15 October 2020
EMA/640921/2020
Committee for Medicinal Products for Human Use (CHMP)

# Extension of indication variation assessment report

Invented name: Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/II/0027

Marketing authorisation holder (MAH) sanofi-aventis groupe

## 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 |
| ANCOVA | Analysis of covariance |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BL | Baseline |
| 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 |
| Ciclosporin | Cyclosporine, Cyclosporine A, or ciclosporin A |
| $C_{max}$ | Maximum concentration |
| CNS | Central nervous system |
| CRA | Clinical Research Associates |
| CRSwNP | Chronic rhinosinusitis with nasal polyposis |
| CSR | Clinical study report |
| CTD | Common Technical Document |
| $C_{trough}$ | Trough concentration |
| $C_{trough,ss}$ | Trough concentration at steady state |
| DFI | Dermatitis Family Index |
| 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 |
| EOS | End of treatment |
| EOT | End of study |
| E-R | Exposure-Response |
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GISS | Global Individual Signs Score |
| HLT | High-level term |
| HOME | Harmonising Outcome Measures for Eczema |
| IDMC | Independent Data Monitoring Committee |
| IGA | Investigator's Global Assessment |
| IgE | Immunoglobulin E |
| IgG4 | Immunoglobulin G4 |
| IL | Interleukin |
| IL-4Rα | IL-4 receptor alpha |
| IP | Investigational product |
| IRT | Interactive Response Technology |
| ISR | Injection site reaction |
| LDH | Lactate dehydrogenase |
| LLOQ | Lower limit of quantitation |
| LOCF | Last observation carried forward |

| | |
|---|---|
| LS | Least squares |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mFAS | Modified full analysis set |
| MI | Multiple imputation |
| MTX | Methotrexate |
| NA | Not applicable |
| 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 |
| PK | Pharmacokinetic |
| POEM | Patient-Oriented Eczema Measure |
| PPS | Per-protocol set |
| PRO | Patient-reported outcomes |
| PROMIS | Patient Reported Outcomes Measurements Information Systems |
| PSBL | Parent study baseline |
| Q1 | Quartile 1 |
| Q2W | Every 2 weeks |
| Q3 | Quartile 3 |
| Q4W | Every 4 weeks |
| QTcB | QT corrected by Bazett's formula |
| QTcF | QT corrected by Fredericia's formula |
| QOL | Quality of life |
| QW | Once weekly |
| 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 |
| SMQ | Standardized MedDRA query |
| SOC | System organ class |
| TCI | Topical calcineurin inhibitors |
| TCS | Topical corticosteroids |
| TEAE | Treatment-emergent adverse event |
| TG | Triglyceride |
| Th2 | T-helper type 2 |
| 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-aventis groupe submitted to the European Medicines Agency on 15 January 2020 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 the population of atopic dermatitis patients from 6 years to 11 years old. Consequently, the sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The PL is updated accordingly.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

### *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0374/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0374/2019 was not yet completed as some measures were deferred.

### *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: Peter Kiely

| Timetable | Actual dates |
|---|---|
| Submission date | 15 January 2020 |
| Start of procedure | 01 Feb 2020 |
| CHMP Rapporteur Assessment Report | 30 Mar 2020 |
| CHMP Co-Rapporteur Assessment Report | 30 Mar 2020 |
| PRAC Rapporteur Assessment Report | 01 Apr 2020 |
| PRAC members comments | N/A |
| Updated PRAC Rapporteur Assessment Report | 07 Apr 2020 |
| PRAC outcome | 17 Apr 2020 |
| CHMP members comments | 20, 21, 22 Apr 2020 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 23 Apr 2020 |
| Request for supplementary information and extension of timetable adopted by the CHMP on | 30 Apr 2020 |
| MAH's responses submitted to the CHMP on | 19 May 2020 |
| CHMP Rapporteur Assessment Report circulated on | 25 Jun 2020 |
| PRAC Rapporteur Assessment Report circulated on | 26 Jun 2020 |
| PRAC members comments | N/A |
| Updated PRAC Rapporteur Assessment Report circulated on | N/A |
| PRAC RMP advice and assessment overview adopted by PRAC | 09 Jul 2020 |
| CHMP members comments | 09 and 13 Jul 2020 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report circulated on | 16 Jul 2020 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on | 23 Jul 2020 |
| MAH's responses submitted to the CHMP on | 13 Aug 2020 |
| CHMP Rapporteur Assessment Report circulated on | 15 Sep 2020 |
| CHMP members comments | 05 and 06 Oct 2020 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report circulated on | 08 Oct 2020 |
| Opinion | 15 Oct 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Introduction

Dupilumab (DUPIXENT®) is a fully human monoclonal antibody that specifically binds to human interleukin (IL)-4 receptor alpha (IL-4Rα) and blocks both human IL-4 (Type I & Type II) and human IL-13 (Type II) signal transduction. DUPIXENT is approved in the European Union (EU) "for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy".

Dupilumab has been also approved for adults and adolescents with severe asthma with type 2 inflammation and for adults with chronic rhinosinusitis with nasal polyposis in and EU. Dupilumab is to be injected subcutaneously.

This submission proposes to extend the age range for the DUPIXENT indication in atopic dermatitis (AD) from ≥12 years (adolescent and adults) to ≥6 years of age (to include children ≥6 to <12 years of age) as follows: DUPIXENT is indicated for "the treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy".

### 2.1.2. Disease or condition

Atopic dermatitis is a chronic inflammatory skin condition that is characterized clinically by periodic flares of dry, red, itchy skin lesions and pathogenically by a defective skin barrier, recurrent infections, and both local and systemic type 2 immune responses.

Atopic dermatitis is one of the most common skin disorders in infants and children. The disease affects over 20% of children in many industrialized countries. Approximately 45% of all cases of AD begin within the first 6 months of life, 60% begin during the first year, and 85% begin before 5 years of age.

### 2.1.3. Epidemiology

Recent studies have improved our understanding of the epidemiology of childhood AD. In general, more severe eczema correlated with poorer overall health, impaired sleep and increased healthcare utilization. Severe eczema was associated with higher prevalence of comorbid chronic health disorders, including asthma, hay fever and food allergies. The International Study of Asthma and Allergies in Childhood (ISAAC) phase 3 study surveyed over 8 countries and identified a 7.9% global prevalence of eczema in children 6 to 7 years old . The prevalence of AD in developed countries such as the US is expected to increase if the trends from the last 20 years continue. The US Centers for Disease Control and Prevention identified an increase in the prevalence of AD in patients aged 0 to 17 years from 7.4% in 1997 to 1999 to 12.5% in 2009 to 2011. Rising prevalence seems to be paired with rising incidence in the total number of severe intractable cases, which includes more cases of children continuing with disease into the grade school years and increased number of cases persisting into adulthood.

### 2.1.4. Biologic features, aetiology and pathogenesis

There is a paucity of studies comparing adults and children with respect to the cellular and molecular mechanisms of disease in AD due in part to the fact that mechanistic studies involving the collection of skin biopsies and other invasive procedures are generally not feasible or pose ethical challenges in children. 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 polarized inflammatory response induced by the marked activation of the T-helper type 2 (Th2) cell axis plays a central role. Two cytokines, IL-4 and IL-13, are critical in the initiation and maintenance of the Type 2 inflammatory pathway. The elevated IgE responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the Th2 cytokines IL-4 and IL-13. Type 2 helper T-cell-associated 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 defensin 2 and 3. The Th2 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.

Most studies in AD children are limited to studies of peripheral blood, demonstrating 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.

### 2.1.5. Clinical presentation

Clinical presentation of AD in children is similar to that in adults. Lesions typically occur in the flexural areas and facial involvement is common, especially the forehead and periorbital regions. The wrists, hands, ankles, feet, fingers, and toes are also often involved. The eruption is characterized by dry, scaling erythematous papules and plaques, and the formation of large lichenified plaques from lesional chronicity. Pruritus is the hallmark of AD in children, as in adults. The cycle of itching and scratching exacerbates the cellular damage in skin lesions and facilitates secondary infections, which can be serious.

The clinical pattern of AD, however, varies somewhat with age. In infants, for example, involvement of the face, neck, and extensor extremities (elbows, knees) is more characteristic than in older individuals with AD. Persistent, bright red plaques may develop on the cheeks and chin at the time of teething and introduction of solid food, likely related to chronic irritation from saliva and foods. Scalp dermatitis with linear excoriations are common, even with minimal skin involvement. With increasing age, children tend to develop the classic flexural patches and plaques on the antecubital and popliteal fossae. Hand and foot plantar dermatitis is also common. In more severe cases, thickened plaques are seen on the dorsal hands, feet, and knees, often with a lichenified or leathery appearance with prominent skin lines. The surrounding skin is often dry and flaky, and there may be plate-like ichthyosis of the distal extremities, especially in older children.

Children with AD, similar to adults with AD, are more frequently colonized with *Staphylococcus aureus* than their healthy counterparts. The rates of colonization vary among studies and regions and range from 40% to 93% of patients with AD, as compared to 24% to 30% of healthy children. Soft tissue infections also occur, affecting 40% to 60% of patients with AD during their lifetime. Atopic dermatitis has been shown to have an impact on the quality of life (QoL) of paediatric patients, greater than that seen in other common skin disorders like psoriasis and urticaria.

### 2.1.6. Management

Available Therapies for Atopic Dermatitis in Children Aged Children Aged **≥6** to < 12 years

Currently available therapies for children with AD 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 population, 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 as young as infants. However, their long-

term use or large body-surface application is limited by the risk of local side effects (eg, skin atrophy and telangiectasia) as well as systemic adverse reactions, including hypothalamic-pituitary-adrenal axis suppression and Cushing syndrome. Children are more prone to the development of systemic reactions to topically applied medication because of their higher ratio of total body surface area to body weight. Linear growth retardation and delayed weight gain have been reported in children receiving TCS. Cushing syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, and adrenal insufficiency have been reported with chronic use. Moreover, continuous use of TCS can be associated with development of tachyphylaxis (decreased treatment response and requirement for higher doses of higher potency steroids).

Topical calcineurin inhibitors (TCI), 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, (e.g, face, genitals, and flexural areas). The more effective TCI product (tacrolimus ointment 0.1%) is not approved for use in children aged 6 to 11 years old. Crisaborole, a non-steroidal topical phosphodiesterase-4 (PDE4) inhibitor, has been approved for use in paediatric AD patients. Ciclosporin is not approved for AD in pediatric patients but often used off label for severe AD when systemic therapy is required. In addition, other systemic immunosuppressive agents are also commonly used in treatment of severe forms of the disease, including methotrexate, azathioprine and mycophenolate mofetil. A high proportion of patients suffer from relapse or rebound once the therapy is discontinued. The lack of safe and effective systemic treatments means that most patients with moderate-to-severe AD are not well controlled and further illustrates the need for an effective treatment for AD in children that also has a safety profile that is acceptable for chronic administration.

## *2.2. Non-clinical aspects*

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP. Nonclinical safety was assessed as part of the original MAA for atopic dermatitis (AD) indication and are sufficient to support the use in patients from 6 to 11 years of age. It is not expected that the proposed indication would lead to an increase in environmental exposure therefore the conclusions related to the current ERA remain valid.

### 2.2.1. Conclusion on the non-clinical aspects

There are no updated data submitted in this application. In relation to ERA, it is agreed that the indication applied for in this application will not lead to a significant increase in environmental exposure further to the use of dupilumab.

## *2.3. Clinical aspects*

### Introduction

Patients aged ≥6 to <12 years with AD have been included in 3 dupilumab clinical studies where PK and pharmacodynamic (PD) data have been collected (refer to Table 1). A variety of SC dosing regimens was evaluated in these studies including: 2 mg/kg and 4 mg/kg single dose or repeated once weekly (QW) dose, weight-tiered 100 mg/200 mg Q2W (below and above 30 kg), and 300 mg Q4W, as well as weight-tiered 200 mg/300 mg Q2W as an up-titration from 300 mg Q4W in the OLE study R668-AD-1434. Loading doses of two times the respective maintenance doses were administered in the fixed dosing regimens of pivotal study R668-AD-1652.

The proposed indication for children is supported primarily by data from the randomized, placebo-controlled pivotal study R668-AD-1652, assessing efficacy and safety of dupilumab with concomitant

topical corticosteroids (TCS) in children with severe AD aged ≥6 to <12 years and by supportive data from patients aged ≥6 to <12 years :

– E-R and PK data are presented to support the posology in this patient population,

– and additionally by supportive data from patients with severe AD in the phase 2a PK study (R668-AD-1412) and patients aged ≥6 to <12 years with moderate-to-severe AD in the open-label extension (OLE) study (R668-AD-1434) of long-term safety and efficacy.

The proposed posology in patients ≥6 to <12 years of age with severe AD is tiered by body weight with patients ≥15 to <30 kg receiving 300 mg Q4W following a 600 mg loading dose and with patients ≥30 to <60 kg receiving 200 mg Q2W following a 400 mg loading dose.

For children ≥6 to <12 years of age weighing ≥60 kg, the proposed dose regimen is 300 mg Q2W following a loading dose of 600 mg, since this dose regimen has been proven to achieve the desired effective exposure in adults and adolescents weighing ≥60 kg.

## 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

Table 1: Overview of Clinical Efficacy Studies for Dupilumab in the Treatment of Children **≥6** to <12 Years of Age with Severe Atopic Dermatitis

| **Study/Phase/ Data Cut-off Date /Study Status[a]** | **Efficacy Objectives** | **Study Design and Duration** | **Treatment: Dose Regimen/Route of Administration** | **Overall Planned / Enrolled[b]** | **Children (≥6 to <12 years of age) Planned/ Enrolled** |
|---|---|---|---|---|---|
| R668-AD-1652 /Phase 3/ 28 Jun 2019/ Primary analysis completed | The primary objective of this study is to demonstrate the efficacy of dupilumab administered concomitantly with TCS in children ≥6 to <12 years of age with severe AD. Key efficacy results are summarized in Table 4. | Randomized (1:1:1), double-blind, placebo-controlled, parallel-group 16-week treatment duration 12-week follow-up See Section 2.1 | Dupilumab Q2W + TCS treatment group: 100 mg Q2W (patients <30 kg) following a loading dose of 200 mg on day 1 or 200 mg Q2W + TCS (patients ≥30 kg) following a loading dose of 400 mg on day 1<br>Dupilumab Q4W + TCS treatment group: 300 mg Q4W, irrespective of weight following a loading dose of 600 mg on day 1<br>Placebo + TCS group | 330 / 367 | ~330 / 367 |
| R668-AD-1434 /Phase 3/ 22 Jul 2019/ Ongoing | Secondary objectives included assessment of long-term efficacy in pediatric patients as well as to determine immunogenicity after re-treatment. Key efficacy results for patients ≥6 to <12 years of age are summarized in Table 8. | Multicenter, OLE<br>The OLE treatment period for this study is ongoing at time of data cutoff date (22 Jul 2019).<br>See Section 2.3 | Under the original version of the protocol, patients were dosed with 2 mg/kg QW or 4 mg/kg QW. From amendment 1 onwards, patients were dosed with 300 mg Q4W with provision for up-titration (200 mg Q2W for patients <60 kg, 300 mg Q2W for patients ≥60 kg) in case of inadequate clinical response at week 16 | NA[c] / 368 | NA[c] / 368<br>(38 patients ≥6 to <12 years of age will have been exposed to dupilumab for ≥1 year in OLE study) |

| Study/Phase/ Data Cut-off Date /Study Status[a] | Efficacy Objectives | Study Design and Duration | Treatment: Dose Regimen/Route of Administration | Overall Planned / Enrolled[b] | Children (≥6 to <12 years of age) Planned/ Enrolled |
|---|---|---|---|---|---|
| R668-AD-1412 /Phase 2a/ NA/Completed | Secondary objectives were to explore the immunogenicity and efficacy of dupilumab in children ≥6 to <12 years of age with severe AD. Key efficacy results are summarized in Table 6. | Multicenter, open-label, ascending-dose, sequential-cohort Single-dose, followed by 4 weekly doses and 8-week follow-up See Section 2.2 | Part A: Dupilumab SC, 2 mg/kg for dose cohort 1 and 4 mg/kg for dose cohort 2, given as single dose on day 1. Part B: Dupilumab SC, 2 mg/kg for dose cohort 1 and 4 mg/kg for dose cohort 2, given weekly over a 4-week treatment period. | ~80 / 78 | ~40 /38 (38 enrolled in Part A and 37 continued in Part B) |

[a] Study status is based on the time of the data cut-off date for the studies in this submission.
[b] Only data from children (males or females ≥6 to <12 years of age) in each study are presented in this submission.
[c] The number of patients ≥6 to <12 years of age planned was not defined in the protocol.
Abbreviations: AD, atopic dermatitis; NA, Not applicable; OLE, open-label extension; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652, Module 5.3.5.2 R668-AD-1434 Second-step Analysis, and Module 5.3.3.2 R668-AD-1412

### 2.3.1. Pharmacokinetics

In the phase 2a PK study R668-AD-1412, semi dense PK sampling schedules during the single dose and 8-week observation/sampling period, and sparse sampling was used during the repeat-dose (at pre-dose of each study drug administration) and follow-up period.

In the pivotal study R668-AD-1652 and the OLE study R668 AD 1434, a sparse sampling scheme was utilized with samples taken at pre-initiation of treatment, and at pre-dose of each study drug administration (Ctrough) throughout the treatment period. Samples collected in the post-treatment period were limited to those patients who did not roll into the OLE study.

The pharmacokinetics (PK) of dupilumab have been previously characterized as nonlinear with target-mediated disposition.

## Table 2: Tabulated summary of studies

| Study / Report Location/ Study Status | Study Population/Analysis Sets | PK-Related Objective | Study Design and Duration | Treatment: Dose, Route of Administration, Frequency (number of patients randomized) |
|---|---|---|---|---|
| **Atopic Dermatitis – SC Administration (Phase 2)** | | | | |
| R668-AD-1412<br>Module 5.3.3.2 in previous marketing application<br><br>Study Completed | Pediatric patients with moderate-to-severe AD (for adolescents ≥12 to <18 years of age) or severe AD (for children ≥6 to <12 years of age) that was not adequately controlled by topical medications.<br>38 children ≥6 to <12 years of age were included in the PK analysis for this application. | PK of dupilumab in pediatric patients with moderate-to-severe AD (for adolescents ≥12 to <18 years of age) or severe AD (for children ≥6 to <12 years of age). | Phase 2a, multicenter, open-label, ascending dose, sequential cohort study of single dose and repeat doses of SC dupilumab.<br>Part A: single dose and 8-week interspersed semi-dense PK sampling (patients were randomized to 1 of 3 sampling schedules)<br>Part B: 4 weekly doses and a 8-week follow-up with sparse PK sampling | SC doses of dupilumab 2 mg/kg and 4 mg/kg<br>38 children ≥6 to <12 years of age |
| **Atopic Dermatitis – SC Administration (Phase 3)** | | | | |
| R668-AD-1652<br>iCSR2<br>Module 5.3.5.1<br><br>Study Ongoing<br>Primary analysis CSR completed | Patients (≥6 to <12 years of age) with severe AD that cannot be adequately controlled with topical AD medications.<br>362 patients were included in PK analysis. | Trough concentrations and immunogenicity were assessed | Phase 3, global randomized, double-blind, placebo-controlled, repeat dose study<br>Sparse sampling for $C_{trough}$<br>Treatment duration 16 weeks<br>Follow-up 12 weeks | • 120 patients on placebo<br>• 120 patients on Q4W SC doses of dupilumab: 300 mg (regardless of body weight) with loading dose of 600 mg<br>• 122 patients on Q2W SC doses of dupilumab: 200 mg (59 patients weighing ≥30 kg) following a loading dose of 400 mg, or 100 mg (63 patients weighing ≥15 kg to <30 kg) following a loading dose of 200 mg |

| Study / Report Location/ Study Status | Study Population/Analysis Sets | PK-Related Objective | Study Design and Duration | Treatment: Dose, Route of Administration, Frequency (number of patients randomized) |
|---|---|---|---|---|
| R668-AD-1434<br>Module 5.3.5.2<br><br>Study Ongoing | Pediatric patients (≥6 months to <18 years of age) with moderate-to-severe AD who have previously completed a clinical study with dupilumab.<br>368 children ≥6 to <12 years of age were included in the PK analysis for this application. | To assess the $C_{trough}$ of functional dupilumab in serum and immunogenicity in pediatric patients with AD after re-treatment with dupilumab. | Phase 3 open-label extension study<br>Sparse sampling for $C_{trough}$<br>Treatment duration 260 weeks<br>Follow-up 12 weeks | 368 children aged ≥6 to <12 years old were enrolled in the study at the time of the data cut-off date of 22 Jul 2019:<br>112 patients previously on placebo and 256 patients previously on SC doses of dupilumab in parent studies.<br>The initial dose regimen in this study of the 368 patients:<br>• 33 patients started with weight-tiered regimen: 17 for 2 mg/kg QW and 16 for 4 mg/kg QW (all 33 patients were from the parent study R668-AD-1412); their dose regimen was switched to the fixed regimen of 300 mg Q4W starting at protocol amendment 1<br>• 335 patients started with the fixed dose regimen of 335 for 300 mg Q4W<br>• 136/362 (37.6%) of patients that received at least one dose of 300 mg Q4W were up-titrated, per protocol, to 200/300 mg Q2W due to inadequate clinical response at week 16 as of the data cutoff for this application |

AD – atopic dermatitis; $C_{trough}$ – trough concentration at the end of the dosing interval; PK – pharmacokinetics; QW – once weekly; Q2W – once every 2 weeks; Q4W – once every 4 weeks; SC – subcutaneous;

### *2.3.1.1. Bioanalytical methods*

Overview

Analyses included samples from the clinical study R668-AD-1652 (pivotal study) and the ongoing open-label extension study R668-AD-1434 which enrolled pediatric patients ≥6 to 18 years of age with AD who have previously completed a pediatric AD dupilumab clinical study, including parent studies R668-AD-1412 (phase 2 PK study) and R668-AD-1652.

Serum samples for quantitation of functional dupilumab (ie, dupilumab with 1 or both binding sites available for target IL-4Rα binding) in human serum were analyzed using validated enzyme linked immunosorbent assays (ELISA) with a lower limit of quantitation (LLOQ) of functional dupilumab of 0.078 mg/L in undiluted human serum. In this summary, concentrations of functional dupilumab in serum may be referred to as dupilumab for brevity.

Incurred sample reanalysis (ISR) for the functional dupilumab assay was performed in R668-AD-1412 study to support the overall pediatric program, including adolescents ≥12 to <18 years of age and children ≥6 to <12 years of age with AD. ISR passing rate in study R668-AD-1412 was 90.8%.

#### *2.3.1.2. Immunogenicity*

Assessment of ADAs in the R668-AD-1434 and R668-AD-1652 studies for this submission was conducted using the REGN668-AV-13089-VA-01V3 assay previously assessed. 22 out of 360 baseline serum samples from R668-AD-1652 study were positive in the ADA screening assay, resulting in an observed false positive rate of 6.1%. This rate is aligned with the target false positive rate of 5% in the screening assay. This indicates that true ADA positives were not missed during the bioanalysis of these study samples in children (≥6 to <12 years of age) AD population.

Assessment of neutralizing anti-dupilumab antibodies for this submission was conducted using the REGN668-AV-13112-VA-01V2 assay previously assessed. Updates to this method included modification of the assay cut point using a 1% false positive rate.

#### *2.3.1.3. Study R668-AD-1412 (phase 2a PK study)*

Study Design: Study R668-AD-1412 was a phase 2a, multicenter, open-label, ascending dose, sequential cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of single dose and repeat doses of SC dupilumab in pediatric patients with AD not adequately controlled by topical medications.

Thirty-eight children ≥6 to <12 years of age were included in the PK analysis for the current application and the results are summarized below.

The study consisted of a screening period, a baseline visit, Part A (including a single-dose treatment and an 8-week sampling period, where patients were randomized to 1 of 3 interspersed semi-dense PK sampling schedules), and Part B (including a repeat-dose treatment period [4 weekly doses] and an 8-week follow-up period). Posology of dupilumab administered in this study was 2 mg/kg and 4 mg/kg by SC injections.

Results (systemic exposure): 38 children ≥6 to <12 years of age were included in the PK analysis for the current application.The concentration-time profiles for functional dupilumab in serum are best described by an initial absorption phase, followed by a linear β elimination phase and a terminal concentration dependent target-mediated elimination phase. Dupilumab concentrations were typically more than 2-fold greater following 4 mg/kg SC than 2 mg/kg SC. Overall, the PK profile of dupilumab in these pediatric AD patients is consistent with that observed in adults.

#### *2.3.1.4. Study R668-AD-1652 (phase 3 pivotal study)*

Study Design: Study R668-AD-1652 was a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab combined with TCS in patients ≥6 to <12 years of age with severe AD not adequately controlled by topical AD medications.

The study consisted of 4 periods: screening (up to 9 weeks), TCS standardization (2 weeks), treatment (16 weeks) and follow-up (12 weeks). Sampling for PK assessment was performed at baseline and at study weeks 4, 8, 12 and 16 during treatment period, at unscheduled visits during this period, and in case of early termination, at this visit. For patients not entering the OLE study R-668-AD-1434, further PK sampling was performed at study weeks 24 and 28 during the follow-up period.

*Randomisation*

Patients were randomized in a 1:1:1 ratio stratified by baseline body weight (<30 kg and ≥30 kg) to the following treatment groups listed below stratified by baseline body weight (<30 kg and ≥30 kg) and region (North America, Europe):

The fixed weight-tiered dupilumab Q2W treatment group (n=122):

-63 Patients with baseline weight ≥15 to <30 kg: Q2W SC injections of 100 mg dupilumab (0.7 mL of a 150 mg/mL solution) from week 2 to week 14, following a loading dose of 200 mg on day 1
and
-59 Patients with baseline weight ≥30 kg: Q2W SC injections of 200 mg dupilumab (1.14 mL of a 175 mg/mL solution) from week 2 to week 14, following a loading dose of 400 mg on day 1.

Non-weight-tiered dupilumab Q4W treatment group (n=120):
regardless of weight, Q4W SC injections of 300 mg dupilumab (2 mL of a 150 mg/mL solution) from week 4 to week 12, following a loading dose of 600 mg on day 1.

Placebo treatment group (n=120): matching placebo

A the dosing regimens used in this study were selected using simulation from a population PK model based on pediatric PK data from study (R668-AD-1412), with the aim of matching the dupilumab exposure distribution in children aged ≥6 to <12 years to that achieved with the approved 300 mg Q2W regimen in adults, based on the assumption that the exposure response relationships for efficacy endpoints is similar in adults and children aged ≥6 to <12 years.

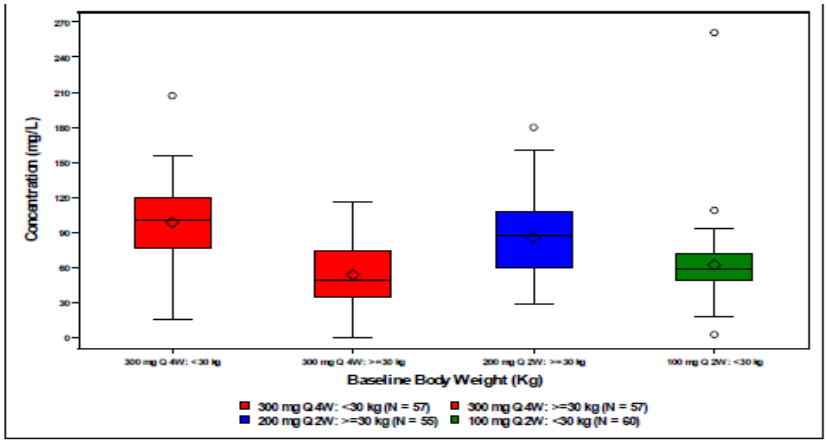
Results (systemic exposure):

Overall, 362 patients were included in PK analysis of Study R668-AD-1652 and the results are summarized below.

Systemic concentrations of dupilumab achieved steady state in all treatment regimens before the primary endpoint at week 16. Steady state was achieved in accordance with the dosing interval and loading dose; the Q2W dosing regimens achieved steady state at or before week 8 and the Q4W regimen achieved steady state at or before week 12. Mean $C_{trough}$ for the Q2W regimen observed at week 4 was about 14% lower than that at week 16. Mean $C_{trough}$ for the Q4W regimen observed at week 4 was about 21% higher than that at week 16.

When comparing the Q2W regimen with the Q4W regimen for each weight subset, differences in exposure by regimen were observed. At week 16, the patients weighing <30 kg had a mean (±SD) $C_{trough}$ of dupilumab on the Q4W regimen (300 mg Q4W) of 98.7±33.2 mg/L while those children on the Q2W regimen (100 mg Q2W) demonstrated a mean $C_{trough}$ of 62.6±32.3 mg/L. In children weighing ≥30 kg, those children on 200 mg Q2W had a mean $C_{trough}$ of 86.0±34.6 mg/L as compared with those patients on the Q4W regimen (300mg Q4W) who had a mean $C_{trough}$ of 53.9±25.7 mg/L. These results demonstrated that the 300 mg Q4W regimen in children ≥15 to <30 kg resulted in $C_{trough}$ similar to those achieved in children ≥30 kg dosed with the 200 mg Q2W regimen. These $C_{trough}$ were higher than those obtained in children ≥30 kg dosed with 300 mg Q4W regimen or <30 kg dosed with the 100 mg Q2W regimen (Figure 1)

Figure 1: Concentrations of Functional Dupilumab in Serum in Week 16 by Patient Body Weight Category and Treatment Group in Children **≥6** to <12 Years of Age with Severe AD (Study R668-AD-1652)




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

Study R668-AD-1434 (OLE study)

Study Design: Study R668-AD-1434 is an ongoing phase 3, open-label extension (OLE) study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat SC doses of dupilumab in pediatric patients ≥6 to 18 years of age with AD who have previously completed a pediatric AD dupilumab clinical study, including parent studies R668-AD-1412 (phase 2 PK study) and R668-AD-1652.

The study consists of a screening period (day 28 to day 1), a treatment period up to the time of local regulatory approval in the appropriate pediatric age group, and a 12-week follow-up period.

Patients from parent study R668-AD-1412 who enrolled in R668-AD-1434 under the original protocol were started on weight-based SC dupilumab regimens of 2 mg/kg or 4 mg/kg QW at the same single dose level they had received in study R668-AD-1412. When R668-AD-1434 amendment 1 was approved, all patients were re-assigned to a fixed dose regimen of 300 mg SC Q4W. At the time of this amendment, most patients from R668-AD-1412 had been enrolled with a median treatment duration of 88 weeks. This amendment also introduced potential for up titration to weight-tiered 200 mg or 300 mg Q2W regimen, based on clinical responses.

Vast majority of patients from parent study R668-AD-1652 enrolled in R668-AD-1434 under protocol amendment 3 and were started on a dose regimen of dupilumab 300 mg SC Q4W without a loading dose. Patients with inadequate clinical response during the treatment with dupilumab 300 mg SC Q4W in study R668-AD-1434, defined as failure to achieve IGA 0 or 1 after 16 weeks of treatment, were to be re-assigned to an up-titrated dosing regimen of either 200 mg SC Q2W (for patients weighing <60 kg) or 300 mg SC Q2W (for patients weighing ≥60 kg).

PK sampling was performed using two different schemes as follows:

For scheme 1, sampling for PK assessment was performed at baseline and at study weeks 4, 12, 36, 60, 84, 104 (EOT) during treatment period, at unscheduled visits during this period, and in case of early termination, at this visit. A further sample was taken study week 120 (EOS) during follow up.

For scheme 2, sampling for PK assessment was performed at baseline and at study weeks 4, 24, 48, 72, 96, 104 (EOT) during treatment period, at unscheduled visits during this period, and in case of early termination, at this visit. A further sample was taken study week 120 (EOS) during follow up.

At the time of the data cut-off, a total of 368 patients from parent studies R668-AD-1412 and R668-AD-1652 aged ≥6 to <12 years at screening of OLE were included in the study.

Results (systemic exposure):

Pharmacokinetic and immunogenicity results are presented below only for patients ≥6 to <12 years of age at the time of enrolment in study R668-AD-1434 who participated in parent study R668 AD-1412 or R668-AD-1652. At the time of the data cut-off, a total of 368 patients from these parent studies aged ≥6 to <12 years were included.

Mean week 16 $C_{trough}$ of dupilumab was 68.9 ± 37.8 mg/L in patients receiving dupilumab SC 300 mg Q4W and were 57% higher in patients up-titrated to the more intensive 200/300 mg SC Q2W regimen (108 ± 53.8 mg/L). Mean week 16 $C_{trough}$ in the subset of patients <30 kg on 300 mg Q4W and ≥30 kg on 200/300 mg Q2W fell between this range at 91.5 ± 37.5 mg/L and 82.3 ± 35.9 mg/L, respectively (Table 3). Mean $C_{trough}$ observed from week 16 through week 52 were approximately at steady state, within a similar range for 2 mg/kg QW and 300 mg Q4W regimens (approximately 50 to 80 mg/L), and higher for patients on 200/300 mg Q2W (approximately 80 to 110 mg/L) or 4 mg/kg QW (approximately 140 to 180 mg/L) regimens.

Table 3: Concentrations of Functional Dupilumab in Serum at Week 16 by Body Weight Category and Treatment Group in Patients **≥6** to <12 Years with AD of Age from Parent Study R668-AD-1652 (Study R668-AD-1434)

| | 300 mg Q4W | | 200/300 mg Q2W | |
|---|---|---|---|---|
| **Body Weight of PK Population** | **N** | **Mean (SD)** | **N** | **Mean (SD)** |
| <30 kg | 89 | 91.5 (37.5) | 10 | 156 (49.3) |
| >= 30 kg | 124 | 52.7 (28.8) | 18 | 82.3 (35.9) |
| Overall | 213 | 68.9 (37.8) | 28 | 108 (53.8) |

N =Number of patients; SD = Standard deviation
Note: Concentrations below the LLOQ were set to 0.

*PK comparison across populations*

The PK of functional dupilumab in serum has previously been extensively described in the adult AD patient population and healthy subjects (initial marketing application). 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. Body weight has been identified as the single most influential covariate that described the variability in dupilumab exposure. As such, an emphasis was primarily placed on presenting and comparing the observed PK of dupilumab in all children ≥6 to <12 years of age to adults as well as a weight normalized comparison of children to adults.

This latter approach was accomplished using population PK modeling. The goal was to select regimens which achieved exposures associated with the highest observed efficacy on primary and secondary endpoints at week 16 and whose exposures at least matched or exceeded the Ctrough at week 16 of the 300 mg Q2W regimen in adults.

*Comparison of dupilumab drug concentrations*

Functional dupilumab Ctrough data over time and at week 16 from the pivotal study R668-AD-1652 in patients ≥6 to <12 years of age treated with dupilumab dosing regimens, including the fixed weight-tiered regimen of 100 mg Q2W (for patients weighing <30 kg) and 200 mg Q2W (for patients weighing ≥ 30 kg) as well as the non-weight-tiered 300 mg Q4W, were compared primarily to the approved dosing regimen in adults of 300 mg Q2W. Adult data were pooled from phase 3 studies (R668-AD-1334 SOLO1 and R668-AD-1416 SOLO2) and the phase 2 study R668-AD-1021.

Dupilumab Ctrough data were also compared to that of the approved regimen in adolescents (200 mg Q2W in patients weighing <60 kg and 300 mg Q2W in patients weighing ≥60 kg) as evaluated in the phase 3 study R668-AD-1526.

Steady-state Ctrough for various dupilumab dosing regimens evaluated in adult, adolescent, and children ≥6 to <12 years old patients with AD are shown in Table 4, Table 5, Table 6. Relative to the mean observed steady-state Ctrough for the approved 300 mg Q2W regimen in adults, steady-state Ctrough values in patients ≥6 to <12 years of age were lower for those <30 kg receiving 100 mg Q2W, but greater in those ≥30 kg receiving 200 mg Q2W. The overall mean steady-state Ctrough in patients ≥6 to

<12 years of age receiving the 300 mg Q4W regimen was also similar to that of adults receiving the approved 300 mg Q2W dose.

Table 4: Comparison of Steady-State Dupilumab Trough Concentrations (mg/L) between Adults, Adolescents, and Children **≥6** to <12 Years of Age by Age Group and Treatment Regimen

| | Adults (N=1772) | | | Adolescents (N=194) | | | Children (≥6-<12yrs) (N=268) | | |
|---|---|---|---|---|---|---|---|---|---|
| **Treatment Group** | **n** | **Mean (SD)** | **Min : Max** | **n** | **Mean (SD)** | **Min : Max** | **n** | **Mean (SD)** | **Min : Max** |
| 100 mg Q2W | 0 | | | 0 | | | 61 | 61.5 (33.1) | 0 : 261 |
| 200 mg Q2W | 53 | 35.2 (24.8) | 0.0390 : 101 | 40 | 51.3 (24.2) | 0 : 100 | 56 | 84.5 (36.2) | 0 : 180 |
| 300 mg Q2W | 711 | 73.6 (38.4) | 0.0390 : 363 | 36 | 57.9 (30.0) | 0 : 112 | 0 | | |
| 100 mg Q4W | 61 | 0.426 (1.18) | 0.0390 : 6.31 | 0 | | | 0 | | |
| 300 mg Q4W | 63 | 13.8 (12.0) | 0.0390 : 38.1 | 80 | 20.3 (15.8) | 0 : 57.1 | 114 | 76.3 (37.2) | 0 : 207 |
| 300 mg QW | 884 | 182 (74.2) | 0.0390 : 447 | 0 | | | 0 | | |
| 2 mg/kg QW* | 0 | | | 20 | 18.5 (12.4) | 0.0390 : 37.0 | 18 | 28.0 (12.9) | 0.0390 : 47.9 |
| 4 mg/kg QW* | 0 | | | 18 | 58.8 (24.4) | 0.184 : 86.7 | 19 | 60.3 (36.3) | 1.73 : 145 |

n=number of patients contributing to each category. N=number of patients.
Adolescents are patients in R668-AD-1526 and R668-AD-1412; Adults are patients in studies R668-AD-1021, R668-AD-1224, R668-AD-1334, R668-AD-1416, R668-AD-1424; Children (≥6 to <12 years) are patients in studies R668-AD-1652 and R668-AD-1412
* Trough concentrations for R668-AD-1412 are at week 12 and are not at steady state

Table 5: Summary of Concentration of Functional Dupilumab in Serum at Week 16 by Body Weight Stratum in Children **≥6** to <12 Years of Age with Severe AD (Study R668-AD-1652)

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

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

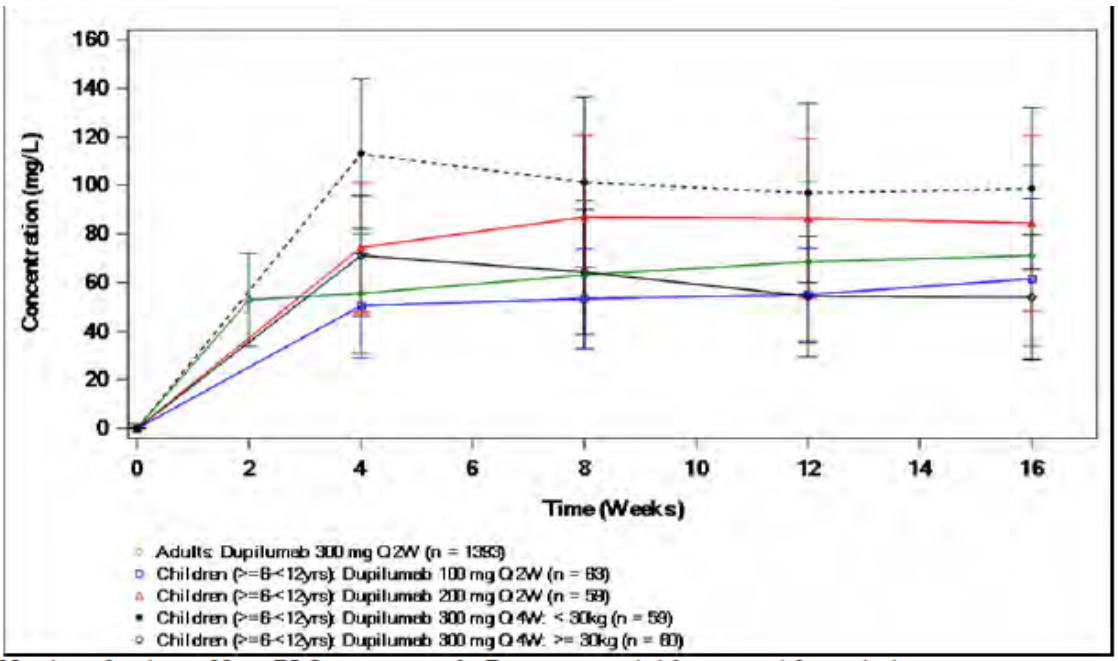
Table 6: Sensitivity Analysis of Concentration of Functional Dupilumab in Serum at Week 16 by Body Weight Categories and Treatment Group in Children **≥6** to <12 Years of Age with Severe AD (Study R668-AD-1652)

| | Concentrations of Functional Dupilumab in Serum (mg/L) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo (N=116) | | 300 mg Q4W (N=114) | | 100 or 200 mg Q2W (N=117) | | 200 mg Q2W (N=56) | | 100 mg Q2W (N=61) | |
| Body Weight Category | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| <10 kg | 0 | -- | 0 | -- | 0 | -- | 0 | -- | 0 | -- |
| 10 - 20 kg | 9 | 0 (0) | 6 | 110 (19.6) | 10 | 96.1 (61.1) | 0 | -- | 10 | 96.1 (61.1) |
| 20 - 30 kg | 48 | 0 (0) | 51 | 97.3 (34.4) | 51 | 54.8 (18.8) | 1 | 0 (---) | 50 | 55.8 (17.3) |
| 30 - 40 kg | 39 | 0 (0) | 38 | 63.7 (23.7) | 32 | 102 (32.1) | 32 | 102 (32.1) | 0 | -- |
| 40 - 50 kg | 13 | 0 (0) | 14 | 38.2 (17.4) | 16 | 67.2 (29.5) | 15 | 71.6 (24.3) | 1 | 0 (---) |
| >= 50 kg | 7 | 0 (0) | 5 | 23.7 (11.7) | 8 | 47.8 (12.5) | 8 | 47.8 (12.5) | 0 | -- |

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

When analyzed by pre-specified weight tiers, steady-state Ctrough were lower in patients weighing ≥30 kg as compared with patients weighing <30 kg (Figure 2).

