27 June 2019
EMA/463030/2019
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/0012

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
AI Autoinjector
ALP Alkaline phosphatase
BMI Body mass index
BUN Blood urea nitrogen
CNS Central nervous system
CPK Creatine phosphokinase
CsA Ciclosporin, cyclosporin A, cyclosporine, or cyclosporine A
CSR Clinical study report
DLP Data lock point
EAIR Exposure-adjusted incidence rate
ECG Electrocardiogram
EOT End of treatment
EU European Union
HLT High-level term
HSV Herpes simplex virus
IDMC Independent Data Monitoring Committee
Ig Immunoglobulin
IL Interleukin
ISR Injection site reaction
LDH Lactate dehydrogenase
MedDRA Medical Dictionary for Regulatory Activities
nP/100 PY Number of patients per 100 patient-years
OLE Open-label extension
PCSV Potentially clinically significant value
PDE4 Phosphodiesterase-4
PFP Pre-filled pen
PFS Pre-filled syringe
PK Pharmacokinetic(s)

PT Preferred term
QW Once weekly
Q2W Every 2 weeks
Q4W Every 4 weeks
Q8W Every 8 weeks
RBC Red blood cell
SAE Serious adverse event
SAF Safety analysis set
SAP Statistical analysis plan
SC Subcutaneous(ly)
SCS Summary of Clinical Safety
SD Standard deviation
SMQ Standardized MedDRA query
SOC System organ class
TARC Thymus and activation-regulated chemokine
TCI Topical calcineurin inhibitor
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

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 16 October 2018 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 extend the adult atopic dermatitis indication to the paediatric, 12 years to 17 years (adolescent) patients under Article 8 of the Paediatric Regulation (1901/2006). This study is submitted in accordance with the requirement of Article 46.

The requested variation proposed 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) P0169/2014 on the agreement of a paediatric investigation plan (PIP). A waiver was granted for the paediatric population from birth to less than 6 months on the grounds that the specific medicinal product is likely to be unsafe

At the time of submission of the application, the PIP EMEA-001501-PIP01-13 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 applicant 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 applicant 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	16 October 2018
Start of procedure:	3 November 2018
CHMP Rapporteur Assessment Report	20 December 2018
CHMP Co-Rapporteur Assessment Report	20 December 2018
PRAC Rapporteur Assessment Report	21 December 2018
PRAC members comments	9 January 2019
Updated PRAC Rapporteur Assessment Report	10 January 2019
PRAC Outcome	17 January 2019
CHMP members comments	21 January 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	24 January 2019
Request for supplementary information (RSI)	31 January 2019
CHMP Rapporteur Assessment Report	28 May 2019
PRAC members comments	n/a
CHMP members comments	17 Jun 2019
Updated CHMP Rapporteur Assessment Report	19 Jun 2019
Opinion	27 Jun 2019

2. Scientific discussion

2.1. 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. Dupilumab is being developed for atopic dermatitis (AD) in pediatric populations, following the approval in adult patients with moderate-to-severe AD. Dupilumab has been approved in multiple regions for the treatment of adult patients with moderate-to-severe AD.

The ongoing pediatric clinical program has been designed to assess the safety and efficacy of dupilumab in patients 6 months to <18 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies were not advisable.

A Paediatric Investigation Plan (PIP) for dupilumab, solution for injection, subcutaneous use, for the "treatment of atopic dermatitis" was submitted to the EMA on 31 July 2013 (EMEA-001501- PIP01-13). The EMA issued a positive decision on 7 July 2014 (P/0169/2014) for the condition "treatment of atopic dermatitis".
• A waiver was granted for the paediatric population from birth to less than 6 months on the grounds that the specific medicinal product is likely to be unsafe.
• A deferral for one or more measures was granted for the paediatric population from 6 months to 18 years of age for the treatment of atopic dermatitis.
Lastly, a request for PIP modification was submitted on 1st February 2018 and the EMA decision (P/0125/2018) was issued on 15 June 2018.
The purpose of this application is to support a change in the target indication to include adolescents with moderate-to-severe AD based on the results from study R668-AD-1526 with patients aged ≥ 12 to <18 years and supporting data from 3 other studies (R668-AD-1412; R668-AD1607; R668-AD-1434).

The proposed indication is:
Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, however an updated carcinogenicity report was provided in this application. This was considered acceptable by the CHMP.

2.2.1. Toxicology

Carcinogenicity

The purpose of this amendment was to reflect an updated literature search cut-off date in support of subsequent marketing applications for the atopic dermatitis indication in adolescent (≥12 to <18 years of age) patients.

A literature search for any articles published between October 1, 2017 and June 6, 2018 was performed, and no new publications were identified that would change the conclusions of the original document. No changes have been made to the original document.

The conclusion stated in the original application remains the same.

In summary, the weight-of-evidence for the available literature data related to IL-4Rα inhibition, and animal toxicology data with surrogate antibodies REGN1103 and REGN646, do not support an increased risk of cancer for dupilumab. Hence, the MAH maintains that no additional nonclinical studies are necessary to evaluate the carcinogenic potential of dupilumab. This is agreed by CHMP.

2.2.2. Ecotoxicity / environmental risk assessment

Dupilumab is a water soluble monoclonal antibody which undergoes extensive *in vivo* metabolism. The human excretion products of dupilumab are predicted to be rapidly and readily degraded in sewage collection and treatment systems and in the environment. Therefore, dupilumab is unlikely to result in a significant risk to the environment. Therefore according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) dupixent is exempt from submission of an ERA. This is acceptable by CHMP.

2.2.3. Discussion on non-clinical aspects

There are no updated non clinical data in this application that need assessment.

2.2.4. Conclusion on the non-clinical aspects

Not applicable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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.

Table 1: Tabular overview of clinical studies

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]	Adolescents Planned / Enrolled
R668-AD-1526 /Phase 3/ 05 Apr 2018/ Primary analysis completed	The primary objective of this study is to demonstrate the efficacy of dupilumab as a monotherapy in patients ≥12 to <18 years of age with moderate-to-severe AD.	Randomized (1:1:1), double-blind, placebo-controlled, parallel-group 16-week treatment duration 12-week follow-up	Dupilumab Q2W treatment group: 200 mg Q2W (patients <60 kg) or 300 mg Q2W (patients ≥60 kg) Dupilumab Q4W treatment group: 300 mg Q4W, irrespective of weight Placebo group	~240 / 251	~240 / 251
R668-AD-1434 /Phase 3/ 21 Apr 2018/ Ongoing	Secondary objectives included assessment of long-term efficacy in adolescent patients ≥12 to <18 years of age as well as to determine immunogenicity after re-treatment.	Multicenter, OLE The OLE treatment period for a particular pediatric age group in a particular geographic region will last until regulatory approval of dupilumab for AD in that age group in that region.	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] / 275 (34 patients aged ≥12 to <18 years of age will have been exposed to dupilumab for ≥1 year)	NA[c] / 275
R668-AD-1412 /Phase 2a/ NA/Completed	Secondary objectives were to explore the immunogenicity and efficacy of dupilumab in adolescent patients ≥12 to <18 years of age. .	Multicenter, open-label, ascending-dose, sequential-cohort Single-dose, followed by 4 weekly doses and 8-week follow-up	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 / 40

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]	Adolescents Planned / Enrolled
R668-AD-1607 /Phase 1b/ 28 Sep 2017/ Part A[d] – Primary analysis completed Part B - Ongoing	Secondary objectives included assessment of efficacy of 200 mg and 300 mg dupilumab administered Q2W SC using either an AI device or PFS in patients with AD. .	Randomized, open-label 12-week treatment duration 12-week follow-up	Part A: 200 mg Q2W after a loading dose of 400 mg on day 1 Part B: 300 mg Q2W after a loading dose of 600 mg on day 1	Part A: 84 / 85	NA[d] / 18

[a] Study status is based on the time of the data cut-off date for the studies in this submission.
[b] Only data from the adolescent patients (males or females ≥12 to <18 years of age) with moderate-to-severe AD in each study are presented in this submission.
[c] The number of adolescent patients planned was not defined in the protocol.
[d] Only Part A data are presented in this submission.
Abbreviations: AD, atopic dermatitis; AI, autoinjector; NA, Not applicable; OLE, open-label extension; PFS, prefilled syringe; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneously.

The clinical development program of dupilumab in the treatment of adolescent AD comprises 4 clinical studies. R668-AD-1526 is the pivotal phase 3 monotherapy study in patients aged 12-18 years with moderate-to-severe AD not adequately controlled with currently available topical treatments. Supportive data are derived from a phase 2a, open-label pharmacokinetic (PK)/safety study (R668-AD-1412), an pediatric open-label extension study (R668-AD-1434) and an open-label autoinjector (AI) study (R668-AD-1607, note: data assessed as part of the extension of indication in asthma). Thus, relevant patient exposure includes 292 adolescent patients stemming from studies R668-AD-1526, R668-AD-1412 and R668-AD-1434.

The clinical development program was designed to assess the safety and efficacy of dupilumab in adolescent patients with moderate-to-severe AD not adequately controlled with currently available topical treatments. The patient population comprised adolescents with AD, as defined by the American Academy of Dermatology Consensus Criteria (Eichenfield, 2004) (Eichenfield, 2014). These patients had moderate-to-severe AD lesions affecting a large portion of their body surface area (BSA). They experienced high levels of AD symptoms, including pruritus. Their disease could not be adequately controlled with topical prescription medications. This population included patients who had been, or would typically be, candidates for systemic AD therapies. Efficacy assessments included measurements of the extent and intensity of AD signs, severity of AD symptoms, the impact of AD on QOL, and anxiety and depression scores.

2.3.2. Pharmacokinetics

Adolescent patients with moderate-to-severe AD have been included in 4 dupilumab clinical studies where PK and pharmacodynamic (PD) data have been collected (refer to Table 1). A variety of subcutaneous (SC) dosing regimens was evaluated in these studies including: 2 mg/kg and 4 mg/kg single dose or repeated QW dose, 200 mg Q2W, 300 mg Q2W, and 300 mg Q4W.

The indication in adolescents with moderate-to-severe AD is based primarily on the phase 3 randomized controlled study R668-AD-1526 assessing efficacy and safety of dupilumab in adolescent patients; exposure-response (E-R) and PK data are presented to support the dosing regimen in adolescent patients. The proposed to-be-marketed dosing regimen for adolescents with AD is tiered by body weight with patients <60 kg receiving 200 mg Q2W following a 400 mg loading dose, and patients ≥ 60 kg receiving 300mg Q2W following a 600 mg loading dose (referred to as the 200/300 mg Q2W regimen). This tiered regimen was

selected for the phase 3 pivotal trial, R668-AD-1526, using simulation from a population PK model based on phase 2 pediatric data with the aim of bridging the dupilumab exposure distribution in adolescent patients to that achieved with the standard 300 mg Q2W regimen in adults.

With respect to PK, in the current application the distribution of trough concentrations was assessed at week 16 for the 200/300 mg Q2W versus the 300 mg Q4W regimens. The nature of PK sampling varied from dense sampling in the R668-AD-1607 study, to semi-dense sampling in the R668-AD-1412 study, to sparse sampling in the R668-AD-1434 and R668-AD-1526 studies

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 1)				
R668-AD-1607 Module 5.3.5.2 Study (Part A) Completed	Patients with moderate-to-severe AD ≥12 years of age (46 males, 39 females), 18 patients <18 years old All patients (85) were included in the PK analysis set.	Compare systemic exposure of dupilumab administered using AI device versus PFS.	Phase 1b multicenter, randomized, open-label study consisting of a screening period (up to 28 days), a 12-week treatment period, and a 12-week post-treatment follow-up period. The study was conducted in 2 parts: Part A and Part B. Dense sampling for dupilumab (C_{max}, $AUC_{0-\tau}$, C_{trough}) Treatment duration 12 weeks Follow-up 12 weeks	SC loading dose of 400 mg, and 200 mg dupilumab SC Q2W dosing for 12 weeks (n=85 for Part A [200 mg in 1 mL autoinjector and PFS])
Atopic Dermatitis – SC Administration (Phase 2)				
R668-AD-1412 Module 5.3.3.2 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. 40 adolescents were included in the PK analysis set.	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. Part A: single dose and 8-week semi-dense PK sampling Part B: 4 weekly doses Follow-up 8 weeks	SC doses of dupilumab 2 mg/kg and 4 mg/kg 78 patients enrolled, 40 adolescents ≥12 to <18 years of age and 38 children ≥6 to <12 years of age

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 3)				
R668-AD-1526 Module 5.3.5.1 Study Ongoing Primary analysis CSR completed	Patients (≥12 to <18 years of age) with moderate-to-severe AD whose disease cannot be adequately controlled with topical medications or for whom topical treatment is medically inadvisable. 250 patients were included in PK analysis set.	Trough concentrations and immunogenicity were assessed but not as a primary or secondary objective	Phase 3, global randomized, double-blind, placebo-controlled, parallel group, repeat dose study Sparse sampling for C_{trough} Treatment duration 16 weeks Follow-up 12 weeks	85 patients on placebo 82 patients on SC doses of dupilumab: 300 mg (39) or 200 mg (43) Q2W (weight based, ≥60 kg or <60 kg) following a loading dose of 600 mg or 400 mg, respectively 83 patients on dupilumab 300 mg Q4W (regardless of weight) with loading dose of 600 mg Overall, approximately 120 patients ≥60 kg and 120 <60 kg
R668-AD-1434 Module 5.3.5.2 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. 275 patients were included in the PK analysis set.	To assess the trough concentrations of functional dupilumab in serum in pediatric patients with AD after re-treatment with dupilumab.	Phase 3 open-label extension study Sparse sampling for C_{trough} Treatment duration 260 weeks Follow-up 12 weeks	69 patients previously on placebo and 206 patients previously on SC doses of dupilumab. Dupilumab SC 300 Q4W (n=275) up-titrated to 300 mg Q2W (n=85) or 200 mg Q2W (n=56) for patients ≥6 to <18 years.
EFC13579 Module 5.3.5.1 asthma marketing application Study Completed	Adolescent patients (≥12 years to <18 years of age) with persistent asthma on background therapy with inhaled corticosteroids in combination with 1 or 2 other controller medicines. 107 adolescent patients were included in the PK analysis set.	To evaluate dupilumab systemic exposure and incidence of ADA	Phase 3 randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab. Sparse sampling for C_{trough} Treatment duration 52 weeks Follow-up 12 weeks	40 patients on placebo 67 patients on SC doses of dupilumab: 200mg Q2W (n=34) or 300 mg Q2W (n=33)

AD – atopic dermatitis; C_{trough} – trough concentration at the end of the dosing interval; SC – subcutaneous;

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

Bioanalytical methods

Determination of functional dupilumab

The quantitative measurement of functional dupilumab was conducted using the validated enzyme linked immunosorbent assay (ELISA) method REGN668-AV-13074-VA-01V2. This method was already described and assessed during the original AD marketing application.

Incurred sample reanalysis (ISR) for the functional dupilumab assay was performed in R668-AD-1021 (to support adult population in the R668-AD-1607 study) and in R668-AD-1412 to support the pediatric population in the current submission. The data for the ISRs of the R668-AD-1021 and R668-AD-1412 studies are provided in their respective sample bioanalytical reports (BARs). ISR passing rate (reanalysis results within ±30% variability of the original result) in study R668-AD-1021 was 88.7% and ISR passing rate in study R668-AD-1412 was 90.8%. Thus, all ISRs performed met acceptance criteria, indicating that the assays generated robust data in both the adult (R668-AD-1607 Part A) and the pediatric (R668-AD-1412, R668-AD-1434, and R668-AD-1526) study populations.

Determination of anti-dupilumab antibodies

REGN668-AV-13089-VA-01V3 Validation of a Bioanalytical Method for Detection of Anti-REGN668 Antibodies in Human Serum

- Objectives and Methods:

This bioanalytical method is a non-quantitative, titer-based, electrochemiluminescent bridging immunoassay, which was thoroughly investigated with respect to a set of pre-defined validation parameters specified in the Bioanalytical Validation Protocol with the objective of demonstrating that it is suitable and reliable for the detection of ADA.

- Results:

REGN-AV-13089-VA-01V2 of this method has been described in the original marketing application for AD. Additional data were generated and the validation report of this method was amended to generate REGN668-AV-13089-VA-01V3. Updates to this method were discussed in the marketing application for asthma. The ADA assay cut points (described in the original marketing application for AD) for this assay which were based on the AD population were employed in the bioanalysis of the clinical samples of studies R668-AD-1607 Part A, R668-AD-1412, R668-AD-1434, and R668-AD-1526.

REGN668-AV-15153-VA-01V1 - Validation of a Bioanalytical Method for Detection of Anti-REGN668 Antibodies in Human Serum Using a Modified REGN668

- Objectives and Methods:

This bioanalytical method was thoroughly investigated with respect to a set of pre-defined validation parameters specified in the Bioanalytical Validation Protocol .

- Results:

The assay method, the ADA assay cut points for this method, and the 2 assay strategy employed using this ADA assay are all described in the Module 2.7.1 of the marketing application for asthma. The ADA assay cut points were calculated using the baseline samples from patients with high background responses from asthma population and employed in the bioanalysis of the clinical samples in the R668-AD-1412 study.

Neutralizing anti-dupilumab antibodies

REGN668-AV-13112-VA-01V2 Validation of a Competitive Ligand Binding Assay for Detection of Neutralizing Anti-REGN668 (Dupilumab) Antibodies in Human Serum

The method applied for the detection of functional dupilumab appears to correspond to the method used in the initial marketing authorization application for AD and this method has been accurately validated (REGN668-AV-13074).

Additional data analyses were included in the amended validation report (REGN668-AV-13112-VA-01V2) submitted in the marketing application for asthma. Updates to this method included modification of the assay cut point using a 1% false positive rate.

Clinical studies with collection of PK and PD data

Study R668-AD-1412

The PK of dupilumab in the pediatric population were first evaluated in pediatric patients with moderate-to-severe AD following single and repeated dose of 2 mg/kg and 4 mg/kg. The concentration-time profiles for functional dupilumab in serum suggest concentration dependent elimination, consistent with target-mediated drug disposition. 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 generally consistent with that observed in adults with moderate-to-severe AD.

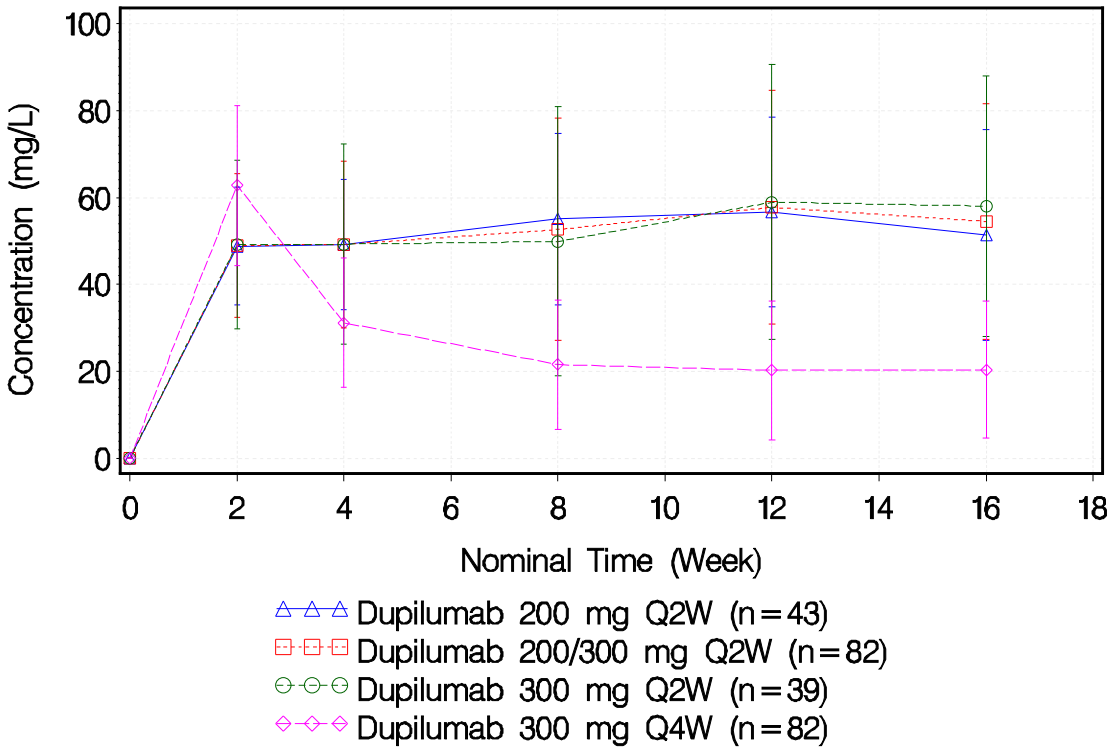
Study R668-AD-1526

In the phase 3 study, adolescent patients with AD were treated with dupilumab 200/300 mg Q2W (tiered by body weight) or 300 mg Q4W, administered via a prefilled syringe (PFS). The choice of dose was based on R668-AD-1412 and 200 mg <60 kg and 300 mg >=60 kg with the aim of achieving a single normalized exposure across this patient population.

The study consisted of 3 periods: screening of up to 5 weeks, treatment period of 16 weeks, and follow-up of 12 weeks. Samples for assessment of drug concentrations were collected on days 1, 15, 29, 57, 85, 113, and 197 and samples for ADA on days 1, 29, 113, and 197.

Systemic concentrations of dupilumab appeared to achieve steady state at or before week 12 (see figure below). Using the week 16 dupilumab concentrations as a representation of steady state, the mean steady state trough concentrations were approximately 3-fold higher for the 200 mg/300 mg Q2W regimen compared to the 300 mg Q4W regimen (54.5±27.0 mg/L vs 19.8±15.9 mg/L).

Figure 1: Mean (±SD) Trough Concentrations of Functional Dupilumab in Serum vs Week by Dose Group



Note: all concentrations are trough concentrations except week 2 in the Q4W dose group.

For the Q2W regimen, similar exposure was achieved for patients <60 kg who received 200 mg compared to patients ≥60 kg who received 300 mg. As expected when administering the same dosing regimen across all body weights, the 300 mg Q4W regimen resulted in lower Ctrough in patients ≥60 kg as compared to patients <60 kg. Overall, a larger number of adolescent patients receiving the Q4W regimen showed week 16 Ctrough of dupilumab at or near the LLOQ (0.078 mg/L).

There is no clear evidence of a clinically meaningful impact of immunogenicity on dupilumab exposure. Anti-drug antibody/NAb-positive patients exhibited individual concentration-time profiles in the range of ADA/NAb-negative patients for the 200 mg/300 mg Q2W and 300 mg Q4W regimens. Scatter plots of the continuous endpoints, EASI and NRS percent change from baseline, show that the efficacy profiles of ADA/NAb-positive patients fall within the distribution of ADA/NAb-negative patients receiving the 200 mg/300 mg Q2W regimen. Inspection of individual profiles of NAb-positive adolescent patients showed that there was no clear association between ADA/NAb positivity, drug concentration, and drug effect.

Study R668-AD-1434

Study R668-AD-1434 is an open-label extension (OLE) study in pediatric patients who had previously enrolled in other dupilumab pediatric AD studies. Samples for drug concentration assessments for the patients ≥12 years to <18 years were collected on days 1, 113, 365, 533, 729, 1065, 1401, and 1821. Only results from adolescent patients ≥12 years to <18 years of age are reported here. Samples for ADA analysis were collected at baseline, and weeks 4, 12, 24, 36, and 48 for patients recruited from parent study R668-AD-1412 and for patients recruited from R668-AD-1607 and R668-AD-1526, samples were collected at baseline and week 16.

At the time of the data cut-off for this report, a total of 275 patients aged ≥12 to <18 years from parent studies R668-AD-1412, R668-AD-1526, and R668-AD-1607 were included in the study.

Adolescent patients receiving a 2 mg/kg QW regimen achieved mean steady state trough concentration at week 48 of 73 mg/L versus 161 mg/L (approximately 2-fold higher) for the 4 mg/kg QW regimen.

The mean concentration of dupilumab at week 16 in adolescent patients from parent studies R668-AD-1526 and R668-AD-1607 who received 300 mg Q4W in R668-AD-1434 was 15.9 mg/L. In those adolescent

patients who were up-titrated to 200 mg/300 mg Q2W due to inadequate response, mean Ctrough at week 16 was approximately 45 mg/L.

A summary of adolescent patients enrolled into study R688-AD-1434 from previous studies is provided in Table 6.

Table 6: Summary of Baseline Characteristics of Patients that Enrolled from Previous Studies - Adolescents ≥12 to <18 Years of Age (SAF)

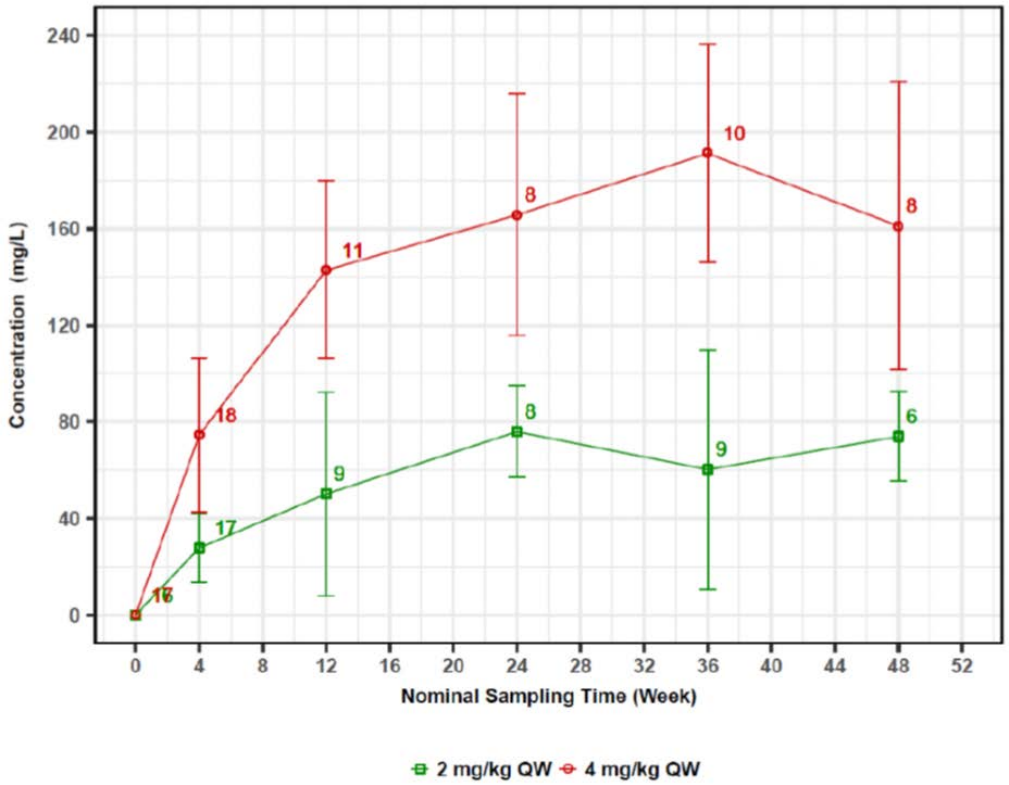
	Total (N=275)
Treatment received in previous study	
Dupilumab	206 (74.9%)
Placebo	69 (25.1%)
Patients Enrolled from the Previous Study	
R668-AD-1412	36 (13.1%)
2 mg/kg QW	17 (6.2%)
4 mg/kg QW	19 (6.9%)
R668-AD-1526	201 (73.1%)
Placebo	69 (25.1)
200 mg Q2W	36 (13.1%)
300mg Q4W	67 (24.4%)
300mg Q2W	29 (10.5%)
R668-AD-1607	38 (13.8%)
300 mg Q2W	27 (9.8%)
200 mg Q2W	11 (4.0%)

Abbreviations: AD, atopic dermatitis, QW, weekly; Q2W, every 2 weeks, Q4W, every 4 weeks.
Source: Post-text Table 4.2.1/1a

A high proportion of patients were White (69.5%) and male (58.9%), but other races and ethnicities were adequately represented. The mean (SD) age of patients was 14.6 ±1.7 years. More than 40% of patients were overweight (BMI ≥85 percentile for age and gender).

Adolescent patients receiving a 2 mg/kg QW regimen achieved mean steady-state trough concentration of 73 mg/L at week 48 versus 161 mg/L (approximately 2-fold higher) for the 4 mg/kg QW regimen (Figure 18). The mean trough concentration of dupilumab at week 16 in adolescent patients from parent studies R668-AD-1526 and R668-AD-1607 who received 300 mg Q4W in R668-AD-1434 was 15.9 mg/L (Table 35). In those adolescent patients who were up-titrated to 200 mg/300 mg Q2W due to inadequate response, mean trough concentration at week 16 was approximately 55 mg/L.

Figure 18: Mean (±SD) Concentrations of Functional Dupilumab in Serum by Nominal Time and Treatment Group in Patients with AD Who Initially Received 2 mg/kg QW or 4 mg/kg QW in Parent Study R668-AD-1412 (Study R668-AD-1434) – Adolescent ≥12 to <18 Years of Age (PK Analysis Set)



Note: Numbers inside the plot represent number of patients in each visit. Data up to week 48 was used for analysis. Patients rolled over from parent study R668-AD-1412. All 36 patients provided at least 1 sample during the analysis period. Blood sampling is described in the Synopsis of Appendix 5
Source: Figure 1 of Clinical Pharmacology report (Appendix 5)

Table 35: Descriptive Statistics of Mean Functional Dupilumab Concentrations in Serum (mg/L) by Nominal Time and Treatment Group in Adolescent Patients with AD from Parent Studies R668-AD-1526 and R668-AD-1607 Who Initially Received 300 mg Q4W (Study R668-AD-1434) - Adolescent ≥12 to <18 Years of Age (PK Analysis Set)

Analysis Visit	n	Mean	SD	CV%	SE	Min	Q1	Median	Q3	Max
Dupilumab 300 mg Q4W										
Baseline	100	16.4	0.815	28.76	175.07	2.88	0.0	0	22	143.0
Week 16	58	15.9	16.46	103.42	2.16	0.0	2	12.6	21	84.4
Dupilumab 300 mg Q4W->200 mg Q2W										
Week 16	21	45.3	18.91	41.74	4.13	0.0	36	45.9	58	78.4
Dupilumab 300 mg Q4W->300 mg Q2W										
Week 16	19	44.8	23.11	51.61	5.30	17.0	24	45.0	58	96.6

Note: Patients rolled over from parent studies R668-AD-1526 and R668-AD-1607.
Abbreviations: n, number of patients; SD, standard deviation; SE, standard error; CV, coefficient of variation; Q1, first quartile; Q3, third quartile, Q2W, every 2 weeks, Q4W, every 4 weeks.
Source: Table 6 of Clinical Pharmacology report (Appendix 5)

In those adolescent patients who were up-titrated to the proposed to-be-marketed 200 mg/300 mg Q2W regimen for adolescents, mean trough concentration at week 16 was approximately 45 mg/L. However, there was considerable variability in trough concentrations at week 16 in adolescents receiving the weight-tiered 200 mg/300 mg Q2W dosing regimen (CV% 41.7-51.6%).

Study EFC13579 (Asthma)

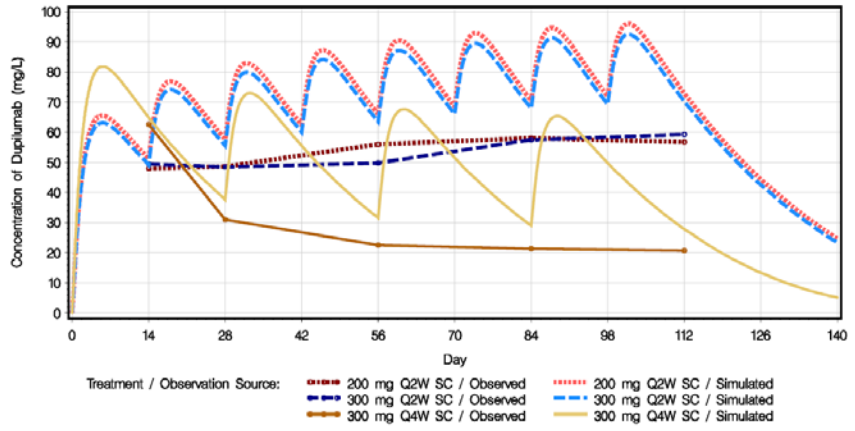
Study EFC13579 was a randomized, double-blind, placebo-controlled, parallel group, multi-national study, using dupilumab or placebo as add-on therapy to inhaled corticosteroids in combination with one or 2 other controller medicines (eg, LABA, long-acting muscarinic antagonists [LAMAs], leukotriene receptor antagonist [LTRA], methylxanthines) in the treatment of patients aged ≥12 years with persistent asthma.

Following SC administration of dupilumab, Ctrough values increased with each subsequent dose administration until week 12 to 16 when steady state appeared to have been achieved. The steady state exposure increase from 200 mg Q2W to 300 mg Q2W was slightly greater than dose proportional in adults, suggesting that saturation of the target-mediated elimination may not have been completely achieved in all patients at the 200 mg Q2W dose level. Mean dupilumab exposure was higher in adolescents than adults, as a consequence of lower mean body weight, but was well within the safety exposure margin established in adults at 300 mg QW.

Population PK modelling

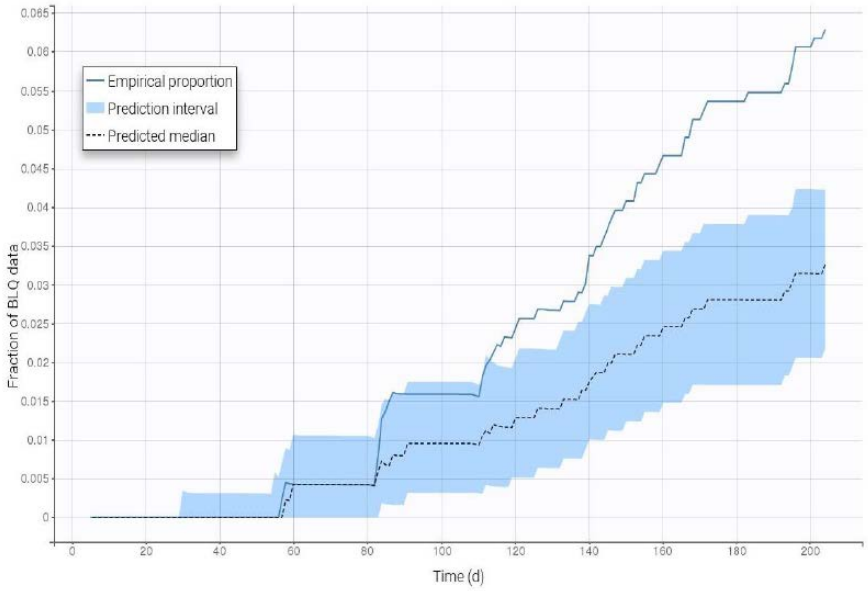
The population PK model utilizing the parameter estimates from the original marketing application for adults with moderate-to-severe AD was used to predict the concentration-time course in adolescents after administration of Q2W and Q4W regimens and the results compared to the observed adolescent data from study R668-AD-1526. A 2-compartment population PK model with parallel linear and nonlinear (Michaelis-Menten) elimination was used. A transit-compartment model was used to describe the absorption phase.

Figure 5: **Mean of Simulated and Observed Concentration of Functional Dupilumab over Time by Treatment with Simulations Based on Adult Model and Adolescent Distribution of Weight**



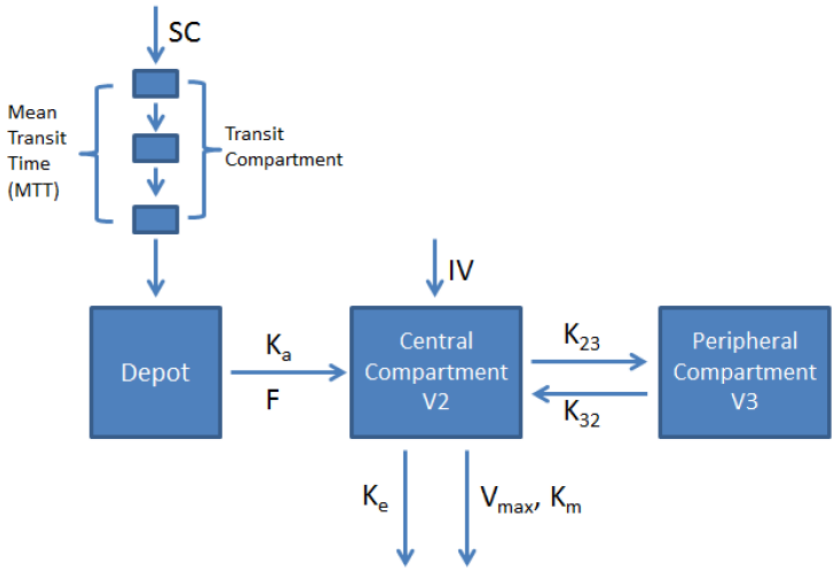
Note: Patients with titers above 1000 were excluded from analyses. Fifteen patients who received an incorrect number of doses are excluded from the calculation of the observed means.

Figure 2: BLQ Visual Predictive Checks for Base Adult Model Applied to Adolescent Data



BLQ = Below quantifiable limit

Subsequently, the adult PK model structure was fitted to the adolescent data, whereby some parameters of the model were re-estimated using only data from the adolescent study R668-AD-1526, including target-mediated elimination (Vm), together with inter-patient variability for this parameter. This modification was implemented to optimize prediction of values below the level of quantitation and the target-mediated phase of the PK profile in the adolescent patients. The statistically significant covariates identified in adults were tested to confirm their significance in the adolescent population.



F – bioavailability; K_a – absorption rate constant; MTT - mean transit time; V_2 – central compartment volume; V_3 – peripheral compartment volume; k_{23}, k_{32} – inter-compartmental rate constants; K_e – elimination rate constant; V_m – maximum target-mediated rate of elimination; K_m – Michaelis-Menten constant.
Source: Population PK Report Figure 1.

The table 3 below shows the parameter estimated for the final covariate model, based on the adolescent data from study R668-AD-1526 and the previously estimated values for adults. Covariates were incorporated into the model or rejected based on forward inclusion (p= 0.05) and backward elimination (p= 0.005) criteria.

In adolescent patients, the covariate coefficients for ADA, body mass index (BMI), EASI score, and weight were statistically significant and similar to those in the adult model. The effects of albumin on central volume and race on elimination rate in adults were not replicated in adolescents, possibly due to a considerably smaller sample size. Population PK parameters were essentially the same in the base and covariate adolescent models. Both base and covariate adult Pop PK models were replicated with small and inconsequential numeric differences in population PK parameters.

Table 3: Population PK Parameters of Adolescent and Adult Covariate Models Parametrized Utilizing Clearance

Parameter Name	Adolescent Covariate Model		Adult Covariate Model	
	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)
PK parameter				
V_2 (L)	2.45 (0.0583)	2.48 (2.35, 2.60)	2.73 (0.0220)	2.74 (2.69, 2.78)
CL (L/d)	0.132 (0.00656)	0.122 (0.109, 0.132)	0.130 (0.00200)	0.129 (0.125, 0.134)
V_m (mg/L/d)	1.37 (0.0797)	1.41 (1.29, 1.54)	1.07 (fixed)	---
k_{23} (1/d)	0.211 (fixed)	---	0.211 (fixed)	---
k_{32} (1/d)	0.310 (fixed)	---	0.310 (fixed)	---
k_a (1/d)	0.306 (fixed)	---	0.306 (fixed)	---
MTT (d)	0.105 (fixed)	---	0.105 (fixed)	---
K_m (mg/L)	0.01 (fixed)	---	0.01 (fixed)	---
F (unitless)	0.642 (fixed)	---	0.642 (fixed)	---
Covariates				
V_2 ~ weight	0.747 (0.0757)	0.760 (0.583, 0.880)	0.811 (0.035)	0.811 (0.735, 0.884)
V_2 ~ albumin	---	---	−0.550 (0.096)	-0.544 (-0.741, -0.362)
CL ~ weight	0.712 (0.174)	0.622 (0.331, 0.924)	0.806 (0.074)	0.790 (0.605, 0.937)
CL ~ BMI	0.437 (0.212)	0.500 (0.0852, 0.877)	0.372 (0.086)	0.406 (0.203, 0.586)
CL ~ ADA	0.195 (0.0563)	0.212 (0.0884, 0.323)	0.164 (0.029)	0.168 (0.0897, 0.239)
CL ~ EASI	0.348 (0.0527)	0.353 (0.218, 0.469)	0.140 (0.021)	0.140 (0.0968, 0.198)
CL ~ ALB	---	---	-0.800 (0.110)	-0.805 (-1.01, -0.562)
CL ~ race (white)	---	---	−0.118 (0.018)	-0.109 (-0.157, -0.0637)
Omega Matrix				
σ ($\ln(V_2)$)	0.138 (0.0156)	0.137 (0.0747, 0.183)	0.212 (0.0069)	0.212 (0.191, 0.230)
σ ($\ln(k_e)$)	0.257 (0.0156)	0.252 (0.227, 0.293)	0.272 (0.0065)	0.271 (0.254, 0.287)
Corr ($\ln(k_e)$,$\ln(V_2)$)	--	---	0.237 (0.045)	0.247
Residual SD				
σ prop. (CV%)	10.0 (0.00569)	9.56 (7.05, 12.3)	12.4 (0.18)	12.4 (11.7, 13.1)
σ add. (mg/L)	2.32 (0.222)	2.40 (1.65, 3.43)	6.06 (0.240)	6.11 (4.87, 6.99)
Derived Parameters [b]				
ke (L/d)	0.0539	---	0.0476	---
Q (L/d)	0.517	---	0.576	---
V_3 (L)	1.67	---	1.86	---

BMI = Body mass index; EASI = Eczema Area and Severity Index; --- = not calculated for fixed, derived, or not included parameters
Note: Bootstrap confidence intervals for the correlation coefficient are not provided as PsN software summarizes covariance.

Model diagnostics (base and final model)

Diagnostic plots show a good model fit with some imperfections in predicted BLQ frequencies and simulated concentrations for the BLQ values.

Figure 11: Observed vs. Population and Individual Predicted Concentrations for Base Adolescent Model

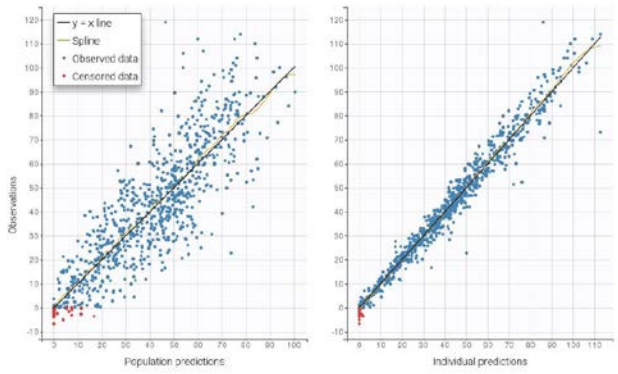
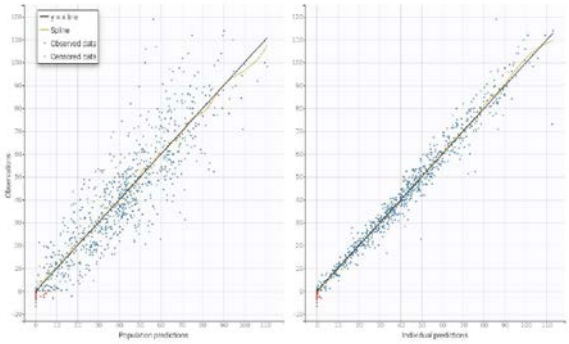


Figure 24: Observed vs. Population and Individual Predicted Concentrations for Adolescent Covariate Model



VPC demonstrated good predictability, ie median observed concentrations of dupilumab were within predicted confidence intervals.

Figure 16: Visual Predictive Checks for Primary Base Adolescent Model by Treatment vs. Actual Day

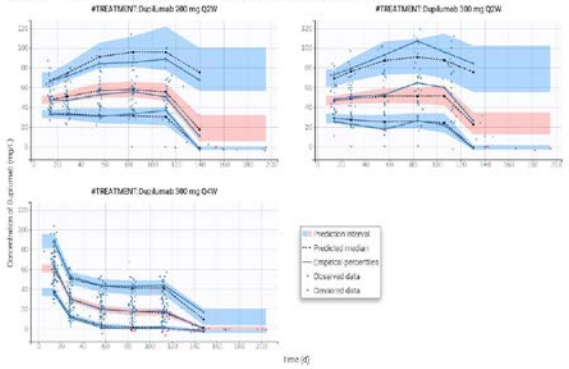
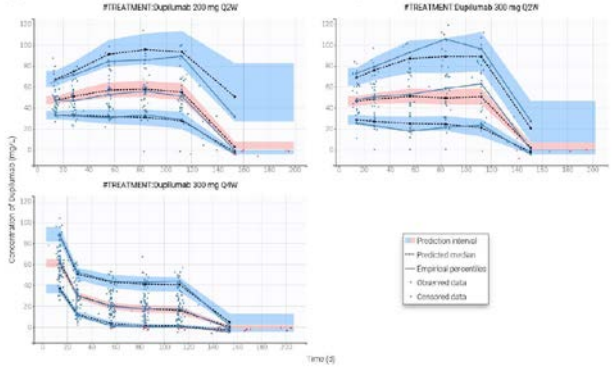


Figure 29: Visual Predictive Checks for Adolescent Covariate Model by Treatment vs. Actual Day



Shrinkage in variance of ETAs for ke and V2 was 21.9% and 51.4%, respectively, in the base model. The corresponding shrinkage in SD was ~12% and ~30%. In the final model, shrinkage was 25.3% and 54.3% in variance of ETAs for ke and V2 respectively. The corresponding shrinkage in SD of ETA is ~14% and ~32%.

VPC plots indicate a slight under-prediction following 300 mg Q2W treatment. Overall model diagnostics showed no major model deficiencies indicating that the population PK model describes the data acceptably well.

In this line it is noticed that Omega (V2) estimated from the final model is wider compared to Omega (V2) estimated from the base model which is considered not plausible. In addition, shrinkage on V2 was high (54.3%) and also rises from the base to the final pop PK model. Thus, the MAH was asked to justify covariate selection. This is further addressed later on in the discussion part.

Overall, it is agreed that the base and covariate PK models adequately described the PK of dupilumab in adolescent patients with moderate-to-severe AD. Diagnostic plots for both base and covariate models showed an acceptable fit. Bootstrapping validated the parameter estimates.

To support the adequacy of the proposed dosing regimen for adolescents, the applicant was asked to conduct simulations to show the probability of attaining the recommended target concentration/exposure for efficacy, over the body weight distribution observed in adolescent patients, when receiving the proposed to-be-marketed weight-tiered 200 mg/300 mg Q2W dosing regimen as well as the 300 mg Q4W regimen.

The PK parameters estimated for the adolescent patients were used to calculate the Cmax, Cmin, and AUC values after the first dose and at steady state for the proposed dosing regimen 200 mg and 300mg Q2W, as well as for 300mg Q4W.

Table 13: Summary of Simulated Exposure to Dupilumab by Treatment Regimen – Covariate Adolescent Model

Variable	Treatment																				
	200 mg Q2W SC							300 mg Q2W SC							300 mg Q4W SC						
	N	Mean	SE	SD	Q1	Median	Q3	N	Mean	SE	SD	Q1	Median	Q3	N	Mean	SE	SD	Q1	Median	Q3
C_{max} (mg/L)	3860	65.6	0.207	12.8	56.3	64.0	73.7	4140	66.1	0.241	15.5	55.6	66.3	76.4	4000	83.2	0.391	24.7	65.2	81.1	99.2
t_{max} (day)	3860	5.23	0.00668	0.415	4.95	5.25	5.50	4140	5.23	0.00652	0.420	4.95	5.25	5.50	4000	5.32	0.00711	0.450	5.05	5.30	5.65
C_{trough} (mg/L)	3860	47.9	0.180	11.2	40.0	46.6	54.7	4140	48.4	0.206	13.2	39.4	48.3	57.3	4000	32.1	0.250	15.8	20.8	30.2	41.4
AUC (mg/L)	3860	762	2.46	153	652	743	859	4140	768	2.87	185	643	772	890	4000	1619	8.56	541	1226	1574	1966
C_{maxSS} (mg/L)	3860	86.1	0.464	28.8	65.5	81.1	101	4140	87.0	0.494	31.8	64.8	83.9	105	4000	55.5	0.398	25.2	37.0	52.0	69.5
t_{maxSS} (day)	3860	3.65	0.00154	0.0956	3.60	3.65	3.70	4140	3.65	0.00148	0.0951	3.60	3.65	3.70	4000	4.62	0.00328	0.207	4.50	4.65	4.75
$C_{troughSS}$ (mg/L)	3860	61.6	0.431	26.8	42.6	57.0	75.4	4140	62.3	0.445	28.7	41.4	58.6	78.2	4000	17.5	0.261	16.5	5.48	13.5	24.6
AUC_{SS} (mg/L)	3860	1066	6.31	392	788	997	1273	4140	1077	6.64	427	774	1030	1320	4000	1047	9.41	595	619	946	1356

Note: N is the number of simulations. AUC is calculated per treatment interval.

Simulated exposure to Dupilumab by treatment regimens supports the chosen 60 kg threshold for differential dosing (200 mg < 60kg; 300 mg ≥ 60 kg).

Absorption

In the adult AD patient population, dupilumab is well absorbed with a reported bioavailability of 64%.

Bioavailability (F) seems not to be re-estimated in the adolescent population and is fixed to the population value estimated from the adult population.

Bioequivalence

Dupilumab drug product at the 300 mg strength has already been approved for AD and consists of a 150 mg/mL solution in a pre-filled syringe (PFS) with or without needle shield. The proposed to-be-marketed drug product at 200 mg strength in the current application is a 175 mg/mL solution with 2 presentations, a PFS with needle shield or a PFS assembled into a pre-filled pen (PFP), also referred to as autoinjector (AI). Of the two presentations, the dupilumab 200 mg PFS was used for clinical studies in asthma, for which an extension of indication and extension of application to include the new 200 mg strength (EMEA/H/C/004390/X/04/G) was recently approved. The proposed to-be-marketed 200 mg PFP is assembled with the same bulk PFS (without plunger rod) and contains the same dupilumab drug substance, same drug formulation, and same solution volume for injection as the PFS used in the asthma pivotal studies. The potential effect of drug product presentation (PFP or PFS) on dupilumab PK and safety was evaluated in an actual-use study in patients with AD (Study R668-AD-1607). Study R668-AD-1607 is a 2-part study with Part A conducted for the 200 mg dupilumab dose and Part B for the 300 mg dupilumab dose; as such only Part A results are presented.

Study R668-AD-1607 (Part A)

Study R668-AD-1607 was an open-label, randomized, actual use study of dupilumab PFP (referred to as an AI device in the study protocol) in adult and adolescent patients with AD. The study was conducted in 2 parts: Part A and Part B. The primary objective of Part A was to assess technical performance of the 1 mL (200 mg dose) PFP. The primary objective of Part B was to assess technical performance of the 2 mL (300 mg dose) PFP. Results from Part B are not presented in this document and will be submitted for review at a later date. In Part A, 85 patients were randomized to receive dupilumab 200 mg Q2W via PFP device or PFS, with a loading dose of 400 mg on day 1. Of the 85 patients enrolled in Part A, 18 were adolescents, of which

8 received dupilumab using the PFP and 10 using PFS. Randomization was stratified by Day 1 injection site (abdomen, upper thighs, or upper arms) and by weight category (≤70 kg, >70 to <100 kg, and ≥100 kg).

The geometric mean ratios of dupilumab exposure with 90% CIs were calculated after first dose and at steady state. This study was not powered to demonstrate bioequivalence.

Pharmacokinetic Results

Following repeated q2w administration of dupilumab at 200 mg, the AUC0-14, Cmax and Ctrough values were comparable at steady state (Table 6 below). The geometric mean ratios (90% CI) for AUC0-14 (PFP/PFS) were 0.903 (0.767 to 1.063) after the seventh dose on Day 85, with similar geometric mean ratios observed for Cmax and Ctrough (Table 7). After the loading dose administration on Day 1, geometric mean ratios (PFP/PFS, 90% CI) for Cmax and AUC0-14 were 0.741 (0.655 to 0.839) and 0.723 (0.635 to 0.823), respectively. The PK in these adolescent patients was similar for the 2 devices and consistent with that observed in adults.

The site of injection did not appear to have a meaningful influence on dupilumab exposure for either the PFS or the PFP. Neither weight nor injection site had an impact on the comparison of PFP and PFS. Taking the data in totality, concentrations of functional dupilumab in serum were similar when administered using the PFP and PFS (200 mg devices). Minor differences were within the observed variability of exposure across the program. The study was not powered for bioequivalence.

