment-Emergent PCSV During 16-Week Treatment Period – White Blood Cells – Part B (SAF)

Parameter (unit) Treatment-emergent PCSV Category	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Patients with at least 1 treatment-emergent PCSV	15/77 (19.5%)	22/82 (26.8%)
Leukocytes (10^9/L)		
<3.0 Giga/L and ≥3.0 Giga/L at baseline (≥2 - <6 years) or <4.0 Giga/L and ≥4.0 Giga/L at baseline (6 - 23 months)	0/77	0/82
>16 Giga/L and ≤16 Giga/L at baseline (≥2 - <6 years) or >20 Giga/L and ≤20 Giga/L at baseline (6 - 23 months)	5/77 (6.5%)	7/82 (8.5%)
Eosinophils (10^9/L)		
(>0.5 Giga/L and >ULN) and (≤0.5 Giga/L or ≤ULN at baseline)	9/77 (11.7%)	13/82 (15.9%)
Lymphocytes (10^9/L)		
<1.0 Giga/L and ≥1.0 Giga/L at baseline (≥1 to <6 yrs) or <2.0 Giga/L and ≥2.0 Giga/L at baseline (≥6 months to <1 yrs)	1/77 (1.3%)	0/82
>10.5 Giga/L and ≤10.5 Giga/L at baseline (≥1 to <6 yrs) or >17 Giga/L and ≤17 Giga/L at baseline (≥6 months to <1 yrs)	0/77	1/82 (1.2%)
Neutrophils (10^9/L)		
<1.2 Giga/L and ≥1.2 Giga/L at baseline	1/77 (1.3%)	2/82 (2.4%)

Abbreviations: PCSV=potentially clinically significant value; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids; ULN=upper limit of normal.
A patient who had 2 or more post-baseline PCSV for the same test was counted only once and by the worst PCSV.
% was calculated using the number of patients with PCSV over the number of patients assessed.
Source: PTT 9.1.3.2/1A

R668-AD-1434

A total of 14/42 (33.3%) patients had at least 1 treatment-emergent PCSV in WBC parameters during the OLE. These were PCSVs for eosinophils (12/42 [28.6%]) and neutrophils (2/42 [4.8%]). The most common PCSV related to WBC parameters was for raised eosinophil count, which was reported in 12/42 (28.6%) patients. In 7/12 of these patients, the raised counts reverted to be within the normal reference range with continued treatment. Of the 5 patients with a raised eosinophil count that did not resolve, 3 patients had eosinophils within the normal range at baseline; 1 patient had a value above normal range at baseline and all subsequent visits; and 1 had values above normal range at the first visit at which eosinophils were assessed (week 4), and at all except 1 of the subsequent visits. No TEAEs were reported for eosinophilia in any of these patients, and these PCSVs did not lead to treatment discontinuation. Two patients had a PCSV for low neutrophils, 1 of which resolved over time and 1 of which was flagged at the last laboratory assessment, and therefore remained ongoing; both patients continued to receive study treatment. No patient had a TEAE related to neutrophil counts and no PCSV for low neutrophils led to treatment discontinuation.

Chemistry

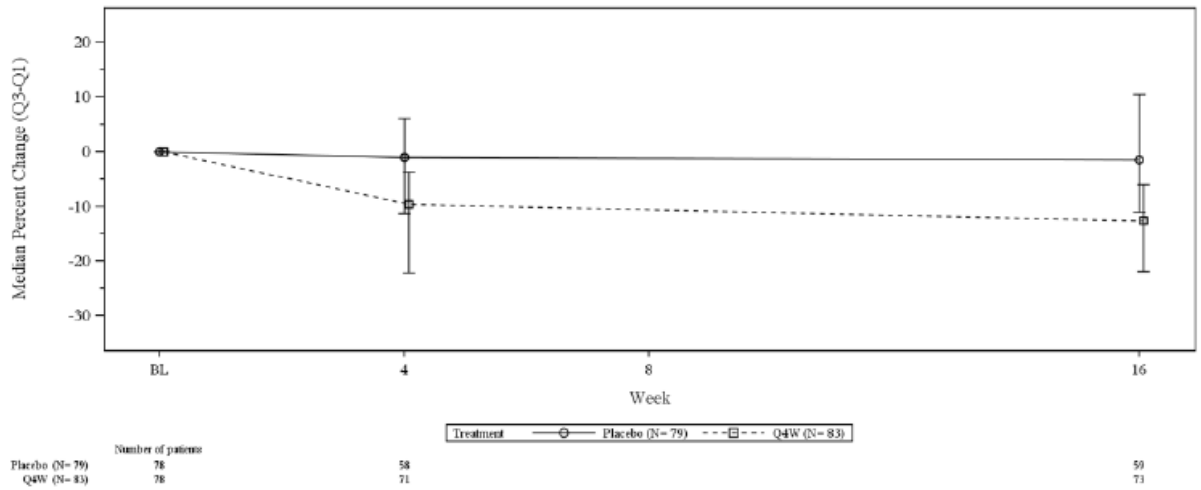
Mean/Median Changes from Baseline

R668-AD-1539 Part B

No clinically meaningful trend towards an increase or decrease in mean or median values over time was seen in either treatment group for the majority of chemistry parameters for metabolic, electrolyte, renal, liver, or lipid function.

As shown in *Figure **41***, a reduction from baseline in LDH was observed in the dupilumab + TCS group as early as week 4, the first post-treatment time point assessed in the study, compared to no change in the placebo + TCS group (p=0.0001).

Figure 41 Median (Q3-Q1) Percent Change from Baseline in Lactate Dehydrogenase (U/L) by Visit through Week 16 in Study R668-AD-1539 Part B, LOCF with Censoring after Rescue Treatment Use – SAF



Abbreviations: BL = Baseline; Q1 = First quartile; Q3 = Third quartile; Q4W = dupilumab 200/300 mg once every 4 weeks; SAF = Safety Analysis Set; TCS = Topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1539 Part B Post-text Figure 11.5.4/1

R668-AD-1434

No meaningful change from baseline in serum chemistry parameters during the treatment period was observed, except for LDH consistent with the finding in study R668-AD-1539 Part B (see above).

Potentially Clinically Significant Values

R668-AD-1539 Part B

There were no clinically meaningful differences between the 2 treatment groups in the number of patients with treatment-emergent PCSVs for any of the chemistry parameters.

Metabolic, electrolyte, renal, liver, or lipid function

No clinically meaningful trend towards an increase or decrease in mean or median values over time was seen in either treatment group for the majority of chemistry parameters for metabolic, electrolyte, renal, liver, or lipid function in either of the conducted studies.

Vital signs

Mean/Median Changes from Baseline

All studies

In study R668-AD-1539 Part B, Part A and R668-AD-1434 there were no clinically meaningful trends in mean or median changes from baseline in vital sign parameters in either treatment group.

Potentially Clinically Significant Values

R668-AD-1539 Part B

In study R668-AD-1539 Part B, there were no clinically meaningful differences between the treatment groups in incidence of treatment-emergent PCSVs related to vital signs. At least 1 treatment-emergent PCSV was found in 46/78 patients (59.0%) in the placebo + TCS group and 46/83 patients (55.4%) in the dupilumab + TCS group, see *Table **86***. Apart from the increase in respiratory rate, all PCSVs were seen either at similar rates across the 2 treatment groups or were higher in the placebo group.

Table 86 Summary of Patients with at Least One Treatment-Emergent PCSV During 16-Week Treatment Period – Vital Signs – in Study R668-AD-1539 Part B (SAF)

Parameter (unit) Treatment-emergent PCSV Category	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Patients with at least 1 treatment-emergent PCSV	46/78 (59.0%)	46/83 (55.4%)
Respiratory Rate (breaths/min)		
> 34 bpm and <=34 pbm at baseline (1 - <6 years) or >40 bpm and <=40 pbm at baseline (6 months - <1 year)	1/78 (1.3%)	7/83 (8.4%)
< 20 bpm and >=20 pbm at baseline (1 - <6 years) or < 24 bpm and >=24 pbm at baseline (6 months - <1 year)	14/78 (17.9%)	18/83 (21.7%)

Parameter (unit) Treatment-emergent PCSV Category	Placebo + TCS (N=78)	Dupilumab 200/300mg Q4W + TCS (N=83)
Heart Rate (beats/min)		
<= 59 bpm and decrease from BL >= 20 bpm (3-<6 years) or <= 63 bpm and decrease from BL >= 20 bpm (1- <3 years) or <= 72 bpm and decrease from BL >= 20 bpm (6 months - <1 year)	5/78 (6.4%)	4/83 (4.8%)
>=140 bpm and increase from BL >= 20bpm (3-<6 years) or >=140 bpm and increase from BL >= 20bpm (1- <3 years) or >=175 bpm and increase from BL >= 20 bpm (6 months - <1 year)	8/78 (10.3%)	3/83 (3.6%)
Systolic Blood Pressure (mmHg)		
<= 70 mmHg and decrease from baseline >= 20 mmHg (6 months to <6 yrs)	4/78 (5.1%)	5/83 (6.0%)
>=121 mmHg and increase from BL >= 20 mmHg (3-<6 years) or >=116 mmHg and increase from BL >= 20mmHg (1 - <3 years) or >=110 mmHg and increase from BL >= 20 mmHg (>=6 months to 1 yrs)	17/78 (21.8%)	11/83 (13.3%)
Diastolic Blood Pressure (mmHg)		
<= 34 mmHg and decrease from baseline >= 10 mmHg (>=6 months to <6 yrs)	0/78	0/83
>=83 mmHg and increase from BL >= 10mmHg (3-<6 years) or >=77 mmHg and increase from BL >= 10mmHg (1 - <3 years) or >=72 mmHg and increase from BL >= 10 mmHg (>=6 months to 1 yrs)	25/78 (32.1%)	22/83 (26.5%)
Temperature (C)		
Rectal, Ear and Temporal: >=39.0 C; Oral or Pacifier: >39.0 C; Axillary or skin infrared: >39.0 C	1/78 (1.3%)	0/83

Abbreviations: PCSV=potentially clinically significant value; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
A patient who had 2 or more post-baseline PCSV for the same test was counted only once and by the worst PCSV.
% was calculated using the number of patients with PCSV over the number of patients assessed.
Source: Module 5.3.5.1 R668-AD-1539 Part B Table 80.