Figure 2: Mean (± SD) Trough Concentrations of Functional Dupilumab in Serum (mg/L) vs. Nominal Time (Week) in Patients **≥6** to <12 Years of Age with Severe AD Receiving Dupilumab 100 mg Q2W, 200 mg Q2W, or 300 mg Q4W by Body Weight Compared to Adult AD Patients Receiving 300 mg Q2W




n=Number of patients. Note: BLQs were set to 0. Data up to week 16 were used for analysis.
Children (≥6 to <12 Years) are patients in study R668-AD-1652; Adults are patients in studies R668-AD-1021, R668-AD-1416, R668-AD-1334, and R668-AD-1424

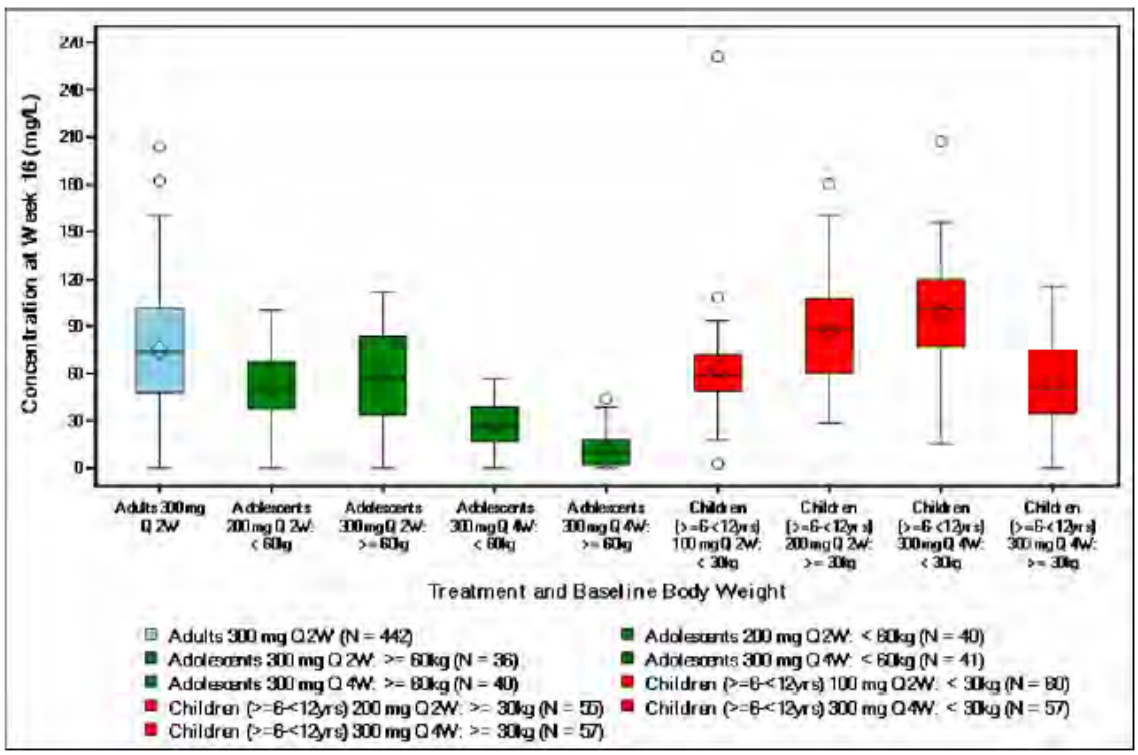
The observed distribution of dupilumab steady-state Ctrough in patients ≥6 to <12 years of age at week 16 was visually compared to the adult 300 mg Q2W regimen as well as regimens previously evaluated in the pivotal study (R668-AD-1526) in adolescent patients (Figure 2). The 300 mg Q4W regimen in patients ≥6 to <12 years of age was summarized separately in those ≥30 kg or <30 kg to facilitate comparison to the equivalent weight groups receiving 100 mg or 200 mg Q2W.

When comparing dosing regimens within the population of children ≥6 to <12 years of age, generally the Ctrough distribution of 200 mg Q2W in patients ≥30 kg and 300 mg Q4W in patients <30 kg was similar to each other and higher than the Ctrough distribution of 300 mg Q4W in patients ≥30 kg and 100 mg Q2W in patients <30 kg. When comparing across populations, the mean ± SD steady-state Ctrough at week 16 in patients ≥30 kg receiving 300 mg Q4W (53.9±25.7 mg/L) and patients <30 kg receiving the 100 mg Q2W (62.6±32.3 mg/L) were lower than adults receiving 300 mg Q2W (73.6 ±38.4 mg). In contrast, mean ±SD steady-state Ctrough in patients <30 kg receiving 300 mg Q4W (98.7±33.2 mg/L) and patients ≥30 kg receiving 200 mg Q2W (86.0±34.6 mg/L) were similar to or greater than the steady-state Ctrough observed in adults (Figure 3).

According to the MAH, these observed PK data support the following posology in children ≥6 to <12 years of age: 200 mg Q2W regimen in the children weighing ≥30 kg and 300 mg Q4W regimen in children <30 kg as the dosing regimens achieving drug concentrations that are at least similar to or greater than that achieved by the standard 300 mg Q2W regimen in adults.

For children ≥6 to <12 years of age weighing ≥60 kg, the proposed dose regimen is 300 mg Q2W following an initial dose of 600 mg, since weight is the primary covariate affecting the PK of dupilumab and this dose regimen has been proven to achieve the desired effective exposure in adults and adolescents weighing >60 kg.

Figure 3: Box-Plot of Functional Dupilumab Trough Concentration in Serum at Week 16 by Patient Age Group, Treatment and Baseline Body Weight Category




Note: BLQ values were set to 0.
Adults are patients in Studies R668-AD-1334 and R668-AD-1416; Adolescent are patients in Study R668-AD-1526; Children (≥6 to <12yrs) are patients in study R668-AD-1652.
A single adult patient (R668-AD-1416-616005003) with an outlier concentration of 363 mg/L has been excluded from the plot for better visualization of distribution of concentrations.

*Model-Based Comparison of Dupilumab PK in Children ≥6 to <12 Years of Age and Adult Patients with AD*

Concentration time profiles of dupilumab were simulated using a population PK model in children ≥6 to <12 years of age <30 kg receiving 300 mg Q4W or ≥30 kg receiving 200 mg Q2W, as well as adults receiving 300 mg Q2W regimens. Regimens were simulated with loading doses of 600 mg (300 mg QW, Q2W, or Q4W) or 400 mg (200 mg Q2W). The analysis assessed both central tendency and variability as

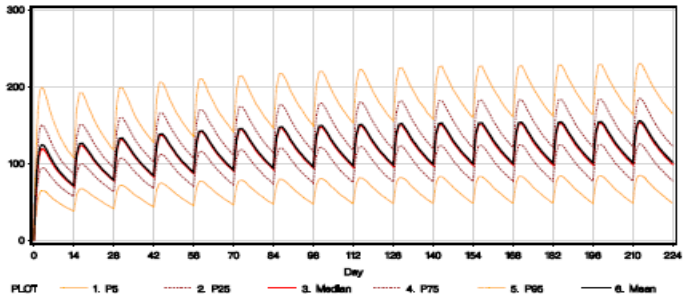
shown by the 90% prediction interval (interval between 5th and 95th percentile) in dupilumab exposure (Table 1and Figure 4). From the model-based analysis, the following observations can be made:

The 5th percentile of Ctrough at steady state in children ≥6 to <12 years of age receiving the 200 mg Q2W at body weight ≥30 kg and 300 mg Q4W at body weight <30 kg is similar to, or greater than, that of adults receiving the 300 mg Q2W regimen (Table 3).

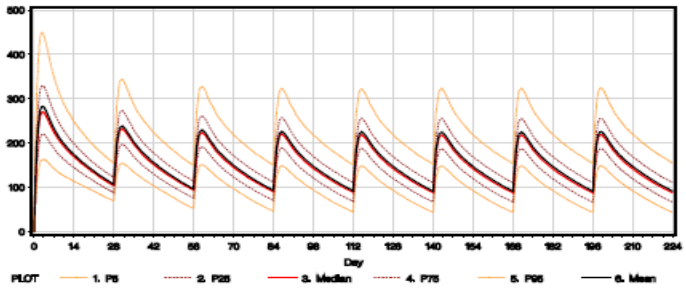
The 95th percentile of Cmax at steady state is lower in children ≥6 to <12 years of age receiving the 200 mg Q2W at body weight ≥30 kg and 300 mg Q4W regimen at body weight <30 kg compared to adults receiving the 300 mg QW regimen. Tables 31 and 32 compare exposures with and without loading doses.

Figure 4: Simulated Concentration of Functional Dupilumab (mg/L) Over Time (Percentiles, Median, and Mean) in Children (Panel A and Panel B) vs. Adults (Panel C)

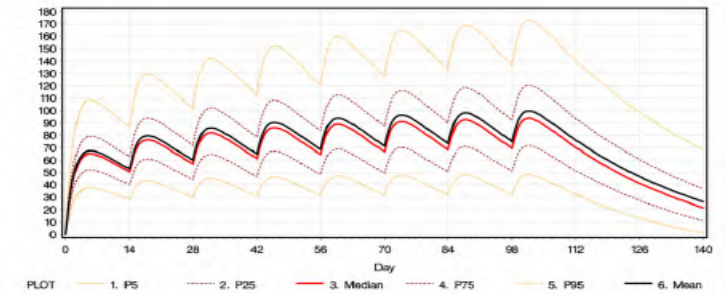
Panel A: Children ≥30 kg Receiving Dupilumab 200 mg Q2W




Panel B: Children <30 kg Receiving 300 mg Q4W




Panel C: Adults Receiving 300 mg Q2W




Source: Module 5.3.3.5 POP PK Report R668-PM-19142-SR-01V1 Figure 41 for Panel A, Figure 43 for Panel B, and Figure 6 panel B adolescent marketing application Module 2.7.2 for Panel C

Figure 42: Simulated Concentration of Functional Dupilumab over Time (300 mg Q4W SC, Weight < 30 kg, No Loading Dose)

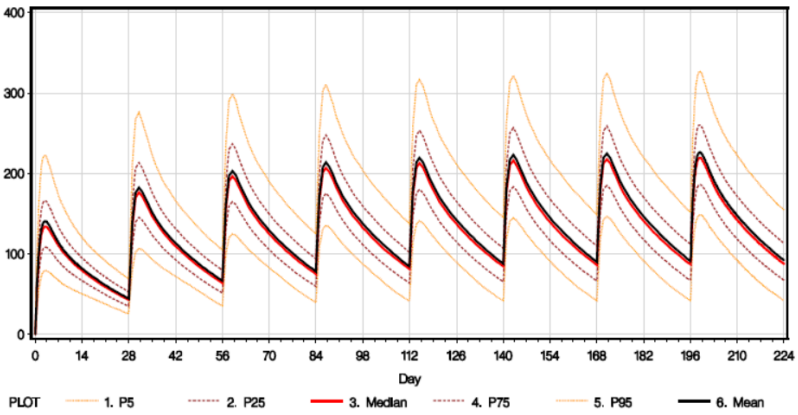



Table 7: Summary of Simulated Exposure to Dupilumab by Treatment Group and Weight in Children ≥6 to <12 Years of Age with AD, Adolescents and Adults

| Variable | >6 to ≤ 12 Years Old | | Adolescents | | Adults | |
|---|---|---|---|---|---|---|
| | 300 mg Q4W SC <30 kg | 200 mg Q2W SC ≥30 kg | 200 mg Q2W SC <60 kg | 300 mg Q2W SC ≥60 kg | 300 mg Q2W SC | 300 mg QW SC |
| $C_{troughSS}$ (mg/L) | 87.7 (43.1, 155) | 98.5 (47.9, 164) | 57.0 (27.9, 113) | 58.6 (22.8, 115) | 72.9 (32.7, 153) | 189 (96.1, 351) |
| $C_{maxSS}$ (mg/L) | 219 (149, 325) | 153 (84.2, 230) | 81.1 (49.1, 142) | 83.9 (40.9, 144) | 97.2 (49.9, 187) | 205 (108, 372) |
| $AUC_{SS}$ (mg*day/L) | 4073 (2689, 6241) | 3548 (1904, 5502) | 1994 (1126, 3637) | 2060 (946, 3730) | 2477 (1203, 4819) | 5564 (2893, 10194) |

Parameters as Median (P05, P95)
Note: $C_{maxSS}$, $C_{troughSS}$ and $AUC_{SS}$ were calculated over the last 28 days of the 16-week treatment period (Q2W or Q4W) to allow for comparison between treatment groups (based on base models developed using phase 3 data).
Source: Module 5.3.3.5 POP PK Report R668-PM-19142-SR-01V1 Table 22, Table 23, and Table 33.

Table 8: Summary of Simulated Exposure to Dupilumab by Treatment Group and Weight (Loading Dose is Given)

| Variable | Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 100 mg Q2W SC | | | | 200 mg Q2W SC | | | | 300 mg Q4W SC | | | | | | | |
| | Weight | | | | Weight | | | | Weight | | | | | | | |
| | < 30 kg | | | | >=30 kg | | | | < 30 kg | | | | >=30 kg | | | |
| | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 |
| First Dose | | | | | | | | | | | | | | | | |
| $C_{trough}$ (mg/L) | 50.3 | 28.9 | 48.8 | 76.7 | 71.0 | 37.5 | 69.9 | 107 | 107 | 69.1 | 104 | 155 | 65.1 | 33.1 | 64.7 | 99.2 |
| $C_{max}$ (mg/L) | 91.7 | 51.7 | 87.7 | 145 | 124 | 64.3 | 119 | 199 | 283 | 163 | 270 | 450 | 187 | 97.7 | 179 | 299 |
| $T_{max}$ (day) | 957 | 546 | 925 | 1482 | 1311 | 690 | 1272 | 2023 | 4987 | 3206 | 4840 | 7222 | 3219 | 1746 | 3185 | 4799 |
| Steady State | | | | | | | | | | | | | | | | |
| $C_{troughSS}$ (mg/L) | 66.6 | 35.5 | 62.8 | 110 | 101 | 47.9 | 98.5 | 164 | 91.4 | 43.1 | 87.7 | 155 | 48.5 | 14.8 | 46.4 | 90.6 |
| $C_{maxSS}$ (mg/L) | 107 | 64.0 | 103 | 161 | 155 | 84.2 | 153 | 230 | 226 | 149 | 219 | 325 | 138 | 68.0 | 138 | 209 |
| $AUC_{SS}$ (mg.d/L) | 2451 | 1438 | 2346 | 3828 | 3614 | 1904 | 3548 | 5502 | 4219 | 2689 | 4073 | 6241 | 2464 | 1147 | 2447 | 3902 |

Note: Exposure after the first dose was calculated for the first 14 and 28 days in the Q2W and Q4W treatment groups respectively. Steady-state exposure was calculated per 28 days to simplify comparison across treatments.

Table 9: Summary of Simulated Exposure to Dupilumab by Treatment Group and Weight (Loading Dose is not Given)

| Variable | Treatment | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 100 mg Q2W SC | | | | 200 mg Q2W SC | | | | 300 mg Q4W SC | | | | | | | |
| | Weight | | | | Weight | | | | Weight | | | | | | | |
| | < 30 kg | | | | >=30 kg | | | | < 30 kg | | | | >=30 kg | | | |
| | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 | Mean | P05 | Median | P95 |
| **First Dose** | | | | | | | | | | | | | | | | |
| $C_{trough}$ (mg/L) | 19.4 | 7.93 | 18.8 | 32.7 | 29.5 | 12.8 | 29.1 | 47.6 | 44.2 | 25.3 | 42.5 | 69.2 | 22.9 | 7.28 | 22.4 | 40.4 |
| $C_{max}$ (mg/L) | 44.6 | 23.9 | 42.8 | 71.3 | 60.1 | 30.3 | 57.6 | 99.5 | 141 | 78.8 | 134 | 223 | 91.9 | 47.4 | 88.1 | 150 |
| $T_{max}$ (day) | 436 | 223 | 420 | 702 | 607 | 300 | 589 | 980 | 2353 | 1410 | 2279 | 3511 | 1454 | 733 | 1430 | 2254 |
| **Steady State** | | | | | | | | | | | | | | | | |
| $C_{troughSS}$ (mg/L) | 66.4 | 34.5 | 63.2 | 109 | 101 | 48.0 | 98.6 | 159 | 91.8 | 42.0 | 87.2 | 154 | 47.4 | 14.9 | 44.9 | 87.4 |
| $C_{maxSS}$ (mg/L) | 107 | 64.0 | 104 | 162 | 155 | 85.0 | 155 | 226 | 226 | 148 | 219 | 327 | 137 | 70.8 | 135 | 209 |
| $AUC_{SS}$ (mg.d/L) | 2448 | 1430 | 2366 | 3786 | 3600 | 1911 | 3581 | 5365 | 4232 | 2709 | 4078 | 6304 | 2428 | 1151 | 2400 | 3853 |

Note: Exposure after the first dose was calculated for the first 14 and 28 days in the Q2W and Q4W treatment groups respectively. Steady-state exposure was calculated per 28 days to simplify comparison across treatments.

*Population PK Analysis*

*Methods:*

Data from the study R668-AD-1652 were used to form the population PK datasets only.

NONMEM and/or Monolix formatted data files were created from the clinical (dosing, sampling date/time, and covariate data) and bioanalytical databases (functional dupilumab concentration data).

The PK model structure used to describe the adult and adolescent data was fitted to the data from children aged ≥6 to <12 years, whereby the parameters of the model were re-estimated using only data from the pivotal study R668-AD-1652.

The statistically significant covariates identified in adults and adolescents were tested to confirm their significance in the children aged ≥6 to <12 years. The results of these analyses were compared to those from adults with moderate-to-severe AD.

The PK model was used to simulate the median, and 5th and 95th percentiles of dupilumab concentration over time in children aged ≥6 to <12 years receiving various dosing regimens in comparison to adults receiving the 300 mg Q2W dosing regimen. Exposure metrics including Ctrough, maximum concentration (Cmax) and area under the curve (AUC) at steady state were determined to allow PK comparison between dosing regimens in children aged ≥6 to <12 years to the approved 300 mg Q2W regimen in adults. The AUC was calculated over the last 28 days of the 16-week treatment period (Q2W or Q4W) to allow for comparison between treatment groups.

Given the relatively small size of population PK dataset in patients >6 to ≤12 years of age (N=241 patients) compared to the adult dataset (N=2115 patients), a full covariate analysis was not undertaken. Covariates identified as significant in the adult population PK model were tested in a forward inclusion/backward elimination model building procedure for children >6 to ≤12 years of age.

241 patients were randomized to the following treatment groups: 1) dupilumab every 2 weeks (Q2W): 100 mg for patients <30 kg (n = 63) or 200 mg for patients ≥30 kg (n = 59); 2) dupilumab every 4-weeks (Q4W): 300 mg (n = 119). Two patients were excluded from the analysis. In the 100 mg Q2W group, one patient, was originally randomized to placebo and erroneously received one dose of 100 mg Q2W at week 2; this patient had only one quantifiable observation. In the 200 mg Q2W group, another patient, exhibited concentrations below the LLOQ over the entire time course of treatment. This patient had a baseline weight of <30 kg and was mis-stratified to the 200 mg Q2W group ≥30. The patient received one loading dose and as a result of mis-stratification, discontinued the drug, but remained in the study. Overall, 239 of 241 patients were used in the analysis.

Population parameter estimates for this pediatric population were compared to previous models in adult and adolescent patients as a cross-validation using both the base and covariate models.

*Pop PK Analysis Data Set:*

239 of 241 patients were used in population PK analysis. The number of included and excluded patients by study, treatment group, and overall is presented in the table below.

Table 10: Accounting of Patient on Active Treatment by Treatment Group and Overall

| Treatment | Inclusion | | | | All Patients |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | N |
| **Dupilumab 100 mg Q2W** | 1 | 0.4 | 62 | 25.7 | 63 |
| **Dupilumab 200 mg Q2W** | 1 | 0.4 | 58 | 24.1 | 59 |
| **Dupilumab 300 mg Q4W** | 0 | 0.0 | 119 | 49.4 | 119 |
| **All Treatments** | 2 | 0.8 | 239 | 99.2 | 241 |

n = Number of patients; N = Total number of patients; Yes = Included patients; No = Excluded patients.

The number of samples by study and treatment group is summarized in the table below. Samples collected before the first dose are not used in the analysis and are excluded from the summary.

Table 11: Accounting of Samples in Patients on Active Treatment by Treatment Group and Overall

| Treatment | Inclusion | | | | All Samples |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | N |
| **Dupilumab 100 mg Q2W** | 7 | 0.7 | 235 | 25.0 | 242 |
| **Dupilumab 200 mg Q2W** | 4 | 0.4 | 225 | 23.9 | 229 |
| **Dupilumab 300 mg Q4W** | 4 | 0.4 | 465 | 49.5 | 469 |
| **All Treatments** | 15 | 1.6 | 925 | 98.4 | 940 |

n = Number of samples; N = Total number of samples; Yes = Included samples; No = Excluded samples.
Notes: Samples collected before the first dose are excluded.

Baseline values of covariates are summarized in the tables below by treatment group and overall. Distribution by gender is balance throughout treatment groups.

Table 12: Summary of Baseline Demographics and Continuous Covariates in Patients on Active Treatment by Treatment Group and Overall

| Treatment / Variable | | N | Mean | SD | Min | P5 | Q1 | Median | Q3 | P95 | Max |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (yr) | Dupilumab 100 mg Q2W | 63 | 7.60 | 1.36 | 6.00 | 6.00 | 6.00 | 7.00 | 9.00 | 10.0 | 10.0 |
| | Dupilumab 200 mg Q2W | 59 | 9.46 | 1.42 | 6.00 | 7.00 | 9.00 | 10.0 | 11.0 | 11.0 | 11.0 |
| | Dupilumab 300 mg Q4W | 119 | 8.50 | 1.74 | 6.00 | 6.00 | 7.00 | 9.00 | 10.0 | 11.0 | 11.0 |
| | All Treatments | 241 | 8.50 | 1.70 | 6.00 | 6.00 | 7.00 | 9.00 | 10.0 | 11.0 | 11.0 |
| Weight (kg) | Dupilumab 100 mg Q2W | 63 | 24.8 | 4.45 | 17.7 | 18.1 | 22.1 | 24.6 | 27.6 | 29.5 | 46.8 |
| | Dupilumab 200 mg Q2W | 59 | 40.0 | 10.1 | 27.9 | 30.4 | 32.5 | 37.0 | 43.9 | 60.1 | 79.1 |
| | Dupilumab 300 mg Q4W | 119 | 31.1 | 9.45 | 18.3 | 19.7 | 23.2 | 30.0 | 35.4 | 50.9 | 65.8 |
| | All Treatments | 241 | 31.6 | 10.2 | 17.7 | 19.5 | 24.0 | 29.5 | 36.0 | 52.3 | 79.1 |
| BMI (kg/m**2) | Dupilumab 100 mg Q2W | 63 | 16.1 | 1.76 | 12.7 | 13.4 | 14.9 | 16.2 | 16.7 | 18.4 | 22.6 |
| | Dupilumab 200 mg Q2W | 59 | 20.2 | 4.03 | 15.4 | 15.5 | 17.1 | 19.5 | 22.1 | 29.6 | 35.2 |
| | Dupilumab 300 mg Q4W | 119 | 17.6 | 2.96 | 12.8 | 14.1 | 15.6 | 17.0 | 18.9 | 24.4 | 28.0 |
| | All Treatments | 241 | 17.8 | 3.35 | 12.7 | 14.2 | 15.6 | 16.9 | 19.4 | 24.1 | 35.2 |
| Albumin (g/L) | Dupilumab 100 mg Q2W | 63 | 46.0 | 3.45 | 37.0 | 42.0 | 44.0 | 46.0 | 49.0 | 52.0 | 54.0 |
| | Dupilumab 200 mg Q2W | 59 | 46.1 | 3.04 | 36.0 | 40.0 | 44.0 | 47.0 | 48.0 | 51.0 | 51.0 |
| | Dupilumab 300 mg Q4W | 119 | 46.0 | 3.14 | 36.0 | 41.0 | 44.0 | 46.0 | 48.0 | 51.0 | 53.0 |
| | All Treatments | 241 | 46.0 | 3.19 | 36.0 | 41.0 | 44.0 | 46.0 | 48.0 | 51.0 | 54.0 |
| EASI (Unitless) | Dupilumab 100 mg Q2W | 63 | 38.2 | 10.1 | 21.0 | 23.8 | 31.2 | 36.2 | 46.5 | 56.0 | 59.7 |
| | Dupilumab 200 mg Q2W | 59 | 36.8 | 12.0 | 17.5 | 22.2 | 27.3 | 34.5 | 44.4 | 58.8 | 66.0 |
| | Dupilumab 300 mg Q4W | 119 | 37.2 | 12.2 | 21.1 | 21.6 | 27.8 | 35.1 | 45.2 | 60.8 | 69.6 |
| | All Treatments | 241 | 37.4 | 11.6 | 17.5 | 22.2 | 28.0 | 35.4 | 45.4 | 59.4 | 69.6 |

BMI = Body mass index; EASI = Eczema Area and Severity Index; N = Number of samples; SD = Standard deviation

Table 13: Summary of Race in Patients on Active Treatment by Treatment Group and Overall

| Treatment | Race | | | | | | | | All Patients |
|---|---|---|---|---|---|---|---|---|---|
| | Asian | | Black | | Other | | White | | |
| | n | % | n | % | n | % | n | % | N |
| Dupilumab 100 mg Q2W | 6 | 9.5 | 12 | 19.0 | 2 | 3.2 | 43 | 68.3 | 63 |
| Dupilumab 200 mg Q2W | 4 | 6.8 | 9 | 15.3 | 2 | 3.4 | 44 | 74.6 | 59 |
| Dupilumab 300 mg Q4W | 5 | 4.2 | 19 | 16.0 | 9 | 7.6 | 86 | 72.3 | 119 |
| All Treatments | 15 | 6.2 | 40 | 16.6 | 13 | 5.4 | 173 | 71.8 | 241 |

n = Number of samples; N = Total number of samples

Table 14: Summary of ADA Positivity in Patients on Active Treatment by Treatment Group and Overall

| Treatment | ADA | | | | All Patients |
|---|---|---|---|---|---|
| | No | | Yes | | |
| | n | % | n | % | N |
| Dupilumab 100 mg Q2W | 60 | 95.2 | 3 | 4.8 | 63 |
| Dupilumab 200 mg Q2W | 56 | 94.9 | 3 | 5.1 | 59 |
| Dupilumab 300 mg Q4W | 119 | 100.0 | 0 | 0.0 | 119 |
| All Treatments | 235 | 97.5 | 6 | 2.5 | 241 |

n = Number of samples; N = Total number of samples
Notes: All patients had negative or low (<1000) titers. ADA observed at any time are reported.

*Modeling Strategy*

The initial plan was to apply the adolescent base model to the data from children ≥6 to <12 years of age with severe AD. It appeared that PK concentrations were mostly through levels in the beta phase providing little or no information about target-mediated elimination rate (Vm); an implementation of simulating annealing or between-subject variability in Vm was necessary to make this parameter stable, as described below. Having Vm in the model as estimated parameters increased variability in the OFV. The variability in OFV was caused by steep target-mediate phase. For these reasons, Vm was estimated using a single base model run and then using 10 runs with randomly changed initial values of the estimated PK parameters. A Vm estimate of 1.64 mg/L/d, which was close to the median of the 10 estimates and had a low OFV, was chosen and used as a fixed PK parameter for further model developments. During the prior development of the adult covariate model, Vm was also fixed to account for sparse data collected mostly during the beta phase and to reduce variability in OFV to acceptable level.

Similar to the adolescent model, inter-compartmental rates (k23 and k32), mean residence time (MRT), and bioavailability (F) were fixed to the adult values. The absorption rate (ka) was fixed to a value of 0.641 1/d estimated using semi-sparse data of ≥6 to <12 years of age subpopulation of study R668-AD-1412. This allowed accounting for potential changes in ka with age and predicting Cmax with higher precision. The estimated absorption rate in children ≥6 to <12 years of age was higher than the adult value and consistent with the higher reported absorption rates in children. The data from Study R668-AD-1412 were not utilized for the model building because of higher prevalence of ADA due to the dosing regimen and a small representation of patients ≥6 to <12 years of age with severe AD.

*Pop PK Parameters and results:*

A standard two-compartment population PK model with parallel linear and nonlinear (Michaelis-Menten) elimination was used. This model was developed using adult data and replicated in adolescents. Transit-compartment model of absorption was represented in the model by mean transit time (MTT) and absorption rate (ka). The inter-patient variability was implemented in central volume (V2) and elimination rate (ke).

*Final pop PK model:*

Table 15: Covariate Model: Population PL Parameters of Children **≥6** to <12 Years of Age, Adolescent, and Adult

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

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

*Model diagnostics of the final model:*

Diagnostic plots for both base and covariate models demonstrated the good fit. The results were validated using bootstrap, visual predictive checks, comparison of results in children ≥6 to <12 years of age with adolescents and adults, assessment of stability, and sensitivity analyses.

Final model:

Figure 5: Covariate Model: Observed vs. Population and Individual Predicted Concentrations (mg/L)

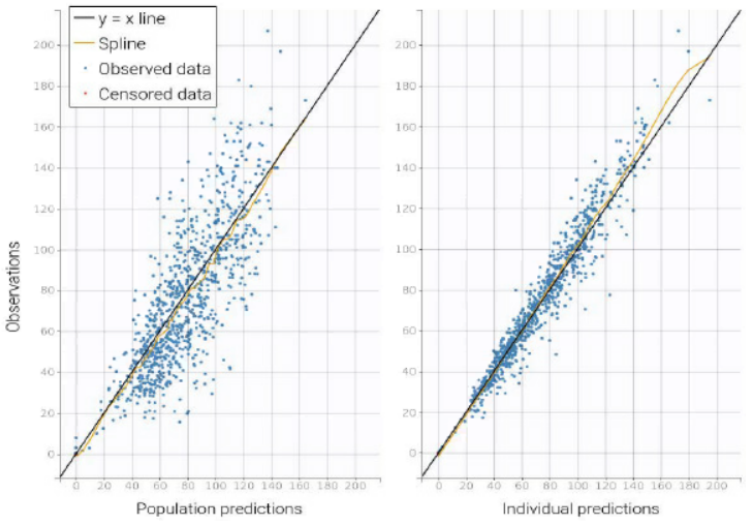
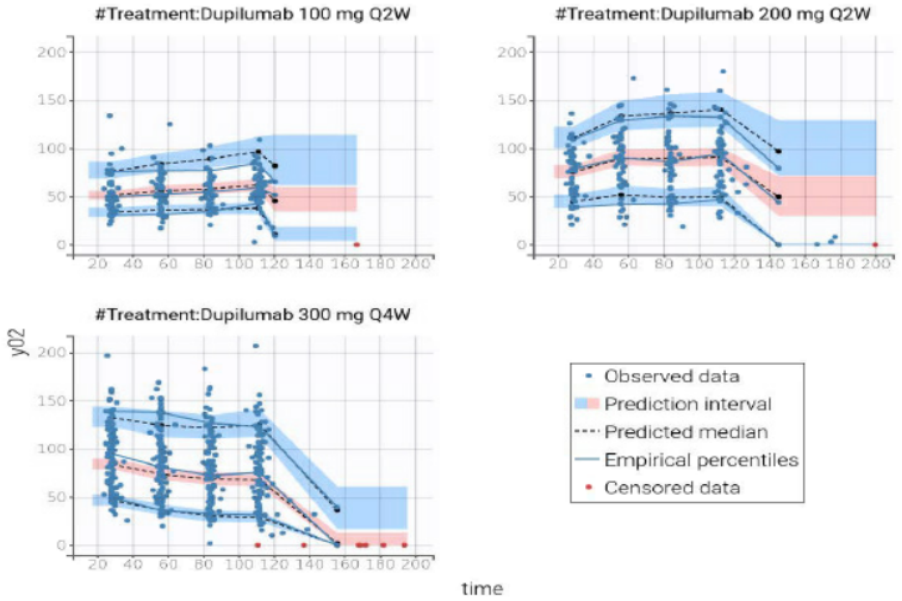


Figure 6: Covariate Model: Visual Predictive Checks by Treatment vs. Actual Day




Notes: y02 – concentration of dupilumab (mg/L); time is expressed in days.

*Covariate selection*

The list of tested covariates included those which were found statistically significant in the adult model, namely weight, BMI, any ADA at any time, race, albumin and EASI score.

Three (albumin, EASI score, and weight) of six covariates which were found statistically significant in adults were also statistically significant in children ≥6 to <12 years of age with no meaningful impact of albumin and EASI on between-subject variability. The statistically significant impact of ADA and body mass index (BMI) on elimination rate and race on central volume in adults was not replicated in children ≥6 to <12 years of age possibly due to considerably smaller sample size, lower prevalence of ADA, and low BMI.

The impact of weight on V2 was similar in children ≥6 to <12 years of age, adolescents, and adults. The impact of albumin on V2 was similar in children ≥6 to <12 years of age and adults. The impact of EASI on ke was similar in children ≥6 to <12 years of age and adults and was ~2-fold higher in adolescents that in children ≥6 to <12 years of age and adults. No dose adjustment for EASI and albumin was done in adults and adolescents. As albumin and EASI explained small portion of between-subject variability and the therapeutic index of dupilumab is wide3,6, the impact of this covariates did not warrant a dose adjustment in children ≥6 to <12 years of age.

When weight is used as a covariate in the population PK model, age does not have a significant impact on V2 and ke indicating that when dupilumab treatment is adjusted for weight there is no need to adjust dosing regimens for age within ≥6 to <12 age group.

*Sensitivity Analyses*

Several sensitivity analyses (SA) were conducted: PK parameter estimated at median weight , profiling of Km, testing age as covariate, using the primary covariate model with all outliers and patients, using parametrization of covariate model using clearance (ke*Vc), using bioavailability of 80.4% , population PK parameters of model with adult absorption rate.

*2.3.1.5. Absorption, distribution and elimination*

The estimated rate of absorption in children ≥6 to <12 years of age (0.641 1/d) was higher than adults (0.306 1/d) and consistent with the higher reported absorption rates in children. The extent of absorption (bioavailability) in children was not estimated due to lack of intravenous (IV) data. In the adult AD patient population, dupilumab is well absorbed with a reported bioavailability of 64%, which was fixed for the paediatric populations (see population PK model).

Estimation of the apparent central compartment volume of distribution ($V_2$) yielded slightly lower values for children ≥6 to <12 years of age vs. adults (2.18±0.087 vs. 2.74±0.021 L, respectively, for a reference body weight of 75 kg in each population). At the median body weight of 29.4 kg, $V_2$ was estimated as 0.999 L.

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 target-mediated clearance ($V_m$) somewhat decreased with age across children ≥6 to <12 years of age, adolescents, and adults; no allometric differences (decrease with weight) in elimination rate ($k_e$) were observed.

The statistically significant impact of ADA and body mass index (BMI) on elimination rate and race on central volume in adults was not replicated in children ≥6 to <12 years of age possibly due to considerably smaller sample size, lower prevalence of ADA, and low BMI.

Based on pop PK results, clearance was estimated to 0.0972 L/d which is slightly lower to Clearance calculated for adolescents (0.128 L/d) and the adult population (0.131 L/d)

*2.3.1.6. Dose proportionality and time dependencies*

Dose proportionality
Dupilumab is, like other monoclonal antibodies, 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 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.

Steady state
In children ≥6 to <12 years of age, systemic concentrations of dupilumab achieved steady state in all treatment regimens before the primary endpoint at week 16. Steady state was achieved in accordance with the dosing interval and loading dose; for Q2W dosing with 200 mg, starting with a loading dose of 400 mg, observed data and population PK analysis determined steady-state concentrations to be achieved at or before week 8. For the 300 mg Q4W regimen, starting with a loading dose of 600 mg, steady state was achieved at or before week 12.

Loading dose and Accumulation
Dupilumab was studied in children ≥6 to <12 years of age with AD when administered with a loading dose as in adult and adolescent patients with AD. Patients weighing <30 kg to be treated with 300 mg Q4W should be administered a total loading dose of 600 mg. Patients weighing ≥30 kg to be treated with 200 mg Q2W should be administered a total loading dose of 400 mg.

Mean $C_{trough}$ for the Q2W regimen observed at week 4 were about 14% lower than that at week 16. In contrast, mean $C_{trough}$ for the Q4W regimen observed at week 4 were about 21% higher than that at week 16.

Despite the higher concentrations after the 600 mg loading dose compared to steady-state concentrations in children <30 kg receiving the 300 mg Q4W regimen, the observed efficacy at week 16 was similar to that observed with the 200 mg Q2W regimen following a 400mg loading dose in children ≥30 kg, indicating no impact of higher concentrations on drug effect at week 16. No safety findings were

associated with the higher drug concentrations after the 600 mg loading dose compared to steady-state concentrations in children <30 kg receiving the 300 mg Q4W regimen.

#### *2.3.1.7. Special populations*

Covariates (Intrinsic and Extrinsic Factors) Affecting Pharmacokinetics

Three of six covariates which were found statistically significant in adults were also statistically significant in children ≥6 to <12 years of age, as indicated by population PK modelling.

Body weight is the primary covariate affecting the PK of dupilumab, and fixed weight-tiered dosing regimens were previously used to adjust exposure differences caused by body weight across the adolescent patient population with AD.
The impact of weight on volume of distribution V2 was similar in children ⩾6 to <12 years of age, adolescents, and adults. Dupilumab regimens of 300 mg Q4W in patients <30 kg and 200 mg Q2W in patients ≥30 kg exhibited similar exposures in the pivotal study R668-AD-1652 and higher exposures than those of 100 mg Q2W in patients <30 kg and 300 mg Q4W in patients ≥30 kg (refer to Figures 1 and 2 in section *PK comparison across populations*).

Based on population PK analysis, age had no clinically meaningful impact on dupilumab PK in children ≥6 to <12 years of age after accounting for differences in body size by weight.

Based on the population PK analysis, baseline EASI score had a positive, statistically significant association with the nonlinear elimination rate of dupilumab in children ≥6 to <12 years of age. This correlation was consistent with that previously observed in adult and adolescent patients with AD but was not considered clinically meaningful. The impact of EASI on elimination rate ke was similar in children ≥6 to <12 years of age and adults and was ~2-fold higher in adolescents that in children ≥6 to <12 years of age and adults. Patients with lower disease burden at baseline exhibit slightly higher exposure of dupilumab, but the difference is small and does not warrant a dose adjustment.

The impact of albumin on $V_2$ was similar in children ≥6 to <12 years of age and adults.

### 2.3.2. Pharmacodynamics

The human monoclonal immunoglobulin-G4 (IgG4) antibody 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*

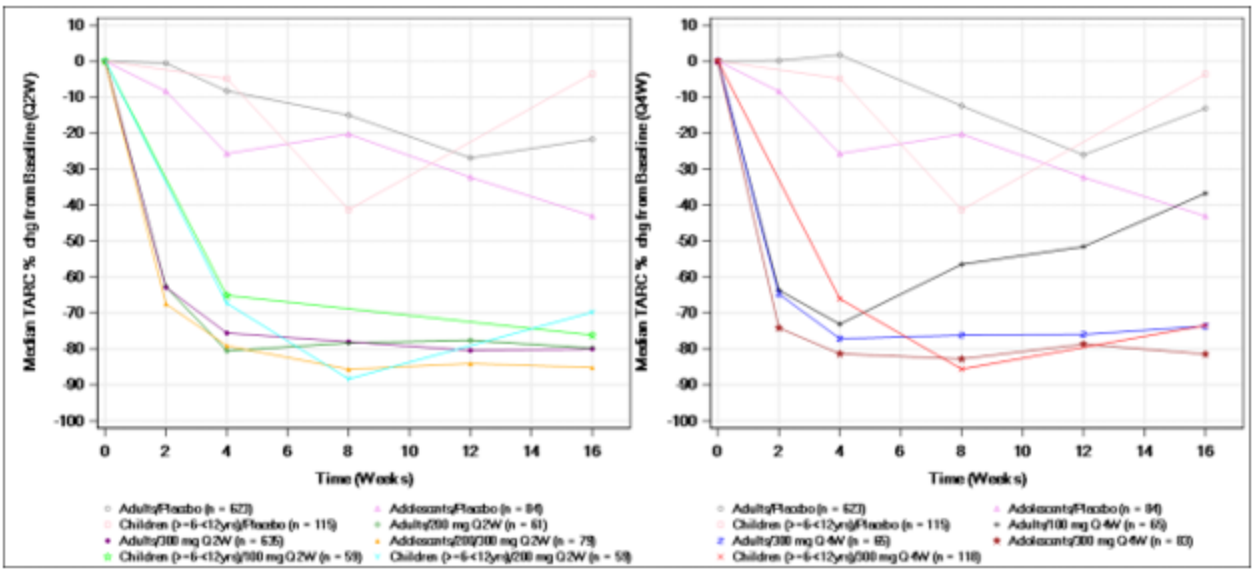
TARC

The time course of Thymus and Activation-Regulated Chemokine (TARC) percent change from baseline over time was analyzed as a biomarker/PD of AD disease severity over time and PD marker of efficacy. Median TARC concentration profiles in children aged ≥6 to <12 years with AD were compared to that of adults and adolescents with AD by dupilumab treatment regimen as a measure of disease activity over time.

Pharmacodynamic profiles of TARC in children ≥6 to <12 years of age (Figure 7) show a similar median magnitude of effect over time by dose regimen to that of adolescents and adults at approved dose regimens.

Figure 7

**Comparison of the Median Percentage Change from Baseline in TARC by Dupilumab Treatment Group (Left Panel: Q2W vs. Placebo; Right Panel: Q4W vs. Placebo) Across Studies R668-AD-1021 (Adults), R668-AD-1334 (Adults), R668-AD-1416 (Adults), R668-AD-1526 (Adolescents), and R668-AD-1652 (Children ≥6 to <12 Years of Age)**



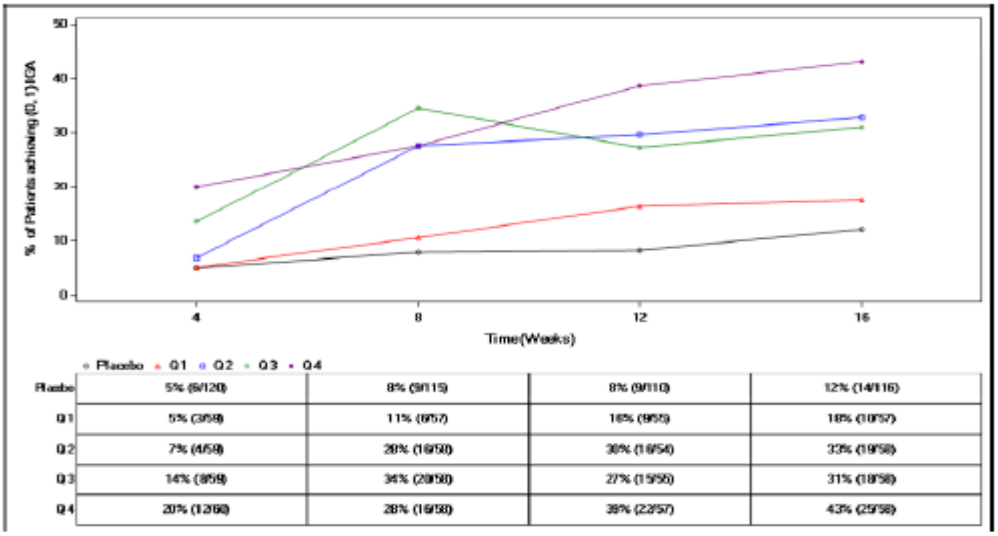

n=Number of patients. Common Nominal Time-points up to Week 16 are used for Analysis.
Adolescents: R668-AD-1526; Children (>=6 to <12 Years): R668-AD-1652; Adults: R668-AD-1021, R668-AD-1416, R668-AD-1334, R668-AD-1424
Placebo subjects from studies R668-AD-1021, R668-AD-1526 and R668-AD-1652 contribute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

### Proportion of patients with IGA 0 or 1

Percent of patients achieving IGA 0 or 1 at week 16 is one key efficacy endpoint of study R688-AD-1652. An increase in the proportion of patients achieving IGA 0 or 1 over time was seen for all quartiles of functional dupilumab concentrations with a trend of increasing drug effect with increasing quartile of $C_{trough}$ of dupilumab (Figure 8).

