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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

### Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/0000

### 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
AE	Adverse event
AESI	Adverse event of special interest
AKC	Atopic keratoconjunctivitis
ALT	Alanine Aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of covariance
anti-dsDNA	Anti-nuclear antibody against double-stranded DNA
anti-TPO	Anti-thyroid peroxidase
ARGUS	A Pharmacovigilance and Risk Management Safety Software System
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BSA	Body surface area
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMQ	Customized MedDRA query
CPK	Creatine phosphokinase
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CsA	Ciclosporin or Cyclosporine A
CYP	Cytochrome P450
DLQI	Dermatology Life Quality Index
EAIR	Exposure-adjusted incidence rate
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EDC	Electronic data capture
EQ-5D	European Quality of Life-5 Dimensions
EQVAS	European Quality of Life visual analog scale
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GISS	Global Individual Signs Score
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – subscale for anxiety
HADS-D	Hospital Anxiety and Depression Scale – subscale for depression
HbA1c	Haemoglobin A1c
HbcAb	Hepatitis B core antibody
HbsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HLT	High level term
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IFN $\gamma$	Interferon gamma
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
ILC2s	Innate Lymphoid Cells 2
IL-4Ra	Interleukin-4 receptor alpha
IRB	Institutional review board
ISR	Injection site reactions
IVRS	Interactive voice response system
IWRS	Interactive web responses system

KD	Dissociation constant
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-effect model with repeated measures
NRS	Numerical Rating Scale
OLE	Open-label extension
PCS	Pruritus Categorical Scale
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PPS	Per protocol set
PT	Preferred term
QoL	Quality of life
QW	Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous(ly)
SCORAD	SCORing Atopic Dermatitis
SD	Standard deviation
SE	Standard error
SMQ	Standardized MedDRA query
SNOT-22	Sinonasal Outcomes Test-22
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TARC	Thymus and activation-regulated chemokine (CCL-17)
TB	Tuberculosis
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
TEAE	Treatment-emergent adverse event
Th2	Type 2 helper T cell
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential
WOCF	Worst observation carried forward
INN	international nonproprietary name
PFS	pre-filled syringe
PFS-S	pre-filled syringe with safety system
SmPC	Summary of product characteristics
AS	active substance
FAS	formulated active substance
FP	finished product
MCB	master cell bank
WCB	working cell bank
CHO	chinese hamster ovary
TSE	transmissible spongiform encephalopathy
BSE	bovine spongiform encephalopathy
PFMEA	process failure modes and effects analysis
RPN	risk priority number
IPC	in process control
CQA	critical quality attributes
CPP	critical process parameter
GQA	general quality attribute

GPP	general process parameter
PPQ	process performance qualification
ADCC	antibody-dependent cell-mediated cytotoxicity
CDC	complement-dependent cytotoxicity
IgG	Immunoglobulin G
mL	millilitre
L	litre
PS80	polysorbate 80
Ph. Eur.	European Pharmacopoeia

# 1. Background information on the procedure

## 1.1. *Submission of the dossier*

The applicant sanofi-aventis groupe submitted on 4 November 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Dupixent, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy. Dupixent can be used with or without topical therapy.

### **The legal basis for this application refers to:**

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

### ***Information on Paediatric requirements***

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0219/2016 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver:

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 P/0219/2016 was not yet completed as some measures were deferred. 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.

The PDCO issued an opinion on partial compliance for the PIP P/0219/2016.

### ***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.

#### **New active Substance status**

The applicant requested the active substance dupilumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

## **Scientific Advice**

The applicant received Scientific Advice from the CHMP on 20/03/2014, 12/06/2014, 20/11/2014, 17/03/2015, 21/05/2015 and 28/04/2016. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

### **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: Patrick Salmon

- The application was received by the EMA on 4 November 2016.
- The procedure started on 24 November 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 February 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 February 2017.
- During the meeting on 23 March 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2017.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Safety/Efficacy assessment of the product:
  - A GCP inspection at one investigator site in Estonia between 20 February 2017 to 22 February 2017, 1 investigator site in the United States between 6 February 2017 to 8 February 2017 and 1 sponsor site in the United States between 3 April 2017 to 7 April 2017. The outcome of the inspection carried out was issued on 8 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 17-20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dupixent on 20 July 2017.



## **2. Scientific discussion**

### **2.1. Problem statement**

#### **2.1.1. Disease or condition**

Atopic dermatitis (AD) is a chronic or chronically relapsing inflammatory skin disease.

#### **2.1.2. Epidemiology**

An estimated 2% to 10% of adults are affected by AD. Atopic dermatitis is commonly associated with asthma and other atopic/allergic conditions, with which it shares common pathophysiological pathways.

#### **2.1.3. Aetiology and pathogenesis**

The pathophysiology of AD is influenced by genetics and environmental factors and involves a complex interplay between antigens, skin barrier defects, and immune dysregulations, in which a polarized inflammatory response induced by the marked activation of the T-helper type 2 (Th2) cell axis plays a central role. Two cytokines, IL-4 and IL-13, are critical in the initiation and maintenance of the Th2 inflammatory pathway.

#### **2.1.4. Clinical presentation, diagnosis**

AD is characterized by pruritus, xerosis, and eczematous lesions. Especially pruritus and skin infections which are a major complication in AD compromise health and lower the quality of life and can result in sleep disturbance, pain and psychiatric comorbidities such as anxiety, depression, and suicidal ideation.

#### **2.1.5. Management**

Limited treatment options are available. Local therapies often relieve typical symptoms for the duration of their application. Atopic dermatitis is treated primarily with topical corticosteroids (TCS). However, continuous long-term application of TCS, particularly those with higher potency, is not recommended, because of side effects such as skin atrophy, HPA axis suppression and others. The majority of patients with mild AD respond well to topical therapy. However, patients with moderate-to-severe AD often do not achieve adequate control with acceptable doses of topical medications and frequently require systemic therapy. Systemic therapy is indicated in patients who do not respond adequately to topical therapies or for whom topical therapy is inadvisable. Currently available systemic therapies include nonselective immunosuppressants such as systemic corticosteroids or Ciclosporin A, which are associated with severe toxicity and side effects.

## ***About the product***

Dupilumab is a recombinant human IgG4 monoclonal antibody with binding specificity to human interleukin-4 receptor IL-4Ra.

IL-4Ra forms an integral part of two distinct receptors, Type I and Type II receptors, through which IL-4 and IL-13 mediate their effects on type 2 immune responses which involves the cooperation of the innate and adaptive immune systems. Evidence suggests a role for type 2 inflammation in patients with atopic dermatitis, including increased circulating IgE, increased eosinophils, basophils, Innate Lymphoid Cells 2 (ILC2s) and mast cells, and marked increases in several type 2 cytokines and chemokines, such as TSLP, TARC, IL-4, IL-5, and IL-13.

## ***2.2. Quality aspects***

### **2.2.1. Introduction**

Dupilumab finished product is presented as a two (2) milliliter solution for injection containing 150 mg/mL of dupilumab (INN) as active substance.

Other ingredients are: sucrose, L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate and water for injections.

The product is available in a 2 mL single-use pre-filled syringe (PFS) without or with safety system (PFS-S) with a fixed 27 gauge ½ inch, thin wall stainless steel staked needle as described in section 6.5 of the SmPC.

### **2.2.2. Active Substance**

#### ***General information***

Dupilumab is a recombinant human IgG4 monoclonal antibody that binds specifically to the IL-4R alpha sub-unit of the IL-4 and IL-13 receptor complex and, is a new active substance. Dupilumab has a predicted protein molecular weight of 146,897.0 Da and contains a single, conserved N-glycosylation site (Asn<sup>302</sup>) in the Fc region of each heavy chain subunit. Dupilumab heavy chains contain a serine to proline mutation at amino acid 233, which is located in the hinge region of the Fc domain

#### ***Manufacture, characterisation and process controls***

##### ***Description of manufacturing process and process controls***

Dupilumab active substance (AS) manufacturing is performed at Regeneron Pharmaceuticals, Inc., Columbia Turnpike, Rensselaer, USA.