R668-AD-1434

As displayed in *Table* ***87***, 72/180 (39.4%) patients had at least 1 treatment-emergent PCSV for vital signs.

Table 87 Summary of Patients with at Least One Treatment-Emergent PCSV – Vital Signs and Weight – in Study R668-AD-1434 (SAF)

Parameter (unit) Treatment-emergent PCSV Category	Total (N=180)
Patients with at least one treatment-emergent PCSV for vital signs (excluding weight)	71/180 (39.4%)
Heart Rate (beats/min)	
<= 50 bpm and decrease from BL >= 20 bpm (6-<12 years) or <= 59 bpm and decrease from BL >= 20 bpm (3-<6 years) or <= 63 bpm and decrease from BL >= 20 bpm (1- <3 years) or <= 72 bpm and decrease from BL >= 20 bpm (6 months - <1 year)	3/180 (1.7%)
>=120 bpm and increase from BL >= 20 bpm (6-<12 years) or >=140 bpm and increase from BL >= 20 bpm (3-<6 years) or >=140 bpm and increase from BL >= 20 bpm (1- <3 years) or >=175 bpm and increase from BL >= 20 bpm (6 months - <1 year)	11/180 (6.1%)
Diastolic Blood Pressure (mmHg)	
<= 34 mmHg and decrease from baseline >= 10 mmHg (6-<12 yrs) or <= 34 mmHg and decrease from baseline >= 10 mmHg (>=6 months to <6 yrs)	3/179 (1.7%)
>=72 mmHg and increase from BL >= 20 mmHg (6-<12 yrs) or >=83 mmHg and increase from BL >= 10 mmHg (3-<6 yrs) or >=77 mmHg and increase from BL >= 10 mmHg (1 - <3 yrs) or >=72 mmHg and increase from BL >= 10 mmHg (>=6 months to 1 yrs)	29/179 (16.2%)
Respiratory Rate (breaths/min)	
< 16 bpm and >=16 pbm at baseline (6 - <12 years) or < 20 bpm and >=20 pbm at baseline (1 - <6 years) or < 24 bpm and >=24 pbm at baseline (6 months - <1 year)	39/180 (21.7%)
> 30 bpm and <=30 pbm at baseline (6 - <12 years) or > 34 bpm and <=34 pbm at baseline (1 - <6 years) or >40 bpm and <=40 pbm at baseline (6 months - <1 year)	4/180 (2.2%)
Systolic Blood Pressure (mmHg)	
<= 80 mmHg and decrease from baseline >= 20 mmHg (6-<12 yrs) or <= 70 mmHg and decrease from baseline >= 20 mmHg (6 months to <6 yrs)	3/179 (1.7%)
>=108 mmHg and increase from BL >= 20 mmHg (6-<12 years) or >=121 mmHg and increase from BL >= 20 mmHg (3-<6 years) or >=116 mmHg and increase from BL >= 20mmHg (1 - <3 years) or >=110 mmHg and increase from BL >= 20 mmHg (>=6 months to 1 yrs)	16/179 (8.9%)
Temperature (C)	
Rectal, Tympanic: >38.0 C; Oral: >37.5 C; Axillary: >37.2 C and Rectal, Tympanic: <=38.0 C; Oral: <=37.5 C; Axillary: <=37.2 C at Baseline (6-<12 yrs); Rectal, Ear and Temporal: >=39.0 C; Oral or Pacifier: >39.0 C; Axillary or skin infrared: >39.0 C and Rectal, Ear and Temporal: <39.0 C; Oral or Pacifier: <=39.0 C; Axillary or skin infrared: <=39.0 C at Baseline (>=6 months to <6 yrs)	1/173 (0.6%)
Weight (kg)	
>=5% decrease from baseline	7/173 (4.0%)

Abbreviations: PCSV=potentially clinically significant value; Q4W=every 4 weeks; SAF=safety analysis set; TCS=topical corticosteroids.
A patient who had 2 or more post-baseline PCSV for the same test was counted only once and by the worst PCSV.
% was calculated using the number of patients with PCSV over the number of patients assessed.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Table 34

Electrocardiogram

R668-AD-1539 Part B and A

In study R668-AD-1539 Part B and A, there were no clinically meaningful trends in mean or median changes from baseline in ECG parameters in either treatment group.

In study R668-AD-1539 Part B, shifts from normal ECG status at baseline to abnormal at week 16 were reported for 8 patients (13.8%) in the placebo + TCS group and 11 patients (15.5%) in the dupilumab + TCS group.

There were no clinically meaningful differences between the treatment groups in incidence of treatment-emergent PCSVs related to ECG findings. No patient had an ECG abnormality that was reported as a TEAE. In the cohort of patients with QTcF prolongations, there were no adverse events of Ventricular arrhythmia or Syncope.

R668-AD-1434

In study R668-AD-1434, ECG was only assessed prior to protocol amendment 1, and hence was not assessed for the age group included in this submission.

Physical Examination

In study R668-AD-1539 Part B, there were no clinically meaningful shifts from baseline in physical examination findings observed in either treatment group.

Physical examinations in study R668-AD-1434 were performed at baseline and at week 260. As at the data cutoff for the study, no patients aged ≥6 months to <6 years had reached week 260, and so physical examination data are not available. These data will be provided in the final CSR. In study R668-AD-1539 Part A, physical examination findings were consistent with the population under study (AD). There were no shifts from normal at baseline to abnormal post-baseline in physical examination status.

Immunogenicity

Relationship Between Anti-Drug Antibody Response and Adverse Event Profile

R668-AD-1539 Part B

1 patient receiving 300 mg Q4W + TCS developed a treatment-emergent ADA response, a low titer, indeterminate, nAb negative response (see *Table **88*** and *Table **89***).

Table 88 ADA Category and Maximum Titer Category in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

		Dupilumab			
Maximum Titer Category	**Placebo + TCS n (%)**	**200 mg Q4W + TCS n (%)**	**300 mg Q4W + TCS n (%)**	**All Active Doses n (%)**	**Overall n (%)**
ADA Analysis Set	69 (100%)	24 (100%)	50 (100%)	74 (100%)	143 (100%)
TE					
Persistent	0	0	0	0	0
Transient	0	0	0	0	0
Indeterminate	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)
TE & TB					
Low (<1,000)	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)
Moderate (1,000 to 10,000)	0	0	0	0	0
High (>10,000)	0	0	0	0	0

ADA = Anti-drug antibody; n = Number of patients contributing to each category; Q4W = Once every 4 weeks; TE = Treatment-emergent; TB = Treatment-boosted; TCS = Topical corticosteroids
Note: See Section 2.4.3.1 for definitions of ADA categories.

Table 89 Summary of ADA Status and Nab Status in Patients ≥6 Months to <6 Years of Age with Moderate to Severe Atopic Dermatitis (Study R668-AD-1539 Part B)

ADA Status; NAb Status	Placebo + TCS n (%)	Dupilumab 200 mg Q4W + TCS n (%)	Dupilumab 300 mg Q4W + TCS n (%)	Dupilumab All Active Doses n (%)	Overall n (%)
NAb Analysis Set	69 (100%)	24 (100%)	50 (100%)	74 (100%)	143 (100%)
ADA-	67 (97.1%)	24 (100%)	49 (98.0%)	73 (98.6%)	140 (97.9%)
Pre+; NAb-	2 (2.9%)	0	0	0	2 (1.4%)
Pre+; NAb+	0	0	0	0	0
TE & TB+; NAb-	0	0	1 (2.0%)	1 (1.4%)	1 (0.7%)
TE & TB+; NAb+	0	0	0	0	0

ADA = Anti-drug antibody; ADA- = ADA negative; n = Number of patients contributing to each category; NAb = Neutralizing antibody; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay; Q4W = Once every 4 weeks; Pre+ = Pre-existing immunoreactivity; TB = Treatment-boosted; TCS = Topical corticosteroids; TE = Treatment-emergent
Note: Percentages are based on ADA analysis set. Note: See Section 2.4.3.1 for definitions of ADA categories.

R668-AD-1539 Part A

In Part A, 19/40 (47.5%) participants developed treatment-emergent ADA. 3/40 patients had a moderate titer, no high titer was exhibited. Reported TEAEs were in ADA positive patients were 2 events of Anaphylactic reaction, one in each age cohort (see above).

Table 90 ADA Category and Maximum Titer Category (ADA Analysis Set)

Maximum Titer Category	2 - 6 yrs 3 mg/kg N (%)	2 - 6 yrs 6 mg/kg N (%)	6 months - 2 yrs 3 mg/kg N (%)	6 months - 2 yrs 6 mg/kg N (%)	Overall N (%)
ADA Analysis Set	10 (100)	10 (100)	10 (100)	10 (100)	40 (100)
Negative*	5 (50.0)	6 (60.0)	4 (40.0)	5 (50.0)	20 (50.0)
TB Response	0	0	1 (10.0)	0	1 (2.5)
TE Response	5 (50.0)	4 (40.0)	5 (50.0)	5 (50.0)	19 (47.5)
TE and TB Responses					
Low (<1,000)	4 (40.0)	4 (40.0)	5 (50.0)	4 (40.0)	17 (42.5)
Moderate (1,000 to 10,000)	1 (10.0)	0	1 (10.0)	1 (10.0)	3 (7.5)
High (>10,000)	0	0	0	0	0

ADA, Anti-drug Antibody; N, Number of Patients Contributing to Each Category; TB, Treatment-boosted; TE, Treatment-emergent; yrs, Years
Note: Negative* includes both negative and pre-existing responses.
Source: Appendix 16.1.15 Table 7

R668-AD-1434

Immunogenicity results for study R668-AD-1434 are presented in *Table **91***, *Table **92*** and *Table **93***. Overall, the percentage of subjects who were ADA-positive to dupilumab anytime post-baseline post dose was relatively low (22/151, 14.6%).