## Figure 8

**Percent of Patients Achieving IGA 0 or 1 over Time by Quartile of Functional Dupilumab Concentrations in Patients ≥6 Years to <12 Years of Age with AD (Study R668-AD-1652)**




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

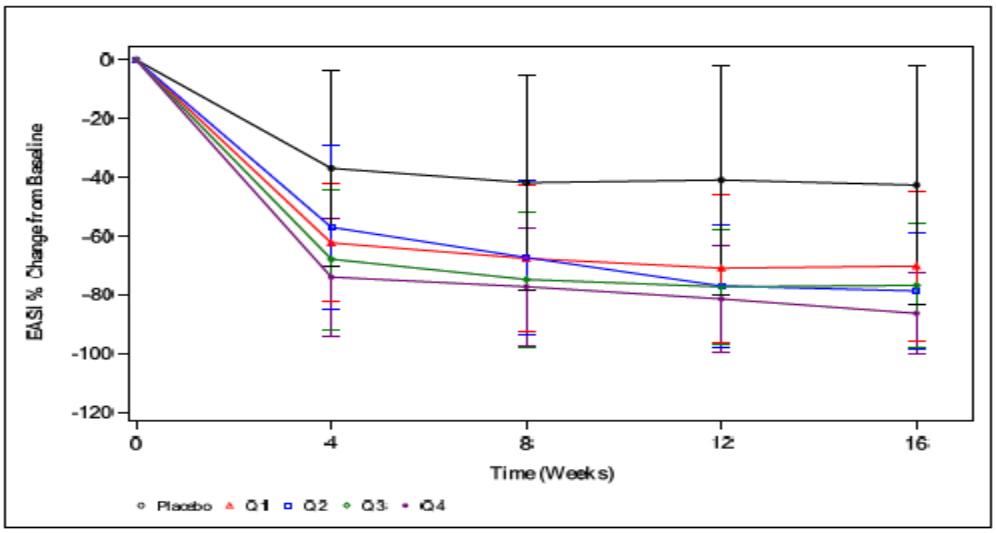
Note: Concentrations below the LLOQ were set to 0. Missing data were imputed as non-responders.
Data up to week 16 are used; number in parentheses in the table is number of patients achieving IGA 0 or 1/ number of patients who contribute to the quartile.
Source: Module 5.3.5.1 R668 AD 1652 Primary Analysis Appendix 5 Clinical Pharmacology Report Figure 8

### EASI – percent change from baseline

Percent change of EASI score from baseline to week 16 is another key efficacy endpoint of study R-688-AD-1652. Drug effect by EASI change from baseline over time was observed for all quartiles of functional dupilumab concentrations with a trend of increasing drug effect with increasing quartile of $C_{trough}$ of dupilumab (Figure 9).

**Figure 9**

**Mean (±SD) EASI Percent Change from Baseline over Time by Quartile of Concentration of Functional Dupilumab in Serum in Patients ≥6 Years to <12 Years of Age with AD (Study R668-AD-1652)**




Note: Concentrations below the LLOQ were set to 0. LOCF Imputation was used.
Concentrations below the LLOQ were set to 0. The quartile ranges for week 16 concentrations (mg/L): Q1 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261).
Source: Module 5.3.5.1 R668 AD 1652 Primary Analysis Appendix 5 Clinical Pharmacology Report Figure 10

Immunogenicity

Samples that were positive in the ADA assay were examined for neutralizing (NAb) activity. For samples testing negative in the ADA assay, NAb results were set to negative. The impact of immunogenicity (ADA category and NAb status) on functional dupilumab concentration was assessed by plotting individual functional dupilumab concentrations by time (weeks), ADA category, and NAb status.

The pivotal study R668-AD-1652 was the primary source for the immunogenicity assessment of dupilumab in children aged ≥6 to <12 years with AD, as it was the largest randomized, controlled study in this population. The OLE study (R668-AD-1434) allowed additional longitudinal monitoring of ADA positive patients and observation of immunogenicity responses over time, especially in those patients who had previously participated in the phase 2a study R668-AD-1412.

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, or if the baseline sample is positive (ie, pre-existing ADA) 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 as follows: Low (titer <1,000), Moderate (1,000≤ titer ≤10,000) and High (titer >10,000).

Study R668-AD-1652 (phase 3 pivotal study)

In the pivotal study R668-AD-1652, the overall prevalence of observed immunogenicity in children aged ≥6 to <12 years with severe AD was low. There were no ADA-positive patients in the 300 mg Q4W + TCS group. The incidence of treatment-emergent ADA in the dupilumab 100 mg Q2W + TCS and dupilumab 200 mg Q2W + TCS groups was 4.9%, and 5.3% respectively and that of placebo + TCS group was 1.7% (Table 4). In these low ADA titer responses, the majority were transient in nature; persistent ADA responses were observed in 1 patient (<1%). There were no high titer responses in the study (Table 16). Two patients in the dupilumab 100 mg Q2W + TCS group (3.3%) and 1 patient in the dupilumab 200 mg Q2W + TCS group (1.8%) showed a positive response in the NAb assay (Table 17).

Table 16

**Summary of ADA Status and ADA Category by Treatment Group in Patients ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)**

| ADA Status and Category | Placebo n (%) | Dupilumab | | | | All Active Doses n (%) | Overall n (%) |
|---|---|---|---|---|---|---|---|
| | | 300 mg Q4W n (%) | 100 or 200 mg Q2W n (%) | 200 mg Q2W n (%) | 100 mg Q2W n (%) | | |
| ADA Analysis Set | 116 (100%) | 114 (100%) | 118 (100%) | 57 (100%) | 61 (100%) | 232 (100%) | 348 (100%) |
| Negative* | 114 (98.3%) | 114 (100%) | 112 (94.9%) | 54 (94.7%) | 58 (95.1%) | 226 (97.4%) | 340 (97.7%) |
| Treatment-Boosted Response | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment-Emergent Response | 2 (1.7%) | 0 | 6 (5.1%) | 3 (5.3%) | 3 (4.9%) | 6 (2.6%) | 8 (2.3%) |
| TE & TB | | | | | | | |
| Persistent | 0 | 0 | 1 (0.8%) | 0 | 1 (1.6%) | 1 (0.4%) | 1 (0.3%) |
| Transient | 1 (0.9%) | 0 | 3 (2.5%) | 2 (3.5%) | 1 (1.6%) | 3 (1.3%) | 4 (1.1%) |
| Indeterminate | 1 (0.9%) | 0 | 2 (1.7%) | 1 (1.8%) | 1 (1.6%) | 2 (0.9%) | 3 (0.9%) |

n = Number of subjects contributing to each category; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre+) responses.
Source: R668 AD 1652 Primary Analysis Appendix 5 Clinical Pharmacology Report Table 8

Table 17: Summary of ADA Status and Nab Status in Children **≥6** to <12 Years of Age with Severe AD (Study R668-AD-1652)

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

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

Table 18

**ADA Category and Maximum Titer Category in Patients ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)**

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

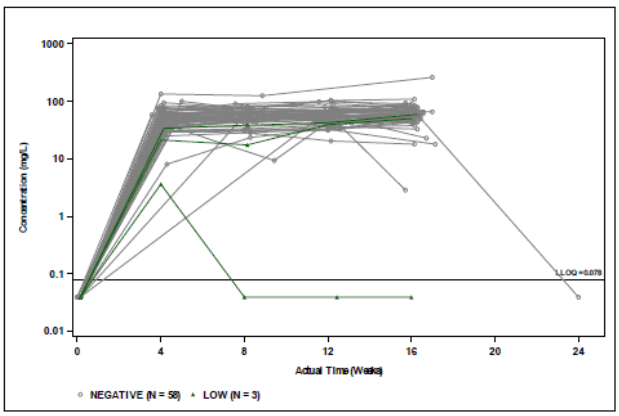
n = Number of subjects contributing to each category; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre+) responses.
Source: R668 AD 1652 Primary Analysis Appendix 5 Clinical Pharmacology Report Table 9

Association of immunogenicity and dupilumab exposure

There was no clear evidence of a clinically meaningful impact of immunogenicity on dupilumab exposure or response in R668-AD-1652. Anti-drug antibody-positive and NAb-positive patients exhibited individual concentration-time profiles in the range of ADA- and NAb-negative patients for the dupilumab Q2W + TCS group (Figure 10, Figure 11).

Figure 10

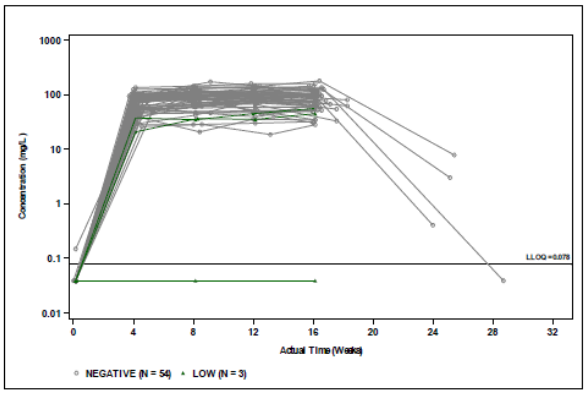
**Figure 18: Individual Concentrations of Functional Dupilumab (Log Scale) in Serum vs. Actual Time by ADA Titer Category in the 100 mg Q2W Group in Children ≥6 Years to <12 Years of Age with AD (Study R668-AD-1652)**




N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were imputed as LLOQ/2.

Figure 11

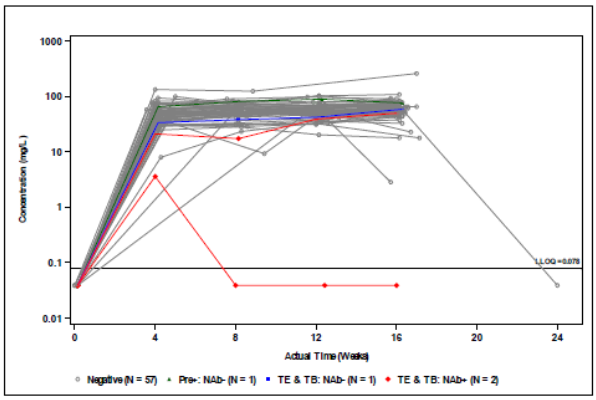
**Figure 19: Individual Concentrations of Functional Dupilumab (Log Scale) in Serum vs. Actual Time by ADA Titer Category in the 200 mg Q2W Group in Children ≥6 Years to <12 Years of Age with AD (Study R668-AD-1652)**




N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were imputed as LLOQ/2.

Figure 12

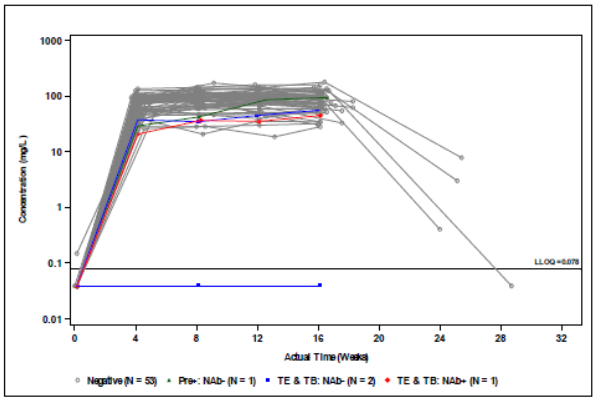
**Figure 20: Individual Concentrations of Functional Dupilumab (Log Scale) in Serum by Actual Time and ADA and NAb Status in the 100 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)**




N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were imputed as LLOQ/2.
Pre+= Pre-existing Immunoreactivity; TE = Treatment-Emergent; TB = Treatment-Boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay
Time is set to 0 when the PK sample collection happened prior to first dose

Figure 13

**Figure 21: Individual Concentrations of Functional Dupilumab (Log Scale) in Serum by Actual Time and ADA and NAB Status in the 200 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)**




N = Number of patients
Note: Concentrations below the LLOQ (horizontal dashed line) were imputed as LLOQ/2.
Pre+ = Pre-existing Immunoreactivity; TE = Treatment-Emergent; TB = Treatment-Boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay
Time is set to 0 when the PK sample collection happened prior to first dose.

In the 100 mg Q2W Group in patients ≥6 years to <12 years of age with AD (Figure 10, Figure 11), one patient fell outside of the distribution. However, this patient was originally randomized to placebo and erroneously received one dose at week 2 of 100 mg Q2W. Therefore, a low titer ADA was not expected to have led to the low concentration-time profile observed.

In the 200 mg Q2W group, in patients ≥6 years to <12 years of age with AD (Figure 12,Figure 12), one patient fell outside of the distribution and exhibited concentrations below the LLOQ over the entire time course of treatment. This patient had a baseline weight of <30 kg and was mis-stratified to the 200 mg Q2W group ≥30. The patient received one loading dose and as a result of mis-stratification, discontinued the drug, but remained in the study. Therefore, the low ADA titer was not expected to have led to the low concentration-time profile observed for this subject.

Association of immunogenicity and concentration-response

There was no clear evidence of a clinically meaningful impact of immunogenicity on dupilumab efficacy. ADA-positive and NAb-positive patients exhibited individual effect-time profiles (both NRS and % EASI change from baseline) in the range of ADA and NAb-negative patients for the dupilumab Q2W + TCS group (Figure 14 to Figure 17).

Figure 14- 17

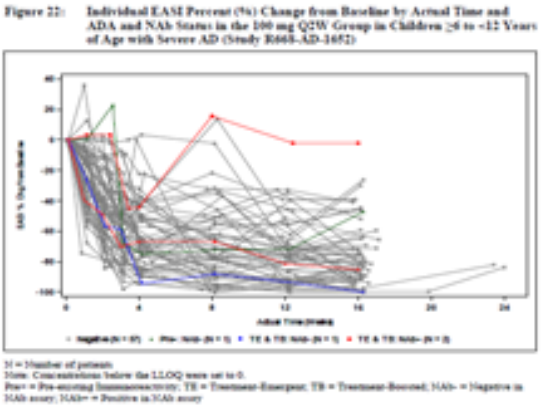


Figure 22: Individual EASI Percent (%) Change from Baseline by Actual Time and ADA and NAb Status in the 100 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)

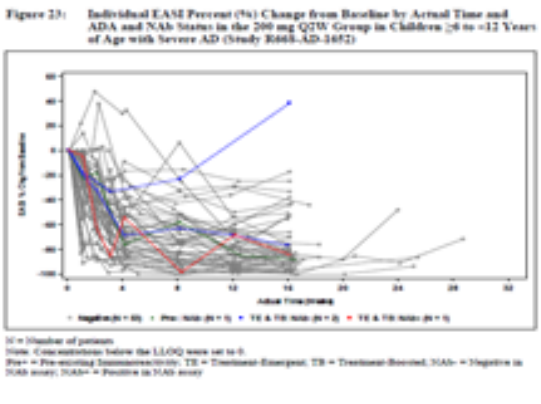


Figure 23: Individual EASI Percent (%) Change from Baseline by Actual Time and ADA and NAb Status in the 200 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)

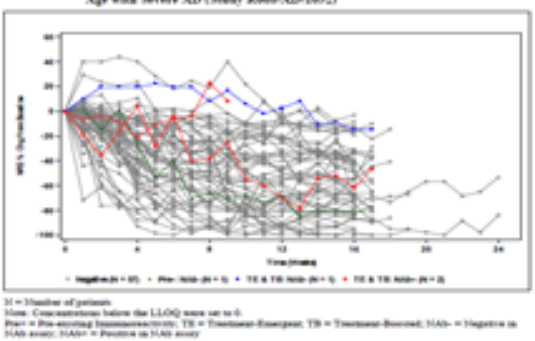


Figure 24: Individual NRS Percent (%) Change from Baseline by Actual Time and ADA and NAb Status in the 100 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)

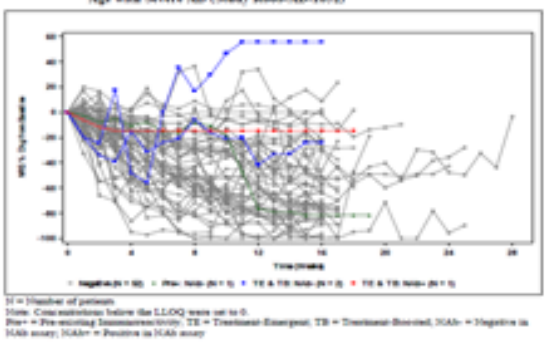


Figure 25: Individual NRS Percent (%) Change from Baseline by Actual Time and ADA and NAb Status in the 200 mg Q2W Group in Children ≥6 to <12 Years of Age with Severe AD (Study R668-AD-1652)

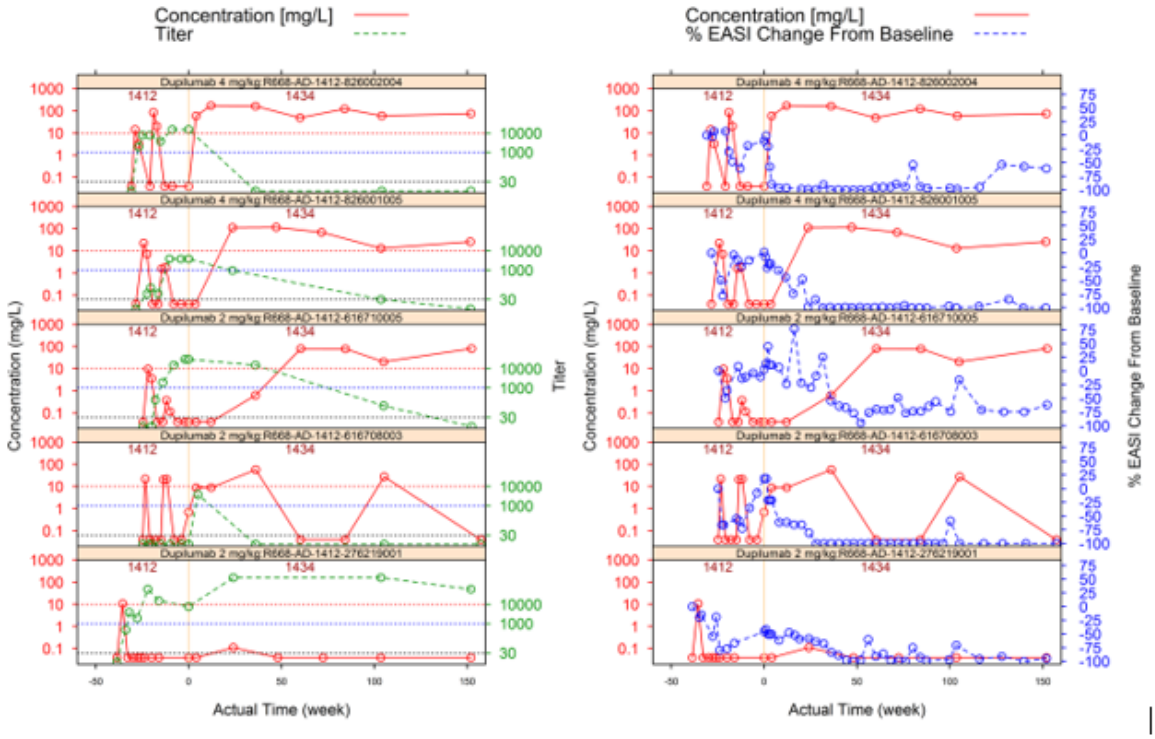
Study R668-AD-1412 (phase 2a PK study)

In the phase 2a PK study R668-AD-1412, patients ≥6 to <12 years received a single dose of dupilumab (2 mg/kg or 4 mg/kg) followed by an 8-week observation period to assess PK, followed by 4 additional weekly doses. This dosing regimen invoked a significant ADA response, with the ADA in 5 patients observed to have moderate or high titers. Overall, in this study, a positive response in the ADA assay at any time was observed in 21 children ≥6 to <12 years of age (56.8%), 11 of which (29.7% of total 37 children ≥6 to <12 years of age) were categorized as having a persistent, treatment-emergent ADA response. The rate of occurrence of persistent ADA was similar across cohorts (33.3% [6/18] patients in the 2 mg/kg cohort and 26.3% [5/19] patients in the 4 mg/kg cohort). The majority of the treatment-emergent positive responses in the ADA assay were categorized as low titer.

As noted above, in 5 patients this treatment regimen resulted in moderate or high ADA titers and those were associated with a substantial reduction in detectable drug concentrations and a lack of notable improvement in EASI score (Figure 10). These patients who continued treatment (in part B and OLE) resulted in declining ADA titers and a corresponding increase in systemic concentrations of dupilumab as well as an improvement in the EASI percent change from baseline. In 1 patient with elevated titers and low concentrations, the efficacy (EASI percent change from baseline) was high and comparable to the other 4 patients. In conclusion, as seen with adolescents, a single dose of dupilumab followed, after 8 weeks (a prolonged pause), by a rechallenge led to a “prime and boost” immune response to dupilumab. These data suggest that with continued dupilumab treatment a portion of patients can be treated through this ADA response with restoration of efficacy.

Figure 18

**Individual Concentrations of Functional Dupilumab, ADA Titer, and Effect as Measured by Percent Change in EASI from Baseline in Patients with Moderate or High Titer from Actual Time Zero of Parent Study R668-AD-1412 through the Last Sample Measured in OLE Study R668-AD-1434**




Note: Patient R668-AD-1412-616708003 was ADA positive at the follow up visit in the parent study which was after OLE study started. All patients from parent study R668-AD-1412 initially received dupilumab 2 or 4 mg/kg QW and were switched to 300 mg Q4W. Patients R668-AD-1412-826002004, R668-AD-1412-616710005 and R668-AD-1412-276219001 were subsequently up-titrated to 200/300 mg Q2W. Patients R668-AD-1412-826001005 and R668-AD-1412-616708003 remained on 300 mg Q4W. Patient R668-AD-1412-616708003 met the criteria to discontinue treatment at week 52, receiving only a single dose of dupilumab 300 mg administered at week 100 thereafter. The remaining patients were on active treatment 3 years into the study.

Study R668-AD-1434 (OLE study)

The ADA status and category of patients in the ADA analysis set are tabulated by parent study in Table 19. The maximum titer and ADA categories of patients in the ADA analysis set are tabulated by parent study in Table 20. The ADA and NAb status of patients in the ADA analysis set are tabulated by parent study in Table 21.

Table 19: Summary of ADA Status and ADA Category by Parent Study in Patients **≥6** to <12 of Age with AD (Study R668-AD-1434)

| | Parent Study | | |
|---|---|---|---|
| **ADA Status and Category** | **R668-AD-1412 N (%)** | **R668-AD-1652 N (%)** | **Overall N (%)** |
| ADA Analysis Set | 33 (100%) | 245 (100%) | 278 (100%) |
| Negative[a] | 19 (57.6%) | 236 (96.3%) | 255 (91.7%) |
| Treatment-Boosted Response | 0 | 0 | 0 |
| Treatment-Emergent Response | 14 (42.4%) | 9 (3.7%) | 23 (8.3%) |
| TE & TB | | | |
| Persistent | 5 (15.2%) | 2 (0.8%) | 7 (2.5%) |
| Transient | 9 (27.3%) | 3 (1.2%) | 12 (4.3%) |
| Indeterminate | 0 | 4 (1.6%) | 4 (1.4%) |

N = Number of patients; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre) responses.

Table 20: ADA Category and Maximum Titer Category of ADA Analysis Set by Parent Study in Patients **≥6** to <12 Years of Age with AD (Study R668-AD-1434)

| | Parent Study | | |
|---|---|---|---|
| **Maximum Titer Category** | **R668-AD-1412 N (%)** | **R668-AD-1652 N (%)** | **Overall N (%)** |
| ADA Analysis Set | 33 (100%) | 245 (100%) | 278 (100%) |
| Negative* | 19 (57.6%) | 236 (96.3%) | 255 (91.7%) |
| Treatment-Boosted Response | 0 | 0 | 0 |
| Treatment-Emergent Response | 14 (42.4%) | 9 (3.7%) | 23 (8.3%) |
| TE & TB | | | |
| Low (<1,000) | 10 (30.3%) | 8 (3.3%) | 18 (6.5%) |
| Moderate (1,000 to 10,000) | 1 (3.0%) | 0 | 1 (0.4%) |
| High (>10,000) | 3 (9.1%) | 1 (0.4%) | 4 (1.4%) |

N = Number of patients; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre) responses.

Table 21: Summary of ADA Status and NAb Status by Parent Study in Patients **≥6** to <12 Years of Age with AD (Study R668-AD-1434)

| | Parent Study | | |
|---|---|---|---|
| **ADA Status; NAb Status** | **R668-AD-1412 N (%)** | **R668-AD-1652 N (%)** | **Overall N (%)** |
| Total ADA Patients | 33 (100%) | 245 (100%) | 278 (100%) |
| Negative | 19 (57.6%) | 229 (93.5%) | 248 (89.2%) |
| Pre+; NAb- | 0 | 7 (2.9%) | 7 (2.5%) |
| Pre+; NAb+ | 0 | 0 | 0 |
| TE & TB; NAb- | 5 (15.2%) | 4 (1.6%) | 9 (3.2%) |
| TE & TB; NAb+ | 9 (27.3%) | 0 | 9 (3.2%) |

N = Number of patients 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.

The overall incidence of treatment-emergent ADA for patients ≥6 to <12 years of age in R668-AD-1434 was 8.3% (23/278) (Table 5). Higher rates of treatment-emergent ADA were observed for patients from parent study R668 AD 1412 (42.4%, 14/33) than from parent study R668-AD-1652 (3.7%, 9/246). Positive ADA in most patients were transient, of a low titer, and negative for NAb. All patients positive for NAb and all but 1 patient with a moderate or ADA high titer were from parent study R668-AD-1412. The elevated immunogenicity in patients from R668-AD-1412 is attributed to intermittent dosing in that study which included an 8-week washout following a single dose not unlike a prime and boost regimen used for vaccinations. This is in contrast to the multiple Q2W or Q4W doses administered continuously for 16 weeks in R668-AD-1652.

The distribution of dupilumab concentrations for ADA positive patients ≥6 to <12 years of age was generally within the range of concentrations of ADA negative patients with the exception of a few patients with high/moderate ADA titers.

Longitudinal assessment indicated that most patients from R668-AD-1412 who entered the current study with moderate or high titers exhibited a decrease in titer values over time with a corresponding increase in dupilumab concentrations. Efficacy, as determined by percent change from baseline in EASI score, also generally improved in these patients with continued troughout the study (Figure 10, presented in section on phase 2 PK study R668-AD-1412).

A single patient from R668-AD-1412 with a high ADA titer level in the parent study exhibited dupilumab concentrations at or near the lower limit of quantification for the duration of the current study. Despite dupilumab concentrations that were not measurable at trough sampling points while on the 2 mg/kg QW regimen, this patient responded to treatment with a maximum change from baseline in EASI score of -100% at week48 in the current study. At Week 94, this patient was transitioned to 300 mg Q4W following approval of amendment 1. EASI score increased following the switch and, based on inadequate response, the patient was uptitrated to the more intense 200 mg Q2W regimen at Week 102 and EASI score subsequently decreased.

### 2.3.3. PK/PD modelling

Exposure-Response Relationships:

*Methods:*

For children ≥6 to <12 years of age with severe AD, the E-R analysis sets consist of the PK analysis set and one non-missing baseline and at least 1 non-missing post dose Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), or pruritus Numerical Rating Scale (NRS) value, as applicable for each E-R assessment.

Exposure-response analyses were based on data from the weight-tiered 100/200 mg Q2W and non-weight-tiered 300 mg Q4W dosing regimens of study R668-AD-1652.

Logistic regression was performed to investigate the E-R relationship between probability of achieving IGA 0 or 1, EASI-50, EASI-75, and EASI-90 with Ctrough at week 16. Missing efficacy data were imputed as non-responders for the binary variables and missing concentration data were imputed using last observation carried forward (LOCF) to account for the effect of censored data due to dropout.

Additionally, quartile analyses were performed to investigate the relationship between efficacy endpoints and quartiles of exposure. Endpoints included the percentage of patients achieving IGA 0 or 1 and the mean (standard deviation [SD]) percent change in EASI from baseline over time by quartile of functional dupilumab concentration. For the endpoint of percentage of patients achieving IGA 0 or 1, missing data were treated as non-responders, and for percent change in EASI from baseline, data after use of rescue treatment were imputed using LOCF. Censored concentration data were imputed using LOCF.

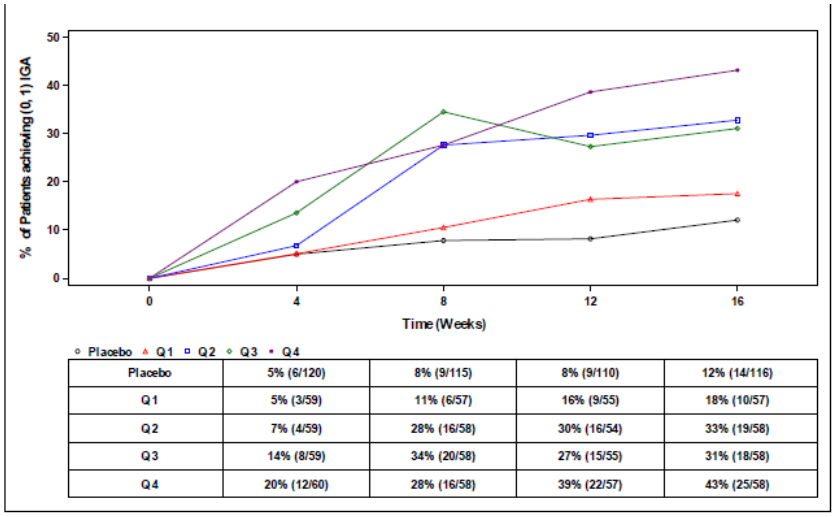
The E-R analysis related to safety was conducted using a logistic regression method to assess the relationship between the incidence of conjunctivitis over 16 weeks and Ctrough at week 16.

*Results:*

Exposure-efficacy relationships

Efficacy endpoint: percent achieving IGA0 or 1

Figure 15: Percent of Patients Achieving (0,1) IGA Score by Nominal Time (Weekl) and Quartile of Functional Dupilumab Concentrations Children ≥6 to <12 Years of Age with AD (Primary) (Study R668-AD-1652)

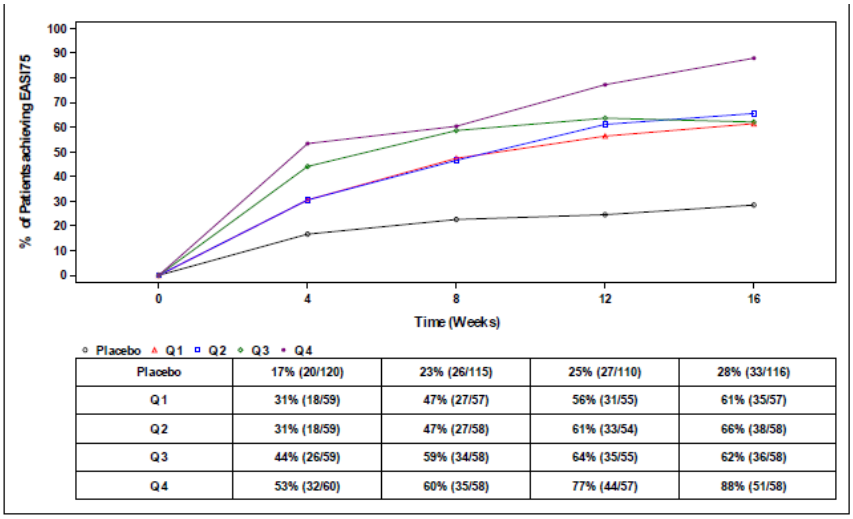



| | | | | |
|---|---|---|---|---|
| Placebo | 5% (6/120) | 8% (9/115) | 8% (9/110) | 12% (14/116) |
| Q1 | 5% (3/59) | 11% (6/57) | 16% (9/55) | 18% (10/57) |
| Q2 | 7% (4/59) | 28% (16/58) | 30% (16/54) | 33% (19/58) |
| Q3 | 14% (8/59) | 34% (20/58) | 27% (15/55) | 31% (18/58) |
| Q4 | 20% (12/60)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

Note: Concentrations below the LLOQ were set to 0.
Data up to Week 16 are used and concentrations are imputed using last observation carried forward (LOCF) rule when the efficacy endpoint is available and concentration is missing at planned PK sample collection visit; 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 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261)

Efficacy endpoint: percent achieving EASI-75

Figure 16: Mean (±SD) EASI-75 by Week and Quartile of Concentration of Functional Dupilumab in Seerum in Children ≥6 to <12 Years of Age with AD (Primary) (Study R668-AD-1652)



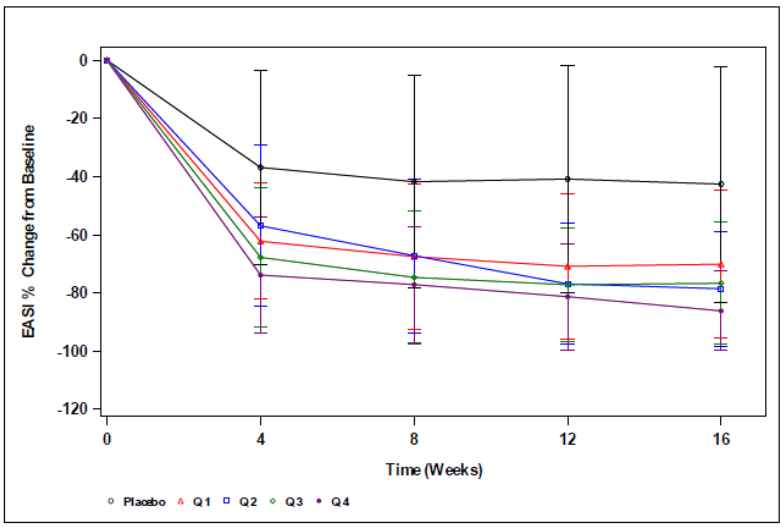

| | | | | |
|---|---|---|---|---|
| Placebo | 17% (20/120) | 23% (26/115) | 25% (27/110) | 28% (33/116) |
| Q1 | 31% (18/59) | 47% (27/57) | 56% (31/55) | 61% (35/57) |
| Q2 | 31% (18/59) | 47% (27/58) | 61% (33/54) | 66% (38/58) |
| Q3 | 44% (26/59) | 59% (34/58) | 64% (35/55) | 62% (36/58) |
| Q4 | 53% (32/60) | 60% (35/58) | 77% (44/57) | 88% (51/58) |

Note: BLQs were set to 0.
Note: Data up to Week 16 are used and concentrations are imputed using last observation carried forward (LOCF) rule when the efficacy endpoint is available and concentration is missing at planned PK sample collection visit; 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 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261).

Efficacy endpoint: percent change from baseline in EASI

Figure 17

**Figure 10: Mean (±SD) EASI % Change from Baseline by Week and Quartile of Concentration of Functional Dupilumab in Serum in Children ≥6 to <12 Years of Age with AD (LOCF Imputation) (Study R668-AD-1652)**

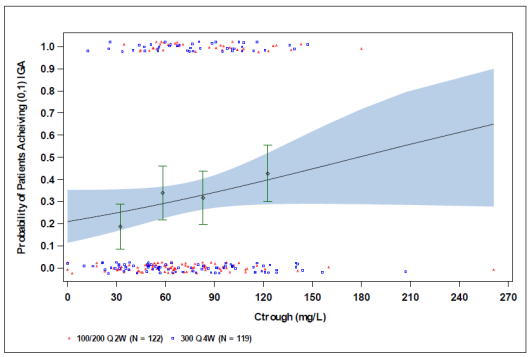



Note: Concentrations below the LLOQ were set to 0. The quartile ranges for Week 16 concentrations (mg/L): Q1 (0-49.7), Q2 (49.7-67.5), Q3 (67.5-97.3), Q4 (97.3-261).

Logistic regression of binary endpoints (IGA 0 or 1, EASI-75, EASI-50, EASI-90)

Figure 18

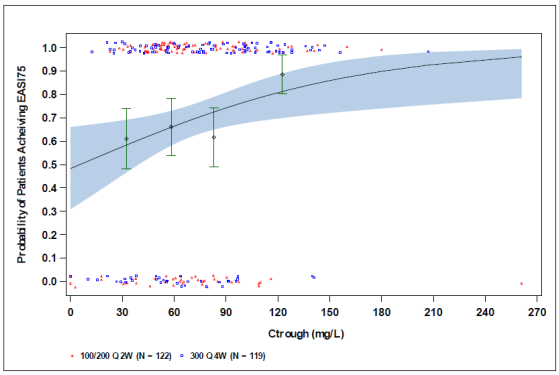
**Figure 15: Logistic Regression Relating Probability of Patients Achieving an (0,1) IGA Score with Dupilumab Trough Concentrations at Week 16 in Children ≥6 to <12 Years of Age with Severe AD (P-Value (Regression): 0.0467) (Study R668-AD-1652)**




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

Figure 19

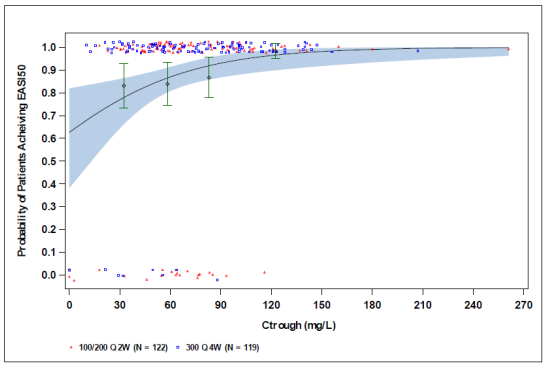
**Figure 16: Logistic Regression Relating Probability of Patients Achieving EASI-75 with Dupilumab Trough Concentrations at Week 16 in Children ≥6 to <12 Years of Age with Severe AD (P-Value (Regression): 0.0040) (Study R668-AD-1652)**




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

Figure 20

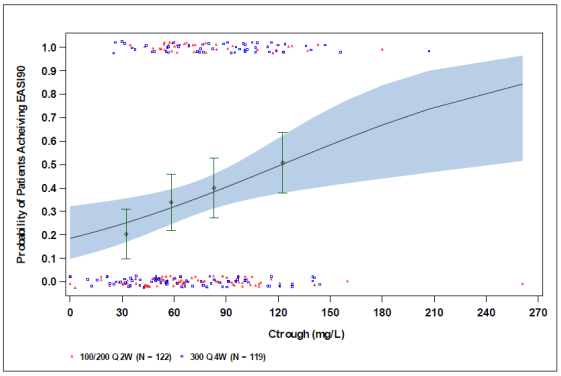
**Figure 41: Logistic Regression Relating Probability of Patients Achieving EASI-50 with Dupilumab Trough Concentrations at Week 16 in Children ≥6 to <12 Years of Age with Severe AD (P-Value (Regression): 0.0011) (Study R668-AD-1652)**




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

Figure 21

**Figure 42: Logistic Regression Relating Probability of Patients Achieving EASI-90 with Dupilumab Trough Concentrations at Week 16 in Children ≥6 to <12 Years of Age with Severe AD (P-Value (Regression): 0.0017) (Study R668-AD-1652)**

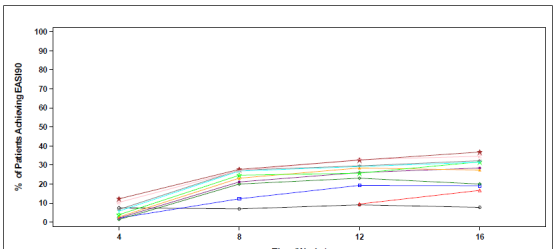



N = Number of patients
Note: Concentrations below the LLOQ were set to 0.
Concentrations are imputed using LOCF rule when the efficacy endpoint is available and concentration is missing at planned PK visit.
Mean Regression line - blue, confidence area around regression line - grey. Non-responders (0)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

Cumulative decile concentration analyses for the most stringent efficacy endpoint (EASI-90 and IGA 0 or 1), and endpoint EASI-50:

Figure 22

**Figure 13: Percent of Patients Achieving EASI-90 by Time and Week 16 Cumulative Dupilumab Concentration Deciles in Children ≥6 to <12 Years of Age with Severe AD (Primary) (Study R668-AD-1652)**

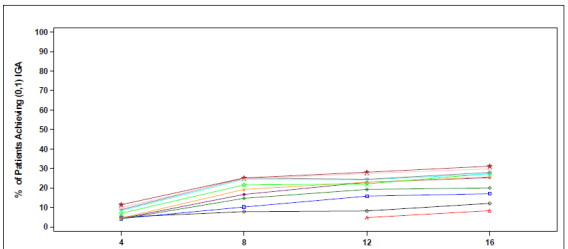



| | | | | |
|---|---|---|---|---|
| Placebo | 7.5% (9/120) | 7.0% (8/115) | 9.1% (10/110) | 7.8% (9/116) |
| <=33 mg/L | | | 9.5% (2/21) | 16.7% (4/24) |
| <=46 mg/L | 2.1% (1/47) | 12.2% (6/49) | 19.3% (11/57) | 19.1% (9/47) |
| <=54 mg/L | 1.4% (1/73) | 20.0% (15/75) | 23.1% (18/78) | 20.0% (14/70) |
| <=61 mg/L | 2.2% (2/93) | 21.1% (19/90) | 26.0% (25/96) | 28.4% (27/95) |
| <=68 mg/L | 2.7% (3/110) | 23.1% (24/104) | 28.4% (31/109) | 27.4% (32/117) |
| <=79 mg/L | 3.9% (5/129) | 24.6% (32/130) | 25.7% (35/136) | 31.7% (44/139) |
| <=92 mg/L | 5.8% (9/156) | 26.8% (44/164) | 29.2% (47/161) | 31.5% (51/162) |
| <=102 mg/L | 6.6% (12/181) | 27.3% (50/183) | 29.5% (52/176) | 32.3% (60/186) |
| <=120 mg/L | 10.4% (22/212) | 27.1% (55/203) | 32.8% (66/201) | 34.8% (72/208) |
| <=261 mg/L | 12.2% (29/237) | 27.7% (64/231) | 32.6% (72/221) | 36.8% (85/231) |

Note: Concentrations below the LLOQ were set to 0.
Data up to Week 16 are used and concentrations are imputed using last observation carried forward (LOCF) rule when the efficacy endpoint is available and concentration is missing at planned PK sample collection visit; Number in parentheses in the table is number of patients achieving EASI-90 / number of patients who contribute to the decile.