Regeneron currently maintains suites for the manufacture of AS. These suites utilise equivalent or identical equipment. Commercial supply is planned to be manufactured in these suites. Other sites for specified testing are described in the application.

The manufacture of dupilumab AS represents a standard manufacturing process for the manufacture of monoclonal antibodies. It is achieved in three main parts, the upstream process, which produces the antibody, the downstream process, which purifies the antibody and the formulation of the active substance (formulated active substance- FAS).

Dupilumab is produced by a cell culture process with recombinant Chinese hamster ovary (CHO) cells that have been engineered to constitutively express dupilumab heavy and light chains. Dupilumab protein is expressed by the cells and is secreted into the culture medium.

The recombinant protein product is harvested and purified leveraging standard chromatographic and membrane based techniques and includes several steps ensuring adventitious agent safety.

At the conclusion of purification, the AS is sterile-filtered and dispensed for long-term storage until needed for formulation.

Dupilumab FAS is produced at a final concentration of 150 mg/mL. The AS batches are thawed, pooled and mixed. This is followed by mixing with dilution buffer and excipient buffer, filtration and further mixing. The dupilumab FAS is then dispensed into bottles with caps and transferred to storage until shipment to the finished product (FP) filling site.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, where relevant, are described for each step for AS and FAS. A cumulative assessment of risk and importance was performed.

The applicant has provided a description of the composition and preparation of all buffers and solutions listed in this section as well as chromatography/filter conditions. The AS and FAS manufacturing processes are considered acceptable.

### ***Control of materials***

The antibody is produced in CHO cells. The anti-IL4R $\alpha$  antibody, dupilumab, was generated by immunization of Regeneron's VelocImmune® mice followed by screening for antibodies specific to human IL4R $\alpha$ . One antibody was chosen and DNA encoding the antibody variable domains was cloned to yield the fully human antibody dupilumab. The cDNA encoding the dupilumab heavy chain and light chain genes was then cloned into expression plasmids and transfected into a CHO host cell line. After transfection and stable integration of the dupilumab expression plasmids into the host cell genome, enabling the constitutive expression of dupilumab, the dupilumab expression cell line was isolated using Regeneron's proprietary cell expression technologies.

The dupilumab MCB will be used to generate new WCBs for routine production of dupilumab AS. An appropriate number of vials were manufactured, cryopreserved and stored at three separate facilities. Three dupilumab WCBs have been prepared from the MCB. The WCB first used in manufacturing AS and used for the manufacturing of dupilumab AS for Phase 3 clinical trials will continue to be used for routine commercial manufacturing, as available. New WCBs were prepared and a protocol for generation & qualification of new WCBs has been provided. Adventitious agent testing of the MCB and WCB was conducted, as per ICH Q5A requirements. The genetic stability of dupilumab production cell line was investigated through the MCB and WCB cell banking process. No evidence of viral or microbial contamination was observed.

Incoming raw materials (chemical materials, chromatography resins and filters) are adequately controlled (acceptable specifications have been provided for all raw materials). Compendial raw materials are tested in accordance with the corresponding monograph, while specifications for non-compendial raw materials are presented. A leachable/extractable risk assessment was performed for all materials used in dupilumab AS and FAS manufacturing processes. The dupilumab manufacturing

process does not use raw materials of direct animal origin, other than CHO cells. TSE/BSE certificates were provided, as applicable.

### ***Control of critical steps and intermediates***

All AS and FAS manufacturing processes steps include controls within the IPC program for assurance of operational and performance consistency, as well as adherence to product safety requirements for each step.

When evaluating parameters and attributes for inclusion in the IPC program, a process failure modes and effects analysis (PFMEA) approach was applied. Potential failure modes were rated on a 1 to 10 scale for severity, likelihood and detectability, with higher scores representing higher relative risk. The product of the severity, likelihood, and detectability scores was calculated, generating a risk priority number (RPN). Failure modes were sorted from highest (greatest risk) to lowest (lowest risk) RPN.

Once a parameter or attribute was chosen for inclusion in the IPC program, it was formally classified as either a critical quality attribute (CQA), a critical process parameter (CPP) a general quality attribute (GQA) or a general process parameter (GPP).

All quality attributes monitored at AS and FAS release are considered COAs. GPPs and GOAs were assigned action limits and CPPs and COAs were assigned acceptance criteria. Actions taken if limits are exceeded are specified.

### ***Process validation***

All key components of the commercial Dupilumab AS and FAS manufacturing processes were prospectively evaluated and validated through laboratory and full scale studies.

Two Dupilumab AS manufacturing processes have been validated, the commercial processes and an earlier process for some of the clinical studies. The two processes differ only in certain downstream purification steps

In general, acceptance criteria for all critical parameters and attributes were met for cell culture, unprocessed bulk material, harvest and purification process steps and released batches.

The applicant has also performed validation of the FAS manufacturing process. A variety of values for operational parameters have been used in order to establish their acceptable range. Release data for PPO FAS lots have been provided. All batches met acceptance criteria in place at the time of testing.

The dupilumab process-related impurity clearance studies provide evidence of the robust, reproducible process-related impurity clearance capability of the downstream purification process. All AS lots produced during investigation of PPOs met the release specifications at the time for all product-related impurities. In conclusion, the AS and FAS manufacturing process has been validated adequately.

### ***Characterisation***

Dupilumab AS lots were characterised, including determination of primary, secondary, and tertiary structure, charge variants, purity, and potency.

For product-related impurities, the applicant has provided adequate description of their characterisation, their effect on the potency of the product and their control strategy, during manufacture, at release and over the intended shelf life of the product.

Process-related impurities were adequately described and clearance capabilities of the manufacturing process shown. Sound rationale has been provided for not testing some process-related impurities. These are based on in-process testing data, assessment of worst case scenario and recommended acceptable daily exposure levels. The process-related impurities that are not routinely tested for are

common to both the commercial and clinical processes and therefore have been present in clinical trial material.

### **Specification**

The specifications for Dupilumab AS and FAS are provided and cover control of identity, purity and impurities, potency and other general tests.

The process used for setting and justification of specifications and specification ranges and limits has been adequately described. In brief, clinically-qualified values were used where possible. The applicant also leveraged historical data from AS and FAS lots by establishing tolerance interval limits. Stability data was used to support end-of-shelf specifications.

Parameters and acceptance criteria of FAS specifications are acceptable.

### **Analytical methods**

The analytical procedures have been provided for testing the AS and formulated AS at release and during stability and are sufficiently described in the dossier and validated.

The potency assay is performed as an AS, FAS and bulk PFS release test.

### **Batch analysis**

Dupilumab FAS includes several formulations examined in clinical trials, as well as the commercial FAS composition.

Results of batch release testing demonstrated that the commercial manufacturing process is capable of producing AS and FAS of consistent and comparable quality at the time of batch release. The applicant has additionally demonstrated the comparability of dupilumab AS manufactured by earlier iterations of the manufacturing process supplying clinical trials.

### **Reference materials**

Dupilumab primary and working reference standards are qualified using AS and FAS release testing as well as additional characterisation. A current in-house primary reference standard has been appropriately characterised and is prepared from a lot representative of production and clinical materials. In-house working reference standards used in the testing of production lots are calibrated against this primary reference material. Future RS material will be qualified and characterised as above according to a defined process. Also, distinct reference materials for process-related impurities have been established and described sufficiently.

### **Stability**

The stability results indicate that the AS and FAS are sufficiently stable and justify the proposed shelf lives in the proposed containers.

Dupilumab AS and FAS stability studies have been carried out according to ICH recommended long term and accelerated storage conditions. Test articles are packaged in small scale packaging that acceptably simulates that used for long term storage of dupilumab AS. The representative real-time stability is based on AS batches and FAS batches produced with the commercial process. Supportive long-term stability studies were also provided.