Table 6 - Summary of pharmacokinetic parameters for functional dupilumab by treatment in AD Patients (Study R668-AD-1607)

Study Day	Parameter	Treatment	N	Mean	Median	SD	Geometric Mean
1	AUC_{0-14} (mg•day/L)	Dupilumab 200 mg Q2W PFP	42	397	374	163	362
		Dupilumab 200 mg Q2W PFS	43	525	488	232	484
	C_{max} (mg/L)	Dupilumab 200 mg Q2W PFP	42	38.8	35.3	17.9	35.1
		Dupilumab 200 mg Q2W PFS	43	49.4	48.0	21.2	45.9
	C_{trough} (mg/L)	Dupilumab 200 mg Q2W PFP	42	25.8	25.9	13.5	21.9
		Dupilumab 200 mg Q2W PFS	43	31.1	29.1	14.6	27.9
	t_{max} (day)	Dupilumab 200 mg Q2W PFP	42	---	6.89	---	---
		Dupilumab 200 mg Q2W PFS	43	---	6.91	---	---
85	AUC_{0-14} (mg•day/L)	Dupilumab 200 mg Q2W PFP	37	665	676	317	588
		Dupilumab 200 mg Q2W PFS	38	733	663	402	630
	C_{max} (mg/L)	Dupilumab 200 mg Q2W PFP	37	59.6	54.9	31.9	52.7
		Dupilumab 200 mg Q2W PFS	38	64.4	58.7	31.9	57.5
	C_{trough} (mg/L)	Dupilumab 200 mg Q2W PFP	37	40.1	36.5	24.9	34.0
		Dupilumab 200 mg Q2W PFS	38	44.7	42.4	27.3	37.8
	t_{max} (day)	Dupilumab 200 mg Q2W PFP	37	---	88.2	---	---
		Dupilumab 200 mg Q2W PFS	38	---	90.1	---	---

N = Number of patients; PFP = Prefilled pen; PFS = Prefilled syringe; --- = Not applicable
Notes: AUC_{0-14} is the area under the concentration-time curve from time zero to 14 days, relative to the day listed in the Study Day column.
C_{trough} is the concentration observed at nominal 14 days following dose.

Table 7 - Estimates of Geometric Mean Ratios (AI/PFS) for functional dupilumab exposure following 200 mg q2w administration (Study R668-AD-1607)

Study Day	PK Parameter	Geometric Mean Ratio	90% CI
Day 1	AUC_{0-14}	0.723	0.635 – 0.823
	C_{max}	0.741	0.655 – 0.839
	C_{trough}	0.757	0.638 – 0.897
Day 85	AUC_{0-14}	0.903	0.767 – 1.063
	C_{max}	0.890	0.779 – 1.017
	C_{trough}	0.872	0.722 – 1.053

AI = Auto-injector; PFS = Prefilled syringe

Notes: AUC_{0-14} is the area under the concentration-time curve from time zero to 14 days, relative to the day listed in the study day column. C_{trough} is the concentration observed at nominal 14 days following dose.

The to-be-marketed 200 mg PFP is assembled with the same bulk PFS and contains the same dupilumab drug substance, same drug formulation, and same solution volume for injection as the PFS which was used in the asthma pivotal studies. In Study R668-AD-1607, the potential effect of drug product presentation (PFP or PFS) on dupilumab PK was investigated. In Part A of this study, patients with moderate to severe AD received dupilumab 200 mg q2w via PFP device or PFS, with a loading dose of 400 mg on Day 1. The study was not formally powered to show PK comparability/bioequivalence between PFS and PFP. The comparison of systemic dupilumab exposure between PFS and PFP was included as secondary objective in the study.

The geometric mean ratio for AUC(0-14) was 0.723 (90% CI: 0.635-0.823) at study day 1 and 0.903 (90% CI: 0.767-1.063) at study day 85 (steady state). The geometric mean ratio for Cmax was 0.741 (90% CI: 0.655-0.839) at study day 1 and 0.890 (90% CI: 0.779-1.017) at study day 85 (steady state). At both time points the 90% confidence interval of the geometric mean ratios for AUC(0-14) and Cmax were not contained within the acceptance interval of 0.8 – 1.25

The comparison of the two presentations was discussed during procedure EMEA/H/C/004390/X/04/G (extension application for asthma and adults and adolescents). The PFP comparability is considered acceptable as this issue has been resolved.

Distribution

Estimation of the central compartment volume of distribution (V2) yielded similar values for adolescents vs. adults (2.54±0.0473 vs. 2.76±0.021 L, respectively).

Elimination

Clearance was calculated to 0.128 L/d, derived from population PK.

Derived values for clearance for the adolescent population (0.128 L/d) and adult population (0.130 L/d) are deemed comparable

Dose proportionality and time dependencies

No new information is being provided in this subsequent marketing application regarding dose proportionality, steady-state and accumulation.

Special populations

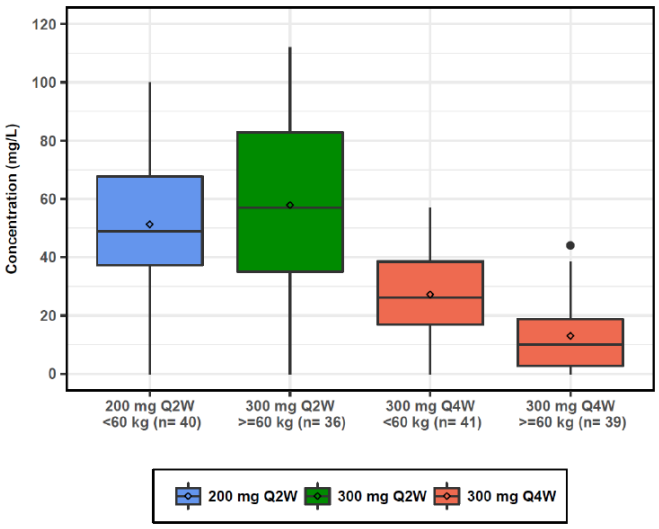
Covariates (Intrinsic and Extrinsic Factors) Affecting Pharmacokinetics

Body Weight

Since weight is the primary covariate affecting the PK of dupilumab, a tiered weight-based regimen was used to normalize exposure across the adolescent population. The mean week-16 dupilumab concentrations and

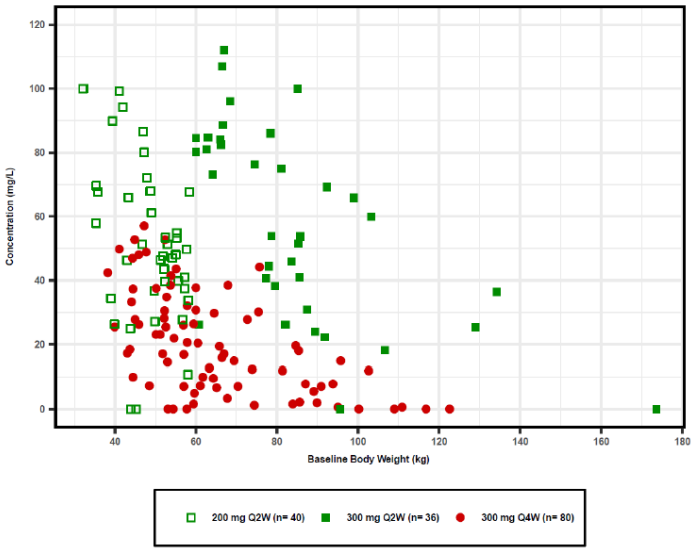
distribution following the 2-tier weight-based 200/300 mg Q2W regimen for patients below and above 60 kg is depicted below.

Figure 7: Concentrations of Functional Dupilumab in Serum (mg/L) at Week 16 vs. Body Weight (kg) by Dose Group in Adolescent Patients with Moderate-to-Severe AD (R668-AD-1526).



n = number of patients
Source: Module 5.3.5.1 R668-AD-1526 Figure 23

Figure 15: Scatter Plot of Concentrations of Functional Dupilumab in Serum at Week 16 vs. Patient Body Weight by Dose Group in Adolescent Patients with AD (Study R668-AD-1526)



n = Number of patients
Note: Concentrations below the LLOQ (0.078 mg/L), were set to 0.
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 20.

In contrast, as would be expected when the same dose was administered across the entire range of body weights, lower trough concentrations were observed at the higher weight category of ≥60 kg compared to the <60 kg weight category for the 300 mg once every 4 weeks (Q4W) regimen.

Age

Population PK analysis in adolescent patients shows that, once weight is accounted for, age in the adolescent range (12 to 18 years) is not a statistically significant covariate and has no effect on PK of dupilumab in AD.

Treatment-Emergent Anti-Drug Antibody

See Section Immunogenicity

Disease Activity (EASI Scores)

Based on the population PK analysis, baseline Eczema Area and Severity Index (EASI) score had a statistically significant association with the PK of dupilumab in adolescents, as was observed in adults; patients with more severe disease at baseline exhibit lower exposure, although the association of baseline EASI alone on exposure was not clinically meaningful.

PK comparison across populations

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. As noted in the initial application and the subsequent asthma application, body weight has been identified as the single most influential covariate that described the variability in dupilumab exposure. As such, an emphasis was placed on presenting and comparing the observed PK of dupilumab in adolescents to adults as well as a weight normalized comparison. This latter approach was accomplished using a population PK approach.

Comparison of the mean concentration-time profiles of functional dupilumab illustrates a high degree of consistency in exposure across the studies conducted using similar dosing regimens in adult and adolescent patients with AD. Any difference in exposure between adult and pediatric patients is likely accounted for by differences in body weight. In addition to comparisons between adolescent and adult patients with AD, the PK profiles of functional dupilumab were compared between adolescent patients with AD and asthma.

Dupilumab Drug Concentrations in Adolescent and Adult Patients with Atopic Dermatitis or Asthma

Data from studies in pediatric patients treated with dupilumab dosing regimens of either 200 mg Q2W or 300 mg Q2W (R668-AD-1607, EFC13579, R668-AD-1526, R668-AD- 1434) are compared with results from studies in adult patients treated with the same dupilumab dosing regimens (R668-AD-1021, R668-AD-1334, R668-AD-1416).

The time to steady state for dupilumab was previously reported as 10 weeks and 12 weeks following QW and Q2W regimens, respectively. Based on these findings, Ctrough at various time points beyond week 12 can be used as a reasonable approximation of the steady state concentrations and thus compared across studies. As shown in the table 4 below, the observed CtroughSS values for the Q2W regimen in adolescent patients are within the range of the CtroughSS values for the 300 mg Q2W regimen in adults.

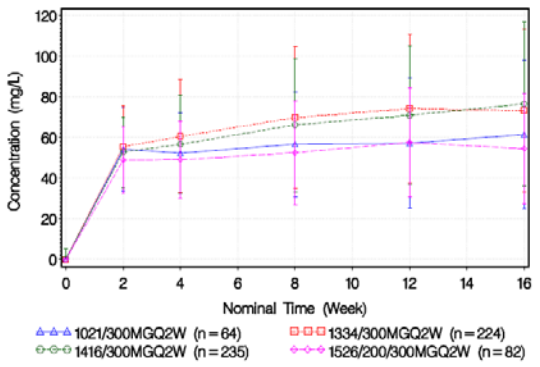
Table 4: Comparison of Dupilumab Trough Concentrations (mg/L) between Adults and Adolescents by Study and Treatment Regimen

	Adolescents					Adults				
	R668-AD-1412	**R668-AD-1607**	**EFC 13579**	**R668-AD-1526**	**R668-AD-1434**	**R668-AD-1607**	**EFC 13579**	**R668-AD-1334**	**R668-AD-1416**	**R668-AD-1021**
Population	AD	AD	Asthma	AD	AD	AD	Asthma	AD	AD	AD
	Week 12	Week 14	Week 16	Week 16	Week 16	Week 14	Week 16	Week 16	Week 16	Week 16
200mg Q2W	-	45.6[a] (34.2)	60.2[b] (26.9)	51.6[b] (24.0)	45.3* (18.9)	41.1 (29.0)	36.5 (22.2)	-	-	35.9 (24.6)
N		17	18	40	21	37	560			52
300mg Q2W	-	-	65.5[c] (36.2)	57.9[c] (30.0)	44.8* (23.1)	-	67.8 (34.9)	73.3 (40.0)	76.6 (40.5)	61.5 (36.7)
N			15	36	19		559	219	219	61
300mg Q4W	-	-	-	19.8 (15.9)	15.9 (16.5)	-	-	-	-	13.8 (12.1)
N				81	58					63
2mg/kg QW	18.5 (12.4)	-	-	-	73.9** (18.5)	-	-	-	-	-
N	20				6					
4mg/kg QW	58.8 (24.4)	-	-	-	161** (59.6)	-	-	-	-	-
N	18				8					

[a] Mean based on both pre-filled syringe and autoinjector
[b] – in patients <60 kg
[c] – in patients ≥60 kg
* following initial treatment with 300 mg Q4W;
** at week 48

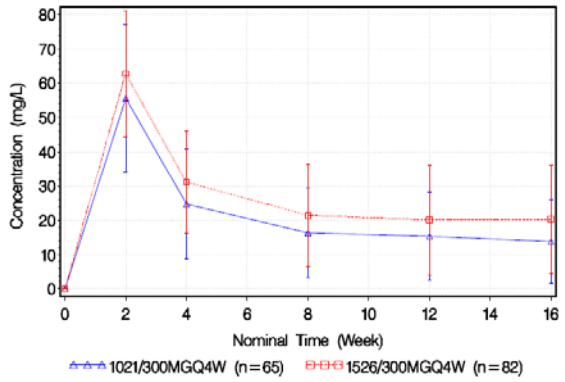
This similarity in dupilumab exposure between adolescents and adult is illustrated graphically for the 200/300 mg Q2W, 300 mg Q2W, and Q4W treatment regimens, respectively.

Figure 3: **Mean (±SD) Concentrations of Functional Dupilumab in Serum (mg/L) vs. Nominal Time (Week) in Adolescent Patients with Moderate-to-Severe AD Receiving 200/300 mg Q2W Compared to Adult AD Patients Receiving 300 mg Q2W.**



n=Number of patients. Note: BLQs were set to 0. Data up to week 16 used for analysis. R668-AD-1526 – adolescents; R668-AD-1021, R668-AD-1334, R668-AD-1416 – adults.
Source: Module 5.3.5.1 R668-AD-1021 CP-01V1 Table 4; Module 5.3.5.1 R668-AD-1334 CP-01V1 Figure 1; Module 5.3.5.1 R668-AD-1416 CP-01V1 Figure 1; Module 5.3.5.1 R668-AD-1526 Figure 21.

Figure 4: **Mean (±SD) Concentrations of Functional Dupilumab in Serum (mg/L) vs. Nominal Time (Week) in Adolescent Patients with Moderate-to-Severe AD Receiving 300 mg Q4W Compared to Adult AD Patients Receiving 300 mg Q4W.**



n=Number of patients. Note: BLQs were set to 0. Data up to week 16 used for analysis. R668-AD-1526 – adolescents; R668-AD-1021 - adults
Source: Module 5.3.5.1 R668-AD-1021 Table 52; Module 5.3.5.1 R668-AD-1526 Figure 21.

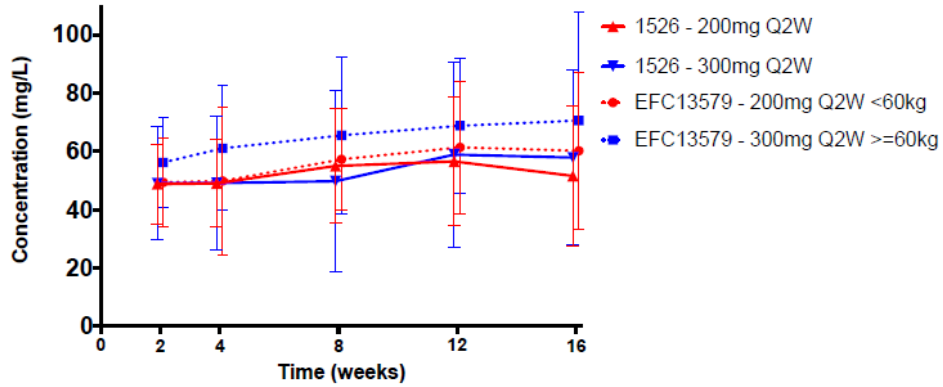
It is agreed that detectable differences in mean dupilumab exposure between adolescents and adult are not considered major given the overall high variability in data which is supported by population PK analysis.

However, in the asthma population, Ctrough (60.2 mg/L) in the adolescent population was higher compared to the adult population (36.5 mg/mL) following 200 mg Q2W with an overall a trend of higher exposure in the adolescent population.

Comparison of Dupilumab PK in Adolescent Patients with Asthma or AD

A comparison of the Q2W regimens between adolescent patients with AD (R668-AD-1526) and asthma (EFC13579) is depicted below. The 200 mg Q2W regimens in adolescent patients <60 kg were similar between the 2 disease populations as were the 300 mg Q2W regimens in adolescents ≥60 kg.

Figure 5: Mean (SD) Trough Concentrations of Functional Dupilumab by Nominal Time, Dose and Study in Adolescent Patients with AD or Asthma.

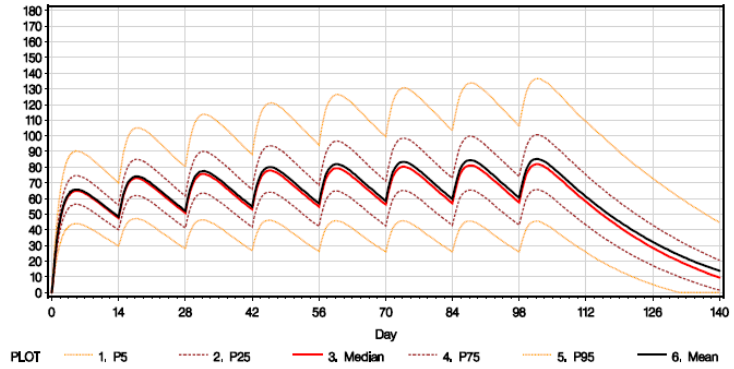


Note – for EFC13579 study in adolescents with asthma, data represents the mean (sd) for the subset of patients receiving 200mg who were <60kg or the subset of patients receiving 300mg who were ≥60kg
Source: Module 5.3.5.1 R668-AD-1526 and Module 5.3.5.3 of asthma marketing application
1526 – adolescents with AD; EFC13579 – adolescents with asthma

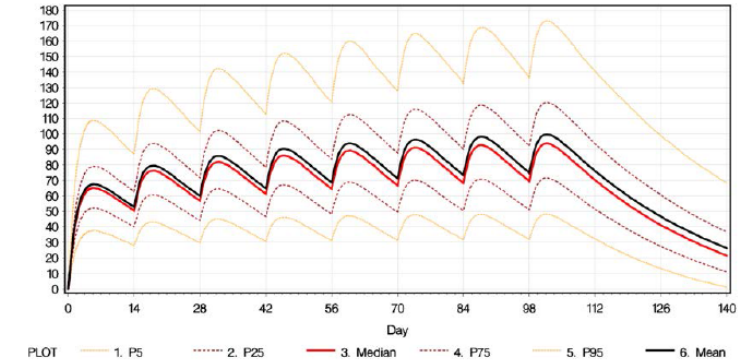
The mean dupilumab concentration reached following 200 mg Q2W was more comparable than mean concentration following 300 mg when opposing AD and Asthma adolescent patients.

Figure 6: Simulated Concentration of Functional Dupilumab Over Time (Percentiles, Median, and Mean) in Adolescent Patients Receiving Dupilumab 200/300 mg Q2W (Panel A) vs. Adults Receiving 300 mg Q2W (Panel B).

A



B



Source: Module 5.3.3.5 Population PK Report Figures 63 and 64.

2.3.3. Pharmacodynamics

Mechanism of action

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

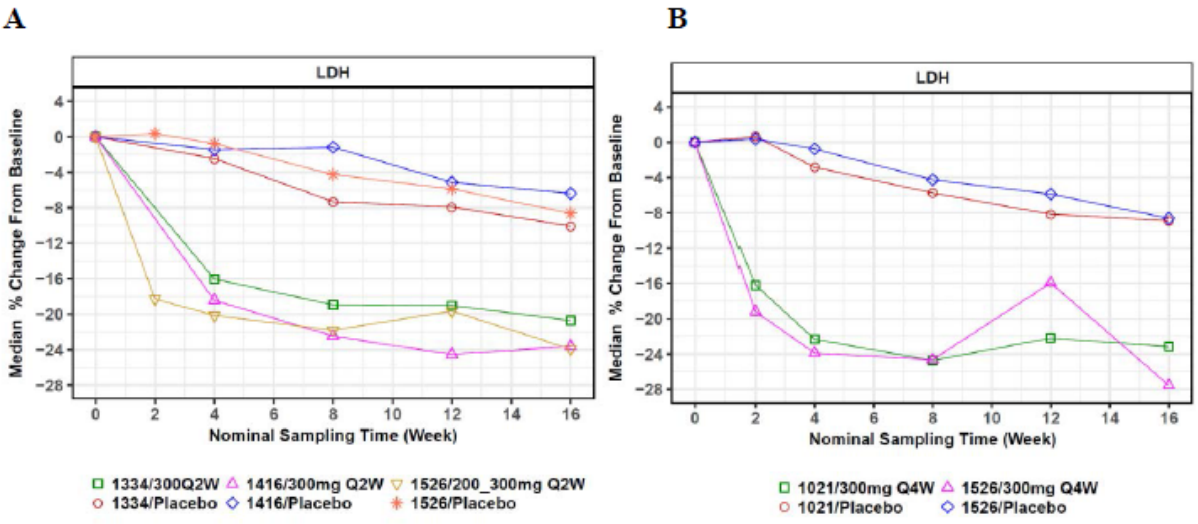
Dupilumab inhibits IL-4 signaling via the Type I receptor (IL 4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine- induced responses, including the release of proinflammatory cytokines, chemokines, and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

Primary and secondary pharmacology

LDH

The time course of lactate dehydrogenase (LDH) was analyzed as a biomarker of AD disease severity over time. Although measured as part of standard chemistry panels for safety monitoring, LDH also serves as a PD marker of efficacy in AD.

Figure 8: Between Study Comparison of the Median Percentage Change from Baseline in Lactate Dehydrogenase by Dupilumab Treatment Group (panel A: Q2W vs placebo; panel B: Q4W vs placebo) Across Studies R668-AD-1021 (adults), 1334 (adults), 1416 (adults) and 1526 (adolescents)



Note: Common nominal time points up to week 16 were used for analysis.
Source: Module 5.3.5.1 R668-AD-1021 Post-text table 3.4.1.1; Module 5.3.5.1 R668-AD-1334 Figure 31; Module 5.3.5.1 R668-AD-1416 Figure 31; Module 5.3.5.1 R668-AD-1526 Figure 20

The pharmacodynamics of LDH shows similar effects of dupilumab between adolescent and adult AD patients.

Immunogenicity

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

The randomized controlled phase 3 study R668-AD-1526 was the primary source for the immunogenicity assessment of dupilumab in adolescents with AD, as it was the largest well-controlled study performed with the proposed to-be-marketed dosing regimen (200mg/300mg Q2W). The open-label, long-term extension study, R668-AD-1434, allowed additional monitoring of ADA positive patients and provided insights into responses over time, especially in those patients who had previously participated in the phase 2 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 and all post baseline ADA titers are reported as less than 4-fold the baseline titer value
- Treatment-boosted - A positive result at baseline in the ADA assay with at least 1 post baseline titer result ≥4-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least 1 positive post baseline result in the ADA assay
    - Persistent - A positive result in the ADA assay detected in at least 2 consecutive post baseline samples separated by at least a 12-week post baseline period [based on nominal sampling time], with no ADA-negative results in-between, regardless of any missing samples
    - Indeterminate - A positive result in the ADA assay at the last collection time point only, regardless of any missing samples

- Transient - Not persistent or indeterminate, regardless of any missing samples

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

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

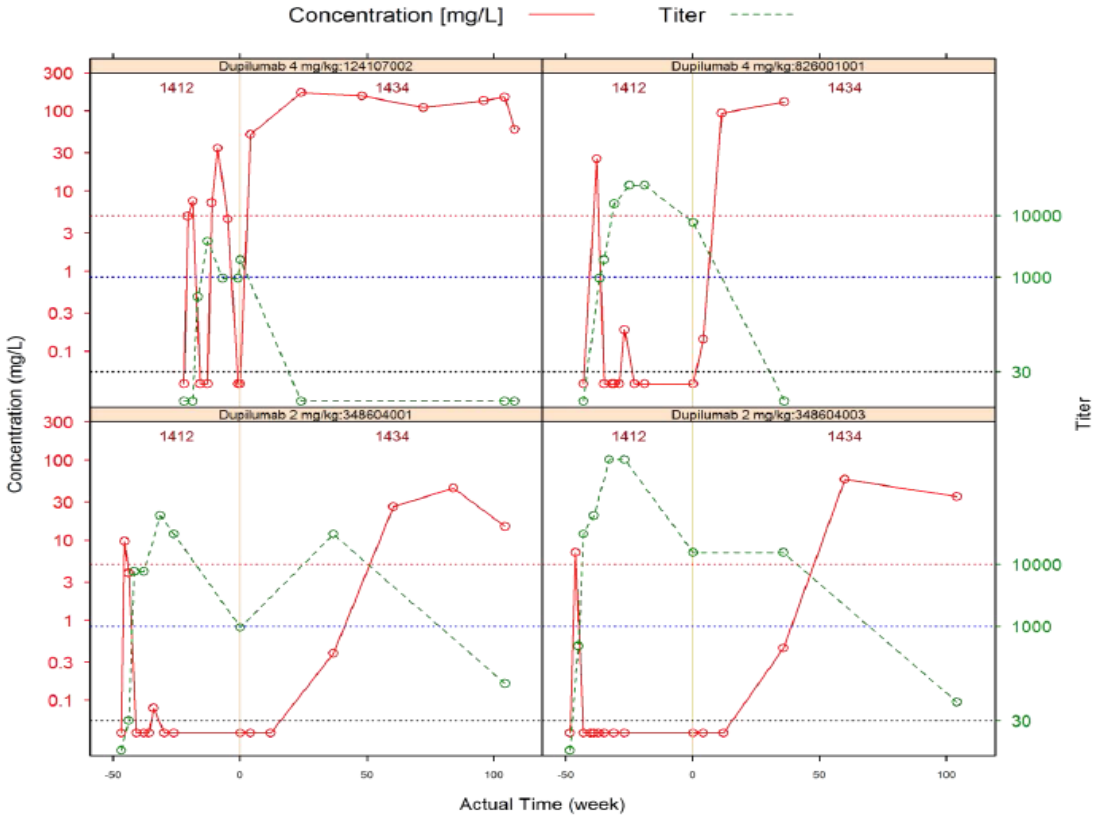
Study R668-AD-1412 (Phase 2a)

Sampling for the assessment of ADA was performed at screening (day -1), days 15, 29, and 57, and then follow-up on days 99 and 141 (end of study), or at early termination.

In this study, adolescent patients received a single dose of dupilumab (2 mg/kg or 4 mg/kg). There was an 8-week delay in the second dose to allow sufficient time to characterize the PK profile, as this was unknown at the time. This was followed by 4 weekly doses of dupilumab QW. This regimen of a single dose, followed by an 8-week pause and then followed by repetitive dosing invoked a significant ADA response. In this study, a treatment-emergent ADA response was observed in 29 patients (72.5%), 20 of which (50% of total 40 patients) were categorized as having a persistent, treatment-emergent response. The majority (23/29, 79.3%) of the treatment-emergent positive responses in the ADA assay were categorized as low titer.

However, in 6 patients this treatment regimen resulted in high or moderate titer responses in the ADA assay that were associated with a substantial reduction in detectable drug concentrations (Figure 14). Notably, in 4 of these patients continued treatment through Part B of the study and, subsequently, the OLE study, resulted in declining titers and a corresponding increase in systemic concentrations of dupilumab (Figure 14) (2 of the remaining adolescent patients with moderate/high titer were not included in this analysis as they did not contribute any longitudinal concentration/ADA titer data in R668-AD-1434 at the time of interim data cutoff). The conclusion from these data is that 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. However, should such a situation occur and efficacy decline, continued dupilumab treatment may allow for improved efficacy over time.

Figure 14: Individual Concentrations of Functional Dupilumab and ADA Titer 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



It is notable that during the development of dupilumab in the adult AD population, various intervals of treatment interval prolongation were assessed as patients rolled into the OLE study from other various parent studies. Although less frequent dosing of dupilumab was associated with a greater frequency of ADA than weekly dosing, these regimens did not produce the high frequencies and high titers of ADA seen with the "prime and boost" regimen used in the R668-AD-1412 study. As opposed to the gap in treatment in adolescents after a single dose, in the adult program, many patients had a gap of treatment of >8 weeks after at least 16 weeks of treatment between the initial study and entry into an extension study. This gap was not associated with the types of ADA responses induced by the "prime and boost" regimen used in the 1412 study. Moreover, this high incidence of treatment-emergent ADA seen in R668-AD-1412 was not seen in R668-AD-1526 where adolescent patients were treated continuously for 16 weeks. The totality of these data suggest that the enhanced formation of ADA in part B of the R668-AD-1412 study in adolescent study is due to the study design rather than the population (adolescents vs adults).

Study R668-AD-1526 (Phase 3)

Samples for assessment of ADA were collected on days 1, 29, 113, and 197.

Including results from the week 4 ADA time point, which was not evaluated in earlier studies, the incidence of treatment-emergent ADA response in the 200 mg/300 mg Q2W group was 16% versus 3.5% for the placebo group and 20.7% for the 300 mg Q4W group. However, most of the treatment-emergent responses for active doses were transient in nature and had low ADA titer, with no high titers observed. Only a few patients exhibited persistent treatment-emergent ADA responses (2.5% for 200 mg/300 mg Q2W, 1.2% for the placebo group, Table 5 and Table 6 below).

Table 5: ADA Category of Patients by Treatment Group in Adolescent Patients with Moderate-to-Severe AD (Study R668-AD-1526).

ADA Category N (%)	Placebo	Dupilumab					Overall
		300 mg Q4W	200 or 300 mg Q2W	200 mg Q2W	300 mg Q2W	All Active Doses	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total ADA Subjects	85 (100%)	82 (100%)	81 (100%)	42 (100%)	39 (100%)	163 (100%)	248 (100%)
Negative/Pre-Existing*	82 (96.5%)	65 (79.3%)	68 (84.0%)	37 (88.1%)	31 (79.5%)	133 (81.6%)	215 (86.7%)
Treatment Boosted Response	0	0	0	0	0	0	0
Treatment Emergent Response	3 (3.5%)	17 (20.7%)	13 (16.0%)	5 (11.9%)	8 (20.5%)	30 (18.4%)	33 (13.3%)
Persistent	1 (1.2%)	2 (2.4%)	2 (2.5%)	1 (2.4%)	1 (2.6%)	4 (2.5%)	5 (2.0%)
Transient	0	10 (12.2%)	10 (12.3%)	3 (7.1%)	7 (17.9%)	20 (12.3%)	20 (8.1%)
Indeterminate	2 (2.4%)	5 (6.1%)	1 (1.2%)	1 (2.4%)	0	6 (3.7%)	8 (3.2%)

n = number of patients. * patients who were either ADA negative at all time points or had pre-existing ADA response.

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Table 6: Maximum Titer Category of Patients by Treatment Group in Adolescent Patients with Moderate-to-Severe AD (Study R668-AD-1526).

Maximum Titer Category n (%)	Placebo	Dupilumab				Overall
		300 mg Q4W	200 or 300 mg Q2W	200 mg Q2W	300 mg Q2W	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total Subjects	85 (100%)	82 (100%)	81 (100%)	42 (100%)	39 (100%)	248 (100%)
Negative/Pre-existing*	82 (96.5%)	65 (79.3%)	68 (84.0%)	37 (88.1%)	31 (79.5%)	215 (86.7%)
Treatment Boosted Response	0	0	0	0	0	0
Treatment Emergent Response	3 (3.5%)	17 (20.7%)	13 (16.0%)	5 (11.9%)	8 (20.5%)	33 (13.3%)
Low (<1,000)	3 (3.5%)	17 (20.7%)	11 (13.6%)	5 (11.9%)	6 (15.4%)	31 (12.5%)
Moderate (1,000 to 10,000)	0	0	2 (2.5%)	0	2 (5.1%)	2 (0.8%)
High (>10,000)	0	0	0	0	0	0

n=Number of patients. * patients who were either ADA negative at all time points or had pre-existing ADA response

Neutralizing ADAs were observed in 4.9%, 4.9%, and 1.2% of patients in the 200 mg/300 mg Q2W, 300 mg Q4W, and placebo treatment groups, respectively.

Table 9: Summary of ADA and NAb Status by Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)

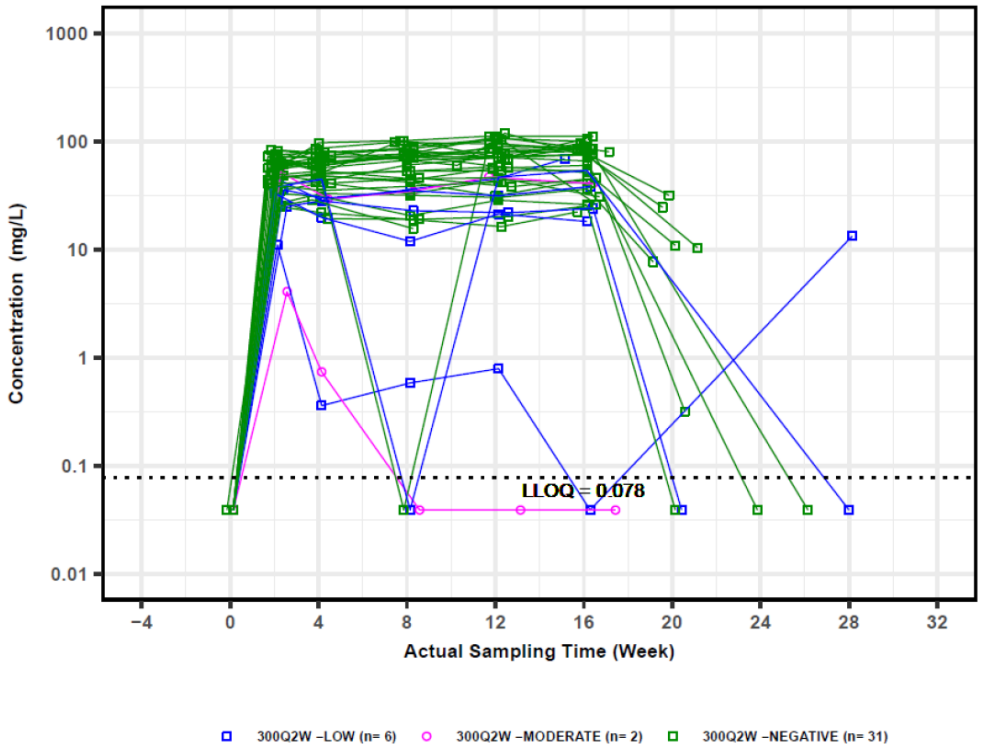
ADA Status and Category; NAb Status	Placebo	Dupilumab				Overall
		300 mg Q4W	200 mg/300 mg Q2W	200 mg Q2W	300 mg Q2W	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total Immunogenicity Patients	85 (100%)	82 (100%)	81 (100%)	42 (100%)	39 (100%)	248 (100%)
Neg; NAb-	82 (96.5%)	65 (79.3%)	68 (84.0%)	37 (88.1%)	31 (79.5%)	215 (86.7%)
Neg; NAb+	0	0	0	0	0	0
TE/TB; NAb-	2 (2.4%)	13 (15.9%)	9 (11.1%)	5 (11.9%)	4 (10.3%)	24 (9.7%)
TE/TB; NAb+	1 (1.2%)	4 (4.9%)	4 (4.9%)	0	4 (10.3%)	9 (3.6%)

n = Number of patients; Neg = Negative or pre-existing immunoreactivity; TE = Treatment-emergent; TB = Treatment-boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay
Note: See Section 2.4.3 for definitions of ADA categories.

In order to allow for integration of these data with other dupilumab studies that did not include an analysis of ADA at week 4, an assessment of ADA was also conducted with the immunogenicity sampling at week 4 censored. With the censoring of these data at week 4, treatment-emergent ADA were observed in 9.9%, 12.2%, and 3.5% of patients in the 200 mg/300 mg Q2W, 300 mg Q4W, and placebo treatment groups, respectively. Neutralizing antibody positivity was unaffected.

There is no clear evidence of a clinically meaningful impact of immunogenicity on dupilumab exposure. Anti-drug antibody/NAb-positive patients exhibited individual concentration-time profiles in the range of ADA/NAb-negative patients for the 200 mg/300 mg Q2W and 300 mg Q4W regimens. Scatter plots of the continuous endpoints, EASI and NRS percent change from baseline, show that the efficacy profiles of ADA/NAb-positive patients fall within the distribution of ADA/NAb-negative patients receiving the 200 mg/300 mg Q2W regimen. Inspection of individual profiles of NAb-positive adolescent patients showed that there was no clear association between ADA/NAb positivity, drug concentration, and drug effect. However, one patient in the 300 mg Q2W dose group, who exhibited persistent ADA with moderate titers and was also positive in the NAb assay, had lower drug concentrations, which reached the LLOQ by week 8 (Figure 31). Another patient in the 300 mg Q2W dose group who exhibited persistent ADA with low titers and was also positive in the NAb assay, showed lower drug concentrations up to week 16, followed by an increase (Figure 31).

Figure 31: Individual Concentrations of Functional Dupilumab (Log Scale) in Serum vs. Actual Time by ADA Titer Category in Adolescent Patients with AD Receiving 300 mg Q2W (Study R668-AD-1526)



n = Number of patients
Note: For concentrations below the LLOQ (0.078 mg/L), a value of LLOQ/2 was imputed.

Figure 45: Mean (±SD) EASI % Change from Baseline and Concentrations of Functional Dupilumab in Serum vs. Week by ADA and NAb Status in the 200 mg Q2W Group in Adolescent Patients with AD (Study R668-AD-1526)

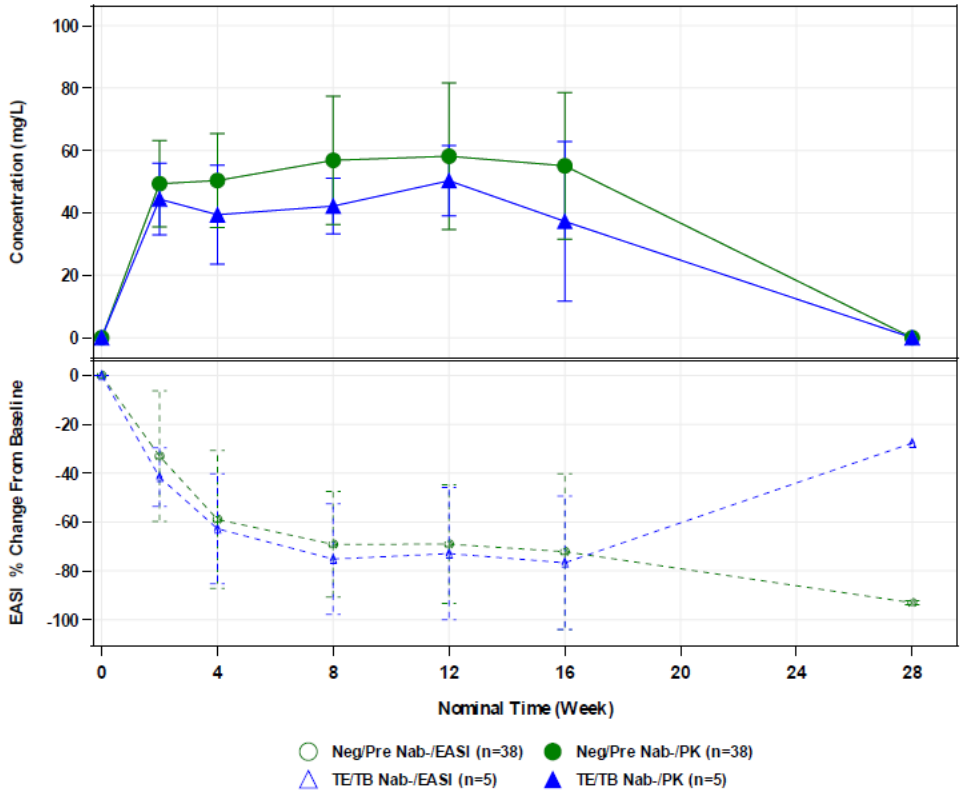


Figure 46: **Mean (±SD) EASI % Change from Baseline and Concentrations of Functional Dupilumab in Serum vs. Week by ADA and NAb Status in the 300 mg Q2W Group in Adolescent Patients with AD (Study R668-AD-1526)**

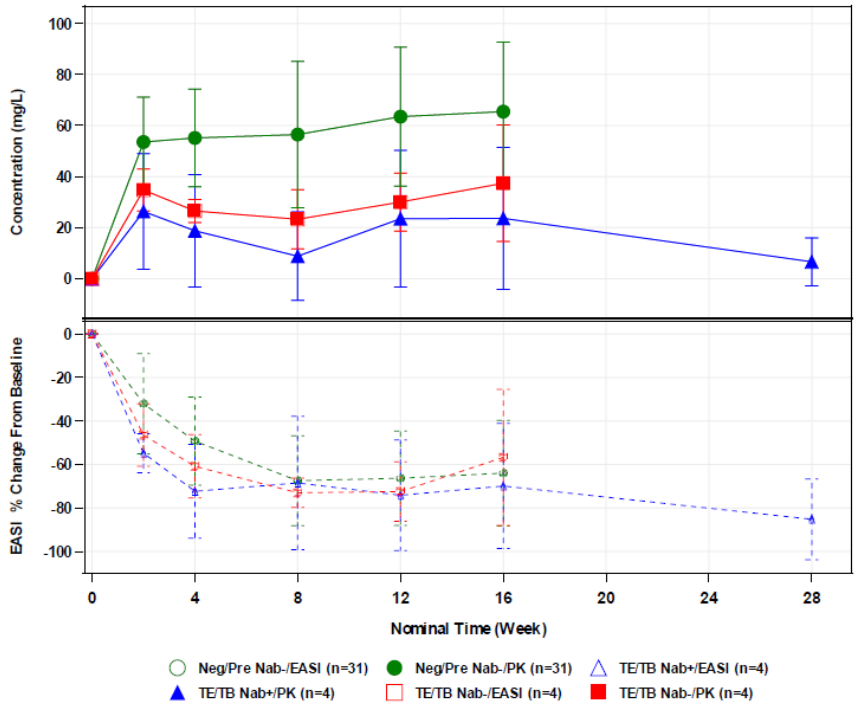


Figure 48: **Mean (±SD) NRS % Change from Baseline and Concentrations of Functional Dupilumab in Serum vs. Week by ADA and NAb Status in the 200 mg Q2W Group in Adolescent Patients with AD (Study R668-AD-1526)**

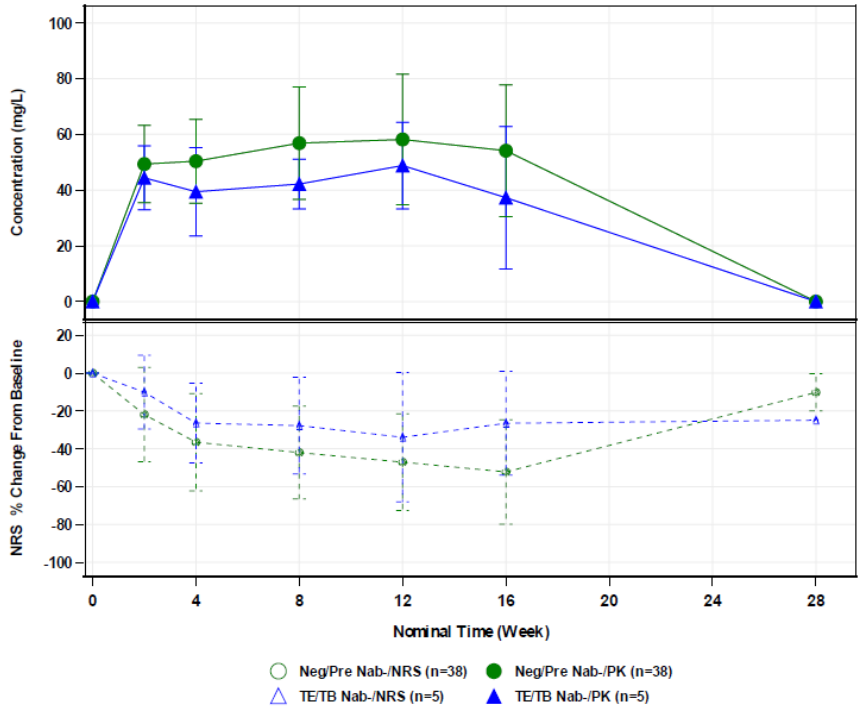
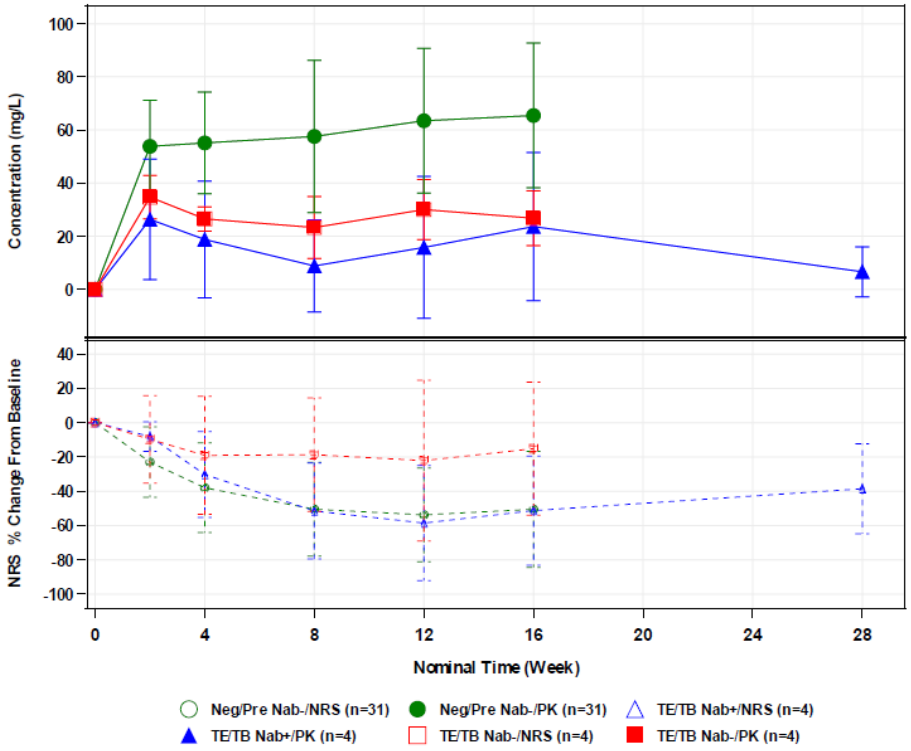


Figure 49: **Mean (±SD) NRS % Change from Baseline and Concentrations of Functional Dupilumab in Serum vs. Week by ADA and NAb Status in the 300 mg Q2W Group in Adolescent Patients with AD (Study R668-AD-1526)**



Study R668-AD-1434 (Phase 3)

Samples for ADA analysis were collected at baseline, and weeks 4, 12, 24, 36, and 48for patients recruited from parent study R668-AD-1412 and for patients recruited from R668-AD-1607 and R668-AD-1526, samples were collected at baseline and week 16.

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

Table 7: **Summary of ADA Status and Category of ADA Analysis Set by Parent Study in Adolescent Patients with AD (Study R668-AD-1434)**

ADA Category	Parent Study						Overall	
	R668-AD-1412		R668-AD-1526		R668-AD-1607			
	n	(%)	n	(%)	n	(%)	n	(%)
Total ADA Patients	35	(100%)	69	(100%)	32	(100%)	136	(100%)
Negative/Pre-existing	16	(45.7%)	55	(79.7%)	29	(90.6%)	100	(73.5%)
Treatment Boosted Response	0		0		0		0	
Treatment Emergent Response	19	(54.3%)	14	(20.3%)	3	(9.4%)	36	(26.5%)
Persistent	4	(11.4%)	3	(4.3%)	1	(3.1%)	8	(5.9%)
Transient	15	(42.9%)	5	(7.2%)	1	(3.1%)	21	(15.4%)
Indeterminate	0		6	(8.7%)	1	(3.1%)	7	(5.1%)

n = Number of patients
Note: 'Negative/Pre-existing' includes ADA negative and pre-existing responses.

Table 9: Summary of ADA Category and NAb Status of NAb Analysis Set by Parent Study in Adolescent Patients with AD (Study R668-AD-1434)

ADA Category; NAb Status	Parent Study						Overall	
	R668-AD-1412		R668-AD-1526		R668-AD-1607			
	n (%)		n (%)		n (%)		n (%)	
Total ADA/NAb Patients	35	(100%)	69	(100%)	32	(100%)	136	(100%)
Neg; NAb-	16	(45.7%)	55	(79.7%)	29	(90.6%)	100	(73.5%)
Neg; NAb+	0		0		0		0	
TE/TB; NAb-	3	(8.6%)	8	(11.6%)	3	(9.4%)	14	(10.3%)
TE/TB; NAb+	16	(45.7%)	6	(8.7%)	0		22	(16.2%)

n = Number of patients; Neg = ADA negative and pre-existing responses; TE = Treatment-emergent; TB = Treatment-boosted; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay

The distribution of dupilumab concentrations for ADA positive patients was generally in the range of concentrations of ADA-negative patients with the exception of a few patients with high/moderate ADA titers. Some patients from R668-AD-1412 who entered this OLE study with moderate or high titers exhibited a decrease in titer values over time with a corresponding increase in systemic dupilumab concentrations.

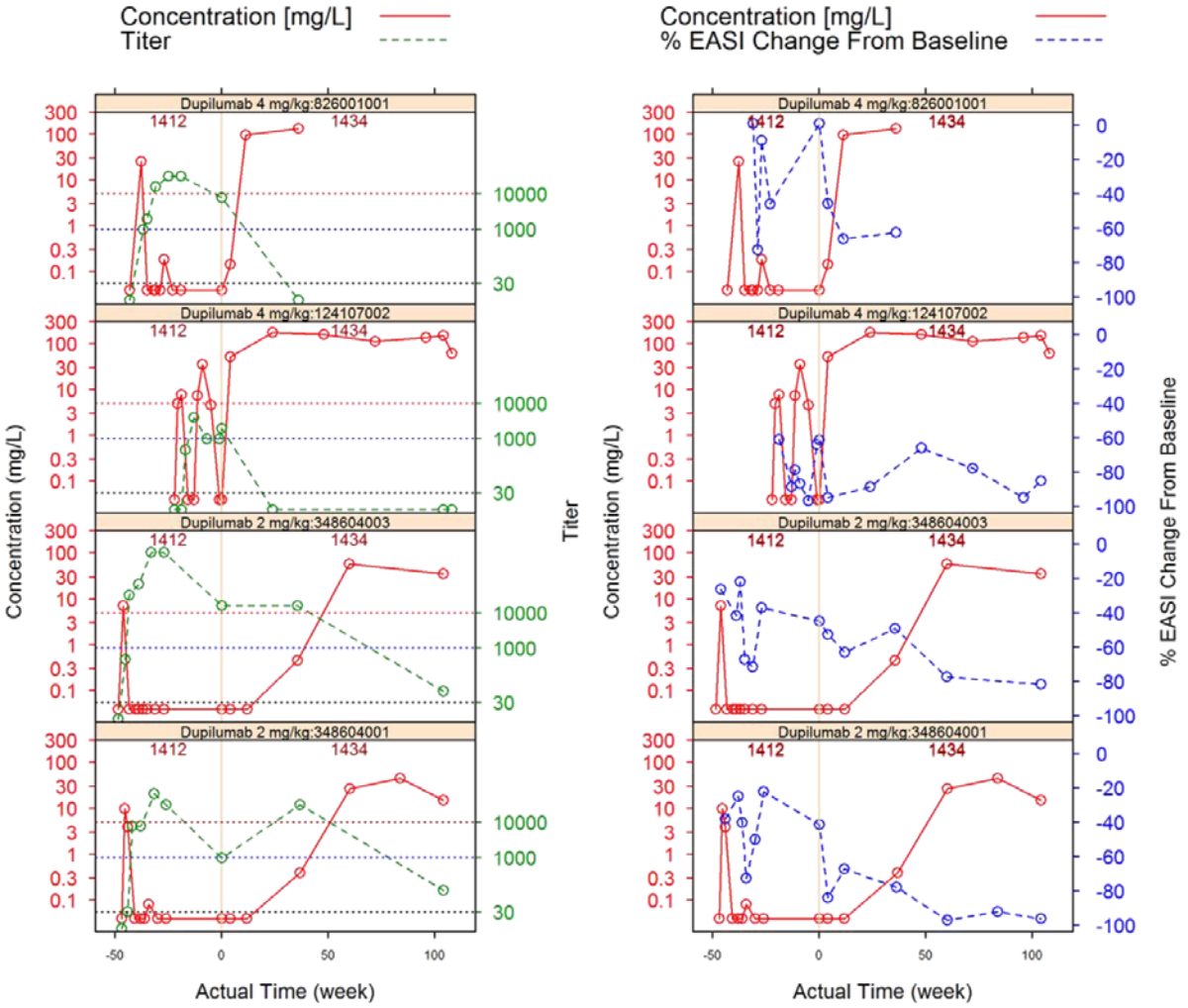
Association of immunogenicity and concentrations of functional dupilumab

The distribution of dupilumab concentrations for ADA-positive patients was generally in the range of concentrations of ADA-negative patients with the exception of a few patients with moderate/high ADA titers.