Figure 23

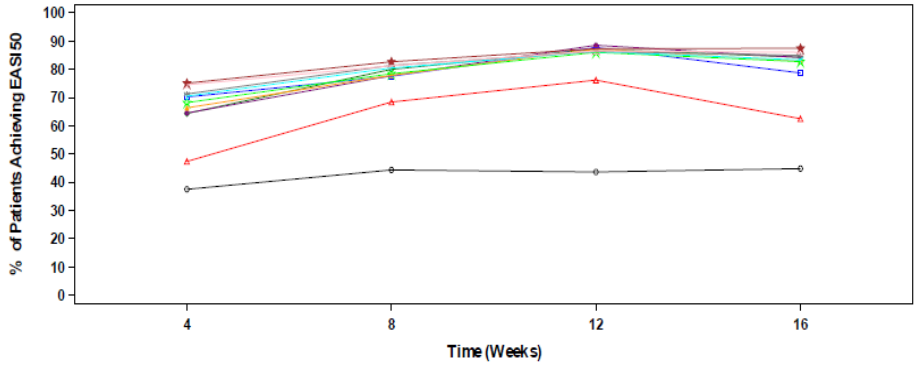
**Figure 14: Percent of Patients Achieving (0,1) IGA Score by Time and Week 16 Cumulative Dupilumab Concentration Deciles in Children ≥6 to <12 Years of Age with Severe AD (Primary) (Study R668-AD-1652)**




| | | | | |
|---|---|---|---|---|
| Placebo | 5.0% (6/120) | 7.8% (9/115) | 8.2% (9/110) | 12.1% (14/116) |
| <=33 mg/L | | | 4.8% (1/21) | 8.3% (2/24) |
| <=46 mg/L | 4.3% (2/47) | 10.2% (5/49) | 15.8% (9/57) | 17.0% (8/47) |
| <=54 mg/L | 4.1% (3/73) | 14.7% (11/75) | 19.2% (15/78) | 20.0% (14/70) |
| <=61 mg/L | 4.3% (4/93) | 16.7% (15/90) | 22.9% (22/96) | 25.3% (24/95) |
| <=68 mg/L | 4.5% (5/110) | 19.2% (20/104) | 22.9% (25/109) | 25.6% (30/117) |
| <=79 mg/L | 7.0% (9/129) | 21.5% (28/130) | 22.1% (30/136) | 27.3% (38/139) |
| <=92 mg/L | 8.3% (13/156) | 24.4% (40/164) | 24.2% (39/161) | 27.2% (44/162) |
| <=102 mg/L | 8.8% (16/181) | 25.1% (46/183) | 24.4% (43/176) | 28.0% (52/186) |
| <=120 mg/L | 9.9% (21/212) | 24.6% (50/203) | 27.4% (55/201) | 29.8% (62/208) |
| <=261 mg/L | 11.4% (27/237) | 25.1% (58/231) | 28.1% (62/221) | 31.2% (72/231) |

Note: Concentrations below the LLOQ were set to 0.
Data up to Week 16 are used and concentrations are imputed using last observation carried forward (LOCF) rule when the efficacy endpoint is available and concentration is missing at planned PK sample collection visit; Number in parentheses in the table is number of patients achieving (0, 1) IGA / number of patients who contribute to the decile.

Figure 24: Percent of Patients Achieving EASI-50 by Time and Week 16 Cumulative Dupilumab Concentration Deciles in Children **≥6** to <12 Years of Age with Severe AD (Primary) (Study R668-AD-1652)




| | | | | |
|---|---|---|---|---|
| Placebo | 37.5% (45/120) | 44.3% (51/115) | 43.6% (48/110) | 44.8% (52/116) |
| <=33 mg/L | 47.4% (9/19) | 68.4% (13/19) | 76.2% (16/21) | 62.5% (15/24) |
| <=46 mg/L | 70.2% (33/47) | 77.6% (38/49) | 87.7% (50/57) | 78.7% (37/47) |
| <=54 mg/L | 64.4% (47/73) | 80.0% (60/75) | 87.2% (68/78) | 84.3% (59/70) |
| <=61 mg/L | 64.5% (60/93) | 77.8% (70/90) | 88.5% (85/96) | 84.2% (80/95) |
| <=68 mg/L | 66.4% (73/110) | 77.9% (81/104) | 87.2% (95/109) | 82.9% (97/117) |
| <=79 mg/L | 68.2% (88/129) | 78.5% (102/130) | 86.0% (117/136) | 82.7% (115/139) |
| <=92 mg/L | 70.5% (110/156) | 80.5% (132/164) | 86.3% (139/161) | 83.3% (135/162) |
| <=102 mg/L | 71.3% (129/181) | 81.4% (149/183) | 86.4% (152/176) | 84.9% (158/186) |
| <=120 mg/L | 74.5% (158/212) | 81.3% (165/203) | 86.6% (174/201) | 86.1% (179/208) |
| <=261 mg/L | 75.1% (178/237) | 82.7% (191/231) | 87.3% (193/221) | 87.4% (202/231) |

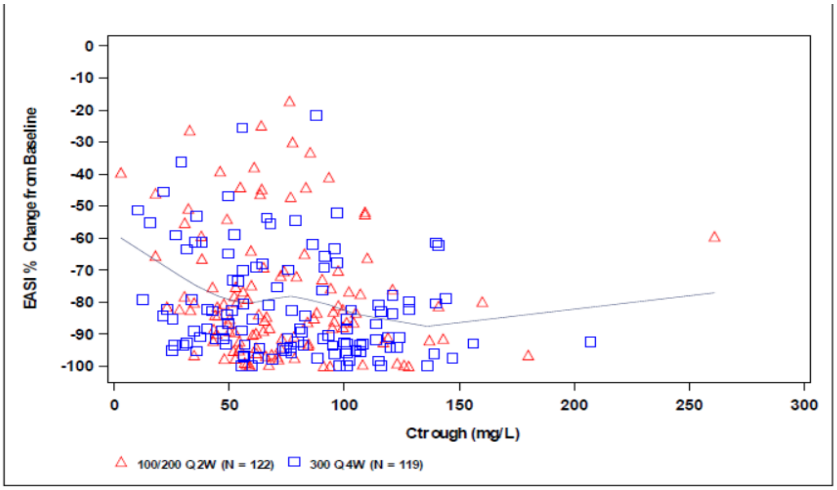
Note: Concentrations below the LLOQ were set to 0.
Data up to Week 16 are used and concentrations are imputed using last observation carried forward (LOCF) rule when the efficacy endpoint is available and concentration is missing at planned PK sample collection visit; Number in parentheses in the table is number of patients achieving EASI-50 / number of patients who contribute to the decile.

EASI-50, the maximal drug effect was achieved at lower concentrations compared to the endpoints of EASI-75, EASI-90, and IGA 0 or 1.

Exposure-response relationships identified moderately positive correlations between higher dupilumab Ctrough and improvement in efficacy endpoints, thus suggesting benefit of dosing regimens that maintain higher Ctrough across patients, with a similar trend for pediatric and adult patients with AD.

A scatter plot of continuous endpoint of EASI percent change from baseline vs. week 16 dupilumab Ctrough indicated a positive E-R relationship, showing increasing drug effect with increasing drug concentration, with an approximate mean percent change from baseline of 30% over the entire concentration range.

Figure 25: Plot of EASI % Change from Baseline with Dupilumab Trough Concentrations at Week 16 in Children ≥6 to <12 Years of Age Receiving 100/200 mg Q2Q or 300 mg Q4Q Regimens with Severe AD (Study R668-AD-1625)




N = Number of patients
Note: Concentrations below the LLOQ were set to 0.
Solid line represents Loess (smooth: 0.5).
Concentrations are imputed using LOCF rule when the efficacy endpoint is available and concentration is missing at planned PK visit.

Exposure-response analysis of the relationship between quartile of dupilumab Ctrough with the primary efficacy endpoint, percentage of patients achieving IGA 0 or 1, showed a trend of increasing drug effect with increasing quartile of Ctrough of dupilumab over time (Figure 8 above).

Similar E-R relationships were observed for other efficacy endpoints including percent of patients achieving EASI-75 (primary imputation method), and EASI percent change from baseline (LOCF method, Figure 10 above).

Sensitivity analyses showed that the same rank ordering of concentration quartiles was preserved for the E-R relationships for the completer analyses.

Cumulative decile concentration analysis showed that for the most stringent efficacy endpoint of EASI-90 and IGA 0 or 1), the time course of drug effect was saturated by week 16 at higher concentrations compared to the least stringent endpoints of EASI-50.

Logistic regression on binary response variables such as the primary and co-primary endpoints of IGA 0 or 1 (Figure 15) and EASI-75 (Figure 16) also demonstrate positive exposure-response relationships, showing increasing effect with increasing steady-state Ctrough of dupilumab.

## 2.3.4. Discussion on clinical pharmacology

Bioanalytical methods

Methods applied for the detection of functional dupilumab and for the detection of anti-dupilumab antibodies and neutralizing antibodies correspond to the methods already utilized and described in previous applications. Incurred sample reanalysis was conducted in study R668-AD-1412 and confirmed that the assay produced robust and reproducible results in the paediatric AD population.

Pharmacokinetics

The package on clinical pharmacology regarding children of this age group with severe AD comprises 3 dupilumab clinical studies where PK and PD data have been collected. A phase 3 pivotal study (R668-AD-1652) was conducted with patients of this age group and the results of two further studies, R668-AD-1412 (Phase 2a PK) and R668-AD-1434 (OLE), provide further supporting data. A variety of subcutaneous (SC) dosing regimens for dupilumab was evaluated in these studies including 2 mg/kg and 4 mg/kg single

dose or repeated QW dose (phase 2 PK study), weight-tiered 100 mg Q2W and 200 mg Q2W (below and above 30 kg) and non-weight-tiered 300 mg Q4W following loading doses of two times the maintenance doses for the respective dosing regimen (pivotal study) as well as weight-tiered 100 mg or 200 mg Q2W as up-titration from 300 mg Q4W (OLE).

A weight-tiered regimen of 100 mg Q2W for children ≥15 to <30 kg and 200 mg Q2W for children ≥30 kg, as well as the non-weight-tiered 300 mg Q4W, were selected for the pivotal study R668-AD-1652 with the aim of matching the dupilumab exposure distribution in children aged ≥6 to <12 years to that achieved with the approved 300 mg Q2W regimen in adults.

Population PK

A population PK analysis for dupilumab in children ≥6 to <12 years of age with severe atopic dermatitis was conducted using data from the Study R668-AD-1652. Appropriate methods were used for model development and evaluation. Dupilumab concentration-time data were described by a two-compartment population PK model with parallel linear and nonlinear Michaelis-Menten (MM) elimination and transit compartments for absorption. Weight was included as a covariate on V2 in all models. EASI on ke and albumin on V2 were identified as additional significant covariates.
Parameters were estimated with good precision in both the base and covariate models, with all RSE <11% and <28%, respectively. Diagnostic plots for both base and covariate models demonstrated an adequate fit to the data.

Re-estimation of PK parameters while using the same model structure for describing adult and adolescent data is supported. However, the re-estimation was conducted based on PK samples from the pivotal study R668-AD-1652 only (N=925). PK data were balanced with respect to sex (50.2% female, 49.8 % male). ADA incidence was highest in the 200 mg Q2W group (5.1%) with overall low incidence (2.4%) and no ADA positivity in the Q4W treatment group.

The base and covariate models adequately described the PK of dupilumab in children aged ≥6 to <12 years with severe AD. Population PK parameters were essentially the same in the base and covariate models. The parameters of the base/covariate models were generally consistent with those previously estimated for adult and adolescent populations with moderate-to-severe AD, although there were some numeric differences. The target-mediated clearance (Vm) somewhat decreased with age across children ≥ 6 to <12 years of age, adolescents, and adults; no allometric differences (decrease with weight) in elimination rate (ke) were observed. Comparisons using the covariate models suggest that central volume (V2) calculated at weight of 75 kg slightly increased with age.
Several PK parameters were fixed (Vm, Km, intercompartmental distribution rates k23 and k32, ke, MTT, and bioavailability F), similar to the model adolescent patients. Ka (0.641 1/d) deviates from the adolescent and adult model (0.306 1/d), whereas F remains to the same fix value of 0.642. It is agreed that a more precise estimation of F is not feasible due to the lack of IV PK data in the paediatric population. In contrast, the absorption rate (ka) was fixed to a value of 0.641 1/d estimated using semi-sparse data of ≥6 to <12 years of age subpopulation of study R668-AD-1412.

It is agreed with the MAH that higher absorption rate is expected in children. However, a higher bioavailabilty F is also likely in this age group as seen for other monoclonal antibodies. Due to the relatively small size of population PK dataset in patients >6 to ≤12 years of age (N=241 patients) compared to the adult dataset (N=2115 patients), a full covariate analysis was not conducted. Three of six covariates which were found statistically significant in adults were also statistically significant in children ≥6 to <12 years of age. The covariate coefficients for albumin, EASI score, and weight were statistically significant similarly to those in the adult model with no meaningful impact of albumin and EASI on between-subject variability. The statistically significant impact of ADA and body mass index (BMI) on elimination rate and race on central volume in adults was not replicated in children ≥6 to <12 years of age possibly due to considerably smaller sample size, lower prevalence of ADA, and low BMI.

The impact of BMI and ke could not be replicated in children from 6 to 12 years of age. Thus, there is no body size related influence incorporated in the pop PK model for the youngest age group. It is argued by CHMP that BMI was notably lower in children ≥6 to <12 years of age than in adolescents and adults (16.9, 22.5, and 24.9 kg/m2, respectively), which can potentially explain the absence of the association of ke and BMI in the youngest age group. However, as body weight or body size related effects are known and expected to have an influence on PK (CL and V), this is not considered plausible to the CHMP. Forest plots have been provided and demonstrated the modest influence of body weight on PK.

The extent of absorption (Bioavailability, F) was not estimated in children ≥6 to <12 years population due to the lack of intravenous (IV) data. Estimation of the apparent central compartment volume of distribution (V2) yielded slightly lower values for children ≥6 to <12 years of age vs. adults (2.18±0.087 vs. 2.74±0.021 L, respectively, for a reference body weight of 75 kg in each population). At the median body weight of 29.4 kg, V2 was estimated as 0.999 L.
Based on pop PK results, clearance was estimated to 0.0972 L/d, which is slightly lower to Clearance calculated for adolescents (0.128 L/d) and the adult population (0.131 L/d).

Overall, the PK of dupilumab is characterized as nonlinear with parallel linear and nonlinear elimination pathways (target-mediated clearance). Clearance slightly decreases with age across children ≥6 to <12 years of age, adolescents, and adults.

Steady state was achieved in all treatment regimens in accordance with dosing intervals and loading doses before week 16.

PK and PD comparison across populations

For children receiving the 300 mg Q4W regimen at any body weight, the 5th percentile and median of CtroughSS were higher than for adolescents receiving the 200/300 mg Q2W regimen but lower than adults receiving the 300 mg Q2W regimen. For the 100 mg Q2W regimen in children at body weight <30 kg, the 5th percentile and median of CtroughSS were lower compared to children receiving the 200 mg Q2W regimen at body weight ≥30 kg and the 300 mg Q4W regimen at body weight <30 kg.

The 95th percentile and median of simulated Cmax at steady state (Cmaxss) in children receiving the 200 mg Q2W regimen at body weight ≥30 kg were higher compared to adolescents receiving the 200/300 mg Q2W regimens and adults receiving the 300 mg Q2W regimen, but lower compared to adults receiving the 300 mg QW regimen. Upon request, the MAH justified that the higher steady-state Cmax predicted in children receiving the 200 mg Q2W regimen at body weight ≥30 kg is unlikely to have safety implications, which can be acceptable as discussed further in the report.

For the 300 mg Q4W regimen in children at body weight <30 kg, the 95th percentile and median of simulated CmaxSS were higher compared to adolescents receiving the 200/300 mg Q2W regimens and adults receiving the 300 mg Q2W regimen. The median of simulated CmaxSS in children at body weight <30 kg receiving the 300 mg Q4W regimen was also higher compared to adults receiving the 300 mg QW regimen but the 95th percentile of CmaxSS was lower. Further, following the loading dose of 600 mg for the 300 mg Q4W regimen in children of any weight, the 95th percentile and median of Cmax were around 2-fold higher than after the 400 mg loading dose for the 200 mg Q2W regimen in children of body weight ≥30 kg. This suggests there may be safety implications for the proposed 600 mg loading dose and 300 mg Q4W regimen for children at body weight <30 kg.

Despite the higher concentrations after the 600 mg loading dose compared to steady-state concentrations in children <30 kg receiving the 300 mg Q4W regimen, the observed efficacy at week 16 was similar to that observed with the 200 mg Q2W regimen following a 400mg loading dose in children ≥30 kg, indicating no impact of higher concentrations on drug effect at week 16. Furthermore, no safety findings were associated with the higher drug concentrations after the 600 mg loading dose compared to steady-state concentrations in children <30 kg receiving the 300 mg Q4W regimen.

The higher steady state Cmax in children ≥15 - <30 kg compared to that of the 300 mg Q2W regimen in adults and 200 or 300 mg Q2W regimen in adolescents is not considered to be a safety concern given the established safety of the dupilumab 300 mg QW regimen in adults and the totality of safety data from R668-AD-1652 and the OLE study R668-AD-1434 with the 300 mg Q4W dose in children ≥15 - <30 kg.

Overall the PK/PD has been appropriately demonstrated across populations of children from 6 to 11 years of age and from 15 to 60 kgs.

Immunogenicity

Immunogenicity was analysed in all clinical studies including children ≥6 to <12 years of age.

In pivotal study R668-AD-1652, the overall prevalence of observed immunogenicity was low (ADA positive 2.3%) and all ADA responses were of low titer. There were no patients positive for ADA in the 300 mg Q4W + TCS group and the incidence of treatment-emergent ADA was 4.9% and 5.3% in the dupilumab 100 mg Q2W + TCS and dupilumab 200 mg Q2W + TCS group, respectively. Only two patients in the dupilumab 100 mg Q2W + TCS group (3.3%) and 1 patient in the dupilumab 200 mg Q2W + TCS group (1.8%) showed positive responses in the NAb assay. It is therefore agreed by CHMP that no clear evidence of a clinically meaningful impact of immunogenicity on dupilumab exposure or response was observed in study R668-AD-1652.

In Study R668-AD-1412, a marked positive response in the ADA assay at any time was observed in 56.8% of children ≥6 to <12 years of age, and 29.7% were categorized having a persistent, treatment-emergent ADA response. The majority of the treatment-emergent positive responses in the ADA assay were categorized as low titers, but in 5 of 37 patients moderate or high titers were observed and those were associated with a substantial reduction in detectable drug concentrations and a lack of notable improvement in EASI score. With continuing treatment through Part B of the study (a repeat-dose treatment period [4 weekly doses] and an 8-week follow-up period) and subsequently in the OLE study, ADA titers declined and a corresponding increase in systemic concentrations of dupilumab as well as an improvement in the EASI percent change from baseline was observed in all but one of the 5 patients having moderate to high ADA titers. Similar results were observed in this study for the group of adolescents ≥12 to <18 years of age but was not observed in the pivotal dupilumab studies R668-AD-1652 and R668-AD-1562 with children and adolescents, respectively. Study R668-AD-1412 utilized a dosing regimen akin to a prime and boost vaccination regimen that could have accounted for the higher incidence of ADA than in any other study in the dupilumab development program.

In the extension study R668-AD-1434, positive ADA in most patients were transient, of a low titer, and negative for NAb. Higher rates of treatment-emergent ADA were observed for patients from parent study R668-AD-1412. Further, all patients positive for Nab and all but 1 patient with moderate or high ADA titer were from parent study R688-AD-1412. Longitudinal assessment of ADA titers over a greater than 2-year period in children ≥6 to <12 years of age who had developed high ADA titers showed that with continuation of treatment, ADA titers declined, with corresponding incline of functional dupilumab concentration and improvement of EASI score.

Exposure-Response

The mean (±SD) EASI and NRS percent (%) change from baseline in conjunction with systemic dupilumab concentrations were found to be non-discriminating of dosing regimens.

The E-R relationships over time, whether assessed by percent change from baseline in EASI, or percent achieving IGA 0 or 1 with quartiles of trough concentrations; or by logistic regression of binary endpoints (EASI-50, EASI-75, EASI-90 and IGA 0 or 1), suggested a trend for increasing drug effects with increasing trough concentration of dupilumab. These E-R findings support the clinical benefit of the regimens resulting in the highest systemic exposure of dupilumab in children ≥6 to <12 years of age:

300 mg Q4W in children <30 kg. This holds partly for the 200 mg Q2W regimen in children ≥30 kg in comparison with the 300 mg Q4W regimen.

To ensure adequate efficacy of dupilumab at different body weights, the MAH was asked to provide exposure-response relationships stratified by body weight and dosing regimen. The requested plots were provided and showed a similar trend of increasing response with increasing concentration in both weight groups.

No relationship with respect to safety can be found; probability of patients developing conjunctivitis (broad term) with dupilumab Ctrough at week 16 showed a slight trend for an inverse E-R relationship with the highest probability of developing conjunctivitis observed at lower drug concentrations. No long-term data is available at this stage to further inform E-R with respect to safety.

Discussion of recommended dose

The proposed posology in patients ≥6 to <12 years of age with severe AD is tiered by body weight with patients ≥15 to <30 kg receiving 300 mg Q4W following a 600 mg loading dose and with patients ≥30 to <60 kg receiving 200 mg Q2W following a 400 mg loading dose.

For children ≥6 to <12 years of age weighing ≥60 kg, the proposed dose regimen is 300 mg Q2W following a loading dose of 600 mg, since this dose regimen has been proven to achieve the desired effective exposure in adults and adolescents weighing ≥60 kg.

Observed PK data support the proposed posology in children ≥6 to <12 years of age: 200 mg Q2W regimen in the children weighing ≥30 kg and 300 mg Q4W regimen in children <30 kg as the dosing regimens achieving drug concentrations that are at least similar to or greater than that achieved by the standard 300 mg Q2W regimen in adults. However, the benefit of the 4 weeks program for children between 6 and 12 years of age, together with comparable efficacy and exposure to adults and the lack of long-term safety data at higher exposure levels needs to be taken into account for dose selection.

Exposure simulations have been provided based on the base pop PK model for age group 6 – 12 years of age. Simulations for body weight cut-off selection (cut-off for switching from 300 mg Q4W to the 200 mg Q2W regimen (proposed as 30 kg) and to the 300 mg Q4W regimen (proposed at 60 kg)) were to be provided taking E-R analysis and data from the OLE study into account. For weight group > 60 kg, there were only few subjects below the age of 12 in this weight category. E-R analysis showed high comparability between 200 mg Q2W and 300 mg Q4W for paediatric patients in the weight group 30-60 kg, characterized by a flat exposure response curve for both dosing regimens considering also body weight quartiles. Simulations showed that steady state exposure (Ctrough) is expected to be lower in each weight category with the 300 mg Q4W regimen compared to the 200 mg Q2W regimen. Exposure-response analyses indicate that the 200 mg Q2W regimen may be associated with improved efficacy. After switching to the 200 mg Q2W regimen, there appeared to be a small increase in IGA0/1 and EASI-75 in the lower weight categories. However, a conclusion that the 200 mg Q2W regimen is more effective than the 300 mg Q4W regimen is not possible due to the limited number of patients with results at Week 52.

Loading dose

Due to the flat dosing regimen that was followed in the Phase 3 study, paediatric patients of low body weight received a very high loading dose of 600mg that exceeds exposures of adolescent and adult patients. Thus, loading dose 600 mg was deemed not justified from the PK point of view by CHMP. Exposure predictions and the data collected support high expected levels. Thus, the MAH was asked to discuss the need for such a high loading dose for paediatrics < 30 and to conduct simulations to select a body weight cut that justifies the need of a loading dose in the 300 mg Q4W setting for all paediatric patients. In response, simulations comprised an alternative modelled scenario: the 600 mg loading dose was split (300 mg administered on D1 and 300 mg on D15 followed by the 300 mg Q4W therapy starting

4 weeks after D15 dose. Simulation results showed that with this amended posology, rapid Ctrough levels will be achieved in this paediatric age group (in both weight categories 15-30 kg and 30–60 kg), while very high Cmax level are avoided.

Figure 26. Simulated Concentration of Functional Dupilumab over Time (Percentiles, Median, and Mean) Treatment Group=300 mg - Day 0, 300 mg Q4W SC - Day 14, Weight Group <30 kg

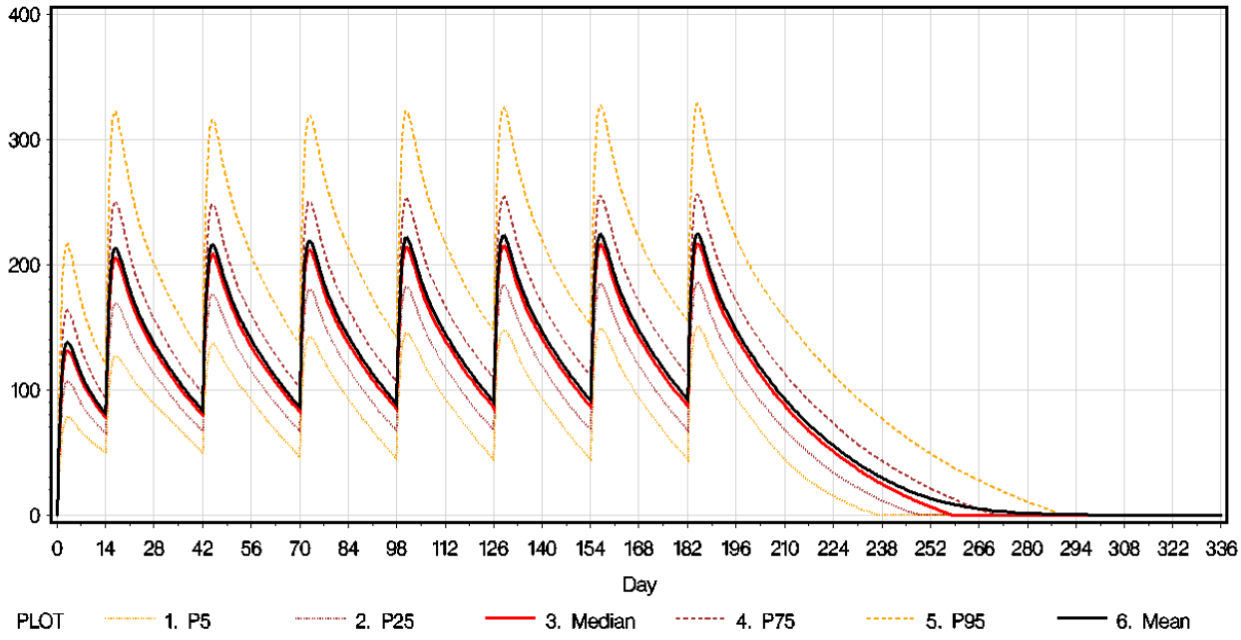
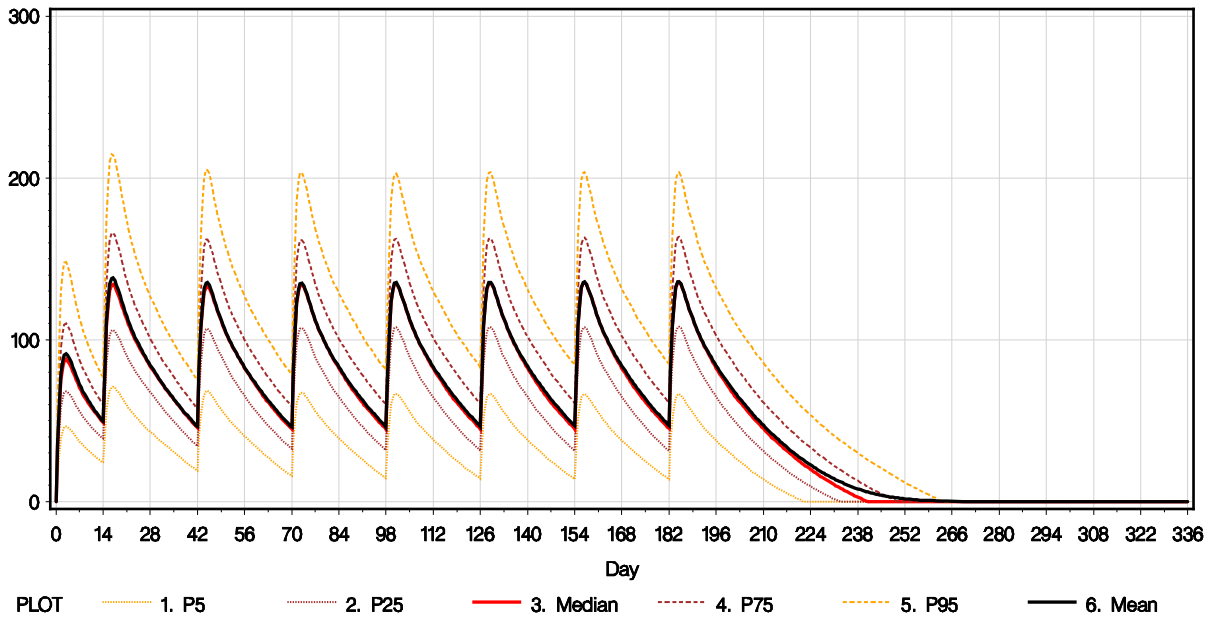



Figure 27. Simulated Concentration of Functional Dupilumab over Time (Percentiles, Median, and Mean) Treatment Group=300 mg - Day 0, 300 mg Q4W SC - Day 14, Weight Group **≥30** kg




In conclusion, a loading dose of 600 mg administered 300 mg at Day 1 and 300 mg at Day 15 will avoid peak concentrations while rapidly achieving efficacy at Cmin levels. This was also shown by exposure

simulations for both weight categories 15-30 kg and 30-60 kg. As such, splitting the loading dose accordingly is deemed the optimal setting for patients below 30 kg.

As patients with a body weight <15 kg were not included in the pivotal study, a statement that dupilumab should not be used paediatric patients weighing <15 kg is included in the SmPC.

Dosing regimen

Further, higher predicted Cmax at steady state in children receiving the 300 mg Q4W regimen at body weight <30 kg compared to adolescents receiving the 200/300 mg Q2W regimens and adults receiving the 300 mg Q2W/Q4W are not considered to be a safety concern given the established safety of the dupilumab 300 mg QW regimen in adults and the totality of safety data from R668-AD-1652 and the OLE study R668-AD-1434 with the 300 mg Q4W dose in children ≥15 - <30 kg. Consequently, a dosing regimen of 300mg Q4W is recommended for approval for patients 15 to 60kg. The posology for patients weighting more than 60 kgs is recommended as initial dose of 300 mg in two injections followed by subsequent doses of 300mg Q2W.

In summary, the recommended dose of dupilumab for children 6 to 11 years of age as stated in the posology section of the SmPC is specified below.

Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with atopic dermatitis

| Body Weight of Patient | Initial Dose | Subsequent Doses |
|---|---|---|
| 15 kg to less than 60 kg | 300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15 | 300 mg every 4 weeks (Q4W)*, starting 4 weeks after Day 15 dose |
| 60 kg or more | 600 mg (two 300 mg injections) | 300 mg every other week (Q2W) |

* The dose may be increased to 200 mg Q2W in patients with body weight of 15 kg to less than 60 kg based on physician's assessment.

### 2.3.5. Conclusions on clinical pharmacology

The MAH provided a comprehensive package on clinical pharmacology to support the dosing regimen in children ⩾6 to <12 years of age with severe AD.
CHMP recommended splitting of the high loading dose of 600 mg for paediatric patients below 60 kg is recommended to avoid early peak concentrations while resulting in rapid attainment of steady state concentrations similarly to the one dose loading of 600 mg as originally proposed and tested in pediatric studies.

The proposed posology in this patient group is tiered by body weight. The recommended doses are 300 mg Q4W with the possibility to increase to 200 mg Q2W (15 kg to < 60 kg), following a loading dose of 300 mg (one 300 mg injection), followed by a second injection of 300 mg 2 weeks later (600 mg loading in total) before staring the Q4W program after 4 weeks.

For patients of this age group (⩾6 to <12 years) weighing ⩾60 kg, the proposed dose regimen is 300 mg Q2W following a loading dose of 600 mg which is equal to the dose regimen in adults and adolescents weighing ⩾60 kg.

## *2.4. Clinical efficacy*

The phase 3, placebo-controlled, pivotal study R668-AD-1652 provides the primary efficacy evaluation in children ≥6 to <12 years of age with AD and is the focus of discussion in this section. The phase 3 OLE study R668-AD-1434 provides additional data to support long-term efficacy in children of this age group

who had participated in a previous dupilumab AD clinical study. The phase 2a open-label PK study R668-AD-1412 provides additional supportive efficacy information.

Studies R668-AD-1434 and R668-AD-1412 allowed, but did not require, concomitant use of topical treatments; therefore, the efficacy data from these studies support the use of dupilumab with or without topical treatment.

In addition, a comparison of the efficacy data in children with that of the adolescent and adult populations is provided.

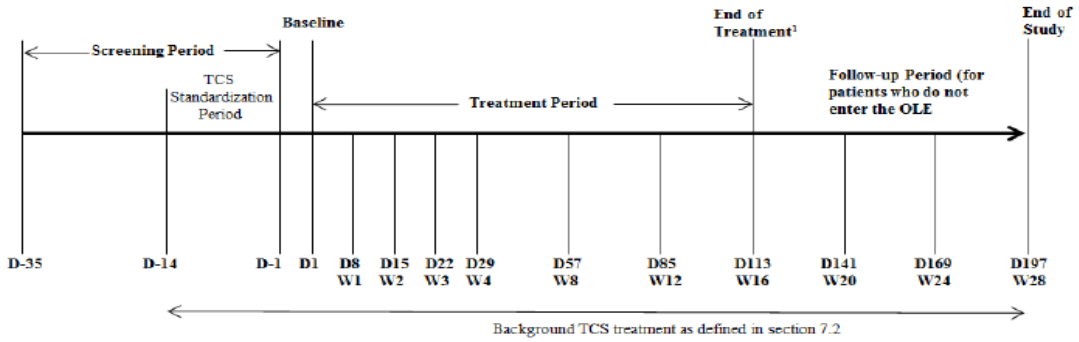
## 2.4.1. Main study

### R668-AD-1652 - Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 16-week Treatment Duration Monotherapy Study

#### Methods

Study R668-AD-1652 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in children ≥6 to <12 years of age with severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable (eg, intolerance, other important side effects, or safety risks). The primary objective of the study was to demonstrate the efficacy of dupilumab in combination with TCS after 16 weeks of treatment in patients ≥6 to <12 years of age with severe AD.

Study Flow Diagram




The study consisted of the following 3 periods: screening of up to 9 weeks, a TCS standardization period of 2 weeks, a treatment period of 16 weeks, and a follow-up period of 12 weeks (for patients who did not enter the OLE). Patients were offered the opportunity to screen for the pediatric OLE study at the end of treatment. Patients who declined to participate in the OLE study were followed for 12 weeks after completion of treatment.

Starting on day −14, all patients initiated a standardized TCS treatment regimen with a medium potency TCS, with adjustments based on clinical response. The use of other concurrent topical therapies for AD was not permitted. However, if medically necessary (ie, IGA score = 4 or to control intolerable AD symptoms), rescue treatment for AD could be provided to study patients as needed at the discretion of the investigator.

#### *Study Participants*

Key Eligibility Criteria

The inclusion/exclusion criteria for R668-AD-1652 were designed to ensure that only children with severe AD, whose disease was not adequately controlled with topical treatment, were included. In addition,

patients with other concomitant diseases or conditions that may have confounded efficacy and safety assessments were excluded from the studies.

The inclusion criteria for this population of children specified male and female patients ≥6 to <12 years of age with chronic AD (present for at least 1 year and meeting the American Academy of Dermatology Consensus Criteria (Eichenfield, 2014). Following a 2-week TCS standardization period, required baseline AD severity scores for eligibility were IGA score = 4, EASI score ≥21, ≥15% BSA involvement with AD, and worst itch weekly average score for maximum itch intensity ≥4.

Patients were also required either to have a documented recent history (within 6 months before the screening visit) of an inadequate response to treatment with topical medications. An inadequate response was defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days. Patients with documented systemic treatment for AD (systemic immunosuppressant drugs such as ciclosporin, MTX, corticosteroids, etc) in the past 6 months were also considered inadequate responders to topical treatments and were potentially eligible for treatment with dupilumab after an appropriate washout period. In addition to application of TCS throughout the study, all patients were required to apply a stable dose of topical emollient (moisturizer) twice daily for at least 7 consecutive days before the baseline visit and throughout the study.

Exclusion criteria designed to prevent confounding of efficacy results included prior participation in a dupilumab clinical study, treatment with any other systemic investigational product, treatment with a topical investigational drug, crisaborole, or TCI within 2 weeks prior to baseline visit, treatment with systemic immunosuppressive/immunomodulating agent or phototherapy for AD within 4 weeks prior to baseline visit, treatment with any cell-depleting agent within 6 months of baseline visit or other biologics within 5 half-lives or 16 weeks, planned use of any prohibited medications or procedures during the treatment period, and presence of any skin comorbidities that could interfere with study assessments.

Exclusion criteria included a baseline body weight <15 kg, known or suspected immunodeficiency, active infections including hepatitis B, hepatitis C, and endoparasitic infections, and treatment with a live vaccine within 4 weeks of the baseline visit.

### *Treatments*

- dupilumab every 2 weeks (Q2W) treatment group:
  - Patients with baseline weight <30 kg received Q2W SC injections of 100 mg dupilumab from week 2 to week 14, following a loading dose of 200 mg on day 1.
  - Patients with baseline weight ≥30 kg received Q2W SC injections of 200 mg dupilumab from week 2 to week 14, following a loading dose of 400 mg on day 1
- dupilumab every 4 weeks (Q4W) treatment group: all patients regardless of weight received Q4W SC injections of 300 mg dupilumab from week 4 to week 12, following a loading dose of 600 mg on day 1.
- placebo treatment group: patients received matching placebo (including doubling the amount of placebo on day 1 to match the loading dose). To maintain blinding, the patients in the <30 kg weight stratum were randomly assigned to receive, in a 1:1 ratio, either Q2W SC injections of placebo matching the 100 mg dupilumab or Q4W SC injections of placebo matching the 300 mg dupilumab. In the ≥30 kg weight stratum, the patients randomized to the placebo group received, in a 1:1 ratio, either Q2W SC injections of placebo matching the 200 mg dupilumab or Q4W SC injections of placebo matching the 300 mg dupilumab.

The study consisted of a 16-week treatment period and a 12-week post-treatment follow-up period.

*Rescue medication*

If medically necessary (ie, IGA score = 4 or to control intolerable AD symptoms), rescue treatment for AD could be provided to study patients as needed at the discretion of the investigator. These rescue therapies included topical therapies (eg, high-potency TCS) as well as oral/systemic medications like corticosteroids and non-steroidal immunosuppressive drugs (eg, cyclosporin, methotrexate [MTX], mycophenolate-mofetil, or azathioprine) for patients who did not respond adequately after at least 7 days of topical treatment.

## *Objectives*

The primary objective of the study was to demonstrate the efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS) in patients ≥6 years to <12 years of age with severe atopic dermatitis (AD). The secondary objective of the study was to assess the safety of dupilumab administered concomitantly with TCS in patients ≥6 years to <12 years of age with severe AD.

## *Outcomes/endpoints*

Primary and Secondary Endpoints

The co-primary endpoints were:

- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16.

The key secondary endpoints were:

- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily worst itch score

Other secondary endpoints were (summary)

- Change from baseline to week 16 in weekly average of daily worst itch score
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Change from baseline to week 16 in percent Body Surface Area (BSA) affected by AD
- Percent change from baseline to week 16 in Scoring Atopic Dermatitis (SCORAD)
- Change from baseline to week 16 in Children's Dermatology Life Quality Index (CDLQI)
- Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)
- Change from baseline to week 16 in Dermatitis Family Index (DFI)
- Change from baseline to week 16 in Patient Reported Outcomes Measurements
- Information Systems (PROMIS) paediatric anxiety short form scale score
- Change from baseline to week 16 in PROMIS paediatric depressive symptoms short form scale score
- Topical treatment for AD – proportion of TCS medication-free days from baseline to week 16
- Mean weekly dose of TCS in grams for medium potency TCS from baseline to week 16
- Mean weekly dose of TCS in grams for high potency TCS from baseline to week 16
- Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16
- Incidence of serious TEAEs through week 16.

Pharmacokinetic Variables

Concentration of functional dupilumab in serum at each time point will be considered to be

- trough values (Ctrough. timepoint).

Anti-Drug Antibody Variables

- Numerous Anti-drug (dupilumab) antibody variables include status (positive or negative) and titer

## Sample size

Overall 240 patients were planned to be enrolled. With 80 Patients per group and a 2-sided 5% significance level, the study can fulfil the following power considerations:

- 97% power to detect a difference between dupilumab Q2W treatment and placebo treatment (both in combination with TCS) in the percentage of IGA score 0 or 1 at week 16, assuming that the percentages are 28% and 5% for dupilumab Q2W and placebo.
- 87% power to detect a difference between dupilumab Q4W treatment and placebo treatment (both in combination with TCS) in the percentage of IGA score 0 or 1 at week 16, assuming that the percentages are 22% and 5% for dupilumab 300 mg Q4W and placebo.
- 99% power to detect a difference in the percentage of patients achieving EASI-75 response at week 16, assuming that the percentages are 68% and 17% for dupilumab Q2W and placebo (both in combination with TCS)
- 99% power to detect a difference in the percentage of patients achieving EASI-75 response at week 16, assuming that the percentages are 62% and 17% for dupilumab Q4W and placebo (both in combination with TCS).

With amendment 3 of the protocol, the sample size was changed from 240 to 330 patients due to potential unblinding of 68 patients.

## Randomisation

Randomization was to be stratified by region (North America and Europe) and baseline weight group (<30 kg and ≥30 kg) to one of the three treatment groups in 1:1:1 allocation. Randomization was performed according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS) to the designated study pharmacist (or qualified designee).

Placebo patients were to receive a matched placebo, including the different doses depending on body weight. Patients in the <30 kg weight stratum were randomly assigned to receive, in a 1:1 ratio, either Q2W SC injections of placebo (0.7 mL) matching the 100 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo (2 mL) matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). Corresponding to that patients with weight ≥ 30 kg were randomized with the same procedure.

## Blinding (masking)

With the exception of the IDMC members, this study remained blinded to all individuals until the prespecified unblinding to conduct the primary analyses.

## Statistical methods

The full analysis set (FAS) includes all randomized patients. The modified full analysis set (mFAS) includes all randomized patients excluding potentially unblinded patients. The primary efficacy analysis population was to be the FAS. Patients were to be analysed as ITT. The mFAS was to be used in a sensitivity analysis for the primary analysis end for selected secondary endpoints.

Primary endpoints were the proportion of patients with EASI-75 at week 16 and the proportion of patients with IGA 0 or 1 at week 16. Further 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 itch score.

Primary endpoints were to be analysed by Cochran-Mantel-Haenszel test stratified for randomization strata was used. For these binary variables withdrawals and patients that were treated by rescue

medication were to be analysed as a non-responder. As a sensitivity analysis, patients that were treated by rescue medication were to be analysed regardless of rescue medication. As a further sensitivity analysis missing values were imputed by last observation carried forward (LOCF).

Continuous variables as the key secondary variables were to be analysed by ANCOVA stratified by region and weight group. Missing values were to be imputed by multiple imputation, where treatment group, randomisation strata and relevant baseline characteristics were used as covariates in the regression model used for the imputation. Data that were collected after rescue medication was to be treated as missing and imputed by multiple imputation. As a sensitivity analysis, patients that were treated by rescue medication were to be analysed regardless of rescue medication. A further sensitivity analysis was to be performed by imputing missing values by LOCF.