Persistently positive ADA response was found in a few patients 5/151 (3.3%); all of these had at least 1 TEAE during the study.

A transient response was found in 11/13 (84.6%) patients and 2/4 (50%) thereof had at least 1 TEAE during the study 5/151 (3.3%) of the patients had a persistently positive ADA response during the study and all reported TEAEs: Nasopharyngitis, upper respiratory tract infection, rhinitis, pyrexia, dermatitis atopic and skin laceration, and injection site pain. Also patients with moderate-to-high titer experienced at least 1 TEAE.

Table 91 Summary of ADA Status and ADA Category by Previous Study in Pediatric Patients ≥6 Months to <6 Years of Age with AD (Study R668-AD-1434)

ADA Status and Category	R668-AD-1539 PART A n (%)	R668-AD-1539 PART B n (%)	Overall n (%)
ADA Analysis Set	35 (100%)	116 (100%)	151 (100%)
Negative	13 (37.1%)	112 (96.6%)	125 (82.8%)
Pre-existing Immunoreactivity	2 (5.7%)	2 (1.7%)	4 (2.6%)
Treatment-Boosted Response	0	0	0
Treatment-Emergent Response	20 (57.1%)	2 (1.7%)	22 (14.6%)

n = Number of patients contributing to each category
Source: Table 5 of the Clinical Pharmacology Report (Appendix 16.1.15).

Table 92 Summary of ADA Status and Maximum Titer Category by Previous Study in Pediatric Patients ≥6 Months to <6 Years of Age with AD (Study R668-AD-1434)

Maximum Titer Category	R668-AD-1539 PART A n (%)	R668-AD-1539 PART B n (%)	Overall n (%)
ADA Analysis Set	35 (100%)	116 (100%)	151 (100%)
TE			
Persistent	5 (14.3%)	0	5 (3.3%)
Transient	13 (37.1%)	0	13 (8.6%)
Indeterminate	2 (5.7%)	2 (1.7%)	4 (2.6%)
TE & TB			
Low (<1,000)	15 (42.9%)	2 (1.7%)	17 (11.3%)
Moderate (1,000 to 10,000)	3 (8.6%)	0	3 (2.0%)
High (>10,000)	1 (2.9%)	0	1 (0.7%)

n = Number of patients contributing to each category; TE = Treatment-emergent; TB = Treatment-boosted
Source: Table 6 of the Clinical Pharmacology Report (Appendix 16.1.15).

Table 93 Summary of ADA Status and NAb Status by Previous Study in Pediatric Patients ≥6 Months to <6 Years of Age with AD (Study R668-AD-1434)

ADA Status; NAb Status	R668-AD-1539 PART A n (%)	R668-AD-1539 PART B n (%)	Overall n (%)
NAb Analysis Set	34 (97.1%)	116 (100%)	150 (99.3%)
ADA-	13 (37.1%)	112 (96.6%)	125 (82.8%)
Pre+; NAb-	2 (5.7%)	2 (1.7%)	4 (2.6%)
Pre+; NAb+	0	0	0
TE & TB+; NAb-	8 (22.9%)	2 (1.7%)	10 (6.6%)
TE & TB+; NAb+	11 (31.4%)	0	11 (7.3%)

n = Number of patients contributing to each category; ADA- = ADA negative; Pre+ = Pre-existing immunoreactivity; TE = Treatment-emergent; TB = Treatment-boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay
Note: Percentages are based on ADA analysis set.
Source: Table 7 of the Clinical Pharmacology Report (Appendix 16.1.15)

Safety in special populations

Subgroup analyses in patients with severe AD

Patients with severe AD were analysed separately as to safety aspects. Please see respective sections above.

Subgroup analyses in patients ≥6 months to < 2 years

R668-AD-1539 Part B

The safety results of the subgroup of patients aged ≥6 months to <2 years are presented in *Table **94*** and *Table **95***. Overall, 10 patients were included in this subgroup, 4/10 in the PBO+TCS group and 6/10 in the DUP+TCS group. The proportion of patients aged <2 years who had at least 1 TEAE during the 16-week treatment period was comparable between the PBO + TCS group (3/4; 75.0%) and the dupilumab + TCS group (4/6; 66.7%). One patient in the DUP + TCS group had a TEAE that led to discontinuation of study drug (see section above). All TEAEs were mild to moderate in intensity. One patient in the DUP + TCS group had a TEAE, which was considered by the investigator to be related to study drug. No deaths or SAEs were reported. 2 TEAEs were reported in more than 1 patient: Upper respiratory tract infection (2 patients) and Dermatitis atopic (2 patients), both in the DUP + TCS group; all other TEAEs were reported by 1 patient each.

Table 94 Overall Summary of TEAEs in Patients Aged <2 years During the 16-Week Treatment Period - Study R668-AD-1539 Part B (SAF)

	Placebo + TCS (N=4)	Dupilumab 200/300mg Q4W + TCS (N=6)
Any TEAE	3 (75.0%)	4 (66.7%)
Any drug related TEAE	0	1 (16.7%)
Any TEAE leading to discontinuation of study drug permanently	0	1 (16.7%)
Maximum intensity for any TEAE, n(%)		
MILD	1 (25.0%)	1 (16.7%)
MODERATE	2 (50.0%)	3 (50.0%)
Any death	0	0
Any TE SAE	0	0
Any drug related TE SAE	0	0
Any TE SAE leading to Discontinuation of study drug permanently	0	0

Abbreviations: Q4W=every 4 weeks; SAE=serious adverse event; SAF=safety analysis set; TCS=topical corticosteroids; TE=treatment-emergent; TEAE=treatment-emergent adverse event.
Module 5.3.5.1 R668-AD-1539 Part B Table 76

Table 95 Summary of TEAEs in Patients Aged <2 years During the 16-Week Treatment Period by Primary SOC and PT - Study R668-AD-1539 Part B (SAF)

Primary System Organ Class Preferred Term	Placebo + TCS (N=4)	Dupilumab 200/300mg Q4W + TCS (N=6)
Number of such events	9	10
Number of patients with at least one such event, n (%)	3 (75.0%)	4 (66.7%)
Infections and infestations	2 (50.0%)	3 (50.0%)

Primary System Organ Class Preferred Term	Placebo + TCS (N=4)	Dupilumab 200/300mg Q4W + TCS (N=6)
Upper respiratory tract infection	0	2 (33.3%)
Impetigo	0	1 (16.7%)
Nasopharyngitis	0	1 (16.7%)
Respiratory tract infection viral	1 (25.0%)	0
Viral upper respiratory tract infection	1 (25.0%)	0
Skin and subcutaneous tissue disorders	1 (25.0%)	2 (33.3%)
Dermatitis atopic	1 (25.0%)	2 (33.3%)
Nail dystrophy	0	1 (16.7%)
Petechiae	1 (25.0%)	0
General disorders and administration site conditions	0	1 (16.7%)
Injection site erythema	0	1 (16.7%)
Investigations	1 (25.0%)	1 (16.7%)
White blood cell count increased	0	1 (16.7%)
Blood creatine phosphokinase increased	1 (25.0%)	0
Respiratory, thoracic and mediastinal disorders	2 (50.0%)	1 (16.7%)
Rhinorrhoea	0	1 (16.7%)
Choking	1 (25.0%)	0
Wheezing	1 (25.0%)	0

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SAF=safety analysis set; SOC=system organ class; TCS=topical corticosteroids; TEAE=treatment-emergent adverse event.
MedDRA (Version 23.1) coding dictionary applied.
At each level of patient summarization, a patient is counted once if the patient reported one or more events.
Module 5.3.5.1 R668-AD-1539 Part B Table 77

R668-AD-1539 Part A

In patients aged ≥6 months to <2 years, 14/20 patients (70.0%) experienced a TEAE in the 4-week post-treatment period, with the same incidence in the 2 dose groups (7/10 [70%]). One patient (5.0%) had a TEAE that was severe in intensity, and 2 patients (10.0%) had events related to the study drug. All but 3 events in 2 patients were transient and had resolved or were resolving at the time of the data cutoff date. There was 1 serious TEAE, which was considered by the investigator to be unrelated to study drug.