Closer inspection of both the dupilumab serum concentration and ADA titer time courses of 4 patients with high or moderate ADA titers showed the ADA titers increase from the start of study R668-AD-1412, where there was a single dose period (8 weeks) followed by a multiple dose period (4 doses administered QW). As the ADA titres reached moderate or high, dupilumab concentration decreased to the LLOQ. Longitudinal assessment of these patients revealed that, with continued treatment over time, ADA titer values declined (some to negative ADA status) with a corresponding increase in dupilumab concentrations to that expected for the treatment regimen. This return to a typical dupilumab concentration generally correlated with a greater percent reduction for baseline EASI (Figure 19).

The 2 remaining adolescent patients with moderate/high titer were not included in this analysis as they did not contribute longitudinal concentration/ADA titer data in this study at the time of interim data cut-off.

Figure 19: Individual Concentrations of Functional Dupilumab, ADA Titer, and Percent EASI Change from Baseline in Patients with Moderate and High Titer from Actual Time Zero of Parent Study R668-AD-1412 through the Last Sample Measured in the OLE Study R668-AD-1434



Note: First treatment start date of study R668-AD-1434 was used to calculate actual time for study R668-AD-1412. The efficacy endpoint corresponding to concentration time points were used for analysis. Percent (%) EASI change was calculated from parent study R668-AD-1412 Part A baseline.
Source: Figure 12 of Clinical Pharmacology report (Appendix 5)

2.3.4. PK/PD modelling

Exposure-Response Analysis

Exposure-response (E-R) analyses were conducted for adolescents with moderate-to-severe AD focusing solely on efficacy and concentration data from the randomized placebo-controlled pivotal study R668-AD-1526 in adolescents.

The primary study endpoint, the percentage of patients achieving an IGA score of 0 or 1, as well as the secondary endpoint, mean (standard deviation [SD]) percent EASI change from baseline, over time by quartile of functional dupilumab concentration was assessed. This was based on data from the 200/300 mg Q2W and 300 mg Q4W regimens of study R668-AD-1526 to explore any E-R relationships. The number of patients in each quartile and time point is shown as well as the percentage of patients receiving the 200/300 mg Q2W dose in each quartile over time. Unlike the analysis in the initial application, this analysis includes

various imputation methods to account for the effect of censored data due to dropout, as well as a completer analysis.

Two imputation methods were employed for the categorical variable of IGA: a primary method whereby missing data were treated as non-responders and a second method, which utilized an LOCF approach for data imputation. Two imputation methods were also employed for the continuous variable of EASI percent change from baseline; LOCF and worst observation carried forward (WOCF).

For missing concentration data from 16 patients, 87% of samples occurred between week 8 and week 16, ie, at or close to steady state. To impute these missing data, the last measured concentration was carried forward in all quartile analyses.

In addition to quartile analysis, logistic regression was performed to investigate the relationship between probability of achieving an IGA score 0 or 1, EASI-50, EASI-75, and EASI-90 with Ctrough at week 16.

A logistic regression analysis was also conducted to assess the relationship between the probability of developing conjunctivitis and Ctrough at week 16.

Per protocol, approximately 240 patients were to be randomized to receive placebo or dupilumab (200 mg Q2W, 300 mg Q2W, or 300 mg Q4W). In actuality, a total of 251 patients were randomized (full analysis set) in a ratio of 1:1:1 to the placebo, Q4W, or Q2W SC treatment regimens (85:83:82, respectively). Of the 251 patients, 250 patients received at least one dose of placebo or study drug and were included in the safety analysis set. Patients (n = 43) with baseline weight <60 kg received 200 mg dupilumab Q2W SC, and patients (n = 39) with baseline weight ≥60 kg received 300 mg dupilumab Q2W SC.
Of the 250 patients in the safety analysis set, 249 patients were included in the PK analysis set. As patients were able to enroll in an open-label extension study at or after the end of treatment (week 16), a total of 10 patients had samples for PK analysis at the last visit (week 28).

Table 1: Accounting of Patients by Analysis Set and Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)

Analysis Set	Not Dosed	Placebo	Dupilumab				All Active Doses	Overall
			300 mg Q4W SC	200 mg/300 mg Q2W SC	200 mg Q2W SC	300 mg Q2W SC		
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Full Analysis Set	1 (100%)	85 (100%)	83 (100%)	82 (100%)	43 (100%)	39 (100%)	165 (100%)	251 (100%)
Safety Analysis Set	0	85 (100%)	83 (100%)	82 (100%)	43 (100%)	39 (100%)	165 (100%)	250 (99.6%)
PK	0	85 (100%)	82 (98.8%)	82 (100%)	43 (100%)	39 (100%)	164 (99.4%)	249 (99.2%)
ADA	0	85 (100%)	82 (98.8%)	81 (98.8%)	42 (97.7%)	39 (100%)	163 (98.8%)	248 (98.8%)

N = Number of patients
Note: Percentages are based on the total in the full analysis set (all randomized patients). See Section 2.3 for definition of the safety, PK, and ADA analysis populations.

A total of 1511 serum samples had a reportable result upon analysis for concentrations of functional dupilumab. Of the samples from dupilumab-treated patients (including prestudy samples), 77.9% had quantifiable functional dupilumab concentrations.

Table 2: Accounting of Samples for Quantification of Functional Dupilumab Concentrations in the PK Analysis Set by Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)

Quantifiable	Placebo	Dupilumab				All Active Doses	Overall
		300 mg Q4W	200 mg/300 mg Q2W	200 mg Q2W	300 mg Q2W		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	506 (100%)	504 (100%)	501 (100%)	262 (100%)	239 (100%)	1005 (100%)	1511 (100%)
Yes	5 (1.0%)	386 (76.6%)	397 (79.2%)	208 (79.4%)	189 (79.1%)	783 (77.9%)	788 (52.2%)
No	501 (99.0%)	118 (23.4%)	104 (20.8%)	54 (20.6%)	50 (20.9%)	222 (22.1%)	723 (47.8%)

n = Number of samples

For the concentration/exposure-response analysis set, 245, 245, and 247 patients in the PK analysis set also had one baseline and at least one post dose EASI, IGA, and pruritus NRS score, respectively. In the placebo group, 5 samples had quantifiable dupilumab concentration. These results from the placebo group did not affect the ability to interpret the results of this study.

Table 3: Accounting of Patients with Reported EASI, IGA, and NRS scores in the Concentration/Exposure-Response Analysis Set by Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)

Analysis Set	Placebo	Dupilumab				All Active Doses	Overall
		300 mg Q4W SC	200 mg/300 mg Q2W SC	200 mg Q2W SC	300 mg Q2W SC		
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
EASI	83 (98.8%)	80 (98.8%)	82 (100%)	43 (100%)	39 (100%)	162 (99.4%)	245 (99.2%)
IGA	83 (98.8%)	80 (98.8%)	82 (100%)	43 (100%)	39 (100%)	162 (99.4%)	245 (99.2%)
NRS	84 (100%)	81 (100%)	82 (100%)	43 (100%)	39 (100%)	163 (100%)	247 (100%)

N = Number of patients
Note: Percentages are based on the total in the concentration/exposure-response analysis set. See Section 2.3 for definition of the concentration/exposure-response analysis sets.

Of the 250 patients in the safety analysis set, 248 patients were included in the ADA and Nab analysis sets. A total of 760 serum samples were available for analysis of ADA and NAb.

Table 4: Accounting of Samples for ADA and NAb Assay in Adolescent Patients by Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)

Samples	Placebo	Dupilumab				All Active Doses	Overall
		300 mg Q4W SC	200 mg/300 mg Q2W SC	200 mg Q2W SC	300 mg Q2W SC		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total Immunogenicity Samples	253 (100%)	254 (100%)	253 (100%)	132 (100%)	121 (100%)	507 (100%)	760 (100%)
ADA Negative	238 (94.1%)	224 (88.2%)	229 (90.5%)	125 (94.7%)	104 (86.0%)	453 (89.3%)	691 (90.9%)
ADA Positive	15 (5.9%)	30 (11.8%)	24 (9.5%)	7 (5.3%)	17 (14.0%)	54 (10.7%)	69 (9.1%)
NAb Negative	252 (99.6%)	250 (98.4%)	248 (98.0%)	132 (100%)	116 (95.9%)	498 (98.2%)	750 (98.7%)
NAb Positive	1 (0.4%)	4 (1.6%)	5 (2.0%)	0	5 (4.1%)	9 (1.8%)	10 (1.3%)

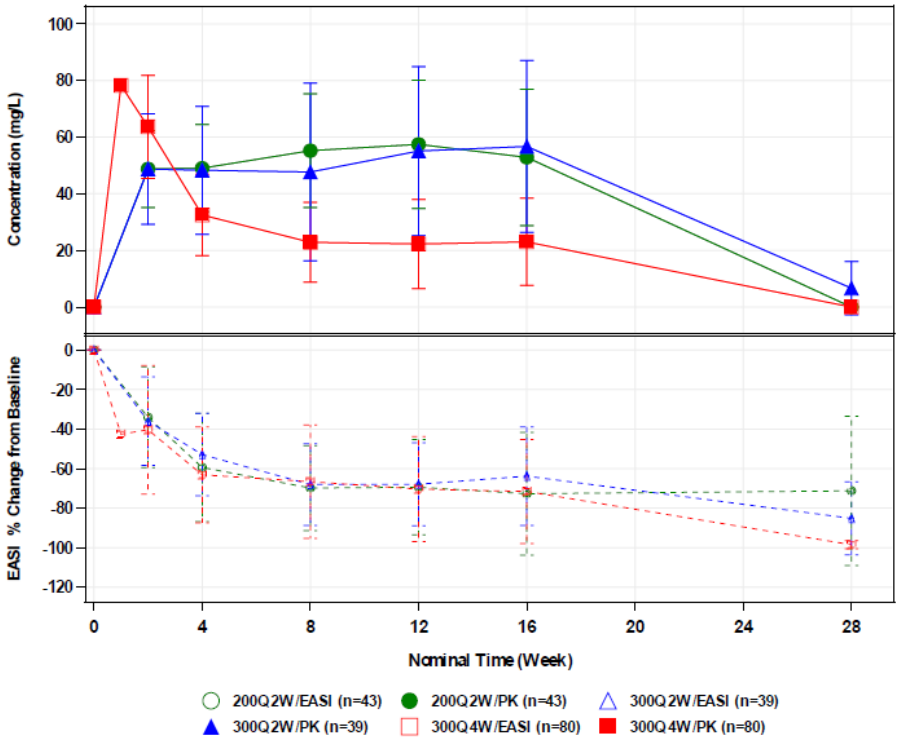
n = Number of samples
Note: Percentages are based on the total in the ADA and NAb analysis sets. See Section 2.3 for definition of ADA and NAb analysis sets.

Results

- E-R analysis regarding efficacy

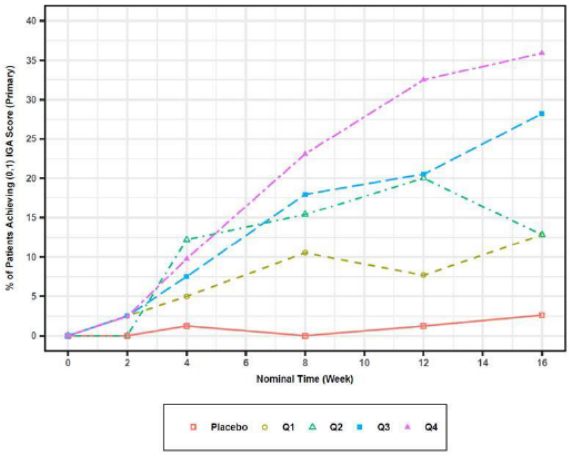
Exposure-response relationships via quartile analysis, where identified, revealed increasing drug effects with increasing serum trough concentration. Specifically, the percent of adolescent patients achieving the primary endpoint (IGA score of 0 or 1) increased with increasing quartile of functional dupilumab concentration. A similar trend was observed for EASI, where increasing percent change from baseline EASI scores was associated with increasing quartiles of dupilumab concentrations. As expected, the percent of patients achieving a given response with the 200/300 mg Q2W relative to the 300 mg Q4W dosing regimen increased with increasing quartiles of concentration. Results of the completer analysis and other imputation methods demonstrated that the rank ordering of concentration quartiles was preserved for the E-R relationships of both IGA and percent EASI change from baseline (see figures below).

Figure 4: **Mean (±SD) EASI % Change from Baseline and Concentrations of Functional Dupilumab in Serum by Week and Treatment Group in Adolescent Patients with AD (Study R668-AD-1526)**



n = Number of patients
Note: Concentrations below the LLOQ (0.078 mg/L) were set to 0.

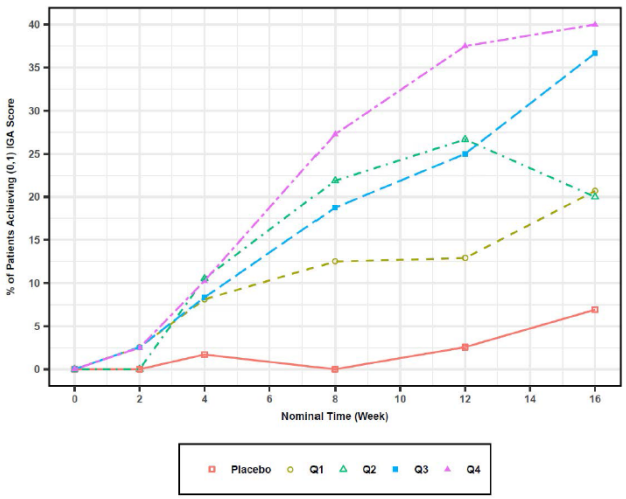
Figure 9: **Percent of Patients Achieving (0 or 1) IGA Score by Nominal Time (Week) and Quartile of Functional Dupilumab Concentrations in Adolescent Patients with Moderate-to-Severe AD (Primary Imputation Method) (Study R668-AD-1526).**



Quartile	WEEK 2	WEEK 4	WEEK 8	WEEK 12	WEEK 16
Placebo	0	1	0	1	2
Q1	1(100%)	3(33%)	4(25%)	3(33%)	5(20%)
Q2	0 (0%)	4(25%)	6(0%)	7(14%)	6(17%)
Q3	1(0%)	3(33%)	7(29%)	10(60%)	12(50%)
Q4	1(100%)	4(75%)	9(100%)	12(92%)	12(100%)

Data up to week 16 used for analysis. Table shows the total number of patients in each concentration quartile who achieved IGA 0 or 1. For each quartile/timepoint, number in parentheses is the percentage of patients receiving 200/300 mg Q2W regimen, calculated as (number of patients inQ2W group / Total active drug treated patients)*100. At week 16, concentration quartiles were: Q1 = 15.3 mg/L, Q2 = 33.6 mg/L, Q3 = 53.4 mg/L, Q4 = 112.0 mg/L.
Source: Module 5.3.5.1 R668-AD-1526 Figure 24.

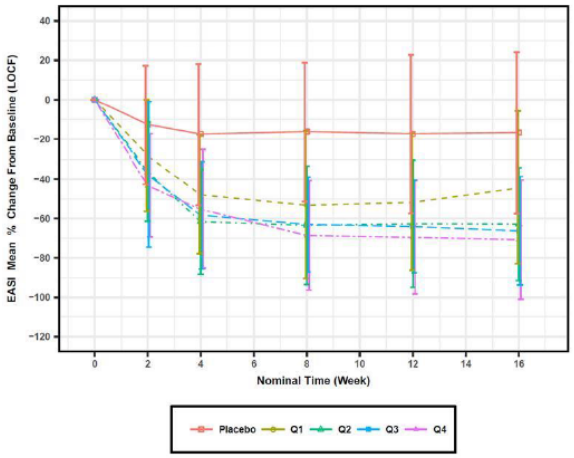
Figure 6: **Percent of Patients Achieving IGA(0,1) by Week and Quartile of Functional Dupilumab Concentrations in Adolescent Patients with AD (Completer) (Study R668-AD-1526)**



Quartile	WEEK 2	WEEK 4	WEEK 8	WEEK 12	WEEK 16
Placebo	0	1	0	1	2
Q1	1(100%)	3(33%)	4(25%)	4(25%)	6(17%)
Q2	0(0%)	4(25%)	7(0%)	8(38%)	6(33%)
Q3	1(0%)	3(33%)	6(33%)	8(50%)	11(45%)
Q4	1(100%)	4(75%)	9(100%)	12(92%)	12(100%)

Note: Data up to week 16 was used for analysis. The table shows the total number of patients in each concentration quartile achieving IGA(0,1). Number in parentheses is the percentage of patients receiving the 200 mg/300 mg Q2W regimen, calculated as number of (Q2W group patients / total active drug-treated patients)*100.

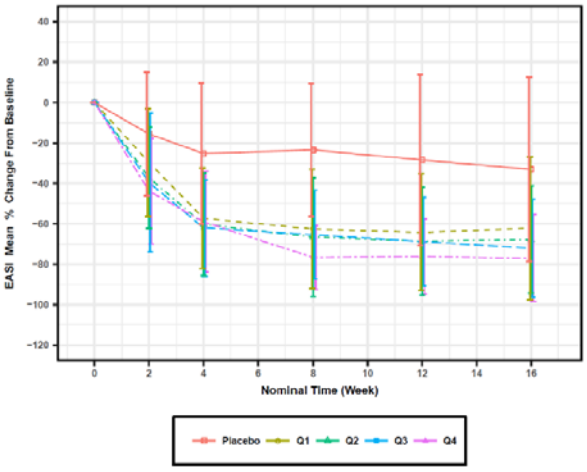
Figure 10: **Mean (±SD) EASI % Change from Baseline by Week and Quartile of Concentration of Functional Dupilumab in Serum in Adolescent Patients with AD (LOCF Imputation) (Study R668-AD-1526)**



Quartile	WEEK 2	WEEK 4	WEEK 8	WEEK 12	WEEK 16
Placebo	84	84	84	84	84
Q1	39(72%)	39(18%)	39(15%)	39(10%)	39(13%)
Q2	41(63%)	41(44%)	41(32%)	41(32%)	41(29%)
Q3	40(40%)	41(61%)	41(56%)	41(61%)	41(61%)
Q4	41(29%)	41(78%)	41(98%)	41(98%)	41(98%)

Data up to week 16 used for analysis. Table shows the total number of patients in each concentration quartile. For each quartile/timepoint number in parentheses is the percentage of patients receiving 200/300mg Q2W regimen, calculated as (number of patients in Q2W group / Total active drug treated patients)*100. At week 16, concentration quartiles were: Q1 = 15.3 mg/L, Q2 = 33.6 mg/L, Q3 = 53.4 mg/L, Q4 = 112.0 mg/L.
Source: Module 5.3.5.1 R668-AD-1526 Figure 25

Figure 8: **Mean (±SD) EASI % Change from Baseline by Week and Quartile of Concentration of Functional Dupilumab in Serum in Adolescent Patients with AD (Completer) (Study R668-AD-1526)**

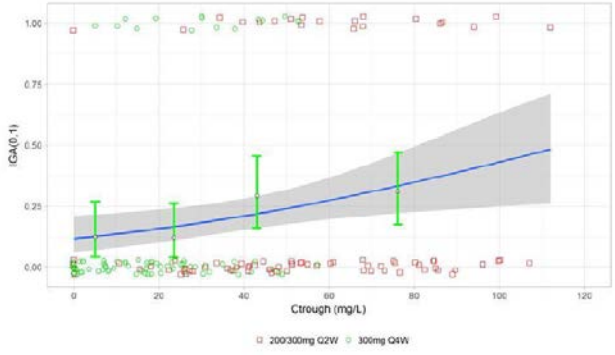


Quartile	WEEK 2	WEEK 4	WEEK 8	WEEK 12	WEEK 16
Placebo	73	59	45	39	29
Q1	39(77%)	37(22%)	32(25%)	31(13%)	29(17%)
Q2	39(62%)	38(47%)	32(28%)	30(43%)	30(37%)
Q3	39(41%)	36(61%)	32(63%)	32(63%)	29(66%)
Q4	40(28%)	39(79%)	33(97%)	32(97%)	30(97%)

Note: Data up to week 16 was used for analysis. Number in parentheses is the percentage of patients receiving the 200 mg/300 mg Q2W regimen, calculated as number of (Q2W group patients / total active drug-treated patients)*100.

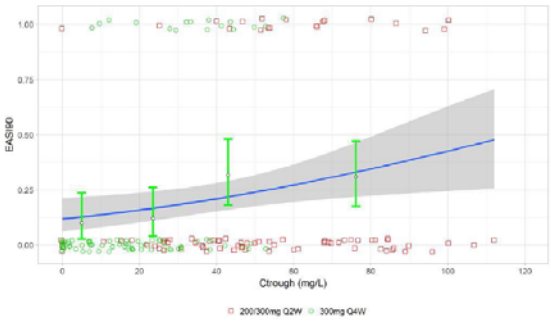
Logistic regression plots on binary efficacy endpoints including IGA 0 or 1, EASI-90, EASI-75, and EASI-50 also supported higher probability of response at higher exposures, which corresponded to the Q2W regimen. The p-values were significant for the inclination of the regression lines of these relationships, with a higher degree of significance observed on the more stringent efficacy endpoints, IGA 0 or 1 and EASI-90, compared to EASI-75 and EASI-50 (see figures below).

Figure 11: **Logistic Regression Relating Probability of Patients Achieving an (0 or 1) IGA Score with Dupilumab Trough Concentrations at Week 16 in Adolescent Patients with Moderate-to-Severe AD (p-value = 0.008) (Study R668-AD-1526)**



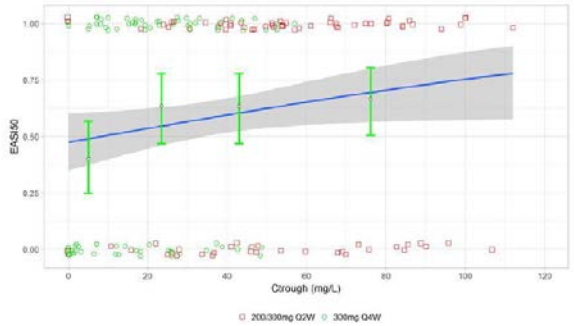
Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively, with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 24.

Figure 12: **Logistic Regression Relating Probability of Achieving EASI-90 with Dupilumab Trough Concentrations at Week 16 in Adolescent Patients with Moderate-to-Severe AD (p-value=0.009) (Study R668-AD-1526)**



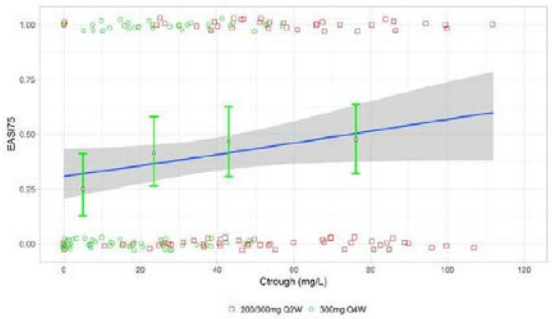
Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 25.

Figure 16: Logistic Regression Relating Probability of Achieving EASI-50 with Dupilumab Trough Concentrations at Week 16 (p-value=0.04) (Study R668-AD-1526)



Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively, with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 27.

Figure 17: Logistic Regression Relating Probability of Achieving EASI-75 with Dupilumab Trough Concentrations at Week 16 (p-value=0.06) (Study R668-AD-1526)



Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively, with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 26.

The data show a positive dupilumab concentration-response relationship for efficacy measures of IGA and EASI in adolescents with moderate-severe atopic dermatitis.

Exposure-response relationships by quartile of dupilumab concentration showed increasing drug effects with increasing trough concentration over time for efficacy endpoints IGA score of 0 to 1 and EASI. The percentage of patients receiving the 200 mg/300 mg Q2W regimen was greatest in the highest quartiles of dupilumab concentration (Q3 and Q4).

Logistic regression plots on binary efficacy endpoints EASI90, EASI50 and IGA(0,1) showed a significant increase in the probability of response at higher exposures which corresponded to the 200 mg/300 mg Q2W dosing regimen. The relationship did not reach significance for the EASI-75 endpoint (p-value=0.06).

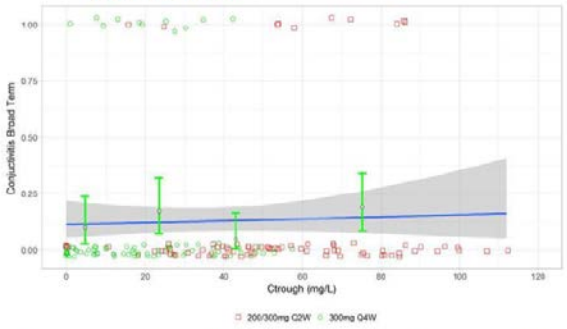
Logistic regression plots on safety endpoints of developing conjunctivitis (narrow term and broad term) showed no significant relationship between dupilumab trough concentration and probability of reporting the adverse event.

At week 16, dupilumab trough concentration quartiles were: Q1 = 15.3 mg/L, Q2 = 33.6 mg/L, Q3 = 53.4 mg/L, Q4 = 112 mg/L.

- E-R analysis regarding safety

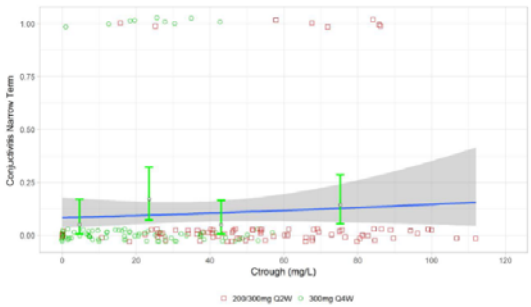
The most commonly reported adverse drug reaction was Conjunctivitis but there was no evidence of a concentration relationship for the probability of developing conjunctivitis.

Figure 13: Logistic Regression Relating Probability of Developing Conjunctivitis (Broad Term) with Dupilumab Trough Concentrations at Week 16 in Adolescent Patients with Moderate-to-Severe AD (p-value = 0.657) (Study R668-AD-1526



Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure
Source: Module 5.3.5.1 R668-AD-1526 CP-01V1 Figure 29.

Figure 28: Logistic Regression Relating Probability of Developing Conjunctivitis (Narrow Term) with Dupilumab Trough Concentrations at Week 16 in Adolescent Patients with Moderate-to-Severe AD (p-value = 0.479) (Study R668-AD-1526)



Note: Mean regression line – blue, confidence area around regression line – grey. Non-responders (0) and responder (1) individual values are jittered and represented at the bottom and at the top of the figure, respectively, with green circles (300 mg Q4W) and red squares (200/300 mg Q2W). The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (open black circles) and confidence intervals (green vertical lines) around the means are presented in the figures by quartile of exposure.

2.3.5. 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. With regard to the applied ADA assay method, the MAH confirmed that the original ADA assay method REGN668-AV-13089-VA-01V2 with the AD population specific cut point was used to analyze all phase 3 studies.

Pharmacokinetics

The package on clinical pharmacology regarding adolescent patients with moderate-to-severe AD comprises 4 dupilumab clinical studies where PK and pharmacodynamic (PD) data have been collected. A variety of subcutaneous (SC) dosing regimens was evaluated in these studies including: 2 mg/kg and 4 mg/kg single dose or repeated QW dose, 200 mg Q2W, 300 mg Q2W, and 300 mg Q4W.

Study R668-AD-1434 is an ongoing, phase 3, OLE study investigating the long-term safety, efficacy, PK, and immunogenicity of dupilumab in paediatric patients with AD who have previously completed a clinical study with dupilumab. Adolescent patients who participated in paediatric studies from dupilumab in AD (R668-AD-1526, R668-AD-1412, and R668-AD-1607) could roll-over into this study. This was a first-step analysis conducted on data from adolescent patients enrolled in this study.

In the PK analysis, the mean trough concentration at Week 16 in adolescent patients, who were up-titrated to the proposed to-be-marketed 200 mg/300 mg Q2W dosing regimen for adolescents, was approximately 45 mg/L. There was considerable variability in trough concentrations at week 16 in adolescents receiving the weight-tiered 200 mg/300 mg Q2W dosing regimen (CV% 41.7-51.6%). This was due to a difference in the duration of treatment with the 300 mg Q4W regimen before being uptitrated to 200/300 mg Q2W regimen in case of inadequate response, as per study protocol. The high variability would not be expected in a standard treatment regimen and therefore is not considered to be of clinical relevance.

Overall, the strategy for data analysis using population PK modelling by external validation and subsequent parameter re-estimation of the adult pop PK model using data collected from adolescent patients is considered appropriate.

The previously developed adult base model predicted dupilumab concentrations in adolescents reasonably well. The incorporation of allometric scaling for the impact of weight on Vc, Ke and Vm, resulted in modest improvements in predictions but the observed adolescent trough concentrations remained lower than those predicted by around 5-10 mg/L. This difference of ~16-25% was considered small and not clinically significant, given the observed efficacy in adolescents receiving 200/300 mg Q2W.

However, the MAH changed the plan to apply the adult base model to the adolescent data. During an examination of the VPC, a somewhat poor prediction of BLQ frequency was observed in addition to a slight over-prediction of observed PK data in adolescents. The MAH considered more appropriate to estimate Vm instead of fixing it based on the adult model. This approach allowed for a better description of the BLQ frequency, but still did not completely address the issue. Of note, patients with high and/or moderate ADA titers were also excluded from the analysis (2 patients overall, patient IDs 814-011-003 and 840-011-004). The MAH re-discussed the influence of BLQ, weight and ADA. It was clarified that low titer ADA has been included in the analysis with no impact on the final VPC, whereas individuals with moderate ADA titers (N=2) and high ADA titer (N=0) were excluded a priori from the analysis. No other potential reasons that might affect dupilumab PK in the adolescent populations were taken into account. Thus, detected deviation in the VPC during external validation of the adult model with adolescent data remains unexplained. Nevertheless, the issue is regarded solved as no major revelvance.

Following the discussion on target-mediated clearance (represented by Vm), the MAH was asked to similarly discuss potential differences between adult and adolescent regarding ka, F as these parameters may differ in other age groups compared to the adult population using modelling and simulation and sensitivity analyses. In response to Q6, the applicant further discussed the impact of fixing F and ka with respect to

both the adult and adolescent population. To justify equal F and ka in both age groups, the MAH provided %change in difference in ka (12%) and apparent volume of distribution (10%) between adults and adolescents. Sensitivity analysis was used to justify that these changes are not clinically relevant. From the %change values a potential increase of 1.1-fold increase in bioavailability could be derived. It is agreed that this has no high impact on any conclusion regarding dosing. Hence, the issue is solved.

To better evaluate allometric effects, the MAH was asked to provide estimated allometric exponents on CL and central volume of distribution based on adult and adolescent data, respectively, using a two compartment model that is parameterized accordingly. As requested, the MAH provided algometric exponents on CL and V2 using the re-parameterized population PK model. Although it is agreed that the impact on weight and V2 are in the same range with respect to both adults and adolescence, it is noted that tested covariate BMI and weight on the same parameter simultaneously are highly correlated with estimation of BMI on CL being not very robust as indicated by bootstrapping. This limits the interpretability and probably confounds the estimation of weight allometric exponent on clearance.

Population PK parameters of adolescents were mostly similar to those in adult models, and similar to those published for other IgG4 monoclonal antibodies. Target-mediated clearance (Vm) was somewhat higher in adolescent than adult patients (base model 1.46 and 1.07 mg/L/d, respectively). It is agreed that this difference is likely inconsequential. In the sensitivity analysis, when additive error was fixed to a 0.01 mg/L, to give greater weight to rare small concentrations and BLQ values in the sparse adolescent data and hence estimate Vm better, the Vm estimate reduced to 1.26 mg/L/d.

In adolescent patients, the covariates of ADA, BMI, EASI score, and weight were statistically significant and consistent with the adult model. The statistically significant impact of albumin on central volume and race on elimination rate in adults was not replicated in adolescents. This is possibly due to the considerably smaller sample size. The narrower range of albumin levels in adolescents than in adults (16 vs. 35 g/L, respectively) may have also contributed. Given that the impact of race on Ke and albumin on V2 in adults was not clinically important, the similarity of PK among adult and adolescent data shown in the covariate analysis is agreed. The covariate effect of EASI score on Ke in adolescents (0.356) is more than double the effect in adults (0.143). However, the overall effect of this covariate in the model was not influential or deemed to be clinically significant. Clarification received revealed that the covariate of weight on ke was a typographical error thus not affecting any result or conclusion.

Overall, it is agreed that the base and covariate PK models adequately described the PK of dupilumab in adolescent patients with moderate-to-severe AD. Diagnostic plots for both base and covariate models showed an acceptable fit. Bootstrapping validated the parameter estimates. In the omega matrix for the adolescent covariate model, the bootstrap CIs for V2 and Ke do not contain the median. This is because in the columns with the parameters of the adolescent base model, the rows of omega matrix were mistakenly switched between ke and V2 of the report. Once correctly labelled, the Confidence Intervals for Omegas of V2 and ke do include the respective median values. This typographical error does not affect any result or conclusion. The inter-individual variability (CV%) of V2 and ke in the base model was 14.3% and 36.5%, respectively. The inter-individual variability (CV%) of V2 and ke in the covariate model was 14.2% and 32.6%, respectively.

The MAH was asked to analyze potential age- and weight-related covariates regarding ka and F in the adolescent patient population. The provided analysis is limited by the sparse amount of PK samples collected from the pivotal study R668-AD-1526. Thus, further analyses and assessing covariate effects on ka and F has not been possible. Omega (V2) estimated from the final model is wider compared to Omega (V2) estimated from the base model which is considered not plausible. In addition, shrinkage on V2 was high (54.3%) and also rises from the base to the final pop PK model. Thus, the MAH was asked to justify covariate selection. The MAH clarified that there was labelling error that led to the issue regarding Omega(V2). In addition the MAH elaborated on the justification of covariate selection on the basis of relatively high shrinkage and is deemed acceptable as they have been in the same range regarding both adults and adolescents and thus, this issue was considered resolved.
VPC plots indicate a slight under-prediction following 300 mg Q2W treatment. Overall model diagnostics showed no major model deficiencies indicating that the population PK model describes the data acceptably well.

The PK parameters estimated for the adolescent patients were used to calculate the Cmax, Cmin, and AUC values after the first dose and at steady state for the proposed dosing regimen 200 mg and 300mg Q2W, as well as for 300mg Q4W.

Estimation of the central compartment volume of distribution (V2) yielded similar values for adolescents vs. adults (2.54±0.0473 vs. 2.76±0.021 L, respectively). Derived values for clearance for the adolescent population (0.128 L/d) and adult population (0.130 L/d) are deemed comparable.

Simulated exposure to Dupilumab by treatment regimens supports the chosen 60 kg threshold for differential dosing (200 mg < 60kg; 300 mg ≥ 60 kg). Simulated mean Ctrough at steady state following 200 mg treatment is calculated to reach 61.6 mg/L which is in accordance to mean Ctrough of 62.3 mg/L simulated following 300 mg treatment in the target adolescent patient population. AUCss is also deemed comparable among the two body weight groups.

Detectable differences in mean dupilumab exposure between adolescents and adult are not considered major given the overall high variability in data which is supported by population PK analysis. The mean dupilumab concentration reached following 200 mg Q2W treatment was more comparable than mean concentrations following 300 mg when opposing AD and Asthma adolescent patients.

To support the adequacy of the proposed dosing regimen for adolescents, the applicant provided logistic regression plots to show the probability of attaining a target trough concentration ("cut off") of 32.7 mg/L over the body weight distribution. These demonstrated that, over the weight range of interest, a much greater percentage of adolescent patients receiving the 200/300 mg Q2W regimen achieve the target trough concentration compared to adolescents receiving the 300 mg Q4W regimen.

Bioequivalence PFP vs. PFS

The comparison of the two presentations was discussed during procedure EMEA/H/C/004390/X/04/G (extension application for asthma and adults and adolescents) and raised again in this application based on the same bioequivalence study. In answer to concerns raised by CHMP, the same clarification provided by the company as for the procedure EMEA/H/C/004390/X/04/G allowed to conclude that the PFP comparability is considered demonstrated.

Immunogenicity

Immunogenicity was analysed in all clinical studies which included adolescent AD patients.

In Study R668-AD-1412, an unexpectedly high ADA response was observed and high or moderate titer responses were associated with a substantial reduction in detectable drug concentrations. However, it is agreed that this significant immune response was most probably invoked due to the unusual study design, where a single dose followed by an 8-week pause and then followed by repetitive dosing was applied. ADA rates seemed to be slightly higher in the adolescent as compared to the adult AD population.

In study R668-AD-1526, 20.5% of patients were found to be positive for treatment-emergent ADA in the 300 mg Q2W dosing group. In the adult AD study R668-AD-1224, this dosing regimen led to a treatment-emergent ADA response in only 5.71% of patients. In the extension study R668-AD-1434, the increased incidence of ADA and NAb was further confirmed in the adolescent as compared to the adult AD population. The applicant has thoroughly discussed the higher ADA rates in the adolescent AD population and elucidated potential reasons for this observation. It is acknowledged that the majority of treatment-emergent ADA response was transient during pivotal study 1526 and that neither high nor persistent ADA titers were detected. With regard to total treatment-emergent responses corrected incidences show similar results compared with the adult AD phase 3 studies. It is acknowledged that the small number of NAb positive patients hampers a thorough analysis as to differences of nAb incidences in the adult and adolescent populations and impacts on PK/efficacy. The justification of the distorted ADA results due to the prime and boost response in patients treated in study 1412 during the OLE study is comprehensible and endorsed. Thus, the immunogenicity profile of adults and adolescents treated with dupilumab was similar. No significant impact of treatment-emergent ADA on exposure, safety or efficacy was observed.

In study R668-AD-1526, with regard to dupilumab exposure and efficacy, the applicant states that ADA status has no clinically relevant impact on these parameters. However, having a closer look into the data, dupilumab exposure in the 300mg Q2W was clearly reduced in ADA positive patients, although there seemed to be no impact on EASI % change from baseline (Figure 46). This appears to be different for NRS % change from baseline. Similar to the observed trend towards reduced dupilumab exposure in ADA positive patients, a lower NRS % change from baseline was observed for ADA positive patients in both the 200 mg and the 300 mg Q2W dosing groups (Figure 48 and 49). The applicant was requested to discuss the impact of ADA status on exposure and efficacy in the adolescent AD population. In addition, in one of the two patients showing considerably lower dupilumab concentrations while exhibiting low ADA titers, dupilumab concentrations were low from week 4 to week 16 but then increased (Figure 31). Although the applicant was unable to determine a specific reason for the increased concentration, the issue is not further pursued. Despite low drug exposure, this ADA positive patient achieved a high response as measured by EASI. It appears that variability in drug exposure may not explain all the between-subject variability in response to drug.

In study R668-Ad-1434, the distribution of dupilumab concentrations for ADA-positive patients was generally in the range of concentrations of ADA-negative patients with the exception of a few patients with moderate or high ADA titers. In these patients, as the ADA titres reached moderate or high levels, dupilumab concentration decreased to the LLOQ. A longitudinal assessment of the ADA titer and dupilumab concentration over time, in 4 patients with moderate/high titers, showed that ADA titers eventually fall with continued dosing, and this decline was associated with a corresponding increase in dupilumab concentrations. The biological reason for the decline in ADA titer over time with continued dupilumab treatment is unclear, but may be a result of tolerance. These 4 patients were off treatment before enrolment into the OLE study.

In order to clarify the duration of ADA positive status following withdrawal of dupixent, the applicant provided data showing the ADA titer of each patient at the end of treatment visit of the parent studies R668-AD-1526 and R668-AD-1412 and at the baseline of the open label extension study R668-AD-1434. The duration between these time points ranged from 1 week to 4 months.

Exposure-Response

The indication in adolescents with moderate-to-severe AD is based primarily on the phase 3 randomized controlled study R668-AD-1526 assessing efficacy and safety of dupilumab in adolescent patients. Exposure-response (E-R) data and analyses are presented to support the dosing regimen in adolescent patients. The primary study endpoint, the percentage of patients achieving an IGA score of 0 or 1, as well as the secondary endpoint, mean (standard deviation [SD]) percent EASI change from baseline, over time by quartile of functional dupilumab concentration has been assessed including various imputation methods to account for the effect of censored data due to dropout, as well as a completer analysis. The MAH was asked to discuss why more than 20% of samples have not been quantifiable in Study R688-AD-1526 following dupilumab dosing taking BLQ samples into account. 17% (1/6) of the samples were collected outside the treatment period of study R668-AD-1526 and are therefore not quantifiable. The issue is regarded to be solved.

The time course of lactate dehydrogenase (LDH) was analyzed as a biomarker of AD disease severity over time. The pharmacodynamics of LDH shows similar effects of dupilumab between adolescent and adult AD patients.

Exposure-response relationships via quartile analysis indicate increasing drug effects with increasing serum trough concentration with respect to efficacy. Specifically, the percent of adolescent patients achieving the primary endpoint (IGA score of 0 or 1) increased with increasing quartile of functional dupilumab concentration. A similar trend was observed for EASI, where increasing percent change from baseline EASI scores was associated with increasing quartiles of dupilumab concentrations, plateauing from Ctrough_ss of 20 – 40 mg/L.

Logistic regression plots on binary efficacy endpoints EASI90, EASI50 and IGA (0,1) showed a significant increase in the probability of response at higher exposures which corresponded to the 200 mg/300 mg Q2W dosing regimen. The relationship did not reach significance for the EASI-75 endpoint (p-value=0.06).

Logistic regression plots on safety endpoints of developing conjunctivitis (narrow term and broad term) showed no significant relationship between dupilumab trough concentration and probability of reporting the adverse event.

At week 16, dupilumab trough concentration quartiles were: Q1 = 15.3 mg/L, Q2 = 33.6 mg/L, Q3 = 53.4 mg/L, Q4 = 112 mg/L. At week 16, dupilumab trough concentration quartiles were: Q1 = 15.3 mg/L, Q2 = 33.6 mg/L, Q3 = 53.4 mg/L, Q4 = 112 mg/L. The 5th percentile of the Ctrough,ss at Week 16 achieved by the standard 300 mg Q2W regimen associated with efficacy in the adult Phase 3 trials is 32.7 mg/L; in the adolescent study R668-AD-1526, Ctrough,ss for the 200/300 mg Q2W regimen is 25.2 mg/L. These values are close or equivalent to the second quartile concentration (33.6 mg/L) at Week 16. In contrast, the 5th percentile for Ctrough,ss at Week 16 achieved by the 300 mg Q4W regimen in adolescents with AD was <0.1 mg/L; the marked reduction compared to the 200/300 mg Q2W regimen is a reflection of the non-linear PK profile of dupilumab.

No evidence of a concentration relationship for the probability of developing conjunctivitis could be detected from exposure quartile analyses with respect to safety.

2.3.6. Conclusions on clinical pharmacology

The MAH provided a comprehensive package on clinical pharmacology to support the dosing regimen in adolescent patients with AD, tiered by body weight with patients <60 kg receiving 200 mg Q2W following a 400 mg loading dose, and patients ≥ 60 kg receiving 300mg Q2W following a 600 mg loading dose.

The PK and PD of dupilumab in adolescent patients with AD were studied and characterised to support this application. Overall, the data suggest that adolescents and adults with moderate-to-severe AD display similar PK when compared at various dosing regimens across phase 2 and phase 3 studies. The similarity in PK between adolescent and adult patients with AD is further supported by the population PK analysis.

No evidence of a concentration relationship for the probability of developing conjunctivitis could be detected from exposure quartile analyses.

ADA rates seemed to be slightly higher in the adolescent as compared to the adult AD population. The applicant has thoroughly discussed the higher ADA rates in the adolescent AD population and elucidated potential reasons for this observation. It is acknowledged that the majority of treatment-emergent ADA response was transient during pivotal study 1526 and that neither high nor persistent ADA titers were detected. With regard to total treatment-emergent responses corrected incidences show similar results compared with the adult AD phase 3 studies. It is acknowledged that the small number of NAb positive patients hampers a thorough analysis as to differences of NAb incidences in the adult and adolescent populations and impacts on PK/efficacy. The justification of the distorted ADA results due to the prime and boost response in patients treated in study 1412 during the OLE study is comprehensible and endorsed. Thus, the immunogenicity profile of adults and adolescents treated with dupilumab was similar. No significant impact of treatment-emergent ADA on exposure, safety or efficacy was observed.

2.4. Clinical efficacy

The clinical development program of dupilumab in the treatment of adolescent AD comprises 4 clinical studies. R668-AD-1526 is the pivotal phase 3 monotherapy study in patients aged 12-18 years with moderate-to-severe AD not adequately controlled with currently available topical treatments. Supportive data are derived from a phase 2a, open-label pharmacokinetic (PK)/safety study (R668-AD-1412), an pediatric open-label extension study (R668-AD-1434) and an open-label autoinjector (AI) study (R668-AD-1607, note: data assessed as part of the extension of indication in asthma).

Patients from the above 3 studies had the option to screen for an OLE study (R668-AD-1434). This phase 3, multicenter, OLE study is enrolling patients from different studies in different age groups, covering the entire spectrum of the pediatric age groups from 6 months to <18 years of age (Section 2.4). For this subsequent marketing application, only data from adolescent patients (≥12 to <18 years of age) are included from study

R668-AD-1434. The primary objective of the study was to evaluate long-term safety of dupilumab in pediatric patients. Additionally, this study provided long-term efficacy data. A total of 275 adolescent patients were included in the study (as of the data cut-off date of 21 Apr 2018). For the OLE study, R668-AD-1434, a first-step CSR was written to support this submission using the data cut-off date of 21 Apr 2018, and a final CSR will be completed at a later date. Additional data from a later data cut-off of December 2018 were provided as part of the response to the request for Supplementary information with approximately 300 patients at baseline.

Figure 1: Dupilumab Studies in the Adolescent Atopic Dermatitis Program

AD = atopic dermatitis; PK = pharmacokinetics; N = number of enrolled and treated adolescent patients (ie, adolescent patients in the safety analysis set [SAF]). Number in parentheses is the number of patients exposed to dupilumab. Source of data: the analysis set tables of individual clinical study reports (CSRs), unless referenced otherwise.
Arrows represent roll-over of patients into the open-label extension (OLE) study R668-AD-1434.
All studies are included in this dossier.
a. Pre-filled pen (PFP) is also referred to as autoinjector (AI).
b. Part A of study R668-AD-1607 also included adult patients; the number listed is for adolescents only.
c. Study R668-AD-1412 also included children ≥6 to <12 years of age; the number of patients listed is for adolescents only.
d. The number of patients randomized and included in the full analysis set (FAS) was 251; 1 patient randomized to the dupilumab 300 mg Q4W group did not receive study treatment and was 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 05 April 2018).
e. Study R668-AD-1434 includes patients ≥6 months to <18 years of age. The number of patients (275) listed included all adolescent patients from the 3 prior studies as of data cutoff for this submission (21 April 2018), including 33 of the 40 patients in the adolescent group from R668-AD-1412, 3 younger patients from R668-AD-1412 who reached 12 years of age at the time rolling over to R668-AD-1434, 201 of 250 patients from R668-AD-1526, 11 of 18 adolescent patients from Part A of R668-AD-1607, and 27 adolescent patients from Part B (300 mg PFP portion of R668-AD-1607; not complete as of data cutoff for this application). Two of the previous studies (R668-AD-1412 and R668-AD-1607) were open label. The third study (R668-AD-1526) had been unblinded, primary analysis completed and results included as part of this application.

The number of patients (275) listed included all adolescent patients from the 3 prior studies as of data cutoff for this submission (21 April 2018), including 33 of the 40 patients in the adolescent group from R668-AD-1412, 3 younger patients from R668-AD-1412 who reached 12 years of age at the time rolling over to R668-AD-1434, 201 of 250 patients from R668-AD-1526, 11 of 18 adolescent patients from Part A of R668-AD-1607, and 27 adolescent patients from Part B of R668-AD-1607 (the primary objective of Part B was to collect actual use data on use of 300 mg PFP and 300 mg PFS; this part of the study was not complete as of data cutoff for this application). Two of the previous studies (R668-AD-1412 and R668-AD-1607) were open label. The third study (R668-AD-1526) had been un-blinded, primary analysis completed and results are included as part of this application.

2.4.1. Dose response study

The efficacy of dupilumab in adolescent patients with AD was first explored in a phase 2a study (R668-AD-1412). Adolescent patients (≥12 to <18 years of age) with moderate-to-severe AD were included in this study. The primary objective of the study was to characterize the safety and PK of dupilumab in patients with AD; efficacy was evaluated as a secondary objective. This was an open-label, uncontrolled study with 2 sequential, ascending-dose cohorts (dose cohort 1 [2 mg/kg] and dose cohort 2 [4 mg/kg]). This study consisted of Part A (single-dose treatment and an 8-week semi-dense PK sampling period), and Part B (including a 4-week repeat-dose treatment period [4 weekly doses] and an 8-week follow-up period).

A total of 40 adolescent patients were enrolled into the study and randomized to the 2 treatment groups (20 patients in the 2 mg/kg group and 20 patients in the 4 mg/kg group).

Methods

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 a single dose (2 mg/kg or 4 mg/kg) of dupilumab administered SC followed by repeat-doses of the same doses weekly for 4 weeks in pediatric patients with moderate-to-severe AD (for adolescents ≥12 to <18 years of age) or severe AD (for pediatric patients ≥6 to <12 years of age) that was not adequately controlled with topical treatments. Approximately 80 patients were planned to be enrolled in this study.

The study consisted of a screening period (day -35 to day -1), a baseline visit, Part A (including a single-dose treatment and an 8-week semi-dense PK sampling period), and Part B (including a 4-week repeat-dose treatment period [4 weekly doses] and an 8-week follow-up period to assess safety, PK and return of clinical signs of AD). Patients who completed this study were offered an opportunity to enroll in an OLE study (patients <18 years old at end of study were offered screening for the pediatric OLE, patients ≥18 years old were offered screening for the adult OLE).

Study participants

Two sequential, ascending-dose cohorts were planned, as follows: dose cohort 1 (2 mg/kg) and dose cohort 2 (4 mg/kg). Within each dose cohort, approximately 36 to 40 patients were to be enrolled in 2 age subsets, as follows: subset A (adolescent ≥12 to <18 years of age; presented in this SCE) and subset B (children ≥6 to <12 years of age; not presented in this SCE). Enrollment and study dosing started with cohort 1A (2 mg/kg, adolescent age subset) and proceeded in sequence to cohort 1B (2 mg/kg, children age subset), cohort 2A (4 mg/kg, adolescent age subset), and cohort 2B (4 mg/kg, children age subset); a safety review of data from the previous cohort(s) was performed before proceeding to the next cohort.

Objective/outcomes

The primary objective of this study was to investigate the safety and PK of SC treatment with dupilumab in pediatric patients with AD. The secondary objective included an assessment of the immunogenicity and efficacy of dupilumab in this patient population.

Concomitant treatments/rescue medication

The use of topical medication for AD (including TCS and TCIs) was permitted during the study.
It was recommended that investigators should select the potency based on the age of the patient, severity of disease and affected region, and that use be consistent with local guidelines.
The use of TCIs was reserved for areas of the body that were more prone to side effects from TCS use (eg, face, intertriginous, and genital areas). If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD was provided to study patients at the discretion of the investigator. This included topical therapies (eg, high-potency TCS) or systemic medications like corticosteroids and non-steroidal immunosuppressive drugs (eg, ciclosporin, MTX, mycophenolate-mofetil, or azathioprine). Efficacy assessments were EASI, IGA of AD severity, pruritus NRS, SCORAD, BSA involvement with AD, and at some study sites AD area photographs.

Results

Patient Disposition

A total of 40 adolescent patients were enrolled into the study (20 patients in the 2 mg/kg group and 20 patients in the 4 mg/kg group).
Most (38/40 [95.0%] patients) completed treatment; 2 patients withdrew (1 due to an adverse event [AE] of animal bite for which rabies vaccine was given, and another patient for fear of study drug injections). Thirty-five (87.5%) patients continued in the pediatric OLE study and 4 (10.0%) patients went on to

participate in the adult OLE study (patients who had turned 18 years old during the study were offered participation in the adult OLE).

Demographics, and Baseline Disease Characteristics

Overall, baseline demographic characteristics were comparable between the 2 dose groups (2 mg/kg and 4 mg/kg). The majority of patients were white (80%) and female (55%); the mean (SD) age of adolescent patients enrolled was 14.5 (1.8) years, the mean (SD) weight was 54.7 (12.2) kg with a weight range from 32 to 81.8 kg, and the mean (SD) BMI was 21.0 (3.7) kg/m2.

Overall, baseline disease characteristics were comparable between the 2 dose groups and consistent overall with moderate-to-severe disease; however, since patients were not randomized into the dose cohorts, some minor differences were observed. The majority of patients had disease onset prior to 5 years of age (85%); the mean (SD) duration of AD was 12.2 (3.4) years; the mean (SD) EASI score was 31.7 (16.0); 47.5% of patients had IGA=3 (moderate disease) and 52.5% had IGA=4 (severe disease); the mean (SD) pruritus NRS score was 6.5 (2.3); and the mean (SD) BSA involvement was 49.0% (24.9).