The applicant committed to complete the stability studies of the primary and supporting dupilumab AS and FAS batches at the long-term storage condition according to the stability protocols provided. In

accordance with EU GMP guidelines<sup>1</sup>, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The forced degradation study confirmed that the current control strategy used for release and stability testing of dupilumab is appropriate and that the methods are capable of detecting the most prominent degradation pathways.

### ***Comparability exercise for Active Substance***

Four production processes have been used to produce dupilumab for clinical studies.

The applicant has adequately outlined the development of the commercial process from earlier processes and has demonstrated comparability with material from these earlier batches used in clinical trials.

### **2.2.3. Finished Medicinal Product**

#### ***Description of the product and pharmaceutical development***

The FP is supplied as a single-use prefilled syringe (PFS) or prefilled syringe assembled with a safety system (PFS-S), containing 2.0 mL of 150 mg/mL dupilumab for subcutaneous injection.

The content of 2 mL of the PFS or PFS-S is intended to be injected, providing a 300 mg dose of dupilumab. The PFS presentation is comprised of a primary container, referred to as a “bulk prefilled syringe”, a transparent plunger rod and a white finger flange to facilitate handling. The bulk PFS is a siliconized, 2.25 mL, clear glass syringe barrel, equipped with a stainless steel 27 gauge needle, an elastomeric plunger stopper and a needle shield. The PFS-S presentation includes a safety system for sharps injury prevention, consisting of a needle guard with a spring for activation. All excipients used in the manufacture of dupilumab FAS/FP are known pharmaceutical ingredients and are compendial grade (Ph.Eur.).

The product has undergone a development process to optimise the formulation and the studies which underpin the choice of formulation are well described in the dossier. Several FP dosage forms were used to supply dupilumab clinical studies.

In addition to the change in presentation, the formulation was adapted over time. Formulation development is adequately described.

Extractable and leachable studies have been carried out on material which comes into contact with the finished product during manufacture and storage. Data has been presented to show that the FP is compatible with the chosen container closure system. The container closure system has been shown to comply with the essential requirements of Annex 1 of the Medical Devices Directive and conforms with the relevant ISO requirements.

As part of the microbial attributes, sterility and endotoxin testing is monitored during batch release testing. The results of the container closure integrity tests demonstrate that the container closure system maintains the sterility of the product and that manufacturing operations and shipping do not impact the container closure integrity.

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<sup>1</sup> 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

## ***Manufacture of the product and process controls***

Dupilumab FAS is supplied frozen and stored until manufacturing of the dupilumab FP.

The manufacturing process is relatively straightforward and involves thawing of formulated AS, pooling and mixing. The FP is then filtered, filled into syringes and fitted with a stopper. At this stage the FP is referred to as bulk pre-filled syringe (PFS). The final PFS is assembled by inserting a plunger rod and finger flange. The PFS-S presentation also has a safety device attached to the finger flange. The manufacturing process is well described.

The manufacturing processes and process controls described can be considered suitable for manufacturing of bulk PFS, PFS and PFS-S.

Validation of the FP manufacturing processes was performed. Overall, the processes can generally be considered adequate to reproducibly produce FP within the defined process parameters. The in-process controls are adequate. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

## ***Product specification***

The FP specifications contain a complete list of release tests and acceptance criteria covering product solution properties, identity, strength, purity, potency and syringe with safety system performance properties. The chosen release tests are sufficient to ensure the quality of the FP and are generally in line with ICH Q6B and the Ph. Eur. monograph on monoclonal antibodies for human use. After revision of some acceptance criteria the proposed acceptance criteria are considered sufficiently justified.

The end-of-shelf-life specification for the dupilumab FP in PFS/PFS-S contains a complete list of stability tests and acceptance criteria covering product, strength, purity, potency and syringe performance properties. Testing at end of shelf life is performed on the finished PFS and PFS-S, respectively.

Specifications for bulk PFS were set and provided.

Appropriate specifications are in place for the FP to control product-related impurities. Stated impurities have been present in clinical trial material.

## ***Analytical methods***

The analytical methods are fully validated. Non-compendial methods have been validated in line with ICH guidance.

## ***Batch analysis***

Representative-scale batch data has been provided for batches of bulk PFS and PFS from each manufacturing site. Furthermore, batches of PFS-S and clinical batches were provided.

All PFS and PFS-S batches complied with the release specifications.

Moreover, acceptance ranges of FP specifications are considered adequately set with regard to the batch analyses results from historic and commercial batches and the justifications on specifications.

## ***Reference materials***

The reference standard is the same as that used for AS.

## ***Stability of the product***

The proposed shelf life is 15 months at 2 – 8° C. Based on available stability data, this shelf-life and storage conditions as stated in the SmPC, are acceptable.

Based on the data provided, the proposed shelf life of 15 months at 2 – 8° C for the FP is acceptable.

In accordance with EU GMP guidelines<sup>1</sup>, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA and the applicant has committed to reporting any confirmed out of trends or failures to conform to stability acceptance criteria at the long-term storage condition of 5 °C within the proposed shelf life, and to evaluate the implications of these data to ensure continued purity, potency, and quality. An out-of-trend stability result is defined as a result or sequence of results that are within the acceptance criterion but are unexpected or atypical, given the known analytical variance and the measured attribute's normal change over time.

Data have been presented to show that if necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. After removal from the refrigerator, Dupixent must be used within 14 days or discarded.

## ***Comparability exercise for finished medicinal drug product***

Comparability has been demonstrated between both finished commercial product manufacturing sites which were also used to supply the Phase 3 studies. Comparability data included a statistical comparison of release and stability data which identified no meaningful differences in batches manufactured at both sites. Therefore batches produced at both sites can be considered comparable. No formal comparability was presented for earlier lyophilized batches, however as these were used only in Phase I studies, comparability data is not considered necessary.

## ***Adventitious agents***

TSE compliance has been demonstrated and there is sufficient information provided on the animal derived material used. Relevant certificates of analysis have been provided for animal derived material.

In general, the viral safety of Dupixent is well addressed. Several steps are taken in order to ensure adventitious agents safety. The cell banking system has been extensively screened for adventitious viruses using a variety of *in vitro* and *in vivo* assays. The tests failed to demonstrate the presence of any virus contaminants in the cell banks with the exception of intracellular A type and extracellular C type retrovirus-like particles which are well known to be present in rodent cells; moreover, the dupilumab manufacturing process demonstrates excess capacity to inactivate/remove such virus like particles.

Dedicated virus safety steps were shown to be effective in removing/inactivating potential viral contaminants. In conclusion, viral and TSE safety has been satisfactorily addressed.

## ***GMO***

Not applicable.



#### **2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

Dupilumab is a recombinant human monoclonal antibody with binding specificity to Human IL-4R $\alpha$  thereby inhibiting both IL-4 and IL-13 signalling. The commercial manufacturing process used to produce dupilumab has been adequately described and validated

The development of dupilumab expressing MCB and WCBs has been described in adequate detail.

The dupilumab AS commercial manufacturing process has been validated.

The applicant has described how quality attributes and process parameters are designated as critical or general IPCs and what the minimum response is with respect to excursions outside of action limit / acceptance criteria/critical action limit.

The chosen release tests are sufficient to ensure the quality of the AS and FAS and are generally in line with ICH Q6B and the Ph. Eur. Monograph on monoclonal antibodies for human use. After revision, the proposed acceptance criteria are considered sufficiently justified.

The applicant proposes an acceptable shelf life for AS and FAS respectively based on stability data from batches manufactured using the commercial process.

The finished product manufacturing process is described. An EU GMP certificate has been provided for the finished product manufacturing site.

It can be concluded that FP specifications comply with Ph. Eur. 2031 Monoclonal antibodies for human use and Ph.Eur. 0520 Parenteral preparations. Characterisation of impurities was adequately described in the dossier and does not give rise to specific concerns.