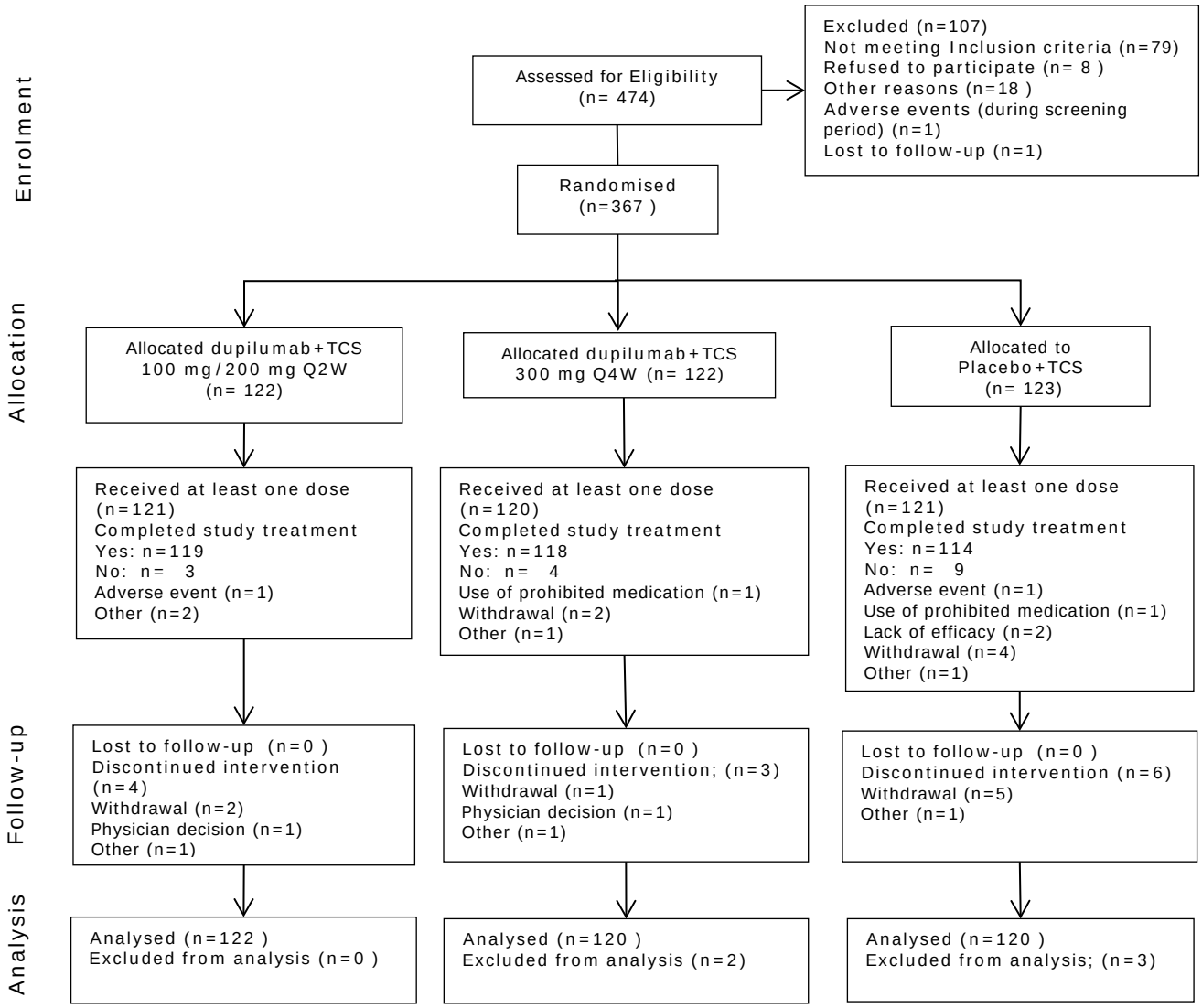
Secondary endpoints that were binary were to be analysed with the same approach as the primary analysis.

Multiple testing was to be considered by the following hierarchical testing procedure:

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

*Results*

## Participant flow




[Not meeting the inclusion /exclusion criteria (n=79); Withdrawal by patient (n=8); Other reasons (n=18)]

## Recruitment

Study Initiation Date: 17 November 2017

Cut-off date for Clinical Study Report: 28 June 2019

## Conduct of the study

### Changes to the conduct of the study

There were 3 amendments to the main study protocol (original dated 28 Feb 2017) and additional country-specific amendments for Germany and the Czech Republic. Amendment 2 only corrected the study number in the header of certain sections of the document and thus is not included in the table below. Amendment 3 for Germany was only submitted to IRBs/ECs and health authorities and implemented at sites that were continuing to enroll patients into the study.

### Changes to the Planned Analyses

The planned other secondary efficacy endpoint of mean weekly dose of TCS in grams for high-potency TCS from baseline to week 16 was not evaluated as part of this CSR. During this study, all patients initiated a standardized TCS treatment regimen with a medium-potency TCS. Use of high-potency TCS was not allowed except as rescue treatment. As a result of the potential unblinding of study site personnel to the treatment assignment for 68 patients, the mFAS was included as an efficacy analysis set.The mFAS includes all randomized patients but excludes patients potentially unblinded to study site personnel. The primary endpoint, co-primary endpoint, and selected secondary endpoints were evaluated in the mFAS as sensitivity analyses.

### Protocol deviations

Overall, 14 (11.4%) patients in the placebo + TCS group, 12 (9.8%) patients in the dupilumab Q4W + TCS group, and 15 (12.3%) patients in the Q2W + TCS group had at least 1 major protocol deviation. The most common type of major protocol deviation was inclusion criteria not met but patient randomized (11/367; 3.0% overall). The incidence of each of the other major protocol deviation categories was low (≤2% overall across the treatment groups) and similar for all treatment groups. The primary efficacy endpoints were evaluated as a supportive analysis using the per-protocol set (PPS), which excluded patients with those major protocol violations deemed to potentially impact the assessment of efficacy. Although not considered a protocol deviation per se, due to an inadvertent operational error, some sites received a packing list accompanying the IMP resupply shipment that had product description written in an open-label fashion.

## Baseline data

A total of 474 patients were screened for study eligibility, 367 of whom were enrolled and randomized in a 1:1:1 ratio. The most common causes for patients failing screening were inclusion/exclusion criteria not met and “other.” A high proportion of the patients completed the study treatment (95.6%). The proportion of patients who did not complete the study treatment was higher in the placebo + TCS group (7.3%) than in the combined dupilumab treatment group (2.9%). No patients in any treatment group withdrew from study treatment due to lack of efficacy. At the time of the data cut-off (28 Jun 2019), most randomized patients (96.2%, with approximately an equal number of patients from each of the 3 treatment arms), transitioned into the R668-AD-1434 OLE study.

### Demographics

Patient demographic characteristics were balanced among the treatment groups. More than half of patients were white (69.2%) but other races and ethnicities were adequately represented in the patient population. The patient population was balanced with respect to sex. The mean (SD) age of the patients

was 8.5 (±1.72) years. The number of patients in the 2 age subgroups (≥6 to <9 and ≥9 to <12 years of age) was balanced across the 3 treatment groups.

Randomization was stratified by baseline weight with a required weight distribution of 50% of patients <30 kg and 50% ≥30 kg. The mean weight of patients was 31.5 kg, with 50.4% <30 kg and 49.6% 30 kg.

### Baseline Disease Characteristics

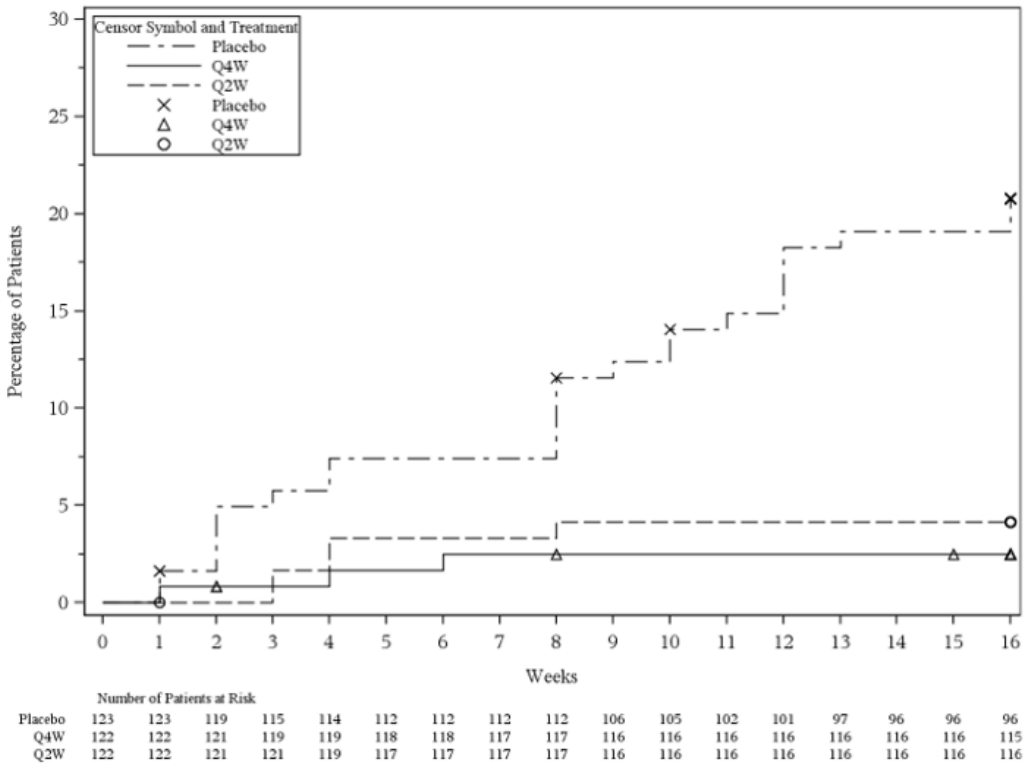
Overall, baseline disease characteristics were similar between the placebo + TCS and combined dupilumab + TCS treatment group with respect to the extent of disease, the intensity of signs, severity of symptoms, and the duration of AD.

### Rescue Medications

Approximately 3.3% of the patients received rescue mediation during the 16-week treatment. A higher proportion of patients in the placebo + TCS group received at least 1 rescue medication during the 16-week treatment period (19.5%) compared to the dupilumab 300 mg Q4W + TCS group 2.5%) and dupilumab Q2W + TCS group (4.1%).

By week 2, a higher proportion of patients in the placebo group than the dupilumab + TCS treatment groups received systemic or topical rescue medications and among the dupilumab + TCS treatment groups the Q2W + TCS group had a higher rate of rescue medication use than the Q4W + TCS group by week 3. Kaplan-Meier curves of time to first rescue treatment (topical or systemic) are shown in Figure 28. Less than 20% of patients in any treatment group required rescue treatment.

Figure 28: Kaplan-Meier Curves of Time to First Rescue Treatment Use During 16-week Treatment Period in Study R668-AD-1652 - FAS




Abbreviations: FAS, full analysis set; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Figure 4.4.1/1

### Treatment Compliance

The mean injection compliance was high overall (≥99.82% in each treatment group) and was similar across the 3 treatment groups.

## Numbers analysed

### Sample Size and Efficacy Analysis Sets

The primary analysis for all efficacy endpoints was performed using the FAS. The FAS included all randomized patients (367) and was analyzed based on the treatment allocated by the interactive voice response system/interactive web response system. Due to the potential unblinding of study site personnel to the treatment assignment of 68 patients, the mFAS was added which excluded data from these patients (19 patients in the placebo + TCS group, 30 patients in the Q2W + TCS group, and 19 patients in the Q4W + TCS group. The mFAS was used for supportive analysis of the primary and co-primary endpoints, key secondary, and selected other secondary endpoints.

## Outcomes and estimation

### Comparison of Efficacy Results of all Studies

This section discusses the primary/co-primary efficacy endpoints, key secondary efficacy endpoints, and other secondary efficacy endpoints of pivotal study R668-AD-1652. As previously noted, a full comparison of efficacy results across R668-AD-1412 and R668-AD-1434 is not included given the many differences between the studies (eg, study design, number of patients, length of treatment period, dose regimens, and the use of concomitant topical therapies).

In the pivotal study, R668-AD-1652, a hierarchical procedure was used to control the overall Type-I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dosing regimens (Q2W and Q4W) versus placebo. Each hypothesis was formally tested only if the preceding one was significant at the 2-sided 0.05 significance level. The hierarchical testing order and an overview of the efficacy results is shown in Table 17. All p-values were <0.0001, except for the proportion of patients with IGA 0 or 1 at week 16 for the 100 mg/200 mg Q2W group in the FAS (p=0.0004).

Superiority of dupilumab (300 mg Q4W and 100/200 mg Q2W) + TCS over placebo + TCS was demonstrated for primary/coprimary endpoints (IGA 0 or 1, EASI-75 [co-primary for EU]) and key secondary endpoints at week 16 (mean percent change in EASI, mean percent change in worst itch score) in the FAS. Statistical significance was also achieved for all remaining other secondary endpoints in the prespecified hierarchy for both dose regimens.

Table 22: Statistical Hierarchy for Multiplicity Control and Overview of Results in Study R668-AD-1652

| Level | Efficacy Endpoints at Week 16 | Placebo + TCS | | Dupilumab[2,3] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 300 mg Q4W+TCS | | | 100/200 mg Q2W+TCS | | |
| | | FAS (N=123) | mFAS (N=104) | | FAS (N=122) | mFAS (N=103) | | FAS (N=122) | mFAS (N=92) |
| Primary | Proportion of patients with IGA 0 or 1 on a 5-point scale), n (%) | 14 (11.4%) | 14 (13.5%) | 7 | 40 (32.8%) | 33 (32.0%) | 1 | 36 (29.5%) | 29 (31.5%) |
| Co-primary[1] | Proportion of patients with EASI-75 (≥75% improvement from baseline), n (%) | 33 (26.8%) | 32 (30.8%) | 8 | 85 (69.7%) | 75 (72.8%) | 2 | 82 (67.2%) | 65 (70.7%) |
| Secondary | Percent change from baseline in EASI, LS mean percent change (SE) | -48.6 (2.46) | -52.6 (2.60) | 9 | -82.1 (2.37) | -82.1 (2.41) | 3 | -78.4 (2.35) | -79.2 (2.54) |
| | Proportion of patients with EASI-50 (≥50% improvement from baseline), n (%) | 53 (43.1%) | 47 (45.2%) | 10 | 111 (91.0%) | 93 (90.3%) | 4 | 101 (82.8%) | 77 (83.7%) |
| | Percent change from baseline in weekly average of daily worst itch score, LS mean percent change (SE) | -25.9 (2.90) | -25.3 (3.11) | 11 | -54.6 (2.89) | -54.3 (3.04) | 5 | -57.0 (2.77) | -54.8 (3.18) |
| | Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4, n (%) | 15 (12.3%) | 14 (13.6%) | 12 | 61 (50.8%) | 51 (50.5%) | 6 | 70 (58.3%) | 51 (56.7%) |
| | Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3, n (%) | 26 (21.1%) | 22 (21.2%) | 15 | 73 (60.3%) | 62 (60.8%) | 13 | 81 (67.5%) | 58 (64.4%) |
| | Proportion of patients with EASI-90 (≥90% improvement from baseline), n (%) | 9 (7.3%) | 9 (8.7%) | 16 | 51 (41.8%) | 47 (45.6%) | 14 | 37 (30.3%) | 32 (34.8%) |
| | Change from baseline in POEM, LS mean change (SE) | -5.3 (0.69) | -5.6 (0.77) | 20 | -13.6 (0.65) | -13.4 (0.71) | 17 | -13.4 (0.65) | -13.4 (0.75) |
| | Change from baseline in CDLQI, LS mean change (SE) | -6.4 (0.51) | -6.4 (0.59) | 21 | -10.6 (0.47) | -10.8 (0.51) | 18 | -10.7 (0.46) | -11.1 (0.54) |

## Primary efficacy endpoints

The proportion of patients with IGA 0 or 1 at week 16 was the primary endpoint for the US and US-reference market countries and a primary endpoint for the EU and EU Reference Market Countries. The proportion of patients with EASI-75 at week 16 was the other co-primary endpoint for the EU and EU Reference Market Countries, and a key secondary endpoint for US and US-reference market countries.

### Proportion of Patients with IGA 0 or 1

The proportion of patients in the FAS with IGA 0 or 1 at week 16 was higher in the dupilumab Q2W + TCS (29.5%) and Q4W + TCS (32.8%) treatment groups than in the placebo + TCS group (11.4%). Both comparisons were considered clinically meaningful and statistically significant ($p=0.0004$ and $p<0.0001$, respectively). The 2 dupilumab + TCS treatment groups (Q2W and Q4W) were comparable with respect to the proportion of patients in the FAS with IGA 0 or 1 at week 16.

Table 23: Proportion of Patients with IGA 0 or 1 at Week 16 in Study R668-AD-1652; Patient Considered Non-Responder after Rescue Treatment Use - FAS

| Treatment | Patients with IGA 0 or 1 at Week 16 n (%) | 95% CI | Difference vs Placebo (%) (95% CI) [1] | P-value vs Placebo [2] | Mantel-Fleiss Criterion vs Placebo [3] |
|---|---|---|---|---|---|
| Dupilumab 100mg or 200mg Q2W + TCS (N=122) | 36 (29.5) | (21.60, 38.44) | 18.1 (8.28, 27.97) | 0.0004 | 24.9 |
| Dupilumab 300mg Q4W + TCS (N=122) | 40 (32.8) | (24.56, 41.87) | 21.4 (11.36, 31.45) | <0.0001 | 26.9 |
| Placebo + TCS (N=123) | 14 (11.4) | (6.36, 18.36) | | | |

[1] Difference is dupilumab minus placebo. CI was calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by region [North America vs Europe] and baseline weight group [<30 kg vs ≥30 kg].
[3] If the value is >5, then Mantel-Fleiss criterion is met.
Note: Values after first rescue treatment used were set to missing. Patients with missing score at week 16 were considered as a non-responder.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.1.1.1/1

In a sensitivity analysis using all observed values, with patients with missing values counted as non-responders, the proportion of patients with IGA 0 or 1 at week 16 was greater in the dupilumab Q2W + TCS treatment group (29.5%) and the dupilumab Q4W + TCS group (33.6%) than the placebo + TCS group (12.2%). Both comparisons were consistent with the primary analysis. Likewise, the sensitivity analysis using the last observation carried forward (LOCF) was consistent with the primary analysis and the sensitivity analysis using all observed values. This showed that the methodology used for handling missing data did not impact the results.

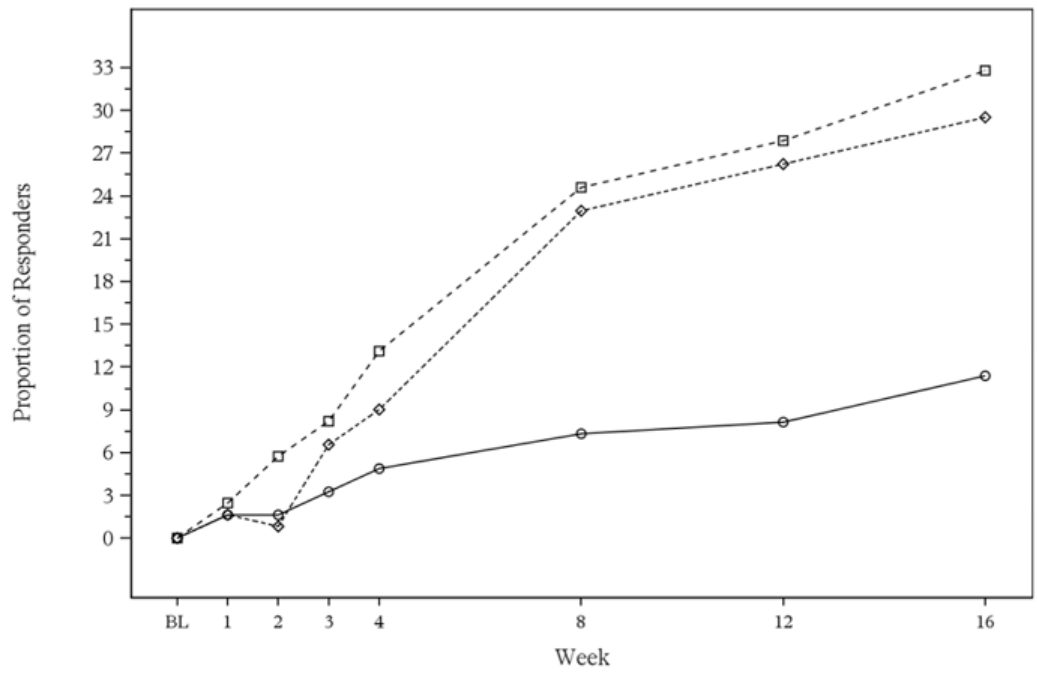
Table 24: Sensivity Analysis of Proportion of Patients Achieving IGA 0 or 1 at Week 16 in Study R668-AD-1652; All Observed Values Regardless of Rescue Treatment Use - FAS

| Treatment | Patients with IGA 0 or 1 at Week 16 n (%) | 95% CI | Difference vs Placebo (%) (95% CI) [1] | P-value vs Placebo [2] |
|---|---|---|---|---|
| Dupilumab 100mg or 200mg Q2W + TCS (N=122) | 36 (29.5) | (21.60, 38.44) | 17.3 (7.37, 27.26) | 0.0008 |
| Dupilumab 300mg Q4W + TCS (N=122) | 41 (33.6) | (25.31, 42.72) | 21.4 (11.23, 31.59) | <0.0001 |
| Placebo + TCS (N=123) | 15 (12.2) | (6.99, 19.32) | | |

[1] Difference is dupilumab minus placebo. CI was calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by region [North America vs Europe] and baseline weight group [<30 kg vs ≥30 kg].
Note: Patients with missing score at each visit were considered as a non-responder.
Abbreviations: CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.1.1.1/5

As shown in Figure 5 the proportion of patients achieving IGA scores of 0 or 1 was numerically higher in the dupilumab Q4W + TCS and Q2W + TCS treatment groups than in the placebo group beginning at week 2 and week 3, respectively. The separation was sustained throughout the 16 weeks of the treatment period. The 2 dupilumab +TCS treatment groups were generally comparable with respect to this outcome, with the Q4W + TCS group having a slightly higher percentage of responders than the Q2W + TCS group starting at approximately week 2 (5.7% vs 0.8%, respectively) through week 16 (32.8% vs 29.5%, respectively).

Figure 29: Proportion of Patients Achieving IGA 0 or 1 Through Week 16 in Study R668-AD-1652-FAS




Number of responder

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo (N=123) | 0 | 2(2) | 2(2) | 4(3) | 6(5) | 9(7) | 10(8) | 14(11) |
| Q4W (N=122) | 0 | 3(2) | 7(6) | 10(8) | 16(13) | 30(25) | 34(28) | 40(33) |
| Q2W (N=122) | 0 | 2(2) | 1(1) | 8(7) | 11(9) | 28(23) | 32(26) | 36(30) |

Note: Values after first rescue treatment used were set to missing. Patients with missing score at each visit were considered as a non-responder

Abbreviations: BL, baseline; FAS, full analysis set; IGA, Investigator's Global Assessment; Q2W, every 2 weeks; Q4W, every 4 weeks.

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 Q2W + TCS (67.2%) and Q4W + TCS (69.7%) groups than in the placebo + TCS group (26.8%). Both comparisons were clinically meaningful and statistically significant ($p<0.0001$). The dupilumab Q2W + TCS group was comparable to the dupilumab Q4W + TCS group for the proportion of patients with EASI-75 at week 16.

Table 25: Proportion of Patients Achieving EASI-75 **(≥75%** improvement from Baseline) at Week 16 in Study R668-AD-1652; Patient Considered Non-Responder After Rescue Treatment Use - FAS

| Treatment | Patients with EASI-75 at Week 16 n (%) | 95% CI | Difference vs Placebo (%) (95% CI) [1] | P-value vs Placebo [2] | Mantel-Fleiss Criterion vs Placebo [3] |
|---|---|---|---|---|---|
| Dupilumab 100mg or 200mg Q2W + TCS (N=122) | 82 (67.2) | (58.13, 75.44) | 40.4 (28.95, 51.82) | <0.0001 | 53.7 |
| Dupilumab 300mg Q4W + TCS (N=122) | 85 (69.7) | (60.70, 77.67) | 42.8 (31.54, 54.15) | <0.0001 | 54.3 |
| Placebo + TCS (N=123) | 33 (26.8) | (19.24, 35.57) | | | |

[1] Difference is dupilumab minus placebo. CI was calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by region [North America vs Europe] and baseline weight group [<30 kg vs ≥30 kg].
[3] If the value is >5, then Mantel-Fleiss criterion is met.
Note: Values after first rescue treatment used were set to missing. Patients with missing score at week 16 were considered as a non-responder
Abbreviations: CI, confidence interval; EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; FAS, full analysis set; Q2W, every 2 weeks, Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.1.2.1/1

## Key secondary endpoints

The proportion of patients with EASI-75 at week 16 was a key secondary endpoint for the US and US reference market countries and a co-primary endpoint for EU and EU reference market countries. This endpoint is presented above.

### Percent Change in EASI Score from Baseline to Week 16

The least square (LS) mean percent change (reduction indicates improvement) from baseline to week 16 in EASI score was greater in the dupilumab Q2W + TCS (−78.4%) and Q4W + TCS (−82.1%) groups than in the placebo + TCS group (−48.6%) (Table 26). The LS mean difference in the percent change from baseline to week 16 in EASI score was clinically meaningful and statistically significant between each dupilumab + TCS group versus the placebo + TCS group ($p<0.0001$). The dupilumab Q2W + TCS group was comparable to the dupilumab Q4W + TCS group for the mean percent change in EASI score from baseline to week 16.

Table 26: Primary Analysis of Percent Change from Baseline in EASI Score at Week 16 in Study R668-AD-1652; MI Method with Data Set to Missing After Rescue Treatment Use -FAS

| Treatment | LS Mean %Change (SE) | LS Mean %Change 95% CI | Mean %Change (SD) | Baseline Mean (SD) | Number of Observed/ Imputed Subjects | Contrast | P-value [1] | LS Mean Difference (95% CI) [1] |
|---|---|---|---|---|---|---|---|---|
| Dupilumab 100 mg or 200 mg Q2W + TCS (N=122) | -78.4 (2.35) | (-83.0 , -73.8) | -77.6 (19.49) | 37.29 (10.862) | 116/6 | Dupilumab 100 mg or 200 mg Q2W + TCS vs Placebo + TCS | <0.0001 | -29.8 (-36.33, -23.24) |
| Dupilumab 300 mg Q4W + TCS (N=122) | -82.1 (2.37) | (-86.7 , -77.4) | -81.2 (16.52) | 37.35 (12.450) | 116/6 | Dupilumab 300 mg Q4W + TCS vs Placebo + TCS | <0.0001 | -33.4 (-40.06, -26.82) |
| Placebo + TCS (N=123) | -48.6 (2.46) | (-53.4 , -43.8) | -47.7 (33.54) | 38.96 (12.012) | 95/28 | | | |

Note: No imputation will be made for patients with baseline missing.
[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] and baseline weight group [<30 kg vs ≥30 kg]) as fixed factors.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; LS, least squares; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.2.1.1/1

### Percent Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch Score from Baseline to Week 16

The LS mean percent change (reduction indicates improvement) from baseline to week 16 in weekly average of daily worst itch score was greater in the dupilumab Q2W + TCS (−57.0%) and Q4W + TCS (−54.6%) groups than in the placebo + TCS group (−25.9%)- The LS mean difference in the percent

change from baseline to week 16 in worst itch score was statistically significant between each dupilumab + TCS group and the placebo + TCS group (p<0.0001). The dupilumab Q2W + TCS group was comparable to the dupilumab Q4W + TCS group for the percent change from baseline in weekly average of worst itch score at week 16.

Table 27: Primary Analysis of Percent Change from Baseline in Weekly Average of Daily Worst Itch Score at Week 16 in Study R668-AD-1652; MI Method with Censoring After Rescue Treatment Use - FAS

| Treatment | LS Mean %Change (SE) | LS Mean %Change 95% CI | Mean %Change (SD) | Baseline Mean (SD) | Number of Observed/ Imputed Subjects | Contrast | P-value [1] | LS Mean Difference (95% CI) [1] |
|---|---|---|---|---|---|---|---|---|
| Dupilumab 100 mg or 200 mg Q2W + TCS (N=122) | -57.0 (2.77) | (-62.4 , -51.5) | -56.5 (28.24) | 7.78 (1.521) | 111/9 | Dupilumab 100mg or 200mg Q2W + TCS vs Placebo + TCS | <0.0001 | -31.0 (-38.76, -23.26) |
| Dupilumab 300 mg Q4W + TCS (N=122) | -54.6 (2.89) | (-60.3 , -48.9) | -54.1 (29.23) | 7.81 (1.583) | 112/10 | Dupilumab 300 mg Q4W + TCS vs Placebo + TCS | <0.0001 | -28.6 (-36.47, -20.82) |
| Placebo + TCS (N=123) | -25.9 (2.90) | (-31.6 , -20.3) | -25.4 (27.68) | 7.73 (1.540) | 93/30 | | | |

[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] and baseline weight group [<30 kg vs ≥30 kg]) as fixed factors.
Note: No imputation will be made for patients with baseline missing.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; LS, least squares; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.2.2.1/1

## Other Secondary Efficacy Endpoints

### Proportion of Patients with Improvement (Reduction ≥4 Points) of Weekly Average of Daily Worst Itch Score from Baseline to Week 16

The proportion of patients in the FAS achieving a reduction of ≥4 points from baseline in the weekly average of daily worst itch score at week 16 was higher in the dupilumab Q2W + TCS (58.3%) and Q4W + TCS (50.8%) groups than in the placebo + TCS group (12.3%). Both comparisons were statistically significant (p<0.0001). The dupilumab Q2W + TCS group had a numerically greater response than the dupilumab Q4W + TCS group for the proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of daily worst itch score at week 16.

Table 28: Primary Analysis of Proportion of Patients Achieving Reduction of ≥4 Points from Baseline in Weekly Average of Faily Worst Itch Score at Week 16 in Study R668-AD-1652; Patients Considered Non-Responder After Rescue Treatment Use – FAS

| Treatment | Patients with Reduction of NRS Score from Baseline ≥4 at Week 16 n/N1(%) | 95% CI | Difference vs Placebo (%) (95% CI) [1] | P-value vs Placebo [2] |
|---|---|---|---|---|
| Dupilumab 100mg or 200mg Q2W + TCS (N=122) | 70/120 (58.3) | (48.98, 67.26) | 46.0 (35.47, 56.61) | <0.0001 |
| Dupilumab 300mg Q4W + TCS (N=122) | 61/120 (50.8) | (41.55, 60.07) | 38.5 (27.86, 49.21) | <0.0001 |
| Placebo + TCS (N=123) | 15/122 (12.3) | (7.05, 19.47) | | |

[1] Difference is dupilumab minus placebo. CI was calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by region [North America vs Europe] and baseline weight group [<30 kg vs ≥30 kg].
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 score at week 16 were considered as a non-responder.
Abbreviations: CI, confidence interval; FAS, full analysis set; NRS, Numeric Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Table 6.2.4.1/1

## Ancillary analyses

### Efficacy Data Supporting the Dose Recommendation

The efficacy data from the phase 3 study (R668-AD-1652) show that both dupilumab dose regimens, Q2W (100 mg in patients <30 kg, 200 mg in patients ≥30 kg + TCS) and Q4W (300 mg Q4W + TCS; all patients irrespective of body weight) result in statistically significant, clinically meaningful improvements in signs, symptoms, and quality of life in children ≥6 to <12 years of age with severe AD. Comparison of the efficacy responses between the Q2W + TCS and Q4W + TCS dose regimens on the primary and key secondary endpoints suggested that the regimens used in the 2 arms were similar on the continuous endpoints (mean % change in EASI score from baseline, mean % change in worst itch score from baseline) and the categorical endpoints (IGA 0 or 1, worst itch score reduction of ≥3 or ≥4 points from baseline). The regimens used in the 2 arms were also similar for other secondary endpoints like EASI-50 and EASI-90.

In patients <30 kg, the 100 mg Q2W regimen was underperforming compared to the 300 mg Q4W regimen. The proportion of patients who achieved the primary endpoint of IGA 0 or 1 at week 16 in the <30 kg dupilumab 100 mg Q2W + TCS group was 13/63 (20.6%) whereas 18/61 (29.5%) patients weighing <30 kg who received 300 mg Q4W + TCS achieved IGA 0 or 1 at week 16. A similar trend favoring the 300 mg Q4W dose over the 100 mg Q2W in the <30 kg weight strata were observed for the endpoints of percent change in EASI, proportion of patients achieving EASI-50, proportion of patients achieving EASI-90, and percent change in SCORAD.

In the ≥30kg weight stratum, numerical differences in efficacy favoring the 200 mg Q2W dose regimen in contrast to the 300 mg Q4W dose regimen were observed, particularly with respect to pruritus.

Although the objective of the weight-tiered regimen in R668-AD-1652 was to normalize exposure across weight groups and achieve trough concentration at steady state ($C_{trough,ss}$) comparable to the 300 mg Q2W dose in adults, the 100 mg Q2W regimen in children <30 kg resulted in lower observed mean trough concentrations at week 16 (62.6 mg/L) compared to the 200 mg Q2W regimen in children ≥30 kg (86.0 mg/L).

According to the MAH, both efficacy data as analyzed by baseline weight strata and clinical pharmacology data support the proposed posology in patients ≥6 to <12 years of age with AD: in those ≥15 to <30 kg, an initial dose of 600 mg followed by 300 mg Q4W; in those ≥30 to <60 kg, an initial dose of 400 mg followed by 200 mg Q2W. For children ≥6 to <12 years of age weighing ≥60 kg, the proposed dose regimen is 300 mg Q2W following an initial dose of 600 mg, since weight is the primary covariate affecting the PK of dupilumab and this dose regimen has been proven to achieve the desired effective exposure and efficacy responses in adults and adolescents weighing >60 kg.

Table 29: Supportive Analysis of Efficacy Results at Week 16 by Baseline Weight Group in Study R668-AD-1652, Patient Considered Non-Responder After Rescue Treatment Use - FAS

| Efficacy Endpoints at Week 16 | Placebo + TCS | | Dupilumab + TCS | | | |
|---|---|---|---|---|---|---|
| | | | <30 kg | | ≥30 kg | |
| | <30 kg | ≥30 kg | 300 mg Q4W | 100 mg Q2W | 300 mg Q4W | 200 mg Q2W |
| | (N=61) | (N=62) | (N=61) | (N=63) | (N=61) | (N=59) |
| Proportion of patients with IGA 0 or 1 on a 5-point scale), n (%)[a,c] | 8 (13.1%) | 6 (9.7%) | 18 (29.5%) (p=0.0277) | 13 (20.6%) (p=0.2663) | 22 (36.1%) | 23 (39.0%) |
| Proportion of patients with EASI-75 (≥75% improvement from baseline), n (%)[a,c] | 17 (27.9%) | 16 (25.8%) | 46 (75.4%) | 38 (60.3%) | 39 (63.9%) | 44 (74.6%) |
| Percent change from baseline in EASI, LS mean percent change (SE)[b,d] | -49.1 (3.30) | -48.3 (3.63) | -84.3 (3.08) | -76.7 (3.04) | -79.9 (3.57) | -80.4 (3.61) |
| Percent change from baseline in weekly average of daily worst itch score, LS mean percent change (SE) [b,d] | -27.0 (4.24) | -25.0 (3.95) | -55.1 (3.94) | -56.1 (3.86) | -54.3 (4.19) | -58.2 (4.01) |
| Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4, n (%)[a,c] | 7/60 (11.7%) | 8/62 (12.9%) | 33/61 (54.1%) | 35/63 (55.6%) | 28/59 (47.5%) | 35/57 (61.4%) |
| Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥3, n (%)[a,c] | 11/61 (18.0%) | 15/62 (24.2%) | 38/61 (62.3%) | 43/63 (68.3%) | 35/60 (58.3%) | 38/57 (66.7%) |
| Proportion of patients with EASI-50 (≥50% improvement from baseline), n (%)[a,c] | 26 (42.6%) | 27 (43.5%) | 58 (95.1%) | 50 (79.4%) | 53 (86.9%) | 51 (86.4%) |
| Proportion of patients with EASI-90 (≥90% improvement from baseline), n (%)[a,c] | 4 (6.6%) | 5 (8.1%) | 28 (45.9%) | 16 (25.4%) | 23 (37.7%) | 21 (35.6%) |

One patient with baseline weight <30 kg who was mis-randomized to 200 mg dupilumab Q2W was summarized in baseline weight <30 kg 100mg dupilumab Q2W group.
Note: Subgroup-by-weight analysis were not tested formally in the testing hierarchy. All nominal p-values (vs placebo) were ≤0.005, except for the proportion of patients <30 kg with IGA 0 or 1 at week 16 for the 300 mg Q4W group (nominal p=0.0277) and the 100 mg Q2W group (nominal p=0.2663).
[a] Note: Value after first rescue treatment used were set to missing. Patients with missing score at each visit were considered as a non-responder.
[b] Note: No imputation was made for patients with baseline missing.
[c] Difference is dupilumab minus placebo (within weight stratum). For calculation of CI and p-value, Chi-square test was used.
[d] 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]) as fixed factors.
Abbreviations: ANCOVA, analysis of covariance; CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; EASI, Eczema Area and Severity Index; EASI-50, 50% reduction in EASI; EASI-75, 75% reduction in EASI; EASI-90, 90% reduction in EASI; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Post-text Tables 12.1.1/2, 12.1.2/1, 12.1.2/2, 12.1.2/3, 12.1.2/4, 12.1.2/5, 12.1.2/6, 12.1.2/7, 12.1.2/8, and 12.1.2/9

## *Summary of main study(ies)*

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 30: Summary of Efficacy for trial R668-AD-1652

| Title: Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 15-week Treatment duration Monotherapy Study | | |
|---|---|---|
| Study identifier | R668-AD-1652 | |
| Design | Randomized, Phase III study, Double-blind, Placebo-Controlled, multicenter Study | |
| | Duration of main phase: | 16 weeks treatment period |

| | | | |
|---|---|---|---|
| | Duration of Run-in phase:<br>Duration of Extension phase: | | 17 Nov 2017<br>Ongoing (R668-AD-1434) |
| Hypothesis | Superiority | | |
| Treatments groups | Dupilumab Q2W + TCS | | Patients with baseline weight <30 kg: Q2W SC injections of 100 mg dupilumab from week 2 to week 14, following a loading dose of 200 mg on day 1.<br>Patients with baseline weight ⩾30 kg: Q2W SC injections of 200 mg dupilumab from week 2 to week 14, following a loading dose of 400 mg on day 1.<br>N = 122 |
| | Dupilumab Q4W + TCS | | All patients regardless of weight: Q4W SC injections of 300 mg dupilumab from week 4 to week 12, following a loading dose of 600 mg on day 1.<br>N = 122 |
| | Placebo + TCS | | Patients with baseline weight <30 kg: in a 1:1 ratio, either Q2W SC injections of placebo matching the 100 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).<br>Patients with baseline weight ⩾30 kg: in a 1:1 ratio, either Q2W SC injections of placebo matching the 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or Q4W SC injections of placebo matching the 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).<br>N = 123 |
| Endpoints and definitions | Primary endpoint | EASI-75 | Proportion of patients with EASI-75 (⩾75% improvement from baseline) at week 16 |
| | Primary endpoint | IGA 0 or 1 | Proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16 |
| | Key Secondary endpoint | Change in EASI Score | Percent change from baseline in EASI Score from Baseline to Week 16 |
| | Key secondary endpoint | EASI-50 | Proportion of patients with EASI-50 at week 16 |
| | Key secondary endpoint | Change in Weekly Average of Daily Worst Itch Score | Percent Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch Score |

| | | | | | |
|---|---|---|---|---|---|
| | Key-secondary endpoint | Daily worst itch score >= 4 | Proportion of patients with improvement (Reduction) of weekly average of daily worst itch score >= 4 from baseline at week 16 | | |
| Database lock | 28 January 2019 | | | | |
| Results and Analysis | | | | | |
| Analysis description | Primary Analysis | | | | |
| Analysis population and time point description | Intent to treat | | | | |
| Descriptive statistics and estimate variability | Treatment group | Dupilumab Q2W + TCS | Dupilumab Q4W + TCS | Placebo +TCS | |
| | Number of subject | 122 | 122 | 123 | |
| | EASI-75 (%) | 67.2 | 69.7 | 26.8 | |
| | 95%CI | 58.1; 51.8 | 60.7; 77.7 | 19.2; 35.6 | |
| | IGA 0 or 1 (%) | 29.5 | 32.8 | 11.4 | |
| | 95%CI | 21.6; 38.4 | 24.6; 41.9 | 6.4; 18.4 | |
| | EASI-50 (%) | 82.8 | 91.0 | 43.1 | |
| | 95% CI | (74.9, 89.0) | (84.4, 95.4) | (34.2, 52.3) | |
| | Change in EASI Score, LS Mean % Change (SD) | -78.4 (2.35) | -82.1 (2.37) | -48.6 (2.46) | |
| | 95%CI | (-83.0, -73.8) | (-86.7, -77.4) | (-53.4, -43.8) | |
| | Change in Weekly Average of Daily Worst Itch Score, LS Mean % Change (SD) | -57.0 (2.77) | -54.6 (2.89) | -25.9 (2.90) | |
| | 95%CI | (-62.4, -51.5) | (-60.3, -48.9) | (-31.6, -20.3) | |
| | Daily worst itch score >= 4 | 58.3 | 50.8 | 12.3 | |
| | 95%CI | (49.0, 67.3) | (41.6, 60.1) | (7.1, 19.5) | |
| Effect estimate per comparison | Primary endpoint<br><br>EASI-75 | Comparison groups | Dupilumab Q2W vs. Placebo | Dupilumab Q4W vs. Placebo | |
| | | Response rate difference | 40.4 | 42.8 | |
| | | 95%CI | 29.0; 51.8 | 31.5; 54.1 | |

| | | | | |
|---|---|---|---|---|
| | | P-value | <0.0001 | <0.0001 |
| | Primary endpoint<br><br>IGA 0 or 1 | Response rate difference | 18.1 | 21.4 |
| | | 95%CI | 8.3; 28.0 | 11.4; 31.5 |
| | | P-value | 0.0004 | <0.0001 |
| | Change in EASI Score, LS Mean Difference | LS Mean Difference | -29.8 | -33.4 |
| | | 95%CI | (-36.33, -23.24) | (-40.06, -26.82) |
| | | P-value | <0.0001 | <0.0001 |
| | EASI-75 | LS Mean Difference | 39.7 | 47.9 |
| | | 95%CI | (28.68, 50.72) | (37.77, 58.01) |
| | | P-value | <0.0001 | <0.0001 |
| | Change in Weekly Average of Daily Worst Itch Score | LS Mean Difference | -31.0 | -28.6 |
| | | 95%CI | (-38.76, -23.26) | (-36.47, -20.82) |
| | | P-value | <0.0001 | <0.0001 |
| | Daily worst itch score >= 4 | LS Mean Difference | 46.0 | 38.5 |
| | | 95%CI | (35.5, 56.6) | (27.9, 49.2) |
| | | P-value | <0.0001 | <0.0001 |
| Notes | The analysis indicates a statistical significant superiority with regard to EASI-75, IGA 0 or 1 and the key secondary endpoints of Dupilumab vs Placebo in the ITT population. | | | |
| Analysis description | Sensitivity analysis for primary analysis on the mFAS population | | | |
| Descriptive statistics and estimate variability | Treatment group | Dupilumab Q2W + TCS | Dupilumab Q4W + TCS | Placebo +TCS |
| | Number of subject | 92 | 103 | 104 |
| | EASI-75 (%) | 70.7 | 72.8 | 30.8 |
| | 95%CI | 60.2; 79.7 | 63.2; 81.1 | 22.1; 40.6 |
| | IGA 0 or 1 (%) | 31.5 | 32.0 | 13.5 |
| | 95%CI | 22.2; 42.0 | 23.2; 42.0 | 7.6; 21.6 |
| Effect estimate per comparison | Co-Primary endpoint<br><br>EASI-75 | Comparison groups | Dupilumab Q2W vs. Placebo | Dupilumab Q4W vs. Placebo |
| | | Response rate difference | 39.9 | 42 |
| | | 95%CI | 27.0; 52.7 | 29.7; 54.4 |
| | | P-value | <0.0001 | <0.0001 |
| | Co-Primary endpoint | Response rate difference | 18.1 | 18.6 |
| | | 95%CI | 6.5; 29.6 | 7.4; 29.7 |

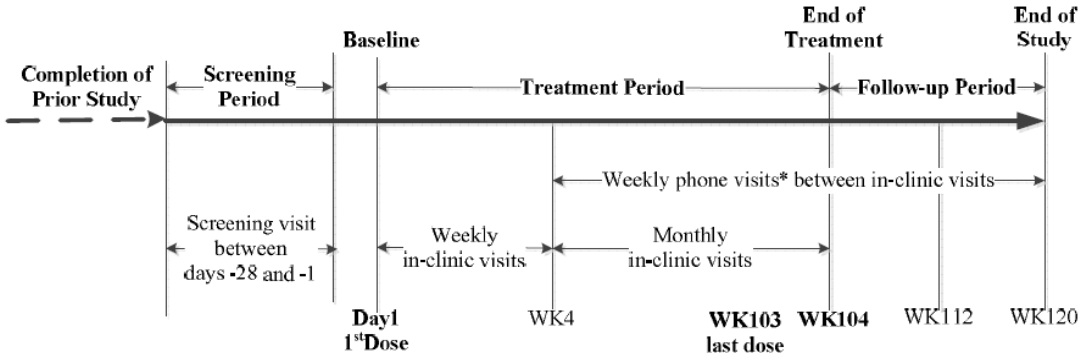
| | | | | |
|---|---|---|---|---|
| | IGA 0 or 1 | P-value | 0.0031 | 0.0013 |
| *Notes* | The sensitivity analysis confirms the result of the primary analysis, where patients that were potentially unblinded were excluded from the analysis. | | | |

## 2.4.2. Supportive studies

R668-AD-1434 An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of Dupilumab in Patients **≥6** Months to <18 Years of Age with Atopic Dermatitis.