Efficacy Results

Efficacy analyses were performed using the safety analysis set (SAF), which included all patients who received any study drug.

Dupilumab administered as a single dose of either 2 mg/kg or 4 mg/kg induced significant and rapid reduction of disease activity in patients at week 2 (34% and 51% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses, respectively). Starting at week 8, patients received repeated weekly doses of dupilumab for 4 weeks, which led to a further improvement in disease severity in patients in both dose groups (67% and 70% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses, respectively at week 12).

There did not appear to be a clear dose response as the 2 dose cohorts showed similar efficacy on the various endpoints evaluated during the study. Efficacy results from this study are summarized in Table 7.

Table 7: Summary of Key Efficacy Parameters for R668-AD-1412 – SAF (Adolescent Patients Aged ≥12 to <18 Years)

	2 mg/kg (N=20)			4 mg/kg (N=20)		
Time Point	**Week 2**	**Week 12**	**Week 20**	**Week 2**	**Week 12**	**Week 20**
Mean percent change in EASI score from baseline (SD)	-33.9 (19.93)	-66.4 (29.25)	-51.2 (33.71)	-50.9 (29.40)	-69.7 (24.48)	-60.6 (29.43)
Proportion of patients achieving EASI-50, n (%)	4 (20.0%)	14 (70.0%)	10 (50.0%)	13 (65.0%)	15 (75.0%)	12 (60.0%)
Proportion of patients achieving EASI-75, n (%)	1 (5.0%)	11 (55.0%)	6 (30.0%)	6 (30.0%)	8 (40.0%)	7 (35.0%)
Proportion of patients achieving IGA 0 or 1, n (%)	0	2 (10.0%)	1 (5.0%)	2 (10.0%)	7 (35.0%)	4 (20.0%)
Mean percent change in pruritus NRS score from baseline (SD)	3.9 (49.04)	-30.8 (68.35)	-17.2 (83.24)	-36.0 (30.88)	-37.6 (34.42)	-33.5 (37.41)
Mean percent change in SCORAD score from baseline (SD)	-21.7 (16.69)	-47.7 (27.27)	-37.5 (23.73)	-35.0 (24.06)	-43.4 (25.38)	-40.0 (28.68)
Mean percent change from baseline in Percent BSA Involvement with AD (SD)	-25.0 (24.2)	-61.0 (31.1)	-47.3 (38.2)	-33.1 (33.2)	-60.4 (34.0)	-49.3 (40.4)

Note: Data after rescue treatment use during the Part B period were set to missing. Then the observed mean with its SD were displayed for continuous variables. Patients with missing value after dropout or rescue treatment use during Part B period were considered as non-responders for categorical variables.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-50, 50% reduction in EASI; EASI-75, 75% reduction in EASI; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation.

Protocol Deviations

A total of 27 (67.5%) adolescent patients had a protocol deviation; 3 (7.5%) adolescent patients had a major protocol deviation

Table 8: Summary of Protocol Deviations - Adolescent >=12 to <18 years of age (SAF)

	2 mg/kg SC (N=20)	4 mg/kg SC (N=20)	Total (N=40)
Number of Protocol Deviations	21	45	66
Number of Major Protocol Deviations	1	2	3
Number of Minor Protocol Deviations	20	43	63
Patients with Any Protocol Deviations, n (%)	13 (65.0%)	14 (70.0%)	27 (67.5%)
Patients with Any Major Protocol Deviation	1 (5.0%)	2 (10.0%)	3 (7.5%)
Patients with Any Minor Protocol Deviation	12 (60.0%)	14 (70.0%)	26 (65.0%)
Type of Major Protocol Deviations			
Exclusion Criteria met but subject randomized	1 (5.0%)	0	1 (2.5%)
Visit performed out of window	0	2 (10.0%)	2 (5.0%)

Abbreviations: SAF, safety analysis set; SC, subcutaneous

The 3 major deviations included exclusion criteria met but subject randomized (1 patient in the 2 mg/kg dose cohort experienced an active chronic or acute infection requiring treatment with systemic antibiotics

within 4 weeks before the baseline visit [eyelid infection]) and visit performed out of window (2 patients in the 4 mg/kg dose cohort).
This was an exploratory efficacy study so it is acceptable as an open-label design and was not powered for comparison of treatment arms with each other however is sufficient for the intended objectives.
Of the 40 included patients of study 1412, the majority (95%) completed the treatment and most patients (97.5%) transitioned into the OLE study, thereof 10 % into the adult OLE study.

Both doses induced a reduction in disease activity regarding the reduction in EASI score from baseline at week 2 (34% and 51%); there did not appear to be a clear dose response as the 2 dose cohorts showed similar efficacy on the various endpoints evaluated during the study, however, effects on IGA reduction were less pronounced and more apparent in the 4 mg/kg group than in the 2 mg/kg dose group. The treatment effect on IGA after 12-20 weeks is comparable to that of the 200/300mg Q4W dose group.

A statistically significant improvement in EASI is demonstrated form week 10 with a maximal effect at week 12 for both cohorts. At week 12 which represents the end of active treatment the effects diminish to week 20 but are still statistically significant. Similar to EASI the effects are statistically significantly higher at week 10 for both groupsHowever, % change from baseline is considered clinically relevant and diminishes at week 20 following withdrawal of treatment.

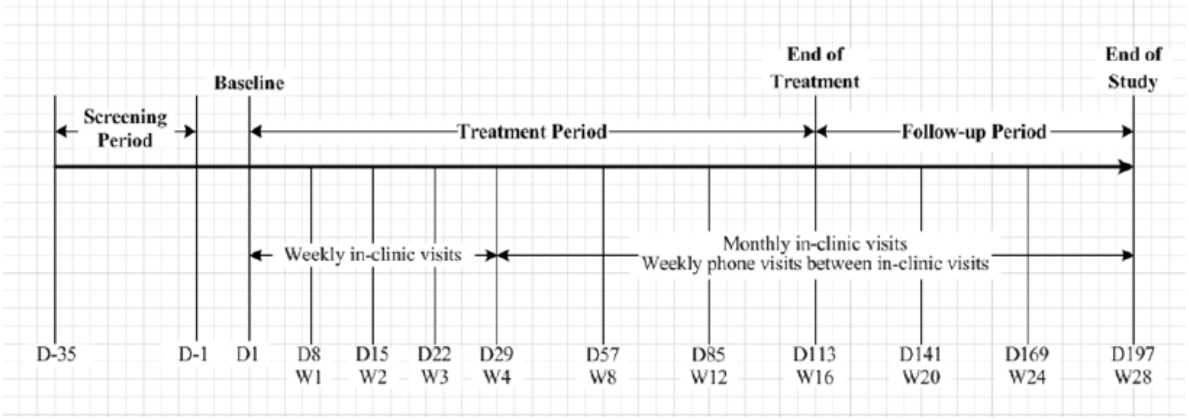
2.4.2. Main study

Study title : R668-AD-1526 – Phase 3, 16-Week Treatment, Double-Blind, Placebo-Controlled Monotherapy Study

Methods

R668-AD-1526 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab monotherapy in adolescent patients (≥12 to <18 years of age), with moderate- to-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 study consisted of the following 3 periods: screening of up to 5 weeks, a treatment period of 16 weeks, and a follow-up period of 12 weeks. 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.



D = study day; W = study week
Note: Weekly phone visits started at week 4 and continued up to week 16. No weekly phone visits occurred or were planned to occur during the follow-up period, as per Section 4.4.

Study participants

Key Inclusion and Exclusion Criteria

The inclusion/exclusion criteria for R668-AD-1526 were designed to ensure that only patients with moderate-to-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 the adolescent population specified male and female patients, ≥12 to <18 years of age with chronic AD (present for at least 1 year and meeting the American Academy of Dermatology Consensus Criteria (Eichenfield, 2014).
Required baseline AD severity scores were IGA score ≥3, EASI score ≥16, ≥10% BSA involvement with AD, and pruritus NRS average score for maximum itch intensity of ≥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 or deemed not to be appropriate candidates for such topical therapies (eg, because of important potential side effects from TCS). 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 or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever was shorter.
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. 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, recent treatment with systemic biologic therapy or immunosuppressive agent, 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 to protect patient safety included a baseline body weight <30 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

Approximately 240 study patients were planned to be randomized to 1 of the following treatment groups:
- Dupilumab Q2W treatment group: 200 mg Q2W for patients <60 kg or 300 mg Q2W for patients ≥60 kg following an initial dose of 400 mg or 600 mg, respectively
- Dupilumab Q4W treatment group: 300 mg Q4W, irrespective of weight following an initial dose of 600 mg
- Placebo group

Concomitant treatment/rescue medication

The rescue therapies included topical therapies (eg, medium-/high-potency TCS) as well as oral/systemic medications like corticosteroids and non-steroidal immunosuppressive drugs (eg, ciclosporin, methotrexate [MTX], mycophenolate-mofetil, or azathioprine) for patients who did not respond adequately after at least 7 days of topical treatment.
Topical calcineurin inhibitors were permitted for use for rescue, alone or in combination with TCS, but the use of TCIs was reserved for problem areas only (eg, face, neck, intertriginous, and genital areas, etc).
Investigators may also have considered rescue with crisaborole (ie, after the point in the study where crisaborole was approved, and the protocol was amended to reflect this option as a rescue medication).

Objectives

The primary objective of the study was to demonstrate the efficacy of dupilumab as a monotherapy after 16 weeks of treatment in patients ≥12 to <18 years of age with moderate-to-severe AD.

Outcomes/endpoints

The **primary endpoint** in the study was the proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16.
The co-primary endpoints in the study for EU and EU reference market countries 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

Key secondary endpoints
- Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (this was not a secondary endpoint for EU and EU reference market countries as it was already a co-primary endpoint)
- Percent change in EASI score from baseline to week 16
- Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline at week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline at week 16

Other secondary endpoints
- Proportion of patients with EASI-50 at week 16
- Proportion of patients with EASI-90 at week 16
- Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline during the 16-week treatment period
- Time to onset of effect on pruritus as measured by proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline during the 16-week treatment period
- Change from baseline to week 16 in percent BSA affected by AD
- Percent change from baseline to week 16 in SCORAD
- Change from baseline to week 16 in CDLQI
- Change from baseline to week 16 in POEM
- Change from baseline to week 16 in weekly average of daily peak Pruritus NRS
- Percent change from baseline to week 4 in weekly average of daily peak Pruritus NRS
- Change from baseline to week 16 in HADS
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 4
- Incidence of skin-infection TEAEs (excluding herpetic infections) through week 16*
- Incidence of serious TEAEs through week 16

*Adjudicated by study medical director.

Other efficacy endpoints include:
- Proportion of patients with SCORAD-50 (≥50% reduction in SCORAD from baseline) response at week 16
- Proportion of patients with SCORAD-75 (≥75% reduction in SCORAD from baseline) response at week 16
- Proportion of patients with SCORAD-90 (≥90% reduction in SCORAD from baseline) response at week 16
- Patient global assessment of disease: proportion of patients with no symptom and proportion of patients with no symptom or mild symptoms at week 16
- Patient global assessment of treatment: proportion of patients who rated their eczema symptoms as "much better" at week 16
- Pruritus categorical scale: proportion of patients who achieved absence of pruritus or mild pruritus at week 16
- Proportion of patients who achieved reduction of IGA score by ≥2 from baseline to week 16
- Change in ACQ-5 score from baseline at week 16

- Change in weekly averaged TNSS score from baseline at week 16
- Change from baseline to week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Number of missed school days assessment during the treatment period
- Mean score of injection site pain as assessed by Visual analogue scale (VAS) for all visits through week 16

Pharmacokinetic Variables

Serum samples for measuring functional dupilumab concentrations were collected at time points.

Antibody Variables

Serum samples for anti-dupilumab antibody were collected at time points.

- Total patients with pre-existing immunoreactivity

Pre-existing immunoreactivity defined as either an ADA positive response in the assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 4-fold over baseline titer levels

- Total patients with treatment-emergent response

Treatment-emergent response was defined as a positive response in the ADA assay post first dose when baseline results were negative or missing. The treatment-emergent responses were further characterized as Persistent, Indeterminate, or Transient

– Persistent Response – Treatment-emergent ADA positive response with 2 or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between

– Indeterminate Response - as a treatment-emergent response with only the last collected sample positive in the ADA assay

– Transient Response - a treatment-emergent ADA positive assay response that was not considered persistent or indeterminate.

- Total patients with treatment-boosted response

Treatment-boosted response defined as a positive response in the ADA assay post first dose that was greater than or equal to 4-fold over baseline titer levels, when baseline results were positive

- Titer Values (Titer value category)

– Low (titer <1,000)

– Moderate (1,000≤ titer ≤10,000)

– High (titer >10,000)

Samples positive in the ADA assay were further characterized for ADA titers and for the presence of neutralizing antibody (NAb) response.

- Total patients positive in the NAb assay

Treatment-emergent or treatment boosted ADA positive patients that were positive in the NAb assay at any time point analyzed.

Serum samples for measurements of biomarkers to study the pharmacodynamic (PD) activity of dupilumab in pediatric AD patients were collected at time points.

Sample size

The final analysis was planned for 240 patients who were enrolled into 3 study groups: dupilumab Q2W (200mg Q2W or 300 mg Q2W), dupilumab Q4W (300mg Q4W), or placebo group in North America.

With 80 patients per group, at the 2-sided 5% significance level, the study has:

- 98% power to detect a difference of 28% between dupilumab Q2W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 37% and 9% for dupilumab Q2W and placebo, respectively.
- 88% power to detect a difference of 20% between dupilumab Q4W treatment and placebo treatment in the percentage of patients who achieve an IGA score 0 to 1 at week 16, assuming that the percentages are 29% and 9% for dupilumab Q4W and placebo, respectively.

- 99% power to detect a difference of 35% between dupilumab Q2W treatment and placebo treatment in the percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 48% and 13% for dupilumab Q2W and placebo, respectively.
- 99% power to detect a difference of 32% between dupilumab Q4W treatment and placebo treatment in percentages of patients achieving EASI-75 response at week 16, assuming that the percentages are 45% and 13% for dupilumab Q4W and placebo, respectively.
- Additional power calculation based on the key secondary endpoint "proportion of patients with improvement (reduction) of Pruritus NRS ≥4 from baseline to week 16", with 80 patients per group, the study will provide:
- 97% power at a 0.05 level to detect a difference of 27% in the percentages of patients achieving Pruritus NRS reduction ≥4 at week 16, assuming that the percentages are 38% and 11% for dupilumab Q2W and placebo, respectively.
- 95% power at a 0.05 level to detect a difference of 25% in the percentages of patients achieving weekly average of daily peak Pruritus NRS reduction ≥4 at week 16, assuming that the percentages are 36% and 11% for dupilumab Q4W and placebo, respectively.

The assumptions used for the power calculations were estimated based on results from the R668-AD-1334 and R668-AD-1416 studies (phase 3 studies for adult AD patients), and the R668-AD-1021 study (a phase 2b dose-ranging study in adults with AD).
Based on the result from the R668-AD-1021 study, the efficacy profile of dupilumab 200 mg Q2W is similar to dupilumab 300 mg Q2W. In the absence of data of dupilumab in pediatric patients with AD, the data observed in the adult studies R668-AD-1334, R668-AD-1416, and R668-AD-1021 are used for these sample size calculations. This is a conservative assumption as it is expected that the effect of dupilumab in children will be greater than that seen in adults. Children have disease for a shorter duration than adults and the disease is more Th2 driven in acute phase while it becomes more type 1 helper T cell in chronic phase (Thepen 1996, Gittler 2012). In addition, children with AD in general respond better to systemic therapies than adults (Schmitt 2007). A recent study compared the differences between activated and polarized T-cell subsets in blood of adult and pediatric patients with AD. The study found that AD is Th2 dominated in children while it extends to additional helper T cell subsets, particularly Th22, in adults (Czarnowicki 2015).

Randomisation

Randomization (1:1:1) was stratified by baseline weight group (<60 kg and ≥60 kg) and baseline disease severity (moderate [IGA=3] vs severe [IGA=4] AD).

Blinding (masking)

With the exception of the IDMC members, this study remained blinded to all individuals until the pre-specified unblinding to conduct the primary analyses.
To maintain the blind, all patients received Q2W injections of dupilumab or placebo starting at day 1. During weeks in which dupilumab was not administered in the Q4W dosing regimen, patients received placebo. Anti-drug antibody and drug concentration results were not communicated to the sites, and the sponsor's operational team did not have access to results associated with patient identification until after the final database lock.

Statistical methods

The full analysis set was planned to be used for the efficacy analysis, where all randomized patients were considered as they were allocated at randomization. For the efficacy analysis each study group of dupilumab treatment was planned to be compared with the placebo group by all efficacy variables. A supportive analysis of the primary endpoint was performed using the per protocol set (PPS).

For all binary primary and key-secondary endpoints the Cochran-Mantel-Haenszel test adjusted by randomization strata (baseline disease severity and weight group) was used for each comparison. The

patients were planned to be classified as a non-responder if rescue medication was used before week 16 or if the patient withdraw from study.

Continuous key-secondary endpoints were planned to be analysed by ANCOVA, where treatment and randomisation strata (baseline disease severity and weight group) were included in the model. Missing values were planned to be imputed 40 times by multiple imputation. Patients receiving rescue treatment will be treated as missing and in this case data will not be imputed.

For multiplicity adjustment, a hierarchical procedure was used to control the overall Type-1 error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens versus placebo. Each hypothesis will be formally tested only if the preceding one is significant at the 2-sided 0.05 significance level. The order of hypothesis tests for the primary and key secondary endpoints is presented in the following Table:

Table 3: Statistical Hierarchy for Multiplicity Control

		Dupilumab	
	Endpoints	**q4w group**	**q2w group**
Primary endpoint	Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16	10	1
Co-primary endpoint for ex-US countries, key secondary for US	Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16	9	2
Key Secondary endpoints	Percent change in EASI score from baseline to week 16	11	3
	Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS	12	4
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline to week 16	13	5
	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16	14	6
Secondary endpoints	Proportion of patients with EASI-50 at week 16	15	7
	Proportion of patients with EASI-90 at week 16	16	8

Sensitivity analysis:
In case of Mantel-Fleiss (MF) criterion did not met, sensitivity analyses including each factor separately in CMH test was conducted. Sensitivity analysis using the last observation carried forward (LOCF) approach to determine patient's status at week 16 was conducted to assess the robustness of the primary efficacy analysis with regards to handling of missing data. The efficacy data was set to missing after rescue treatment was used, and the LOCF method was used to determine patients' status at week 16. In addition, the Cochran-Mantel-Haenszel method adjusted by randomization strata was also performed on all observed data regardless if rescue treatment was used. A patient with missing data was counted as a non-responder.

Results

Participant flow

Overall patient disposition in R668-AD-1526 is shown in Table 11. A total of 295 patients were screened for study eligibility , 251 of whom were enrolled and randomized in a 1:1:1 ratio . The most common causes for patients failing screening were lack of adequate disease severity and lack of willingness to comply with study visits and procedures.

One of the randomized patients was not treated; this patient did not meet one of the study eligibility criteria and was withdrawn due to protocol violation. A high proportion of the patients completed the study treatment (92.0%). The proportion of patients who withdrew from study treatment was higher in the placebo group (10.6%) than in the combined dupilumab treatment group (6.6%). A lack of study drug efficacy was the most common reason recorded for withdrawal from the study treatment for patients in the placebo group; no patients in the combined dupilumab treatment group withdrew from the study treatment due to lack of study drug efficacy.

At the time of the data cut-off (05 Apr 2018), the majority of randomized patients (80.1%), with approximately equal number of patients from each of the 3 treatment groups, transitioned into the R668-AD-1434 OLE study. A small number of patients discontinued from the study (6.0%). Withdrawal of consent was the most frequently cited reason for premature discontinuation from study.

Figure 2: Participant flow (R668-AD-1526)

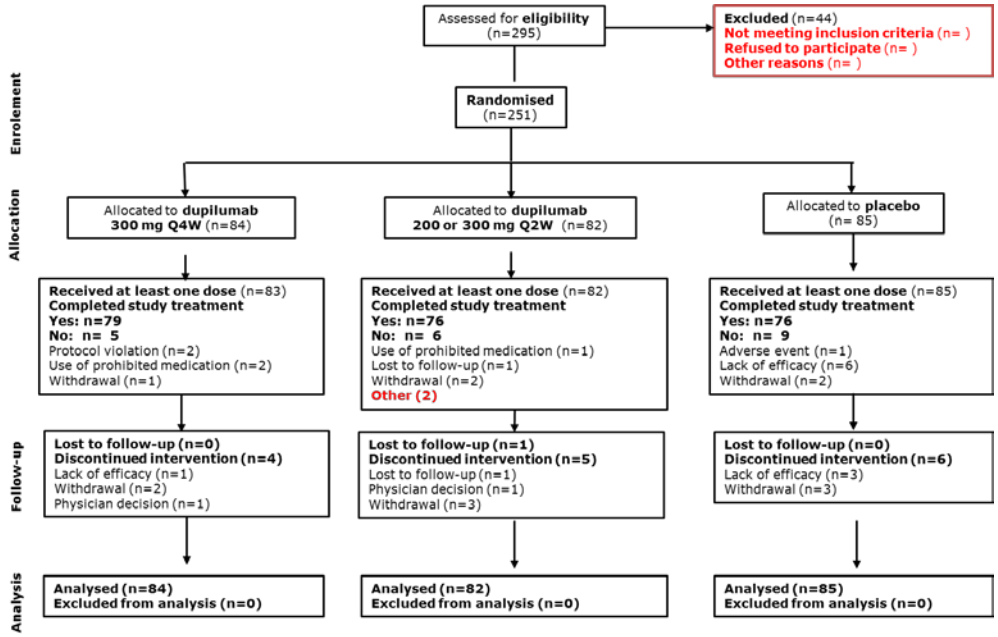


Table 11: Summary of Patient Accountability and Study Disposition in R668-AD-1526 – All Randomized Patients

		Dupilumab			
	Placebo (N=85)	300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	Total (N=251)
Received study medication, n (%)	85 (100%)	83 (98.8%)	82 (100%)	165 (99.4%)	250 (99.6%)
Patient randomized but not treated, n (%)	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Complete the study treatment, n (%)					
Yes	76 (89.4%)	79 (94.0%)	76 (92.7%)	155 (93.4%)	231 (92.0%)
No	9 (10.6%)	5 (6.0%)	6 (7.3%)	11 (6.6%)	20 (8.0%)
Adverse event	1 (1.2%)	0	0	2 (1.2%)	3 (1.2%)

	Placebo (N=85)	300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	Total (N=251)
Lack of efficacy	6 (7.1%)	0	0	0	6 (2.4%)
Protocol violation	0	2 (2.4%)	0	2 (1.2%)	2 (0.8%)
Other	2 (2.4%)	3 (3.6%)	4 (4.9%)	7 (4.2%)	9 (3.6%)
Lost to follow-up	0	0	1 (1.2%)	1 (0.6%)	1 (0.4%)
Use of prohibited medication	0	2 (2.4%)	1 (1.2%)	3 (1.8%)	3 (1.2%)
Withdrawal by subject	2 (2.4%)	1 (1.2%)	2 (2.4%)	3 (1.8%)	5 (2.0%)
Transition into another study, n (%)					
Yes	69 (81.2%)	67 (79.8%)	65 (79.3%)	132 (79.5%)	201 (80.1%)
R668-AD-1434	69 (81.2%)	67 (79.8%)	65 (79.3%)	132 (79.5%)	201 (80.1%)
No	16 (18.8%)	17 (20.2%)	17 (20.7%)	34 (20.5%)	50 (19.9%)
Completed week 16 n (%)	80 (94.1%)	81 (96.4%)	79 (96.3%)	160 (96.4%)	240 (95.6%)
Completed week 28 (end of study), n (%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (1.8%)	4 (1.6%)
Ongoing, n (%)	9 (10.6%)	11 (13.1%)	11 (13.4%)	22 (13.3%)	31 (12.4%)
Discontinuation from study with reason, n (%)	6 (7.1%)	4 (4.8%)	5 (6.1%)	9 (5.4%)	15 (6.0%)
Adverse event	0	0	0	0	0
Death	0	0	0	0	0
Lack of efficacy	3 (3.5%)	1 (1.2%)	0	1 (0.6%)	4 (1.6%)
Lost to follow-up	0	0	1 (1.2%)	1 (0.6%)	1 (0.4%)
Physician decision	0	1 (1.2%)	1 (1.2%)	2 (1.2%)	2 (0.8%)
Protocol violation	0	0	0	0	0
Withdrawal by subject	3 (3.5%)	2 (2.4%)	3 (3.7%)	5 (3.0%)	8 (3.2%)
Other	0	0	0	0	0

Note: The percentage is based on the number of randomized patients in each treatment group as denominator.
Patients could roll over into OLE after 16 weeks.
Abbreviations: OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks.
Source: Module 5.3.5.1 R668-AD-1526 Primary Analysis Post-text Tables 1.1.2/2 and 1.1.2/1

The participant flow shows that nearly all randomized patients of the individual dose groups received their study treatment. 6.6% (11/166) of the patients treated with dupilumab did not complete the study treatment, thereof showed 1 patient lack of efficacy in the 300 mg Q4W group, the remaining 6 patients with lack of efficacy were assigned to the placebo group. 80% of the patients of this pivotal study transitioned into the OLE study R668-AD-1434. All other aspects such as discontinuation rate, patient withdrawals etc. were balanced between the treatment groups.

Recruitment

Study Initiation Date (first patient enrolled): 21 March 2017

Cut-off date for Clinical Study Report: 05 Apr 2018

Conduct of the study

Amendments

For studies with multiple protocol amendments, only the study conduct reflected in the latest protocol amendment prior to the database lock date is presented in this section. All amendments to the study design

are documented in the individual CSRs. There were 3 amendments, amendment 1 being the most substantial, to the study protocol of study R-668-AD-1526 following discussion with PDCO and in accordance with the agreed PIP.

Key aspects of the amendment 1 are presented below:

- Addition of a 200 mg Q2W regimen (with a loading dose of 400 mg on day 1) to the Q2W treatment group. Patients below 60 kg will receive 200 mg Q2W, while patients ≥60 kg will receive 300 mg Q2W (with a loading dose of 600 mg on day 1).
- Increase sample size from 180 patients to 240 patients.
- Change duration of treatment period from 12 weeks to 16 weeks. The treatment duration was increased to enable detection of maximum therapeutic effect of dupilumab and maximize the likelihood to detect a statistically significant difference versus placebo on the primary endpoint.

- Revised AESI according to study results and dupilumab safety profile observed in the adult AD population.

Changes to the Planned Analyses

Throughout the conduct of the study, any type of conjunctivitis or blepharitis (severe or serious or lasting ≥4 weeks) was considered an AESI required to be reported within 24 hours of identification. However, for the statistical analysis, the time frame, "lasting ≥4 weeks," was removed from the final definition for this AESI criterion for conjunctivitis or blepharitis, as described in the SAP and according to the recent revision of the list of AESIs across the dupilumab program in AD. The rationale for this change was based on the information received during the course of the study for the conjunctivitis/blepharitis events lasting longer than 28 days. These events were not found to be clinically meaningful, as none of these events led to treatment discontinuation, or had been classified as severe or serious.

Protocol deviations

Overall, 7.1% of patients in the placebo group, 19% of patients in the dupilumab Q4W group, and 9.8% of patients in the Q2W group had at least 1 major protocol deviation The most common type of major protocol deviation was inadequate informed consent administration (3.2% overall). The incidence of each of the other major protocol deviation categories was low (≤2% overall across the treatment groups).

Table 9: Summary of Protocol Deviations – All Randomized Patients

		Dupilumab			
	Placebo (N=85)	300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	Total (N=251)
Number of Protocol Deviations	312	300	259	559	871
Number of Major Protocol Deviations	9	21	8	29	38
Number of Minor Protocol Deviations	303	279	251	530	833
Patients with Any Protocol Deviation	66 (77.6%)	75 (89.3%)	60 (73.2%)	135 (81.3%)	201 (80.1%)
Patients with Any Major Protocol Deviation	6 (7.1%)	16 (19.0%)	8 (9.8%)	24 (14.5%)	30 (12.0%)
Patients with Any Minor Protocol Deviation	66 (77.6%)	73 (86.9%)	60 (73.2%)	133 (80.1%)	199 (79.3%)
Type of Major Protocol Deviation	6 (7.1%)	16 (19.0%)	8 (9.8%)	24 (14.5%)	30 (12.0%)
Inadequate informed consent administration	3 (3.5%)	3 (3.6%)	2 (2.4%)	5 (3.0%)	8 (3.2%)
Inclusion criteria not met but subject randomized	1 (1.2%)	4 (4.8%)	0	4 (2.4%)	5 (2.0%)
Procedure not performed	1 (1.2%)	2 (2.4%)	2 (2.4%)	4 (2.4%)	5 (2.0%)
Other: epro compliance	2 (2.4%)	0	2 (2.4%)	2 (1.2%)	4 (1.6%)

		Dupilumab			
	Placebo (N=85)	300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	Total (N=251)
Other: randomization	0	3 (3.6%)	1 (1.2%)	4 (2.4%)	4 (1.6%)
Prohibited medications	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (1.8%)	4 (1.6%)
Personnel not qualified and/or designated to perform study-related activities.	0	3 (3.6%)	0	3 (1.8%)	3 (1.2%)
Handling of investigational product was not performed in accordance with the protocol	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Inadequate source documents	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Randomization error-subject randomized to wrong treatment	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)

The percentage is based on the number of randomized patients in each treatment group as denominator.

Baseline data

Patient Disposition, Demographics, and Baseline Disease Characteristics

As of the data cut-off date of 05 Apr 2018, a total of 251 patients were enrolled into the study and randomized (85 patients in the placebo group, 82 patients in the dupilumab Q2W group, and 84 patients in the Q4W group).

A total of 231 patients completed treatment, and 20 patients discontinued treatment for the following primary reasons: lack of efficacy (6 patients in the placebo group) and other reasons (7 patients in dupilumab treatment groups and 2 patients in the placebo group). A total of 201 patients (80.1%) rolled over into the pediatric OLE study, R668-AD-1434.

Overall, demographics and baseline disease characteristics were similar between the 3 treatment Groups. The majority of patients were white (62.5%). Male and female patients represented 59.0% and 41.0% of the population, respectively.

Most patients had disease onset prior to 5 years of age (84.9%), and the mean (SD) duration of AD was 12.2 (3.20) years. The mean (SD) EASI score was 35.5 (14.16).

The proportion of patients with IGA scores of 3 (moderate disease) and 4 (severe disease) were 46.2% and 53.8%, respectively. The mean (SD) pruritus NRS score was 7.6 (1.66) and the mean (SD) BSA involvement was 56.5% (22.97).

A detailed description of patient disposition, demographics and baseline disease characteristics for patients in this study is presented below.

Demographics

Patient demographic characteristics were balanced among the treatment groups (Table 12). More than half of patients were white (62.5%) but a substantial number of patients of other races and ethnicities were also included in the patient population. Likewise, more than half of patients were male (59.0%) but female patients were adequately represented in the patient population. The mean (SD) age of the patients was 14.5 (1.7) years. The number of patients in the 2 age subgroups (≥12 to <15 years and ≥15 to 18 years) was balanced across the 3 treatment groups. More than 40% of the patients were classified as overweight (BMI ≥85 percentile for age and gender). This observation is consistent with reports in the literature describing that a higher proportion of adolescent patients with AD are overweight compared with the normal population (Silverberg, 2014).The proportion of overweight patients was balanced across the 3 treatment groups. Of the 2 countries from which patients enrolled (Canada and the US), most patients were in the US.

Table 10: Summary of Baseline Demographic Characteristics for R668-AD-1526 – FAS

Parameter	Placebo (N=85)	Dupilumab 300 mg Q4W (N=84)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=166)	Total (N=251)
Age (years) descriptive					
n	85	84	82	166	251
Mean (SD)	14.5 (1.78)	14.4 (1.59)	14.5 (1.74)	14.5 (1.66)	14.5 (1.70)
Q1	13.0	13.0	13.0	13.0	13.0
Median	15.0	14.0	14.0	14.0	14.0
Q3	16.0	16.0	16.0	16.0	16.0
Min : Max	12 : 17	12 : 17	12 : 17	12 : 17	12 : 17
Age group (years), n (%)					
≥12-<15	41 (48.2%)	45 (53.6%)	43 (52.4%)	88 (53.0%)	129 (51.4%)
≥15-<18	44 (51.8%)	39 (46.4%)	39 (47.6%)	78 (47.0%)	122 (48.6%)
Ethnicity, n (%)					
Not Hispanic or Latino	72 (84.7%)	64 (76.2%)	69 (84.1%)	133 (80.1%)	205 (81.7%)
Hispanic or Latino	13 (15.3%)	20 (23.8%)	13 (15.9%)	33 (19.9%)	46 (18.3%)
Race, n (%)					
White	48 (56.5%)	55 (65.5%)	54 (65.9%)	109 (65.7%)	157 (62.5%)
Black or African American	15 (17.6%)	8 (9.5%)	7 (8.5%)	15 (9.0%)	30 (12.0%)
Asian	13 (15.3%)	13 (15.5%)	12 (14.6%)	25 (15.1%)	38 (15.1%)
Other	6 (7.1%)	8 (9.5%)	7 (8.5%)	15 (9.0%)	21 (8. 4%)
Not Reported/Missing	3 (3.5%)	0	2 (2.4%)	2 (1.2%)	5 (2.0%)
Sex, n (%)					
Male	53 (62.4%)	51 (61.9%)	43 (52.4%)	95 (57.2%)	148 (59.0%)
Female	32 (37.6%)	32 (38.1%)	39 (47.6%)	71 (42.8%)	103 (41.0%)
Height (cm) descriptive					
n	85	84	82	166	251
Mean (SD)	162.4 (10.99)	164.0 (10.32)	161.2 (10.22)	162.6 (10.33)	162.6 (10.54)
Q1	156.0	157.0	155.0	155.5	155.5
Median	160.2	163.0	160.0	162.5	162.0
Q3	167.6	171.7	167.6	170.0	169.0
Min : Max	133 : 198	138 : 188	137 : 185	137 : 188	133 : 198
Weight (kg) descriptive					
n	85	83	82	166	251
Mean (SD)	64.4 (21.52)	65.8 (20.08)	65.6 (24.46)	65.7 (22.28)	65.2 (21.99)
Q1	49.5	52.3	48.9	50.2	49.9
Median	58.9	59.8	58.1	59.4	59.4

Q3	76.0	75.2	79.5	78.4	78.0
Min : Max	31 : 148	38 : 123	32 : 174	32 : 174	31 : 174
Weight group, n (%)					
<60 kg	43 (50.6%)	42 (50.0%)	43 (52.4%)	85 (51.2%)	128 (51.0%)
≥60 kg	42 (49.4%)	42 (50.0%)	39 (47.6%)	81 (48.8%)	123 (49.0%)
BMI (kg/m^2) descriptive					
n	85	84	82	166	251
Mean (SD)	23.9 (6.03)	24.1 (5.92)	24.9 (7.87)	24.5 (6.94)	24.3 (6.64)
Q1	19.5	19.7	19.7	19.7	19.6
Median	22.1	22.9	22.5	22.6	22.5
Q3	28.2	25.7	29.8	27.6	28.1
Min : Max	16 : 48	16 : 39	15 : 67	15 : 67	15 : 67

BMI group, n (%)					
<85 percentile of population	49 (57.6%)	47 (56.0%)	46 (56.1%)	93 (56.0%)	142 (56.6%)
≥85 percentile of population	36 (42.4%)	37 (44.0%)	36 (43.9%)	72 (44.0%)	109 (43.4%)
Country, n (%)					
Canada	11 (12.9%)	9 (10.7%)	11 (13.4%)	20 (12.0%)	31 (12.4%)
United States	74 (87.1%)	75 (89. 3%)	71 (86.6%)	146 (88.0%)	220 (87.6%)

Abbreviations: BMI, body mass index; max, maximum; min, minimum; SAF, safety analysis set; SC, subcutaneously; SD, standard deviation; Q1, first quartile; Q2W, every 2 weeks; Q3, third quartile; Q4W, every 4 weeks.

Baseline Disease Characteristics

Overall, the treatment groups were balanced between placebo and treatment groups for the extent of disease (as measured by BSA), intensity of signs (as measured by EASI and IGA), severity of symptoms (as measured by pruritus NRS), and the duration of AD (Table 13). Most patients were diagnosed with AD before 5 years of age. This is consistent with the age of onset of AD in adolescents as reported in the literature (Kay, 1994).

The baseline disease characteristics as measured by AD assessments were consistent with moderate-to-severe AD. A significant proportion of patients had disease onset prior to 5 years of age (84.9%). The mean (SD) duration of AD was 12.2 (3.20) years. The mean (SD) EASI score was 35.5 (14.16). Approximately 46.2% of patients had IGA=3 (moderate disease) and 53.8% had IGA=4 (severe disease). The mean (SD) peak pruritus NRS score was 7.6 (1.66). The mean (SD) BSA involvement was 56.5 (22.97).

At baseline, the high CDLQI and HADS scores indicated an impaired QOL and low mental health of the enrolled AD patients, respectively (Table 11).

Table 11: Summary of Baseline Disease Characteristics for R668-AD-1526 – FAS

Parameter	Placebo (N=85)	Dupilumab			Total (N=251)
		300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	
Chronic AD diagnosis, n (%)					
Before the age of 5 years old	73 (85.9%)	70 (83.3%)	70 (85.4%)	140 (84.3%)	213 (84.9%)
Between the age of 5 and 9 years old	7 (8.2%)	9 (10.7%)	11 (13.4%)	20 (12.0%)	27 (10.8%)
Between the age of 10 and 19 years old	5 (5.9%)	5 (6.0%)	1 (1.2%)	6 (3.6%)	11 (4.4%)
Duration of AD (years)					
n	85	84	82	166	251
Mean (SD)	12.3 (3.44)	11.9 (3.18)	12.5 (2.97)	12.2 (3.08)	12.2 (3.20)
Q1	11.0	11.0	11.0	11.0	11.0
Median	13.0	12.5	13.0	13.0	13.0
Q3	15.0	14.0	15.0	14.0	15.0
Min : Max	1 : 17	1 : 16	4 : 17	1 : 17	1 : 17
n (%) of patients with duration of AD (years)					
<13 years	39 (45.9%)	42 (50.0%)	38 (46.3%)	80 (48.2%)	119 (47.4%)
≥13 years	46 (54.1%)	42 (50.0%)	44 (53.7%)	86 (51.8%)	132 (52.6%)
EASI score					
n	85	84	82	166	251
Mean (SD)	35.5 (13.97)	35.8 (14.82)	35.3 (13.84)	35.5 (14.30)	35.5 (14.16)
Q1	23.3	22.5	23.5	23.3	23.3
Median	31.7	33.5	32.5	33.2	32.8
Q3	47.6	46.0	44.1	45.3	45.6
Min : Max	17 : 71	16 : 71	16 : 71	16 : 71	16 : 71
IGA score					
n	85	84	82	166	251
Mean (SD)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)	3.5 (0.50)
Q1	3.0	3.0	3.0	3.0	3.0
Median	4.0	4.0	4.0	4.0	4.0
Q3	4.0	4.0	4.0	4.0	4.0
Min : Max	3 : 4	3 : 4	3 : 4	3 : 4	3 : 4
Number n (%) of patients with IGA score					
IGA=3	39 (45.9%)	38 (45.2%)	39 (47.6%)	77 (46.4%)	116 (46.2%)
IGA=4	46 (54.1%)	46 (54.8%)	43 (52.4%)	89 (53.6%)	135 (53.8%)
Peak pruritus NRS					
n	85	84	82	166	251
Mean (SD)	7.7 (1.62)	7.5 (1.84)	7.5 (1.52)	7.5 (1.68)	7.6 (1.66)
Q1	6.6	6.3	6.3	6.3	6.4

Parameter	Placebo (N=85)	Dupilumab 300 mg Q4W (N=84)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=166)	Total (N=251)
Median	8.0	8.0	7.6	7.7	7.9
Q3	9.0	9.0	8.9	8.9	8.9
Min : Max	4 : 10	2 : 10	4 : 10	2 : 10	2 : 10
NRS ≥3	85 (100%)	83 (98.8%)	82 (100%)	165 (99.4%)	250 (99.6%)
NRS ≥4	84 (98.8%)	83 (98.8%)	82 (100%)	165 (99.4%)	249 (99.2%)
n (%) patients with peak pruritus NRS					
<7	24 (28.2%)	29 (34.5%)	29 (35.4%)	58 (34.9%)	82 (32.7%)
≥7	61 (71.8%)	55 (65.5%)	53 (64.6%)	108 (65.1%)	169 (67.3%)
n (%) patients with PCS					
Absence of pruritus	0	0	0	0	0
Mild pruritus	12 (14.1%)	10 (11.9%)	9 (11.0%)	19 (11.4%)	31 (12.4%)
Moderate pruritus	36 (42.4%)	33 (39.3%)	42 (51.2%)	75 (45.2%)	111 (44.2%)
Severe pruritus	37 (43.5%)	41 (48.8%)	31 (37.8%)	72 (43.4%)	109 (43.4%)
BSA of atopic dermatitis					
n	85	84	82	166	251
Mean (SD)	56.4 (24.13)	56.9 (23.51)	56.0 (21.40)	56.5 (22.43)	56.5 (22.97)
Q1	38.0	39.5	40.0	40.0	39.0
Median	52.0	58.5	53.5	54.0	53.9
Q3	76.0	75.8	69.0	72.5	73.5
Min : Max	15 : 98	13 : 99	20 : 98	13 : 99	13 : 99
SCORAD score					
n	85	84	82	166	251
Mean (SD)	70.4 (13.25)	69.8 (14.12)	70.6 (13.89)	70.2 (13.97)	70.3 (13.70)
Q1	61.8	60.1	59.2	59.7	59.7
Median	70.4	68.8	68.6	68.8	69.4
Q3	79.5	81.3	82.8	81.6	81.3
Min : Max	41 : 101	39 : 99	45 : 98	39 : 99	39 : 101
PGAD, n (%)					
No symptoms (Score=1)	0	0	1 (1.2%)	1 (0.6%)	1 (0.4%)
Mild symptoms (Score=2)	10 (11.8%)	5 (6.0%)	7 (8.5%)	12 (7.2%)	22 (8.8%)
Moderate symptoms (Score=3)	20 (23.5%)	32 (38.1%)	22 (26.8%)	54 (32.5%)	74 (29.5%)
Severe symptoms (Score=4)	30 (35.3%)	26 (31.0%)	32 (39.0%)	58 (34.9%)	88 (35.1%)
Very severe symptoms (Score=5)	25 (29.4%)	21 (25.0%)	20 (24.4%)	41 (24.7%)	66 (26.3%)
POEM					
n	85	84	82	166	251

Parameter	Placebo (N=85)	Dupilumab			Total (N=251)
		300 mg Q4W (N=84)	200 mg or 300 mg Q2W (N=82)	Combined (N=166)	
Mean (SD)	21.1 (5.38)	21.1 (5.47)	21.0 (5.01)	21.0 (5.23)	21.0 (5.27)
Q1	19.0	18.0	17.0	17.0	18.0
Median	21.0	22.0	21.0	22.0	21.0
Q3	25.0	25.0	25.0	25.0	25.0
Min : Max	3 : 28	7 : 28	9 : 28	7 : 28	3 : 28
CDLQI Total Score					
n	85	84	82	166	251
Mean (SD)	13.1 (6.72)	14.8 (7.38)	13.0 (6.21)	13.9 (6.87)	13.6 (6.82)
Q1	8.0	9.0	8.0	9.0	8.0
Median	12.0	14.0	12.0	13.0	12.0
Q3	18.0	21.0	17.0	20.0	20.0
Min : Max	2 : 29	3 : 28	3 : 30	3 : 30	2 : 30
Total HADS					
n	85	84	82	166	251
Mean (SD)	11.6 (7.76)	13.3 (8.17)	12.6 (8.04)	12.9 (8.09)	12.5 (7.99)
Q1	6.0	7.0	6.0	7.0	6.0
Median	10.0	12.0	11.5	12.0	11.0
Q3	16.0	19.0	17.0	18.0	17.0
Min : Max	0 : 39	0 : 32	0 : 38	0 : 38	0 : 39
HADS Anxiety Scale					
n	85	84	82	166	251
Mean (SD)	7.4 (4.41)	8.0 (4.87)	8.1 (4.62)	8.1 (4.73)	7.8 (4.63)
Q1	4.0	4.0	5.0	5.0	4.0
Median	7.0	7.5	8.0	8.0	8.0
Q3	10.0	11.0	11.0	11.0	11.0
Min : Max	0 : 21	0 : 20	0 : 21	0 : 21	0 : 21
≥9	31 (36.5%)	37 (44.0%)	37 (45.1%)	74 (44.6%)	105 (41.8%)
≥12	11 (12.9%)	19 (22.6%)	19 (23.2%)	38 (22.9%)	49 (19.5%)
HADS Depression Scale					
n	85	84	82	166	251
Mean (SD)	4.3 (3.86)	5.2 (4.17)	4.4 (4.15)	4.8 (4.17)	4.6 (4.07)
Q1	1.0	2.0	1.0	1.0	1.0
Median	3.0	4.0	4.0	4.0	4.0
Q3	6.0	8.0	7.0	8.0	7.0
Min : Max	0 : 18	0 : 16	0 : 17	0 : 17	0 : 18
≥7	19 (22.4%)	27 (32.1%)	25 (30.5%)	52 (31.3%)	71 (28.3%)
≥10	7 (8.2%)	17 (20.2%)	10 (12.2%)	27 (16.3%)	34 (13.5%)
Weekly averaged TNSS					
n	60	50	59	109	169
Mean (SD)	4.0 (3.14)	4.5 (3.66)	4.3 (3.34)	4.4 (3.47)	4.3 (3.35)

Parameter	Placebo (N=85)	Dupilumab 300 mg Q4W (N=84)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=166)	Total (N=251)
Q1	1.5	1.8	2.0	2.0	1.9
Median	3.7	3.7	3.7	3.7	3.7
Q3	5.7	6.3	6.8	6.5	6.0
Min : Max	0 : 14	0 : 15	0 : 15	0 : 15	0 : 15
ACQ-5					
n	48	43	46	89	137
Mean (SD)	1.1 (1.25)	1.0 (0.99)	1.2 (1.21)	1.1 (1.11)	1.1 (1.16)
Q1	0.3	0.4	0.2	0.2	0.2
Median	0.6	0.6	0.8	0.8	0.6
Q3	1.7	1.4	2.2	1.6	1.6
Min : Max	0 : 5	0 : 4	0 : 4	0 : 4	0 : 5
Inadequate response to topical medications					
Yes	80 (94.1%)	79 (94.0%)	79 (96.3%)	158 (95.2%)	238 (94.8%)
No	5 (5.9%)	5 (6.0%)	3 (3.7%)	8 (4.8%)	13 (5.2%)
Significant skin atrophy	1 (1.2%)	0	0	0	1 (0.4%)
Hypersensitivity reactions	1 (1.2%)	1 (1.2%)	0	1 (0.6%)	2 (0.8%)
Systemic effects	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Other	4 (4.7%)	3 (3.6%)	3 (3.7%)	6 (3.6%)	10 (4.0%)

Abbreviations: ACQ-5, Asthma Control Questionnaire; AD, atopic dermatitis; BSA body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; NRS, Numerical Rating Scale; PCS, Pruritus Categorical Score; PGAD, Patient Global Assessment of Disease; POEM, Patient-Oriented Eczema Measure; Q1, quartile 1; Q2W, every 2 weeks; Q3, quartile 3; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SD, standard deviation; TNSS, Total Nasal Symptoms Score.

History of Atopic / Allergic Disease

A high proportion of patients enrolled in the study also had one or more comorbid atopic/allergic condition (92%) (Table 14). The most commonly reported atopic co-morbidities were asthma, allergic rhinitis, and food allergy. These conditions are typical of the general AD population, reflecting the common underlying type 2 helper T cell-mediated pathophysiology of these diseases.
The next most common atopic/allergic condition other than AD was other allergies (69.2%), which encompassed allergy to house dust mite, animals, plants, molds, medications, etc. (Table 14).

Overall, the treatment groups were balanced in terms of proportion of patients with at least one or more comorbid allergic condition. Of note, 22.8% of all patients indicated a current history of allergic conjunctivitis (a higher percentage of patients in the combined dupilumab treatment group [24.8%] indicated a current history of allergic conjunctivitis compared to patients in the placebo group [18.8%]).
Based on the specific atopic disease questionnaire, the proportion of patients with a family history of atopic/allergic conditions was similar between treatment groups (Table 12). The most common atopic/allergic condition in patient family history was AD.
All patients randomized met the eligibility criteria for AD duration and severity.

Table 12: Summary of History of Atopic / Allergic Disease for R668-AD-1526 – SAF

Parameter	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=165)	Total (N=250)
Number (%) of Patients with Current History of Atopic/Allergic Conditions					
Atopic dermatitis	85 (100%)	83 (100%)	82 (100%)	165 (100%)	250 (100%)
Other allergies	62 (72.9%)	53 (63.9%)	58 (70.7%)	111 (67.3%)	173 (69.2%)
Allergic rhinitis	57 (67.1%)	48 (57.8%)	59 (72.0%)	107 (64.8%)	164 (65.6%)
Food allergy	48 (56.5%)	52 (62.7%)	52 (63.4%)	104 (63.0%)	152 (60.8%)
Asthma	46 (54.1%)	42 (50.6%)	46 (56.1%)	88 (53.3%)	134 (53.6%)
Hives	22 (25.9%)	28 (33.7%)	22 (26.8%)	50 (30.3%)	72 (28.8%)
Allergic conjunctivitis (keratoconjunctivitis)	16 (18.8%)	21 (25.3%)	20 (24.4%)	41 (24.8%)	57 (22.8%)
Chronic rhinosinusitis	7 (8.2%)	6 (7.2%)	6 (7.3%)	12 (7.3%)	19 (7.6%)
Nasal polyps	2 (2.4%)	1 (1.2%)	2 (2.4%)	3 (1.8%)	5 (2.0%)
Eosinophilic esophagitis	0	0	1 (1.2%)	1 (0.6%)	1 (0.4%)
Number (%) of patients with current history of atopic/allergic conditions excluding atopic dermatitis	**78 (91.8%)**	**73 (88.0%)**	**79 (96.3%)**	**152 (92.1%)**	**230 (92.0%)**
Number (%) of Patients with Family History of Atopic/Allergic Conditions					
Atopic dermatitis	49 (57.6%)	49 (59.0%)	49 (59.8%)	98 (59.4%)	147 (58.8%)
Asthma	41 (48.2%)	41 (49.4%)	35 (42.7%)	76 (46.1%)	117 (46.8%)
Allergic rhinitis	38 (44.7%)	33 (39.8%)	39 (47.6%)	72 (43.6%)	110 (44.0%)
Other allergies	32 (37.6%)	33 (39.8%)	41 (50.0%)	74 (44.8%)	106 (42.4%)
Food allergy	24 (28.2%)	27 (32.5%)	29 (35.4%)	56 (33.9%)	80 (32.0%)
Hives	17 (20.0%)	19 (22.9%)	20 (24.4%)	39 (23.6%)	56 (22.4%)
Allergic conjunctivitis (keratoconjunctivitis)	16 (18.8%)	21 (25.3%)	10 (12.2%)	31 (18.8%)	47 (18.8%)
Chronic rhinosinusitis	15 (17.6%)	6 (7.2%)	7 (8.5%)	13 (7.9%)	28 (11.2%)
Nasal polyps	4 (4.7%)	2 (2.4%)	4 (4.9%)	6 (3.6%)	10 (4.0%)
Eosinophilic esophagitis	3 (3.5%)	2 (2.4%)	0	2 (1.2%)	5 (2.0%)
Number (%) of Patients with currently resolved Atopic/Allergic Conditions					
Asthma	8 (9.4%)	5 (6.0%)	5 (6.1%)	10 (6.1%)	18 (7.2%)
Allergic conjunctivitis (Keratoconjunctivitis)	2 (2.4%)	1 (1.2%)	3 (3.7%)	4 (2.4%)	6 (2.4%)
Hives	1 (1.2%)	3 (3.6%)	2 (2.4%)	5 (3.0%)	6 (2.4%)
Food allergy	2 (2.4%)	1 (1.2%)	1 (1.2%)	2 (1.2%)	4 (1.6%)
Other allergies	1 (1.2%)	1 (1.2%)	1 (1.2%)	2 (1.2%)	3 (1.2%)
Allergic rhinitis	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Chronic rhinosinusitis	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)
Eosinophilic esophagitis	0	1 (1.2%)	0	1 (0.6%)	1 (0.4%)

Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set.

History of Systemic Treatments Used for Atopic Dermatitis

Overall, 27.6% of patients reported prior systemic corticosteroid use and 20.8% of patients indicated prior systemic non-steroidal immunosuppressants use (Table 15).