Batch data from a significant number of lots has been provided which provides assurance that the manufacturing process at both sites is capable of manufacturing a consistent product.

Based on the data provided, the proposed shelf life of 15 months at 2 – 8° C for the FP is acceptable.

The TSE/virus safety of dupilumab is sufficiently demonstrated.

#### **2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

#### **2.2.6. Recommendation(s) for future quality development**

Not applicable

### **2.3. *Non-clinical aspects***

#### **2.3.1. Introduction**

The MAA for dupilumab was supported by a comprehensive battery of pharmacology, pharmacokinetics and toxicology tests.

## 2.3.2. Pharmacology

### ***Primary pharmacodynamic studies***

#### Primary pharmacology *in vitro*

The initial experiments demonstrated that dupilumab had a high affinity for human IL-4R $\alpha$ , with a KD of 12 pM to the dimeric form of the receptor. However, subsequent surface plasma resonance experiments using the Biacore system suggested a much diminished ability to bind IL-4R $\alpha$  of mouse or monkey origin. Therefore, surrogate antibodies were generated, REGN1103 and REGN646, which bind to IL-4R $\alpha$  of mouse and monkey origin respectively. These surrogate antibodies were shown to have affinities in a similar range as that of dupilumab in humans.

Further *in vitro* characterisation of dupilumab and the surrogate antibodies was performed. Dupilumab was shown to bind to CD20 positive lymphocytes which was blocked by pre-incubation with excess IL-4. Increased cell surface expression of CD23 was also inhibited by dupilumab in human PBMCs and in the Ramos lymphoma cell line. Inhibition of secretion of TARC, a type 2 chemokine whose secretion is mediated by IL-4 or IL-13, was also inhibited by dupilumab in PBMCs isolated from donors.

Given that dupilumab is a human IgG4 molecule, Fc-effector function is not expected. In accordance, using cell lines expressing IL-4R $\alpha$ , no ADCC or CDC activity of dupilumab against target cells could be detected.

Functional characterisation studies with the surrogate antibodies were also performed. REGN1103, the mouse surrogate antibody, inhibited IL-4- and IL-13-dependent proliferation of cell lines at IC50's of 1.9 nM and 11 pM respectively. Similar experiments to those performed with dupilumab were also performed for REGN646, the monkey surrogate antibody. REGN646 inhibited IL-4 and IL-13-mediated signalling as measured by STAT6 mediated luciferase expression or TARC secretion. Flow cytometry analysis showed a comparable staining pattern of human and monkey lymphocytes by dupilumab and REGN646, respectively.

#### Primary pharmacology *in vivo*

Due to the lack of an *in vivo* model of atopic dermatitis the proof of principle experiments have been performed using classical models of type 2 immune response which have been shown to be mediated at least in part through signalling via IL-4 and IL-13. To this end, a genetically engineered transgenic mouse was established which expresses human IL-4 and IL-4R $\alpha$  and was validated as a system in human to evaluate the efficacy of dupilumab *in vivo*. Using this transgenic mouse, efficacy of dupilumab was demonstrated in a model of IL-25 induced Type-2-driven inflammation. Maximum pharmacodynamic response was evident at 25 mg/kg of dupilumab as shown by examining goblet cell metaplasia, total serum IgE levels as well as lung histopathology score. In a model of house dust mite (HDM) allergen lung inflammation efficacy was seen with sub-cutaneous administration of 25 mg/kg of dupilumab twice weekly for a period of 4 weeks. Dupilumab treatment reduced the total levels of IgE in HDM treated mice to that of control untreated animals, as well as inhibiting the activation of eosinophils and goblet cell metaplasia.

Additional *in vivo* studies in wild-type mice were conducted with REGN1103, a surrogate monoclonal antibody specific for murine IL-4R $\alpha$ . Efficacy of REGN1103 in mice was studied in HDM-induced lung inflammation. When given in parallel to allergen exposition over four weeks, REGN1103 achieved the expected pharmacologic effect. Treatment was associated with reduced pulmonary eosinophil

infiltration, reduced in goblet cell metaplasia and less total IgE and HDM-specific IgG1 in serum. The study provides a proof-of-concept for the inhibition of IL-4Ra in hyperactive type 2 immune responses.

#### Secondary pharmacodynamics

No secondary pharmacodynamics studies were performed because no test article-related adverse primary pharmacodynamics or changes to safety pharmacology parameters were observed in nonclinical pharmacology and toxicology studies, indicating absence of off-target effect.

### ***Safety pharmacology programme***

In line with ICH S6(R1) safety pharmacology endpoints were evaluated as part of the repeat-dose toxicity studies in cynomolgus monkeys. No dupilumab-related effects were observed on cardiovascular, respiratory or CNS function.

### **2.3.3. Pharmacokinetics**

The pharmacokinetics of dupilumab were evaluated in single-dose PK studies in rats and cynomolgus monkeys after IV and SC administration to provide PK information in the absence of target-mediated clearance. PK/TK of REGN646 were evaluated after single and repeated IV or SC administration in cynomolgus monkeys; TK of REGN1103 was evaluated after SC administration in mice. The SC route is the proposed clinical route of administration.

PK characteristics of dupilumab after single IV and SC administration in rats and cynomolgus were typical for a monoclonal antibody and consistent with a lack of target binding. In both species, the concentration-time profile of dupilumab was characterized by an initial distribution or absorption phase following IV or SC administration, respectively, followed by a single elimination phase. The mean half-life of dupilumab ranged from 4.8 – 7 days in rats and 11.7 to 20.5 days in cynomolgus and was comparable following IV or SC administration. The bioavailability following SC dosing was high (84.2 % in rats, > 92% in cynomolgus).

PK of REGN646 in cynomolgus was characterized by non-linear kinetics, which is consistent with target-mediated disposition. After single IV administration (ranging from 1 – 15 mg/kg), C<sub>max</sub> increased approximately dose-proportionally while AUC<sub>inf</sub> increased in a greater than dose-proportional manner. Elimination of REGN646 was biphasic, with a long  $\beta$  elimination phase and a more rapid terminal target elimination phase. Consistently, the mean beta elimination half-life of REGN646 at serum concentrations above the target-saturation ranged from 7.2 to 9.1 days while the mean terminal elimination half-life was 1.5 – 2.1 at concentrations where target-mediated elimination is the primary clearance process. The absolute bioavailability of REGN646 following SC administration was approx. 70.0%. After repeated once weekly doses of 25 and 100 mg/kg/week, accumulation of REGN646 was observed, ranging from 2.2 to 4.6-fold.

REGN1103 showed non-linear kinetics in mice; increases in exposure were greater than dose-proportional at lower doses and approximately dose-proportional at doses  $\geq$  25 mg/kg/week.

In accordance with ICH S6 (R1), studies on distribution, metabolism and excretion were not conducted.

### **2.3.4. Toxicology**

Dupilumab is specific for human IL-4Ra and does not adequately interact with IL-4Ra from non-clinical species. Therefore the toxicity of IL-4Ra blockade was evaluated using surrogate antibodies specific for

cynomolgus or mouse IL-4Ra. The pharmacologic activity of these surrogate antibodies was adequately characterized and is considered comparable to that of dupilumab.

### ***Repeat dose toxicity***

Repeated dose studies of up to 26 weeks duration were conducted with REGN646 in cynomolgus monkeys. In these studies, once weekly IV or SC treatment with REGN646 at doses up to 100 mg/kg was well tolerated. No REGN646-related adverse effects were noted. Lymphocytic infiltrates were observed at the SC injection sites. These are considered a reaction to injection of high concentration of human protein.

Of note, no immunological effects of REGN646 were observed in the repeat-dose toxicity studies. There were no test-article-related changes in peripheral blood lymphocyte subpopulations. In addition, there were no treatment-related changes in serum IgM, IgG and IgE, with the exception of the 13-week study. In this study, lower IgE serum levels were observed in individual monkeys who had received saturating doses of REGN646. However, this finding is considered a pharmacologic effect of IL-4Ra blockade. Furthermore, REGN646 treatment did not affect the development of an antibody response to immunization with KLH. The primary and secondary IgM and IgG response against KLH in REGN646-treated cynomolgus was comparable to that of control animals.