Table 96 Summary of Treatment-Emergent Adverse Events in Patients ≥6 months to <2 Years Old by System Organ Class and Preferred Term to Week 4 - R668-AD-1539 Part A (Safety Analysis Set)

Primary System Organ Class Preferred Term	3 mg/kg (N=10)	6 mg/kg (N=10)	Combined (N=20)
Patients with at least one TEAE	7 (70.0%)	7 (70.0%)	14 (70.0%)
Infections and infestations	3 (30.0%)	4 (40.0%)	7 (35.0%)
Nasopharyngitis	1 (10.0%)	2 (20.0%)	3 (15.0%)
Impetigo	1 (10.0%)	1 (10.0%)	2 (10.0%)
Upper respiratory tract infection	1 (10.0%)	1 (10.0%)	2 (10.0%)
Folliculitis	1 (10.0%)	0	1 (5.0%)
Gastrointestinal disorders	3 (30.0%)	1 (10.0%)	4 (20.0%)
Diarrhoea	1 (10.0%)	1 (10.0%)	2 (10.0%)
Constipation	1 (10.0%)	0	1 (5.0%)
Teething	1 (10.0%)	0	1 (5.0%)

Skin and subcutaneous tissue disorders	1 (10.0%)	2 (20.0%)	3 (15.0%)
Dermatitis atopic	0	1 (10.0%)	1 (5.0%)
Urticaria	1 (10.0%)	1 (10.0%)	2 (10.0%)
General disorders and administration site conditions	1 (10.0%)	1 (10.0%)	2 (10.0%)
Pyrexia	1 (10.0%)	0	1 (5.0%)
Injection site erythema	0	1 (10.0%)	1 (5.0%)
Immune system disorders	1 (10.0%)	0	1 (5.0%)
Anaphylactic reaction	1 (10.0%)	0	1 (5.0%)
Respiratory, thoracic and mediastinal disorders	0	1 (10.0%)	1 (5.0%)
Cough	0	1 (10.0%)	1 (5.0%)
Blood and lymphatic system disorders	0	1 (10.0%)	1 (5.0%)
Thrombocytosis	0	1 (10.0%)	1 (5.0%)
Eye disorders	0	1 (10.0%)	1 (5.0%)
Lacrimation increased	0	1 (10.0%)	1 (5.0%)
Musculoskeletal and connective tissue disorders	1 (10.0%)	0	1 (5.0%)
Joint swelling	1 (10.0%)	0	1 (5.0%)

MedDRA (Version 21.1) dictionary applied.
Abbreviations: TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1539 Part A Post-text Table 7.2.1.1

R668-AD-1434

*Table **97*** and *Table **98*** present the safety results of patients ≥6 months to <2 years. A total of 15 (15/19; 78.9%) patients aged <2 years had at least 1 TEAE during the study (***Table 97***). The events were all mild to moderate in intensity and none led to permanent discontinuation of study drug. The majority of events were deemed unrelated to the study drug by the investigator. None of the patients aged <2 years had SAEs and no deaths were reported. The most common TEAEs by PT (≥20%) were Nasopharyngitis (7/19 [36.8%]), Upper respiratory tract infection (7/19 [36.8%]), Dermatitis atopic (6/19 [31.6%]), Urticaria (5/19 [26.3%]), Food allergy (5/19 [26.3%]), Viral upper respiratory tract infection (4/19 [21.1%]), and Cough (4/19 [21.1%]). One patient (1/19) had an Injection site reaction (Injection site pain).

Table 97 Overall Summary of Treatment Emergent Adverse Events in Patients <2 Years of Age - Study R668-AD-1434 (SAF)

	Total (N=19)
Patients with any TEAE	15 (78.9%)
Patients with any drug related TEAE	3 (15.8%)
Patients with any TEAE leading to Permanent Study Drug Discontinuation	0
Patients with any TEAE with Maximum Intensity	
MILD	4 (21.1%)
MODERATE	11 (57.9%)
Patients with TEAE resulting in Death	0
Patients with any Serious TEAE	0
Patients with any drug related Serious TEAE	0
Patients with Serious TEAE leading to Permanent Study Drug Discontinuation	0

Abbreviations: SAE, serious adverse event; SAF, safety analysis population; TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.2 R668-AD-1434 Third-step Analysis Table 40

Table 98 Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported in ≥2 Patients Aged <2 Years - Study R668-AD-1434 (SAF)

Primary System Organ Class Preferred Term	Total (N=19)
Number of TEAEs	188
Patients with at least one TEAE	15 (78.9%)
Infections and infestations	15 (78.9%)
Nasopharyngitis	7 (36.8%)
Upper respiratory tract infection	7 (36.8%)
Viral upper respiratory tract infection	4 (21.1%)
Ear infection	2 (10.5%)
Rhinitis	2 (10.5%)
Respiratory, thoracic and mediastinal disorders	8 (42.1%)
Cough	4 (21.1%)
Nasal congestion	2 (10.5%)
Rhinitis allergic	2 (10.5%)
Rhinorrhoea	2 (10.5%)
Skin and subcutaneous tissue disorders	8 (42.1%)
Dermatitis atopic	6 (31.6%)
Urticaria	5 (26.3%)
Rash	3 (15.8%)
Immune system disorders	6 (31.6%)
Food allergy	5 (26.3%)
Milk allergy	2 (10.5%)
General disorders and administration site conditions	5 (26.3%)
Pyrexia	3 (15.8%)
Gastrointestinal disorders	3 (15.8%)
Diarrhoea	2 (10.5%)

Abbreviations: SAF, safety analysis population; TEAE, treatment-emergent adverse event
Source: Module 5.3.5.2 R668 AD 1434 Third-step Analysis Table 41

Safety profile of children ≥6 months to <6 years of age in comparison to other study populations with AD

The applicant provided a comparison of Adverse Events across the dupilumab development program in adults, adolescents and children (see ***Table 99***). For this comparison, primarily the conducted pivotal studies were used based on the premise that similar pathophysiology, study designs and exposures to dupilumab are given.

Approved dose regimens providing similar trough concentrations are listed in the *Table* ***99*** below.

Table 99 Overview of Treatment-Emergent Adverse Events and Conjunctivitis (Narrow CMQ) Across Studies in Children, Adolescents and Adults with AD

	Children ≥6 months to <6 years		Children ≥6 to <12 years		Adolescents		Adults	
	R668-AD-1539 Part B Study		R668-AD-1652 Study		R668-AD-1526 Study		Pooled SOLO and R668-AD-1021[1]	
Number (%) patients	Placebo (N=78)	Dupilumab 200/300mg Q4W (N=83)	Placebo (N=120	Dupilumab 300mg Q4W (N=120	Placebo (N=85)	Dupilumab 200/300mg Q2W (N=82)	Placebo (N=517)	Dupilumab 300mg Q2W (N=529)
Any TEAE	58 (74.4%)	53 (63.9%)	88 (73.3%)	78 (65.0%)	59 (69.4%)	53 (72.0%)	369 (71.4%)	377 (71.3%)
Any drug related TEAE	5 (6.4%)	9 (10.8%)	13 (10.8%)	24 (20.0%)	13 (15.3%)	18 (22.0%)	106 (20.5%)	151 (28.5%)
Any TEAE leading to discontinuation	1 (1.3%)	1 (1.2%)	2 (1.7%)	0	1 (1.2%)	0	10 (1.9%)	10 (1.9%)
Maximum intensity for any TEAE								
MILD	22 (28.2%)	30 (36.1%)	52 (43.3%)	45 (37.5%)	29 (34.1%)	20 (24.4%)	140 (27.1%)	192 (36.3%)
MODERATE	26 (33.3%)	21 (25.3%)	29 (24.2%)	33 (27.5%)	29 (34.1%)	37 (45.1%)	180 (34.8%)	161 (30.4%)
SEVERE	10 (12.8%)	2 (2.4%)	7 (5.8%)	0	1 (1.2%)	2 (2.4%)	49 (9.5%)	24 (4.5%)
Any death	0	0	0	0	0	0	0	1 (0.2%)
Any TE SAE	4 (5.1%)	0	2 (1.7%)	2 (1.7%)	1 (1.2%)	0	32 (6.2%)	15 (2.8%)
Any drug related TE SAE	0	0	0	0	0	0	4 (0.8%)	2 (0.4%)
Treatment emergent conjunctivitis (narrow CMQ)								
No. patients with conjunctivitis	0	4 (4.8%)	5 (4.2%)	8 (6.7%)	4 (4.7%)	8 (9.8%)	11 (2.1%)	49 (9.3%)
Preferred term								
Conjunctivitis	0	3 (3.6%)	3 (2.5%)	5 (4.2%)	1 (1.2%)	4 (4.9%)	3 (0.6%)	21 (4.0%)
Conjunctivitis allergic	0	1 (1.2%)	1 (0.8%)	3 (2.5%)	3 (3.5%)	3 (3.7%)	5 (1.0%)	16 (3.0%)
Conjunctivitis bacterial	0	0	1 (0.8%)	0	0	0	2 (0.4%)	7 (1.3%)
Conjunctivitis viral	0	0	0	0	0	1 (1.2%)	1 (0.2%)	4 (0.8%)
Atopic keratoconjunctivitis	0	0	0	0	0	0	0	1 (0.2%)

Post marketing experience

Dupilumab is not currently approved in patients <6 years of age with AD. However, a cumulative search with a data lock point of 28 Sep 2021 was performed in the Sanofi global safety database to identify all post-marketing cases describing use of dupilumab in patients <6 years of age with AD. There were 735 post-marketing cases reported for DUPIXENT cumulatively up to the data lock point of 28 Sep 2021 in this population. For reference, post-marketing exposure to 30 Sep 2021 is estimated to be 522.786 patient years.

Of the 735 reports received, 727 (99%) were non-serious. Eight of the 735 cases were serious; no fatal cases were reported. No trends or patterns were identified upon review of the serious cases. Over 75% of the post-marketing cases reported use of dupilumab in an underaged patient, and the majority did not report any other event. Consequently, the most frequently reported SOC was Injury, poisoning, and procedural complications consisting mainly of reports of 'Off-label use' and 'Product use issue'. The other most frequently reported SOCs were Skin and subcutaneous tissue disorders (Atopic Dermatitis and Pruritus were the most commonly reported PTs) and General disorders and administration site conditions (Injection Site Reactions including Injection site pain were the most commonly reported PTs).

The post-marketing data do not suggest any new safety concerns for dupilumab.

2.6.1. Discussion on clinical safety

The safety analysis sets (SAF) for each study included all patients who had received at least 1 dose of study drug. The safety data of the studies were not pooled except for patient disposition/exposure, which is reasonable as regards the difference of study designs. Results are first presented and discussed for the pivotal study R668-AD-1539 Part B, followed by R668-AD-1539 Part A and the open-label extension study R668-AD-1434.