This is a phase 3, open-label extension (OLE) study investigating the long term safety, efficacy, pharmacokinetics (PK), and immunogenicity of repeat monthly subcutaneous (SC) doses of dupilumab in paediatric patients with AD who had previously completed a clinical study with dupilumab in patients with AD.
The study was ongoing at the time of data cut-off on 22 Jul 2019. Children ≥6 years to <12 years old who participated in paediatric studies from dupilumab in AD (R668-AD-1652 and R668-AD-1412) could roll-over into this OLE study. The study duration is up to 2 years which provides long-term safety data in paediatric patients treated with dupilumab.
Paediatric patients who participated in a prior clinical study of dupilumab in AD were eligible to participate in this extension study.

Study Flow Diagram




* Patients and their parents/caregivers have the option to come to the clinic for these visits.

Children aged ≥6 years to <12 years who were enrolled into this study subsequent to implementation of protocol version R668-AD-1434 amendment 1 were started on 300 mg SC administered every 4 weeks (Q4W). Patients who were already enrolled in this study at the time of implementation of protocol version R668-AD-1434 amendment 1 and who were at the time on either 2 mg/kg or 4 mg/kg were switched to 300 mg Q4W.

If medically necessary (i.e., to control intolerable AD symptoms, treatment of flares of disease, etc), rescue treatment for AD may have been provided to study patients at the discretion of the investigator.

In case patients were not controlled with topical rescue medications and they needed to be rescued with systemic medications or in case the investigator deemed that rescue should be initiated with systemic medication, the following procedure was followed:

For patients who were being treated with 300 mg Q4W dose regimen, these patients were up titrated as follows:
1. Patients weighing ≥60 kg: 300 mg Q2W

2. Patients weighing <60 kg: 200 mg Q2W

Endpoints:

The primary endpoint in the study was the incidence and rate (events per patient-year) of treatment-emergent adverse events (TEAEs) through the last study visit.

The secondary endpoints related to safety were:
- Incidence and rate (events per patient-year) of treatment emergent serious adverse events (SAEs)
- Incidence and rate (events per patient-year) of TEAEs of special interest

Study Population

The intended study population includes paediatric patients with moderate-to-severe AD, aged ≥6 to <18 years at the time of screening, who have participated in a prior dupilumab study, for children ≥6 years and <12 years' old these were Study R668-AD-1652 (Phase 3 study) and Study R668-AD-1412 (A Phase 2a Study).

Inclusion Criteria (summary)

A patient must meet the following criteria to be eligible for inclusion in the study: Male or female, ≥6 to <18 years of age at the time of screening Participated in a prior dupilumab study in pediatric patients with AD and adequately completed the visits and assessments required for both the treatment and follow-up periods, as defined in the prior study protocol

Exclusion Criteria (summary)

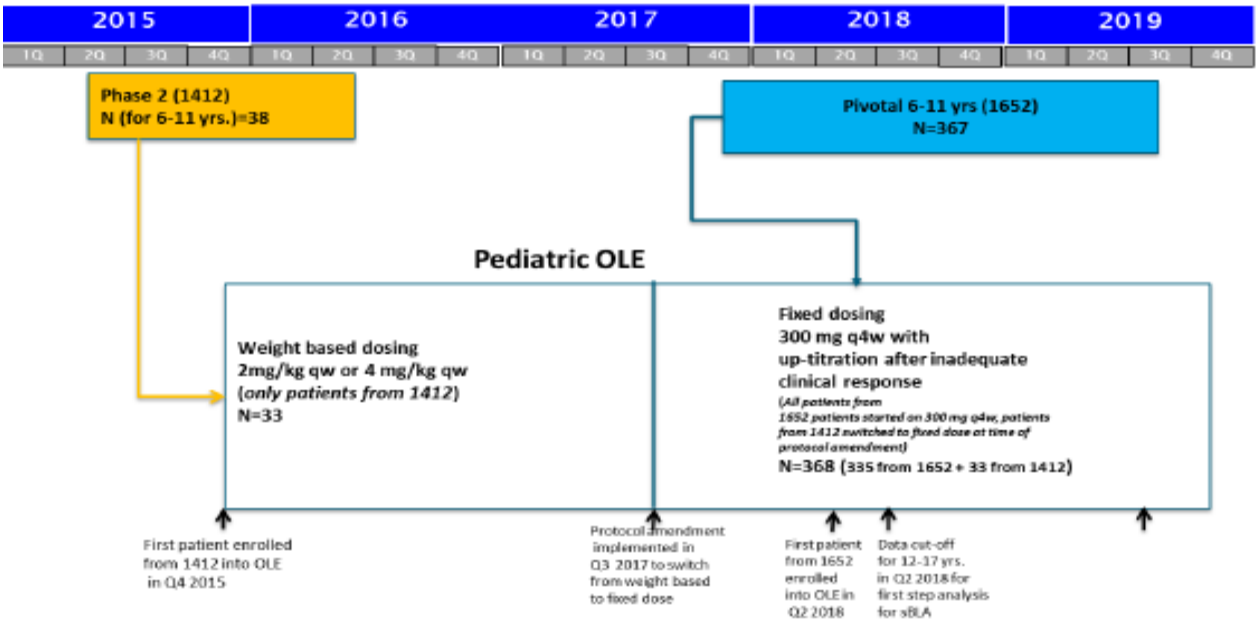
- Patients who, during their participation in a prior dupilumab study in pediatric patients with AD, developed a serious adverse event (SAE) deemed related to dupilumab, or an AE leading to treatment discontinuation which in the opinion of the investigator or of the medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient.

- Treatment with an investigational drug, other than dupilumab, within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit Patients who have used the following treatments within 4 weeks before the baseline visit: Systemic corticosteroids, Immunosuppressive/immunomodulating drugs (e.g. cyclosporine, mycophenolate mofetil, IFN-γ, Janus kinase inhibitors, azathioprine or methotrexate) or Phototherapy, Treatment with biologics, other than dupilumab, Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit

- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit.

- Known or suspected immunodeficiency
- Patients with an established diagnosis of hepatitis B or C viral infection
- Patients who are on current treatment for hepatic disease
- Presence of abnormalities in laboratory test results at screening

Timeline of Patients Feeding into the OLE from Parent Studies




*2.4.2.1. Persistence of Efficacy in Children* ***≥6*** *to <12 Years of Age Treated for >16 Weeks*

Evidence for the persistence of efficacy beyond 16 weeks of treatment with dupilumab in a population of children ≥6 to <12 years of age is provided by data from OLE study R668-AD-1434. Data for each endpoint that support persistence of efficacy are presented in the subsections below. For all endpoints, data after week 88 should be interpreted with caution as the number of patients included in the analysis progressively decreased after this time point (as patients transitioned to fixed dosing of 300 mg Q4W [followed by up-titration to 200 mg or 300 mg Q2W in some patients] after re-consenting to protocol amendment 1). The clinical benefit provided at week 16 was shown to be incrementally improved at week 52 and then sustained with continued treatment.

At the baseline of the OLE study, the mean (SD) EASI score was 15.70 (15.883) and the mean (SD) IGA score was 2.5 (1.04); overall, 29.9% of patients had IGA=3 (moderate disease) and 19.6% had IGA=4 (severe disease); and the mean (SD) BSA involvement was 28.6% (25.52). Efficacy results for the overall study population (N=368), including patients receiving fixed dosing of 300 mg Q4W, are summarized in Table 31. Efficacy data from the 368 patients enrolled in the study demonstrated a substantial clinical benefit of dupilumab in children ≥6 to <12 years of age at week 16. The clinical benefit shown at week 16 in the overall study population was sustained at later time points, including in the subset of patients with data through week 104.

Table 31: Summary of Key Efficacy Results for R668-AD-1434-SAF (Overall Study Population of Children **≥6** to <12 Years of Age, N=368)

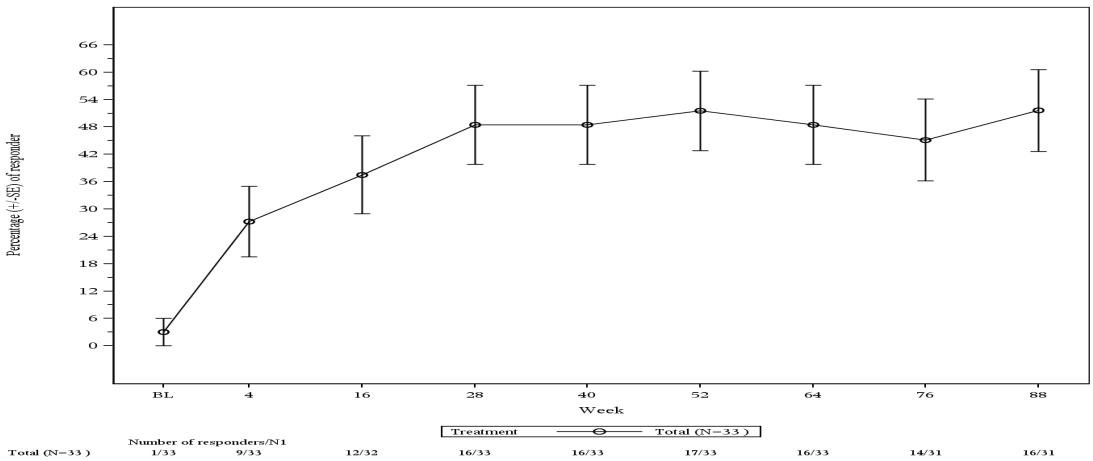
| | Total (N=368) | | | | | |
|---|---|---|---|---|---|---|
| | **Baseline of Current Study** | **Week 4** | **Week 16** | **Week 28** | **Week 52** | **Week 104** |
| Proportion of patients achieving IGA 0 or 1, n/N1 (%) | 65/368 (17.7%) | 80/315 (25.4%) | 96/281 (34.2%) | 75/191 (39.3%) | 20/40 (50.0%) | 17/33 (51.5%) |
| Proportion of patients achieving EASI-75 relative to baseline of parent study, n/N1 (%) | 151/368 (41.0%) | 170/315 (54.0%) | 195/281 (69.4%) | 139/191 (72.8%) | 33/40 (82.5%) | 23/30 (76.7%) |
| Proportion of patients achieving EASI-50 relative to baseline of parent study, n/N1 (%) | 251/368 (68.2%) | 261/315 (82.9%) | 254/281 (90.4%) | 181/191 (94.8%) | 37/40 (92.5%) | 29/30 (96.7%) |
| Proportion of patients achieving EASI-90 relative to baseline of parent study, n/N1 (%) | 77/368 (20.9%) | 93/315 (29.5%) | 108/281 (38.4%) | 86/191 (45.0%) | 22/40 (55.0%) | 19/30 (63.3%) |
| Mean % reduction in EASI score from baseline of parent study (SD) | -59.05 (36.556) | -71.04 (26.062) | -78.56 (23.708) | -82.20 (17.838) | -87.36 (16.705) | -87.25 (18.215) |
| Median % change from baseline of OLE in EASI score (Q1-Q3) [1] | -- | -28.41 (-61.76, 8.04) | -50.12 (-76.19, -8.33) | -65.75 (-87.88, -36.02) | -88.09 (-98.33, -68.95) | -90.45 (-100.00, -63.47) |

[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 a 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; 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 Post-text Tables 6.1.1.1/1b, 6.2.1.1/1b, 6.2.2.1/1b, 6.2.3.1/1b, 6.2.6.1/1b, and 6.2.7.1/1b

### *2.4.2.2. Proportion of Patients Achieving an IGA Score of 0 or 1 at Each Visit in R668-AD1434*

At baseline of the OLE study, only 1 (3.0%) of 33 patients (≥6 to <12 years of age) who rolled over from R668-AD-1412 had an IGA score of 0 or 1. This low proportion of patients with disease control at baseline is expected because these patients had a treatment interruption of ≥8 weeks between the last dose in the parent study and the baseline of OLE study. At week 16, a considerable proportion of patients (12/32 [37.5%]) had achieved IGA 0 or 1, which increased to 17/33 (51.5%) patients at week 52. All 33 patients who rolled over from study R668-AD-1412 were continuing with weight-based dosing at week 52. Response rates at later time points were generally comparable, suggesting sustained efficacy of dupilumab treatment. The slight variability in response rates between week 52 and week 76 resulted from patients with remission being discontinued from study drug at week 52, losing remission during the period of treatment interruption, and then re-gaining remission once study drug was re-initiated around week 76.

Figure 30: Proportion (±SE) of Patients Achieving an IGA Score of 0 or 1 at Each Visit – Children **≥6** to <12 Years of Age (SAF – Patients Who Received Weight-based Dosing Under Original R668-AD-1434 Protocol)



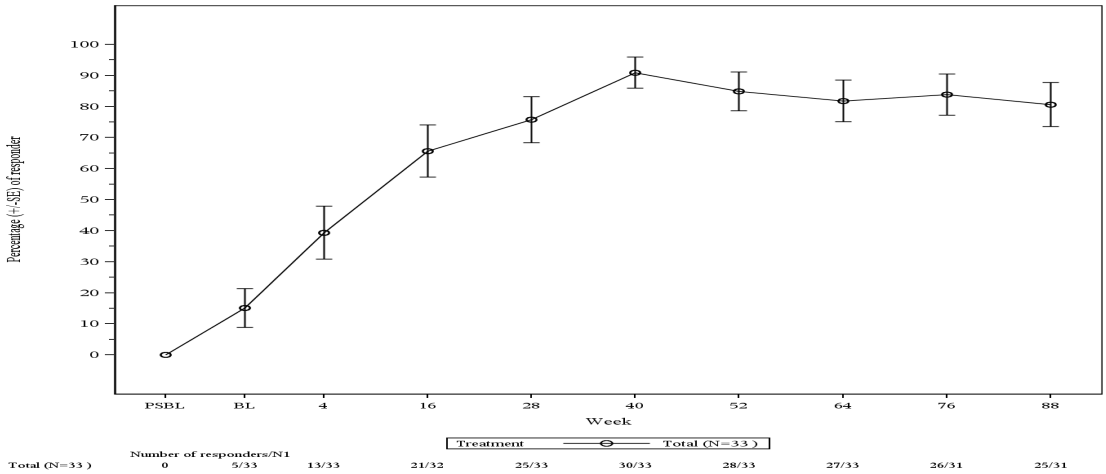

Note: N1 stands for the number of patients with non-missing score at each visit.

Only data up to the first visit when patient received 300 mg Q4W were included for analysis.
Abbreviations: BL, baseline; IGA, Investigator's Global Assessment; Q4W, every 4 weeks; SAF, safety analysis set; SE, standard error.

### *2.4.2.3. Proportion of Patients Achieving EASI-75 Relative to Baseline of R668-AD-1412 at each Visit in R668-AD-1434*

The proportion of patients with EASI-75 (defined as a ≥75% reduction in EASI score from baseline EASI score of study R668-AD-1412) at baseline of the OLE was 5/33 (15.2%). At week 16, a considerable proportion of patients (21/32 [65.6%]) had achieved EASI-75, which increased to 28/33 (84.8%) patients at week 52. Response rates at later time points were generally comparable suggesting sustained efficacy of dupilumab treatment (Figure 31).

Figure 31: Proportion (±SE) of Patients Achieving an EASI-75 Relative to Baseline of R668-AD-1412 at Each Visit - Children **≥6** to <12 Years of Age (SAF – Patients Who Received Weight-based Dosing Under Original R668-AD-1434 Protocol)



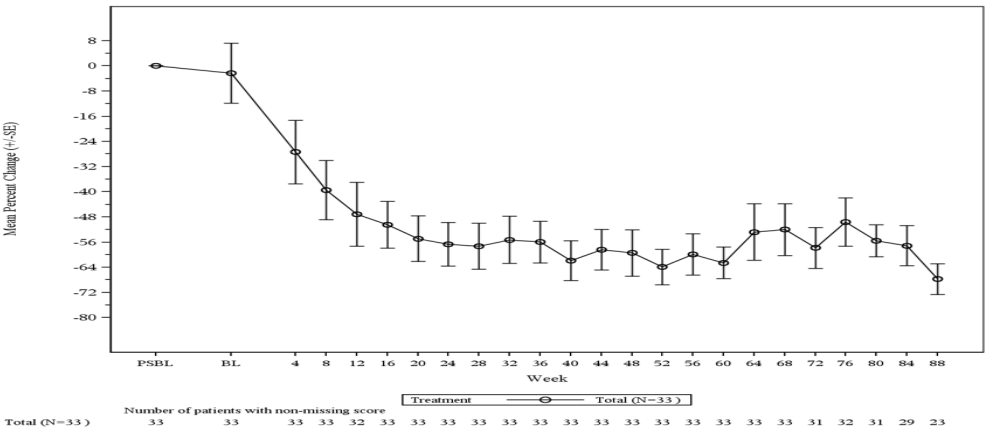

Note: N1 stands for the number of patients with non-missing score at each visit.
Only data up to the first visit when patient received 300 mg Q4W were included for analysis.
Abbreviations: BL, baseline; EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; PSBL, parent study baseline, Q4W, every 4 weeks; SAF, safety analysis set; SE, standard error.

### *2.4.2.4. Other long-term efficacy assessments*

#### Mean Percent Change in Peak Pruritus NRS Score from the Baseline of R668-AD-1412 in R668-AD-1434

At baseline of the parent study, R668-AD-1412, the mean (SD) peak pruritus NRS score was 6.67 (±2.354). At baseline of the OLE, patients had comparable levels of pruritus intensity with a mean (SD) peak pruritis NRS score of 5.94 (±2.573). There was a rapid reduction in pruritus NRS score during the OLE (mean [SD] percent change of −27.35% [±57.927] from baseline of R668-AD-1412 by week 4). The mean (SD) percent change in pruritus NRS score was −50.52% (±42.556) at week 16 and −63.87% (±32.372) at week 52. Although there was some variability, this reduction was largely maintained during the later time points of analysis (Figure 32).

Figure 32: Mean Percent Change (±SE) in Pruritus NRS Scores from Baseline of R668-AD-1412 - Children **≥6** to <12 Years of Age (SAF – Patients Who Received Weight-based Dosing Under Original R668-AD-1434 Protocol)




Abbreviations: BL, baseline; NRS, Numeric Rating Scale; PSBL, parent study baseline; SAF, safety analysis set; SE, standard error.

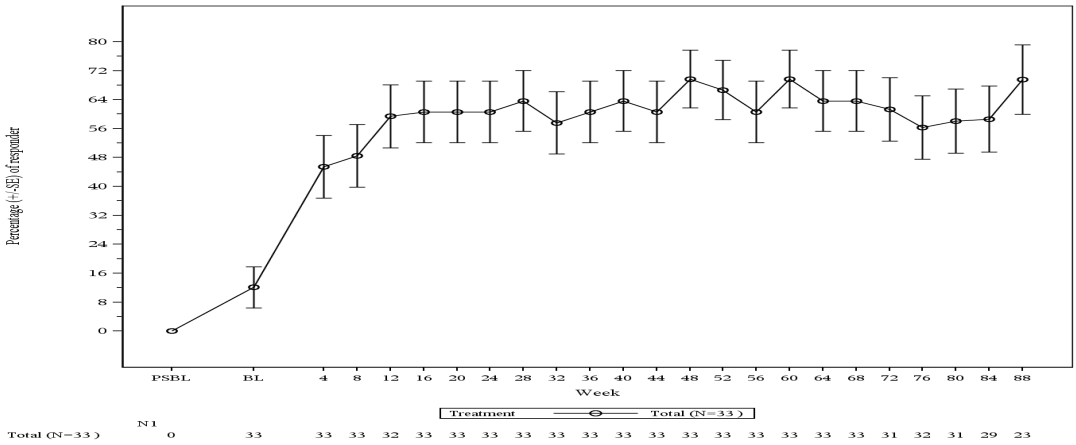
Mean Percent Change in Peak Pruritus NRS Score from the Baseline of R668-AD-1434

At baseline of the OLE, the mean (SD) pruritus NRS score was 5.94 (±2.573). A mean (SD) percent reduction in pruritis NRS score from baseline of the OLE was observed at week 4 (−23.11% [±52.540]), which was further reduced at week 16 (−46.62% [±43.247]) and week 52 (−54.90% [±55.521]). Although there was variability, this reduction was maintained throughout the remainder of the analysis period.

Proportion of Patients Achieving a Reduction of **≥4** Points from Baseline of R668-AD-1412 in Pruritus NRS Score or Achieving NRS Score of 0 at Each Visit in R668-AD-1434

At baseline of R668-AD-1412, the mean (SD) peak pruritus NRS score was 6.67 (±2.354) points. A total of 4/33 (12.1%) patients had achieved reduction in pruritus NRS score ≥4 points or a score of 0 at the baseline of the OLE. There was a reduction in pruritus severity during the OLE (15/33 [45.5%] where patients had reduction in pruritus NRS score ≥4 points from the baseline of R668-AD-1412 or a score of 0 by week 4. Increase in responder rates were seen by week 16 (20/33 [60.6%]) and by week 52 (22/33 [66.7%] patients).

Figure 33:Proportion (±SE) of Patients with Improvement (Reduction) of Pruritus **≥4** Points from Baseline of R668-AD-1412 or Achieving an NRS Score of 0 at Each Visit - Children **≥6** to <12 Years of Age (SAF – Patients Who Received Weight-based Dosing Under Original R668-AD-1434 Protocol)




Note: N1 stands for the number of patients with non-missing score at each visit

Abbreviations: BL, baseline of open-label extension; NRS, Numeric Rating Scale; PSBL, parent study baseline; SAF, safety analysis set; SE, standard error.

### *2.4.2.5. Antidrug antibodies*

The overall incidence of treatment-emergent ADA for patients ≥6 to <12 years of age in R668-AD-1434 was 8.3% (23/278). A higher rate of treatment-emergent ADA responses was observed in patients from parent study R668-AD-1412 (42.4%, 14/33) than in patients from parent study R668-AD-1652 (3.7%, 9/248). The higher rate of treatment-emergent ADA in patients from parent study R668-AD-1412 may be explained by the differences in dosing regimen for each study: in R668-AD-1412, a single 2 mg/kg QW or 4 mg/kg QW dupilumab dose was administered followed by an 8-week delay prior to receiving additional treatment with 2 mg/kg QW or 4 mg/kg QW for 4 additional doses, whereas in R668-AD-1652, dupilumab 100/200 mg Q2W (<30/≥30 kg), 300 mg Q4W, or placebo were administered in a 1:1:1 ratio for 16 weeks.

The overall incidence of patients with persistent ADA was 2.5% (7/278).

Table 32: Summary of ADA Status and ADA Category by Parent Study in Children with AD – Children **≥6** to <12 Years of Age

| | Parent Study | | |
|---|---|---|---|
| | R668-AD-1412 | R668-AD-1652 | Overall |
| **ADA Status and Category** | **n (%)** | **n (%)** | **n (%)** |
| ADA Analysis Set | 33 (100%) | 245 (100%) | 289 (100%) |
| Negative[a] | 19 (57.6%) | 236 (96.3%) | 255 (91.7%) |
| Treatment-Boosted Response | 0 | 0 | 0 |
| Treatment-Emergent Response | 14 (42.4%) | 9 (3.7%) | 23 (8.2%) |
| TE & TB | | | |
| Persistent | 5 (15.2%) | 2 (0.8%) | 7 (2.5%) |
| Transient | 9 (27.3%) | 3 (1.2%) | 12 (4.3%) |
| Indeterminate | 0 | 4 (1.6%) | 4 (1.4%) |

N = Number of patients; TE = Treatment-emergent; TB = Treatment-boosted

Note: Negative* includes both negative and pre-existing (Pre) responses.

Source: Table 5 of the Clinical Pharmacology Report (Appendix5)

Table 33: ADA Category and Maximum Titer Category of ADA Analysis Set by Parent Study in Patients ≥6 to <12 Years of Age (Study R668-AD-1434)

| | Parent Study | | |
|---|---|---|---|
| | R668-AD-1412 | R668-AD-1652 | Overall |
| Maximum Titer Category | n (%) | n (%) | n (%) |
| ADA Analysis Set | 33 (100%) | 245 (100%) | 278 (100%) |
| Negative[a] | 19 (57.6%) | 236 (96.3%) | 255 (91.7%) |
| Treatment-Boosted Response | 0 | 0 | 0 |
| Treatment-Emergent Response | 14 (42.4%) | 9 (3.7%) | 23 (8.2%) |
| TE & TB | | | |
| Low (<1,000) | 10 (30.3%) | 8 (3.3%) | 18 (6.5%) |
| Moderate (1,000 to 10,000) | 1 (3.0%) | 0 | 1 (0.4%) |
| High (>10,000) | 3 (9.1%) | 1 (0.4%) | 4 (1.4%) |

N = Number of patients; TE = Treatment-emergent; TB = Treatment-boosted
Note: Negative* includes both negative and pre-existing (Pre) responses.
Source: Table 6 of the Clinical Pharmacology Report (Appendix5)

Table 34: Summary of ADA Status and NAb Status by Parent Study in Patients ≥6 to<12 Years of Age with AD (Study R668-AD-1434)

| | Parent Study | | |
|---|---|---|---|
| | R668-AD-1412 | R668-AD-1652 | Overall |
| ADA Status; NAb Status | n (%) | n (%) | n (%) |
| Total ADA Patients | 33 (100%) | 245 (100%) | 278 (100%) |
| Negative | 19 (57.6%) | 229 (93.5%) | 248 (89.2%) |
| Pre+; NAb- | 0 | 7 (2.9%) | 7 (2.5%) |
| Pre+; NAb+ | 0 | 0 | 0 |
| TE & TB; NAb- | 5 (15.2%) | 9 (3.7%) | 14 (5.0%) |
| TE & TB; NAb+ | 9 (27.3%) | 0 | 9 (3.2%) |

N = Number of patients 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 5)

## 2.4.3. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The pivotal study R668-AD-1652 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in children ≥6 to <12 years of age with severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable. After an appropriate wash out phase of systemic agents and medium potency TCS with standardization period, a treatment period of 16 weeks followed.
367 patients were enrolled and randomized to three different treatment arms receiving dupilumab Q2W + TCS (adapted to weight), dupilumab Q4W + TCS or placebo+ TCS. A participation in the subsequent OLE study was offered to patients meeting the eligibility criteria.
The eligibility criteria and the design of pivotal study R668-AD-1652 are deemed appropriate.

The study treatment consisted of 3 treatment arms differing in treatment frequency and doses. The Q2W + TCS treatment arm provided two different dose regimens according to body weight (patients <30 kg received Q2W SC injections of 100 mg dupilumab from week 2 to week 14, following a loading dose of 200 mg, patients >30 kg received Q2W SC injections of 200 mg dupilumab from week 2 to week 14, following a loading dose of 400 mg. The second arm provided a treatment scheme of 300 mg Q4W, following a loading dose of 600 mg regardless of weight and the third one matching placebo+TCS. Rescue therapy was provided if clinically necessary and patients applying systemic drugs were permanently discontinued.

## *Efficacy data and additional analyses*

Efficacy assessments included EASI, IGA of AD severity, worst itch score, and BSA involvement with AD. As to the endpoints both the IGA and EASI scales are established outcome measures and correlation with disease severity and activity is acknowledged. The worst itch (WI-NRS) scale as patient-reported outcome (PRO) measure and modified peak pruritus Numeric Rating Scale (NRS) was newly applied in the pivotal phase 3 study; as the peak pruritus NRS is a valid and fit-for-purpose tool to measure itch severity this is an accepted complementary 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 to the CHMP and in line with the objectives of this study.

Supportive data as to long-term efficacy comes from the phase 3 OLE study R668-AD-1434; additional PK and efficacy data is provided by the phase 2a open-label PK study R668-AD-1412. Both studies supplied data for the EoI procedure for Dupixent for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy (EMEA/H/C/004390/II/0012).

The patient population, the study design, the endpoints and the treatment regimens are considered adequately chosen to demonstrate effects of dupilumab treatment in the proposed indication for patients with severe AD and they are in line with PDCO's decisions. Concerning the protocol amendments introduced changes, were based on PIP modifications and approved by PDCO.

*Outcome/ Endpoints*

As to the efficacy results the proportion of patients achieving the primary endpoint IGA scores of 0 or 1 was significantly higher in the dupilumab Q4W + TCS (32.8%) and Q2W + TCS (29.5%) treatment groups compared with the placebo + TCS group (11.4%). This effect was consistent in several analyses using FAS, mFAS, PPS (primary and sensitivity analysis) and persistent throughout the 16 weeks of treatment. Noticeable is the slightly higher percentage of responders in the Q4W +TCS group after treatment initiation compared to the Q2W + TCS group (5.7% vs. 0.8%) which probably is attributable to the higher loading dose in this treatment group.

The co-primary endpoints were met in both dupilumab treatment groups. The proportion of patients achieving EASI-75 at week 16 was significantly higher in the Q4W + TCS (69.7%) and Q2W + TCS (67.2%) treatment groups compared with the placebo + TCS group (26.8%) also with consistent results obtained by the above-mentioned analyses.

Key secondary endpoints as Percent Change in EASI Score from Baseline to Week 16 and Percent Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch Score from Baseline to Week 16 showed statistically significant results indicating a quick and sustained treatment effect of both dupilumab + TCS groups compared to the placebo + TCS group throughout the performed analyses. As seen for the co-primary endpoint, better efficacy results were achieved for the Q4W + TCS group regarding the Percent Change in EASI Score from Baseline to Week 16. Results pertaining to the reduction of the Daily Worst Itch Score were minimally better in the Q2W group than in the Q4W group (LS Mean % Change -56.5 vs. -54.5).

Similarly, the proportion of patients achieving a reduction of ≥4 points from baseline in the weekly average of daily worst itch score at week 16 was significantly higher in the dupilumab Q2W + TCS (58.3%) and Q4W + TCS (50.8%) groups than in the placebo + TCS group (12.3%). The paediatric population showed even better efficacy results than the adult one across the pivotal studies (cf. table 36). The onset of action for both dupilumab + TCS treatment groups was rapid, as demonstrated by the differences from placebo on assessments of rash and pruritus observed as early as week 2.
For the placebo + TCS group, less than 50% of patients achieved NRS reduction of at ≥3 or ≥4 points during the 16- week treatment period. The robustness of these results was confirmed by multiple sensitivity analyses, including analyses of all observed values, without censoring the data after rescue, although considerably more placebo + TCS patients received rescue treatment (19.5%) during the study

than dupilumab + TCS-treated patients (3.3% combined; 4.1% dupilumab Q2W + TCS; 2.5% dupilumab Q4W + TCS).

Topical corticosteroids represent the mainstay of pharmacologic treatment of AD. To evaluate the effect of dupilumab treatment on the use of topical TCS treatment, the proportion of TCS medication-free days and the mean weekly dose of TCS were evaluated as efficacy endpoints. Following the 16-week treatment period, there was a significantly higher mean proportion of topical AD medication-free days in both dupilumab + TCS groups compared to the placebo + TCS group (nominal $p<0.01$). The mean weekly dose of low / medium potency TCS was also shown to be significantly lower for the dupilumab + TCS treatment groups than in the placebo + TCS group (nominal $p<0.01$). A higher proportion of TCS medication-free days, lower mean weekly dose of TCS, and lower proportion of patients requiring rescue treatment suggests a potential steroid-sparing effect of dupilumab in patients ≥6 to <12 years of age treated with dupilumab + TCS.

*Ancillary analyses*

Ancillary analyses were conducted for weight strata as to patients weighing less or more than 30 kg. Analysis of efficacy response in the different weight strata revealed different clinical benefits resulting from different treatment schemes.

Patients ≥30 kg experienced a slightly better efficacy while receiving the Q2W + TCS regimen measured by a higher proportion of patients achieving the primary endpoints IGA 0 or 1, EASI-75 and 3 secondary pruritus-related endpoints. However, regarding the primary endpoint and several key secondary endpoints this effect was relatively small and relates mainly to the co-primary endpoint EASI-75 and the two secondary endpoints 'proportion of patients with reduction of weekly average of daily worst itch score ≥ 3 or 4'. The key secondary endpoint 'Percent Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch Score from Baseline to Week 16', however, was nearly comparable.

In the <30 kg weight stratum the primary endpoints were met by a higher proportion of patients assigned to the Q4W + TCS regimen whereas the outcome regarding the reduction of pruritus was slightly more favourable for the Q2W + TCS treatment scheme. However, apart from the secondary endpoint 3-point reduction in the pruritus NRS score both of the other endpoints related to pruritus assessment were comparable between both dupilumab dose groups. In general, a less frequent dosing regimen is supposed to enhance treatment compliance due to a reduced treatment burden in the paediatric population in a real world setting. Thus, the Q4W regimen is favoured for all patient of this age class.

Data on persistence of efficacy beyond 16 weeks of treatment with dupilumab comes from the OLE study R668-AD-1434. The primary objective of the OLE study has been to evaluate long-term safety of dupilumab in paediatric patients with AD, as well as long-term, uncontrolled efficacy data.
A total of 368 children (≥6 to <12 years of age) were enrolled in the OLE study and provided data (as of the data cut-off date of 22 Jul 2019). The MAH then introduced an amendment (amendment 1) to switch all patients to a 300mg Q4W treatment. The earliest visit a patient from R668-AD-1412 reconsented to amendment 1 was at week 88 of the OLE study R668-AD-1434 as previously described in the clinical section; hence, these patients had been on QW dosing for a considerable duration. All patients from R668-AD-1652 rolled into the OLE under protocol amendment 1 and were started on fixed dosing 300 mg Q4W. This approach is based on the PIP. However, this is not in line with the agreed posology in the SmPC as discussed in the clinical pharmacology section.

The MAH also introduced up-titration in case of inadequate clinical response at 300mg Q4W to 200 or 300 mg Q2W, based on body weight <60 kg or ≥60 kg, respectively. This flexibility allows possible demonstration of efficacy with a higher concentration in patients who are not achieving an adequate response, although based on uncontrolled data. This is considered adequately addressed in the SmPC as the dose may be increased to 200 mg Q2W in 6 to 11 years patients with body weight of 15 kg to less than 60 kg based on physician's assessment.

Of the 368 patients ≥6 to <12 years of age enrolled in the study, 282 had completed 16 weeks, 217 had completed 26 weeks, and 39 patients had completed at least 52 weeks of treatment period. Hence, the number of patients in the total study population with data after week 28 is limited in this ongoing study. Additionally, the majority (33/40) received weight-based dosing (2 mg/kg QW or 4 mg/kg QW). The clinical benefit seemed to be consistent overtime based on continuous improvement of the (co-) primary and key secondary endpoints. The proportion of patients in the total study population who achieved IGA 0 or 1 was 17.7% at baseline of the OLE, 34.2% at week 16, 50.0% at week 52, and 51.5% at week 104, and the proportion who achieved EASI-75 was 41.0% at baseline, 69.4% at week 16, 82.5% at week 52, and 76.7% at week 104.
The mean percent change in EASI score from the baseline of the parent study was −59.05% at baseline of the OLE, −78.56% at week 16, and −87.36% at week 52. The secondary endpoints such as pruritus, SCORAD, POEM, IGA and QoL also demonstrated a positive effect in treatment.

In context with the results of the PK/PD data (i.e. the high comparability of the E-R analysis regarding both regimens), the comparable efficacy results on the more stringent parameter IGA 0/1, the slightly better safety profile of the Q4W regimen as well as the lower treatment burden that results from a four weekly administration, lead to the CHMP recommendation of a uniform posology for all paediatric AD patients aged 6-11 years. The MAH agreed with this recommendation. Additionally, flexibility for dose increase in patients from 15 to 60 kgs is introduced as discussed above and in the clinical pharmacology section.
For patients weighing more than 60 kgs the same loading dose and dose regimen is recommended similarly than for adolescents and adults populations.

### 2.4.4. Conclusions on the clinical efficacy

The superiority of dupilumab over placebo is demonstrated for all three dose regimens regarding the primary and key secondary endpoints, and both the Q2W and Q4W regimens achieved convincing results with a slightly better global efficacy of the Q4W regimen.

Based on the provided data, the efficacy of dupilumab in the agreed indication is acknowledged.

## *2.5. Clinical safety*

### *Introduction*

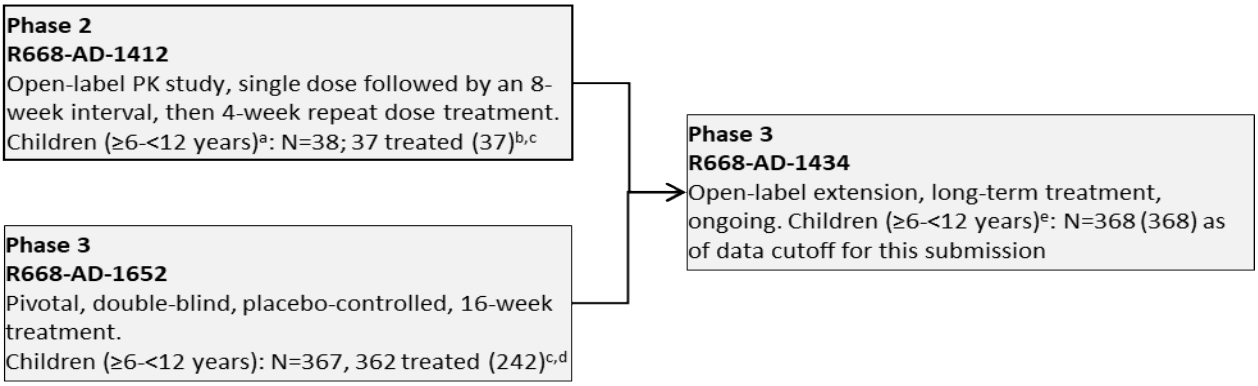
Summary of the existing safety profile of dupilumab

In summary, the adult AD data indicate that dupilumab was generally well tolerated and had a favorable safety profile in the treatment of patients with moderate-to-severe AD, including the subset of patients for whom treatment with ciclosporin would be medically inappropriate. Aside from the incidence of ISRs, there was no clear difference between the safety profile of the dupilumab 300 mg Q2W dose regimen and that of the 300 mg QW dose regimen. Long-term treatment in the 52-week placebo-controlled R668-AD-1224 study and the R668-AD-1225 OLE study did not reveal additional safety concerns associated with dupilumab.

Regarding the adolescent AD data, dupilumab treatment was well tolerated in general. No new safety concerns had arisen from data collected in the adolescent population and the previously known safety profile of the adult AD population was confirmed

The safety analysis of patients with AD is based primarily on the placebo-controlled phase 3 study (R668-AD-1652) and is supported by data from the completed phase 2a pharmacokinetic (PK)/safety study (R668-AD-1412), and the paediatric OLE (R668-AD-1434). A summary of the 3 studies in children

with AD aged ≥6 to <12 years is provided below.




a. Study R668-AD-1412 also included adolescents ≥12 to <18 years of age; the number of patients listed is for children ≥6 to <12 years of age only.
b. The number of patients included in the FAS was 38; 1 patient did not receive study treatment and was not included in the SAF.
c. Number in parentheses is the number of patients exposed to dupilumab.
d. The number of patients randomized and included in the FAS was 367; 5 randomized patients (2 in the 300 mg dupilumab Q4W + TCS group and 3 in the placebo + TCS group) did not receive study treatment and were not included in the SAF. Data presented in this dossier include results based on the prespecified primary analysis of efficacy (the data cutoff date was the day of last visit of the last patient in the treatment period, which was 28 Jun 2019.
e. Study R668-AD-1434 includes patients ≥6 months to <18 years of age. The number of patients (368) listed included all patients ≥6 to <12 years of age from the 2 prior studies as of data cutoff for this submission (22 Jul 2019), including 33 of the 38 patients ≥6 to <12 years of age from R668-AD-1412, 353 of 367 patients from R668-AD-1652. One of the previous studies (R668-AD-1412) was open-label. The second study (R668-AD-1652) had been unblinded, primary analysis completed, and results included as part of this application.
cf. The number of patients who progressed into R668-AD-1434.

## *Patient exposure*

Table 35: Overall Number of Children Aged **≥6** to <12 Years Included in the Safety Analysis Set

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

[a] The number of patients randomized and included in the full analysis set (FAS) was 367; 3 patients randomized to the dupilumab + TCS Q2W and Q4W and 2 patients randomized to placebo + TCS did not receive study treatment and were not included in the safety analysis set (SAF).
[b] Eight patients in the placebo + TCS group withdrew from R668-AD-1652 and did not enter the OLE study.
[c] The number of patients randomized and included in the full analysis set (FAS) was 38; 1 patient randomized to the dupilumab 4 mg/kg QW did not receive study treatment and was not included in the SAF.
[d] One patient in the dupilumab 4 mg/kg QW withdrew from R668-AD-1412 and did not enter the OLE study. One patient in the dupilumab 2 mg/kg QW and 2 patients in the dupilumab 4 mg/kg QW group who completed R668-AD-1412 did not enter the OLE study.
Source: Module 5.3.5.3 R668-AD-Children: Pooled Exposure Table 1.1.1/1 and Table 5.2.1/1

The sample size of the SAF for each of the studies included in this submission is presented in Table 36.

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Table 36: 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-1652 | 367 | 0 | 367 | 5 | TOTAL | 362 |
| | 123 | 0 | 123 | 2 | Placebo + TCS | 120 |
| | 122 | 0 | 122 | 2 | Dupilumab 300 mg Q4W + TCS | 120 |
| | 122 | 0 | 122 | 1 | Dupilumab 100/200 mg Q2W + TCS | 122 |
| R668-AD-1434 [1] | 368 | NA | NA | NA | TOTAL | 368 |
| R668-AD-1412 [2] | 38 | NA | NA | NA | TOTAL | 37 |
| | | | | | Dupilumab 2 mg/kg QW | 18 |
| | | | | | Dupilumab 4 mg/kg QW | 19 |

Abbreviations: NA, not applicable; QW, once weekly; Q2W, every 2 weeks; 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 included all patients from the studies R668-AD-1652 and R668-AD-1412 as of data cutoff for this submission (22 Jul 2019), including 33 of the 37 patients in the ≥6 to <12 years of age group from R668-AD-1412 and 353 of 362 patients from R668-AD-1652.