In summary, no adverse effects were observed in the repeat-dose studies. In all studies, the NOAEL was the highest dose administered and was associated with a Ctrough of 4150 µg/ml and an AUC<sub>0-168h</sub> of 791,000 µg\*h/ml at 100 mg/kg SC in the chronic toxicity study.

### ***Genotoxicity***

Genotoxicity studies have not been conducted, in accordance with ICH S6(R1).

### ***Carcinogenicity***

No carcinogenicity studies were conducted. However, an assessment of the carcinogenic potential of dupilumab was made based on literature data on the role of the IL-4/IL-13 pathway in tumour development and on non-clinical data for both REGN646 and REGN1103.

The majority of literature data indicate that IL-4 and IL-13 mediate pro-tumorigenic effects either by directly promoting tumour cell proliferation or indirectly via the activation of immunomodulatory cells. Such effects would be inhibited by anti-IL-4Ra treatment. In addition, results from the repeated-dose toxicity studies in mice and cynomolgus do not indicate a carcinogenic risk. The applied weight of evidence approach is in accordance with ICH S6(R1). It can be agreed that chronic treatment with dupilumab is not associated with an increased risk of cancer. In contrast, blockade of IL-4Ra signalling may contribute to inhibition of tumour growth.

### ***Reproduction Toxicity***

The effect of IL-4Ra inhibition on fertility and early embryonic development was evaluated in mice treated with the surrogate mAb. Subcutaneous administration of REGN1103 to adult male and female mice at 25, 75, or 200 mg/kg/week did not result in any compound-related mortality. There were no REGN1103-related clinical signs, effects on body weight or food consumption, macroscopic observations or microscopic findings. In addition, there were no compound-related effects on mating,

fertility, estrous cycling, embryo survival or any of the male reproductive assessments (organ weights). Therefore, dupilumab is not expected to have an effect on fertility.

In the cynomolgus enhanced pre-/post-natal development study, there were no REGN646-related maternal effects. The incidence of embryo-fetal loss was higher in REGN646-treated groups (32.4% combined 25 and 100 mg/kg groups) than in the control group (25%) but was within the range of historical control data reported at the test facility (6.7 – 38.9%). In the surviving offspring, there were no REGN646-related findings.

### 2.3.5. 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

### 2.3.6. Discussion on non-clinical aspects

The provided pharmacology studies have demonstrated that dupilumab has a high affinity for the human IL-4R $\alpha$  receptor and a much lower affinity for IL-4R $\alpha$  of mouse and monkey origin necessitating the generation of surrogate antibodies. The surrogate antibodies, REGN1103 and REGN646 demonstrated affinities to mouse and monkey IL-4R $\alpha$  respectively in a comparable, albeit lower, range to that of dupilumab to hIL-4R $\alpha$ . The staining pattern of human and monkey lymphocytes by dupilumab and REGN646, respectively was comparable. *In vitro* functionality of these antibodies was demonstrated in cells of the respective species with inhibition of IL-4 or IL-13 dependent signalling. Although no preclinical models of atopic dermatitis were available a transgenic mouse expressing hIL-4 and hIL-4R $\alpha$  was generated and used for proof of efficacy studies with dupilumab in models of type 2 immune responses. Similar *in vivo* experiments were performed demonstrating efficacy with the mouse surrogate REGN1103 antibody. Taken together the studies provide a comprehensive basis for the potential mechanism of action of dupilumab in atopic dermatitis as well as establishing the appropriateness of the surrogate antibodies for the toxicity studies.

In rats and monkeys dupilumab exhibited linear kinetics as expected in species that do not bind dupilumab with high affinity. No target-mediated clearance was observed and total dupilumab exposure was approximately dose proportional. In monkeys REGN646, the monkey surrogate anti-IL-4R $\alpha$  antibody, displayed non-linear kinetics. The concentration-time profiles of REGN646 are characterized by an initial distribution phase following IV administration, or an absorption phase following SC administration, followed by a target-saturating beta elimination phase and a terminal target-mediated elimination phase. The target-mediated elimination is most notable at the lower concentrations. Low volumes of distribution are seen along with long elimination half-life, which are typical pharmacokinetic characteristics of monoclonal Abs. The presence of ADA in animals in the REGN646 monkey study clearly impacted the rate of drug clearance observed in the study especially at lower concentrations, and there was no evidence of toxicity associated with the occurrence of ADA.

Since dupilumab and the surrogate antibodies, REGN1103 and REGN646, are large proteins that are above the glomerular filtration cut-off threshold, they are primarily eliminated by proteolytic catabolism that results in smaller peptides and amino acids that can be reused for new protein synthesis. The clearance of therapeutic monoclonal antibodies typically does not involve cytochrome P450 (CYP450)-mediated metabolism or interaction with cell membrane transporters, therefore pharmacokinetic interactions with small molecule drugs are limited. However, published literature suggests IL-4 plays a role in the regulation of CYP. The clinical significance of this is unclear. In a

clinical drug-drug interaction study (R668-Ad-1433) in AD patients, the effects of dupilumab on the PK of CYP substrates were evaluated. The data generated from this study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

To support the safety of dupilumab, a toxicology programme was conducted in accordance with current guidance and considered adequate. Given the lack of cross-reactivity of dupilumab with IL-4R $\alpha$  from non-clinical species, surrogate mAbs were used, which is acceptable. The repeated-dose toxicity studies IL-4R $\alpha$  blockade did not reveal any adverse effects. Given that the toxicity studies were conducted with a surrogate antibody a direct comparison of exposure multiples in the toxicity studies with exposure of dupilumab in humans is not considered meaningful. However, the C<sub>trough</sub> at the end of treatment in the chronic toxicity study corresponds to 52x of IC<sub>90</sub> determined for REGN646-mediated inhibition of IL-4-stimulated TARC secretion in vitro. This indicates that a sufficiently high exposure to REGN646 was maintained throughout the study.

The effect of IL-4R $\alpha$  blockade on reproductive and developmental toxicity was evaluated in a fertility study in mice which and in an ePPND study in cynomolgus monkeys. No adverse effects were noted.

### **2.3.7. Conclusion on the non-clinical aspects**

The non-clinical studies are sufficient to support the marketing authorisation of dupilumab.