A slightly higher proportion of patients in the dupilumab Q4W group received prior systemic corticosteroids compared to patients in the placebo group and the dupilumab Q2W group. A similar proportion of patients in

all treatment groups indicated prior systemic non-steroidal immunosuppressants. The most commonly used non-steroidal immunosuppressants were ciclosporin and methotrexate (12.8% and 10.4%, overall, respectively). The high proportion of adolescents who had received systemic immunosuppressant therapy is indicative of the severity of disease in this population.
A high proportion of patients had a history of prior ciclosporin treatment. More than half (66.7%) of these patients used ciclosporin for longer than 12 weeks during their most recent course of treatment. The most common reason for discontinuing the most recent use of ciclosporin for all treatment groups was inadequate efficacy (54.4%).

Table 13: Summary of Prior Use of Systemic Corticosteroids and Systemic Non-steroidal Immunosuppressant Medications for AD in R668-AD-1526 – SAF

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

Abbreviations: AD, atopic dermatitis; Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set.

Previous Medications and Procedures
All patients in the SAF received at least 1 prior medication. The most commonly (≥50% in any treatment group) used prior medications (by therapeutic class) were dermatological preparations of corticosteroids, antihistamines for systemic use, drugs for obstructive airway disease, and emollients and protectives.
Overall, 27.6% of patients reported prior systemic corticosteroid use and 20.8% of patients indicated prior systemic non-steroidal immunosuppressants use.
A higher proportion of patients in the dupilumab Q4W group received prior systemic corticosteroids compared to patients in the placebo group and the dupilumab Q2W group. A similar proportion of patients in all treatment groups indicated prior systemic non-steroidal immunosuppressants. The most commonly used systemic non-steroidal immunosuppressants were ciclosporin and methotrexate (12.8% and 10.4%, overall, respectively).

Rescue Medications
Approximately 37.5% of the patients received rescue mediation during the 16-week treatment period (Table 14). A higher proportion of patients in the placebo group received at least 1 rescue medication during the 16-week treatment period, followed by patients in the dupilumab 300 mg Q4W group and then by patients in the dupilumab Q2W group.
The most commonly (>50% of patients in the placebo group) used dermatological rescue medication by therapeutic class was dermatological preparations of corticosteroids (Table 16).
The majority of patients who used systemic corticosteroids, and all patients who used systemic non-steroidal immunosuppressants, were in the placebo group (Table 14). Other rescue medications used are listed in Table 14.

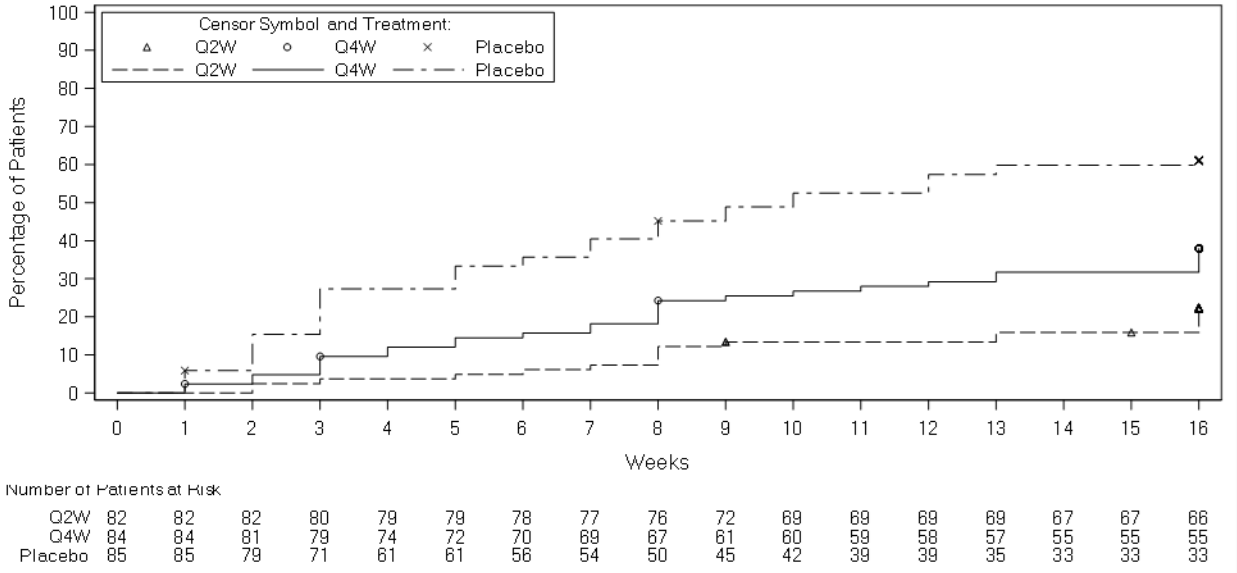
Table 14: Summary of Rescue Medication Taken during the 16-Week Treatment Period in R668-AD-1526 – FAS

Therapeutic Class Chemical Class/WHODDE 201712	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=165)	Total (N=250)
Patients with at least one rescue medication	50 (58.8%)	27 (32.1%)	17 (20.7%)	44 (26.5%)	94 (37.5%)
Corticosteroids, dermatological preparations	47 (55.3%)	26 (31.0%)	14 (17.1%)	40 (24.1%)	87 (34.7%)
Corticosteroids, moderately potent (Group II)	32 (37.6%)	18 (21.4%)	6 (7.3%)	24 (14.5%)	56 (22.3%)
Corticosteroids, potent (Group III)	16 (18.8%)	6 (7.1%)	8 (9.8%)	14 (8.4%)	30 (12.0%)
Corticosteroids, very potent (Group IV)	12 (14.1%)	6 (7.1%)	1 (1.2%)	7 (4.2%)	19 (7.6%)
Corticosteroids, weak (Group I)	6 (7.1%)	7 (8.3%)	2 (2.4%)	9 (5.4%)	15 (6.0%)
Other dermatological preparations	7 (8.2%)	1 (1.2%)	3 (3.7%)	4 (2.4%)	11 (4.4%)
Agents for dermatitis, excluding corticosteroids	7 (8.2%)	1 (1.2%)	3 (3.7%)	4 (2.4%)	11 (4.4%)
Corticosteroids for systemic use	5 (5.9%)	0	2 (2.4%)	2 (1.2%)	7 (2.8%)
Glucocorticoids	5 (5.9%)	0	2 (2.4%)	2 (1.2%)	7 (2.8%)
Immunosuppressants	3 (3.5%)	0	0	0	3 (1.2%)
Calcineurin inhibitors	2 (2.4%)	0	0	0	2 (0.8%)
Selective immunosuppressants	1 (1.2%)	0	0	0	1 (0.4%)

Abbreviations: FAS, full analysis set; Q2W, every 2 weeks; Q4W, every 4 weeks; WHODD, World Health Organization Drug Dictionary Enhanced.

By week 16, a higher proportion of patients in the placebo group than the dupilumab treatment groups received systemic or topical rescue medications and among the dupilumab treated groups the Q4W group had a higher rate of rescue medication use than the Q2W group. The median time to first rescue treatment use (topical or systemic) was approximately 9 weeks for the placebo group. Less than 50% of patients in either of the dupilumab dose groups required rescue treatment. Kaplan-Meier curves of time to first rescue treatment (topical or systemic) are shown in Figure 3.

Figure 3: Kaplan-Meier Curves of Time to First Rescue Treatment Use (Topical or Systemic) – FAS



Abbreviations: FAS, full analysis set; Q2W, every 2 weeks; Q4W, every 4 weeks.

During the 16-week treatment period, the mean proportion of rescue medication-free days was lower in the placebo group, followed by the dupilumab Q4W and dupilumab Q2W groups. No patients in any of the treatment groups underwent any rescue procedures during the 16-week treatment period.

Treatment Compliance

The mean injection compliance was high overall (>97.5% in each treatment group) and was similar across the 3 treatment groups .

Patients were required to apply stable doses of a moisturizer (emollient) twice daily for at least 7 days before the baseline visit and at least 7 days after the baseline visit (day -7 to day 8).

The mean (SD) background treatment compliance was similar across the 3 treatment groups with a mean (SD) compliance of >89% in each treatment group.

Numbers analysed

Sample Size and Efficacy Analysis Sets

The primary analysis for all efficacy endpoints was performed as planned by using the full analysis set (FAS). The FAS included all randomized patients and was analyzed based on the treatment allocated by the interactive voice response system/interactive web response system.

As a supportive analysis, the primary efficacy endpoint (and co-primary efficacy endpoint in the EU, EU reference countries,) was also analyzed using the per-protocol set (PPS). The PPS included all patients in the FAS except those patients who had major protocol deviations that were deemed to potentially impact the assessment of efficacy. Most of the patients (>90% in each treatment group, >95% overall) in the FAS were included in the PPS.

Outcomes and estimation

This section discusses the primary/co-primary efficacy endpoints, key secondary efficacy endpoints, and other secondary efficacy endpoints of pivotal study R668-AD-1526.

A hierarchical procedure was used as planned to control the overall Type-I error rate at 0.05 for the primary endpoint and the secondary endpoints across the 2 dupilumab dose regimens 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 results is shown in Table 19 (all comparisons are against the placebo group). The p-value, if not shown, for the efficacy endpoints in the testing hierarchies was <0.0001.

Superiority of dupilumab over placebo was demonstrated for all primary endpoints (IGA 0 or 1, co-primary EASI-75 for EU) and key secondary endpoints at week 16 (mean % change in EASI, mean % change in weekly average of daily peak pruritus NRS, proportion of patients with NRS reduction ≥3 from baseline, proportion of patients with NRS reduction ≥4 from baseline). The pre-specified hierarchical testing procedure broke down at the thirty-third endpoint: change from baseline in HADS score at week 16 for the dupilumab Q2W dose. The Q2W regimen was numerically superior to the Q4W regimen on most primary and key secondary categorical endpoints.

Table 19: Statistical Hierarchy for Multiplicity Control and Overview of Results

Level	Efficacy Endpoints (EPs) at Week 16	Placebo (N=85)	Dupilumab Q4W (N=84)		Dupilumab Q2W (N=82)	
Primary/ Co-primary Endpoints	Proportion of patients with IGA 0 to 1 (on a 5-point scale)	2 (2.4%)	10	15 (17.9%) 15.5% p = 0.0007	1	20 (24.4%) 22.0%
	Proportion of patients with EASI-75 (≥75% improvement from baseline)	7 (8.2%)	9	32 (38.1%) 29.9%	2	34 (41.5%) 33.2%
Key Secondary Endpoints	Percent change in EASI score from baseline to week 16	-23.6 (5.49)	11	-64.8 (4.51) -41.2	3	-65.9 (3.99) -42.3
	Percent change from baseline to week 16 in weekly average of peak daily Pruritus NRS	-19.0 (4.09)	12	-45.5 (3.54) -26.5	4	-47.9 (3.43) -29.0
	Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥3 from baseline to week 16	8/85 (9.4%)	13	32/83 (38.6%) 29.1%	5	40/82 (48.8%) 39.4%
	Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to week 16	4/84 (4.8%)	14	22/83 (26.5%) 21.7% p = 0.0001	6	30/82 (36.6%) 31.8%
	Proportion of patients with EASI-50	11 (12.9)	15	46 (54.8%)	7	50 (61.0%)

Level	Efficacy Endpoints (EPs) at Week 16	Placebo (N=85)		Dupilumab Q4W (N=84)		Dupilumab Q2W (N=82)
Other secondary endpoints in 1st Family				41.8%		48.0%
	Proportion of patients with EASI-90	2 (2.4)	16	16 (19.0%) 16.7% p = 0.0004	8	19 (23.2%) 20.8%
Other secondary endpoints in 2nd Family	Time to onset of effect in weeks on pruritus during the 16-week treatment period (≥3 point reduction of weekly average of peak Pruritus NRS from baseline)	Not reached	25	6 1.88 p = 0.0029	17	5.4 2.25 p = 0.0001
	Time to onset of effect in weeks on pruritus during the 16-week treatment period (≥4 point reduction of weekly average of peak Pruritus NRS from baseline)	Not reached	26	11 2.34 p = 0.0010	17	11.4 2.40 p = 0.0007
	Change from baseline in percent BSA affected by AD	-11.66 (2.720)	27	-33.41 (2.330) -21.75	19	-30.11 (2.337) -18.44
	Percent change from baseline in SCORAD	-17.6 (3.76)	28	-47.5 (3.21) -29.9	20	-51.6 (3.23) -34.0
	Change from baseline in CDLQI	-5.1 (0.62)	29	-8.8 (0.53) -3.7	21	-8.5 (0.50) -3.4
	Change from baseline in POEM	-3.8 (0.96)	30	-9.5 (0.86) -5.7	22	-10.1 (0.76) -6.3
	Change from baseline in weekly average of peak daily Pruritus NRS	-1.54 (0.303)	31	-3.44 (0.260) -1.90	23	-3.70 (0.250) -2.16
	Percent change from baseline to week 4 in weekly average of peak daily Pruritus NRS	-12.5 (3.06)	32	-33.1 (3.05) -20.6	24	-34.7 (2.99) -22.2

Primary/Co-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 co-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 (and a Reduction from Baseline of ≥2 Points) at Week 16

The proportion of patients in the FAS with IGA 0 or 1 (and reduction from baseline of ≥2 points) at week 16 was higher in the dupilumab Q2W group (24.4%) and the dupilumab Q4W group (17.9%) than in the placebo group (2.4%) (Table 20). Both comparisons were statistically significant and clinically meaningful.

The dupilumab Q2W treatment group was numerically superior to the dupilumab Q4W treatment group for the proportion of patients in the FAS with IGA 0 or 1 at week 16 (Table 20).

Table 15: Proportion of Patients with IGA 0 or 1 at Week 16 in Study R668-AD-1526; Patient Considered Non-Responder after Rescue Treatment Use – FAS

Treatment	Patients with IGA 0 or 1 at Week 16 (%)	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]	Mantel-Fleiss Criterion vs Placebo [3]
Dupilumab 200 mg or 300 mg Q2W (N=82)	20 (24.4)	22.0 (12.20, 31.87)	<0.0001	10.9
Dupilumab 300 mg Q4W (N=84)	15 (17.9)	15.5 (6.70, 24.31)	0.0007	8.4
Placebo (N=85)	2 (2.4)			

[1] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].
[3] If the value is >5, then Mantel-Fleiss criterion is met, so the chi-square approximation for the distribution of the Mantel-Haenszel statistics used in the Cochran-Mantel-Haenszel test is valid.
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.

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 (and reduction from baseline of ≥2 points) at week 16 was greater in the dupilumab Q2W treatment group (24.4%) and the dupilumab Q4W group (20.2%) than the placebo group (4.7%) (Table 21). 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 them ethodology used for handling missing data did not impact the results.

Table 16: Sensitivity Analysis of Proportion of Patients Achieving IGA 0 to 1 at Week 16 in Study R668-AD-1526; All Observed Values Regardless of Rescue Treatment Use – FAS

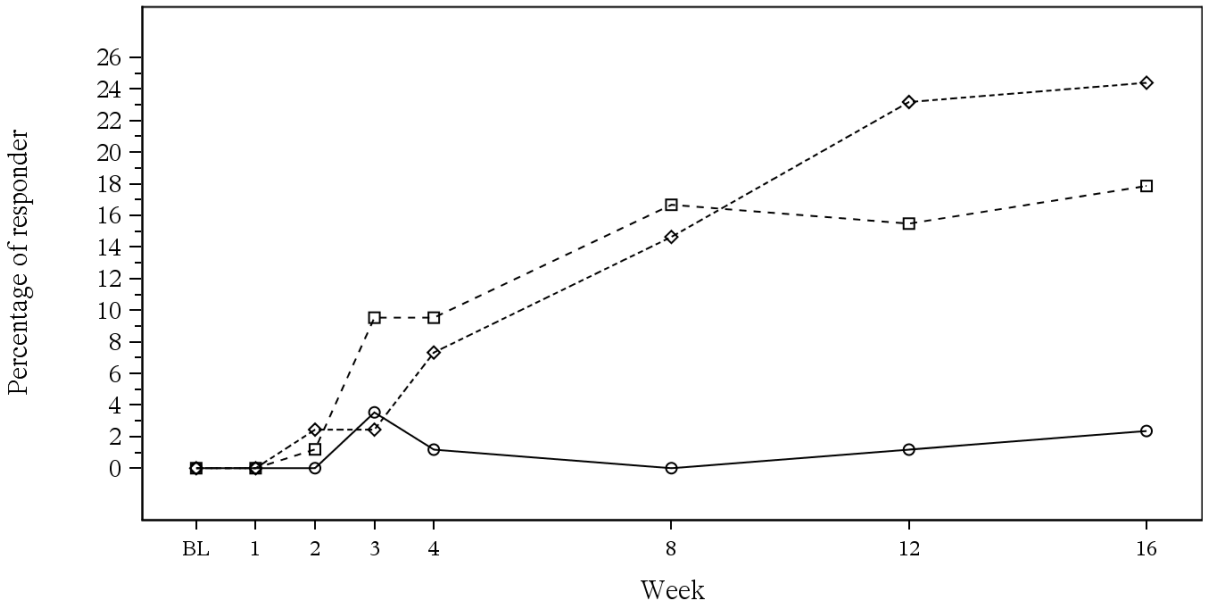
Treatment	Patients with IGA 0 or 1 at Week 16 n (%)	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200 mg or 300 mg Q2W (N=82)	20 (24.4)	19.7 (9.36, 30.01)	0.0003
Dupilumab 300 mg Q4W (N=84)	17 (20.2)	15.5 (5.83, 25.23)	0.0017
Placebo (N=85)	4 (4.7)		

[1] Difference is dupilumab minus placebo. CI = Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 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.

A supportive analysis of the primary endpoint was performed using the PPS. The proportion of patients in the PPS with IGA 0 or 1 (and reduction from baseline of ≥2 points) at week 16 was higher in the dupilumab Q2W treatment group vs the placebo group (25.3% vs 2.4%, respectively; nominal p<0.0001) and higher for the dupilumab Q4W group vs the placebo group (18.2% vs 2.4%, respectively; nominal p=0.0006).
As shown in Figure 3, the proportion of patients achieving IGA scores of 0 to 1 (and reduction from baseline of ≥2 points) was numerically higher in both the dupilumab treatment arms than in the placebo group beginning at week 4. The separation was sustained throughout the 16 weeks of the treatment period.

The proportion of patients achieving IGA 0 or 1 (and reduction from baseline of ≥2 points) in the dupilumab Q2W dosing arm was higher at week 12 compared to the dupilumab Q4W dosing arm (~23% of patients vs ~15% of patient, respectively) and this numerical superiority of Q2W over Q4W was sustained at week 16.

Figure 4: Proportion of Patients Achieving IGA 0 to 1 through Week 16 in Study R668-AD-1526– FAS



Number of responder								
Placebo (N= 85)	0	0	0	3(4)	1(1)	0	1(1)	2(2)
Q4W (N= 84)	0	0	1(1)	8(10)	8(10)	14(17)	13(15)	15(18)
Q2W (N= 82)	0	0	2(2)	2(2)	6(7)	12(15)	19(23)	20(24)

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 with EASI-75 at week 16 was higher in the dupilumab Q2W group (41.5%) and the dupilumab Q4W group (38.1%) than in the placebo group (8.2%) (Table 17). Both comparisons were statistically significant and clinically meaningful. The dupilumab Q2W treatment group was comparable to the dupilumab Q4W treatment group for the proportion of patients with EASI-75 at week 16 (Table 17).

Table 17: Proportion of Patients Achieving EASI-75 (≥75% Improvement from Baseline) at Week 16 in Study R668-AD-1526; Patient Considered Non-Responder after Rescue Treatment Use – FAS

Treatment	Patients with EASI-75 at Week 16 n (%)	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]	Mantel-Fleiss Criterion vs Placebo [3]
Dupilumab 200 mg or 300 mg Q2W (N=82)	34 (41.5)	33.2 (21.07, 45.39)	<0.0001	20.2
Dupilumab 300 mg Q4W (N=84)	32 (38.1)	29.9 (17.94, 41.78)	<0.0001	19.4
Placebo (N=85)	7 (8.2)			

[1] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].
[3] If the value is >5, then Mantel-Fleiss criterion is met, so the chi-square approximation for the distribution of the Mantel-Haenszel statistics used in the Cochran-Mantel-Haenszel test is valid.
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; IGA, Investigator's Global Assessment; Q2W, every 2 weeks, Q4W, every 4 weeks.

In a sensitivity analysis using all observed values, with patients with missing values counted as non-responders, the proportion of patients with EASI-75 at week 16 was higher for the dupilumab Q2W group (45.1%) and the dupilumab Q4W group (47.6%) than for the placebo group (15.3%) (Table 18). Comparisons for each dupilumab treatment group were consistent with the primary analysis.
Likewise, the sensitivity analysis LOCF was consistent with the primary analysis and the sensitivity analysis for all observed data. This showed that the methodology used for handling missing data did not impact the results.

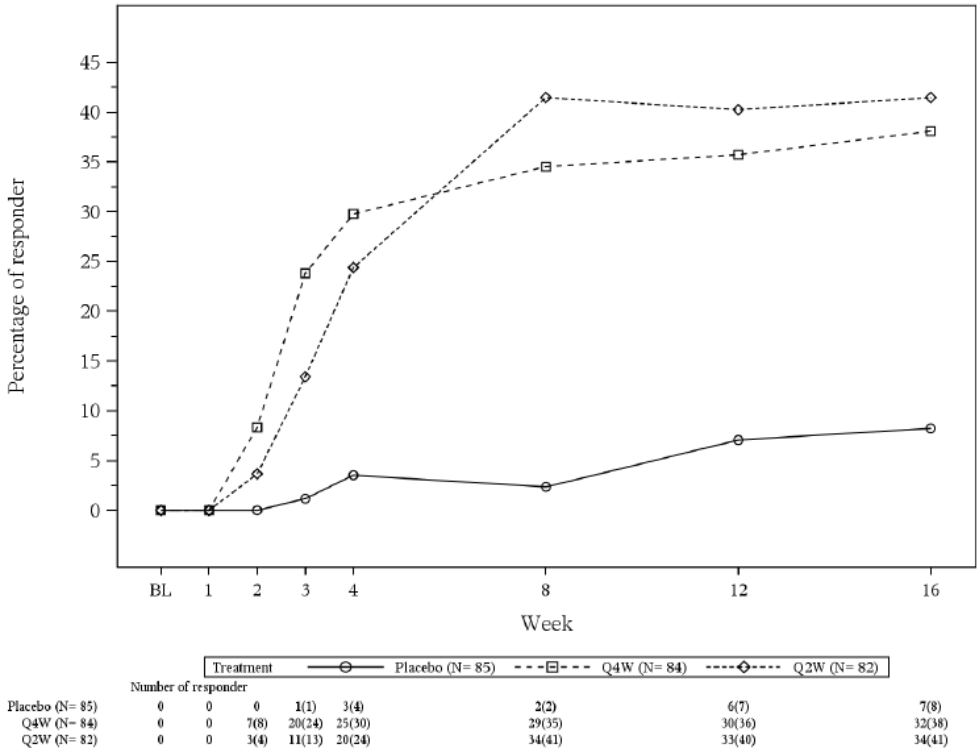
Table 18: Sensitivity Analysis of Proportion of Patients Achieving EASI-75 (≥75% Improvement from Baseline) at Week 16, All Observed Values Regardless of Treatment Use in Study R668-AD-1526 – FAS

Treatment	Patients with EASI-75 at Week 16 n (%)	Difference vs Placebo (%) (95% CI) [1]	P-value vs Placebo [2]
Dupilumab 200 mg or 300 mg Q2W (N=82)	37 (45.1)	29.8 (16.62, 43.04)	<0.0001
Dupilumab 300 mg Q4W (N=84)	40 (47.6)	32.3 (19.19, 45.46)	<0.0001
Placebo (N=85)	13 (15.3)		

[1] Difference is dupilumab minus placebo. Confidence interval calculated using normal approximation.
[2] P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg].
Note: 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; IGA, Investigator's Global Assessment; Q2W, every 2 weeks, Q4W, every 4 weeks.

A supportive analysis of the co-primary endpoint was performed in the PPS. The proportion of patients in the PPS with EASI-75 at week 16 was higher in the dupilumab Q2W group vs the placebo group (43.0% vs 8.3%, respectively; nominal p<0.0001) and the dupilumab Q4W group vs the placebo group (40.3% vs 8.3%, respectively; nominal p<0.0001). As shown in Figure 4, during the study treatment period up to week 16, there was a clear separation in the proportion of patients achieving EASI-75 between the dupilumab and placebo groups. The first time point during the treatment period at and subsequent to which the dupilumab Q2W group was persistently nominally statistically significant compared to the placebo group was at week 3 (p=0.0025). For the dupilumab Q4W group, this time point was week 2 (p=0.0066). The 2 dose regimens of dupilumab tested (ie, Q2W and Q4W) were comparable with respect to this outcome, with the Q2W groups having a slightly higher percentage of responders starting at approximately week 8 and remaining as such through week 16.

Figure 5: Proportion of Patients Achieving EASI-75 from Baseline through Week 16 in Study R668-AD-1526; Patient Considered Non-Responder after Rescue Treatment Use – FAS



Abbreviations: BL, baseline; EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; FAS, full analysis set; Q2W, every 2 weeks, Q4W, every 4 weeks.

Key Secondary Efficacy Endpoints Percent Change in EASI Score from Baseline to Week 16

The mean reduction in EASI score from baseline to week 16 was greater in the dupilumab Q2W group (least squares [LS] mean [standard error (SE)] vs baseline, -65.9%, [3.99%]) and dupilumab Q4W group (LS mean [SE] vs baseline, -64.8%, [4.51%]), than the placebo group (LS mean [SE] vs baseline, -23.6%, [5.49%]) (Table 24). The LS mean difference in percent change from baseline for each of the dupilumab treatment groups compared to the placebo group was clinically meaningful and statistically significant. The dupilumab Q2W treatment group was comparable to the dupilumab Q4W treatment group for percent change in EASI score from baseline to week 16 (Tables 19 and 20).

Table 19: Primary Analysis of Percent Change from Baseline in EASI Score at Week 16 in Study R668-AD-1526; MI Method with Data Set to Missing after Rescue Treatment Use – FAS

Treatment	LS Mean % Change (SE)	Mean % Change (SD)	Baseline Mean (SD)	Num. of Observed / Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200 mg or 300 mg Q2W (N=82)	-65.9 (3.99)	-65.5 (26.69)	35.26 (13.836)	66/16	Dupilumab 200 mg or 300 mg Q2W vs Placebo	<0.0001	-42.3 (-55.60, 29.04)
Dupilumab 300 mg Q4W (N=84)	-64.8 (4.51)	-64.4 (26.86)	35.78 (14.822)	55/29	Dupilumab 300 mg Q4W vs Placebo	<0.0001	-41.2 (-54.44, 28.02)
Placebo (N=85)	-23.6 (5.49)	-23.2 (33.60)	35.53 (13.971)	33/52			

[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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.
Note: Seed number 12345 and 54321 with imputation size 40.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error.

A sensitivity analysis of percent change from baseline in EASI score at week 16 regardless of rescue treatment for the FAS (Table 20) was consistent with the primary analysis. Likewise, the following sensitivity analyses conducted in the FAS were also consistent with the primary analysis: LOCF and worst observation carried forward (WOCF). This showed that the methodology used for handling missing data did not impact the results.

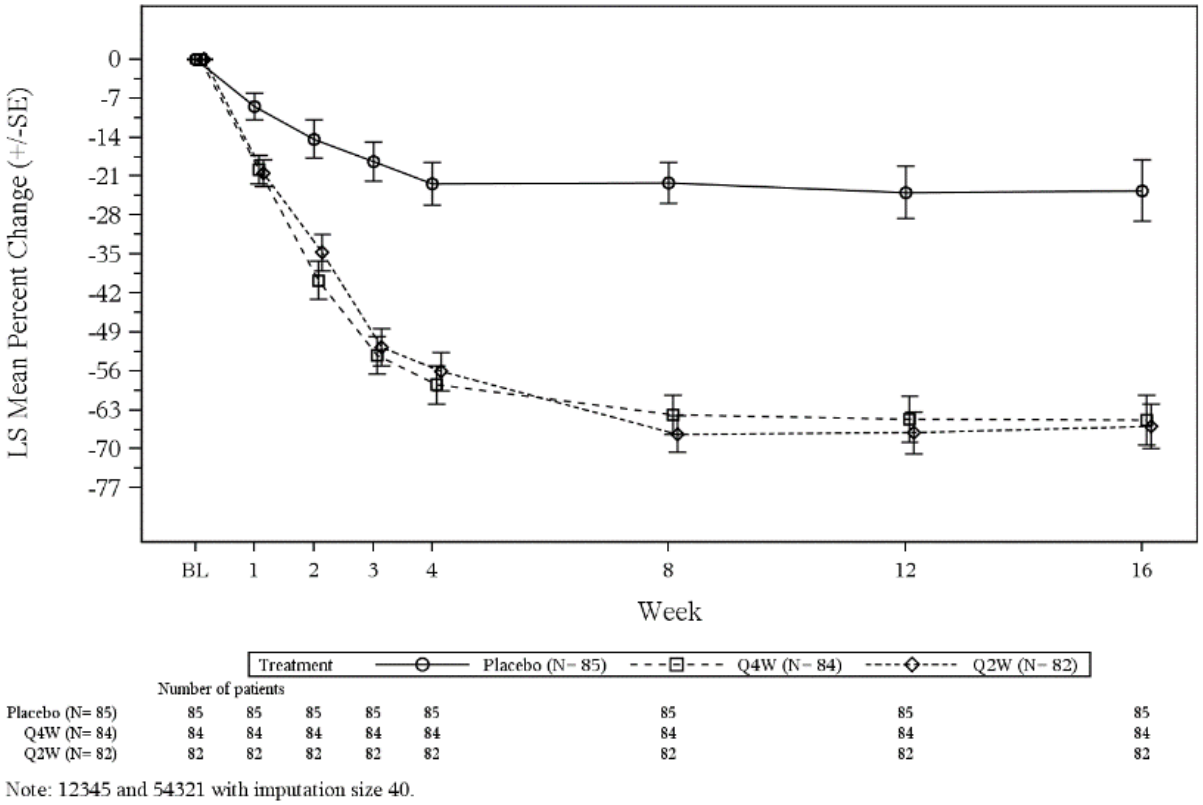
Table 20: Sensitivity Analysis of Percent Change from Baseline in EASI Score at Week 16, MI Method Regardless of Rescue Treatment Use in Study R668-AD-1526 - FAS

Treatment	LS Mean %Change (SE)	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200 mg or 300 mg Q2W (N=82)	-66.2 (3.56)	-65.9 (27.18)	35.26 (13.836)	78/4	Dupilumab 200 mg or 300 mg Q2W vs Placebo	<0.0001	-34.9 (-44.76, 25.11)
Dupilumab 300 mg Q4W (N=84)	-66.1 (3.51)	-65.7 (27.51)	35.78 (14.822)	81/3	Dupilumab 300 mg Q4W vs Placebo	<0.0001	-34.8 (-44.54, 25.08)
Placebo (N=85)	-31.3 (3.54)	-30.9 (38.07)	35.53 (13.971)	82/3			

[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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.
Note: Seed number 12345 and 54321 with imputation size 40.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EASI, Eczema Area and Severity Index; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error.

As shown in Figure 6, during the study treatment period up to week 16, there was a clear separation in the mean percent change in EASI between the dupilumab and placebo groups. The rapid onset to the effect was sustained across the 16-week treatment period. The 2 dose regimens of dupilumab tested were comparable with respect to this outcome. Similar results to the primary analysis were observed in analyses performed with or without censoring after rescue treatment use.

Figure 6: Percent Change in EASI Score from Baseline through Week 16 in Study R668-AD-1526: MI Method with Data Set to Missing after Rescue Treatment Use – FAS



Number of patients								
Placebo (N= 85)	85	85	85	85	85	85	85	85
Q4W (N= 84)	84	84	84	84	84	84	84	84
Q2W (N= 82)	82	82	82	82	82	82	82	82

Note: 12345 and 54321 with imputation size 40.

Abbreviations: BL, baseline; EASI, Eczema Area and Severity Index; FAS, full analysis set; LS, least squares; MI, multiple imputation; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Percent Change in Weekly Average of Peak Daily Pruritus NRS Score from Baseline to Week 16

The percent change from baseline to week 16 in weekly average of peak daily pruritus NRS was greater in the dupilumab Q2W group (LS mean [SE] vs baseline, -47.9% [3.43%]) and dupilumab 300 mg Q4W group (LS mean [SE] vs baseline, -45.5% [3.54%]) than the placebo group (LS mean [SE] vs baseline, -19.0% [4.09%]) (Table 26). The LS mean difference in percent change from baseline vs placebo was -29.0% for dupilumab Q2W and -26.5% for dupilumab Q4W. The comparisons for each dupilumab group versus the placebo group were statistically significant (Table 26).

The dupilumab Q2W group was comparable to the dupilumab Q4W group for the percent change from baseline in weekly average of peak pruritus NRS at week 16 (Table 21).

Table 21: Primary Analysis of Percent Change from Baseline in Weekly Average of Peak Daily Pruritus NRS at Week 16 in Study R668-AD-1526; MI Method with Censoring after Rescue Treatment Use – FAS

Treatment	LS Mean %Change (SE)	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200 mg or 300 mg Q2W (N=82)	-47.9 (3.43)	-47.6 (29.25)	7.52 (1.519)	66/16	Dupilumab 200 mg or 300 mg Q2W vs Placebo	<0.0001	-29.0 (-39.54, -18.38)
Dupilumab 300 mg Q4W (N=84)	-45.5 (3.54)	-45.1 (26.65)	7.49 (1.836)	53/31	Dupilumab 300 mg Q4W vs Placebo	<0.0001	-26.5 (-37.45, -15.63)
Placebo (N=85)	-19.0 (4.09)	-19.2 (22.15)	7.73 (1.624)	31/54			

[1] The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs Placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.
Note: Seed number 12345 and 54321 with imputation size 40.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; LS, least squares; MI, multiple imputation; NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error.

In a sensitivity analysis using all observed values, regardless of whether rescue treatment was used or data were collected after study withdrawal, using the MI method, a significant decrease in weekly average of peak daily pruritus NRS score from baseline to week 16 was observed in the dupilumab Q2W group (Table 27). The LS mean difference in percent change from baseline vs placebo was -27.3% for dupilumab Q2W and -25.5% for dupilumab Q4W. The comparison of each dupilumab treatment group vs the placebo group was consistent with the primary analysis (Table 22)

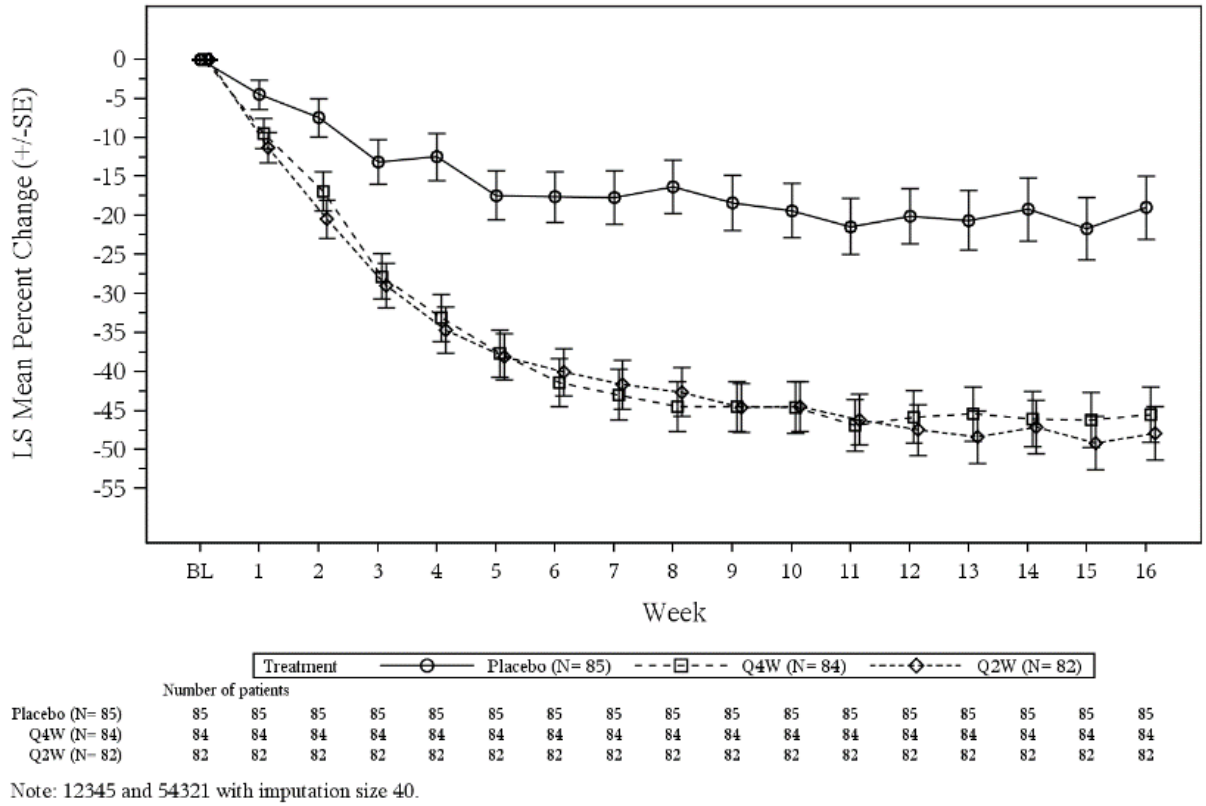
Table 22: Sensitivity Analysis of Percent Change from Baseline in Weekly Average of Peak Daily Pruritus NRS at Week 16; MI Method Regardless of Rescue Treatment Use in Study R668-AD-1526 – FAS

Treatment	LS Mean %Change (SE)	Mean %Change (SD)	Baseline Mean (SD)	Num. of Observed/ Imputed Subjects	Contrast	P-value [1]	LS Mean Difference (95% CI) [1]
Dupilumab 200 mg or 300 mg Q2W (N=82)	-48.1 (3.27)	-47.8 (29.64)	7.52 (1.519)	78/4	Dupilumab 200 mg or 300 mg Q2W vs Placebo	<0.0001	-27.3 (-36.29, -18.24)
Dupilumab 300 mg Q4W (N=84)	-46.3 (3.27)	-45.9 (30.58)	7.49 (1.836)	79/5	Dupilumab 300 mg Q4W vs Placebo	<0.0001	-25.5 (-34.46, -16.48)
Placebo (N=85)	-20.9 (3.24)	-21.0 (26.99)	7.73 (1.624)	76/9			

[1] The confidence interval (CI) with p-value is based on treatment difference (Dupilumab group vs Placebo) of the LS mean percent change using ANCOVA model with baseline measurement as covariate and the treatment, randomization strata (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors.
Note: Seed number 12345 and 54321 with imputation size 40.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least squares; MI, multiple imputation; NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; SE, standard error.

As shown in Figure 6, during the study treatment period up to week 16, there was a clear separation in the percent change in weekly average of peak daily pruritus NRS score between the dupilumab groups and the placebo group. Thus, this effect was rapid and sustained. The 2 dose regimens of dupilumab tested were comparable with respect to this outcome.

Figure 7: Percent Change from Baseline in Weekly Average of Peak Daily Pruritus NRS Score from Baseline to Week 16 in Study R668-AD-1526; MI Method with Data Set to Missing after Rescue Treatment Use – FAS



Number of patients																
Placebo (N= 85)	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
Q4W (N= 84)	84	84	84	84	84	84	84	84	84	84	84	84	84	84	84	84
Q2W (N= 82)	82	82	82	82	82	82	82	82	82	82	82	82	82	82	82	82

Note: 12345 and 54321 with imputation size 40.

Abbreviations: BL, baseline; FAS, full analysis set; LS, least squares; MI, multiple imputation; NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Proportion of Patients with Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus NRS from Baseline to Week 16

The proportion of patients achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS score at week 16 was higher in the dupilumab Q2W group (48.8%) and dupilumab Q4W (38.6%) group than in the placebo group (9.4%). Both comparisons were statistically significant.

The dupilumab Q2W group was numerically superior to the dupilumab Q4W group for the proportion of patients achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS at week 16.

In a sensitivity analysis using all observed values, with patients with missing values counted as non-responders, the proportion of patients achieving a reduction of ≥3 points from baseline in weekly average of peak daily pruritus NRS scores at week 16 was higher in the dupilumab Q4W (54.2%) and dupilumab Q2W (58.5%) groups than in the placebo group (22.4%). Both comparisons were statistically significant statistically and consistent with the primary analysis.

Proportion of Patients with Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus NRS from Baseline to Week 16

The proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at week 16 was significantly higher in the dupilumab Q2W (36.6%) and dupilumab Q4W (26.5%) groups than the placebo group (4.8%). Both comparisons were statistically significant.
The dupilumab Q2W group was numerically superior to the dupilumab Q4W group for the proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS at week 16.

In a sensitivity analysis using all observed values, with patients with missing values counted as non-responders, the proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at week 16 was higher in the dupilumab Q2W (42.7%) and dupilumab Q4W (39.8%) groups than the placebo group (15.5%). Both comparisons were consistent with the primary analysis.

Other Secondary Efficacy Endpoints

Other EASI Endpoints

Analysis of other secondary EASI endpoints supported the primary and key secondary efficacy endpoint results that showed dupilumab monotherapy was more effective than placebo at improving both the severity and the extent of AD. The proportion of patients with EASI-50 (≥50% improvement from baseline) at week 16 was higher in the dupilumab Q2W (61.0%) and dupilumab Q4W groups (54.8%) than in the placebo group (12.9%). Both comparisons were statistically significant. The dupilumab Q2W treatment group was numerically superior to the dupilumab Q4W group. The proportions of patients achieving EASI-90 (≥90% improvement from baseline) at week 16 were higher in the dupilumab Q2W (23.2%) and dupilumab Q4W (19.0%) groups than in the placebo group (2.4%). Both comparisons were statistically significant. The dupilumab Q2W treatment group was numerically superior to the dupilumab Q4W group.

During the study treatment period up to week 16, there was a clear separation in the proportion of patients achieving EASI-50 between the dupilumab and placebo groups. The proportion of patients achieving EASI-50 was greater in the dupilumab groups than in the placebo group at every weekly assessment during the study treatment period. The proportion of patients achieving EASI-50 was higher in the Q2W group than the Q4W group at week 8 (approximately 68% vs. 58%, respectively) and this numerical superiority of Q2W over Q4W was maintained through week 16.
Similar results to the primary analysis were observed in sensitivity analyses performed using all observed values regardless of rescue treatment use and using LOCF.

During the study treatment period up to week 16, there was a clear separation in the proportion of patients achieving EASI-90 between the dupilumab and placebo groups. The first time point during the treatment period at and subsequent to which the dupilumab Q2W and Q4W groups were persistently nominally significant compared to placebo was at week 4 ($p=0.0388$ and $p=0.0061$), respectively.
Similar results to the primary analysis were observed in sensitivity analyses performed using all observed values regardless of rescue treatment use and using LOCF.

Other Secondary Pruritus NRS Endpoints

Results of other secondary peak pruritus NRS endpoints supported the results of the key secondary efficacy endpoints that demonstrated dupilumab monotherapy was more effective than placebo in reducing the weekly average of peak pruritus in AD patients, with effects seen within 4 weeks of treatment.
The mean baseline weekly average of peak daily pruritus NRS score was similar across the 3 treatment groups.
A greater mean change in weekly average of peak daily pruritus NRS score from baseline to week 16 was observed for the dupilumab Q2W group (LS mean [SE] vs baseline, -3.7 [0.250]) and the dupilumab Q4W group (LS mean [SE] vs baseline, -3.44 [0.260]) compared to the placebo group (LS mean [SE] vs baseline,

-1.54 [0.303]). The LS mean difference in change from baseline vs placebo was -2.16 (-2.935, -1.389) for the dupilumab Q2W group and -1.90 (-2.705, -1.098) for the dupilumab Q4W group. Both comparisons were statistically significant. The decrease in weekly average of peak daily pruritus NRS score from baseline to week 16 was comparable for the 2 dupilumab groups.
The LS mean percent change (SE) in weekly average of peak daily pruritus NRS score from baseline to week 4 was -34.7% (2.99) in the dupilumab Q2W group, -33.1% (3.05) in the dupilumab Q4W group and -12.5% (3.06) in the placebo group. The LS mean difference in change from baseline vs placebo was -22.2% (-30.55, -13.85) for the dupilumab Q2W group and -20.6% (-29.11, -12.14) for the dupilumab Q4W group. Both comparisons were statistically significant. The decrease from baseline to week 4 in weekly average of peak daily pruritus NRS was comparable between the 2 dose regimens.
The median time (weeks) to onset of effect on pruritus (time at which 50% of patients in the treatment group achieved a ≥3 point reduction of weekly average of peak pruritus NRS from baseline) during the 16-week treatment period was approximately 5 and 6 weeks for the dupilumab Q2W and dupilumab Q4W groups, respectively. mFor the placebo group, less than 50% of patients achieved NRS reduction of at least 3 points during the 16-week treatment period and hence the median time to onset of effect on pruritus could not be computed. Compared to the placebo group, the hazard ratio (95% CI) for reduction of pruritus during the 16-week treatment period (≥3 point reduction of NRS from baseline) was 2.249 (1.490 - 3.393) for the dupilumab Q2W group and 1.877 (1.240 - 2.843) for the dupilumab Q4W group. Both comparisons were statistically significant. The median time to achieve a ≥3 point reduction in weekly average of peak pruritus NRS from baseline was comparable for the 2 dupilumab groups. The median time (weeks) to onset of effect on pruritus (time at which 50% of patients in the treatment group achieved a ≥4 point reduction of weekly average of peak pruritus NRS from baseline) during the 16-week treatment period was approximately 11 weeks for both dupilumab treatment groups. For the placebo group, less than 50% of patients achieved NRS reduction of at least 4 points during the 16-week treatment period and hence the median time to onset of effect on pruritus could not be computed. Compared to the placebo group, the hazard ratio (95% CI) for time to onset of effect on pruritus during the 16-week treatment period (≥4 point reduction of NRS from baseline) was 2.401 (1.448 - 3.983) for the dupilumab Q2W group and 2.340 (1.411 - 3.882) for the dupilumab Q4W group. Both comparisons were statistically significant.
The median time to achieve a ≥4 point reduction in weekly average of peak pruritus NRS from baseline was comparable for the 2 dupilumab groups.

The proportion of patients achieving improvement (reduction) of weekly average peak dailypruritus NRS of ≥4 points from baseline to week 4 was higher in the dupilumab Q2W (22.0%) and the dupilumab Q4W (20.5%) groups than in the placebo group (4.8%). Both comparisons were nominally statistically significant.
The proportion of patients achieving improvement (reduction) of weekly average peak daily pruritus NRS of ≥4 points from baseline to week 4 was comparable between the 2 dose regimens.

Other AD Severity and Patient-Reported Outcome Measure Endpoints

Other secondary efficacy endpoints incorporated additional measurements of AD severity and provided further support for the results of the primary and key secondary efficacy endpoints. Results from the pivotal phase 3 study in adolescents showed that dupilumab monotherapy was more effective than placebo at improving the extent and severity of AD lesions, as assessed by SCORAD and BSA involvement with AD. This was demonstrated by larger reductions or percent reductions from baseline in these assessment scores at week 16 in the dupilumab groups than the placebo group. The LS mean difference in change or percent change from baseline for each assessment score at week 16 was statistically significant when compared to placebo for both dose regimens.
Results of additional patient-reported assessments included as other secondary efficacy endpoints demonstrated that dupilumab monotherapy was more effective than placebo at improving primary AD symptoms (eg, pruritus, sleep disturbance, skin bleeding, cracking, oozing, flaking, etc), as well as health-related quality of life, as assessed by the POEM and CDLQI, respectively. This was demonstrated by larger reductions from baseline in these assessment scores at week 16 in the dupilumab groups than the placebo group. The LS mean difference in change from baseline for each assessment score at week 16 was statistically significant when compared to placebo for both dose regimens.

The pre-specified hierarchical testing procedure broke down at the thirty-third endpoint: change from baseline in HADS total score at week 16 for the dupilumab Q2W dose. The mean (SD) baseline HADS total score was 12.6 (8.04) for patients in the dupilumab Q2W group, 13.3 (8.17) for patients in the dupilumab Q4W group, and 11.6 (7.76) for patients in the placebo group. While numerically a trend towards decreased LS mean change in HADS total score was evident for both dupilumab treatment groups, the LS mean difference compared to placebo was not significant for the dupilumab Q2W group, but was nominally significant for the dupilumab Q4W group (Table 23).

Table 23: Other AD Severity and Patient-Reported Outcomes (Percent Change from Baseline in SCORAD at Week 16; Change from Baseline in Percent BSA Involvement with AD at Week 16; Change from Baseline in POEM at Week 16; Change from Baseline in CDLQI at Week 16; and Change from Baseline in HADS at Week 16) in Study R688-AD-1526 - FAS

	Placebo (N=85)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab 300 mg Q4W (N=84)
Percent change from baseline in SCORAD at Week 16			
LS mean % change (SE)	-17.6 (3.76)	-51.6 (3.23)	-47.5 (3.21)
LS mean difference (95% CI)		-34.0 (-43.41, -24.58)	-29.9 (-39.98, -19.83)
P-value vs placebo		<0.0001	<0.0001
Change from baseline in Percent BSA involvement with AD at Week 16			
LS mean change (SE)	-11.66 (2.720)	-30.11 (2.337)	-33.41 (2.330)
LS mean difference (95% CI)		-18.44 (-25.117, -11.770)	-21.75 (-28.950, -14.552)
P-value vs placebo		<0.0001	<0.0001
Change from baseline in POEM at Week 16			
LS mean change (SE)	-3.8 (0.96)	-10.1 (0.76)	-9.5 (0.86)
LS mean difference (95% CI)		-6.3 (-8.63, -4.01)	-5.7 (-8.24, -3.23)
P-value vs placebo		<0.0001	<0.0001
Change from baseline in CDLQI at Week 16			
LS mean change (SE)	-5.1 (0.62)	-8.5 (0.50)	-8.8 (0.53)
LS mean difference (95% CI)		-3.4 (-5.01, -1.80)	-3.7 (-5.20, -2.18)
P-value vs placebo		<0.0001	<0.0001
Change from baseline in HADS total score at Week 16			
LS mean change (SE)	-2.5 (0.80)	-3.8 (0.68)	-5.2 (0.73)
LS mean difference (95% CI)		-1.3 (-3.30, 0.76)	-2.7 (-4.79, -0.56)
P-value vs placebo		0.2203	0.0133

Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; FAS, full analysis set; LS, least squares; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SCORAD, SCORing Atopic Dermatitis; SE, standard error.

In a post-hoc analysis developed for the SCE, a larger proportion of patients in the dupilumab groups had a clinically meaningful reduction in CDLQI total score and POEM total score (each defined as ≥6 point reduction) from baseline to week 16 compared to placebo groups for both dose regimens .

Table 24: Post-hoc Analyses Endpoints: Patients Achieving CDLQI Reduction ≥6 from Baseline at Week 16; Patients Achieving POEM Reduction ≥6 from Baseline at Week 16 in Study R688-AD-1526 – CDLQI and POEM Analysis Sets

	Placebo (N=85)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab 300 mg Q4W (N=83)
Patients achieving CDLQI improvement ≥6 from baseline at Week 16 in patients with CLDQI ≥6 at baseline			
Patients with CDLQI ≥6 at baseline, n	76	71	71
Patients achieving ≥6 point improvement at week 16, n/N3 (%)	15/76 (19.7%)	43/71 (60.6%)*	42/71 (59.2%)*
Patients achieving POEM improvement ≥6 from baseline at Week 16 in patients with POEM ≥6 at baseline			
Patients with POEM ≥6 at baseline, n	84	82	83
Patients achieving ≥6 point improvement at week 16, n/N3 (%)	8/84 (9.5%)	52/82 (63.4%)*	39/83 (47.0%)*

Values are first rescue treatment used were set to missing. Patients with missing score at week 16 were considered as a non-responder.
N3: number of patients with baseline POEM or CDLQI score ≥6.
P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity (IGA=3 vs. IGA=4) and baseline weight group (<60 kg vs. ≥60 kg)
*P-value <0.0001 vs, placebo
Abbreviations: CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; LS, least squares; POEM, Patient-Oriented Eczema Measure; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Ancillary analyses

Comparison of Results in Subpopulations Within the Phase 3 Pivotal Study

Subgroup analyses of the primary and key secondary efficacy endpoints were performed on the dataset of the phase 3 pivotal study (R668-AD-1526). Subgroup analyses by age, gender, ethnicity, race, duration of AD, age of onset of AD, family history of AD, baseline body weight, body mass index (BMI), baseline IGA score, baseline EASI score, baseline peak pruritus NRS, baseline BSA involvement in AD, previous use of systemic immunosuppressants, previous use of ciclosporin, previous use of MTX, history of asthma, history of allergic rhinitis, and history of food allergies were planned and performed for the primary and key secondary efficacy endpoints. Demographic characteristics were analyzed by subgroups of age, gender, ethnicity, race, duration of AD, baseline weight group, and overweight determined by baseline BMI. The demographics were comparable across the 3 treatment arms at baseline in the FAS.