[2] For study R668-AD-1412, only pediatric patients aged ≥6 to <12 years are included in this Table and within the analyses described in this Module 2.7.4. Additional patients ≥12 to <18 years of age were included in the study but are not described in this document.

Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Tables 2 and 4, Module 5.3.5.2 R668-AD-1434 Second-step Analysis Post-text Table 1.1.1/1b, Module 5.3.3.2 R668-AD-1412 Table 8.

Study R668-AD-1652

Patient accountability in study R668-AD-1652 is presented in

Table 37.

The dupilumab 100 mg or 200 mg Q2W + TCS treatment group included patients with <30 kg body weight who received 100 mg Q2W + TCS (63 patients) and patients with ≥30 kg body weight who received 200 mg Q2W + TCS (59 patients).

Table 37: Summary of Patient Accountability and Study Disposition in Study R668-AD-1652 – All Randomized Patients

| | | Dupilumab | | | |
|---|---|---|---|---|---|
| | Placebo + TCS (N=123) [1] | 300 mg Q4W + TCS (N=122) | 100 mg or 200 mg Q2W + TCS (N=122) | Combined (N=244) | Total (N=367) |
| Received study medication, n (%) | 121 (98.4 %) | 120 (98.4%) | 121 (99.2%) | 241 (98.8%) | 362 (98.6%) |
| Patient randomized but not treated, n (%) | 2 (1.6%) | 2 (1.6%) | 1 (0.8%) | 3 (1.2%) | 5 (1.4%) |
| Completed the study treatment, n (%) | | | | | |
| Yes | 114 (92.7%) | 118 (96.7%) | 119 (97.5%) | 237 (97.1%) | 351 (95.6%) |
| No | 9 (7.3%) | 4 (3.3%) | 3 (2.5%) | 7 (2.9%) | 16 (4.4%) |
| Adverse event | 1 (0.8%) | 0 | 1 (0.8%) | 1 (0.4%) | 2 (0.5%) |
| Lack of efficacy | 2 (1.6%) | 0 | 0 | 0 | 2 (0.5%) |
| Other | 6 (4.9%) | 4 (3.3%) | 2 (1.6%) | 6 (2.5%) | 12 (3.3%) |
| Patient misstratified | 0 | 0 | 1 (0.8%) | 1 (0.4%) | 1 (0.3%) |
| Patient randomized in error | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | 2 (0.8%) | 3 (0.8%) |
| Use of prohibited medication | 1 (0.8%) | 1 (0.8%) | 0 | 1 (0.4%) | 2 (0.5%) |
| Withdrew consent | 4 (3.3%) | 2 (1.6%) | 0 | 2 (0.8%) | 6 (1.6%) |
| Transition into another study, n (%) | | | | | |
| Yes (Transitioned in R668-AD-1434) | 117 (95.1%) | 119 (97.5%) | 117 (95.9%) | 236 (96.7%) | 353 (96.2%) |
| No | 6 (4.9%) | 3 (2.5%) | 5 (4.1%) | 8 (3.3%) | 14 (3.8%) |
| Completed week 28 (end of study), n (%) | 0 | 0 | 0 | 0 | 0 |
| Ongoing, n (%) | 0 | 0 | 1 (0.8%) | 1 (0.4%) | 1 (0.3%) |
| Discontinuation from study with reason, n (%) | 6 (4.9%) | 3 (2.5%) | 4 (3.3%) | 7 (2.9%) | 13 (3.5%) |
| Adverse event | 0 | 0 | 0 | 0 | 0 |
| Death | 0 | 0 | 0 | 0 | 0 |
| Lack of efficacy | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 | 0 | 0 |
| Physician decision | 0 | 1 (0.8%) | 1 (0.8%) | 2 (0.8%) | 2 (0.5%) |
| Protocol violation | 0 | 0 | 0 | 0 | 0 |

| | | Dupilumab | | | |
|---|---|---|---|---|---|
| | Placebo + TCS (N=123) [1] | 300 mg Q4W + TCS (N=122) | 100 mg or 200 mg Q2W + TCS (N=122) | Combined (N=244) | Total (N=367) |
| Withdrawal by patient | 5 (4.1%) | 1 (0.8%) | 2 (1.6%) | 3 (1.2%) | 8 (2.2%) |
| Other | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | 2 (0.8%) | 3 (0.8%) |
| Patient randomized in error | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | 2 (0.8%) | 3 (0.8%) |

[1] The placebo + TCS group consisted of patients who received Q4W injections of placebo and patients who received Q2W injections of placebo (in a 1:1 ratio). Patients in the Q4W group did not receive matched placebo
Note: The percentage is based on the number of treated patients in each treatment group as denominator.
Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Table 2

Study R668-AD-1434

The primary reasons for discontinuation from OLE Study R668-AD-1434 were as follows: withdrawal by subject: 4/373 (1.1%) , physician decision: 2/373 (0.5%) , ,adverse event: 2/373 (0.5%), lack of efficacy: 2/373 (0.5%), lost to follow-up: 1/373 (0.3%), other: 5/373 (1.4%).

Exposure data were pooled for the 3 studies included in this submission and are presented by treatment duration and dupilumab dose administration in Table 38.

Table 38:Summary of Study Drug Administration (Cumulative) and Duration of Treatment in Children Aged ≥6 to <12 Years from All Studies - SAF

| | **Dupilumab** | | | | | |
|---|---|---|---|---|---|---|
| **Exposure Characteristics** | **2 mg/kg QW (N = 18)** | **4 mg/kg QW (N = 19)** | **300 mg Q4W + TCS (N = 371)** | **100 mg Q2W + TCS (N = 63)** | **200 mg Q2W + TCS (N = 59)** | **All Combined [3] (N = 391)** |
| Number of treated patients [1] | 18 | 19 | 371 | 63 | 59 | 391 |
| Number of study doses administered | | | | | | |
| Mean (SD) | 76.1 (24.88) | 72.7 (33.49) | 6.7 (4.29) | 8.9 (0.39) | 8.8 (0.95) | 19.8 (27.01) |
| Q1 | 57.0 | 57.0 | 4.0 | 9.0 | 9.0 | 8.0 |
| Median | 85.0 | 89.0 | 6.0 | 9.0 | 9.0 | 13.0 |
| Q3 | 93.0 | 96.0 | 9.0 | 9.0 | 9.0 | 18.0 |
| Min-Max | 5 : 105 | 5 : 101 | 1 : 22 | 7 : 9 | 2 : 9 | 1 : 141 |
| Number of doses administered, cumulative, n (%) | | | | | | |
| ≥1 | 18 (100%) | 19 (100%) | 371 (100%) | 63 (100%) | 59 (100%) | 391 (100%) |
| ≥4 | 18 (100%) | 19 (100%) | 286 (77.1%) | 63 (100%) | 58 (98.3%) | 360 (92.1%) |
| ≥8 | 17 (94.4%) | 16 (84.2%) | 134 (36.1%) | 61 (96.8%) | 57 (96.6%) | 301 (77.0%) |
| ≥12 | 17 (94.4%) | 16 (84.2%) | 64 (17.3%) | 0 | 0 | 217 (55.5%) |
| ≥16 | 17 (94.4%) | 16 (84.2%) | 9 (2.4%) | 0 | 0 | 140 (35.8%) |
| ≥24 | 17 (94.4%) | 16 (84.2%) | 0 | 0 | 0 | 47 (12.0%) |

| Exposure Characteristics | Dupilumab | | | | | |
|---|---|---|---|---|---|---|
| | 2 mg/kg QW (N = 18) | 4 mg/kg QW (N = 19) | 300 mg Q4W + TCS (N = 371) | 100 mg Q2W + TCS (N = 63) | 200 mg Q2W + TCS (N = 59) | All Combined [3] (N = 391) |
| ≥48 | 17 (94.4%) | 16 (84.2%) | 0 | 0 | 0 | 33 (8.4%) |
| ≥52 | 17 (94.4%) | 16 (84.2%) | 0 | 0 | 0 | 33 (8.4%) |
| ≥76 | 11 (61.1%) | 13 (68.4%) | 0 | 0 | 0 | 24 (6.1%) |
| ≥100 | 3 (16.7%) | 2 (10.5%) | 0 | 0 | 0 | 21 (5.4%) |
| ≥124 | 0 | 0 | 0 | 0 | 0 | 8 (2.0%) |
| ≥148 | 0 | 0 | 0 | 0 | 0 | 0 |
| Summary of treatment duration [2] (weeks) | | | | | | |
| Mean (SD) | 78.4 (26.64) | 73.9 (34.21) | 25.9 (16.80) | 15.8 (0.83) | 15.8 (1.91) | 44.0 (35.71) |
| Q1 | 57.0 | 56.9 | 15.9 | 15.9 | 15.9 | 20.4 |
| Median | 85.4 | 93.0 | 23.9 | 16.0 | 16.0 | 39.9 |
| Q3 | 94.0 | 97.1 | 36.1 | 16.1 | 16.1 | 52.0 |
| Min-Max | 5 : 109 | 5 : 102 | 3 : 88 | 11 : 17 | 2 : 17 | 4 : 193 |
| Treatment duration [2] (weeks) cumulative, n (%) | | | | | | |
| ≥1 week | 18 (100%) | 19 (100%) | 371 (100%) | 63 (100%) | 59 (100%) | 391 (100%) |
| ≥4 weeks | 18 (100%) | 19 (100%) | 364 (98.1%) | 63 (100%) | 58 (98.3%) | 391 (100%) |
| ≥8 weeks | 17 (94.4%) | 16 (84.2%) | 306 (82.5%) | 63 (100%) | 58 (98.3%) | 366 (93.6%) |
| ≥12 weeks | 17 (94.4%) | 16 (84.2%) | 291 (78.4%) | 62 (98.4%) | 58 (98.3%) | 356 (91.0%) |
| ≥16 weeks | 17 (94.4%) | 16 (84.2%) | 276 (74.4%) | 47 (74.6%) | 44 (74.6%) | 351 (89.8%) |
| ≥26 weeks | 17 (94.4%) | 16 (84.2%) | 175 (47.2%) | 0 | 0 | 273 (69.8%) |
| ≥39 weeks | 17 (94.4%) | 16 (84.2%) | 85 (22.9%) | 0 | 0 | 200 (51.2%) |
| ≥52 weeks | 17 (94.4%) | 16 (84.2%) | 28 (7.5%) | 0 | 0 | 101 (25.8%) |
| ≥78 weeks | 11 (61.1%) | 11 (57.9%) | 5 (1.3%) | 0 | 0 | 28 (7.2%) |
| ≥104 weeks | 4 (22.2%) | 0 | 0 | 0 | 0 | 25 (6.4%) |
| ≥130 weeks | 0 | 0 | 0 | 0 | 0 | 21 (5.4%) |

[1] Including a total of 3 studies: R668-AD-1652, R668-AD-1412, and R668-AD-1434.

[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 a given dupilumab dose for a patient who entered study R668-AD-1434 was calculated as the sum of duration of treatment exposure to dupilumab in the previous study plus duration of treatment exposure to dupilumab in the OLE study. The 391 patients include all patients who received at least 1 dose of dupilumab in either the parent study or the OLE study: 354 patients from R668-AD-1652 (6 patients in the placebo + TCS group did not rollover to the OLE study) and 37 patients from R668-AD-1412.

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.

### *Adverse events*

Study R668-AD-1652

A higher proportion of patients in the placebo + TCS group reported TEAEs during the 16-week treatment period than in the dupilumab + TCS groups; frequencies of TEAEs were similar in the dupilumab + TCS groups (Table 39). Most TEAEs were mild to moderate in intensity and deemed not related to study drug by the investigator. The number of SAEs reported was low: 2/120 patients (1.7%) in the placebo + TCS group (Asthma and Dermatitis Atopic) and 2/120 patients (1.7%) in the dupilumab Q4W group (Food Allergy and Urinary Tract Infection). All 4 SAEs were deemed unrelated to the study drug by the investigator. No deaths were reported. 2/120 (1.7%) patients reported TEAEs leading to permanent study drug discontinuation in the placebo +TCS group and 2/122 patients (1.6%) in the dupilumab Q2W +TCS group. There were no discontinuations due to TEAEs in the dupilumab Q4W group.

Table 39: Summary of Treatment-Emergent Adverse Events During the 16-Week Treatment Period in Study R668-AD-1652 – SAF

| | | **Dupilumab** | | |
|---|---|---|---|---|
| Number of patients (%) | **Placebo + TCS (N=120)** | **300 mg Q4W + TCS (N=120)** | **100 mg or 200 mg Q2W + TCS (N=122)** | **Combined (N=242)** |
| Any TEAE | 88 (73.3%) | 78 (65.0%) | 82 (67.2%) | 160 (66.1%) |
| Any drug-related TEAE | 13 (10.8%) | 24 (20.0%) | 30 (24.6%) | 54 (22.3%) |
| Any TEAE leading to discontinuation of study drug permanently | 2 (1.7%) | 0 | 2 (1.6%) | 2 (0.8%) |
| Maximum intensity for any TEAE | | | | |
| Mild | 52 (43.3%) | 45 (37.5%) | 48 (39.3%) | 93 (38.4%) |
| Moderate | 29 (24.2%) | 33 (27.5%) | 31 (25.4%) | 64 (26.4%) |
| Severe | 7 (5.8%) | 0 | 3 (2.5%) | 3 (1.2%) |
| Any death | 0 | 0 | 0 | 0 |
| Any treatment-emergent SAE | 2 (1.7%) | 2 (1.7%) | 0 | 2 (0.8%) |
| Any drug-related, treatment-emergent SAE | 0 | 0 | 0 | 0 |
| Any treatment-emergent SAE leading to permanent discontinuation of study drug | 0 | 0 | 0 | 0 |

Note: At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SAF, safety analysis set; TCS, topical corticosteroids; TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Table 56

Study R668-AD-1434

Open-Label Extension study R668-AD-1434 included safety data from a heterogeneous population with respect to dosing and dupilumab exposure, ranging from 300 mg Q4W to 4 mg/kg QW (resulting in mean drug levels comparable to 300 mg QW). Adverse event data for this study were summarized for the total patient population as of the data cutoff date for the submission (n=368) and for the population of patients

that rolled over from parent study R668-AD-1412 (n=39, of which 33 patients had ≥52 weeks of treatment with dupilumab.

In the OLE study (n=368), more than half of the patients (219/368 [59.5%]) experienced at least 1 TEAE (Table 40). Most events were mild to moderate in intensity and deemed unrelated to the study drug by the investigator. There were 9/368 (2.4%) patients who experienced SAEs during the study, and none of them were assessed as related to the study drug by the Investigator. No patient permanently discontinued from the study due to SAEs. A total of 2/368 (0.5%) patients reported AEs that led to permanent discontinuation of study drug. No deaths were reported during the study.

Table 40: Overall Summary of Treatment-Emergent Adverse Events in Study R668-AD-1434 – Children **≥6** to <12 Years of Age (SAF)

| | **Total (N=368)** |
|---|---|
| Patients with any TEAE | 219 (59.5%) |
| Patients with any drug related TEAE | 52 (14.1%) |
| Patients with any TEAE leading to permanent study drug discontinuation | 2 (0.5%) |
| Patients with any TEAE with maximum intensity | |
| Mild | 101 (27.4%) |
| Moderate | 106 (28.8%) |
| Severe | 12 (3.3%) |
| Patients with TEAEs resulting in death | 0 |
| Patients with any serious TEAEs | 9 (2.4%) |
| Patients with any drug-related serious TEAEs | 0 |
| Patients with serious TEAEs leading to permanent study drug discontinuation | 0 |

Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; SAE, serious adverse event; SAF, safety analysis set; TEAE, treatment-emergent adverse event.
Source: Module 5.3.5.2 R668-AD-1434 Second-step Analysis Table 22

### *Treatment-Emergent Treatment-Related Adverse Events*

Study R668-AD-1652

The proportion of patients who had at least 1 treatment-related TEAE (relatedness assessed by the investigator) during the 16-week treatment period was comparable across dupilumab treatment groups, and was higher than for patients in the placebo + TCS group (Table 41). This was primarily driven by a higher incidence of ISRs in all dupilumab treatment groups compared to the placebo + TCS group. The incidence of Conjunctivitis was also higher in all dupilumab groups compared to the placebo + TCS group.

Table 41: Summary of Treatment-Emergent Treatment-Related Adverse Events by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1652 with **≥2%** Incidence in Any Treatment Group – SAF

| Primary System Organ Class<br>Preferred Term<br>(MedDRA Version 22.0) | Placebo + TCS (N=120) | Dupilumab<br>300 mg Q4W + TCS (N=120) | Dupilumab<br>100 mg or 200 mg Q2W + TCS (N=122) | Dupilumab<br>Combined (N=242) |
|---|---|---|---|---|
| Number of patients with at least 1 related TEAE, n (%) | 13 (10.8%) | 24 (20.0%) | 30 (24.6%) | 54 (22.3%) |
| General disorders and administration site conditions | 6 (5.0%) | 10 (8.3%) | 12 (9.8%) | 22 (9.1%) |
| Injection site erythema | 2 (1.7%) | 3 (2.5%) | 7 (5.7%) | 10 (4.1%) |
| Injection site swelling | 1 (0.8%) | 2 (1.7%) | 6 (4.9%) | 8 (3.3%) |
| Injection site pain | 1 (0.8%) | 3 (2.5%) | 1 (0.8%) | 4 (1.7%) |
| Infections and infestations | 4 (3.3%) | 9 (7.5%) | 12 (9.8%) | 21 (8.7%) |
| Conjunctivitis | 1 (0.8%) | 4 (3.3%) | 6 (4.9%) | 10 (4.1%) |
| Conjunctivitis bacterial | 0 | 0 | 3 (2.5%) | 3 (1.2%) |
| Upper respiratory tract infection | 0 | 3 (2.5%) | 0 | 3 (1.2%) |

Note: At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event; TCS, topical corticosteroids.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Table 59

Study R668-AD-1434

In the OLE study R668-AD-1434, 52/368 (14.1%) of patients experienced TEAEs considered related to treatment by the investigator. Events that were reported in ≥5 patients included the PTs of Conjunctivitis Allergic (7/368 [1.9%] patients), Injection Site Erythema (6/368 [1.6%] patients), and Injection Site Pain (5/368 [1.4%] patients).

## *Serious adverse event/deaths/other significant events*

### Treatment-Emergent Serious Adverse Events

Study R668-AD-1652

In study R668-AD-1652, 4/362 (1.1%) patients experienced SAEs, 2 in the dupilumab Q4W + TCS group and 2 in the placebo + TCS group. None of the SAEs were deemed related to the study drug by the investigator. None of the reported SAEs led to permanent treatment discontinuation. Table 42 presents SAE and AE leading to permanent discontinuation.

Table 42: Serious Adverse Events and Adverse Events Leading to Permanent Study Drug Discontinuation Reported in Study R668-AD-1652

| Treatment | Patient ID | Preferred Term | Verbatim Term | Serious | Severity | Relationship to Study Drug | Action Taken with IP | Outcome |
|---|---|---|---|---|---|---|---|---|
| **SAEs** | | | | | | | | |
| Placebo | 616314004 | Asthma | Asthma Exacerbation | Yes | Moderate | Not related | Dose not changed | Recovered |
| Q4W | 840302011 | Urinary tract infection | Worsening of urinary tract infection | Yes | Moderate | Not related | Dose not changed | Recovered |
| Q4W | 203304005 | Food allergy | Allergic hives after nuts | Yes | Moderate | Not related | Dose not changed | Recovered |
| Placebo | 276313001 | Dermatitis atopic | Worsening of atopic dermatitis | Yes | Moderate | Not related | Dose not changed | Recovered |
| Q4W | 203303001 | Bone contusion | Contusion of the cervical spine | Yes | Mild | Not related | Not applicable | Recovered |
| Q2W | 203304004 | Gastroenteritis | Gastroenteritis | TES | Moderate | Not related | Not applicable | Recovered |
| **AEs leading to Permanent Study Drug Discontinuation** | | | | | | | | |
| Q2W | 840302004 | Food allergy | Allergic reaction to peanuts | No | Moderate | Not related | Drug withdrawn due to use of prohibited medication | Recovered |
| Q2W | 840322024 | Conjunctivitis bacterial | Right and left eye conjunctivitis (bacterial) | No | Moderate | Related | Drug withdrawn due to AE | Not recovered |
| Placebo | 840317008 | Asthma | Asthma exacerbation | No | Moderate | Not related | Drug withdrawn due to AE | Recovered |
| Placebo | 840319004 | Dermatitis atopic | Atopic dermatitis flare | No | Severe | Not related | Drug withdrawn due to Lack of Efficacy | Not recovered |

Abbreviations: AE, adverse events; SAE, serious adverse event; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Listings 2.7.2 and 2.7.3

Study R668-AD-1434

In study R668-AD-1434, 9/368 (2.4%) patients experienced SAEs including 2 patients with Anaphylactic Reaction. Both events were also considered AESIs. No other events were experienced by >1 patient. No SAEs were considered related to dupilumab as alternative causes were present for each SAE. None of the reported SAEs led to permanent treatment discontinuation. All SAEs resolved over time with treatment.

Deaths

There were no deaths in the AD program in patients.

## *Adverse Events of Special Interest*

Study R668-AD-1652

A total of 5/362 (1.4%) patients experienced treatment emergent AESIs. One patient in the placebo + TCS group reported 1 AESI (Enterobiasis). Two patients in the dupilumab Q4W + TCS treatment group reported 1 AESI each (Ascariasis and Food Allergy).Two patients (1.6%) in the dupilumab Q2W + TCS treatment group reported 1 AESI each (Conjunctivitis Allergic and Keratitis). One AESI was classified as moderate in severity (Food Allergy) and 1 was classified as severe (Conjunctivitis Allergic); all others were classified as mild. All AESIs were resolved apart from the case of Keratitis, which was listed as not recovered/not resolved. No AESIs resulted in study drug discontinuation.

Study R668-AD-1434

A total of 11/368 (3.0%) patients experienced treatment-emergent AESIs in study R668-AD-1434, 2 of which were serious AESIs (2 events of Anaphylactic Reaction). None of the events of Anaphylactic Reaction were considered related to study drug. Four patients had helminthic infections (Enterobiasis and Strongyloidiasis). These AESIs resolved after treatment with antihelminthic medication. Three patients had Keratitis (2 events of Keratitis and 1 event of Atopic Keratoconjunctivitis) and 1 patient had Conjunctivitis Bacterial. These events of Keratitis (1 mild case and 1 moderate case) and Conjunctivitis (1 severe case) resolved over time with treatment and did not lead to discontinuation of study drug. One child had an AESI of Food Allergy.

Analysis of Adverse Events by Organ System

Infections and Infestations: A higher proportion of patients in the placebo + TCS group (61/120 [50.8%]) had TEAEs in this SOC than in the dupilumab Q4W + TCS group (52/120 [43.3%]) and in the dupilumab Q2W + TCS group (49/122 [40.2%]). No single PT contributed to this difference. The most common PTs in this SOC were Nasopharyngitis and Upper Respiratory Tract Infection. Nasopharyngitis occurred more often in the dupilumab Q4W + TCS group (15/120 patients [12.5%]) than in the placebo + TCS group (8/120 patients [6.7%]). There was no significant difference between the treatment groups in the occurrence of Upper Respiratory Tract infection.

Skin and Subcutaneous Tissue Disorders: The proportion of patients with TEAEs in this SOC was similar between the placebo + TCS group (23/120 [19.2%]) and the combined dupilumab + TCS groups (39/242 [16.1%]). However, the PT Dermatitis Atopic (which was also the most common PT in this SOC) was reported more frequently in the placebo + TCS group (17/120 [14.2%]) than in the combined dupilumab + TCS groups (18/242 [7.4%]). The next most common PT was Urticaria, with no significant difference between the treatment groups.

Gastrointestinal Disorders: The proportion of patients with TEAEs in this SOC was similar between the placebo + TCS group (17/120 [14.2%]) and the combined dupilumab + TCS groups (34/242 [14.0%]). The most common PTs in this SOC were Vomiting and Diarrhoea, both with no significant differences between the treatment groups.

General Disorders and Administration Site Conditions: The proportion of patients with TEAEs in this SOC was similar between the placebo + TCS group (15/120 [12.5%]) and the combined dupilumab + TCS groups (34/120 [14.0%]). The most common PTs in this SOC were Injection Site Erythema and Injection Site Swelling, both events occurred more often in the combined dupilumab + TCS treatment groups (12/242 patients [5.0%] and 10/242 patients [4.1%], respectively) than in the placebo + TCS group (2/120 patients [1.7%] and 1/120 patients [0.8%], respectively).

Respiratory, Thoracic and Mediastinal Disorders: The proportion of patients with TEAEs in this SOC was higher in the placebo + TCS group (31/120 [25.8%]) than in the combined dupilumab + TCS groups (29/242 [12.0%]), mainly due to the PT Asthma, which occurred in 12/120 (10.0%) patients in the placebo + TCS group compared to 6/242 (2.5%) patients in the combined dupilumab + TCS groups. The most common PTs in this SOC were Cough and Rhinitis Allergic, both with no significant differences between the treatment groups.

Eye Disorders: The proportion of patients with TEAEs in this SOC was higher in the dupilumab Q2W + TCS group (15/122 [12.3%]) than in the placebo + TCS group (8/120 [6.7%]) and the dupilumab Q4W + TCS group (7/120 [5.8%]). The only PT in this SOC reported by ≥2% of patients was Conjunctivitis Allergic with no significant difference between the treatment groups.

Nervous System Disorders: The proportion of patients with TEAEs in this SOC was higher in the placebo + TCS group (15/120 [12.5%]) than in the combined dupilumab + TCS treatment groups (18/242 [7.4%]). No single PT contributed to this difference. The only PT in this SOC reported by ≥2% of patients was Headache, with no significant difference between the treatment groups.

*Conjunctivitis Events*

A broad customized MedDRA query (CMQ) containing 14 terms and a narrow standardized MedDRA query (SMQ) containing 5 terms that included “Conjunctivitis” were used for an *ad-hoc* analysis to obtain a better understanding.

In study R668-AD-1652, using the narrow SMQ, the proportion of patients with at least 1 conjunctivitis-related event during the 16-week treatment period was higher in the dupilumab Q2W + TCS group (18/122

patients [14.8%]) than in the placebo + TCS (5/120 patients [4.2%) group or in the dupilumab Q4W + TCS (8/120 patients [6.7%]) group (Table 43).

Table 43: Summary of Patients with Treatment-Emergent Conjunctivitis (Narrow Search) during the 16-Week Treatment Period in Study R668-AD-1434 – SAF

| **Preferred Term**<br>**MedDRA Version 21.1** | **Total (N=368)** | Total(N=368)<br>nP/PY<br>(nP/100 PY) [1] |
|---|---|---|
| **Number of TEAEs** | 59 | |
| **Patients with at least one TEAE** | 42 (11.4%) | 42/242.1 (17.34) |
| Conjunctivitis allergic | 24 (6.5%) | 24/259.9 (9.23) |
| Conjunctivitis bacterial | 10 (2.7%) | 10/261.4 (3.83) |
| Conjunctivitis | 8 (2.2%) | 8/266.6 (3.00) |
| Conjunctivitis viral | 3 (0.8%) | 3/271.5 (1.10) |
| Atopic keratoconjunctivitis | 1 (0.3%) | 1/272.2 (0.37) |

Patients who experienced more than 1 TEAE were counted only once in each category
[1] Total patient years were calculated as the sum of study observational period over all patients.
Abbreviations: CMQ, customized MedDRA query; MedDRA, medical dictionary for regulatory activities; nP, number patients with events; SAF, safety analysis population; TEAE, treatment-emergent adverse event.
Search terms for Narrow CMQ were: Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral and Atopic keratoconjunctivitis
Source: Module 5.3.5.1 R668 AD 1434 Second-Step Analysis Table 27

Similar results were observed using the broad CMQ. None of these conjunctivitis events from the narrow and broad search were serious and most events were of mild or moderate severity and resolved with conventional treatment while the patient remained on the study drug. One event of Conjunctivitis Bacterial led to study drug discontinuation.

In study R668-AD-1434, a search performed using the Conjunctivitis narrow CMQ showed 42/368 patients (11.4%) had a Conjunctivitis event in the OLE (Table 43). One patient had a severe TEAE of Conjunctivitis Bacterial. None of the events were serious or led to treatment discontinuation.

*Events of Injection Site Reaction*

In study R668-AD-1652, the proportion of patients with at least 1 Injection Site Reaction events during the 16-week treatment period was higher in the dupilumab groups (12/120 patients [10.0%] in the Q4W + TCS group and 13/122 patients [10.7%] in the Q2W + TCS group) than in the placebo +TCS (7/120 patients [5.8%]). This difference was mainly driven by the PTs of Injection Site Erythema and Injection Site Swelling.

In Study R668-AD-1434, 17/368 patients (4.6%) experienced TEAEs of Injection Site Reaction. Most of these events were mild to moderate in severity, transient in duration with resolution over time, and none were serious or led to treatment.

## *Adverse Drug Reactions*

A review of all TEAEs per the methods did not identify any new ADRs in the population of children with AD aged ≥6 to <12 years as compared to the adult and adolescent AD patient population who received dupilumab treatment. Only the known ADRs of Injection Site Reactions and Conjunctivitis occurred more frequently in the dupilumab groups than in the placebo group. No event of Injection Site Reaction was severe, serious, or led to study drug discontinuation, and the incidence was comparable in the dupilumab groups. Likewise, no event of Conjunctivitis was serious; most Conjunctivitis events were of mild to

moderate severity and resolved with conventional treatments while the patient remained on the study drug. The following sections provide further details on these cases related to these specific ADRs.

## *Laboratory findings*

Overall, mean and median hematology, chemistry, and urinalysis values were generally consistent with baseline values across each of the respectively studies. While some patients reported fluctuations in LDH values and eosinophils during treatment with dupilumab, none of these cases were associated with TEAEs and were not clinically significant. Moreover, these laboratory values were consistent with those previously observed in adult trials.

## *Hematology*

### Mean / Median Changes from Baseline

#### Red Blood Cells and Platelets

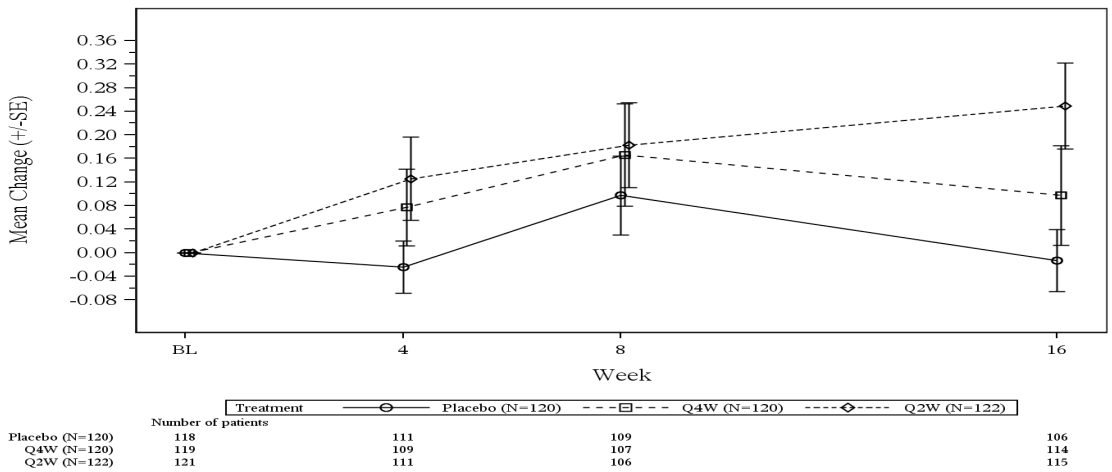
During the treatment period of study R668-AD-1652, there were no clinically meaningful trends or differences between treatment groups in mean or median changes from baseline in any red blood cell parameter. There were no meaningful changes from baseline in RBC parameters in studies R668-AD-1434 and R668-AD-1412.

#### White Blood Cells

In study R668-AD-1652, 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 (basophils, lymphocytes, monocytes, leukocytes, and neutrophils) during the treatment period.

A TEAE related to elevated eosinophil counts was reported in 1/122 patients (0.8%) in the dupilumab Q2W + TCS group. This patient had a TEAE of Eosinophilia, moderate in intensity and considered unrelated to study drug due to an eosinophil count of 0.78 × $10^9$/L at week 4 (result at baseline: 0.43 × $10^9$/L). The eosinophil counts subsequently returned towards baseline and was 0.55 × $10^9$/L at EOT. There were no associated clinical sequelae and the patient remained on study drug.

Figure 34: Mean Change (SE) in Eosinophils ($10^9$/L) from Baseline Through Week 16 Treatment Period during the 16-Week Treatment Period in Study R668-AD-1652 – SAF




Q2W = Once every 2 weeks; Q4W = Once every 4 weeks; SAF = Safety Analysis Set; SE = Standard error.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Post-text Figure 9.1.1/2

In study R668-AD-1434, there was no meaningful change from baseline in basophils, lymphocytes, monocytes, leukocytes, or neutrophils during the treatment period.

Clinically Meaningful Values

Red Blood Cells and Platelets

In study R668-AD-1652, there were no meaningful differences in treatment emergent potentially clinically significant value (PCSVs) in red blood cell or platelet parameters between the dupilumab + TCS and placebo + TCS groups. The proportion of patients with at least 1 treatment emergent PCSVs during the treatment period was low across treatment groups: 2/120 (1.7%) in the placebo + TCS group, 2/119 (1.7%) in the dupilumab Q4W + TCS group, and 5/122 (4.1%) in the dupilumab Q2W + TCS group. No patients had relevant laboratory test abnormalities related to RBCs or platelets that were considered TEAEs.

In study R668-AD-1434, 4/281 (1.4%) patients in the SAF had at least 1 treatment emergent hematologic PCSV in hematologic (RBCs and platelets) parameters during the OLE. No patients had relevant laboratory test abnormalities related to RBCs or platelets that were considered TEAEs.

White Blood Cells

In study R668-AD-1652, the proportion of patients in the dupilumab groups with treatment-emergent PCSVs in white blood cell parameters were either similar (dupilumab Q2W + TCS group, 52/122 [42.6%]) or lower (dupilumab Q4W + TCS group, 34/119 [28.6%]) than of those in the placebo + TCS group (52/120 [43.3%]). These results were mainly driven by the eosinophil PCSVs: 28/122 (23.0%) patients in the dupilumab Q2W + TCS group, 14/119 (11.8%) in the dupilumab Q4W + TCS group, and 24/119 (20.2%) in the placebo + TCS group had a treatment-emergent increase in eosinophil count that was classified as PCSV. No patients had relevant laboratory test abnormalities related to white blood cell parameters that were considered TEAEs.

In study R668-AD-1434, 90/281 (32.0%) patients in the SAF had at least 1 treatment emergent PCSV in hematologic (WBCs) parameters. The most common PCSV related to WBC parameters were elevated eosinophil counts, which was reported in 44/279 (15.8%) patients. Most of these abnormalities resolved over time. Two patients with a PCSV associated with elevated eosinophil count had TEAEs of Eosinophilia. The next most common PCSV related to WBC parameters was elevated total leukocyte count, which was reported in 21/281 (7.5%) patients. Most of these patients were still within the normal lab range for total leukocyte count. None of these events were considered TEAEs.

### *Chemistry*

Mean/Median Changes from Baseline

In study R668-AD-1652, there were no clinically meaningful trends in mean or median changes from baseline in most chemistry parameters in any treatment group for metabolic, electrolyte, renal function, liver function, or lipid parameters. Mean (SD) baseline LDH values were 284.3 (71.15) in the placebo + TCS group, 292.8 (85.85) in the dupilumab Q4W + TCS group, and 296.3 (84.12) in the dupilumab Q2W + TCS group. There were mean and median decreases from baseline in LDH for patients in both dupilumab + TCS groups during the treatment period. This is a known phenomenon as elevated LDH levels are associated with AD disease activity and severity (Kou, 2012).

### *Urinalysis*

In study R668-AD-1652 and R668-AD-1434, there were no clinically meaningful trends in mean or median changes from baseline in urinalysis parameters in any treatment group.

Vital Signs

Clinically Significant Values

In study R668-AD-1652, at least 1 treatment emergent PCSV was found in 65/120 patients (54.2%) in the placebo + TCS group, 66/120 patients (55.0%) in the dupilumab Q4W + TCS group, and 71/122 patients (58.2%) in the dupilumab Q2W + TCS group. Clinically significant observations in heart rate and temperature were rare across the studies. Clinically significant observations in other vital sign parameters are discussed below. No AEs or SAEs related to hypertension were reported during study R668-AD-1652 and study R668-AD-1434.

Electrocardiogram

Across studies R668-AD-1652 and R668-AD-1434, there were no clinically meaningful trends in mean or median changes from baseline in ECG parameters in any treatment group.

## *Immunological events*

In the pivotal study R668-AD-1652, the incidence of treatment-emergent ADA response was low. There was no evidence of a clinically meaningful impact of immunogenicity on dupilumab exposure or response.

In the OLE study R668-AD-1434, the distribution of dupilumab concentrations for ADA positive patients was generally in the range of concentrations of ADA negative patients.

Relationship Between Anti-Drug Antibody Response and Adverse Event Profile

In study R668-AD-1652, there were no ADA-positive patients in the dupilumab Q4W + TCS group. In the Q2W + TCS group, 3/6 (50.0%) ADA positive patients and 79/112 (70.5%) of ADA negative patients reported at least 1 TEAE (Table 17). Two cases of Atopic Dermatitis and 1 case of Conjunctivitis were reported in ADA-positive patients.

In OLE study R668-AD-1434, 23/279 (8.2%) patients had a treatment-emergent positive ADA response during the study and a total of 7/279 (2.5%) patients had a persistently positive ADA response during the study. The TEAEs (by PT) observed in >1 patient with a persistently positive ADA response during the study were Nasopharyngitis (3 patients), Dermatitis Atopic (3 patients), Viral Upper Respiratory Tract Infection (2 patients), Herpes Simplex (2 patients), Dermatitis Infected (2 patients), Hordeolum (2 patients), Oropharyngeal Pain (2 patients), Pyrexia (2 patients), Abdominal Pain (2 patients), and Seasonal Allergy (2 patients). Additionally, 2/7 (28.6%) patients with persistent ADA response had a TEAE under Injection Site Reactions (HLT). None of these patients experienced any TEAEs with the PT of Anaphylactic Reaction during the study. A total of 5/279 (1.7%) patients had a moderate (1/279) or high titer (4/279) ADA response during the study.

## *Safety in special populations*

- Weight Strata Analyses in R688-AD-1652

An analysis of safety by weight strata was provided by the MAH with the initial submission to support the initially proposed posology of dupilumab 300 mg Q4W in patients weighing<30 kg and 200 mg Q2W in patients weighing ≥30 kg. Randomization in this study was stratified by baseline weight (<30 kg, ≥30 kg) and, within the Q2W + TCS treatment group, patients received different doses of dupilumab in these different strata (patients <30 kg: 100 mg Q2W; patients ≥30 kg: 200 mg Q2W). All patients randomized to the dupilumab Q4W + TCS treatment group received dupilumab 300 mg Q4W regardless of baseline weight. Table 44 provides an overview of AEs by weight strata.

Overview of Adverse Events by Weight Strata

In the <30 kg weight stratum, a higher proportion (46/63, 73%) of patients in the dupilumab Q2W (100 mg) + TCS group reported TEAEs during the 16-week treatment period than in the dupilumab Q4W + TCS (39/60, 65.0%) or the placebo + TCS (43/60, 71.7%) group (Table 44). Most of the TEAEs were mild to moderate in intensity. No deaths were reported. There were 2/60 (3.3%) SAEs reported in the dupilumab Q4W + TCS group of this weight stratum. No SAE was considered related to study drug and no patients permanently discontinued the study drug due to SAEs.

Table 44: Summary of Patients with Treatment-Emergent Adverse Events during the 16-week Treatment Period in Study R668-AD-1652 by Baseline Weight <30 kg (SAF)

| | Baseline Weight <30 kg | | |
|---|---|---|---|
| | Placebo + TCS (N=60) | 300 mg Q4W + TCS (N=60) | 100 mg Q2W + TCS (N=63) |
| Any TEAE | 43 (71.7%) | 39 (65.0%) | 46 (73.0%) |
| Any drug related TEAE | 5 (8.3%) | 13 (21.7%) | 18 (28.6%) |
| Any TEAE leading to discontinuation of study drug permanently | 2 (3.3%) | 0 | 1 (1.6%) |
| Maximum intensity for any TEAE, n(%) | | | |
| Mild | 25 (41.7%) | 25 (41.7%) | 23 (36.5%) |
| Moderate | 14 (23.3%) | 14 (23.3%) | 21 (33.3%) |
| Severe | 4 (6.7%) | 0 | 2 (3.2%) |
| Any death | 0 | | 0 |
| Any TE SAE | 0 | 2 (3.3%) | 0 |
| Any drug related TE SAE | 0 | 0 | 0 |
| Any TE SAE leading to Discontinuation of study drug permanently | 0 | 0 | 0 |

Note: One patient with baseline weight <30 kg who was mis-randomized to 200mg dupilumab Q2W was summarized in baseline weight <30 kg 100 mg dupilumab Q2W group.
Abbreviations: PTT, Post-text table; Q2W, Once every 2 weeks; Q4W, Once every 4 weeks; SAE, Serious adverse event; SAF, Safety Analysis Set; TCS, Topical corticosteroids; TEAE, Treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Table 69

In the ≥30 kg weight stratum, a higher proportion (45/60, 75%) of patients in the placebo + TCS group reported TEAEs during the 16-week treatment period than in the dupilumab Q4W + TCS (39/60, 65%) or the 200 mg dupilumab Q2W + TCS (36/59, 61.9%) group (Table 45). Most of the TEAEs were mild to moderate in intensity. No deaths were reported. There were 2/60 (3.3%) SAEs reported in the placebo + TCS group of this weight stratum. No SAE was considered related to study drug and no patients permanently discontinued the study drug due to SAEs.

Table 45:Supportive Analysis of Number of Patients with Treatment-Emergent Adverse Events during the 16-Week Period in Study R668-AD-1652 by Baseline Weight **≥30** kg– SAF

| | Baseline Weight **≥30** kg | | |
|---|---|---|---|
| | Placebo + TCS (N=60) | 300 mg Q4W + TCS (N=60) | 200 mg Q2W + TCS (N=59) |
| Any TEAE | 45 (75.0%) | 39 (65.0%) | 36 (61.0%) |
| Any drug related TEAE | 8 (13.3%) | 11 (18.3%) | 12 (20.3%) |
| Any TEAE leading to discontinuation of study drug permanently | 0 | 0 | 1 (1.7%) |
| Maximum intensity for any TEAE, n(%) | | | |
| Mild | 27 (45.0%) | 20 (33.3%) | 25 (42.4%) |
| Moderate | 15 (25.0%) | 19 (31.7%) | 10 (16.9%) |
| Severe | 3 (5.0%) | 0 | 1 (1.7%) |
| Any death | 0 | 0 | 0 |
| Any TE SAE | 2 (3.3%) | 0 | 0 |
| Any drug related TE SAE | 0 | 0 | 0 |
| Any TE SAE leading to Discontinuation of study drug permanently | 0 | 0 | 0 |

Note: One patient with baseline weight ≥30 kg who was randomized to placebo but received one 100mg dupilumab inadvertently was summarized in baseline weight ≥30 kg 200 mg dupilumab Q2W group.
Abbreviations: PTT, Post-text table; Q2W, Once every 2 weeks; Q4W, Once every 4 weeks; SAE, Serious adverse event; SAF, Safety Analysis Set; TCS, Topical corticosteroids; TEAE, Treatment-emergent adverse event.
Source: Module 5.3.5.1 R668-AD-1652 Primary Analysis Table 70

Frequency of Treatment-Emergent Adverse Events by Weight Strata

*Less than 30 kg Weight Stratum*

The SOCs in which TEAEs were reported by ≥10% of patients in any treatment group of the <30 kg weight stratum were as follows:

Infections and Infestations: There was no significant difference between the 2 dupilumab treatment groups: (26/60 patients [43.3%] in the Q4W + TCS group and 28/63 patients [44.4%] in the dupilumab Q2W [100 mg] + TCS group). In the placebo + TCS group, 30/60 patients (50.0%) had TEAEs in this SOC.