## **2.4. Clinical aspects**

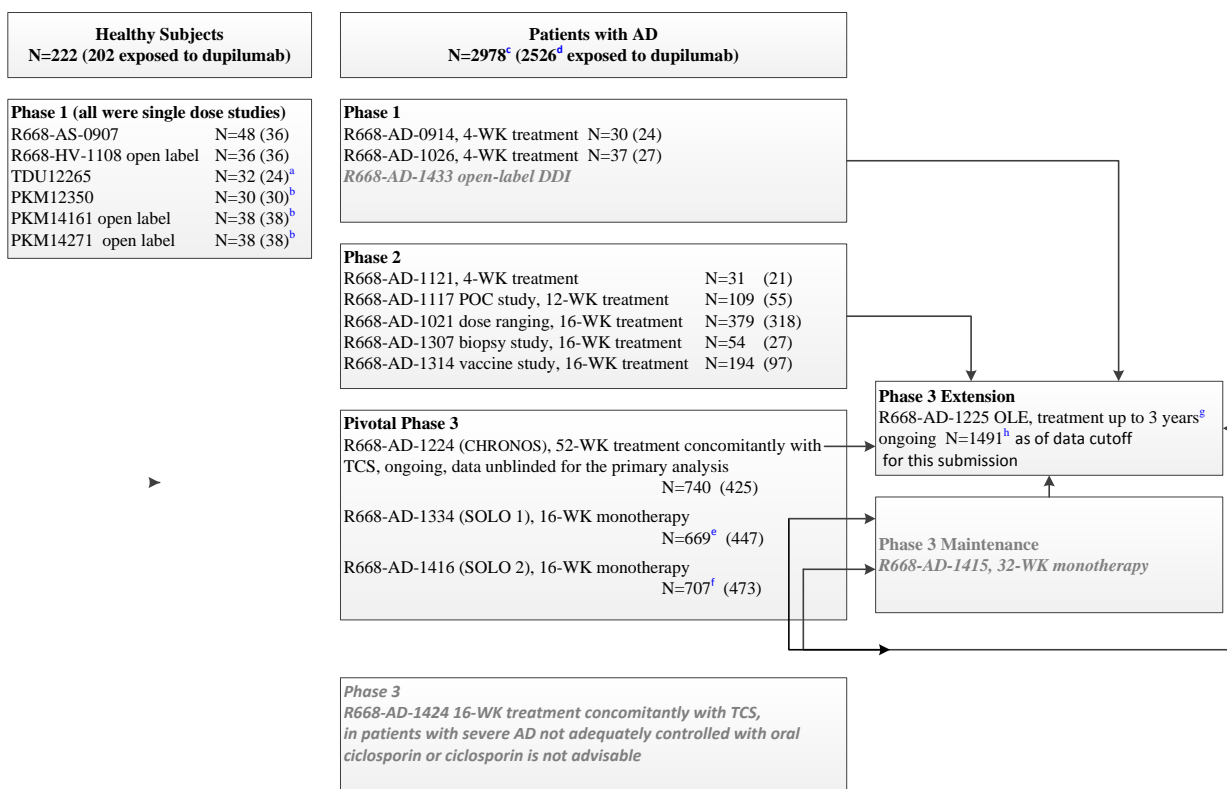
### **2.4.1. Introduction**

#### ***GCP***

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

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

- Tabular overview of clinical studies



## 2.4.2. Pharmacokinetics

The PK of dupilumab in healthy subjects has been evaluated in three Phase I studies (R668-AS-0907, R668-HV-1108 and TDU12265) and three formulation comparison studies (Study PKM12350, PKM14161, PKM14271). Population PK analysis has also been conducted.

### Absorption

Dupilumab is generally well absorbed following SC administration with an absolute bioavailability of 64% based on population PK analysis. After a single SC administration of 75 mg to 600 mg dupilumab, the median t<sub>max</sub> was 3 to 7 days in healthy subjects.

Steady-state is generally achieved by week 16 for both the 300 mg Q2W and 300 mg QW dosing. Comparison of the mean concentration-time profiles for both R668-AD-1224 where dosing with 300 mg Q2W and 300 mg QW was maintained for 52 weeks, and R668-AD-1225 where mean data from the 300 mg QW regimen up to 68 weeks are available, suggests that the steady-state trough concentrations achieved by week 16 are in the range of those measured in other studies and are maintained for up to 1 year. A very slight increase in mean C<sub>trough</sub> values (R668-AD-1225) could be detected.

After 51 weeks of dosing in study R668-AD-1224, mean C<sub>trough</sub> was 78.6 mg/L and 188 mg/L for the 300 Q2W and 300 mg QW regimens, respectively. Generally, C<sub>trough</sub> values showed a high variability with a standard deviation from the mean of about 40 (Q2W) and over 70 (QW). The 600 mg loading dose enabled a more rapid increase in exposure allowing approximately 75% of the steady-state concentration to be reached by week 4.

Mean trough concentration of functional dupilumab in serum were consistent across studies conducted using similar dosing regimens in patients with moderate-severe AD.



In conclusion, the PK of dupilumab is characterized as nonlinear with target-mediated clearance. Following different dosing regimens of both IV and SC administration, the concentration-time profile of functional dupilumab was characterized by an initial distribution phase (IV) or absorption phase (SC,  $F = 0.642$ ) followed by a bi-phasic elimination. Bioavailability  $F$  was estimated based on population PK analysis.

## ***Distribution***

In study TDU12265, following a single SC dose of 75 mg to 600 mg of dupilumab, the estimated apparent steady-state volume of distribution ranged from 6.6 L to 10.7 L. Based on POP PK analysis, the central volume of distribution ( $V_2$ ) was 2.74 L and peripheral volume of distribution ( $V_3$ ) was 1.86 L, resulting in a total volume of distribution of 4.6 L. This small volume of distribution is in line with what is expected from a monoclonal antibody.

## ***Elimination***

As a monoclonal antibody, the metabolism of dupilumab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids; eliminated by kidneys is not expected. Hence no metabolism or excretion studies were conducted. Clearance via the linear, concentration-independent elimination pathway was estimated by population PK modelling (central volume  $\times k_e$ ). For the typical patients this resulted in a linear clearance estimate of  $2.74 \text{ L} \times 0.0477 \text{ 1/d} = 0.131 \text{ L/d}$ . Total clearance estimates increase as concentration decreases.

## ***Dose proportionality and time dependency***

Following single administration of dupilumab, a greater-than dose proportional increase in systemic exposure was observed. In healthy volunteers, for a 12-fold increase in IV dose from 1 mg/kg to 12 mg/kg, a 38-fold increase in AUC<sub>last</sub> was observed. For an 8-fold increase in SC single dose from 75 mg to 600 mg, a 30-fold increase in AUC<sub>last</sub> was observed in healthy male Japanese subjects. These observations are consistent with nonlinear PK due to target-mediated clearance. Following IV and SC administration  $C_{max}$  increased in a slightly greater than dose proportional manner. Intravenous doses of 1, 3, 8, and 12 mg/kg resulted in  $C_{max}/\text{Dose}$  values of 25.8, 31.3, 33.7, and 35.2 1/L, respectively.

## ***Special populations***

### Population PK Analysis

Samples collected from all Phase 1-3 studies except R688-AD-1225 have been included in the establishment of a two compartment model. Placebo subjects were excluded from all datasets. In total, a comprehensive data base of 18243 samples has been collected from 2041 subjects for model selection and validation (sensitivity analyses) and covariate analyses. The base model for population-based analyses was a 2-compartment model with 3 serial transit compartments characterizing the absorption process, bioavailability ( $F_1$ ) from the depot following SC administration to the central compartment that was described by a central volume of distribution ( $V_2$ ). The inter-compartmental rates ( $k_{23}$  and  $k_{32}$ ) were used to characterize the inter-compartmental distribution. The linear elimination pathway was described using a Michaelis-Menten (M-M) model to represent target-mediated drug disposition, parameterized by the maximal rate of clearance ( $V_m$ ) and the Michaelis constant ( $K_m$ ). A first order rate constant was used to describe the SC absorption of dupilumab. A transit compartmental model was used to describe the lag time in absorption of dupilumab.



As only sparse samples have been collected from AD patients, the model selection was conducted in a step-wise process aiming at optimal parameter estimation and selection of the best model structure. Except V2 and Ke, the parameters were fixed to the values estimated from the phase 1 and phase 2 data. Model evaluation showed no major artefacts or time effects. VPC plots indicate that the high variability among Ctrough values is moderately but acceptably well covered. Shrinkage estimates (Model 1) for V2, ke, Vm, Ka, and MTT were 10.4%, 25.2%, 22.9%, 23.2%, and 54.9% respectively. As the value for MMT is very high, this underlines the request to reconsider the introduction of lag-time (transit compartments) in the model structure. For Model 4, Shrinkage of ke and the central volume V2 was estimated to 41% and 35%. Given that these values are estimated based on mainly sparse trough concentration values, and no major artefacts in the parameter distribution could be detected, this is acceptable. Sensitivity analyses where all data sets and BLQ values have been integrated resulted in even higher shrinkage values and generally confirmed the model robustness in terms of parameter estimation and covariate finding.