Subgroup analyses of baseline characteristics were performed, including age, gender, ethnicity, race, duration of AD, age of onset of AD, family history of AD, baseline body weight, BMI, baseline IGA score, baseline EASI score, baseline peak NRS, baseline BSA involvement in AD, previous use of systemic immunosuppressants, previous use of ciclosporin, previous use of methotrexate, history of asthma, history of allergic rhinitis, and history of food allergies. The baseline characteristics were comparable across the 3 treatment arms in the FAS.

In general, the number of patients across the different race categories was too small for meaningful conclusions to be drawn, except for White patients.

In addition, the numbers of patients who had previously used systemic ciclosporin (n = 18 to 20 per treatment group) or methotrexate (n = 9 to 19 per treatment group) were too small for meaningful conclusions to be drawn. However, the pooled number of patients who had previously used any systemic immunosuppressive drug including ciclosporin or methotrexate (n = 40 to 53 per treatment group) was

sufficient to show that dupilumab consistently improved signs and symptoms of AD in this subgroup of patients. Key conclusions from the subgroup analyses of the primary and key secondary efficacy endpoints were as follows:

- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the proportion of patients who achieved IGA of 0 or 1 at week 16 across all subgroups assessed. No interactions (ie, $p<0.05$) were identified. This included consistent results for this endpoint across weight and BMI categories and irrespective of prior use of systemic immunosuppressants.

- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the proportion of patients who achieved EASI-75 at week 16 across all subgroups assessed, except for Q2W in patients with prior exposure to ciclosporin. No interactions (ie, $p<0.05$) were identified, except for the subgroup of patients who had prior exposure to ciclosporin, which could have been driven by the small number of patients who had prior exposure to ciclosporin. Of note, in patients who had previous exposure to one or more systemic non-steroidal immunosuppressants (cyclosporine, azathioprine, methotrexate, mycophenolate-mofetil) and/or systemic steroids, (n=40 to 53 per treatment group), both dupilumab dose regimens provided a better response than placebo for this endpoint.

- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the percent change in EASI score from baseline to week 16 across all subgroups. No interactions (ie, $p<0.05$) were identified, except for the subgroups of patients based on duration of AD and prior exposure to ciclosporin. The interaction for the subgroup based on prior exposure to ciclosporin could have been driven by the small number of patients who had prior exposure to ciclosporin. Of note, in patients who had previous exposure to one or more systemic non-steroidal immunosuppressants (cyclosporine, azathioprine, methotrexate, mycophenolate-mofetil) and/or systemic steroids, (n=40 to 53 per treatment group), both dupilumab dose regimens provided a better response than placebo for this endpoint.

- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the percent change in weekly average of peak daily pruritus NRS score from baseline to week 16 across all subgroups assessed and no interactions (ie, $p<0.05$) were identified.
- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the proportion of patients who achieved improvement (reduction of ≥ 3 points) of weekly average of peak daily pruritus NRS from baseline to week 16 across all subgroups, except Q4W in the patients race category of 'other'. No interactions (ie, $p<0.05$) were identified. This included consistent results for this endpoint across weight and BMI categories and irrespective of prior use of systemic immunosuppressants.
- Dupilumab (Q2W and Q4W) demonstrated a consistent effect on the proportion of patients who achieved improvement (reduction of ≥ 4 points) of weekly average of peak daily pruritus NRS from baseline to week 16 across all subgroups, except Q4W in African American patients. No interactions (ie, $p<0.05$) were identified. This included consistent results for this endpoint across weight and BMI categories and irrespective of prior use of systemic immunosuppressants.

Table 25: Summary of Key Efficacy Results for R668-AD-1526 – FAS

Endpoint	Placebo	Dupilumab	
		200 mg or 300 mg Q2W	300 mg Q4W
N	85	82	84
Primary/Co-primary Endpoint(s)			
Proportion of Patients with IGA 0 or 1 at week 16, n %	2 (2.4%)	20 (24.4%)	15 (17.9%)
Proportion of Patients with EASI-75 at week 16, n %	7 (8.2%)	34 (41.5%)	32 (38.1%)
Key Secondary Endpoints			
LS Mean Percent Change in EASI Score from Baseline to week 16, % (SE)	-23.6% (5.49)	-65.9% (3.99)	-64.8% (4.51)
LS Mean Percent Change in Average Peak Daily Pruritus NRS, % (SE)	-19.0% (4.09)	-47.9 (3.43)	-45.5 (3.54)
Proportion of Patients with Improvement (Reduction of ≥3 Points) of Weekly Average of Peak Daily Pruritus NRS from Baseline to Week 16, n/N1[a] (%)	8/85 (9.4)	40/82 (48.8)	32/83 (38.6)
Proportion of Patients with Improvement (Reduction ≥4 Points) of Weekly Average of Peak Daily Pruritus NRS from Baseline to Week 16, n/N1[b] (%)	4/84 (4.8)	30/82 (36.6)	22/83 (26.5)

All p-values were <0.0001, except for the proportion of patients with IGA 0 or 1 at week 16 for the 300 mg Q4W group (p=0.0007) and the proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus from baseline to week 16 (p=0.0001).
a N1 stands for the number of patients with baseline NRS score ≥3
b N1 stands for the number of patients with baseline NRS score ≥4
Categorical endpoints: P-values were derived by Cochran-Mantel-Haenszel test stratified by baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]. Patients with missing values at week 16 were counted as non-responders.
Continuous endpoints: P-values were 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 (baseline disease severity [IGA=3 vs IGA=4] and baseline weight group [<60 kg vs ≥60 kg]) as fixed factors. Missing values were imputed by the multiple imputation method.
Abbreviations: EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; FAS, full analysis set; IGA, Investigator's Global Assessment; LS, least square; NRS, numerical rating scale; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

Summary of main study

The following table 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).

- **Summary of Efficacy for trial R668-AD-1526**

Title: A Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of Dupilumab Monotherapy in Patients ≥12 to <18 Years of Age, with Moderate-to-Severe Atopic Dermatitis		
Study identifier	R668-AD-1526	
Design	randomized, double-blind, placebo-controlled, parallel-group design	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	16 weeks (21-03-2017 – 05-04-2018) 5 weeks Not applicable

Hypothesis	Superiority		
Treatments groups	Dupilumab 200 mg or 300 mg Q2W		Dupilumab 200 mg Q2W for patients <60 kg or 300 mg Q2W for patients ≥60 kg plus 400 mg or 600 mg on day 1
	Dupilumab 300 mg Q4W irrespective of weight		Dupilumab 300 mg Q4W plus 600 mg on day 1 N=84
	Matching Placebo		Placebo Q2W plus doubling the dose of placebo on day 1
Endpoints and definitions	Co-Primary endpoint	IGA 0 or 1 at week 16	Proportion of patients with IGA 0 or 1 (on a 5 point scale) at week 16
		Easi-75 at week 16	Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16
	Key Secondary endpoints	Change in EASI score to week 16	Percent change in EASI score from baseline to week 16
		Change pruritus NRS to week 16	Percent change from baseline to week 16 in weekly average of daily peak Pruritus numerical rating scale (NRS)
		Pruritus NRS reduction ≥3 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline at week 16
		Pruritus NRS reduction ≥4 at week 16	Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline at week 16
		Proportion pts with EASI-50	Proportion of patients with EASI-50 at week 16
		Proportion pts with EASI-90	Proportion of patients with EASI-90 at week 16
Database lock	5 April 2018		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT population was used for primary and secondary analyses reported below			
Descriptive statistics and estimate variability	Treatment group	Dupilumab 200 mg or 300 mg Q2W	Dupilumab 300 mg Q4W	Placebo
	Number of subject	82	83	85
	IGA 0 or 1 at week 16 (n(%))	20 (24.4)	15 (17.9)	2(2.4)
	95% CI (%)	(15.59, 35.14)	(10.35, 27.85)	(0.30, 8.31)
	Easi-75 at week 16 (n(%))	34(41.5)	32(38.1)	7(8.2)
	95% CI (%)	(30.72, 52.92)	(27.65, 49.42)	(3.35, 16.19)

Effect estimate per comparison	Co-primary endpoint IGA 0 or 1 at week 16	Comparison groups	Dupilumab 200 mg or 300 mg Q2W vs.	Dupilumab 300 mg Q4W vs. Placebo
		Difference in %	22.0	15.5
		P-value	<0.0001	0.0007

	Co-Primary endpoint Easi-75 at week 16	Difference in %	33.2	29.9
		P-value	<0.0001	<0.0001
Notes				
Analysis description	**Secondary analysis**			
Descriptive statistics and estimate variability	Treatment group	Dupilumab 200 mg or 300 mg Q2W	Dupilumab 300 mg Q4W	Placebo
	Number of subject	82	84	85
	Change in EASI score to week 16 (LS Mean %Change (SE))	-65.9 (3.99)	-64.8 (4.51)	-23.6 (5.49)
	95% CI (%)	(-73.72, -58.08)	(-73.64, -55.96)	(-34.36,-12.84)
	Change pruritus NRS to week 16 (LS Mean %Change	-47.9 (3.43)	-45.5 (3.54)	-19.0 (4.09)
	95% CI (%)	(-54.62, -41.18)	(-52.44, -38.56)	(-27.02, -10.98)
	Pruritus NRS reduction ≥3 at week 16 (n/N1(%))	40/82 (48.8%)	32/83 (38.6%)	8/85 (9.4%)
	95% CI (%)	(37.60, 60.09)	(28.11, 49.93)	(4.14, 17.69)
	Pruritus NRS reduction ≥4 at week 16 (n/N1(%))	30/82 (36.6%)	22/83 (26.5%)	4/84 (4.8%)
	95% CI (%)	(26.23, 47.97)	(17.41, 37.33)	(1.35, 11.74)
	Proportion pts with EASI-50	50 (61.0%)	46 (54.8%)	11 (12.9%)
	95% CI (%)	(49.57, 71.56)	(43.52, 65.66)	(6.64, 21.98)
	Proportion pts with EASI-90	19 (23.2%)	16 (19.0%)	2 (2.4%)
	95% CI (%)	(14.56, 33.80)	(11.30, 29.08)	(0.29, 8.24)
Effect estimate per comparison	Secondary endpoint Change in EASI score to week 16	Comparison groups	Dupilumab 200 mg or 300 mg Q2W	Dupilumab 300 mg Q4W
		Least means square (SE)	-42.3	-41.2
		P-value	<0.0001	<0.0001
	Secondary endpoint Change pruritus	Least means square (SE)	-29.0	-26.5
		P-value	<0.0001	<0.0001
	Secondary endpoint Pruritus NRS reduction ≥3 at	Difference in %	39.4	29.1
		P-value	<0.0001	<0.0001
	Secondary endpoint Pruritus NRS	Difference in %	31.8	21.7
		P-value	<0.0001	0.0001

	reduction ≥4 at week 16			
	Proportion pts EASI-50	Difference in %	48.0	41.8
		P-value	<0.0001	<0.0001
	Proportion pts		20.8	16.7
			<0.0001	0.0004
Notes				

Supportive studies

R668-AD-1607 – Phase 1b, 12-Week Treatment, Open-Label, Autoinjector Study

Study Design

Study R668-AD-1607 was a phase 1b, multicenter, randomized, open-label, two-part study designed to support the registration of dupilumab AI devices in adults and adolescents. The patient population consisted of patients ≥12 years with moderate-to-severe AD, whose disease was not adequately controlled with topical AD medication (TCS with/without TCIs) or for whom topical AD therapies were otherwise inadvisable (eg, because of side effects or safety risks). Approximately 168 patients were planned to be enrolled in the study.

The study consisted of a screening period (4 weeks), treatment period (12 weeks), and post-treatment follow-up period (12 weeks). In Part A, patients with moderate-to-severe AD were randomized to receive dupilumab 200 mg via AI device or dupilumab 200 mg via PFS, after a loading dose of 400 mg on day 1. In Part B, patients with moderate-to-severe AD were randomized to receive dupilumab 300 mg via AI device or dupilumab 300 mg via PFS, after a loading dose of 600 mg on day 1. Adolescent patients (≥12 to <18 years of age) who completed this study were offered the opportunity to enroll in the pediatric OLE study.

Since the dupilumab AI devices had not been tested in any clinical settings that would replicate their actual use (ie, actual administration of the product repeatedly using the to-be-marketed AI presentation), an actual-use study was conducted to support their registration.

Study objective

The primary objective of the study was to collect 12 weeks of actual-use data assessing technical performance and user interactions of the dupilumab AI device when used by patients (or caregivers for injections in upper arms) with AD over a 12-week treatment period. The efficacy of dupilumab administered Q2W SC using AI device and PFS in patients with AD was assessed as a secondary objective.

Concomitant treatments

All patients used a standardized regimen of TCS using a treatment algorithm specified in the protocol. If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD could have been provided to study patients at the discretion of the investigator. This included topical therapies (eg, high-potency TCS) or systemic medications like corticosteroids and non-steroidal immunosuppressive drugs (eg, ciclsporin, MTX, mycophenolate-mofetil, or azathioprine).

Efficacy outcomes/endpoints

Efficacy assessments performed were EASI, IGA of AD severity, pruritus NRS, and BSA involvement with AD. In this submission, the results for Part A of the study, which included data on the 200 mg dupilumab dose in the 1 mL AI up to the cut-off date of 28 Sep 2017, are presented. All patients in Part A had completed the end-of-treatment visit at the time of the data cut-off date (28 Sep 2017) and data are provided in the Part A CSR included in this dossier. All patients in Part B (300 mg; 2 mL AI) of the study had completed the end-of-treatment visit at the time of the data cut-off date for this submission (21 Apr 2018); however, the

data analysis was not complete and, thus, complete results are not presented. All adolescent and adult patients from Part A were included in the summary of results submitted in this application.

Results

Patient Disposition/ Demographics,
A total of 85 patients, including 18 adolescents (≥12 to <18 years of age), were enrolled and randomized (42 in the AI group, and 43 in the PFS group) in Part A of the study. A total of 78/85 (91.8%) completed treatment through day 99 in Part A, and 7 (8.2%) withdrew from treatment; the primary reason of which was AE (3 [3.5%] patients). Out of a total of 18 adolescent patients enrolled in the study, 7 patients had entered the pediatric OLE study, R668-AD-1434, by the time of the data cut-off date (28 Sep 2017). At the time of the data cut-off date for R668-AD-1434 (21 Apr 2018), 11 out of the 18 patients had entered the OLE study.

Baseline Disease Characteristics
The majority of patients were white (64.3% in the AI group, 76.7% in PFS group); 50.0% were males in the AI group, 58.1% were male in the PFS group; the mean (SD) age was 38.9 (19.4) years in the AI group, 33.3 (16.5) years in the PFS group; the mean (SD) weight was 77.6 (20.3) kg with a weight range of 43.5 to 122.0 kg in the AI group, 80.2 (26.1) kg with a weight range of 31.7 to 148.7 kg in the PFS group; and the mean (SD) BMI was 27.0 (5.5) kg/m2 in the AI group, 27.9 (8.4) kg/m2 in the PFS group.

Overall, baseline disease characteristics were similar between the AI and PFS groups and consistent with moderate-to-severe disease. A significant proportion of patients had disease onset prior to 5 years of age (38.1% in the AI group, 48.8% in the PFS group); the mean (SD) duration of AD was 23.3 (18.9) years in the AI group, 20.4 (12.4) years in the PFS group; the mean (SD) EASI score was 31.1 (13.1) in the AI group, 31.0 (12.6) in the PFS group; 50.0% of patients had IGA=3 (moderate disease) and 50.0% had IGA=4 (severe disease) in the AI group, 51.2% of patients had IGA=3 (moderate disease) and 48.8% had IGA=4 (severe disease) in the PFS group; the mean (SD) pruritus NRS score was 7.5 (1.6) in the AI group, 7.0 (1.8) in the PFS group; and the mean (SD) BSA involvement was 47.2 (24.8) in the AI group, 47.8 (20.7) in the PFS group.

Primary and Secondary Endpoints

The primary endpoint in the study was the number and type of validated AI device-associated product technical failures (PTF) during the treatment period divided by total number of actual injections. The total number of actual AI injections included the injections actually taken and the attempted injections which failed to be completed due to possible device malfunction, and reported as a product technical complaint (PTC). The secondary endpoints included: Number and percentage of patients with an AI device-associated PTF; number and type of AI device-associated PTCs divided by total number of actual injections; number and percentage of patients with an AI device-associated PTC.

There were no validated PTFs reported among 322 injections with the 200 mg AI in 42 AD patients, and 333 injections with the 200 mg PFS in 43 AD patients over 12 weeks.
There were 6 PTCs for the 200 mg AI device which consisted primarily of failed drug deliveries that resulted from user error, and which could be perceived as the patient not receiving the full dose (e.g., releasing the AI too early, not waiting for the second click of the AI, not feeling the injection, lifting the AI up too soon, and fluid oozing out when the cap was removed).
There was 1 PTC for the 200 mg PFS device which was a complaint of the needle bending during injection.

Efficacy Results
The results from the efficacy parameters for all ages in the study are summarized in Table 6. All efficacy and device-related endpoints were evaluated on the modified intent-to treat (mITT) analysis set. The mITT population included all randomized patients who received at least 1 injection of study drug.

Both dupilumab 200 mg devices demonstrated efficacy across multiple clinical outcomes, reflecting improvements in objective signs of AD and pruritus. Efficacy endpoints (percent change from baseline in weekly average of peak daily pruritus NRS and EASI scores [continuous variables] and proportion of patients with reduction of weekly average of peak daily pruritus NRS ≥3 from baseline) between the AI and PFS treatment groups were comparable with overlapping95% CIs around the point estimates.
Overall, the efficacy results with both devices were consistent with the magnitude of efficacy seen in other AD studies with dupilumab.

Table 26: Summary of Key Efficacy Parameters for R668-AD-1607 Part A– mITT Population (Adult and Adolescent Patients)

	Dupilumab 200 mg Q2W AI (N=42)			Dupilumab 200 mg Q2W PFS (N=43)		
Time Point	**Week 2**	**Week 8**	**Week 12**	**Week 2**	**Week 8**	**Week 12**
Mean percent change in EASI score from baseline (SD)	-38.7 (32.1)	-64.3 (37.3)	-73.9 (35.8)	-44.6 (32.0)	-73.6 (21.7)	-81.1 (20.2)
Proportion of patients achieving EASI-75, n (%)	8 (19.0)	19 (45.2)	24 (57.1)	9 (20.9)	24 (55.8)	29 (67.4)
Proportion of patients achieving IGA 0 or 1, n (%)	1 (2.4)	12 (28.6)	16 (38.1)	5 (11.6)	14 (32.6)	22 (51.2)
Mean percent change in weekly average of peak daily pruritus NRS score from baseline at each visit (SD)	-28.2 (24.4)	-56.3 (33.8)	-62.7 (29.8)	-27.7 (20.0)	-55.6 (26.6)	-58.9 (27.7)
Mean absolute change from baseline in percent BSA involvement with AD (SD)	-10.1 (16.5)	-23.1 (20.9)	-28.8 (21.6)	-14.2 (16.4)	-27.5 (22.4)	-35.7 (18.0)

Note: Patients with a missing value at a visit were considered as non-responders for categorical endpoints. No missing values were imputed for continuous endpoints.
Abbreviations: AD, atopic dermatitis; AI, autoinjector; BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; IGA, Investigator's Global Assessment; mITT, modified intent-to-treat population; NRS, Numerical Rating Scale; PFS, prefilled syringe; Q2W, every 2 weeks; SD, standard deviation.

Table 27: Summary of Efficacy Parameters for R668-AD-1607 Part A – mITT Population (Adolescent Patients Only, Post-Hoc Analysis)

	Dupilumab 200 mg Q2W (AI and PFS combined) (N=18)		
Time Point	**Week 2**	**Week 8**	**Week 12**
Mean percent change in EASI score from baseline (SD)	-31.1 (36.3)	-62.1 (46.3)	-73.7 (46.7)
Proportion of patients achieving EASI-75, n (%)	3 (16.7)	11 (61.1)	12 (66.7)
Proportion of patients achieving IGA 0 or 1, n (%)	0	6 (33.3)	8 (44.4)
Mean percent change in weekly average of peak daily pruritus NRS score from baseline at each visit (SD)	-24.3 (19.3)	-49.8 (34.2)	-56.1 (30.6)
Mean absolute change from baseline in percent BSA	-7.1 (15.7)	-28.4 (27.1)	-37.1 (26.0)

	Dupilumab 200 mg Q2W (AI and PFS combined) (N=18)
involvement with AD (SD)	

Abbreviations: AD, atopic dermatitis; AI, autoinjector; BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-75, 75% reduction in EASI; IGA, Investigator's Global Assessment; mITT, modified intent-to-treat population; NRS, Numerical Rating Scale; PFS, prefilled syringe; Q2W, every 2 weeks; SD, standard deviation.

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

Study Design

Study R668-AD-1434 was a phase 3, OLE study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in pediatric patients with AD who had previously completed a clinical study with dupilumab in patients with AD. The patient population consisted of pediatric patients ≥6 months to <18 years of age with AD who participated in a prior clinical study of dupilumab in AD (including R668-AD-1412, R688-AD-1607, and R668-AD-1526).

The first-step CSR focuses on data from patients aged ≥12 to <18 years only, in order to support the application for dupilumab in adolescents with AD.

Methods/Study objectives

The primary objective of the study was to assess the long-term safety of dupilumab in pediatric patients with AD. Long-term efficacy was evaluated as a secondary objective. The study consisted of a screening period (day -28 to day -1), a treatment period up to the time of regional regulatory approval, and a 12-week follow-up period.

Under the original protocol (published on 04 May 2015), the dose regimen for patients ≥12 years to <18 years old was 2 mg/kg QW or 4 mg/kg QW. Under protocol amendment 1 (published on 27 Mar 2017), the dose regimen for patients ≥12 years to <18 years old was changed from weekly weight-based dosing (2 mg/kg or 4 mg/kg) to a fixed dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at week 16 as follows:

- Patients weighing ≥60 kg: 300 mg Q2W
- Patients weighing <60 kg: 200 mg Q2W

Inadequate clinical response was defined as failure to achieve an IGA score of 0 or 1 (disease severity of "almost clear", or "clear") for at least 16 weeks from the date of initiation of treatment with the 300 mg Q4W regimen. Patients were up-titrated to the Q2W earlier than 16 weeks when the Q2W regimen was administered as rescue treatment, or later than 16 weeks (as long as they had received at least 16 weeks of treatment with Q4W regimen).

Concomitant treatments

The use of topical medication for AD (including TCS and TCIs) was permitted during the study. It was recommended that investigators should select the potency based on the age of the patient, severity of disease and affected region, and that use be consistent with local guidelines.
The use of TCIs was reserved for areas of the body that were more prone to side effects from TCS use (eg, face, intertriginous, and genital areas). If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD could be provided to study patients at the discretion of the investigator. This included topical therapies (eg, high-potency TCS) or systemic medications like corticosteroids and non-steroidal immunosuppressive drugs (eg, ciclosporin, MTX, mycophenolate mofetil, or azathioprine).

Outcomes/endpoints

Efficacy assessments included EASI, IGA of AD severity, pruritus NRS, SCORAD, BSA involvement with AD, POEM, CDLQI, assessment of AD flares, and maintenance of treatment effect. Pruritus NRS and POEM assessments were removed from the study in protocol amendment 1. Therefore, pruritus NRS and POEM data were summarized only for patients who consented to the original protocol (n=36).

The efficacy results presented in the first-step CSR included in support of this subsequent marketing application focused on patients who rolled over from R668-AD-1412 and received weight-based dosing (2 mg/kg QW or 4 mg/kg QW) under the original protocol (n=36), for the duration of the study during which they received weight-based dosing (note: from amendment 1 onwards, these patients were switched to a fixed dose [300 mg Q4W followed by up-titration in case of inadequate response][]; the efficacy analysis does not include the period when these patients received the fixed dose). The reasons for this approach are as follows:

1. The key efficacy objective of this OLE study was to evaluate the long-term efficacy of dupilumab. At the time of the data cut-off date for the first-step analysis of (21 Apr 2018) all the patients that had completed at least 52 weeks were enrolled from the R668-AD-1412 study.
2. Patients who rolled over from R668-AD-1412 received weight-based dosing (2 mg/kg QW or 4 mg/kg QW) for a significant duration (median duration of treatment exposure was around 89 weeks), before being switched to a fixed dose (300 mg Q4W) under amendment 1. In contrast, patients who rolled over from R668-AD-1526 and R668-AD-1607 received the fixed dose from the time they enrolled into the study.

3. Focusing on patients with weight-based dosing allowed evaluation of efficacy results in the OLE study from a dose regimen that provided exposure that was equivalent to the dose planned to be proposed for approval in adolescent patients (200/300 mg Q2W).

Patient Disposition/ Demographics/ Baseline Disease Characteristics

A total of 275 adolescent patients were enrolled in this study: 36 from study R668-AD-1412, 201 from study R668-AD-1526, and 38 from study R668-AD-1607 (see Table 1).
Overall, 4 patients discontinued treatment for the following reasons: withdrawal by patient (2/4), lost to follow-up (1/4), and physician decision (1/4)

Of the 275 patients enrolled in this study, the majority of patients were white (69.5%). Male and female patients represented 58.9% and 41.1% of the population, respectively; the mean (SD) age was 14.6 (1.7) years, mean (SD) weight was 65.0 (20.6) kg with a weight range from 32.2 to 149.0 kg, and a mean (SD) BMI of 24.2 (6.1) kg/m2.
A number of patients had disease onset prior to 1 year of age (18.9%). The mean (SD) duration of AD was 12.5 (3.2) years. At the baseline of the OLE study, the mean (SD) EASI score was 19.9 (15.4); overall, 49.5% of patients had IGA=3 (moderate disease) and 23.3% had IGA=4 (severe disease); and the mean (SD) BSA involvement was 34.2% (25.3).

In the subgroup of 36 patients who rolled over from R668-AD-1412 and received weight-based dosing under the original protocol, the majority of patients were white (88.9%). Male and female patients represented 47.2% and 52.8% of the population, respectively; the mean (SD) age was 14.5 (1.9) years, mean (SD) weight was 55.1 (12.0) kg with a weight range from 35.0 to 81.7 kg, and a mean (SD) BMI of 21.0 (3.7) kg/m2. The number of patients who had disease onset prior to 1 year of age was 44.4%.
The mean (SD) duration of AD was 12.6 (2.9) years. At the baseline of the OLE study, the mean (SD) EASI score was 23.4 (17.6); overall, 61.1% of patients had IGA=3 (moderate disease) and 25.0% had IGA=4 (severe disease); the mean (SD) pruritus NRS score was 4.9 (2.8) and the mean (SD) BSA involvement was 38.3% (26.0).

The mean (SD) duration of time that patients were off treatment before starting in the OLE study was 61.8 (50.08) days for the total patient population (n=275) and 136.8 (54.5) days for the subgroup of 36 patients who rolled over from R668-AD-1412 and received weight-based dosing.
If patients had a treatment gap of <6 weeks, they were expected to maintain concentrations of dupilumab in serum that were sufficient to maintain target saturation during the transition. If patients had a treatment gap >13 weeks, concentrations of dupilumab in serum were expected to be undetectable at time of enrollment into the OLE study.
If patients had a treatment gap between 6 and 13 weeks, the concentration of dupilumab in serum was expected to fall below the level of target saturation but still remain above the lower limit of quantitation. The majority of patients in the total study population (113), and all 36 patients in the subgroup of patients who

rolled over from R668-AD-1412 and received weight-based dosing, had a treatment gap of at least 6 weeks before entering into the OLE and this could be one of the factors explaining the relatively high disease severity at baseline of the OLE study.

Topical immunosuppressants were permitted concomitant medications during the study. A total of 176/275 (64.0%) of patients used TCS and 33/275 (12.0%) used TCI during the study.

Efficacy Results
Efficacy analyses were performed using the safety analysis set (SAF), which included all patients who received any study drug.

Efficacy Results in the Total Study Population (N=275)

At the time of the first-step analysis, of the 275 adolescent patients enrolled in the study, 142 patients had completed 16 weeks, 69 patients had completed 26 weeks, and 34 patients had completed at least 52 weeks of treatment period.

The efficacy data from the overall study population of 275 patients demonstrated a substantial clinical benefit of dupilumab to adolescent patients, as shown by improvements in the proportion of patients who achieved IGA 0 or 1, and the proportion of patients who achieved EASI-50, EASI-75 and EASI-90 relative to the parent study baseline (Table 28).

Table 28: Summary of Key Efficacy Results for R668-AD-1434 – SAF (Total Study Population, N=275)

	Total (N=275)				
	Baseline of Current Study	**Week 4**	**Week 16**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	23/275 (8.4%)	38/246 (15.4%)	45/143 (31.5%)	14/34 (41.2%)	14/32 (43.8%)
Proportion of patients achieving EASI-75 relative to baseline of previous study, n/N1 (%)	60/275 (21.8%)	110/245 (44.9%)	87/143 (60.8%)	28/34 (82.4%)	29/32 (90.6%)
Proportion of patients achieving EASI-50 relative to baseline of previous study, n/N1 (%)	133/275 (48.4%)	171/245 (69.8%)	124/143 (86.7%)	32/34 (94.1%)	32/32 (100%)
Proportion of patients achieving EASI-90 relative to baseline of previous study, n/N1 (%)	29/275 (10.5%)	49/245 (20.0%)	48/143 (33.6%)	18/34 (52.9%)	15/32 (46.9%)
Mean % reduction in EASI score from baseline of Previous study (SD)	-43.49 (38.012)	-63.35 (29.469)	-72.89 (28.783)	-84.49 (16.915)	-87.78 (11.161)
Median[1] % change from baseline of current study in EASI score (Q1-Q3)		-32.69 (-56.12, -4.34)	-58.24 (-84.54, -24.92)	-89.51 (-95.31, -70.83)	-85.87 (-93.59, -75.13)

[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 responders. N1 stands for the number of patients with observed data at the visit.

A later data cut-off (December 2018) set of data was provided as part of the response to Request for Supplementary Information. The data set included approximately 300 patients at baseline and 106 patients at week 52 and confirms the long term efficacy of dupiluab treatment.

Table 29 - Key efficacy parameters for all patients in the SAF based on updated OLE data (Dec 2018 cut-off)

	Baseline	**Week 4**	**Week 16**	**Week 52**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	27/299 (9.0%)	43/298 (14.4%)	77/295 (26.1%)	46/106 (43.4%)
Proportion of patients achieving EASI- 75 relative to baseline of previous study, n/N1 (%)	65/299 (21.7%)	128/297 (43.1%)	171/295 (58.0%)	84/104 (80.8%)
Proportion of patients achieving EASI- 50 relative to baseline of previous study, n/N1 (%)	144/299 (48.2%)	206/297 (69.4%)	251/295 (85.1%)	97/104 (93.3%)
Proportion of patients achieving EASI- 90 relative to baseline of previous study, n/N1 (%)	33/299 (11.0%)	60/297 (20.2%)	88/295 (29.8%)	58/104 (55.8%)
Mean % reduction in EASI score from baseline of Previous study (SD)	-54.0 (29.96)	-66.4 (28.71)	-73.1 (23.69)	-86.0 (19.72)

Efficacy Results in the Subgroup of Patients who Rolled Over from R668-AD-1412 and Received Weight-based Dosing Under the Original Protocol (N=36)

A total of 25/36 (69.4%) of patients used TCS and 10/36 (27.8%) used TCI during the study.
Key efficacy endpoint results for the study are summarized in Table 9. Dupilumab provided substantial and sustained clinical benefit to adolescent patients as measured by both investigator-assessed and patient-reported outcomes.
This was shown by the proportion of patients achieving IGA 0 or 1 (0/36 (0%) at baseline, 15/36 (41.7%) at week 16, 14/34 (41.2%) at week 52) and EASI-75 (2/36 (5.6%) at baseline, 25/36 (69.4%) at week 16 and 28/34 (82.4%) at week 52). The reduction in mean percentage EASI score from baseline of previous study was 28.6% at baseline of OLE, 81.9% at week 16 and 84.5% at week 52. The reduction in mean percentage pruritus NRS score from baseline of previous study was 21.7% at baseline of OLE, 63.9% at week 16 and 67.2% at week 52 (Table 30).

Table 30: Summary of Key Efficacy Results for R668-AD-1434 – SAF (Adolescents ≥12 to <18 years Receiving Weight-Based Dosing Under Original Protocol, N=36)

			Total (N=36)		
	Baseline of OLE	**Week 4**	**Week 16**	**Week 52**	**Week 104**
Proportion of patients achieving IGA 0 or 1, n/N1 (%)	0/36	8/36 (22.2%)	15/36 (41.7%)	14/34 (41.2%)	11/17 (64.7%)
Proportion of patients achieving EASI-75 relative to baseline of previous study, n/N1 (%)	2/36 (5.6%)	20/36 (55.6%)	25/36 (69.4%)	28/34 (82.4%)	15/17 (88.2%)
Proportion of patients achieving EASI-50 relative to baseline of previous study, n/N1 (%)	11/36 (30.6%)	26/36 (72.2%)	35/36 (97.2%)	32/34 (94.1%)	17/17 (100%)
Proportion of patients achieving EASI-90 relative to baseline of previous study, n/N1 (%)	2/36 (5.6%)	8/36 (22.2%)	16/36 (44.4%)	18/34 (52.9%)	8/17 (47.1%)
Mean % change in EASI score from baseline of Previous study (SD)	-28.62 (34.439)	-69.85 (23.483)	-81.87 (17.272)	-84.49 (16.915)	-87.34 (11.107)
Median[1] % change in EASI score from	NA	-54.50 (-85.59,	-82.38 (-94.81,	-89.51 (-95.31,	-85.71 (-93.75,

			Total (N=36)		
	Baseline of OLE	**Week 4**	**Week 16**	**Week 52**	**Week 104**
baseline of OLE (Q1-Q3)		-36.14)	-60.76)	-70.83)	-74.07)
Proportion of patients achieving pruritus NRS reduction ≥3 from baseline of Previous Study or achieving NRS of 0, n/N1 (%) (N=36)	14/36 (38.9%)	26/36 (72.2%)	26/34 (76.5%)	26/34 (76.5%)	6/8 (75.0%)
Proportion of patients achieving pruritus NRS reduction ≥4 from baseline of Previous Study or achieving NRS of 0, n/N1 (%) (N=36)	9/36 (25.0%)	20/36 (55.6%)	23/34 (67.6%)	24/34 (70.6%)	6/8 (75.0%)
Mean % change from baseline of previous study in pruritus NRS score (SD) (N=36)	-21.72 (58.115)	-49.94 (29.732)	-63.85 (22.794)	-67.16 (23.248)	-79.20 (13.173)

[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: the efficacy analysis does not include the period when these patients switched to the fixed dose of 300 mg Q4W under amendment 1.
2/36 patients discontinued from the study prior to week 52. By week 104, 17 patients had transitioned from weight based dosing to a fixed dose, after re-consenting to protocol amendment 1. Since this table only provided data for patients who received weight based dosing under the original protocol, these patients were excluded from the original analysis set.
Abbreviations: AD, atopic dermatitis; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-75, 75R reduction in EASI; IGA, Investigator's Global Assessment; NA: Not applicable; SAF, safety analysis set; SCORAD, SCORing Atopic Dermatitis.

Proportion of Patients with IGA 0 or 1 at Each Visit

At baseline of the OLE, none of the patients who rolled over from study R668-AD-1412 had an IGA score of 0 or 1. This is expected because these patients had a treatment interruption of at least 8 weeks between the last dose in the R668-AD-1412 and the baseline of the OLE. At week 16, a considerable proportion of patients (15/36 [41.7%]) had achieved IGA 0 or 1.

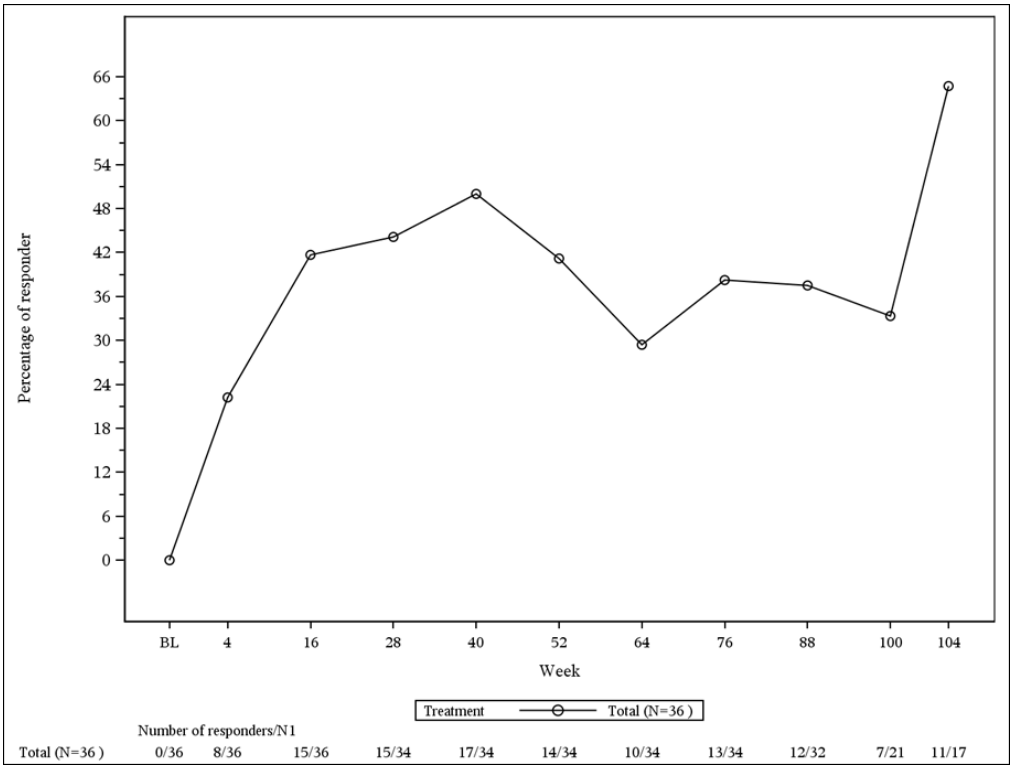
Response rates at later time points, though somewhat variable due to the small patient numbers analyzed, were comparable to those at week 16, suggesting sustained efficacy of dupilumab treatment. The variability in response rates between week 52 and week 76 also resulted from patients with remission 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 64.

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 after re consenting to

protocol amendment 1). (Note - when the term “fixed dosing” is used this refers to a dose regimen of 300 mg Q4W followed by up-titration to Q2W [200 mg or 300 mg] regimen in some patients)().

Proportion of Patients Achieving an IGA Score of 0 or 1 at Each Visit – Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)

Figure 8: Proportion of Patients Achieving an IGA Score of 0 or 1 at Each Visit – Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



Abbreviations: BL, baseline.
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.

As per study protocol, patients who achieved an IGA score of 0 or 1 for a 12-week period leading up to week 52 were discontinued from study drug. Once these patients were discontinued from study drug, disease activity was closely monitored, and dupilumab was re-initiated if these patients had a relapse of disease defined as IGA score ≥2. At the time of data cut-off date for this submission (21 Apr 2018), 14 patients who achieved an IGA score of 0 or 1 for a 12-week period after week 40 were discontinued from study drug. In 12 of the 14 patients, the disease returned and treatment had to be re-initiated, demonstrating the need for continuous treatment with dupilumab. The median time to re-initiation of study drug was 16 weeks.

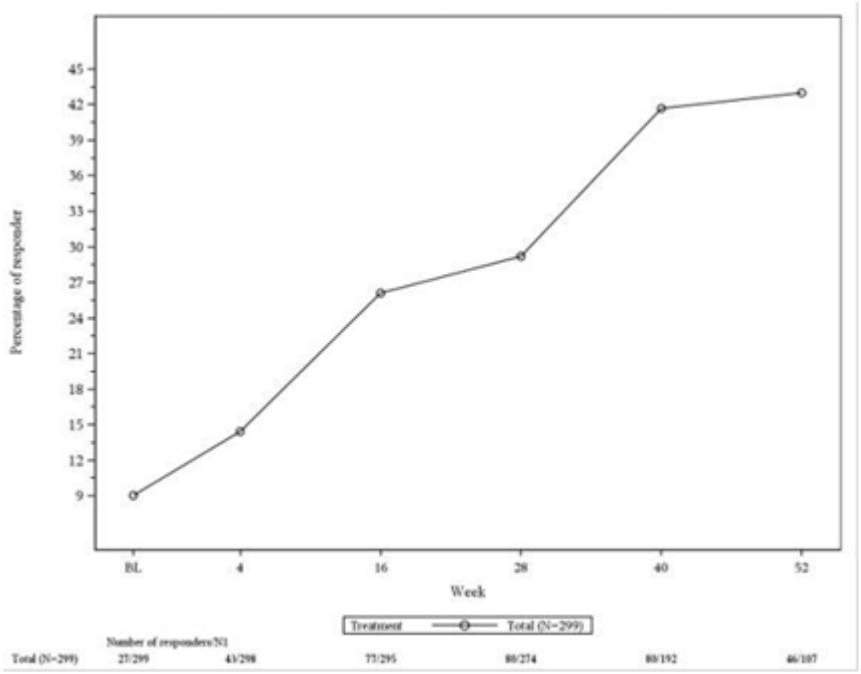
Table 31: Summary of Patients with IGA 0 or 1 for At Least 12 Weeks Leading Up to Week 52 - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)

	Total (N=275)
Number of Patients who completed Week 52	34
Number of Patients with IGA of 0 or 1 for at least 12 weeks leading up to week 52	14/34 (41.2%)
Number of Patients who re-initiated study drug	12/14 (85.7%)
Time to re-initiation of study drug (weeks) [1]	
n	11
Mean (SD)	24.36 (19.402)
Q1	12.00
Median	16.00
Q3	47.00
Min : Max	7.0 : 64.0

[1] One patient had re-initiation of study drug at unscheduled visit; hence time to re-initiation of study drug could not be determined.
Percentages were calculated based on number of patients who completed week 52.

As per updated OLE data (Data cut off Dec 2018) at baseline 27 out of 299 patients enrolled (9.0%) had an IGA score of 0 or 1. These patients came from the pivotal phase 3 study R668-AD-1526. At Week 16, a considerably higher proportion of patients (77/295 [26.1%]) had achieved IGA 0 or 1. There was a trend towards numerically higher response rates at Week 52 as compared to Week 16 with 46/107 (43.4%) patients achieving IGA 0/1.

Figure 9 Updated OLE data (Data cut off Dec 2018) - Proportion of patients achieving IGA score of 0 or 1 by visit adolescent ⩾12 to <18 years of age (Safety analysis set)



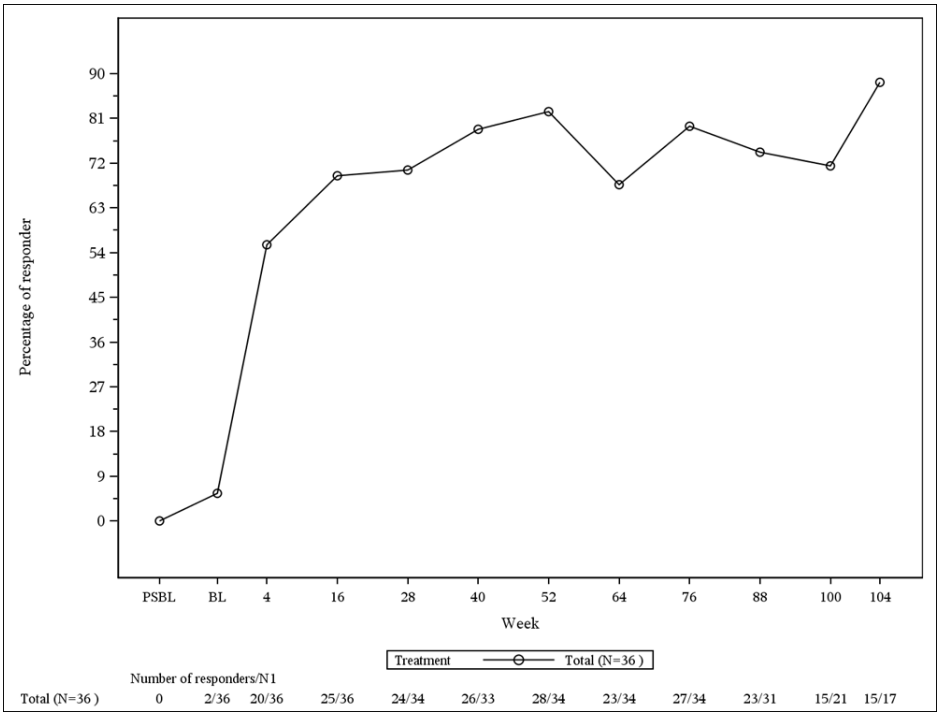
Proportion of Patients Achieving an EASI-75 Relative to Baseline of R668-AD- 1412
The proportion of patients with EASI-75 (defined as a ≥75% reduction in EASI score from baseline EASI score of study R668-AD-1412) at baseline of the OLE was 2/36 (5.6%)

At week 16, a considerable proportion of patients (25/36 [69.4%]) had achieved EASI-75. Response rates at later time points were comparable to that at week 16, suggesting sustained efficacy of dupilumab treatment.

The variability in response rates between week 52 and week 76 also 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 64.

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 after re consenting to protocol amendment 1).

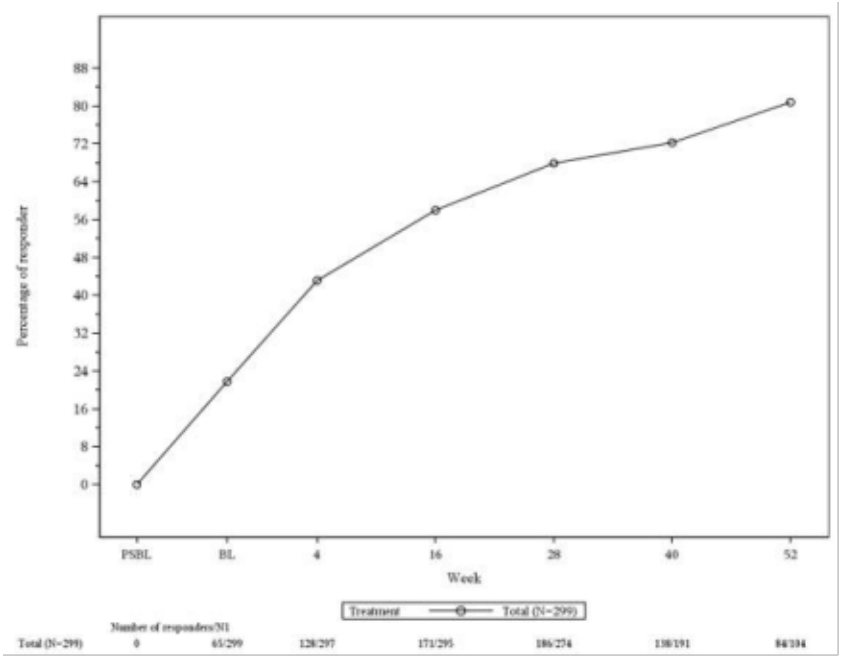
Figure 10: Proportion of Patients Achieving an EASI-75 Relative to Baseline of R668-AD-1412 at Each Visit - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



Abbreviations: BL, baseline; PSBL, parent study baseline
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.

As per updated OLE data (Data cut off Dec 2018) at baseline of the OLE, 65 out of 299 patients enrolled (21.7.0%) had achieved an EASI75 response from baseline of the previous study. At Week 16, a considerably higher proportion of patients (171/295 [58.0%]) had achieved EASI75. There was a trend towards numerically higher response rates at Week 52 as compared to Week 16 with 84/104 (80.8%) patients achieving EASI75.

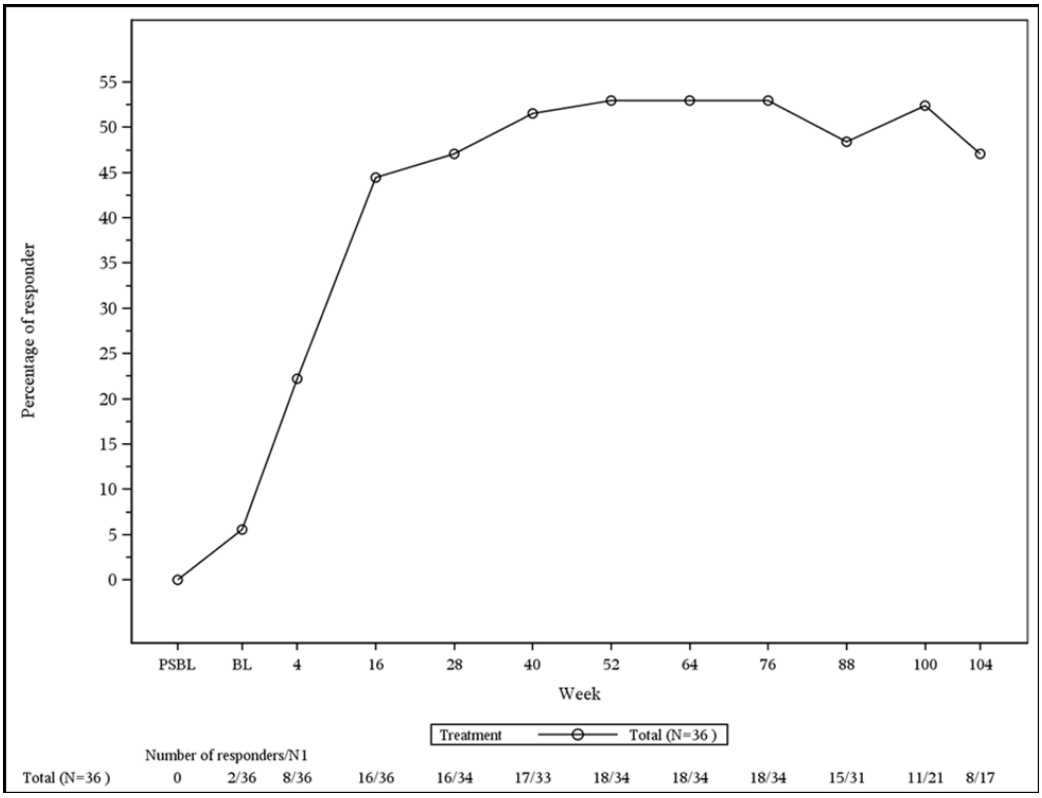
Figure 11: Updated OLE data (Data cut off Dec 2018) - Proportion of patients achieving an EASI-75 relative to Baseline of previous study by visit adolescent ≥12 to <18 years of age (Safety analysis set)



Proportion of Patients Achieving an EASI-90 Relative to Baseline of R668-AD-1412

At baseline of the OLE, 2/36 (5.6%) patients had achieved EASI-90 relative to baseline of R668-AD-1412. A considerable increase in response rate was seen during the treatment period of the OLE, and by week 16, 16/36 (44.4%) of patients had achieved EASI-90 response. Further increases in the proportion of patients who achieved EASI-90 were observed between week 16 and week 52 (at week 52, 18/34 [52.9%] patients had achieved EASI-90). This response rate was sustained for the remainder of the analysis period.

Figure 12: Proportion of Patients Achieving EASI-90 Relative to Baseline of R668-AD-1412 at Each Visit - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



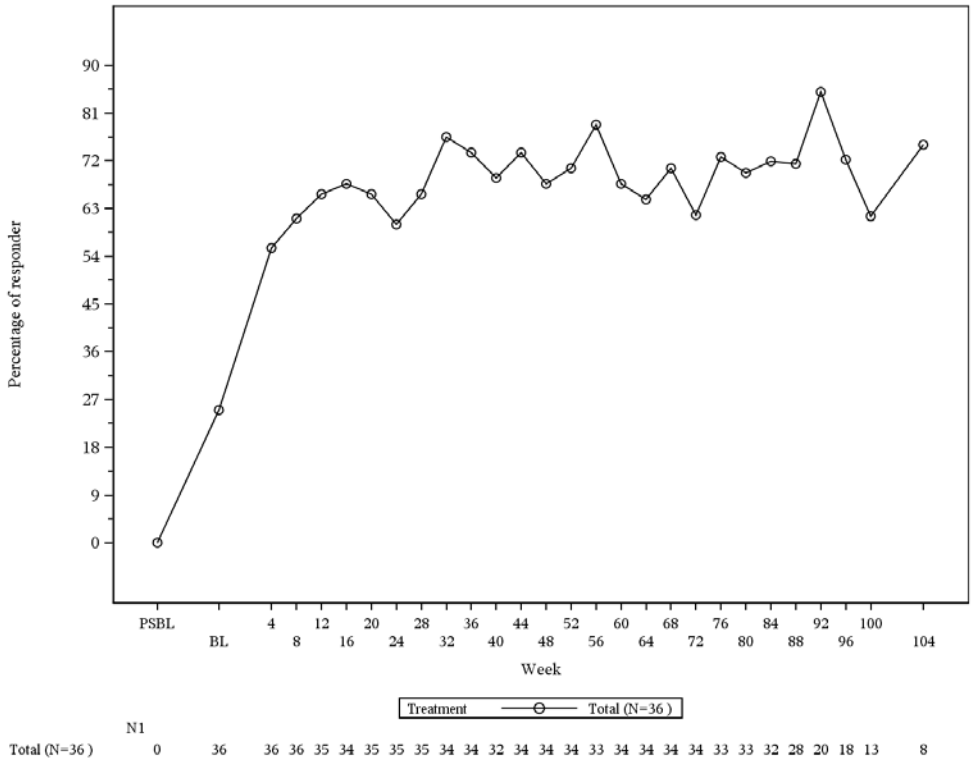
Abbreviations: BL, baseline; PSBL, parent study baseline.
Note: N1 stands for the number of patients with non-missing score at each visit.
Only data up to the first visit when patient received 300 mg Q4W were included for analysis.