Disposition

Overall, 162 patients were enrolled in study R668-AD-1539 Part B. 79/162 received PBO+TCS and 83/162 received DUP 200/300 mg Q4W+TCS. Patients had a good treatment compliance, and the majority of both treatment groups entered the OLE study R-668-AD-1434. Only one patient assigned to the DUP+TCS group discontinued the treatment due to an Adverse Event, for further details, see information below.

In R668-AD-1539 Part A, a total 40 patients were enrolled. One patient withdrew from study participation.

The majority of patients continued dupilumab treatment in the still ongoing OLE study R668-AD-1434. In this study, at data cut-off, no participant had completed the study, 167/180 (92.8%) were being treated, and 13/180 (7.2%) had discontinued from the study, mainly due to withdrawal of consent for different reasons.

Exposure

The treatment exposure was balanced between both treatment groups of the pivotal study R668-AD-1539 Part B. The majority of patients in the PBO+TCS group (93.6%) and in the DUP+TCS group (96.4%) received the planned 4 doses within a mean treatment duration of 111 days (15.9 weeks).

In R668-AD-1539 Part A, all 40 patients were exposed to a single weight-based dose of 3 mg/kg or 6 mg/kg. For both age cohorts, the median duration was similar (65% ≥ 29 days).

In study R668-AD-1434, the extent of exposure for the 180 included patients varied between 4 and <208 weeks, the mean overall treatment exposure was 37.23 weeks (SD 43.02), median 21.0 weeks. The majority of patients (131/180 (72.8%) received dupilumab ≥ 16 weeks. Long-term safety data with an overall cumulative treatment exposure of ≥ 52 weeks is available from 27/180 (15%) patients. Exposure data according to the claimed dose regimen is available for 118 (65.6%) patients; 58 (32.2%) received dupilumab ≥16 weeks, and 7 (3.9%) patients for ≥52 weeks.

Overall, 139/180 (77.2%) patients received the dose regimen of 200/300 mg Q4W corresponding to the claimed posology without switching the dose regimen; additional 23/180 patients coming from parent study R668-AD-1539 Part A changed to the fixed dose. The dose was changed under protocol amendment 4 for these patients from weight-based to fixed dose tiered by body weight, irrespective of age (200 mg Q4W for patients 5 to <15 kg, 300 mg Q4W for patients 15 to <30 kg, or 200 mg Q2W for patients 30 to <60kg).

As regards pooled exposure data of all three studies (SAF), overall 193 patients had received at least 1 dose of dupilumab in the pooled studies. Until data cut-off of 31 July 2021, 164/193 (85.0%) had completed at least 16 weeks of treatment, and 31/193 (16.1%) patients had completed at least 52 weeks of treatment. Updated safety data include additional 18 patients completed 52 weeks of treatment resulting in a total number of 48 patients completing 52 weeks of treatment. Combining both exposures of the parent and the OLE study, overall 90/180 (50%) patients were exposed for ≥52 weeks, which is considered acceptable. Based on the analysis, no new safety concerns arise from the updated safety data.

Adverse events

In Part B, a higher proportion of the PBO+TCS group experienced any treatment-emergent adverse events compared with the verum group and more drug-related TEAEs were reported in the DUP+TCS group of patients with moderate-to-severe AD as well as in the subgroup with severe AD. One patient in each group discontinued the study due to a treatment-emergent Adverse event (TEAE). The majority of events was mild to moderate, severe TEAEs occurred more frequently in the PBO+TCS. No treatment-emergent Serious adverse event (SAE) was reported in the DUP+TCS group; SAE observed in the placebo

group were assessed unrelated. In the subgroup with severe AD, results were similar; here, patients experienced slightly more mild and less drug-related TEAE compared with the moderate-to-severe study population. Preferred terms (PT) that were reported with a higher frequency in the verum group were Molluscum contagiosum, Conjunctivitis, Gastroenteritis viral, and Rhinorrhea. These results are consistent between the subgroup with severe AD and the total SAF. The proportion of patients who had at least one treatment-related TEAE was higher in the DUP+TCS group than in the PBO+TCS group, and also the subgroup with severe AD. This difference was mainly driven by higher incidences of PTs Conjunctivitis, Eosinophilia and Blepharitis, known ADRs in the AD population.

In Part A, in cohort 1 (≥2 to <6 years) the TEAE frequency was balanced between the two dose groups. 2/10 (20%) of the 6 mg/kg cohort and 3/10 (30%) of the 3 mg/kg cohort experienced unrelated TEAE of mild-to-moderate intensity in the 4-week treatment period. In the younger patient cohort 2 (≥6 months to <2 years), 7/10 (70%) of each dose group experienced TEAEs. Two dupilumab-related TEAEs occurred in the 6 mg/kg cohort (injection site erythema and diarrhea). SAEs were reported once in each age cohort (anaphylactic reactions due to a food allergy), case reports suggest that both events were unrelated. The balance of incidences suggests no dose-response relationship; however, patient numbers of this study are too limited for a sound interpretation of this aspect.

In study R668-AD-1434, 60.6% had at least one TEAE, drug-related TEAEs were relatively rare, serious and severe TEAEs were very rare. Result in the subgroup with severe AD were comparable, patients had less mild, more moderate, however, no severe events. Most were reported in SOC Infections and infestations where respiratory tract infections dominated. 6.7% of the participants had atopic dermatitis during the study, however, the frequency diminished over time when compared with Part B, also considering that 75 patients had received PBO in the parent study resulting in a later onset of treatment benefit. A few patients reported hypersentitivity events which were of uncomplicated nature. Overall, incidences were similar between SOCs of the parent studies and the OLE study. In the severe AD subgroup, patients experienced slightly more events, especially infections and infestations, however, incidences within the different SOCs were comparable. Three SAEs were reported, thus, the frequency of severe TEAEs was low. The observed blepharitis and urticaria were considered related to dupilumab, the latter lead to discontinuation of the study drug. Blepharitis is a known uncommon eye disorder associated with dupilumab treatment and as such listed in SmPC section 4.8. All three events resolved over time. Most frequently reported treatment-related adverse events were eye disorders such as conjunctivitis and blepharitis as well as Urticaria, however, the frequencies were very low. The SAE frequency was very low; 2 SAEs of anaphylactic reaction and pneumonia occurred during the OLE study that were considered unrelated and didn't lead to study drug discontinuation. No deaths were reported throughout the pivotal and the open-label extension study.

AESI

The pre-specified medically significant events are considered acceptable due to their potential causal association with dupilumab based on the mode of action or the known safety profile.

In Part B, 1 patient presented with 1 AESI of non-serious, severe, bilateral, ulcerating blepharitis that was ongoing at the time of transition into the OLE study. Skin infections occurred with a higher frequency in the placebo group, no serious skin infections were observed in the verum group and infection types were typical for the investigated population. Herpes infections were balanced between the treatment groups. Conjunctivitis events (broad and narrow CMQ) occurred with a higher frequency in the verum group (7.2% vs. 1.3% and 4.8% vs. 0), a known ADR in the AD population under dupilumab treatment. Urticaria was reported in 4/78 (5.1%) patients assigned to the PBO+TCS group compared with 1/83 (1.2%) patients in the DUP+TCS group and in study R668-AD-1539 Part A, 1 patient in each dose group in cohort 1 experienced Urticaria. In study R668-AD-1434, overall 13/180 (7.2%) patients experienced TEAEs associated with Urticaria, 5 events occurred in patients <2 years. One Urticaria events in a 4-year-

old male patient was severe, related and led to discontinuation of the study drug. Urticaria events do not meet the criteria for ADR determination for the time being as reasoned by the MAH.

The overall frequency of AESI was very low (1.7%) in this study.

Discontinuation of the study drug

Overall, 2 patients assigned to the dupilumab treatment group discontinued their dupilumab treatment, one during the parent study R668-AD-1539 Part B due to an Atopic dermatitis flare and the other during participation in R668-AD-1434 due to a non-serious, severe and dupilumab-related TEAE of urticaria. These low discontinuation rates suggest a good tolerability in the studied population.

Laboratory findings and vital signs

In Part B, there were no patients that had relevant laboratory test abnormalities associated with SAEs or TEAEs leading to discontinuation of the study drug. Individual patients had an increase in eosinophil counts in the dupilumab + TCS group with a peak at week 4, and decreasing until week 16.

Treatment-emergent potentially clinically significant values (PCSV), defined as laboratory values outside the reference range under study drug treatment with potential clinical implications, were lower in the DUP+TCS group compared with the PBO+TCS group as regards RBCs and platelets. With regard to WBCs, 15.9% vs. 11.7% had a PCSV of increased eosinophil count. 4 TEAEs of eosinophilia (2), neutropenia (1) and leukocytosis (1) were reported, however, these events resolved over time and were not associated with clinical symptoms. During OLE study, PCSV related to raised eosinophil count was reported in 28.6% of the study participants, mostly of transient nature, and without any associated TEAEs. A transient increase in blood eosinophil counts is a known ADR in the adult and paediatric population resulting from dupilumab's mode of action. As such, it is listed in section 4.8 of the SmPC, and the description of this adverse reaction has been updated with the results from study AD-1539.

As to clinical chemistry, a decrease in LDH, a biomarker associated with AD disease activity and severity, was observed in the verum group, which is a known pharmacodynamic effect of dupilumab and as such described in SmPC section 5.1.

Vital signs, ECG parameters or results of physical examination were not meaningfully altered during the course of the studies. The observed changes may be interpreted within the context of physiological changes or study procedures.

Immunogenicity

In Part B, 1/74 (1.4%) patients exhibited a low titer, Nab negative response. Based on this low frequency of ADA response, a correlation between the occurrence and nature of TEAEs and immunogenicity is not feasible.