### Covariates and Special Populations

The influence of selected demographic factors (body weight, body mass index [BMI], age, sex, race), population (healthy subjects, AD patients), baseline laboratory test results (creatinine clearance, aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], albumin), baseline Eczema Area and Severity Index (EASI) score, and anti-drug antibody (ADA) status were investigated in the covariate model. Weight was included as a covariate in all models. Covariates were tested using a typical stepwise forward addition ( $p < 0.01$ ) and backward deletion ( $p < 0.001$ ) method using the derived Model 4. Data base for covariate testing was mainly data collected from Phase 3 studies. Sensitivity analyses supported the identified covariates on PK parameter Ke and central volume (V2).

Weight and albumin (on V2) and BMI, ADA, race and EASI score were statistically significant covariates on ke. Body weight had the most notable effect on variability in V2 (-27.3% and +35.6% change in V2) and BMI the greatest effect on ke (-9.29 and +14.4% change in ke). In the overall population PK analysis data set, weight ranged from 39.8 to 175 kg with mean weight of 76.6 kg. Mean BMI was calculated to 26.2, resulting from values ranging from 16.2 to 62.7. Individual post-hoc estimates of exposure at steady state (Studies R668- AD-1334, R668-1416 and R668-AD-1224) underline the body weight effect on exposure. Mean C trough value in body weight group < 70 kg is more than halved compared to the group weighing 100 kg and more (101 mg/L vs 41.8 mg/L; 300 mg Q2W). The same holds for AUC exposure (1670 mg\*day/L vs 729 mg\*day/L). The effect of BMI groups on dupilumab exposure in steady state is equally pronounced (Ctrough: 97.5 mg/L vs 48 mg/L; AUC: 1600 mg\*day/L vs 830 mg\*day/L). While dupilumab trough concentrations were lower in subjects with higher body weight, there was no meaningful impact on efficacy.

Based on the population PK analysis, mild to moderate renal impairment (predicted creatinine clearance of  $>30 \leq 80$  mL/min) did not affect the PK of dupilumab. No formal study was conducted in special populations, such as patients with renal or hepatic impairment. Thus the impact of severely impaired renal and hepatic function on PK is unknown.

Gender was equally distributed among the study population (F: 41%, M: 59%); no differences in PK have been detected. Race has been identified as significant covariate based on model 4. Comparison of Asian vs. remaining population, African American/Black vs. remaining population and White vs. remaining population showed no major differences in individual ke and Vc. The PK of dupilumab was evaluated in healthy Japanese male subjects in study TDU12265. There were no obvious differences in the PK of dupilumab between healthy Japanese and Caucasian subjects (R668-AS-0907). However, a 300 mg single dose resulted in maximum mean dupilumab levels of ~38 mg/L in Japanese male healthy subjects (TDU12265) compared to 30 mg/L in all other healthy subjects at day 7. Results from

the phase 3 study (R668-AD-1334) showed that exposure to functional dupilumab is similar for the subset of Asian AD patients and the non-Asian AD patient population.

The patients' age ranged from 18 years to 88 years. Only 61 patients were over 65 years of age (Studies R668-AD-1334, R668-1416 and R668-AD-1224). Population PK analysis did not indicate age to affect the PK of dupilumab (Ke, Vc).

### ***Pharmacokinetic interaction studies***

As a monoclonal antibody, dupilumab is not anticipated to directly interact with cytochrome P450 (CYP) enzymes thus no typical drug-drug interactions of dupilumab with other drugs via are expected. It is agreed that no influence of concomitant TCS can be detected based on comparison of PK data from patients involved in monotherapy studies SOLO1 and SOLO2 vs study R668-AD-1224.

Limited *in vitro* data suggested that IL-4 and IL-13 may modulate the expression (and potentially the activities) of some CYP isoforms resulting in dysregulated drug metabolism that could influence the exposure of concomitant medications. A clinical study (R668-AD-1433) designed to examine the effects of dupilumab on the PK of selected CYP substrates in adult patients with moderate-to-severe AD has been completed. This study did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

### **2.4.3. Pharmacodynamics**

#### ***Mechanism of action***

The pathophysiology of atopic dermatitis 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 Type 2/T-helper type 2 (Th2) cell axis plays a central role. The primary skin defect may be an immunologic disturbance that causes IgE-mediated sensitization, with epithelial-barrier dysfunction that is the consequence of both genetic mutations and local inflammation.

Two cytokines, interleukin (IL)-4 (IL-4) and IL-13, are critical in the initiation and maintenance of the type2/Th2 inflammatory pathway. Downstream effects of IL-4 and IL-13 are dependent on IL-4 receptor alpha (IL-4R $\alpha$ ) signaling, which is inhibited by dupilumab. Dupilumab is a recombinant human IgG4 monoclonal antibody that binds specifically to the alpha sub-unit of the Type I and II interleukin-4 receptors (IL-4R $\alpha$ ). Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4R $\alpha$ / $\gamma$ c), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4R $\alpha$ /IL-13R $\alpha$ ).

#### ***Primary and Secondary pharmacology***

The Type2/Th2 cytokines produced by skin-infiltrating leukocytes, including IL-4, IL-5, and IL-13, act on keratinocytes and other cell types to induce production of chemokines, including chemokine (C-C motif) ligand 17 (CCL17, also known as thymus and activation regulated chemokine [TARC]) and CCL26 (eotaxin-3), which are chemo attractants for Th2 cells and eosinophils. *In vitro*, dupilumab blocks TARC and eotaxins 3 induction by IL-4 and IL-13 in human blood. In addition, both IL-4 and IL-13 are present at elevated levels in individuals with allergic disease including AD. Lactate dehydrogenase (LDH) was also used as a PD biomarker and was determined in all studies as part of the standard laboratory testing. The PD of dupilumab was assessed in phase 1, phase 2, and phase 3 studies. Immunogenicity was assessed in all studies.

IL-4 and IL-13 levels increase in a transient manner following dupilumab treatment. This supports the dupilumab-mediated modulation of IL-4 and IL-13 signalling by blocking IL-4R $\alpha$ .

A dose- and concentration-dependent normalization of Serum TARC, Total IgE, and LDH following dupilumab treatment could be detected. A greater proportion of patients in the dupilumab treatment groups compared to the placebo group achieved normal total serum IgE (ULN defined as 119 kU/L) at week 16 in the R668-AD-1224 study; however, the proportion of patients was low (8.2% for the 300 mg QW group, 6.7% for the 300 mg Q2W group compared to 1.4% for the placebo group). After 52 weeks of treatment, total IgE was normalized in 11.7% and 15.9% of patients receiving dupilumab 300 mg Q2W and 300 mg QW, respectively, compared to 4.4% of patients receiving placebo.

Almost all patients treated with dupilumab achieved normal LDH at both week 16 and week 52 compared to approximately 50% of patients in the placebo group.

The percent change from baseline in LDH, TARC, and total IgE at week 16 for the 300 mg Q2W and 300 mg QW dose regimens for patients in the following weight categories: <70 kg,  $\geq$ 70 to <100 kg, and  $\geq$ 100 kg has been assessed. Data indicate that there are only small differences in mean PD response between patients in the different body weight groups.

### Immunogenicity

Immunogenicity assessments and monitoring were performed for all clinical studies. Overall, ADA incidence throughout the studies is rather low and comparable among the treatment groups. In the 16-week studies, approximately 7% of subjects treated with DUPIXENT and 2% of subjects on placebo developed antibodies to dupilumab, while in the 52-week study, approximately 7% of subjects treated with DUPIXENT + TCS and 8% of subjects on placebo + TCS developed antibodies to dupilumab. Majority of the ADA positive patients exhibited low titers (<1000). Less than 2% of patients treated with dupilumab + TCS and 3% of patients treated with placebo + TCS exhibited ADA positive responses lasting more than 12 weeks. Except in a few cases with high ADA titers, development of anti-drug antibodies was generally not associated with loss of efficacy. Of the subjects that developed antibodies in the 16-week studies, approximately 2% of all subjects treated with DUPIXENT and approximately 0.5% of all subjects on placebo had antibodies that were classified as neutralizing. Of the subjects that developed antibodies in the 52-week study, approximately 1% of all subjects treated with DUPIXENT and approximately 0.7% of all subjects on placebo had antibodies that were classified as neutralizing.