Gastrointestinal Disorders: There was no significant difference between the 2 dupilumab treatment groups (6/60 patients [10.0%] in the Q4W + TCS group and 7/63 patients [11.1%] in the Q2W [100 mg] + TCS group). In the placebo + TCS group, 30/60 patients (16.7%) had TEAEs in this SOC.

General Disorders and Administration Site Conditions: A higher proportion of patients in the dupilumab Q4W + TCS group (10/60 patients [16.7%]) had TEAEs in this SOC than in the Q2W (100 mg) + TCS group (7/63 patients [11.1%]). This difference was not driven by any particular PTs. In the placebo + TCS group, 10/60 patients (16.7%) had TEAEs in this SOC.

Nervous System Disorders: There was no significant difference between the 2 dupilumab treatment groups (2/60 patients [3.3%] in the Q4W + TCS group and 3/63 patients [4.8%] in the Q2W [100 mg] + TCS group). In the placebo + TCS group, 7/60 patients (11.7%) had TEAEs in this SOC.

Skin and Subcutaneous Tissue Disorders: A higher proportion of patients in the dupilumab Q2W (100 mg) + TCS group (13/63 patients [20.6%] had TEAEs in this SOC) than in the Q4W + TCS group (9/60 patients [15.0%]). In the placebo + TCS group, 10/60 patients (16.7%) had TEAEs in this SOC. However, the PT Dermatitis Atopic was reported more frequently in the dupilumab Q2W (100 mg) + TCS group (8/63 patients [12.7%]) than in the dupilumab Q4W + TCS group (4/60 patients [6.7%]). This PT was reported in (7/60 patients [11.7%]) in the placebo + TCS group.

Eye Disorders: A higher proportion of patients in the dupilumab Q2W (100 mg) + TCS group (10/63 patients [15.9%]) had TEAEs in this SOC than in the dupilumab Q4W + TCS group (4/60 patients [6.7%]). The PT Conjunctivitis Allergic was reported in 4/63 patients (6.3%) in the dupilumab Q2W (100 mg) + TCS group compared to 2/60 patients (3.3%) in the dupilumab Q4W + TCS group. In the placebo + TCS group, 1/60 patient (1.7%) had TEAEs in this SOC.

Respiratory, Thoracic and Mediastinal Disorders: A higher proportion of patients in the dupilumab Q2W (100 mg) + TCS group (10/63 patients [15.9%]) had TEAEs in this SOC than in the Q4W + TCS group (3/60 patients [5.0%]). In the placebo + TCS group, 16/60 patients ([26.7%) had TEAEs in this SOC. The PT Asthma was reported in 4/63 patients (6.3%) in the dupilumab Q2W (100 mg) + TCS group compared to 0/60 patients in the dupilumab Q4W + TCS group (and 7/60 patients [11.7%] in the placebo + TCS group).

The TEAEs that occurred with a higher frequency (≥2%) in the dupilumab Q4W (300 mg) + TCS group compared to the Q2W (100 mg) + TCS group were Upper Respiratory Tract Infection, Rhinitis, Injection Site Oedema, Erythema, and Alopecia.

The TEAEs that occurred with a higher frequency (≥2% in the dupilumab Q2W (100 mg) + TCS group compared to the Q4W (300 mg) group were Conjunctivitis Bacterial, Molluscum Contagiosum, Conjunctivitis, Herpes Virus Infection, Sinusitis, Gastritis, Injection Site Erythema, Injection Site Swelling, Dermatitis Atopic, Skin Exfoliation, Conjunctivitis Allergic, Cough, Rhinitis Allergic, Asthma, and Food Allergy.

*More than 30 kg Weight Stratum*

The SOCs in which TEAEs were reported by ≥10% of patients in any treatment group of this weight stratum were the following:

Infections and Infestations: A higher proportion of patients in the dupilumab Q4W + TCS group (26/60 patients [43.3%]) had TEAEs in this SOC than and in the dupilumab Q2W (200 mg) + TCS group (21/59 patients [35.6%]). The PT Nasopharyngitis was reported in 9/60 patients (15.0%) in the dupilumab Q4W (300 mg) + TCS group compared to 2/59 patients (3.4%) in the dupilumab Q2W (200 mg) + TCS group. In the placebo + TCS group, 31/60 patients (51.7%) had TEAEs in this SOC.

Gastrointestinal Disorders: There was no significant difference between the 2 dupilumab treatment groups (11/60 patients [18.3%] in the Q4W + TCS group and 10/59 patients [16.9%] in the Q2W [200 mg] + TCS group). In the placebo + TCS group, 7/60 patients (11.7%) had TEAEs in this SOC.

General Disorders and Administration Site Conditions: A higher proportion of patients in in the dupilumab Q2W (200 mg) + TCS group (10/59 patients [16.9%]) had TEAEs in this SOC than in the Q4W + TCS group (7/60 patients [11.7%]). The PT Injection Site Oedema was reported in 2/59 patients (3.4%) in the dupilumab Q2W (200 mg) + TCS group compared to 0/60 patients in the dupilumab Q4W (300 mg) + TCS group. In the placebo + TCS group, 5/60 patients (8.3%) had TEAEs in this SOC.

Nervous System Disorders: There was no significant difference between the 2 dupilumab treatment groups (6/60 patients [10.0%] in the Q4W + TCS group and 7/59 patients [11.9%] in the Q2W [200 mg] + TCS group). In the placebo + TCS group, 8/60 patients (13.3%) had TEAEs in this SOC.

Skin and Subcutaneous Tissue Disorders: The proportion of patients with TEAEs in this SOC was higher in the dupilumab Q4W + TCS group (11/60 patients [18.3%]) than in the dupilumab Q2W (200 mg) + TCS group (6/59 patients [10.2%]). This difference was not driven by any particular PTs. In the placebo + TCS group, 13/60 patients (21.7%) had TEAEs in this SOC.

Eye Disorders: There was no significant difference between the 2 dupilumab treatment groups (3/60 patients [5.0%] in the Q4W + TCS group and 5/59 patients [8.5%] in the Q2W [200 mg] + TCS group). In the placebo + TCS group, 7/60 patients (11.7%) had TEAEs in this SOC.

Respiratory, Thoracic and Mediastinal Disorders: The proportion of patients with TEAEs in this SOC was higher in the dupilumab Q4W + TCS group (11/60 patients [18.3%]) than in the Q2W (200 mg) + TCS group (5/59 patients [8.5%]). The PTs Asthma, Oropharyngeal Pain, and Rhinorrhoea were each reported in 2/60 patients (3.3%) in the dupilumab Q4W (300 mg) + TCS group compared to 0/59 patients in the dupilumab Q2W (200 mg) + TCS group. In the placebo + TCS group, 15/60 patients (25.0%) had TEAEs in this SOC.

The TEAEs that occurred with a higher frequency (≥2%) in the dupilumab Q4W (300 mg) + TCS group compared to the Q2W (100 mg) + TCS group were Nasopharyngitis, Conjunctivitis, Diarrhoea, Abdominal Pain Upper, Dermatitis Atopic, Urticaria, Asthma, Oropharyngeal Pain, Rhinorrhoea, and Skin Papilloma.

The TEAEs that occurred with a higher frequency (≥2%) in the dupilumab Q2W (100 mg) + TCS group compared to the Q4W (300 mg) + TCS were Bronchitis, Conjunctivitis Bacterial, and Injection Site Oedema.

### *Safety After Re-treatment with Dupilumab*

Effects of re-treatment with dupilumab on safety parameters were evaluated in a subset of patients from OLE study R668-AD-1434 who came from study R668-AD-1412. These patients had a treatment interruption of at least 8 weeks between the last dose of dupilumab in the parent study and the first dose of dupilumab in the OLE study. There were few severe TEAEs and SAEs and no deaths or AEs leading to discontinuation in this subset of patients. The TEAE profile was similar to that observed in both the 16-week, placebo-controlled pivotal study R668-AD-1652 and the overall population in the OLE study R668-AD-1434.

## *Safety related to drug-drug interactions and other interactions*

#### Withdrawal and Rebound

The effect of dupilumab withdrawal was evaluated in the context of disease recurrence following treatment discontinuation. During the 8-week follow-up period of study R668-AD-1412 (weeks 12 to 20) at the end of the 4-week repeat-dosing treatment period, there was a return of AD symptomatology, trending toward but not reaching baseline. These observations indicate that continuous treatment is necessary to achieve and sustain the clinical benefit of dupilumab. No rebound effect (worsening of disease above baseline) after treatment withdrawal was observed in the studies.

### *Discontinuation due to adverse events*

Study R668-AD-1652

A total of 4/362 (1.1%) patients experienced TEAEs leading to permanent study drug discontinuation; 2 in the placebo + TCS group (Asthma and Dermatitis Atopic) and 2 in the dupilumab Q2W + TCS group (Food Allergy and Conjunctivitis Bacterial). For the case of Food Allergy, the patient experienced an allergic reaction after eating ice cream that contained nuts. Because the patient received steroidal medication for the event, study drug treatment was permanently discontinued per protocol. The investigator considered the Food allergy as not related to study drug, as the patient had a pre-existing peanut allergy.

None of these events leading to study drug discontinuation were serious. Among these TEAEs, only 1 was classified as treatment-related (Conjunctivitis Bacterial.

Study R668-AD-1434

A total of 2/368 (0.5%) patients experienced TEAEs leading to permanent study drug discontinuation in patients in study R668-AD-1434 (Optic Disc Drusen and Dermatitis Atopic). Only 1 of these cases (Dermatitis Atopic) was considered related to the study drug.

Study R668-AD-1412

There were no TEAEs leading to study drug discontinuation in patients in study R668-AD-1412.

### *Post marketing experience*

Dupilumab is not currently approved in patients <12 years of age. There were 736 post-marketing cases reported for Dupixent cumulatively up to the data lock point of 22 Jul 2019 in patients <12 years of age this population, 733 of which were non-serious. The post-marketing data seem not to suggest any new safety concerns for dupilumab.

## 2.5.1. Discussion on clinical safety

*Patient accountability and exposure*

The safety analysis of patients with AD is based on the placebo-controlled phase 3 study (R668-AD-1652, 362 treated patients) and is supported by data from the completed phase 2a pharmacokinetic (PK)/safety study (R668-AD-1412, 37 treated patients), and the pediatric ongoing OLE (R668-AD-1434, 368 treated patients). All studies allowed concomitant use of topical treatments (eg, TCS, TCI).

362 out of 367 enrolled patients in the pivotal study R668-AD-1652 were treated with study treatment, and thereof 242 patients were exposed to dupilumab. Patients were assigned to three different dose regimens and stratified by baseline weight (<30 kg, ≥30 kg) and region (North America, Europe). A total of 391 patients were exposed to dupilumab during the parent studies (1412 or 1652) or open-label extension study (1434).

From study R668-AD-1412, 33 patients and from study R668-AD-1652, 335 patients joined OLE study R668-AD-1434. According to the MAH, 284 patients had completed ≥16 weeks of treatment in the OLE study, and 38 patients (all from the parent study R668-AD-1412) had completed ≥52 weeks of treatment.

Safety data was not pooled and the safety analysis is mainly focused on data derived from the pivotal study R668-AD-1652, supported by separate analyses of studies 1412 and 1434; this is acceptable to CHMP considering the size of the database.

Regarding all 362 treated patients included in the pivotal phase 3 study 1652, the proportion of patients receiving different treatment regimens were balanced (120 patients received dupilumab 300 mg Q4W + TCS and 122 patients received dupilumab 100/200 mg Q2W + TCS). The same applies to supportive phase 2 study 1412 (dupilumab 2 mg/kg QW: 18 patients, 4 mg/kg QW: 19 patients).

Overall, the safety data refer to 137 patients who have received at least 52 weeks of dupilumab treatment during both the parent studies R668-AD-1652 and R668-AD-1412 as well as the open label extension study R668-AD-1434. Hence, data volume relating to safety is considered acceptable to the CHMP.

The patient accountability in study 1652 and within the Q2W + TCS subgroups was fairly balanced, almost all the patients completed the study treatment (placebo: 92.7%, Q4W+TCS: 98.4% and Q2W+TCS: 99.2%) and the majority transitioned into OLE study 1434 (placebo: 95.1%, Q4W+TCS: 97.5% and Q2W+TCS: 95.9%).

Exposure data were pooled. The majority of the patients were treated with dupilumab beyond week 16 whereby different proportions are noted: 2 mg/kg: 94.4%, 4 mg/kg: 84.2%, 300 mg Q4W: 74.4%, 100 mg Q2W: 74.6%, 200 mg Q2W: 74.6%. In contrast to the other dose groups the proportion of patients assigned to the 300 mg Q4W arm receiving dupilumab beyond week 12 was merely 78.4%.

The greatest proportion of patients stemming from supportive study 1412 received dupilumab for 52 weeks (33/37). Only 7.5% (28/371) of the patients assigned to the 300 mg/kg Q4W + TCS during study 1652 and 1434 and none of the 100/200mg Q2W + TCS arm study arm reached treatment week 52. For patients assigned to the 100/200mg Q2W + TCS arm study arm no safety data beyond week 26 is available. Hence, long-term safety data beyond treatment week 26 is only available from 175 (Q4W) and 33 patients (2 or 4 mg/kg bw) and beyond treatment week 52 from 28 (Q4W) and 33 (2 or 4 mg/kg bw) patients (table 5), respectively.

*AEs and SAEs*

Overall, more patients assigned to the placebo+TCS group experienced AEs (300 mg Q4W+TCS: 65.0%, 100/200 mg Q2W: 67.2% and Placebo 73.3%) whereby more of the verum treatment groups had TEAEs (300 mg Q4W+TCS: 20.0%, 100/200 mg Q2W: 24.6% and Placebo 10.8%). Most TEAEs were mild to moderate in intensity. Two (2) TE-SAEs occurred in the 300 mg Q4W+TCS group but these did not lead to treatment discontinuation. During OLE study (n=368) 59.5% experienced TEAE, therefore 14.1% were deemed drug-related. 2.4% patients had SAEs but did not permanently discontinue dupilumab.

Summary of Adverse Events

Pivotal, placebo-controlled study R668-AD-1652:

The overall incidence of TEAEs was similar across all treatment groups. No dupilumab-treated patients in the pivotal placebo-controlled study experienced any treatment-emergent SAEs. The incidence of TEAEs leading to permanent treatment discontinuation was low.

There is no indication that dupilumab treatment increased the occurrence of systemic hypersensitivity reactions. There was no report of an anaphylactic reaction considered related to dupilumab.

The incidence of local injection site reactions was higher in the combined dupilumab + TCS groups than in the placebo + TCS group, consistent with SC injection of a protein biologic. There was no significant difference between the 2 dupilumab dose groups. No injection site reactions were severe or serious, and none of the events resulted in permanent treatment discontinuation. There was no increase in infections in general with dupilumab compared to placebo + TCS.

The most common PTs ins the SOC of Infections and Infestations were Nasopharyngitis and Upper Respiratory Tract Infection, ie, very common infections in that age group. The incidence of Conjunctivitis (based on the narrow and broad CMQ search) was higher in both dupilumab groups (with the highest incidence in the dupilumab Q2W + TCS group) than in the placebo + TCS group. All of the reported events were non-serious and mild or moderate in severity (except for 1 severe event of Conjunctivitis Allergic). All the events were transient in nature and resolved over time either spontaneously or with conventional treatment.

There are no new ADRs identified in the AD program for children compared to the adolescent and adult AD program.

The safety profile from the long-term OLE study R668-AD-1434 was consistent with that seen in studies in children with shorter duration of treatment.

Summary for Clinical Laboratory Evaluations

Mean and median chemistry and hematology laboratory values were generally consistent with baseline values at each visit or showed some small random fluctuations from baseline in the pivotal study AD 1652.

A decrease in LDH values was seen over time in the dupilumab dose groups; however, a positive correlation between LDH concentrations and AD severity has been reported in the literature (Kou, 2012)(Mukai, 1990). Decreases in LDH observed in this study could be a result of reduced AD disease activity and severity after dupilumab treatment. This is agreed by CHMP.

Increases in eosinophils were observed in patients treated with dupilumab; however, these increases had no clinical consequences. These eosinophil value changes were consistent with what was previously seen in the adult trials.

Results from laboratory observations in the supportive studies R668-AD-1434 and R668-AD-1412 were consistent with those of the pivotal study.

Immunogenicity

A few patients were positive for ADA during the pivotal study 1652, especially none included in the 300 mg Q4W+placebo treatment arm. No specific AE pattern became obvious due to the low case numbers. In OLE study R668-AD-1434 8.2% patients had a treatment-emergent positive ADA response during the study and 2.5% of the patients had a persistently positive ADA response during the study.

In patients 6 to 12 years of age the immunogenicity profile of dupilumab, given as Q2W or Q4W dosing regimens, with respect to treatment-emergent ADA was low; all titers were low and had no significant effect on the efficacy or safety of dupilumab in children.

Similar to adolescents, longitudinal assessment of ADA titers over a >2-year period in children who had developed high ADA titers (induced by the "prime and boost" regimen used in the R668-AD-1412 study) that resulted in attenuated systemic drug concentrations showed that continued treatment with dupilumab (2 mg/kg or 4 mg/kg once weekly [QW]) resulted in reduction of ADA titers and a corresponding increase in systemic dupilumab concentrations. Efficacy, as determined by percent change from baseline in EASI score, also generally improved in these patients with continued treatment throughout the study. None of these patients exhibited any signs or symptoms of a systemic hypersensitivity or serum sickness during treatment with dupilumab.

Overall, the frequency of ADA-positive patients seems to be significantly lower compared with the adolescent and adult population, the percentage of persistent ADA response is comparable to that of the adolescent AD population included in the dupilumab development programme. CHMP concurs that the

available immunogenicity data do not show a clinically significant effect of ADA on safety. However, long-term safety data is considered sparse. This will be followed up during the post marketing phase.

Higher incidences of both Atopic Dermatitis and Conjunctivitis were observed in ADA-negative patients. The incidence of AEs, such as injection site reactions, were similar between ADA positive and ADA-negative patients. There were no events of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab regardless of ADA or neutralizing antibody status.

*Analyses by weight strata*

Analyses by weight strata were performed for all patients receiving dupilumab. Patients randomized to the Q2W arm weighing <30 kg received 100 mg, patients ≥30 kg: 200 mg. All patients randomized to the dupilumab Q4W + TCS treatment group received dupilumab 300 mg Q4W.

The incidence of SAE after re-treatment was far higher than that one observed in the pivotal study R668-AD-1652 (4/362, 1.1%) or during OLE study R668-AD-1434 (9/368, 2.4%). However, only 33 subjects were analysed regarding effects of re-treatment and hitherto, long-term results of OLE study R668-AD-1434 are limited, so that bias regarding the frequencies are possible.
From the available data, no specific AE pattern was observed after retreatment with dupilumab after a pause of 8 weeks.
The possibility for treatment interruption and re-treatment is already introduced in the SmPC.

*TEAE leading to permanent study drug discontinuation*

During the pivotal study, the overall frequency of permanent study drug discontinuation due to TEAE was very low (1.1%). 2 patients each of the placebo + TCS and of the Q2W + TCS group stopped the treatment. The 2 TEAE in the dupilumab Q2W + TCS group were moderate. Overall, only the bacterial conjunctivitis was assessed to be drug-related which is agreed by CHMP.
A total of 2/368 (0.5%) patients experienced TEAEs leading to permanent study drug discontinuation in patients in study R668-AD-1434 and merely 1 of these cases presenting AD was considered related to the study drug.

## 2.5.2. Conclusions on clinical safety

Based on the provided data, there is no evidence that dupilumab treatment increases the occurrence of systemic hypersensitivity reactions, malignancy and suicidal behaviour in the paediatric population with atopic dermatitis aged 6-11 years. The safety profile was consistent with that observed in the adolescent and adult population. Based on the safety analyses, a uniform posology of 300 mg Q4W in patients 15 to <60kg with the possibility of up-titration to a Q2W regimen as performed during the OLE study has been recommended, to which the MAH agreed. The split loading dose and amended treatment regimen proposed for children weighing 15-60 kg is endorsed by CHMP.

For patients over 60 kgs a loading dose of 600 mg as two 300 mg injections following up by 300 mg every other week (Q2W) is recommended similarly as the recommended dose for adolescents and adult patients.

## 2.5.3. 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.

## 2.6. 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 5.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

### Safety concern

| | |
|---|---|
| Important identified risk | • Systemic hypersensitivity (including events associated with immunogenicity) |
| Important potential risk | • None |
| Missing information | • Use in pregnant and lactating women<br>• Conjunctivitis related events in AD patients<br>• Long-term safety |

AD: Atopic Dermatitis.

As part of this procedure, the applicant agreed to add detail to the discussion on the potential for use in paediatric patients not covered by the authorized indications, to the RMP at the next regulatory opportunity.

### Pharmacovigilance plan

| Study status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| Pregnancy registry (R668-AD-1639) Ongoing | To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes in asthma and AD patients. | Use in pregnant and lactating women | Protocol submission<br><br>Amended protocol (asthma cohorts)<br><br>Final report | Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018) Will also be submitted to other health authorities.<br><br>Submitted for information with EU-RMP v5.0 [Annex 3]<br><br>Will be submitted once available |
| Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing | To measure the prevalence of adverse pregnancy and infant outcomes in | Use in pregnant and lactating women | Protocol submission (amendment 1) | Submitted for information with EU-RMP v5.0 [Annex 3]. |

| | | | | |
|---|---|---|---|---|
| | 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. | | Final report | Will be submitted once available |
| 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) Ongoing | 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 related events in AD patients) | Final report | Q3 2023 |
| 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 | To evaluate the | Long-term safety | Final report | Q4 2020 |

| | | | | |
|---|---|---|---|---|
| extension study to assess the long-term safety of dupilumab in patients ≥12 years of age with asthma (Phase III) (LTS12551) (Cat. 3) | long-term safety and tolerability of dupilumab in patients with asthma. | | | |

AD: Atopic Dermatitis; PK: Pharmacokinetics; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

### *Risk minimisation measures*

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Important identified risk | | |
| Systemic hypersensitivity (including events associated with immunogenicity) | Routine risk minimization measures:<br><br>SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4<br><br>Prescription only medicine<br><br>Additional risk minimization measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Hypersensitivity questionnaire<br><br>Additional pharmacovigilance activities:<br><br>None |
| Important potential risks | | |
| None | | |
| Missing information | | |
| Use in pregnant and lactating women | Routine risk minimization measures:<br><br>SmPC sections 4.6 and 5.3<br><br>PIL section 2<br><br>Prescription only medicine<br><br>Additional risk minimization measures:<br><br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>Pregnancy questionnaire<br><br>Additional pharmacovigilance activities:<br><br>Pregnancy registry study (R668-AD-1639) in asthma and AD patients<br><br>Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients |

| | | |
|---|---|---|
| Conjunctivitis related events in AD patients | Routine risk minimization measures:<br>SmPC sections 4.4 and 4.8<br>PIL sections 2 and 4<br>Prescription only medicine<br>Additional risk minimization measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>Ophthalmology substudy LTS14041 (R668-AD-1225) |
| Long-term safety | Routine risk minimisation measures:<br>Prescription only medicines<br>Additional risk minimisation measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>Studies LTS12551, LTS14041 (R668-AD-1225) and LTS1434 (R668-AD-1434) |

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Minor changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed and accepted by the CHMP.

### 2.7.1. 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.

### 2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dupixent (dupilumab) is included in the additional monitoring list as new active substance and new biological since October 2017.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin disease. It is characterized by eczematous lesions (including erythema, excoriations, lichenification, infiltration, oozing), xerosis and pruritus. These clinical manifestations lead to significant sleep disturbances, severe psychological and sociological sequelae and impaired quality of life especially in patients with moderate to severe AD. The main goals of the treatment are the reduction of inflammation and symptoms, especially of pruritus.

Atopic dermatitis is one of the most common skin disorders in infants and children. The disease affects over 20% of children in many industrialized countries. Approximately 45% of all cases of AD begin within the first 6 months of life, 60% begin during the first year, and 85% begin before 5 years of age.

Recent studies have improved our understanding of the epidemiology of childhood AD. In general, more severe eczema correlated with poorer overall health, impaired sleep and increased healthcare utilization. Severe eczema was associated with higher prevalence of comorbid chronic health disorders, including asthma, hay fever and food allergies. The International Study of Asthma and Allergies in Childhood (ISAAC) phase 3 study surveyed over 8 countries and identified a 7.9% global prevalence of eczema in children 6 to 7 years old . The prevalence of AD in developed countries such as the US is expected to increase if the trends from the last 20 years continue. Rising prevalence seems to be paired with rising incidence in the total number of severe intractable cases, which includes more cases of children continuing with disease into the grade school years and increased number of cases persisting into adulthood.

### 3.1.2. Available therapies and unmet medical need

Currently available therapies for children with AD 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 population, 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 as young as infants. However, their long-term use or large body-surface application is limited by the risk of local side effects (e.g. skin atrophy and telangiectasia) as well as systemic adverse reactions, including hypothalamic-pituitary-adrenal axis suppression and Cushing syndrome. Children are more prone to the development of systemic reactions to topically applied medication because of their higher ratio of total body surface area to body weight. Linear growth retardation and delayed weight gain have been reported in children receiving TCS. Cushing syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, and adrenal insufficiency have been reported with chronic use. Moreover, continuous use of TCS can be associated with development of tachyphylaxis (decreased treatment response and requirement for higher doses of higher potency steroids).

Topical calcineurin inhibitors (TCI), 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, (e.g. face, genitals, and flexural areas). The more effective TCI product (tacrolimus ointment 0.1%) is not approved for use in children aged 6 to 11 years old. Crisaborole, a non-steroidal topical phosphodiesterase-4

(PDE4) inhibitor, has been approved for use in paediatric AD patients. Ciclosporin is not approved for AD in pediatric patients but often used off label for severe AD when systemic therapy is required. In addition, other systemic immunosuppressive agents are also commonly used in treatment of severe forms of the disease, including methotrexate, azathioprine and mycophenolate mofetil. A high proportion of patients suffer from relapse or rebound once the therapy is discontinued. The lack of safe and effective systemic treatments means that most patients with moderate-to-severe AD are not well controlled and further illustrates the need for an effective treatment for AD in children that also has a safety profile that is acceptable for chronic administration.

Thus, there exists a significant unmet medical need for an alternative treatment for -severe AD in children.

### 3.1.3. Main clinical studies

The application is based on the following studies:

A phase 3, placebo-controlled, pivotal study R668-AD-1652 in children ≥6 to <12 years of age with AD and a phase 3 OLE study R668-AD-1434 provides additional data to support long-term efficacy in children of this age group who had participated in a previous dupilumab AD clinical study. In addition, a phase 2a open-label PK study R668-AD-1412 provides additional supportive efficacy information.

The pivotal study R668-AD-1652 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in children ≥6 to <12 years of age with severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable.

In total 367 patients were enrolled and randomized to three different treatment arms differing in treatment frequency and doses. The Q2W + TCS treatment arm provided two different dose regimens according to body weight (patients <30 kg received Q2W SC injections of 100 mg dupilumab from week 2 to week 14, following a loading dose of 200 mg, patients >30 kg received Q2W SC injections of 200 mg dupilumab from week 2 to week 14, following a loading dose of 400 mg. The second arm provided a treatment scheme of 300 mg Q4W, following a loading dose of 600 mg regardless of weight and the third one matching placebo+TCS. Rescue therapy was provided if clinically necessary and patients applying systemic drugs were permanently discontinued.

Studies R668-AD-1434 and R668-AD-1412 allowed, but did not require, concomitant use of topical treatments; therefore, the efficacy data from these studies support the use of dupilumab with or without topical treatment.

Efficacy assessments included EASI, IGA of AD severity, worst itch score, and BSA involvement with AD. As to the endpoints both the IGA and EASI scales are established outcome measures and correlation with disease severity and activity is acknowledged. The worst itch (WI-NRS) scale as patient-reported outcome (PRO) measure and modified peak pruritus Numeric Rating Scale (NRS) was applied in the pivotal phase 3 study. 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.

Supportive data as to long-term efficacy comes from the phase 3 OLE study R668-AD-1434; additional PK and efficacy data is provided by the phase 2a open-label PK study R668-AD-1412. Both studies were assessed in a previous application (EMEA/H/C/004390/II/0012) extending the use from patients to adolescents aged 12 years and older who are candidates for systemic therapy.

## 3.2. Favourable effects

The proportion of patients achieving the primary endpoint IGA scores of 0 or 1 was significantly higher in the dupilumab Q4W + TCS (32.8%) and Q2W + TCS (29.5%) treatment groups compared with the placebo + TCS group (11.4%). This effect was consistent in several analyses using FAS, mFAS, PPS (primary and sensitivity analysis) and persistent throughout the 16 weeks of treatment. A slightly higher percentage of responders in the Q4W +TCS group after treatment initiation compared to the Q2W + TCS group (5.7% vs. 0.8%) was observed, which probably is attributable to the higher loading dose in this treatment group.

The co-primary endpoint was met in both dupilumab treatment groups. The proportion of patients achieving EASI-75 at week 16 was significantly higher in the Q4W + TCS (69.7%) and Q2W + TCS (67.2%) treatment groups compared with the placebo + TCS group (26.8%) also with consistent results obtained by the above-mentioned analyses.

The MAH has demonstrated clinical efficacy and superiority to placebo of all dupilumab dose regimens. The effects of therapy as determined by EASI 75 and IGA 0/1 were observed rather quickly starting immediately and continuously concerning the Q4W regimen and from week 3 regarding the Q2W regimen, respectively.

For the placebo + TCS group, less than 50% of patients achieved NRS reduction of at ≥3 or ≥4 points during the 16- week treatment period. The robustness of these results was confirmed by multiple sensitivity analyses, including analyses of all observed values, without censoring the data after rescue, although considerably more placebo + TCS patients received rescue treatment (19.5%) during the study than dupilumab + TCS-treated patients (3.3% combined; 4.1% dupilumab Q2W + TCS; 2.5% dupilumab Q4W + TCS).

At Week 16, key secondary endpoints (Percent Change in EASI Score, Percent Change in Weekly Average of Daily Worst Itch Score) showed statistically significant results indicating a sustained treatment effect of both dupilumab + TCS groups compared to the placebo + TCS group. As seen for the co-primary endpoint, better efficacy results were achieved for the Q4W + TCS group regarding the Percent Change in EASI Score from Baseline to Week 16. Results pertaining to the reduction of the Daily Worst Itch Score were minimally better in the Q2W group than in the Q4W group (LS Mean % Change -56.5 vs. -54.5).

The proportion of TCS medication-free days and the mean weekly dose of TCS were evaluated as efficacy secondary endpoints. Following the 16-week treatment period, there was a significantly higher mean proportion of topical AD medication-free days in both dupilumab + TCS groups compared to the placebo + TCS group (nominal $p<0.01$). The mean weekly dose of low / medium potency TCS was also shown to be significantly lower for the dupilumab + TCS treatment groups than in the placebo + TCS group (nominal $p<0.01$). A higher proportion of TCS medication-free days, lower mean weekly dose of TCS, and lower proportion of patients requiring rescue treatment suggests a potential steroid-sparing effect of dupilumab in patients ≥6 to <12 years of age treated with dupilumab + TCS.

*Ancillary analyses*

Ancillary analyses were conducted for weight strata as to patients weighing less or more than 30 kg. Analysis of efficacy response in the different weight strata revealed different clinical benefits resulting from different treatment schemes.

Patients ≥30 kg experienced a slightly better efficacy while receiving the Q2W + TCS regimen measured by a higher proportion of patients achieving the primary endpoints IGA 0 or 1, EASI-75 and 3 secondary pruritus-related endpoints. However, the reported difference was not found clinically relevant since the

effect was relatively small for the primary endpoint and several key secondary endpoints this effect and related mainly to the co-primary endpoint EASI-75 and the two secondary endpoints 'proportion of patients with reduction of weekly average of daily worst itch score ≥ 3 or 4'. The key secondary endpoint 'Percent Change from Baseline to Week 16 in Weekly Average of Daily Worst Itch Score from Baseline to Week 16', however, was nearly comparable.

In the <30 kg weight stratum the primary endpoints were met by a higher proportion of patients assigned to the Q4W + TCS regimen. Apart from the secondary endpoint 3-point reduction in the pruritus NRS score both of the other endpoints related to pruritus assessment were comparable between both dupilumab dose groups.

In context with the results of the PK/PD data (i.e. the high comparability of the E-R analysis regarding both regimens), the comparable results regarding the more stringent parameter IGA 0/, the slightly better safety profile of the Q4W regimen as well as the lower treatment burden that results from a four weekly administration, lead to the CHMP recommendation of a uniform posology for all paediatric AD patients aged 6-11 years. Additionally, a less frequent dosing regimen is expected to enhance treatment compliance.

The MAH also introduced up-titration in case of inadequate clinical response to 200 or 300 mg Q2W, based on body weight <60 kg or ≥60 kg, respectively. However, based on PK/PD simulations the recommendation for flexible dosing was amended to allow an increase to 200 mg Q2W in patients with body weight of 15 kg to less than 60 kg based on physician's assessment. This flexibility may allow for possible demonstration of efficacy with a higher concentration in patients who are not achieving an adequate response, although based on uncontrolled data.

Finally, successful re-treatment of relapsed patients following treatment discontinuation was demonstrated during OLE study R668-AD-1434.

## *3.3. Uncertainties and limitations about favourable effects*

Efficacy results of OLE study R668-AD-1434 showed improvements of AD symptoms based on the proportion of patients who achieved the co-primary endpoint as well as the key secondary endpoints. However, long-term efficacy data is limited which brings some limitations regarding longer-term maintenance.

The numbers of dupilumab-treated patients included in this submission are too small regarding the long-term efficacy of the Q2W regimen to recommend this dosing regimen. Additional data submitted during the procedure substantiate the overall safety conclusions but are still considered too sparse regarding the recommendation of a Q2W posology that was favoured by the MAH for children weighing >30 kg.

## *3.4. Unfavourable effects*

Pivotal study 1652:

More patients assigned to the placebo +TCS group experienced TEAEs, whereby more of the verum treatment groups had drug-related TEAEs.

Common TEAEs by PT that occurred with a higher frequency in the dupilumab treatment groups than in the placebo + TCS group were Nasopharyngitis, Conjunctivitis, Molluscum Contagiosum, Injection Site Erythema, Injection Site Swelling, Conjunctivitis Allergic, and Skin Papilloma.

Conjunctivitis occurred slightly more often in the dupilumab treatment groups.

The frequency of injection site reactions was higher in both verum groups.

OLE study 1434:

59.5% experienced TEAE, thereof 14.1% were deemed drug-related. 2.4% patients had SAEs but did not permanently discontinue dupilumab.

As to the TEAE pattern, similar results were obtained. The most common TEAEs by PT (≥5% in all patients) included Nasopharyngitis, Upper Respiratory Tract Infection, Dermatitis Atopic (typically worsening or exacerbation), Cough, Conjunctivitis Allergic, and Headache.

For adverse events of special interest, a total of 11/368 (3.0%) patients experienced treatment-emergent AESIs in study R668-AD-1434, 2 of which were serious AESIs (2 events of Anaphylactic Reaction were considered unrelated to treatment) and 13.9% and 11.4%, respectively (broad/narrow) experienced conjunctitivis.

As for immunogenicity, in OLE study R668-AD-1434 8.2% patients had a treatment-emergent positive ADA response during the study and 2.5% of the patients had a persistently positive ADA response during the study.

Based on the submitted data in paediatric patients 6 to 11 years, no new safety concern was identified. There was no significantly increased risk for dupilumab regarding malignancy, all types of infections, systemic hypersensitivity reactions and suicidal behaviour. The immunogenic potential of dupilumab seemed lower than observed in adults or adolescents since persistent ADA were rare.

## *3.5. Uncertainties and limitations about unfavourable effects*

Conjunctivitis occurred more often during OLE study 1434. However, the observed frequencies are comparable to those observed in the adolescent AD population (pivotal study 1526). Close monitoring will be performed in the post marketing setting.

There were no events of malignancy reported. However, there is insufficient data on long-term exposure to characterise the risk for developing malignancy. This issue had been discussed during the initial MA for AD.

Further uncertainties concern the limited long-term safety data in paediatric patients and the impact of dupilumab on pregnancies and their outcomes.

## *3.6. Effects Table*

Effects Table for Dupixent, Atopic Dermatitis (data cut-off: 28 June 2019)

| Effect | Short description | Unit | PLAC + TCS | DUP 300 mg Q4W + TCS | DUP 100/200 mg Q2W + TCS | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| Favourable Effects | | | | | | | |
| Primary EP IGA 0/1 | Proportion of patients with IGA 0 to 1 | % | 11.4 | 32.8 | 29.5 | Statistically significant and clinically meaningful | Study R668-AD-1652 |
| Co-primary EP EASI | Proportion of patients with EASI -75 (≥75% improvement from | % | 26.8 | 69.7 | 67.2 | Statistically significant and clinically meaningful | Study R668-AD-1652 |

| Effect | Short description | Unit | PLAC + TCS | DUP 300 mg Q4W + TCS | DUP 100/200 mg Q2W + TCS | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| -75 | baseline) | | | | | | |
| Key secondary EP | LS Mean Percent Change in EASI Score from Baseline to week 16 | LS mean perc change | -48.6 | -82.1 | -78.4 | Key secondary endpoints support the effects seen in the (co-)primary EP | Study R668-AD-1652 |
| | LS Mean Percent Change in Weekly Average of Daily Worst Itch Score from Baseline to week 16 | LS mean perc change | -25.9 | -54.6 | -57.0 | | Study R668-AD-1652 |
| Other secondary EP | Proportion of patients with improvement (reduction) of weekly average of daily worst itch score ≥4 | % | 12.3 | 50.8 | 58.3 | Secondary endpoint supports the effects seen in the co-primary EP | Study R668-AD-1652 |
| Unfavourable Effects | | | | | | | |
| TEAEs | SOC Infections and infestations | % | 50.8 | 43.4 | 40.2 | Most TEAE were mild-to-moderate, resolved during treatment period and didn't result in discontinuation of study drug | Study R668-AD-1652 |
| | Nasopharyngitis | % | 6.7 | 12.5 | 6.6 | Frequency in R668-AD 1434: 13.0%, (In adolescents in study R668-AD-1526, 300 mg Q4W: 10.8%) | Study R668-AD-1652 |
| | Injection Site Erythema<br>Injection Site Swelling<br>Injection Site Pain | % | 1.7<br>0.8<br>2.5 | 4.2<br>3.3<br>2.5 | 5.7<br>4.9<br>1.6 | Frequencies slightly higher than in adolescent population. Known ADR, no event of Injection Site Reaction was severe, serious, or led to study drug discontinuation | Study R668-AD-1652 |
| | Conjunctivitis | % | 2.5 | 4.2 | 5.7 | Known ADR, associated with AD | Study R668-AD-1652 |
| | Conjunctivitis Allergic | | 0.8 | 2.5 | 4.1 | | |

| Effect | Short description | Unit | PLAC + TCS | DUP 300 mg Q4W + TCS | DUP 100/200 mg Q2W + TCS | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|---|
| | ADA response | % | 1.7 | 0 | 4.9/ 5.3 | ADA were not associated with special TEAE. Low titers and transient. | Study R668-AD-1652 |

Abbreviations: AD= Atopic Dermatitis, PLAC=Placebo, DUP=Dupilumab, EP= endpoint, ISR=Injection Site Reaction, ADA= Anti-Drug Antibodies, TEAE= Treatment-Emergent Adverse Event, TC=Topical Corticosteroids, URTI= Upper Respiratory Tract Infection, Q2W=biweekly, Q4W=four-weekly, and refer to the list of abberviations.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The superiority of dupilumab over placebo is demonstrated for all three dose regimens regarding the primary and key secondary endpoints, and both the Q2W and Q4W regimens achieved clinically relevant results with a slightly better global efficacy of the Q4W regimen.

The Q4W posology is recommended by CHMP in paediatric AD patients aged 6-11 years weighing from 15 kgs to less than 60kg on the basis of PK/PD data showing a high comparability of the E-R analysis regarding Q2W and Q4W regimens, comparable results between both regimens on the more stringent parameter IGA 0/1, the slightly better safety profile of the Q4W regimen as well as the lower treatment burden that results from a four weekly administration.

In case of inadequate clinical response is observed, up-titration to 200 mg Q2W is also introduced as a posology based on body weight in patients from <15 kg to ≥60 kg. This flexibility allows possible demonstration of efficacy with a higher concentration in patients who are not achieving an adequate response, although based on uncontrolled data.

The split loading dose for children weighing 15-60 kg as proposed by the MAH is considered adequate and relevant to avoid peak concentrations.

For children 6 to 11 years weighing more than 60kg, the same posology as in adolescents weighing more than 60kg is recommended.

The most relevant safety concerns of dupilumab generally relate to infections, injection site reactions, and a formation of anti-drug antibodies resulting in systemic hypersensitivity reactions. Additionally, eye disorders such as conjunctivitis and related conditions were identified as AESI throughout the clinical development programme.

The observed treatment-emergent adverse events were generally mild to moderate and common viral infections prevailed as typical for this age class. Conjunctivitis of different etiology was slightly increased in the dupilumab treatment groups and this relatively rare clinical symptom is a known ADR. The long-term effect of chronic conjunctivitis in these patients is currently unknown. Therefore, cases of conjunctivitis should be further monitored through PSURs.

Dupilumab use was not associated with a higher risk of experiencing TEAEs of systemic hypersensitivity in the paediatric population, as no events occurred during the studies. This suggests a low immunogenic potential of dupilumab in the AD population aged 6-11 years.

Safety profile was generally similar to the profile observed in adolescents and adults.

### 3.7.2. Balance of benefits and risks

The CHMP is the opinion that the favourable effects outweigh the unfavourable effects. The benefit-risk balance in patients from 6 to 11 years old with severe atopic dermatitis is positive.

In these patients, the agreed posology is:

- In patients 15 kg to less than 60 kg an initial dose of 300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15 and then subsequent doses of 300 mg every 4 weeks (Q4W), (starting 4 weeks after Day 15 dose).

The subsequent dose may be increased to 200 mg Q2W based on physician's assessment.

- In patients weighting more than 60 kg an initial dose of 600 mg (two 300 mg injections) and then subsequent doses of 300 mg every other week (Q2W).

### 3.7.3. Additional considerations on the benefit-risk balance

Not applicable

### *3.8. Conclusions*

The overall B/R of Dupixent is positive in the following indication: treatment of severe atopic dermatitis in children 6 to 11 years old who are candidates for systemic therapy.

## 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 expand the indication of severe atopic dermatitis to patients from 6 years to 11 years. Consequently, the sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The PL is updated accordingly.

Minor changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s).

The RMP has been amended accordingly. (version 5.0)

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 <PIP P/0374/2019 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 ‘EMEA/H/C/004390/II/0027’.