In Part A, in 19/40 (47.5%) patients' treatment-emergent ADA were found with comparable incidences across the dose and age cohorts, the majority (42.5%) thereof had low titers, and the minority (7.5%) moderate titers, no high titers were determined. Nab responses were observed in 27.5%.

In R668-AD-1434, a persistently positive ADA response was found in a few patients 5/151 (3.3%). 7/151 (4.6%) patients had moderate or high ADA titers. Almost all patients with any kind of ADA response (indeterminate, transient or persistent) had TEAEs without any specific pattern. One case of serious, severe anaphylactic reaction was reported in a patient with low-titer, transient ADA response; this event was considered unrelated to dupilumab, however, based on the narratives it seems difficult to clearly determine the relationship between trigger and event.

Overall, the immunogenic potential of dupilumab appears to be low in this young paediatric population. During the Dupixent development program it was noticed that single administrations lead to a higher rate

of ADA responses whereas titers reverted after repeated dosing. Immune reactions occurred rarely in the investigated population, and the observed types do not differ from those that were reported in previous studies, thus, no new ADR were observed. It is, however, noted that the overall study population is relatively small which hampers the significance of the study results. Albeit that numbers are very small, there is no apparent increased trend towards immunogenicity in the under 2-year-old age group versus the over 2 years age group.

Post marketing data

735 post-marketing cases were reported up to the data lock point of 28 Sep 2021 in patients <6 years of age with AD following off-label use. 8/735 reports included serious adverse events. The MAH provided an update of post-marketing data until the latest available cut-off (28 Sep 2021), including frequencies as to most frequently reported SOCs. The provided data confirm the known safety profile in some way, however, as no exact PTs are listed, no exact assessment can be made.

Safety in the subgroup <2 years

The overall incidence of TEAEs in the patient subgroup ≥6 months to <2 years is comparable between both treatment groups in study R668-AD-1539 Parts A and B and incidences of individual PTs are comparable to those seen in the overall study population. The same applies to the open-label extension study R668-AD-1434. The most common TEAEs were infections of the respiratory and gastrointestinal tract.

These data are, however, to be interpreted with caution as patient numbers in this subgroup are very limited, i.e. in pivotal study Part B, merely 10 patients were <2 years old, 6 thereof exposed to dupilumab, and in the OLE study R668-AD-1434 only 19 patients. In in Part A, overall 20 patients were aged ≥6 months to <2 years, however, these patients received a single SC dose of dupilumab. As stated in PIP01-13-M07 Summary Report 4.1 at D60, 16/20 joined the open label extension study and have been exposed to dupilumab for over a year. In the latest PIP modification M07, the MAH requested a delay of 2 months in study completion of the pivotal paediatric safety and efficacy study (PIP Study 6) due to slower than expected enrolment until March 2022. The overall reduction of patient numbers from 240 to 120 for pivotal study Part B was agreed based on adequate power calculations. According to the MAH, no age subset had been numerically predefined in the PIP or requested by PDCO and limited patient numbers in this subgroup are the result of recruitment difficulties due to the pandemic and the recommended treatment algorithm with topical therapies prior to commencing Dupixent therapy. As few patients < 2 years were enrolled in the pivotal study, no sufficient long-term data is expectable for these patients within the scope of the OLE study. Based on additional 7 months of data from the OLE study, no new safety concerns arose. At the CHMP request, the MAH proposed to use a running company sponsored disease registry in paediatric patients aged <12 years with AD, entitled 'PEDISTAD', to collect additional relevant safety data for the target population, i.e. to include additional 500 patients aged 6 months to <6 years who are currently receiving systemic or topical treatment and whose disease is not adequately controlled by topical prescription therapies or for whom those therapies are not medically advisable. This approach is supported by the CHMP, the study has been included in the RMP as a category 3 study and the protocol will be submitted for endorsement in Q3 2023.

The interaction of dupilumab treatment and live or live-attenuated vaccines is currently unclear. The MAH will provide further data from the ongoing OLE study R668-AD-1434; that will inform on interaction of dupilumab with inactivated vaccines. At the moment, the concomitant administration is not recommended, which is reflected in section 4.4 of the Product Information. This is considered suboptimal for prescribers as these types of vaccines used for basic immunisation are administered between 12 and 24 months of age depending on national vaccination programmes. Based on the current data situation, vaccinations with live or live-attenuated vaccines are recommended to be completed before initiation of dupilumab treatment. As no dedicated clinical data is available, this is accepted for the time being.

Safety across the paediatric population

The overall TEAE frequencies are similar across the studies, children <12 years tended to experience less adverse events, especially drug-related TEAEs. The TEAE intensity was comparable between the studies. Conjunctivitis cases were scarcer in the youngest study population. The comparison of the results suggests that the safety profile of dupilumab is consistent across the different study populations. It is to be considered that the populations and designs are not exactly comparable regarding disease severity at baseline, concomitant medications and exposures, and thus, the results provide an approximate indication as to consistency of the safety profile.

2.6.2. Conclusions on clinical safety

The safety profile of Dupixent in children ≥6 months to <6 years of age with severe Atopic dermatitis whose disease could not be adequately controlled with topical medications was consistent with the hitherto known safety profile. No new ADRs were identified based on the submitted data. The final CSR of the OLE study will be submitted to provide further long-term safety data. A limitation is the very limited long-term data, especially in paediatric patients <2 years of age. The MAH committed to conduct a registry-based PASS for a further characterisation of the safety profile in infants and young children; overall, 40-60 children are anticipated for participation in this study which is a limited number of patients but is deemed to reflect the general recruitment issues encountered with the pivotal study. This approach is, however, endorsed by the CHMP as this category 3 PASS (included in the RMP) is considered an appropriate risk-proportionate data source.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 9.0 with the following content:

Safety concerns

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity) Conjunctivitis and keratitis related events in AD patients
Important potential risk	None
Missing information	Use in pregnant and lactating women Long-term safety in adult and paediatric patients

AD: Atopic Dermatitis.

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1				
Not applicable				
Category 2				
Not applicable				
Category 3				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes.	Use in pregnant and lactating women	Protocol submission Amended protocol (asthma cohorts) Final report	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018) Submitted for information with EU-RMP v5.0 Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.	Use in pregnant and lactating women	Protocol submission (amendment 1) Final report	Submitted for information with EU-RMP v5.0 Apr-2027
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041)	To assess the long-term safety, efficacy, PK, and immunogenicity of REGN668 in adult patients with moderate-to-severe AD.	Long-term safety (Ophthalmology sub study: additional information on conjunctivitis and keratitis related events in AD patients)	Final report	Q3 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing				
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2024
An open-label study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Phase III) (LTS14424) Ongoing	To assess the long-term safety, tolerability and efficacy of dupilumab in pediatric patients with asthma	Long-term safety of dupilumab in pediatric patients with Asthma	Final report	Sep-2024
A registry-based study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe AD (study code pending protocol development) Planned	To assess the long-term safety of dupilumab in pediatric patients with moderate-to-severe AD.	Long-term safety of dupilumab in paediatric patients (≥6 months to <6 years) with AD	Synopsis v1.0 provided in [Annex 3.1] of EU-RMP v7.1 Protocol submission Annual progress reports Final Report	 Q3 2023 Q4 2024-2031 Q3 2032

AD: Atopic Dermatitis; EU: European Union; PK: Pharmacokinetic; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	None
Conjunctivitis and keratitis related events in AD patients	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ophthalmology substudy in LTS14041 (R668-AD-1225)
Use in pregnant and lactating women	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine A**dditional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639) in asthma and AD patients Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Long-term safety in adult and paediatric patients	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies LTS14041 (R668-AD-1225), LTS1434 (R668-AD-1434), and LTS14424 and PEDISTAD registry-based study (study code pending protocol development)

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Dupilumab 300 mg and 200 mg pre-filled syringes are already approved in the EU and no further strengths or presentations are proposed for use in the new proposed indication. Full user testing was performed previously.

The new indication will cover an additional age category 6-month-old to 5 years old children similarly to the age range of children 6 to 11 years of age already included via Variation EMEA/H/C/004390/II/27). In case of administration at home the parent /caregiver should be properly trained by the doctor/HCP, this is already included in the SmPC. The changes related to the content and layout in the package leaflet are minor (section 1, 2 and 3) and a full user testing or bridging report is not necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

AD is the most common inflammatory skin condition of childhood. It affects 15–30% of children and it is particularly common in industrialised countries worldwide. The disease is characterised by chronic and relapsing pruritic skin lesions that generally develop in early childhood, usually between 3 and 6 months of age. Approximately 60% of patients develop eczematous lesions in the first year of life and 90% by 5 years of age (Huang et al, 2017).

Clinical presentation of AD in infants (≤1 year) involves lesions that often emerge in the first few months of life, affecting the cheeks with pruritic papules and papulovesicles that form oozing plaques with crust. In addition, the scalp, neck, extensor extremities, and trunk may be diffusely affected by inflammatory lesions. After 1 to 2 years, lesions can still be acute; however, lichenified, chronic lesions begin to predominate with a predilection for flexural sites. In addition, hand and foot dermatitis as well as nummular plaques with oozing and crusting on the hands and wrists can appear (Nomura, 2020). Linear excoriations due to scratching are common. The background nonlesional skin is often xerotic, and there may be plate-like ichthyosis of the distal extremities, especially in older children. The cycle of itching and scratching exacerbates the cellular damage in skin lesions and facilitates secondary infections, which can be serious (Boguniewicz, 2018).