Proportion of Patients Achieving a Reduction of ≥4 from Baseline of R668-AD-1412 in Pruritus Numerical Rating Scale or Achieving NRS Score of 0 at Each Visit.

At baseline of study R668-AD-1412, the mean peak Pruritus NRS score was 6.75 (±2.170) Points. A total of 9/36 (25.0%) patients had achieved reduction in Pruritus NRS ≥4 points or a score of 0 at baseline of the OLE. There was a further rapid reduction in Pruritus severity during the OLE (20/36 [55.6%] patients had reduction in Pruritus NRS ≥4 points from baseline of R668-AD-1412 or a score of 0 by week 4).

Additional increases in responder rates were seen by week 16 (23/34 [67.6%]), which was largely maintained during the later time points of analysis. Data after week 88 should be interpreted with caution as the number of patients included in the analysis progressively reduced after this time point (as patients transitioned to fixed dosing after re consenting to protocol amendment 1).

Figure 13: Proportion 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 - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



Abbreviations: BL, baseline; PSBL, parent study baseline.
Note: N1 stands for the number of patients with non-missing score at each visit

Proportion of Patients Achieving a Reduction of ≥4 from Baseline of the OLE in Pruritus Numerical Rating Scale Score or Achieving an NRS Score of 0 at Each Visit

At baseline of the OLE, the mean peak Pruritus NRS was 4.92 (±2.802) points the proportion of patients who achieved a reduction in peak Pruritus NRS ≥4 points from baseline of the OLE or achieved an NRS score of 0 increased to 9/36 (25%) patients by week 4 and 13/34 (38.2%) patients by week 16. This level of response was maintained for the remainder of the analysis time period.

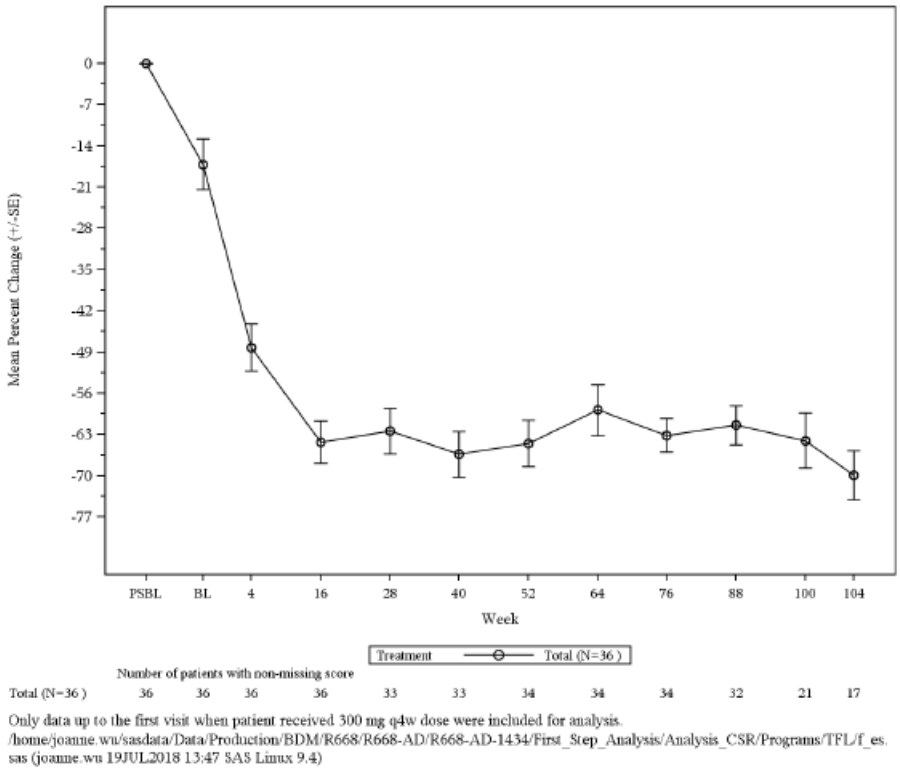
Change from Baseline of the OLE in BSA at Each Visit

The mean (SD) BSA involvement at baseline of the OLE was 38.3% (±25.96). Reductions in BSA involvement were observed at week 4 (mean change of -18.3% [± 18. 43]), at week 16 (mean change of -23.8% [±12.26]), and at week 52 (mean change of -31.2% [±23.77]). The level of reduction seen at week 52 was largely maintained throughout the remaining analysis time points.

Percent Change from Baseline of Previous Study in SCORAD at Each Visit

At baseline of study R668-AD-1412, the mean SCORAD score was 66.04 (±13.973). A reduction in mean value of 17.14% (±25.828) from baseline of study R668-AD-1412 had been achieved at baseline of the OLE. There was a further reduction in SCORAD score during the OLE (reduction in mean value of 48.20% [±23.706] and 64.32% [±21.448] at week 4 and week 16, respectively). The level of reduction seen at week 16 was largely maintained throughout the remaining analysis time points.

Figure 14: Mean Percent Change (±SE) in SCORAD Score from Baseline of R668-AD- 1412 by Visit - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



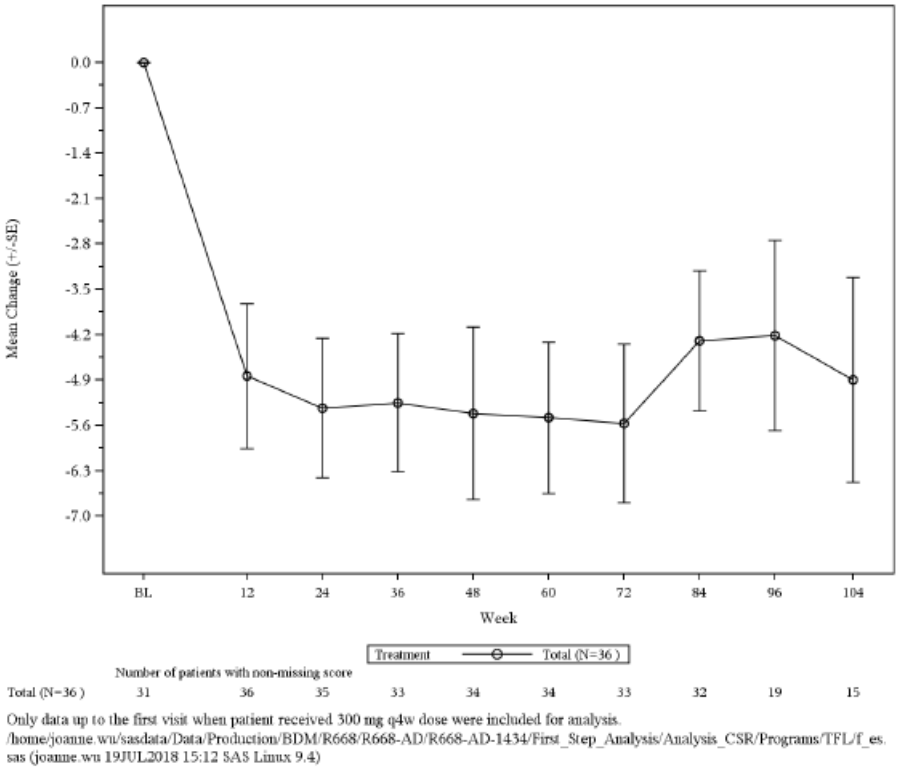
Percent Changes from Baseline of the OLE in SCORAD at Each Visit

At baseline of the OLE, the mean SCORAD was 54.62 (±20.524). The reduction in mean value from the baseline of the OLE in SCORAD was 38.8% (±21.976) at week 4, and 56.7% (±23.798) at week 16. The level of reduction seen at week 16 was largely maintained throughout the remaining analysis time points.

Change from Baseline of the OLE in CDLQI for Patients ≥12 to <18 Years of Age at Each Visit

At baseline of the OLE, the mean CDLQI was 9.1 (±6.85). The mean change in CDLQI from the baseline of the OLE was -4.8 (±6.23) at week 12, a level of reduction which was largely maintained throughout the remaining analysis time points.

Figure 15: Mean Absolute Change (±SE) in CDLQI from Baseline of the OLE by Visit - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)



Change in POEM from Baseline of OLE at Each Visit

At baseline of the OLE, the mean POEM score was 15.4 (±7.62). The mean change in POEM from the baseline of the OLE was -7.3 (±6.41) at week 12, a level of reduction which was largely maintained throughout the remaining analysis time points. Data after week 84 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 after re consenting to protocol amendment 1).

Summary of Sustained Remission Defined by IGA

At the time of data cut-off, 34 of the 36 patients who rolled over from study R668-AD-1412 completed week 52, and 14 of these 34 patients (41.2%) obtained sustained remission from AD.

Sustained remission was defined as maintenance of an IGA score of 0 or 1 for a 12-week period, after week 40. Once sustained remission was reached, the patients were discontinued from study drug, disease activity was closely monitored, and dupilumab was re-initiated if these patients had a relapse of disease defined as IGA score ≥2.

In 12 of the 14 patients who achieved sustained remission, the disease returned and treatment was re-initiated, demonstrating the need for continuous treatment with dupilumab. The median time to re-initiation is shown below. 16 weeks

Summary of Sustained Remission Defined by IGA 0 or 1 for ≥12 Weeks - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)

Table 21: Summary of Sustained Remission Defined by IGA 0 or 1 for ≥12 Weeks - Adolescent ≥12 to <18 Years of Age (SAF – Under Original Protocol)

	Total (N=36)
Number of Patients who completed week 52	34/36 (94.4%)
Number of Patients with Sustained Remission	13/34 (38.2%)
Number of Patient re-initiated study drug after sustained remission	11/13 (84.6%)
Time to re-initiation of study drug after sustained remission (weeks) [1]	
n	11
Mean (SD)	24.4 (19.402)
Q1	12.00
Median	16.00
Q3	47.00
Min : Max	7.0 : 64.0

Note: Patients who had sustained remission of the disease, as defined by maintenance of an Investigator's Global Assessment (IGA) score of 0 or 1 continuously for a 12-week period, after week 40 were discontinued from study drug (for example, a patient who has an IGA score of 0 or 1 through week 40 to week 52, inclusive, was discontinued from the study drug at week 52; similarly, a patient who has an IGA score of 0 or 1 through week 52 to week 64, inclusive, was discontinued from study drug at week 64, and so on)
[1] One patient had re-initiation of study drug at unscheduled visit; hence time to re-initiation of study drug could not be determined.
Only data up to the first visit when patient received 300 mg Q4W dose were included for analysis
Source: Post-text Tables 6.7.4.1/1a

Disease activity was monitored in the patients in whom study drug was re-initiated (n=12).
Efficacy data subsequent to study drug re-initiation was available for 10 out of these 12 patients at the date of the data cut-off for this first-step analysis CSR. Overall, 8 out of these 10 patients achieved an IGA score of 0 or 1 after re-initiation of study drug.

Summary of Patients with Up-Titration of Dupilumab

Per protocol, patients could be up-titrated from 300 mg Q4W to a 200/300 mg Q2W dose in case of inadequate clinical response. Inadequate clinical response was defined as failure to achieve an IGA score of 0 or 1 (disease severity of “almost clear” or “clear”) at or after 16 weeks from the date of initiation of treatment with 300 mg Q4W regimen. Patients could also be up-titrated earlier than 16 weeks also if investigator felt that the patient needed a rescue treatment due to high disease severity (IGA score of at least 3). Patients could be up-titrated as follows:
1. Patients weighing ≥60 kg: 300 mg Q2W
2. Patients weighing <60 kg: 200 mg Q2W

Of the 275 patients, 268 patients received at least 1 Q4W dose. The number of patients who had already been up-titrated by the time of this first-step analysis was 141/268 (52.6%). Importantly, 97/268 (36.2%) patients needed to be rescued with dupilumab Q2W regimen, as per judgement of the study investigator, prior to completion of 16 weeks of treatment with Q4W regimen as they experienced either intolerable symptoms or high disease severity This suggests that the study investigator considered the Q4W regimen was suboptimal for a substantial proportion of patients.

Discussion on clinical efficacy

Design and conduct of clinical studies

Study design/endpoints/study population of the pivotal study R668-AD-1526
The primary objective of the pivotal study R668-AD-1526 was to demonstrate the efficacy of dupilumab as a monotherapy after 16 weeks of treatment in patients ≥12 to <18 years of age with moderate-to-severe AD.
The co-primary endpoints were defined as proportions of patients with EASI-75 (≥75% improvement from baseline) at week 16 and proportion of patients with IGA 0 or 1 (on a 5-point scale) at week 16. EASI is deemed to provide a realistic assessment of clinical AD symptoms and as it indicates good overall evidence of reliability in rating AD subjects.
Key secondary endpoints were the proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16 (not in the EU, see co-primary endpoint), percent change in EASI score from baseline to week 16, percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS, proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline at week 16 and proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline at week 16.
The co-primary and key secondary endpoints, including standard efficacy variables like the EASI-75 and IGA 0 or 1 which represent a sufficient degree of improvement, are considered adequate and in line with the objectives of this study.

The eligibility criteria of the pivotal study R668-AD-1526 including the definition of inadequate response to topical treatments are endorsed.
240 patients assigned to three different dose groups (200/300 mg Q2W dependent of bodyweight or 300 mg Q4W or placebo Q2W) over a treatment period of 16 weeks were planned for the pivotal study including the opportunity to join a subsequent open-label extension study (OLE R-668-AD-1434). Concomitant therapy was only applicable as rescue therapy to avoid bias regarding the efficacy outcome. Handling of non-responders is endorsed. In general, a shorter monotherapy treatment and thus placebo period (i.e. reduction to 16 weeks treatment period as agreed in the above mentioned PIP modification) is considered acceptable and sufficient to establish the efficacy also from an ethical point of view.

Concerning the protocol amendments introduced changes were based on PIP modifications and approved by PDCO. The protocol amendments are considered to be without adverse influence to the efficacy results. Hence, the study design, the endpoints, the patient population and the treatment are considered to be adequately chosen to demonstrate effects of dupilumab treatment in the proposed indication as they are in line with PDCO's decisions.

An analysis of major protocol deviations and their impact on study participation and efficacy and safety results, respectively, was requested. As the sponsor states, the overall rate of protocol deviations in the study was comparable to that seen in adult phase 3 SOLO trials. This is reassuring as in pediatric trials, given the higher complexity of study procedures including gathering of informed consent/assent, there is a potential to have higher incidence of PDs. A sensitivity analysis was conducted to evaluate the effect of major PDs on the efficacy results on the co-primary endpoints. In this Per protocol analysis (PP), patients with major protocol deviations were excluded. Results from this analysis were consistent with the Intention to Treat (ITT) analysis in which all randomized patients were included in the CSR. This analysis is considered acceptable and the issue is resolved.

Efficacy data and additional analyses

Participant flow/Demographics
R668-AD-1526
The participant flow shows that nearly all randomized patients of the individual dose groups received their study treatment. 6.6% (11/166) of the patients treated with dupilumab did not complete the study

treatment, thereof showed 1 patient lack of efficacy in the 300 mg Q4W group, the remaining 6 patients with lack of efficacy were assigned to the placebo group. 80% of the patients of this pivotal study transitioned into the OLE study R668-AD-1434. All other aspects such as discontinuation rate, patient withdrawals etc. were balanced between the treatment groups.

The demographics were fairly balanced between the treatment groups with a preponderance of white (63%) and male study participants (59%). The majority of patients had a disease manifestation below the age of 5 years (85%) and the mean (SD) duration of AD was 12.2 years.
Baseline disease characteristics were relatively balanced, IGA scores of 3 (moderate disease) and 4 (severe disease) were 46% and 53.8%, respectively, and EASI 35.3-35-5. All other AD assessments like mean (SD) pruritus NRS score was 7.6 (1.66) and the mean (SD) BSA involvement was 56.5% (22.97), BSA etc. were well-balanced, too. Most patients had comorbid allergic conditions; these were evenly distributed across the different treatment groups. Overall, demographics and baseline disease characteristics were similar between the 3 treatment groups.

The mean injection compliance was high overall (>97.5% in each treatment group) and was similar across the 3 treatment groups.

Concomitant/Rescue medication
R668-AD-1526
A third of the patients had prior systemic corticosteroid use and 21% had received systemic immunosuppressant therapy which reflects the disease severity of the population (ciclosporin and methotrexate were received in 12.8% and 10.4%, respectively).
The highest need of rescue medication was recorded in the placebo group (59%), followed by the 300 mg Q4W group (32%) and then by the 200/300 mg Q2W group (21%). These results are comparable with the need of rescue medication during study R668-AD-1334 (SOLO 1, adult AD monotherapy study). Systemic corticosteroids were taken by 2 subjects (2.4%) of the 200/300 mg Q2W group compared to 5.9% of the placebo group and hence, are to be counted as non-responders from the time of rescue medication use. Systemic immunosuppressants were only administered in the placebo group (3.5%).
Approximately 15 % of the 200/300 mg dose group, which is the intended dose for the claimed indication, had used any rescue medication by treatment week 16. The company allowed for use of rescue medications during the study and prior to achievement of the primary endpoint, they were considered as non-responders for the analyses. Results of different sensitivity analyses showed that the methods of analyses including the methodology of data handling after rescue medication did not impact the results as both doses of dupilumab showed statistical significance ($p < 0.05$) over placebo. Results of sensitivity analyses of R668-AD-1434, -1412 and -1607 were consistent with that obtained by the primary analyses.

Outcome/ Endpoints
Co-primary endpoints
In the study R668-AD-1526 the proportion of patients in the FAS with IGA 0 or 1 at week 16 was significantly higher in the dupilumab 200/300 mg Q2W (24.4%) and dupilumab 300 mg Q4W groups (17.9%) than the placebo group (2.4%). The comparisons were statistically significant ($p<0.0001$ for each group).
Efficacy analyses regarding the co-primary endpoint revealed a significantly higher EASI-75 at week 16 in the dupilumab treatment groups (41.5% and 38.1%) compared with the placebo group (8.2%).
Sensitivity analyses using all observed values with patients with missing values counted as non-responders showed similar results.
Patients receiving the Q4W regimen initially showed a slightly higher response rate than patients assigned to the Q2W dose groups until week 9, however, the lines crossed around week 9 and the latter showed a higher treatment efficacy from week 9 until week 16. These efficacy results show a clinically meaningful improvement of AD symptoms in patients with moderate-to-severe disease conditions.

Key secondary endpoints
Percent change in EASI score from baseline to week 16

The LS mean difference in percent change from baseline for each of the dupilumab treatment groups compared to the placebo group was clinically meaningful and statistically significant and both dupilumab treatment groups were comparable with regard to the percent change in EASI score from baseline to week 16.

Percent Change in Weekly Average of Peak Daily Pruritus NRS Score from Baseline to Week 16

The percent change from baseline to week 16 in weekly average of peak daily pruritus NRS was greater in the dupilumab Q2W group (-47.9% [3.43%]) and dupilumab 300 mg Q4W group (-45.5% [3.54%]) than the placebo group (-19.0% [4.09%]) (Table 26). The comparisons for each dupilumab group versus the placebo group were statistically significant. Both treatment groups were comparable for the percent change from baseline in weekly average of peak pruritus NRS at week 16.

The Peak Pruritus NRS is considered a well-defined and reliable patient-reported outcome (PRO) measure for evaluating itch intensity of AD patients providing a significant informative value of treatment response. Similarly, the Proportion of Patients with Improvement (Reduction ≥3 Points) of Weekly Average of Peak Daily Pruritus NRS from Baseline to Week 16 was higher in the dupilumab Q2W group (48.8%) and dupilumab Q4W (38.6%) group than in the placebo group (9.4%) with statistical significance Patients showing an improvement of weekly average of daily peak Pruritus NRS ≥4 from baseline at week 16 . and the proportion of patients achieving a reduction of ≥4 points from baseline in weekly average of peak daily pruritus NRS score at week 16 prevailed again in the dupilumab Q2W (36.6%) and dupilumab Q4W (26.5%) groups compared to placebo group (4.8%). As to both secondary endpoints, the Q2W group was numerically superior to the dupilumab Q4W group. The proportion of patients achieving an EASI-50 was significantly higher in the dupilumab treatment groups than in the placebo group. Additionally, the other efficacy endpoints that were assessed support the favourable efficacy compared to placebo.

The results from the studies R668-AD-1526 show a significant higher and clinically meaningful improvement in severity of AD in the dupilumab 300 mg Q4W and 200/300 mg Q2W groups compared to placebo substantiated by achievement of the co-primary endpoints, whereby the Q2W regimen yields better results in the analysed treatment effects. Hence, the key secondary endpoints support the effects seen in the co-primary endpoints and show a significant reduction of disease burden.

As an active comparator was not used in the trial it is not known how the therapy would compare to Tacrolimus or other systemic therapies in a systemic treatment naïve population. Furthermore the longer term and maintenance of effect was not measured in this study as patients were enrolled into the open label study R668-AD-1434. It is also known that seasons may affect the AD flairs the applicant should clarify the season in which patients were enrolled and treated, this would not have been controlled for at the trial was not for 52 weeks.

Subgroup analyses

A variety of subgroup analyses was performed. The demographics and the baseline characteristics were comparable across the 3 treatment arms in the FAS. The number of patients across the different race categories was too small for meaningful conclusions to be drawn, the same applies to prior ciclosporin/MTX use.

Dupilumab (Q2W and Q4W) demonstrated a consistent effect on key primary and secondary endpoints across all subgroups with exception of the proportion of patients who achieved EASI-75 at week 16 as well as for Q2W in patients with prior exposure to ciclosporin; however, general use of systemic immunosuppressive medication during dupilumab therapy was minimal and dupilumab showed consistently improved signs and symptoms of AD in this subgroup.

Supportive studies

R668-AD-1412

Of the 40 included patients included in study R668-AD-1412 [phase 2a, multicenter, open-label, ascending-dose, sequential-cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of a single dose (2 mg/kg or 4 mg/kg) of dupilumab administered SC followed by repeat-doses of the same doses weekly for 4 weeks in pediatric patients with moderate-to-severe AD (for adolescents ≥12 to <18 years of age) or severe AD (for pediatric patients ≥6 to <12 years of age) that was not

adequately controlled with topical treatments)], the majority (95%) completed the treatment and most patients (97.5%) transitioned into the OLE study, thereof 10 % into the adult OLE study. The patients were assigned to one of 2 dose cohorts (2 mg/kg or 4 mg/kg). During Part A of the study, patients received a single SC dose, followed by an 8-week semi-dense PK sampling period. During Part B of the study, patients received 4 weekly SC doses, followed by an 8-week follow-up period. Demographics were similar across age groups and dose cohorts. Baseline AD characteristics differed between the 2 age groups, as expected. However, within each age group, baseline AD characteristics were similar across dose cohorts.

The efficacy data showed that Dupilumab administered as a single dose of either 2 mg/kg or 4 mg/kg induced significant and rapid reduction of disease activity in patients at week 2 (34% and 51% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses respectively). Repeated weekly doses of dupilumab led to a further improvement in disease severity in patients in both dose cohorts (67% and 70% reduction in EASI score from baseline for 2 mg/kg and 4 mg/kg doses respectively at week 12).

Improvement in the other efficacy endpoints such as percent change from baseline in SCORing Atopic Dermatitis (SCORAD) score, percent change from baseline in Pruritus Numerical Rating Scale (NRS) and percentage of patients with an IGA score of 0 or 1 and the change from baseline in % BSA affected by AD was were noted. The data showed that statistically significant responses were seen by week 8 and reached a maximum at week 12. Following withdrawal of treatment during the follow up period the effects persisted by were diminished from week 12 to week 20.
There were no systematic differences in the efficacy observed within the 2 age sub-groups that were studied in the adolescent population (≥12 to <15 and ≥15 to <18 years of age). This was expected as the exposure was normalized by the weight based dosing and there is no evidence in the literature to suggest that that disease pathophysiology is different between these subgroups.

However, there are limitations with the study as it was relatively small 40 adolescent patients and for only 12 weeks duration. More significantly, patients were allowed to use concomitant medications such as topical TCS or TCI or oral medications when needed, this would have confounded the results. As the trial was exploratory, low patient numbers and relatively short duration is not considered to further pursue comparative efficacy in patients who did not receive any rescue medication.

In Study R668-AD-1607, the potential effect of drug product presentation (PFP or PFS) on dupilumab PK was investigated. In this study, patients with moderate to severe AD received dupilumab 200 mg q2w via PFP device or PFS, with a loading dose of 400 mg on Day 1. The study was not formally powered to show PK comparability/bioequivalence between PFS and PFP. The primary endpoint in the study was the number and type of validated AI device-associated product technical failures (PTF) during the treatment period divided by total number of actual injections. The comparison of systemic dupilumab exposure between PFS and PFP was included as secondary objective in the study. R668-AD-1607 data has previously been submitted to support an extension of application in adult and adolescent asthma patients to include a new 200 mg strength (EMEA/H/C/004390/X/04/G). The bioequivalence of the PFP compared to the PFS was questioned and resolved with updated information.

OLE study R668-AD-1434 (An ongoing open label extension study to assess the long term safety and efficacy of Dupilumab in patients ≥ 6 months to ≤18 years with atopic dermatitis) recruited patients from studies R668-AD-1526, R668-AD-1607 and R668-AD-1412. Included patients were treated with 2 mg/kg QW or 4 mg/kg QW, the dose was subsequently amended to a fixed dose of 300 mg Q4W with the possibility of up-titration to 200/300 mg Q2W dependent on the bodyweight in case of inadequate clinical response at week 16. Q4W Concomitant topical medication was allowed. Efficacy assessments included EASI, IGA of AD severity, pruritus NRS, SCORAD, BSA involvement with AD, POEM, CDLQI, assessment of AD flares, and maintenance of treatment effect. The presented efficacy results are based and focused on patients stemming from parent study R668-AD-1412 (n=36) which received a stable weight-based dose regimen over 22 months on average. According to the MAH this approach was chosen to minimize bias caused by administration of different dose regimens (intra- and inter-patient dosing) during the other parent studies R668-AD-1526 and R668-AD-1607.

A first-step analysis was conducted on data from adolescent patients (≥12 to <18 years old) enrolled in this study, with a data cut-off date of 21 Apr 2018. At the time of the first-step analysis, of the 275 adolescent patients enrolled in the study, 142 had completed 16 weeks, 69 had completed 26 weeks, and 34 patients had completed at least 52 weeks of treatment. This clinical study report is focused on adolescent patients.

34 of the included 275 patients have completed 52 treatment weeks. Thereof 41.2% (14/34) reached the co-primary endpoints by achieving IGA 0 or 1; the proportion of patients with EASI-75 relative to baseline of the previous study was 82.4% (28/34). The majority (76%) applied concomitant topical TCS/TCI.The proportions reaching the co-primary endpoints were higher after week 16 than during the pivotal study R668-AD-1526 which is explicable by several influencing factors as residual dupilumab concentrations resulting from the treatments obtained during the parent studies, higher disease severity at baseline of study R668-AD-1526 as compared to baseline of study R668-AD-1434, concomitant topical medication during R668-AD-1434 , study design, data set etc.. Efficacy results of the requested updated subgroup analysis on the co-primary endpoints showed lower treatment effects regarding the achievement of IGA score of 0 or 1 at Week 16 in obese patients, in patients who had received a previous therapy with systemic immunosuppressants and in those presenting higher eosinophil counts at baseline suggesting a higher disease activity. These conditions, however, did not influence the dupilumab treatment effect on the proportion of patients with EASI-75 at week 16.
The majority of patients applied TCS with a moderate potency during all three studies and the number of patients on topic medication for AD decreased over time during study R668-AD-1412. The mean duration of TCS during the treatment period was lower in the dupilumab 200/300 mg Q2W group than in the 300 mg Q4W and the placebo group suggesting a better efficacy. During pivotal study R668-AD-1526 patients in the dupilumab groups needed rescue medication to a lesser extent than the placebo group. Based on the different study designs the confounding effect of concomitant medication on efficacy is non-existent (1526) or not separable.

Rescue therapy was allowed if medically necessary (ie, to control intolerable AD symptoms, treatment of flares of disease, etc) to study patients at the discretion of the investigator. It was recommended that investigators performed an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in patients with an IGA score ≥3.
The Applicant reported that 16 patients required rescue therapy (5.8%) of which 12 (4.4%) used systemic corticosteroids. The provided data show that all of the 16 patients received at least temporarily the 300 mg Q4W regimen and nearly all patients (14/16) were switched to the higher dose regimen (300 mg Q2W), suggesting the need for a higher exposure. patients The proportion of patients that needed up-titration of dupilumab from the previous Q4W regimen to the weight-based Q2W regimen (36.2% until week 16) reflects higher dupilumab concentrations were needed to control disease activity in this AD patient population

More long-term continuous data would have been available if patients had been enrolled without treatment interruption to show maintenance of effect and also whether patients whom did not receive IGA0/1 achieved better efficacy with continued treatment.

As per study protocol, patients who achieved an IGA score of 0 or 1 for a 12-week period leading up to week 52 were discontinued from study drug. Once these patients were discontinued from study drug, disease activity was closely monitored, and dupilumab was re-initiated if these patients had a relapse of disease defined as IGA score ≥2. At the time of data cut-off date for this submission (21 Apr 2018), 14 patients who achieved an IGA score of 0 or 1 for a 12-week period after week 40 were discontinued from study drug. In 12 of the 14 patients, the disease returned and treatment had to be re-initiated, demonstrating the need for continuous treatment with dupilumab. The median time to re-initiation of study drug was 16 weeks. While the company showed that AD will flare again as the median time was 16 weeks, in some patients continuous therapy may not be required further clarification was requested from the applicant and this should be reflected in the SPC. The applicant does not recommend the treatment strategy of treatment interruption with up to 12 weeks duration. The analysis performed by the applicant indicated that after 8 weeks, the patients had lost around 25% of the response achieved from treatment with dupilumab. The justification provided by the applicant can be accepted. There are insufficient data to recommend other treatment regimens.

A later data cut-off (December 2018) set of data was provided as part of the response to the request from the Rapporteurs for more long-term treatment efficacy data. This data set included at baseline approximately 300 patients, and 104 patients at week 52. The results as measured by various investigator-assessed measures provided with the additional data confirm a beneficial efficacy of dupilumab in the adolescent target population.

In summary, efficacy results in the total study population included in OLE study R668-AD-1434 showed improvements of AD symptoms based on the proportion of patients who achieved the co-primary endpoints as well as key secondary endpoints which is supported by long-term study data on key efficacy parameters of 299 patients; thus, a consistent positive efficacy is evidenced.

2.4.3. Conclusions on the clinical efficacy

A total of 205 adolescent patients were exposed to dupilumab in the parent studies R668-AD-1526 or R668-AD-1412 and 299 patients during the OLE study R668-AD-1434 (and 104 patients having reached week 52 – data provided during the procedure).

The applicant has demonstrated clinical efficacy of dupilumab administered as 300 mg Q4W, 200/300mg Q2W or weight-based dose regimen of 2 and 4 mg/kg/bw/QW, respectively, as monotherapy or in combination with TCS in patients who suffer from moderate-to-severe AD and are insufficiently controlled on topical therapies for AD.

The superiority to placebo is demonstrated for these three dupilumab doses, and especially the results from the studies R668-AD-1526 show a significant higher and clinically meaningful improvement in severity of AD in the dupilumab 300 mg Q4W and 200/300 mg Q2W groups compared to placebo, whereby the Q2W regimen yields better results regarding the analysed treatment effects. Also significant efficacy was demonstrated in the key secondary endpoints such as pruritus, SCORAD, Change in ACQ-5, GISS, POEM, HADS and CDLQI. The effects demonstrated are considered to be clinically relevant.

The therapeutic effects were seen as early as 2 weeks with a near maximal effect demonstrated at 12 to 16 weeks. In summary, efficacy results of OLE study R668-AD-1434 showed improvements of AD symptoms based on the proportion of patients who achieved the co-primary endpoints as well as key secondary endpoints which is substantiated by long-term efficacy data with 109 and 28 patients with an overall treatment exposure of ≥52 ≥104 weeks, respectively.

OLE study R668-AD-1434 recruited patients from studies R668-AD-1526, R668-AD-1607 and R668-AD-1412. Included patients were treated with 2 mg/kg QW or 4 mg/kg QW, the dose was subsequently amended to a fixed dose of 300 mg Q4W with the possibility of up-titration to 200/300 mg Q2W dependent on the bodyweight in case of inadequate clinical response at week 16.Concomitant topical medication was allowed. Efficacy assessments included EASI, IGA of AD severity, pruritus NRS, SCORAD, BSA involvement with AD, POEM, CDLQI, assessment of AD flares, and maintenance of treatment effect.

The presented efficacy results in the dossier are based and focused on patients stemming from parent study R668-AD-1412 (n=36) which received a stable weight-based dose regimen over 22 months on average. According to the MAH this approach was chosen to minimize bias caused by administration of different dose regimens (intra- and inter-patient dosing) during the other parent studies R668-AD-1526 and R668-AD-1607.

34 of the included 275 patients had completed 52 treatment weeks. Thereof 41.2% (14/34) reached the co-primary endpoint by achieving IGA 0 or 1; the proportion of patients with EASI-75 relative to baseline of the previous study was 82.4% (28/34). The majority (76%) applied concomitant topical TCS/TCI.The proportions reaching the co-primary endpoints were higher after week 16 than during the pivotal study R668-AD-1526 but these results might be influenced by residual dupilumab concentrations resulting from the treatments obtained during the parent studies (54% (149/275) had a treatment gap of 6-13 weeks

before entering the OLE study); it remains unclear however, how many patients had shorter treatment interruptions.

Efficacy results in the subgroup of patients who rolled over from R668-AD-1412 were exactly the same as in the OLE study whereby more patients used TCS/TCI (97.2%).
The proportion of patients that needed up-titration of dupilumab from the previous Q4W regimen to the weight-based Q2W regimen (36.2% until week 16) reflects higher dupilumab concentrations were needed to control disease activity in this AD patient population. patients This is addressed by a weight based posology The patients enrolled from study 1412 which was a weight-based regimen, appear to achieve increasingly improved results over time for IGA 0/1, EASI 75 and 90, as well as pruritus NRS reduction ≥4. Improvement from baseline is expected as these patients had a treatment interruption of at least 8 weeks between the last dose in the R668-AD-1412 and the baseline of the OLE. Although the numbers of patients are decreasing over time, consistent or improved results are seen between weeks 52 to 104.

In summary, efficacy results in the total study population included in OLE study R668-AD-1434 showed improvements in AD symptoms based on the proportion of patients who achieved the co-primary endpoints as well as key secondary endpoints. Long-term efficacy data was limited to 34 patients completing week 52 and merely 134 patients reached week 16 in the original dossier. Further data provided during the procedure (104 and 295 patients completing week 52 and week 16 respectively) confirmed the long term efficacy of dupilumab treatment and the above data is a mixture of patients who continued on treatment, those who taken off treatment and subsequently were retreated following relapse of control.

2.5. Clinical safety

Introduction

Dupilumab is administered as a subcutaneous (SC) injection and, as with all biologics administered SC, would be expected to cause injection site reactions (ISRs) in some patients.
Data on the incidence of ISRs were collected as part of the safety program and severe ISRs lasting longer than 24 hours were handled as adverse events of special interest (AESI) in the dupilumab program. In the clinical AD program, study exclusion criteria designed to protect patient safety were developed based on the above theoretical concerns and the occurrence of events related to these concerns were monitored during the clinical studies.

The purpose of this Summary of Clinical Safety (SCS) is to provide an analysis of safety data from all adolescent AD patients exposed to dupilumab at the time of database lock for the individual studies (see details below). The safety analysis of adolescent patients with AD described in this SCS is based primarily on the placebo-controlled phase 3 study (R668-AD-1526) and is supported by data from the completed phase 2a pharmacokinetic (PK)/safety study (R668-AD-1412), the autoinjector device (AI) study (R668-AD-1607), and the pediatric open-label extension (OLE) (R668-AD-1434) (Figure 1). The numbers of patients treated in these studies are presented in Table 1.

Studies R668-AD-1434, R668-AD-1412, and R668-AD-1607 allowed concomitant use of topical treatments (eg, TCS, TCI) during the studies; therefore, the safety data from these studies provide support for dupilumab to be used with or without topical treatment.

Table 32: Overall Number of Adolescent Patients Included in the Safety Analysis Set

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

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

Overview of Safety Assessments and Analyses

The data from the 4 clinical studies that comprise the dupilumab program for adolescents with moderate-to-severe AD have not been pooled given the significant differences across these studies. Instead, the SCS is based predominantly on safety data derived from the double-blind, placebo controlled study R668-AD-1526 and is supported by data from the open-label studies R668-AD-1412, R668-AD-1434, and R668-AD-1607.

The dupilumab dosing regimens varied between studies and only a subset of adolescents received the proposed authorisation dose e.g. 82 in R668-AD-1526 (16 weeks study) and 141 in a long term extension study after up-titration from 300mg Q4W dose.

The general safety data have not been pooled which is agreed due to the divergent study conditions (design/dose/duration of treatment etc.). The approach of a primary analysis of the pivotal phase 3 study R668-AD-1526 supported by data from the three studies R668-AD-1412, R668-AD-1434, and R668-AD-1607 is endorsed. Only the supportive studies allowed concomitant use of topical treatments (eg, TCS, TCI). All analyses are focused on the adolescent study population (≥12 to <18 years of age with moderate-to-severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable). The subgroup analyses are agreed.

Patient exposure

Disposition

The sample size of the SAF for each of the studies included in this submission is presented in Table 33 below.

Table 33: 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-1526	251	0	251	1	TOTAL	250
					Placebo	85
					Dupilumab 300 mg Q4W	83
					Dupilumab 200/300 mg Q2W	82
R668-AD-1434 [1]	275	NA	NA	NA	TOTAL	275
R668-AD-1412 [2]	40	40	NA	NA	TOTAL	40
					Dupilumab 2 mg/kg QW	20
					Dupilumab 4 mg/kg QW	20
R668-AD-1607 [3]	85	0	85	0	TOTAL	85
					200 mg Q2W, AI	42
					200 mg Q2W, PFS	43

Abbreviations: AI, autoinjector; NA, not applicable; PFS, pre-filled syringe; 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 adolescent patients from the 3 prior studies as of data cutoff for this submission (21 Apr 2018), including 33 of the 40 patients in the adolescent group from R668-AD-1412, 3 patients from R668-AD-1412 who reached 12 years of age at the time they rolled over to R668-AD-1434, 201 of 250 patients from R668-AD-1526, 11 of 18 adolescent patients from Part A of R668-AD-1607, and 27 adolescent patients from Part B of R668-AD-1607.
[2] For study R668-AD-1412, only adolescent patients are included in this Table and within the analyses described in this Summary of Clinical Safety. Additional patients 6 to <12 years of age were included in the study but are not described in this document.
[3] For study R668-AD-1607, all patients (adolescent and adult) from Part A are included in this Table and within the analyses described in this Summary of Clinical Safety. Of the 85 total patients, 18 patients were adolescents. .

Exposure

Exposure data were pooled for the 4 studies included in this submission and are presented by treatment duration and dupilumab dose administration in Table 34.

Table 34: Summary of Study Drug Administration (Cumulative) and Duration of Treatment in Adolescent Patients from All Studies - SAF

	Dupilumab					
Exposure Characteristics	2 mg/kg QW (N = 21)	4 mg/kg QW (N = 22)	300 mg Q4W (N = 284)	200 mg Q2W (N = 99)	300 mg Q2W (N = 89)	All Combined [3] (N = 322)
Number of treated patients [1]	21	22	284	99	89	322
Number of study doses administered						
Mean (SD)	74.4 (39.53)	73.0 (34.61)	5.0 (4.12)	8.5 (4.88)	8.0 (5.30)	19.1 (27.00)

Exposure Characteristics	Dupilumab					
	2 mg/kg QW (N = 21)	4 mg/kg QW (N = 22)	300 mg Q4W (N = 284)	200 mg Q2W (N = 99)	300 mg Q2W (N = 89)	All Combined [3] (N = 322)
Q1	56.0	58.0	1.0	5.0	3.0	6.0
Median	93.0	81.0	4.0	9.0	9.0	11.0
Q3	108.0	100.0	9.0	9.0	11.0	15.0
Min-Max	5:109	1:109	1:18	1:23	1:22	1:113
Number of doses administered, cumulative, n (%)						
≥1	21 (100%)	22 (100%)	284(100%)	99 (100%)	89 (100%)	322 (100%)
≥4	21 (100%)	21 (95.5%)	148 (52.1%)	83 (83.8%)	66 (74.2%)	282 (87.6%)
≥8	17 (81.0%)	19 (86.4%)	80 (28.2%)	68 (68.7%)	49 (55.1%)	233 (72.4%)
≥12	17 (81.0%)	19 (86.4%)	25 (8.8%)	17 (17.2%)	20 (22.5%)	144 (44.7%)
≥16	17 (81.0%)	19 (86.4%)	1 (0.4%)	10 (10.1%)	9 (10.1%)	80 (24.8%)
≥24	17 (81.0%)	18 (81.8%)	0	0	0	36 (11.2%)
≥48	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥52	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥76	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥100	8 (38.1%)	6 (27.3%)	0	0	0	17 (5.3%)
≥124	0	0	0	0	0	0
≥148	0	0	0	0	0	0
Summary of treatment duration [2] (weeks)						
n	21	22	284	99	89	322
Mean (SD)	75.4 (39.91)	75.4 (35.74)	14.4 (9.52)	16.0 (9.34)	15.4 (10.03)	32.0 (28.73)
Q1	57.1	58.0	4.1	10.0	7.6	16.0
Median	93.3	90.6	15.9	15.9	15.9	24.0
Q3	108.7	101.3	20.1	18.0	20.1	36.3
Min-Max	5:109	1:109	2:52	2:44	2:42	1:125
Treatment duration [2] (weeks) cumulative, n (%)						
≥1 week	21 (100%)	22 (100%)	284 (100%)	99 (100%)	89 (100%)	322 (100%)
≥4 weeks	21 (100%)	21 (95.5%)	271 (95.4%)	94 (94.9%)	75 (84.3%)	320 (99.4%)

Exposure Characteristics	Dupilumab					
	2 mg/kg QW (N = 21)	4 mg/kg QW (N = 22)	300 mg Q4W (N = 284)	200 mg Q2W (N = 99)	300 mg Q2W (N = 89)	All Combined [3] (N = 322)
≥8 weeks	17 (81.0%)	19 (86.4%)	193 (68.0%)	80 (80.8%)	65 (73.0%)	295 (91.6%)
≥12 weeks	17 (81.0%)	19 (86.4%)	168 (59.2%)	71 (71.7%)	55 (61.8%)	272 (84.5%)
≥16 weeks	17 (81.0%)	19 (86.4%)	137 (48.2%)	47 (47.5%)	44 (49.4%)	246 (76.4%)
≥26 weeks	17 (81.0%)	18 (81.8%)	34 (12.0%)	13 (13.1%)	16 (18.0%)	141 (43.8%)
≥39 weeks	16 (76.2%)	18 (81.8%)	4 (1.4%)	5 (5.1%)	2 (2.2%)	73 (22.7%)
≥52 weeks	16 (76.2%)	18 (81.8%)	1 (0.4%)	0	0	35 (10.9%) [4]
≥78 weeks	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥104 weeks	7 (33.3%)	4 (18.2%)	0	0	0	27 (8.4%)
≥130 weeks	0	0	0	0	0	0

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

Adverse events

Overview of Adverse Events

Study R668-AD-1526

The proportion of patients reporting TEAEs was similar during the 16-week treatment period between the placebo group and the combined dupilumab treatment groups. Most TEAEs were mild to moderate in intensity and deemed not related to study drug by the investigator (Table 35).
There was a higher proportion of patients with treatment-related TEAEs in the dupilumab Q2W group (22.0%) compared to the dupilumab Q4W group (14.5%) and the placebo group (15.3%). There were no SAEs reported in either dupilumab treatment group and no deaths reported in the study.

Table 35: Summary of Treatment-Emergent Adverse Events During the 16-Week Treatment Period in Study R668-AD-1526 – SAF

		Dupilumab		
Number of patients (%)	**Placebo (N=85)**	**300 mg Q4W (N=83)**	**200 mg or 300 mg Q2W (N=82)**	**Combined (N=165)**
Any TEAE	59 (69.4%)	53 (63.9%)	59 (72.0%)	112 (67.9%)
Any drug-related TEAE	13 (15.3%)	12 (14.5%)	18 (22.0%)	30 (18.2%)
Any TEAE leading to discontinuation of study drug permanently [1]	1 (1.2%)	0	0	0
Maximum intensity for any TEAE				
Mild	29 (34.1%)	26 (31.3%)	20 (24.4%)	46 (27.9%)
Moderate	29 (34.1%)	24 (28.9%)	37 (45.1%)	61 (37.0%)
Severe	1 (1.2%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Any death	0	0	0	0
Any treatment-emergent SAE	1 (1.2%)	0	0	0
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

[1] There were 2 patients in the dupilumab Q2W arm who discontinued treatment during the study period due to AEs unrelated to dupilumab. These patients re-initiated study drug during the OLE study R668-AD-1434. These 2 patients are not counted under AEs leading to discontinuation of study drug permanently.

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; TEAE, treatment-emergent adverse event.

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=275) and for the population of patients that rolled over from parent study R668-AD-1412 (n=36, of which 34 patients had ≥52 weeks of treatment with dupilumab).

In the OLE study (n=275), approximately half of the patients experienced at least 1 TEAE. Most of the events were mild to moderate in intensity and deemed unrelated to the study drug by the investigator. There were 4 patients who experienced an SAE during the study. There were no AEs that led to permanent discontinuation of study drug and no deaths reported during the study. There were further data provided with a later data cut-off (December 2018) during the procedure (n=299, enrolled with 109 and 21 patients with an overall treatment exposure of ≥52 ≥104 weeks respectively).

For those patients who rolled over into the OLE from R668-AD-1412 and received weight-based dosing (n=36, of which 34 patients had ≥52 weeks of treatment with dupilumab), a total of 97.2% (35/36) of patients experienced a TEAE, of which 27.8% (10/36) had a dupilumab-related TEAE. Most TEAEs were mild or moderate in severity, with 11.1% (4/36) of patients experiencing a severe TEAE. A total of 8.3% (3/36) experienced SAEs; however, none of the SAEs was considered to be related to study drug. No TEAEs led to study drug discontinuation.

Study R668-AD-1412

In study R668-AD-1412 (n = 40), the number of adolescent patients experiencing at least 1 TEAE was higher in the 4 mg/kg dose cohort (80% [16/20]) than in the 2 mg/kg cohort (55.0% [11/20]), which was driven primarily by Nasopharyngitis. Two patients in the 4 mg/kg cohort each reported 1 severe (non serious) TEAE of Dermatitis Atopic. Two adolescents experienced SAEs in the study: 1 patient in the 4 mg/kg cohort had SAEs of Dermatitis Infected and Staphylococcal Skin Infection, and 1 patient in the 2 mg/kg cohort experienced Palpitations and an additional SAE of Dermatitis Infected. There were no deaths or TEAEs leading to discontinuation of study drug.

Study R668-AD-1607 Part A

Among adolescent patients, 61.1% (11/18) of patients experienced TEAEs, with only 16.7% (3/18) of patients experiencing TEAEs considered related to study drug. There were no SAEs, severe TEAEs, or TEAEs leading to discontinuation of study drug among adolescent patients in Part A of study R668-AD-1607.

Treatment-Emergent Treatment-Related Adverse Events Study R668-AD-1526

The proportion of patients who had at least 1 treatment-related TEAE (relatedness assessed by the investigator) during the 16-week treatment period was higher for patients in the dupilumab Q2W treatment group than for patients in the placebo group or the dupilumab Q4W treatment group (Table 36). This was primarily driven by a higher incidence of ISRs in the dupilumab Q2W group compared to the other 2 groups. The incidence of Conjunctivitis was also higher in the dupilumab Q2W group as compared to the placebo group. Safety findings of treatment-related TEAEs during the entire study period (approximately 28 weeks) were similar to the 16-week treatment period.

Table 36: Summary of Treatment-Emergent Treatment-Related Adverse Events by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1526 with ≥2% Incidence in Any Treatment Group – SAF

		Dupilumab		
Primary System Organ Class Preferred Term (MedDRA Version 20.1)	Placebo (N=85)	300 mg Q4W (N=83)	200 mg or 300 mg Q2W (N=83)	Combined (N=165)
Number of treatment-related TEAEs	23	18	39	57
Patients with at least 1 related TEAE, n (%)	13 (15.3%)	12 (14.5%)	18 (22.0%)	30 (18.2%)
Infections and infestations	4 (4.7%)	6 (7.2%)	7 (8.5%)	13 (7.9%)
Conjunctivitis	0	1 (1.2%)	3 (3.7%)	4 (2.4%)
Herpes simplex	0	2 (2.4%)	0	2 (1.2%)
Upper respiratory tract infection	2 (2.4%)	0	2 (2.4%)	2 (1.2%)
General disorders and administration site conditions	4 (4.7%)	3 (3.6%)	8 (9.8%)	11 (6.7%)
Injection site pain	1 (1.2%)	0	3 (3.7%)	3 (1.8%)
Injection site swelling	1 (1.2%)	0	3 (3.7%)	3 (1.8%)
Injection site erythema	1 (1.2%)	0	2 (2.4%)	2 (1.2%)
Injection site pruritus	2 (2.4%)	0	2 (2.4%)	2 (1.2%)
Injection site warmth	0	0	2 (2.4%)	2 (1.2%)
Eye disorders	2 (2.4%)	3 (3.6%)	3 (3.7%)	6 (3.6%)
Conjunctivitis allergic	2 (2.4%)	3 (3.6%)	3 (3.7%)	6 (3.6%)

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.

Study R668-AD-1434
In the OLE study R668-AD-1434, 9.5% (26/275) of patients in the adolescent age group experienced a TEAE considered related to treatment by the investigator. The most frequently reported treatment-related TEAEs fell under the SOC General Disorders and Administration Site Conditions (3.3% [9/275] of patients) and included ISRs. Injection Site Mass and Injection Site Edema were each reported by 3 patients (1.1%), and Injection Site Erythema and Injection Site Swelling were each reported by 2 patients (0.7%). Other treatment-related TEAEs reported in 2 or more patients included the PTs of Nasopharyngitis, Oral Herpes, Dermatitis Atopic, Conjunctivitis Allergic, Dry Eye, and Oropharyngeal Pain (all reported by 2 patients each). Additional data from R668-AD-1434 using a later data cut-off date (December 2018) were provided upon request of the agency. NO new safety concerns in adolescents with atopic dermatitis were identified.

Study R668-AD-1412
In study R668-AD-1412, 12.5% (5/40) of patients in the adolescent age group experienced a TEAE considered related to treatment by the investigator. Treatment-related TEAEs occurred at a higher frequency in the 4 mg/kg dose cohort than in the 2 mg/kg dose cohort (20.0% [4/20] and 5.0% [1/20], respectively). No treatment-related TEAE was reported by >1 adolescent patient; no trends in SOC or PT were observed.

Study R668-AD-1607 Part A
In study R668-AD-1607, 16.5% (14/85) of patients experienced a TEAE considered related to treatment by the investigator. Treatment-related TEAEs occurred at a similar frequency in the AI group and the PFS group (14.3% [6/42] and 18.6% [8/43], respectively). The only events that were reported by ≥2 patients in any treatment group were Injection Site Pruritus (1 patient in the AI group and 2 patients in the PFS group) and Conjunctivitis (no patients in the AI group and 2 patients in the PFS group). All other treatment-related TEAEs were reported by ≤1 patient in any treatment group, and none of them were reported in both groups.

Serious adverse event / deaths / other significant events

Treatment-Emergent Serious Adverse Events
Treatment-emergent SAEs are summarized for each study below. More detailed descriptions of treatment-emergent SAEs are provided in the patient narratives included with each individual CSR.

Study R668-AD-1526
In this double-blind, placebo-controlled study, no patients in the dupilumab treatment groups experienced SAEs. One patient in the placebo treatment group experienced the SAE of Appendicitis.

Study R668-AD-1434
In the OLE study, 4 patients experienced SAEs, including Injection Site Cellulitis, Ankle Fracture, Patent Ductus Arteriosus, and Food Allergy (each reported by 1 patient). None of these events were considered related to study drug or led to discontinuation of study drug. However, the event of Injection Site Cellulitis was considered by the investigator to be related to the study procedure. Of the 4 patients that experienced SAEs, 3 of the patients were those who rolled over into the OLE from R668-AD-1412 and received weight-based dosing.

Study R668-AD-1412
Two adolescent patients (1 in each treatment group) in this open-label study experienced SAEs.
One patient in the 2 mg/kg treatment group experienced SAEs of Dermatitis Infected and Palpitations, and 1 patient in the 4 mg/kg treatment group experienced SAEs of Dermatitis Infected and Staphylococcal Skin Infection. The event of Staphylococcal Skin Infection occurred 7 weeks after the patient's final dose of study treatment and was considered not related to study drug. None of these events were considered related to study drug.