3.1.2. Available therapies and unmet medical need

As non-pharmacological therapeutic measures, moisturizers are the cornerstone of all AD regimens. Xerosis is one of the main clinical features of AD, and results from a dysfunctional epidermal barrier that leads to increased transepidermal water loss. Topical moisturizers combat xerosis through a combination of ingredients that maintain skin hydration, such as emollients. Daily bathing with warm water is beneficial in AD therapy by hydrating the skin and removing serous crusts, allergens, and irritants (Eichenfield et al, 2014). Bleach baths demonstrated efficacy in clinically improving moderate-to-severe AD in children (Wong et al, 2013).

Similar to the adult and adolescent populations, topical treatment is the mainstay of management of AD in children. Topical corticosteroids (TCS) of varying potency represent the cornerstone of topical treatment and some low potency TCS are approved in pediatric patients <1-year-old. However, their long-term use or application to the large body-surface area is limited by the risk of local and systemic side effects, such as Cushing's syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, adrenal insufficiency and tachyphylaxis. Topical calcineurin inhibitors (TCIs), such as tacrolimus and

pimecrolimus, are also available for use in children, mostly as second-line therapy as an alternative to or in combination with TCS. Use of these agents is typically limited to areas that are prone to skin atrophy from application of TCS, (eg, face, genitals, and flexural areas), however, their use bears the risk of skin malignancies and of lymphomas.

Patients with severe disease are often treated off-label with systemic therapies such as corticosteroids and immunosuppressive drugs harboring the risk of severe side effects and lacking dedicated safety and efficacy data. The described limitations result in a large number of pediatric patients with severe AD whose disease cannot be safely controlled by the existing therapies. Therefore, there exists a significant unmet medical need for a treatment that is safe and effective for long-term use, especially for pediatric patients with severe forms of the disease not adequately controlled by topical prescription therapies.

3.1.3. Main clinical studies

This application is supported by 3 clinical studies: the pivotal completed phase 3 study R668-AD 1539-Part B, and two supportive studies R668-AD 1539-Part A (completed Phase 2) and R668-AD-1434 (ongoing open-label extension study, OLE).

R668-AD-1539 Part B was a phase 3, pivotal, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in children aged ≥6 months to <6 years of age with moderate-to-severe Atopic dermatitis (AD) whose disease could not be adequately controlled with topical medications. Patients received the following treatments: Placebo (PBO) + low potency topical corticosteroids (TCS) or dupilumab (DUP) 200 mg/300 mg Q4W + TCS over a period of 16 weeks. The dosing was tiered by body weight, i.e. patients with baseline body weight ≥5 kg to <15 kg received 200 mg Q4W, those with baseline body weight ≥15 kg to <30 kg received 300 mg Q4W.

The co-primary endpoint was the proportion of patients with IGA 0 or 1 at week 16 and the proportion of patients with EASI-75 at week 16. The key secondary endpoints were the percent change in EASI score from baseline to week 16 and the percent change from baseline to week 16 in weekly average of daily worst scratch/itch NRS score.

3.2. Favourable effects

R668-AD-1539 Part B (pivotal phase 3 study)

In the **overall population**, the proportion of all patients achieving IGA scores of 0 or 1 at Week 16 was numerically higher in the DUP+TCS group compared with the PBO+TCS group (23/83, 27.7% vs. 3/79, 3.9%, p<0.0001). The results of the sensitivity analysis considering all observed values regardless of rescue treatment were consistent with the primary analysis (25/83, 30.1% vs. 4/79, 5.1%).

The proportion of all patients achieving EASI-75 at Week 16 was higher in the DUP+TCS group compared with the PBO+TCS group (44/83, 53.0% vs. 8/79, 10.7%, p<0.0001), supported by the results of the sensitivity analysis considering all observed values regardless of rescue treatment (53/83, 63.9% vs. 13/79, 16.5%, p<0.0001).

The Percent Change from Baseline in EASI Score at Week 16 in Study R668-AD-1539 Part B declined by -70 in the DUP+TCS group (mean %Change -63.1) and by -19.6 (mean %Change -11.4) in the PBO+TCS group with a statistically significant LS mean difference in the percent change from baseline to week 16 between both treatment groups, i.e. -50.4 (-62.38, -38.40).

The Percent Change from Baseline to Week 16 in Weekly Average of Worst Scratch/Itch NRS Score from Baseline to Week 16 was −49.4% in the DUP+TCS group vs. −2.2% in the PBO+TCS group, LS mean difference -47.1. This effect was also observed very early.

The proportion of patients with improvement of weekly average of daily worst scratch/itch NRS score ≥4 or ≥3 from Baseline at Week 16 was higher in the DUP+TCS group compared with the PBO+TCS group (≥4 points: 48.1% vs. 8.9%, p<0.0001; ≥3 points: 53.3% vs. 9.9%, p<0.0001) as of week 2.

The analysis of further EASI endpoints, i.e. the proportion of patients in the FAS achieving EASI-50 and -90, or endpoints assessing AD severity as Change from baseline to week 16 in SCORAD/Percent BSA affected by AD, showed that treatment with dupilumab combined with TCS improved AD symptoms more effectively than placebo and TCS. This is also reflected by results regarding observer- or patient-reported assessments related to treatment effects on sleep quality, skin pain, POEM and others.

In the subgroup of patients with **severe AD** (IGA 4 at baseline), the proportion of patients who achieved IGA scores of 0 or 1 at Week 16 was also larger in the verum group (9/63, 14.3% vs. 1/62. 1.7%).

The proportion of patients achieving EASI-75 at Week 16 in the DUP+TCS group was higher compared with the PBO+TCS group (29/63, 46.0% vs. 4/62, 7.8%).

R668-AD-1434 (OLE study)

Proportion of patients achieving IGA 0 or 1 was 12.8% (BL), 21.6% (week 4), 33.1% (week 16), 38.6% (week 52). Proportion of patients with severe AD achieving IGA 0 or 1 was 0 (week 4), 20.8% (Week 16), and 26.9% (Week 52).

Proportion of patients achieving EASI-75 relative to baseline of previous study was 29.4% (BL), 57.4% (week 4), 70.9% (week 16), and 81.8% (week 52).

Mean % change in EASI score from baseline of previous study was -50.26 (BL), -71.05 (week 4), -78.97 (week 16), and 86.11 (week 52).

3.3. Uncertainties and limitations about favourable effects

R668-AD-1539 Part B

The study was not planned and analysed according to the applied indication (severe AD), but rather for the indication moderate-to-severe AD. The provided primary efficacy results performed on the FAS (moderate-to-severe AD) are mainly driven by the patients with moderate AD and, therefore, not entirely transferable to the population with severe AD. The analyses restricted to the subgroup of patients with severe AD was not included in the multiple testing strategy which leads to a lack of type 1 error control for these analyses. Further key analyses restricted to the subgroups indicate a consistent treatment effect in both populations and mitigate the statistical issues in some way. From a clinical perspective however, the totality of evidence from the clinical program is considered adequate to support the nominally statistically significant difference between the dupilumab and placebo arms reported for the severe AD population. In addition, the moderate-to-severe multiplicity-controlled endpoints, at time of final analysis, was made up of 75% of patients (125/162) with severe disease at baseline thus the efficacy results in the overall population was represented in majority by the severe patients. In addition, the current approved indication for patients 6 years-11 years old in the EU is 'severe AD', maintaining continuity across paediatric age groups at this time point is endorsed by the CHMP. Therefore the applied indication (severe AD) was agreed by the CHMP.

A minority of study participants was ≥6 months to <2 years old, further subgroup analyses were performed and a trend towards higher clinical benefit caused by dupilumab treatment is observed in the younger patients in the pivotal and the open-label extension study. Further data for this age group will be submitted with the final results of the OLE study.

R668-AD-1434

48/180 (26.7%) patients ≥6 months to <6 years of age completed at least 52, thus, long-term efficacy is limited. The final CSR will be submitted when available to provide further long-term efficacy data.

3.4. Unfavourable effects

R668-AD-1539 Part B

Common TEAEs by PT that were reported with a higher frequency in the DUP+TCS group were, Rhinorrhea (4.8% vs. 1.3%), Molluscum contagiosum (4.8% vs. 2.6%), Conjunctivitis (3.6% vs. 0), viral Gastroenteritis (3.6% vs. 0), and dental caries (4.8% vs. 0). Conjunctivitis occurred with a higher incidence in the dupilumab treatment groups, however, eye disorders such as conjunctivitis, keratitis and blepharitis were identified as ADRs throughout the clinical development programme in the AD population.

Slightly more drug-related TEAEs were reported in the DUP+TCS group (10.8% vs. 6.4%) in patients with moderate-to-severe AD, as well as in the subgroup with severe AD (12.7% vs. 8.2%).

During study R668-AD-1539 Part B, Urticaria was reported in 4/78 (5.1%) patients assigned to the PBO+TCS group compared with 1/83 (1.2%) patients in the DUP+TCS group and in study R668-AD-1539 Part A, 1 patient in each dose group in cohort 1 experienced Urticaria. In the open-label extension study R668-AD-1434, overall, 13/180 (7.2%) patients experienced TEAEs associated with Urticaria, 5/19 (26.2%) events occurred in patients <2 years. One Urticaria event in 4-year-old male patient was severe, related and led to discontinuation of the study drug.

No events of or clinically symptomatic eosinophilia or malignancy were reported, however, there is insufficient data on long-term exposure to characterise the risk for developing malignancy.

R668-AD-1539 Part A

In Part A, 19/40 (47.5%) participants developed treatment-emergent ADA.

R668-AD-1434

In R668-AD-1434, a persistently positive ADA response was found in 5/151 (3.3%) patients. 4/151 (2.6%) patients had moderate or high ADA titers. One case of serious, severe anaphylactic reaction was reported in a patient with low-titer, transient ADA response; this event was considered unrelated to dupilumab, however, based on the narratives it seems difficult to clearly determine the relationship between trigger and event. TEAEs observed in >1 patient with a persistently positive ADA response during the study were Nasopharyngitis, Upper respiratory tract infection, Rhinitis, Pyrexia, Dermatitis atopic, and Skin laceration.

In conclusion no new safety signals associated with the use of dupilumab in paediatric patients 6 months to < 6 years were identified. The overall safety profile was consistent with that seen in other age groups in the dupilumab development program.

3.5. Uncertainties and limitations about unfavourable effects

The majority of TEAEs were mild to moderate, severe TEAEs occurred more frequently in the PBO+TCS group compared with the DUP+TCS group (12.8% vs. 2.4%). No TE-SAE was reported in the DUP+TCS group.

The observed difference in drug-related TEAEs was mainly driven by higher incidences of PTs Conjunctivitis, Eosinophilia and Blepharitis, which are known ADRs in the AD population. Cases of conjunctivitis should continue to be monitored in the RMP.

Almost all patients with any kind of ADA response (indeterminate, transient or persistent) had TEAEs without any specific pattern. In Part A, 3/40 patients had a moderate titer, no high titer was observed. Reported TEAEs in ADA positive patients were 2 events of anaphylactic reaction, one in each age cohort, these were, however, considered unrelated to dupilumab. Immune reactions occurred rarely in the investigated population, and the observed types do not differ from those that were reported in previous studies. During the Dupixent development program it was noticed that single administrations lead to a higher rate of ADA responses whereas titers reverted after repeated dosing.

The interaction of dupilumab treatment and live or live-attenuated vaccines is currently unclear. The MAH will provide further data from the ongoing OLE study R668-AD-1434 that will inform on interaction of dupilumab with inactivated vaccines. The concomitant administration is not recommended, which is reflected in the Product Information.

The number of paediatric patients in the 6 month – 2-year age group compared to the other age group was relatively low, making it difficult to fully characterise the long-term safety profile. It is appreciated however that there were challenges in recruiting children in this age bracket to the trial, and that the same challenges would exist in another trial. The MAH committed to conduct a registry based PASS study to collect more long-term safety data in the age 6 month - 6-year age group. In addition the final CSR of the OLE study will be submitted to provide further long-term safety data.

3.6. Effects Table

Table 100 Effects Table for Dupixent, Indication: Severe AD in paediatric patients aged ≥ 6 months to <6 years (data cut-off: 16 Sep 2021)

Effect	Short description	Unit	Treatment DUP 200/300 mg + TCS Q4W N=83 N=63*	Control PBO + TCS Q4W N=79 N=62*	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary EP IGA 0/1	Proportion of patients with IGA 0 to 1 at Week 16	N (%)	23 (27.7)	3 (3.9)	Statistically significant and clinically meaningful	Study R668-AD-1539 Part B, **overall population**
Primary EP IGA 0/1	Proportion of patients with IGA 0 to 1 at Week 16	N (%)	9 (14.3)	1 (1.7)	Not planned as key analysis	Study R668-AD-1539 Part B, **severe AD population**
Co-primary EP EASI -75	Proportion of patients with EASI -75[1] at Week 16	N (%)	44 (53.0)	8 (10.7)	Statistically significant and clinically meaningful	Study R668-AD-1539 Part B, **overall population**
Co-primary EP EASI -75	Proportion of patients with EASI -75[1] at Week 16	N (%)	29 (46.0)	4 (7.2)	Not planned as key analysis	Study R668-AD-1539 Part B, **severe AD population**
Key secondary	Percent change in EASI score from baseline at Week	LS mean	-70.0 (4.85)	-19.6 (5.13)	Statistically significant and clinically meaningful	Study R668-AD-1539 Part B, **overall**

Effect	Short description	Unit	Treatment DUP 200/300 mg + TCS Q4W N=83 N=63*	Control PBO + TCS Q4W N=79 N=62*	Uncertainties / Strength of evidence	References
EP	16					**population**
Key secondary EP	Percent change in EASI score from baseline at Week 16	LS mean	-55.4 (5.01)	-10.3 (5.16)	Not planned as key analysis	Study R668-AD-1539 Part B, **severe AD population**
Key secondary EP	Percent change in worst scratch/ itch NRS score from baseline at Week 16	LS mean	-49.4 (5.03)	-2.2 (5.22)	Statistically significant and clinically meaningful	Study R668-AD-1539 Part B, **overall population**
Key secondary EP	Percent change in worst scratch/ itch NRS score from baseline at Week 16	LS mean	-41.8 (5.35)	0.5 (5.40)	Not planned as key analysis	Study R668-AD-1539 Part B, **severe AD population**
Unfavourable Effects						
TEAE PT	Urticaria	%	1.2	5.1		Study R668-AD-1539, Part B (SAF)
Immunogenicity	ADA nAB	%	47.5% 27.5%	-	Low titers and transient, single dose. In Part B 1 patient with TE-ADA, in OLE study overall 3.3% patients with persistently positive ADA response. Overall, no significant effect on safety.	Study R668-AD-1539 Part A

Abbreviations: AD: Atopic Dermatitis, ADA: Anti-Drug Antibodies, DUP: Dupilumab, EASI: Eczema Area and Severity Index, EP: Endpoint, IGA: Investigator's Global Assessment, ISR: Injection Site Reaction, LS: Least Square, N: Number, NRS: Numeric Rating Scale, TEAE: Treatment-Emergent Adverse Event, PBO: Placebo, PT: Preferred Term, Q4W: four-weekly, TCS: Topical Corticosteroids, URTI: Upper respiratory tract infection.

Notes: [1] ≥75% improvement from baseline, * the subset of the severe AD population included N=62 (PCO) and N=63 (DUP)

Efficacy results are taken from Table 4, Summary of Key Efficacy Results for R668-AD-1539 – Part B (FAS); Safety results from Tables 7, 8, 10, 31, 32, 38, Summary on Clinical Safety.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Currently, there is an unmet medical need for systemic therapies in AD in patients <6 years of age. Oral corticosteroids are often used to control severe forms of AD that are inadequately controlled by topical treatments. Additionally, other systemic immunosuppressive agents such as cyclosporine are commonly used off-label due to lacking therapeutic alternatives. However, all of them harbour serious safety issues as to long-term use, especially for paediatric patients. The beneficial treatment effects of dupilumab

200/300 mg Q4W combined with TCS in patients with severe AD who are inadequately controlled by topical therapies has been demonstrated. The provided controlled data on short-term use (16 weeks) showed statistically significant and clinically relevant treatment results in favour of dupilumab.

As immunomodulatory drug with a subcutaneous route of administration, the most relevant safety concerns of dupilumab generally are associated with hypersensitivity reactions, (helminthic) infections, and immunogenicity and effects on the immature system in children <6 years. There were no reported events of anaphylactic reactions (assessed as related to study drug by the investigator) or systemic hypersensitivity reactions in either treatment group. In terms of infections, the overall incidence was higher in the placebo group; no helminthic infections were reported. The observed treatment-emergent adverse events were predominantly mild to moderate and common viral infections prevailed as typical for this age class. Conjunctivitis occurred with a higher incidence in the dupilumab treatment groups, however, eye disorders such as conjunctivitis, keratitis and blepharitis were identified as ADRs throughout the clinical development programme in the AD population. The long-term effect of chronic conjunctivitis in these patients is currently unknown. Therefore, cases of conjunctivitis should continue to be monitored in the RMP.

No events of or clinically symptomatic eosinophilia or malignancy were reported, however, there is insufficient data on long-term exposure to characterise the risk for developing malignancy. This issue has been discussed during the initial MAA for AD, subject to investigation in the OLE study.

The available immunogenicity data did not show a clinically significant effect of ADA on safety, this suggests a low immunogenic potential of dupilumab in the investigated population.

The interaction of dupilumab treatment and live or live-attenuated vaccines is currently unclear. The MAH will provide further data from the ongoing OLE study R668-AD-1434 that will inform on interaction of dupilumab with inactivated vaccines. At the moment, the concomitant administration is not recommended, which is reflected in the Product Information. This is considered suboptimal for prescribers as these types of vaccines used for basic immunisation are administered between 12 and 24 months of age depending on national vaccination programmes. Based on the current data situation, vaccinations with live or live-attenuated vaccines are recommended to be completed before initiation of dupilumab treatment. As no dedicated clinical data is available, this is accepted for the time being.

Overall, the available dataset in patients <2 years is very limited due to recruitment problems which was thoroughly discussed by the MAH. The MAH commits to conduct a category 3 PASS in order to further characterise the safety profile in the 6-month to 2-year age group.

3.7.2. Balance of benefits and risks

The therapeutic need of dupilumab in paediatric patients aged ≥6 months to <6 years with severe AD is acknowledged. The favourable effects outweigh the unfavourable effects. The totality of evidence from the clinical program is considered adequate to support the statistically significant difference between the dupilumab and placebo arms reported for the severe AD population. However, the numbers of paediatric patients in the 6 month – 2-year age group compared to the other age group was still relatively low, making it difficult to fully characterise the long-term safety profile. It is acknowledged, however, that there were challenges in recruiting children in this age bracket to the trial, and that the same challenges would exist in another trial. The long term safety profile will be further characterised in the post-authorisation setting : a registry-based PASS is planned by the MAH. In addition the final CSR of the OLE study will be submitted to provide further long-term efficacy and safety data.

3.8. Conclusions

The overall B/R of dupilumab is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of severe atopic dermatitis in paediatric patients from 6 months to <6 years of age based on final results from Study R668-AD-1539; this is a phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 Months to <6 years with moderate-to-severe atopic dermatitis.
As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 9.0 of the RMP has also been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0329/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-0060'.

Attachments

1. SmPC and Package Leaflet (changes highlighted) as adopted by the CHMP on 26 January 2023.