Study R668-AD-1607 Part A
In this open-label study, treatment-emergent SAEs were experienced by 1 patient in the AI group (Lymphadenopathy) and 1 patient in the PFS group (Sepsis) (both patients were >18 years old).

Deaths
There were no deaths in the adolescent AD program.

Other Significant Adverse Events
Treatment-emergent AEs leading to discontinuation and AESIs are summarized for each study below.

Adverse Events of Special Interest
Treatment-emergent AESIs were defined for each study.

Study R668-AD-1526
Treatment-emergent AESIs were experienced by 2 patients in the Q2W dupilumab group (Suicidal Ideation and Food Allergy [1 event each]) and 1 patient in the Q4W dupilumab group (Keratitis).

Study R668-AD-1434
Treatment-emergent AESIs were experienced by 3 patients in the adolescent group. One patient experienced a non-serious AESI of Conjunctivitis Allergic (which was severe in intensity and hence classified as an AESI), 1 patient experienced a non serious AESI of Depression (which was associated with suicidal ideation and hence classified as an AESI), and 1 patient experienced an SAE of Food Allergy.

Study R668-AD-1412
Treatment-emergent AESIs were experienced by 3 patients in the adolescent group. One patient (4 mg/kg group) experienced a non serious AESI of Allergic Edema(localized edema reported as “swelling hand”) and 2 patients (1 in each treatment group) experienced the serious AESI of Dermatitis Infected.

Study R668-AD-1607 Part A
Treatment-emergent AESIs were experienced by 3 patients in each group in study R688-AD-1607, which included Urticaria, Conjunctivitis Allergic, Conjunctivitis, Vulvovaginal Mycotic Infection, Sepsis, and Hypersensitivity (1 patient each). None of the AESIs were reported by more than 1 patient in either group. The AESI of Sepsis led to discontinuation of study drug. Of note, the events of Conjunctivitis Allergic and Conjunctivitis were non serious TEAEs, but they both occurred for >28 days, which qualified them as AESIs in this study. The events of Conjunctivitis Allergic and Conjunctivitis occurred in patients <18 years old. All other AESIs in this study were reported in patients >18 years old.

The summary of TEAEs reported by more than 2% of patients is described below in table 37.

Table 37: Summary of TEAEs Reported by ≥2% of Patients in Any Dose Cohort by SOC and PT During the 16-Week Treatment Period in Study R668-AD-1526 – SAF

Primary System Organ Class Preferred Term (MedDRA Version 20.1)	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=165)
Patients with at least 1 TEAE, n (%)	59 (69.4%)	53 (63.9%)	59 (72.0%)	112 (67.9%)
Infections and infestations	37 (43.5%)	38 (45.8%)	34 (41.5%)	72 (43.6%)
Upper respiratory tract infection	15 (17.6%)	6 (7.2%)	10 (12.2%)	16 (9.7%)
Nasopharyngitis	4 (4.7%)	9 (10.8%)	3 (3.7%)	12 (7.3%)
Conjunctivitis	1 (1.2%)	3 (3.6%)	4 (4.9%)	7 (4.2%)

Primary System Organ Class Preferred Term (MedDRA Version 20.1)	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=165)
Pharyngitis streptococcal	0	4 (4.8%)	2 (2.4%)	6 (3.6%)
Impetigo	4 (4.7%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Viral upper respiratory tract infection	1 (1.2%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Herpes simplex	1 (1.2%)	4 (4.8%)	0	4 (2.4%)
Conjunctivitis viral	0	2 (2.4%)	1 (1.2%)	3 (1.8%)
Folliculitis	2 (2.4%)	1 (1.2%)	2 (2.4%)	3 (1.8%)
Gastroenteritis viral	1 (1.2%)	0	3 (3.7%)	3 (1.8%)
Influenza	4 (4.7%)	0	3 (3.7%)	3 (1.8%)
Bronchitis	0	0	2 (2.4%)	2 (1.2%)
Conjunctivitis bacterial	0	2 (2.4%)	0	2 (1.2%)
Sinusitis bacterial	0	0	2 (2.4%)	2 (1.2%)
Urinary tract infection viral	0	2 (2.4%)	0	2 (1.2%)
Skin infection	2 (2.4%)	0	1 (1.2%)	1 (0.6%)
Ear infection	3 (3.5%)	0	0	0
Paronychia	3 (3.5%)	0	0	0
Skin and subcutaneous tissue disorders	26 (30.6%)	20 (24.1%)	22 (26.8%)	42 (25.5%)
Dermatitis atopic	21 (24.7%)	15 (18.1%)	15 (18.3%)	30 (18.2%)
Urticaria	4 (4.7%)	2 (2.4%)	4 (4.9%)	6 (3.6%)
Rash	0	2 (2.4%)	1 (1.2%)	3 (1.8%)
Pruritus	2 (2.4%)	1 (1.2%)	0	1 (0.6%)
General disorders and administration site conditions	6 (7.1%)	9 (10.8%)	10 (12.2%)	19 (11.5%)
Injection site pain	1 (1.2%)	1 (1.2%)	3 (3.7%)	4 (2.4%)
Injection site swelling	1 (1.2%)	1 (1.2%)	3 (3.7%)	4 (2.4%)
Injection site pruritus	2 (2.4%)	1 (1.2%)	2 (2.4%)	3 (1.8%)
Malaise	0	3 (3.6%)	0	3 (1.8%)
Fatigue	0	0	2 (2.4%)	2 (1.2%)
Injection site erythema	1 (1.2%)	0	2 (2.4%)	2 (1.2%)
Injection site warmth	0	0	2 (2.4%)	2 (1.2%)
Pyrexia	3 (3.5%)	1 (1.2%)	1 (1.2%)	2 (1.2%)
Nervous system disorders	11 (12.9%)	7 (8.4%)	12 (14.6%)	19 (11.5%)
Headache	9 (10.6%)	4 (4.8%)	9 (11.0%)	13 (7.9%)
Migraine	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (1.8%)
Respiratory, thoracic and mediastinal disorders	13 (15.3%)	9 (10.8%)	6 (7.3%)	15 (9.1%)
Oropharyngeal pain	1 (1.2%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Asthma	2 (2.4%)	1 (1.2%)	2 (2.4%)	3 (1.8%)
Cough	4 (4.7%)	2 (2.4%)	1 (1.2%)	3 (1.8%)

Primary System Organ Class Preferred Term (MedDRA Version 20.1)	Placebo (N=85)	Dupilumab 300 mg Q4W (N=83)	Dupilumab 200 mg or 300 mg Q2W (N=82)	Dupilumab Combined (N=165)
Nasal congestion	4 (4.7%)	1 (1.2%)	2 (2.4%)	3 (1.8%)
Sinus congestion	2 (2.4%)	1 (1.2%)	0	1 (0.6%)
Gastrointestinal disorders	4 (4.7%)	7 (8.4%)	6 (7.3%)	13 (7.9%)
Nausea	1 (1.2%)	2 (2.4%)	2 (2.4%)	4 (2.4%)
Abdominal pain upper	1 (1.2%)	1 (1.2%)	2 (2.4%)	3 (1.8%)
Vomiting	2 (2.4%)	0	0	0
Eye disorders	7 (8.2%)	6 (7.2%)	6 (7.3%)	12 (7.3%)
Conjunctivitis allergic	3 (3.5%)	4 (4.8%)	3 (3.7%)	7 (4.2%)
Injury, poisoning and procedural complications	2 (2.4%)	3 (3.6%)	9 (11.0%)	12 (7.3%)
Ligament sprain	0	0	2 (2.4%)	2 (1.2%)
Procedural pain	0	0	2 (2.4%)	2 (1.2%)
Investigations	2 (2.4%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Blood creatine phosphokinase increased	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (1.8%)
Musculoskeletal and connective tissue disorders	4 (4.7%)	3 (3.6%)	2 (2.4%)	5 (3.0%)
Pain in extremity	2 (2.4%)	2 (2.4%)	1 (1.2%)	3 (1.8%)
Immune system disorders	2 (2.4%)	1 (1.2%)	1 (1.2%)	2 (1.2%)
Food allergy	2 (2.4%)	0	1 (1.2%)	1 (0.6%)

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; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

Study R668-AD-1434

In the OLE study R668-AD-1434, TEAEs occurred in 149/275 (54.2%) patients during the study with an EAIR of 283.051 patients per 100 patient-years (nP/100 PY). The most common TEAEs by PT (≥5% in all patients) included Nasopharyngitis, Upper Respiratory Tract Infection, Dermatitis Atopic (typically worsening or exacerbation), and Headache. Of note, Allergic Conjunctivitis occurred in 2.2% of patients, and Conjunctivitis (unspecified etiology) occurred in 1.8% of patients All other PTs were reported in <5% of patients.

Laboratory findings

Clinical Laboratory Evaluations

No meaningful changes from baseline were observed regarding RBC or WBC. The transient increase in eosinophil counts during the first weeks of treatment is a known phenomenon caused by dupilumab treatment and was extensively discussed during the MAAs for dupilumab in the adult AD and adult/adolescent asthma population. Accordant and appropriate measures were implemented in the RMP and SmPC to avert possible risks in patients with hypereosinophilic conditions. Neither clinically meaningful deviations of clinical chemistry parameters were observed nor electrolyte abnormalities. No harmful impact on the renal or liver function was detected.

Instrumental tests

ECG abnormalities were present during study R668-AD-1434 as 30.6% (11/36) of all patients had at least 1 treatment-emergent PCSV for ECGs mainly with increase of 30-60 ms from baseline in QTc interval (16.7%). None of these PCSVs were reported as a TEAE or led to treatment discontinuation. The QTc PCSVs were not associated with other significant ECG abnormalities or clinical signs and did not lead to additional investigations.

Immunogenicity

The data are presented in the table below.

Table 38: ADA Category for Patients by Treatment Group

		Dupilumab					
ADA Category N (%)	**Placebo**	**300 mg Q4W**	**200 or 300 mg Q2W**	**200 mg Q2W**	**300 mg Q2W**	**All Active Doses**	**Overall**
Total ADA Patients	85 (100%)	82 (100%)	81 (100%)	42 (100%)	39 (100%)	163 (100%)	248 (100%)
Negative/Pre-Existing	82 (96.5%)	65 (79.3%)	68 (84.0%)	37 (88.1%)	31 (79.5%)	133 (81.6%)	215 (86.7%)
Treatment Boosted Response	0	0	0	0	0	0	0
Treatment Emergent Response	3 (3.5%)	17 (20.7%)	13 (16.0%)	5 (11.9%)	8 (20.5%)	30 (18.4%)	33 (13.3%)
Persistent	1 (1.2%)	2 (2.4%)	2 (2.5%)	1 (2.4%)	1 (2.6%)	4 (2.5%)	5 (2.0%)
Transient	0	10 (12.2%)	10 (12.3%)	3 (7.1%)	7 (17.9%)	20 (12.3%)	20 (8.1%)
Indeterminate	2 (2.4%)	5 (6.1%)	1 (1.2%)	1 (2.4%)	0	6 (3.7%)	8 (3.2%)

n = Number of patients

Table 39: Summary of Treatment-Emergent Adverse Events Reported by ≥2 Patients with a Treatment-Emergent Positive ADA Response or a Treatment-Boosted ADA Response in All Patients by ADA Response, SOC, and PT in Study R668-AD-1526 – Anti-Dupilumab Antibody Analysis Set

Primary System Organ Class	**Placebo**		**Dupilumab 300 mg Q4W**		**Dupilumab 200 mg or 300 mg Q2W**	
Preferred Term/MedDRA Version 20.1	**Positive ADA (N=3)**	**Negative ADA (N=82)**	**Positive ADA (N=17)**	**Negative ADA (N=65)**	**Positive ADA (N=13)**	**Negative ADA (N=68)**
Number of patients with at least 1 such event, n (%)	3 (100%)	56 (68.3%)	11 (64.7%)	43 (66.2%)	9 (69.2%)	50 (73.5%)
Infections and infestations	2 (66.7%)	35 (42.7%)	8 (47.1%)	31 (47.7%)	5 (38.5%)	30 (44.1%)
Upper respiratory tract infection	0	15 (18.3%)	0	7 (10.8%)	2 (15.4%)	8 (11.8%)
Nasopharyngitis	1 (33.3%)	3 (3.7%)	3 (17.6%)	7 (10.8%)	1 (7.7%)	4 (5.9%)
Pharyngitis	0	0	1 (5.9%)	0	1 (7.7%)	0
Impetigo	0	4 (4.9%)	2 (11.8%)	1 (1.5%)	0	2 (2.9%)
Influenza	1 (33.3%)	3 (3.7%)	0	0	1 (7.7%)	4 (5.9%)
Skin and subcutaneous tissue disorders	2 (66.7%)	24 (29.3%)	3 (17.6%)	17 (26.2%)	3 (23.1%)	20 (29.4%)
Dermatitis atopic	1 (33.3%)	20 (24.4%)	3 (17.6%)	13 (20.0%)	2 (15.4%)	13 (19.1%)

Primary System Organ Class Preferred Term/MedDRA Version 20.1	Placebo		Dupilumab 300 mg Q4W		Dupilumab 200 mg or 300 mg Q2W	
	Positive ADA (N=3)	Negative ADA (N=82)	Positive ADA (N=17)	Negative ADA (N=65)	Positive ADA (N=13)	Negative ADA (N=68)
Urticaria	1 (33.3%)	3 (3.7%)	0	2 (3.1%)	2 (15.4%)	2 (2.9%)
General disorders and administration site conditions	0	6 (7.3%)	2 (11.8%)	7 (10.8%)	1 (7.7%)	9 (13.2%)
Injection site pain	0	1 (1.2%)	1 (5.9%)	0	1 (7.7%)	2 (2.9%)
Nervous system disorders	1 (33.3%)	10 (12.2%)	1 (5.9%)	6 (9.2%)	2 (15.4%)	9 (13.2%)
Headache	1 (33.3%)	8 (9.8%)	1 (5.9%)	3 (4.6%)	2 (15.4%)	6 (8.8%)
Eye disorders	0	7 (8.5%)	2 (11.8%)	4 (6.2%)	1 (7.7%)	7 (10.3%)
Conjunctivitis allergic	0	3 (3.7%)	1 (5.9%)	3 (4.6%)	1 (7.7%)	3 (4.4%)
Gastrointestinal disorders	1 (33.3%)	3 (3.7%)	3 (17.6%)	4 (6.2%)	2 (15.4%)	5 (7.4%)
Nausea	0	1 (1.2%)	2 (11.8%)	0	1 (7.7%)	2 (2.9%)
Abdominal pain upper	1 (33.3%)	0	0	1 (1.5%)	1 (7.7%)	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	1 (33.3%)	12 (14.6%)	2 (11.8%)	7 (10.8%)	2 (15.4%)	5 (7.4%)
Oropharyngeal pain	1 (33.3%)	0	0	3 (4.6%)	2 (15.4%)	0
Sinus congestion	1 (33.3%)	1 (1.2%)	1 (5.9%)	0	0	0
Musculoskeletal and connective tissue disorders	0	4 (4.9%)	1 (5.9%)	2 (3.1%)	1 (7.7%)	1 (1.5%)
Pain in extremity	0	2 (2.4%)	1 (5.9%)	1 (1.5%)	1 (7.7%)	0

Note: At each level of patient summarization, a patient is counted once if the patient reported 1 or more events.
ADA-positive patients are patients with treatment-emergent or treatment-boosted response. ADA-negative patients are patients with pre-existing immunoreactivity or negative in the ADA assay at all time points
Abbreviations: ADA, anti-drug antibody; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; Q2W, every 2 weeks; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event.

There was a trend towards increased immunogenicity in adolescents as compared to adults.
In all the studies of dupilumab in AD adults' patients, submitted in the original application, which included studies conducted in patients treated with dupilumab for over 52 weeks, the proportion of patients with treatment-emergent positive response in the ADA assay was ⩽10%.

On the other hand, a positive ADA response was observed in 18.4% of adolescents treated with dupilumab in study R668-AD-1526 (16 weeks' duration), in 50 patients (64.9%) in R668-AD-1412 study and in 19.9% of adolescents in the long term extension study (including 109 patients with 52 weeks treatment duration).

In studies in adults only 2 % showed persistent titers whereas in the studies in adolescents the persistent ADA response was reported in 2.5 % in R668-AD-1526 study and in 6% in the long term extension study. There were no adolescents with boosted ADA response.

It is noted that a particularly high ADA response was observed in R668-AD-1412 study. As discussed a positive AD response was reported in up to 50 patients (64.9%) children, 31 of which (40.3% of total 77 patients) were categorized as having a persistent, treatment-emergent ADA response.
In patients with high titer the serum concentration decreased during the initial period; however, with continued treatment over time, ADA titer values declined (some to negative ADA status) with corresponding increase in dupilumab concentrations to a typical steady-state value.
It is noted that a total of 1/3 patient with moderate titer ADA response had TEAEs under Injection Site Reaction (HLT), which were events of Injection Site Pain and Injection Site Swelling. A total of 2/3 patients with high titer ADA response had TEAEs under Injection Site Reaction (HLT), which were events of Injection Site Edema and Injection Site Hemorrhage.

In in Study R668-AD-1526, the proportion of patients reporting at least 1 TEAE was similar in the ADA-positive and ADA-negative patients in both the dupilumab Q4W (11/17 [64.7%]) in ADA positive vs 43/65 [66.2%] in ADA negative) and dupilumab Q2W group (9/13 [(69.2%]) in ADA positive vs 50/68 [73.5%] in ADA negative).

The incidence of commonly reported AEs like Dermatitis Atopic (exacerbation thereof) and Injection Site Reactions was comparable between ADA-positive and ADA-negative patients in both the dupilumab treatment groups.

A total of 8/136 (5.9%) patients had a persistently positive ADA response during the study. Of these, 7/8 (87.5%) had at least 1 TEAE during the study. In comparison, 18/21 (85.7%) patients with a transient response and 7/7 (100%) patients with an indeterminate response had at least 1 TEAE during the study. Due to a small number of patients with persistent titer it is difficult to conclude if there were any differences in the types of TEAEs reported in this population as compared to patients without ADA response.
There were no reports of anaphylactic reaction (using narrow search terms under SMQ anaphylactic reaction) during the study and systemic hypersensitivity was only reported in the context of food allergy.

Safety in special subgroups

Analyses of designated subgroup populations were planned in study R668-AD-1526 only. Subgroups to be considered for comparing safety data included age, gender, ethnicity, race, duration of AD, baseline weight group, and baseline BMI group. There was an inadequate number of patients for meaningful conclusions to be drawn for the subgroups of Hispanic or Latino patients (n=13 to 20 patients per treatment group). In general, the subgroup sample sizes were small and limited the ability to draw definite conclusions from comparative subgroup analyses.

A trend towards higher incidence of TEAEs in the dupilumab Q2W group was observed in patients ≥12 to <15 years of age (79.1%) as compared to patients ≥15 to <18 years of age (64.1%).

This difference across the 2 age subgroups was not observed in the dupilumab Q4W group. Similarly, the incidence of TEAEs with the dupilumab Q2W group was higher in patients <60 kg (81.4%) as compared to patients ≥60 kg (61.5%). This difference across the 2 weight subgroups was also not observed in the dupilumab Q4W group. These differences were driven by a higher incidence of Dermatitis Atopic, ISRs, and Headache in the patients ≥12 to <15 years old and in patients <60 kg.

The incidences of treatment-emergent severe AEs, treatment-related AEs, SAEs, treatment-related SAEs, and TEAEs leading to permanent dose withdrawal was low for all patients in the study. Therefore, no conclusions could be drawn from subgroup analyses of these factors.

Safety When Used with Concomitant TCS and TCI
Dupilumab was well tolerated, where a majority of patients used concomitant topical medications (TCS and TCI). The safety profile was comparable with that in the monotherapy pivotal study R668-AD-1526, the data support the use of dupilumab with or without topical treatment.

Use in Pregnancy and Lactation
There were no pregnancies reported in studies R668-AD-1526, R668-AD-1434, R668-AD-1412, and R668-AD-1607.

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.

Safety related to drug-drug interactions and other interactions

No new data applicable to this submission.

Discontinuation due to adverse events

Only two patients of the pivotal study had a treatment interruption; one case of permanent treatment discontinuation was recorded in the placebo group.

Post marketing experience

Dupilumab is not currently approved in patients <18 years of age. However, a cumulative search with data lock point (DLP) date of 21 Apr 2018 was performed in the Sanofi safety database to identify all post-marketed cases of dupilumab use in patients <18 years of age.
There were 156 post-marketed cases reported for DUPIXENT cumulatively up to the DLP of 21 Apr 2018 in patients less than 18 years of age. Of these, only 2 cases were serious, and no fatal cases were reported.
One patient experienced the serious event coded as “Unevaluable Event”, which was reported as “symptoms have been worsening”. No additional details were provided.
One patient experienced the serious event of Loss of Consciousness, which was reported to have occurred for approximately 5 seconds after the patient’s first dose of dupilumab and was diagnosed by the patient’s physician as vasovagal response. Review of the post-marketed cases identified no new safety concerns.

2.5.1. Discussion on clinical safety

General
The proposed authorisation dose for adolescents with body weight less than 60 kg is 400 mg as the initial dose followed by 200 mg given every other week whereas for adolescents with body weight 60 kg and more the initial dose 600 mg followed by 300 mg given every other week.

The general safety data have not been pooled which is agreed due to the divergent study conditions (design/dose/duration of treatment etc.). The approach of a primary analysis of the pivotal phase 3 study R668-AD-1526 supported by data from the three studies R668-AD-1412, R668-AD-1434, and R668-AD-1607 is acceptable.
All analyses are focused on the adolescent study population (≥12 to <18 years of age with moderate-to-severe AD whose disease could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable). The performed subgroup analyses are generally agreed but the results are considered inconclusive due to the small sample sizes.

Exposure
In total 322 adolescents were exposed to dupilumab (in studies in atopic dermatitis) for the mean duration of exposure of 32 weeks. 109 adolescents received treatment with dupilumab for 52 weeks and 28 subjects received treatment for more than 104 weeks.

The pooled safety data of the 4 studies included in this submission show that 322 patients had received at least 1 dose of dupilumab. The majority (76.4%) had completed at least 16 weeks of treatment (10.9% at least 52 weeks of treatment, 8.4% at least 104 weeks of treatment) with a mean number of 32 treatment weeks and 19 administered doses.
However, only 50% (~240 patients) of the fixed dose groups (300 mg Q4W and 200/300 mg Q2W) were treated over a period of 16 weeks and 82-86% of the 43 patients of the weight-based 2 and 4 mg/kg, respectively, have reached treatment duration of 16 weeks.

The number of administered doses was the highest in the weight-based dose group (38% vs. 27% having received >100 cumulative doses in the 2 mg or 4 mg/kg bw). The lowest exposure was recorded in the 300 mg Q4W group (8.8% (25/284) patients received >12 doses), the 200 and 300 mg Q2W dose groups had a slightly higher exposure of 10% having received >16 cumulative doses. As the mean and median number of study drug administrations and median treatment duration were similar between the placebo and treatment groups the comparative safety profile is complete.

The applicant provided further paediatric long-term safety data derived from the OLE study using a data cut-off of Dec 2018. While long-term treatment with dupilumab is still evolving it is not associated with any new safety concerns in adolescents with atopic dermatitis and it continues to be well tolerated. Additional longer-term safety data will continue to be monitored.

Treatment-emergent Adverse Events (TEAE)
R668-AD-1526
Any TEAE in SOCs Infections and Infestations occurred in comparable frequency in the treatment groups and in the placebo group e.g in 38 (45.8%) in the Q4W group, in 34 (41.5%) in the Q2W group and in 37 (43.5%) in the placebo group. It is noted that these frequencies are higher as compared to those reported in 16 weeks' studies in adults.

A higher incidence of treatment-related TEAEs was recorded in the 200/300 mg Q2W group of the pivotal study R668-AD-1526 compared to the 300 mg Q4W group (22% vs. 14.5% vs 15.3% in the placebo group).

Most treatment-related TEAEs were recorded in the infections and infestations SOC: 8.5% vs. 7.2% vs. 4.7% in the 200/300 mg Q2W, 300 mgQ4W and placebo arms respectively and conjunctivitis was the most common PT (3.7% vs. 1.2% vs. 0%) followed by upper respiratory tract infections (2.4% vs. 0% vs. 2.4%). However, conjunctivitis was a rare clinical symptom and based on the hitherto collected data it is assumed that this phenomenon is also linked to the underlying disease AD itself. In R668-AD-1526 study there was a higher proportion of patients with any TEAEs and treatment-related TEAEs in the dupilumab Q2W group compared to the Q4W group (as discussed the drug concentration was higher in the Q2W group as compared to the Q4W group).

The difference between these two treatment groups was mostly seen for Injection site reactions and Conjunctivitis. Treatment related events in the General disorders SOC were reported in 9.8% of subjects in the dupilumab Q2W group and only in 3.6 % of subjects in Q4W (these were mainly injection site reactions). An additional clear analysis of the relationship of the administered dose (200 or 300 mg dose Q2W) and observed TEAEs during the pivotal phase 3 study was provided by the MAH upon request.

Regarding the overall TEAE incidences of, the lower dose group (200 mg Q2W) had more TEAE (81.4% vs. 61.5% and 63.9%, respectively) and drug-related TEAE (25.6% vs. 17.9% and 14.5%, respectively) than the other dose groups (300 mg Q2W and 300 mg Q4W).
The SOCs of "Infections and Infestations" and "General disorders and administration site conditions had slightly higher incidences not driven by any particular PT. "The SOCs of "Skin and subcutaneous tissue

disorders", "Nervous system disorders" and "Eye disorders" had a higher incidence in the lower dose group (200 mg Q2W vs. 300 mg Q2W) driven by PTs of Dermatitis atopic, Headache and Conjunctivitis allergic.

Noticeable were higher incidences of headache (16.3% vs. 5.1%), atopic dermatitis (23.3% vs. 12.8%) and conjunctivitis allergic (7.0% vs. 0%). However, no SAEs or TEAEs leading to study drug discontinuation were observed and the TEAEs were almost exclusively mild to moderate. As conjunctivitis allergic, headache and injection site reactions are already listed as ADRs in the SmPC, it can be concluded that no new safety issues became apparent after these separate analyses of the different dose regimens.

With regards to the safety profile of the Q2W dosing schedule as compared to Q4W, minor differences were noted between the frequencies of occurrence of some PTs between the Q4W and Q2W group, overall the rates were comparable. However, it must be remembered that the number of events is rather low.

Increasing frequency of administration will cause an increased incidence of injection site reactions/AE's, however the Q2W regimen is expected to be less immunogenic that Q4W.
It is also agreed that the Q2W dose group was numerically superior to the Q4W dose group on most primary/key secondary categorical endpoints (IGA 0 or 1, NRS reduction of ≥3 points from baseline, NRS reduction of ≥4 from baseline), while it was numerically higher the difference is not clinically relevant between the dose regimens.
Moreover, the frequency of TEAE's and SAE's were similar between those aged 12-15 yrs compared to patients aged 15-18 years. For weight cut off < 60 kgs SAES were higher and occurred at a frequency of 2.7% compared to only 0.7% in those > 60 kgs.

A case of herpes simplex was the only new SAE in the updated data from this study using the new cut-off date and occurred in a patient who had been in close contact with an individual with herpes labialis prior to emergence of symptoms. The case was categorized as not related to dupilumab treatment by the investigator.

There was no consistent dose trend or an increasing TEAE incidence with increasing dose. In fact, all of SOCs have a lower incidence in the highest dose group of 300 mg Q2W than 200 mg Q2W and some show a similar incidence between 200 mg Q2W and placebo a higher rate of overall TEAEs in the adolescents weighing <60 kg who were dosed with 200 mg Q2W. This could be attributed to the low numbers of patients. The higher overall TEAE incidence in this cohort (<60 kg cohort) however is being driven by multiple SOCs and appear to be driven by PTs of Dermatitis atopic, Headache and Conjunctivitis allergic respectively. General administration and site disorders are also highest with 200mg Q2W regimen. None of these cases were reported as SAEs or TEAEs leading to discontinuation.

Overall, it appears that patients weighing less than 60kgs have a higher incidence of adverse events compared with those weighing more than 60 kgs with comparable exposure. However, the data is from a relatively small data set it may not be an accurate true estimate.

R668-AD-1434
Approximately 54% of the heterogenous population of OLE study R668-AD-1434 showed any TEAE, every tenth was deemed drug-related. A third of the patients who rolled over from the parent study R668-AD-1412 experienced treatment-related TEAEs. The sponsor was asked to clarify if these were deemed to be related to a change to the fixed dose regime. The applicant derives the apparent higher frequency of related TEAEs recorded in patients stemming from parent study R668-AD-1412 and continuing in the paediatric open-label extension study R668-AD-1434 from a longer duration of exposure/observation. The provided rationale on the basis of exposure-adjusted comparison of incidence of related TEAEs is endorsed since no major differences were detected between patients who rolled over and those of the overall patient population.

In R668-AD-1412

TEAEs were reported in 80 % of patients in the 4mg/kg group as compared to 55% the 2mg/kg group. In this study in both arms the most common AEs reported after both single doses and repeated weekly doses were

Nasopharyngitis and Atopic Dermatitis (exacerbation of AD). The episodes of exacerbation of AD could have resulted from the study design in which patients had an 8-week treatment interruption between single-dose administration during Part A and start of Part B.
Infections occurred twice as frequent in the 4mg/kg group as compared to the 2mg/kg group. The observed difference was driven primarily by Nasopharyngitis which was reported in 40 % of subjects in the 4 mg/kg arm as compared to 10 % of subjects in the 2mg/kg group.

Serious Adverse Events (SAE)
Serious adverse events were rare across the adolescent AD program. No patients in the dupilumab treatment groups of the pivotal study 1526 experienced SAEs. One of the recorded SAE (Injection Site Cellulitis) during the OLE study 1434 was deemed related to dupilumab. No deaths were recorded. Two AESIS were recorded (viral keratitis and conjunctivitis lasting ≥28 days) that were categorised by the investigator as related to dupilumab treatment.

Two patients of study R668-AD-1412 experienced SAE of infected dermatitis. According to the applicant the two SAEs of 'dermatitis infected' reported in R668-AD-1412 were deemed not related to the study drug by the investigator since their onset occurred outside the treatment period with dupilumab. The provided rationale on the basis of the two narratives is accepted.

Laboratory findings
No relevant changes were detected between the placebo and dupilumab groups in hematology, chemistry, and urinary analysis parameters apart from eosinophil and LDH levels.

No meaningful changes from baseline were observed regarding RBC or WBC. The transient increase in eosinophil counts during the first weeks of treatment is a known phenomenon caused by dupilumab treatment and was extensively discussed during the MAAs for dupilumab in the adult AD and adult/adolescent asthma population. Appropriate measures were implemented in the RMP and SmPC to avert possible risks in patients with hypereosinophilic conditions.
Neither clinically meaningful deviations of clinical chemistry parameters were observed nor electrolyte abnormalities. No harmful impact on the renal or liver function was detected.

30.6% (11/36) of all patients had at least 1 treatment-emergent PCSV for ECGs mainly with increase of 30-60 ms from baseline in QTc interval (16.7%). Neither significant ECG abnormalities (prolongation of QTc interval, maximum values did not exceed 500 ms) nor added or associated clinical conspicuities as syncopes or cardiac arrhythmias were detected. These provided data suggest that no negative impact of dupilumab on the cardiac function is to be expected.

Immunogenicity
There was a trend towards increased immunogenicity in adolescents as compared to adults. In all the studies of dupilumab in AD adults patients, submitted in the original application, which included studies conducted in patients treated with dupilumab for over 52 weeks, the proportion of patients with treatment-emergent positive response in the ADA assay was ≤10%.

In the pivotal study R668-AD-1526 most ADA-positive dupilumab- treated patients were detected in the dupilumab 300 mg Q2W and 300 mg Q4W dose group (20.5% and 20.7%, respectively). Thereof, 2.6% and 2.4% were persistent. All active doses developed treatment-emergent ADAs whereof the majority had a transient ADA response and only 5 patients had a persistent one. No distinct AE pattern became obvious amongst the ADA-positive and ADA-negative individuals. No cases of systemic hypersensitivity occurred during the studies in the ADA-positive population. In studies in adults only 2 % showed persistent titers whereas in the studies in adolescents the persistent ADA response was reported in 2.5 % in R668-AD-1526 study and in 6% in the long term extension study. There were no adolescents with boosted ADA response.

Based on the totality of the provided clinical data, the overall immunogenicity incidence and ADA profile in adults and adolescent patients is considered similar, especially for the most clinically relevant ADA endpoints, namely incidence of persistent ADA, high ADA titers and NAb positivity.

From a safety perspective, there were no events of systemic hypersensitivity (i.e., serum sickness and anaphylaxis) that were related to study drug, and as such no further analysis stratifying by ADA status was performed. Regarding other TEAEs, the low N precluded any meaningful analysis on safety by ADA status.

In patients with high titer the serum concentration decreased during the initial period however with continued treatment over time, ADA titer values declined (some to negative ADA status) with a corresponding increase in dupilumab concentrations to a typical steady-state value.
It is noted that a total of 1/3 patients with moderate titer ADA response had TEAEs under Injection Site Reaction (HLT), which were events of Injection Site Pain and Injection Site Swelling. A total of 2/3 patients with high titer ADA response had TEAEs under Injection Site Reaction (HLT), which were events of Injection Site Edema and Injection Site Hemorrhage.
It is agreed that the ADA titres were not associated with any specific SOC, occurred relatively low and majority were non serious.

In relation to the long term extension study, ADA positive subgroup reported a higher incidence of ISRs (7/58 [12.1%]) than the ADA negative subgroup (13/234 [5.6%]), with a numerically increasing incidence observed with increasing ADA titers (low titer 3/46 [6.5%]; moderate titer 1/8 [12.5%]; high titer 3/4 [75%]). This is expected with subcutaneous injection of biologics. None of the ISRs led to permanent study drug discontinuation and all were non-serious except one serious case of Injection site oedema.

Subgroup analyses

No pregnancies were reported during all studies. No rebound effect was observed.

Only two patients of the pivotal study had a treatment interruption; one case of permanent treatment discontinuation was recorded in the placebo group.

A cumulative search regarding post-marketing experience in adolescent patients revealed an off-label use in 156 paediatric patients whereof 2 had unspecified SAE.

In summary, no new safety concerns arose from the adolescent population and the safety profile is considered similar to that observed in adults. No new identified risks are present which should be incorporated in the RMP. The known safety profile was confirmed by updated data derived from OLE study R668-AD-1434.

2.5.2. Conclusions on clinical safety

Overall, dupilumab was well tolerated in the adolescent patient population across the 4 studies included in this submission, including the dose and method of administration proposed for licensing. No new safety concerns arose from the adolescent population and the data were consistent with the hitherto known safety profile of the adult AD population.

Overall, the size of the safety database for dupilumab to support the indication in adolescent patients with moderate to severe atopic dermatitis is PIP-conform concerning the pivotal study. The need of long-term safety data has been addressed. The potential risk of malignancy is addressed in the RMP. Treatment with dupilumab in the AD placebo-controlled studies and the open-label extension studies was generally well tolerated and exhibited a low immunogenic potential.

Sufficient long-term safety data was submitted upon request that substantiate the favourable safety profile in the adolescent population.

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 CHMP received the following PRAC Advice on the submitted Risk Management Plan: The PRAC considered that the risk management plan version 3.0 is acceptable.

The MAH is reminded to consolidate the different RMP versions that are currently under evaluation. In addition, the MAH should implement the changes regarding off-label use within variation II/17. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

Safety concerns

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risks	Malignancy Eosinophilia associated with clinical symptoms in asthma patients
Missing information	Use in paediatric AD and asthma patients <12 years of age Use in pregnant and lactating women Conjunctivitis related events in AD patients Long-term safety Dupilumab effect on live vaccine safety

Pharmacovigilance plan

There are no changes to the pharmacovigilance plan.

Risk minimisation measures

There are no changes to risk minimisation measures.

2.7. Update of the Product information

This application is an Extension of Indication for Dupixent to extend the atopic dermatitis indication to the paediatric adolescent population 12 years to 17 years.

This application is submitted in accordance with the requirement of Article 46.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

2.7.1. User consultation

The MAH will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as recommended during procedure EMEA/H/C/004390/X/004G use within the next two months as agreed previously with CHMP/EMA.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, duplilumab is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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 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 (Ring, 2012) (Eichenfield, 2014) (Geoghegan, 2017).

Atopic dermatitis is the most common childhood inflammatory skin disease, affecting over 20% of the children in many industrialized countries. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three estimated that 5% to 10% of adolescents in most European countries have AD (Sole, 2010). The majority of the adolescents presenting with AD have disease onset early in life. Forty to 60% of the cases of childhood AD persist post-puberty into adolescence (Wuthrich, 1999). Onset in adolescence occurs in a small group (<10%) of the total cases of AD (Bieber, 2017). A significant proportion of adolescent patients suffer from either moderate (17%) or severe (10%) forms of the disease (Johansson, 2015).

There is a paucity of studies comparing adults and adolescents with respect to the cellular and molecular mechanisms of disease in AD, because mechanistic studies involving the collection of skin biopsies and other invasive procedures are generally not feasible or pose ethical challenges in children.

Based on multiple other similarities, however, it has been postulated that the mechanisms are similar. 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 (Gittler, 2012).

Clinical presentation of AD in adolescents 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 (Wasserbauer, 2009) (Rudikoof, 1998). 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 adolescents, as in adults. The cycle of

itching and scratching exacerbates the cellular damage in skin lesions and facilitates secondary infections, which can be serious (Boguniewicz, 2018).

Consistent with the observation that AD in children is dominated by Type 2 inflammation is the demonstration that adolescents with AD also have a higher prevalence of allergic comorbidities such as asthma, allergic rhinitis, and food allergies (Silverberg, 2013).

Atopic dermatitis can be disabling in adolescents due to intractable pruritus and disfiguring skin lesions. The disease can affect the overall quality of life (QOL), cause significant sleep loss, have a negative impact on educational development and social interactions, and at times, cause psychological problems, including major depression, anxiety, and attention deficit hyperactivity disorder (Halvorsen, 2014) (Slattery, 2011). A survey that assessed rates of depressive and anxiety disorders in a clinical sample of adolescents with AD found increased rates of anxiety as compared to community estimates (23% to 40% vs. 3% to 6%). The risk of suicidal ideation has been found to be higher in patient with AD as compared to controls. A cross sectional study showed that 15.5% of dolescent patients with eczema reported suicidal ideation as compared to 9% in general population (Halvorsen, 2014).

In addition, serious skin infections are associated with AD in adolescents, as in adults. More than 90% of patients with AD have *Staphylococcus aureus* colonization on their skin compared with only 10% of healthy individuals (Ong, 2014) which is directly correlated with AD severity.

In addition, adolescent patients with AD may experience episodes of eczema herpeticum, a potentially life-threatening disseminated herpes simplex virus-1 (HSV-1) or, less commonly, HSV-2 infection (Boguniewicz, 2010).

3.1.2. Available therapies and unmet medical need

Currently Available Therapies for Atopic Dermatitis in Adolescent Patients

In general, therapies recommended for the treatment of AD in adults are also used in adolescents, and the treatment guidelines for AD do not specify age ranges in the pediatric population.
Currently available therapies have significant side effects, and various systemic immunosuppressive drugs are used off-label with little evidence to support their use. Similar to the adult population, topical treatment is the mainstay of management of mild-to-moderate AD in adolescents. 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 (Hengge, 2006).

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. Moreover, continuous use of TCS can be associated with development of tachyphylaxis.
Topical calcineurin inhibitors (TCIs) are also available for use in adolescents, mostly as second-line therapy. Use of these agents is typically limited to areas that are prone to skin atrophy from application of TCS, eg, face, genitals, and flexural areas.

Systemic agents approved for the treatment of AD in adolescents include systemic corticosteroids for severe or incapacitating AD intractable to conventional treatments. Ciclosporin A 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 off label in treatment of severe forms of the disease, including methotrexate, azathioprine and mycophenolate mofetil.

Unmet Medical Need in Adolescent Patients

Moderate-to-severe AD is a serious, chronic, debilitating skin disease with substantial impact on day-to-day functioning and wellbeing of affected adolescent patients. It shares pathophysiological pathways with other atopic/allergic conditions such as asthma, allergic rhinitis, and food allergies, which are common comorbidities in patients with AD.

The currently available treatments for AD in adolescent patients have important limitations including unsatisfactory effectiveness, limited data from randomized, controlled clinical trials to guide their use in clinical practice, and important risks and side effects. These limitations result in a large number of adolescent patients with moderate-to-severe AD whose disease cannot be safely controlled by available therapies. Therefore, there exists an unmet medical need for an effective treatment that has a favorable safety profile for long-term use for adolescent patients with moderate and severe forms of the disease not adequately controlled by topical prescription therapies.

3.1.3. Main clinical studies

The clinical development program of dupilumab in the treatment of adolescent AD comprises 4 clinical studies.

R668-AD-1526 is the pivotal phase 3 monotherapy study in patients aged 12-18 years with moderate-to-severe AD not adequately controlled with currently available topical treatments.

Supportive data are derived from a phase 2a, open-label pharmacokinetic (PK)/safety study (R668-AD-1412), an pediatric open-label extension study (R668-AD-1434) and an open-label autoinjector (AI) study (R668-AD-1607, note: data assessed as part of the extension of indication in asthma).

Thus, relevant patient exposure includes 292 adolescent patients stemming from studies R668-AD-1526, R668-AD-1412 and R668-AD-1434.

OLE study R668-AD-1434 recruited patients from studies R668-AD-1526, R668-AD-1607 and R668-AD-1412. Included patients were treated with 2 mg/kg QW or 4 mg/kg QW, the dose was subsequently amended to a fixed dose of 300 mg Q4W with the possibility of up-titration to 200/300 mg Q2W dependent on the bodyweight in case of inadequate clinical response at week 16.

The clinical development program was designed to assess the safety and efficacy of dupilumab in adolescent patients with moderate-to-severe AD not adequately controlled with currently available topical treatments. The patient population comprised adolescents with AD, as defined by the American Academy of Dermatology Consensus Criteria (Eichenfield, 2004) (Eichenfield, 2014). These patients had moderate-to-severe AD lesions affecting a large portion of their body surface area (BSA). They experienced high levels of AD symptoms, including pruritus. Their disease could not be adequately controlled with topical prescription medications.

This population included patients who had been, or would typically be, candidates for systemic AD therapies. Efficacy assessments included measurements of the extent and intensity of AD signs, severity of AD symptoms, impact of AD on QOL, and anxiety and depression scores.

A total of 205 adolescent patients were exposed to dupilumab in the parent studies R668-AD-1526 or R668-AD-1412 and 299 patients during the OLE study R668-AD-1434.

3.2. Favourable effects

The applicant has demonstrated clinical efficacy of dupilumab administered as 300 mg Q4W, 200/300mg Q2W or weight-based dose regimen of 2 and 4 mg/kg/bw/QW, respectively, as monotherapy or in combination with TCS in patients who suffer from moderate-to-severe AD and are insufficiently controlled on topical therapies for AD.

The superiority to placebo is demonstrated for these three dupilumab doses, and especially the results from the studies R668-AD-1526 show a significant higher and clinically meaningful improvement in severity of AD

in the dupilumab 300 mg Q4W and 200/300 mg Q2W groups compared to placebo, whereby the Q2W regimen yields better results regarding the analysed treatment effects. Also significant efficacy was demonstrated in the key secondary endpoints such as pruritus, SCORAD, Change in ACQ-5, GISS, POEM, HADS and CDLQI. The effects demonstrated are considered to be clinically relevant.

The therapeutic effects were seen as early as 2 weeks with a near maximal effect demonstrated at 12 to 16 weeks. In summary, efficacy results of OLE study R668-AD-1434 showed improvements of AD symptoms based on the proportion of patients who achieved the co-primary endpoints as well as key secondary endpoints which is substantiated by long-term efficacy data with 109 and 28 patients with an overall treatment exposure of ≥52 ≥104 weeks, respectively.

34 of the included 275 patients had completed 52 treatment weeks. Thereof 41.2% (14/34) reached the co-primary endpoint by achieving IGA 0 or 1; the proportion of patients with EASI-75 relative to baseline of the previous study was 82.4% (28/34). The majority (76%) applied concomitant topical TCS/TCI.The proportions reaching the co-primary endpoints were higher after week 16 than during the pivotal study R668-AD-1526 but these results might be influenced by residual dupilumab concentrations resulting from the treatments obtained during the parent studies (54% (149/275) had a treatment gap of 6-13 weeks before entering the OLE study); it is unclear however, how many patients had shorter treatment interruptions.

Efficacy results in the subgroup of patients who rolled over from R668-AD-1412 were exactly the same as in the OLE study whereby more patients used TCS/TCI (97.2%).

The proportion of patients that needed up-titration of dupilumab from the previous Q4W regimen to the weight-based Q2W regimen (36.2% until week 16) reflects higher dupilumab concentrations were needed to control disease activity in this AD patient population.

The patients enrolled from study 1412 which was a weight-based regimen, appear to achieve increasingly improved results over time for IGA 0/1, EASI 75 and 90, as well as pruritus NRS reduction ≥4. Improvement from baseline is expected as these patients had a treatment interruption of at least 8 weeks between the last dose in the R668-AD-1412 and the baseline of the OLE. Although the numbers of patients are decreasing over time, consistent or improved results are seen between weeks 52 to 104.

In summary, efficacy results in the total study population included in OLE study R668-AD-1434 showed improvements in AD symptoms based on the proportion of patients who achieved the co-primary endpoints as well as key secondary endpoints..

3.3. Uncertainties and limitations about favourable effects

21% of the patients assigned to the dupilumab 200/300 mg dose group, which is the intended dose for the claimed indication, used rescue medication during the pivotal study R668-AD-1526 and approximately 15 % had used any rescue medication by treatment week 16.

Long-term efficacy data is limited to 34 patients completing week 52 and merely 134 patients reached week 16. The above data is a mixture of patients who continued on treatment, those who taken off treatment and subsequently were retreated following relapse of control.

3.4. Unfavourable effects

A higher incidence of treatment-related TEAE was recorded in the 200/300 mg Q2W group of the pivotal study R668-AD-1526 compared to the 300 mg Q4W group (22% vs. 14.5% vs 15.3% in the placebo group). Most related TEAE were recorded in the infections and infestations SOC: 8.5% vs. 7.2% vs. 4.7% and conjunctivitis was the most common PT (3.7% vs. 1.2% vs. 0%) followed by upper respiratory tract infections (2.4% vs. 0% vs. 2.4%).

A higher incidence of ISRs (9.8% vs. 3.6% vs. 4.7%) was recorded in the dupilumab Q2W treatment group compared with the other 2 groups as already seen in the adult population.

Approximately 54% of the heterogeneous population of OLE study R668-AD-1434 showed any TEAE, every tenth was deemed drug-related. A third of the patients who rolled over from the parent study R668-AD-1412 experienced treatment-related TEAEs.

In the long term extension study 54.2% of subjects reported any TEAEs whereas any drug-related TEAE was reported in 9.5% of subjects.

In the pivotal study R668-AD-1526 most ADA-positive dupilumab- treated patients were detected in the dupilumab 300 mg Q2W and 300 mg Q4W dose group (20.5% and 20.7%, respectively). Thereof, 2.6% and 2.4% were persistent. During study R668-AD-1412, ADA response was observed in 29 patients (72.5%), 50% of which were categorized as having a persistent, treatment-emergent response. The majority (23/29, 79.3%) of the treatment-emergent positive responses in the ADA assay were categorized as low titer.

3.5. Uncertainties and limitations about unfavourable effects

Conjunctivitis was a low incidenceclinical symptom and it is assumed that this symptom is related to AD as primary disease since this phenomenon was not observed in the asthma population.
Based on the weight-of-evidence assessment of the literature, IL-4 and IL-13 actions via the IL-4Rα activation pathway are predominantly protumorigenic. Although there were no cases of malignancy reported in paediatric studies the risk for children could be potentially higher. Malignancy is listed as an important potential risk in the RMP.

Based on the currently available data there was no significantly increased risk detectable for dupilumab regarding malignancy, all types of infections or systemic hypersensitivity reactions. However, the safety profile has to be refined over the next years with more data coming from the ongoing open label extension trials in AD and Asthma.

3.6. Effects Table

Table 40: Effects Table for dupilumab (data cut-off: 05 Apr 2018)

Effect	Short description	Unit	Treatment Q2W	Treatment Q4W	Control PLAC	Uncertainties / Strength of evidence	References
Favourable Effects							
IGA 0/1	Proportion of patients with IGA 0 to 1	%	24.4	17.9	2.4	Dupilumab 300 mg Q4W DIFF vs placebo 95% CI 15.5 (6.70, 24.31) Dupilumab 200/300 mg Q2W diff vs placebo 95% CI 22.0 (12.20, 31.87)	Study R668-AD-1526
EASI -75	Proportion of patients with EASI -75 (≥75% improvement from	%	41.5	38.1	8.2	Dupilumab 300 mg Q4W DIFF vs placebo 95% CI 29.9 (17.94,	Study R668-AD-1526

Effect	Short description	Unit	Treatment Q2W	Treatment Q4W	Control PLAC	Uncertainties / Strength of evidence	References
	baseline)					41.78) Dupilumab 200/300 mg Q2W diff vs placebo 95% CI 33.2 (21.07, 45.39)	
Key secondary endpoints	Perc. Change in EASI baseline-week 16	%	-65.9	-64.8	-23.6	Key secondary endpoints support the effects seen in the co-primary endpoints	Study R668-AD-1526
	Perc. Change baseline-week 16 in NRS	%	-47.9	-45.5	-19		Study R668-AD-1526
	Prop. Of patients baseline-week 16 in NRS improvement NRS≥3	%	48.8	38.6	9.4		Study R668-AD-1526
Unfavourable Effects							
Treatment-related TEAE	Infections and infestations SOC	%	8.5	7.2	4.7	Most adverse drug reactions were mild	Study R668-AD-1526
	ISR		9.8	3.6	4.7	Placebo group percentage higher than Q4W treatment group	Study R668-AD-1526
	Conjunctivitis		3.7	1.2	0	Phenomenon associated with underlying AD disease	Study R668-AD-1526
	Upper respiratory tract infections		2.4	0	2.4	Placebo group percentage higher than Q4W treatment group	Study R668-AD-1526
	ADA response		20.5	20.7	3.5	ADA were not associated with special TEAE. ADA incidence balanced between treatment groups.	Study R668-AD-1526

Abbreviations: PLAC=Placebo, ISR=Injection Site Reaction, ADA= Anti-drug antibodies

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applicant has clearly demonstrated the beneficial treatment effects of dupilumab 200/300 mg Q2W as a monotherapy or combined with TCS in patients with moderate-to-severe AD who are inadequately controlled on topical therapies.

The maintenance data provided on longer term use to 52 weeks was statistically significantly in favour of dupilumab.

The general and most relevant safety concerns of dupilumab identified during the AD program are related to infections, eye disorders (conjunctivitis and related conditions), injection site reactions, antidrug antibodies resulting in systemic hypersensitivity reactions, risk of malignancy, limited long term data in patients treated with the proposed biweekly dose of dupilumab as well as uncertainties about the impact of dupilumab on pregnancies and their outcomes. This will be monitored in the post approval setting as mentioned in the RMP.

In terms of infections the overall rate was slightly higher in the dupilumab treated patients compared with the placebo group. These were generally mild to moderate and common viral infections prevailed. No increased risk for helminth or opportunistic infections was identified. Conjunctivitis was a rare clinical symptom and it is assumed that this symptom is related to AD as primary disease since this phenomenon was not observed in the asthma population. The long term effect of chronic conjunctivitis in these patients is unknown. Cases of conjunctivitis will continue to be further monitored in the post approval setting as described in the RMP.

Dupilumab use was not associated with a higher risk of experiencing TEAEs of systemic hypersensitivity in the adolescent population. No cases of systemic hypersensitivity occurred during the studies in the ADA-positive population. There was a higher rate of ISR events in the dupilumab 300mg Q2W treat population compared with the dupilumab 300mg Q4W group. None of the events were classified as severe or serious. Discontinuation rates due to ISRs were very low. Overall, ISRs seemed to be mild to moderate self-limiting reactions that were well tolerated by patients.

No case of malignancy was present across treatment groups. However, there is insufficient long term exposure data to characterise the risk of developing malignancy particularly at the dose proposed. This issue has been discussed during the initial MA for AD and is part of the RMP and subject to investigation in the OLE studies.

3.7.2. Balance of benefits and risks

Based on the data provided on efficacy and safety, the CHMP is of the opinion that the favourable effects outweigh the unfavourable effects. The benefit-risk profile of dupilumab is considered positive in the paediatric adolescent (12 to 17 years) AD population.

3.7.3. Additional considerations on the benefit-risk balance

None.

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 for Dupixent to extend the atopic dermatitis indication to the paediatric adolescent population 12 years to 17 years. This study is submitted in accordance with the requirement of Article 46.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

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

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA Decision(s) P0169/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. 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

Extension of Indication for Dupixent to extend the atopic dermatitis indication to the paediatric adolescent population 12 years to 17 years. This is also submitted in accordance with the requirement of Article 46.

As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

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

Summary

Please refer to the variation assessment report.