### Exposure-Response

In order to investigate the relationship of measures of drug exposure with response, the exposure-response relationships for the efficacy endpoints (EASI, pruritus Numerical Rating Scale [NRS], Investigator's Global Assessment [IGA]) were also assessed for both dupilumab trough concentration and AUC. The relationship between dupilumab exposure and its effects on the following adverse event (AE) terms was also assessed: Conjunctivitis (narrow), Herpes Simplex, and Herpes through empirical exposure-response analyses that utilized dupilumab concentration from week 0 to week 16 vs incidence of these AEs from baseline to week 16.

Exposure-response analyses were conducted using pooled data from the phase 3 monotherapy studies in order to evaluate the influence of drug concentration on the efficacy and safety of dupilumab; study R668-AD-1224 (long-term treatment [LTT]) was analyzed separately as patients were treated with concomitant topical corticosteroids (TCS).

#### *Exposure – Efficacy Relationship*

No notable difference is observed when comparing mean percent change from baseline EASI score, the proportion of patients achieving IGA 0-1 and the mean percent change from baseline for peak pruritus

NRS for the 300 mg Q2W and 300 mg QW treatment regimens. This analysis found the majority of patients responded well to dupilumab treatment in all 3 studies (R668-AD-1334, R668-AD-1416, R668-AD-1224), whether using a 300 mg Q2W or 300 mg QW regimen. At week 16 when the primary endpoint was assessed, there was no notable difference in mean PD efficacy response between the 300 mg Q2W and the 300 mg QW treatment regimens, thus, no dose-response relationship with regard to efficacy is detectable including the long-term treatment study.

Despite this apparent lack of a dose-response relationship based on mean PD data, the quartile analysis of dupilumab-treated patients from the two phase 3 mono-therapy studies showed a clear exposure-response relationship. With quartiles based on C<sub>trough</sub> at week 16, the lowest quartile of exposure resulted in a smaller reduction from baseline in EASI score (70%) than the highest quartile (81%). Addressing the 300 QW and 300 Q2W regimens separately, a consistent trend of increasing reduction in EASI with increasing quartile of exposure between Q1 and Q4 could be detected. Trends remain when assessing exposure-efficacy by AUC<sub>0-112</sub>. Similarly, the proportion of patients achieving IGA 0-1 increased from 37.1% to 56.6% for the lowest and highest quartile of dupilumab concentrations at day 112, with a consistent difference when assessed by C<sub>trough</sub> or AUC<sub>0-112</sub> and dosing regimens separately. The E/R relationship based on NRS is similar but notably shallower than that observed based on e.g. EASI score, which showed an 11% difference between Q4 and Q1.

Subgroup analysis with focus on body weight showed that for both EASI and IGA, a greater improvement was observed in the lowest quartile of body weight than in the highest quartile. For patients in the lowest quartile of body weight (<64 kg), the mean percent improvement in EASI score at week 16 was 76.2%, in contrast to a mean improvement of 70.7% for patients in the highest quartile of body weight (>88.5 kg). In the lowest quartile of body weight, 51.9% of patients achieved IGA 0-1 compared to 39.8% in the highest quartile of body weight. When assessed across the quartiles Q3 to Q1, the impact of body weight on response is far less. Thus, the overall body weight effect on exposure accounts for a great portion of the overall E/R relationship, while the majority of patients treated with 300 mg Q2W receive significant and possibly their own maximal treatment benefit. Some patients (in the highest body weight quartile) may receive some additional benefit from the higher exposure associated with the more intense 300 mg QW treatment regimen.

Population exposure-efficacy analysis selected BMI (or body weight) on baseline response (E<sub>0</sub>) as major covariate based on a E<sub>max</sub> model that has been established only for the EASI score efficacy parameter. EC<sub>50</sub> values for C<sub>trough</sub> and AUC were estimated to 30 mg/L and 5570 mg\*day/L, respectively. EC<sub>50</sub> C<sub>trough</sub> level is achieved among all bodyweight groups, while the selected AUC-level is far beyond the AUC values reached in any body weight group. No conclusions should be drawn based on the EC<sub>50</sub> levels as they have been estimated with large confidence intervals.

#### *Exposure – Safety Relationship*

The descriptive exposure-response analysis for safety illustrated that the adverse events identified in the phase 3 studies (conjunctivitis, herpes simplex, and oral herpes) were balanced across the quartiles of exposure and no exposure-response relationship could be identified, given the limitations of the safety data.

#### **2.4.4. Discussion on clinical pharmacology**

No major differences in bioavailability due to different cell lines, manufacturing processes or duration of injection (slow rate of 10 minutes vs fast rate of 30 seconds) could be detected in healthy volunteer studies.

No direct comparison between PK in healthy subjects and AD patients were possible as there are only single dose PK data collected from healthy subjects and only multiple dose PK data from AD patients. Among healthy subjects and AD patients, PK is generally deemed comparable on the basis of mean C<sub>trough</sub> values. This is supported by population PK analysis indicating that the PK of functional dupilumab in AD patients and healthy subjects is neither significantly nor meaningfully different.

The terminal elimination phase is described by target-mediated clearance leading to pronounced nonlinear kinetics. Thus terminal half-life varied across the concentration ranges. For the envisaged dosing regimen, the applicant was asked to calculate t<sub>1/2</sub> considering non-linear kinetics and target-mediated effects to be stated in the SmPC for the exposure range (C<sub>min,ss</sub>, C<sub>max,ss</sub>) in the steady state.

The 600 mg loading dose enabled a more rapid increase in exposure allowing approximately 75% of the steady-state concentration to be reached by week 4.

Using data from 5000 subjects, the applicant has used the PK population model to estimate the predicted mean C<sub>max,SS</sub> for both the 300 mg Q2W and 300 mg QW doses of dupilumab. Samples collected from the clinical trials constituted a comprehensive dataset allowing a proper characterization of the PK of dupilumab in the relevant patient population. Low fluctuations between trough and C<sub>max</sub> levels were predicted for both dosing regimens and were adequately justified based on low clearance at target-saturating concentrations.

A clinical study (R668-AD-1433) designed to examine the effects of dupilumab on the PK of selected CYP substrates in adult patients with moderate-to-severe AD has been completed. The results did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.

The chosen PD biomarkers and response parameters are deemed plausible and indicate a proof of concepts. Dupilumab showed no dose-response relationship but a clear exposure response relationship with regard to efficacy. Some patients (in the highest body weight quartile characterized by the lowest exposure) may receive some additional benefit from the higher exposure associated with the more intense 300 mg QW treatment regimen.

Rates of ADA and NAb development appear to be low with dupilumab, with a higher incidence seen in subjects who were administered lower doses of dupilumab or those who received Q2W doses rather than QW doses. Less than 2% of patients treated with dupilumab and 3% of patients treated with placebo exhibited positive responses in the ADA assay that last more than 12 weeks. Of these positive samples, the majority exhibited low titers (<1000) and the distribution of dupilumab concentrations was within the range observed for patients who exhibited negative responses in the ADA assay at all times.

Two patients treated with 300 mg QW, positive in the ADA assay at week 16 with high titers and also positive in the NAb assay had reductions in serum dupilumab concentrations temporally associated with the development of ADA and lost efficacy over time. Neutralizing antibodies were not generally associated with loss of efficacy, except in patients who exhibited high titer ADA responses. Positive responses in the ADA assay were generally not associated with an impact on exposure, safety or efficacy. In the overall exposure pool, less than 0.1% of patients exhibited high titer ADA responses associated with reduced exposure and efficacy. In general, there does not appear to be a marked impact on efficacy scores in subjects who develop ADAs or NABs. Longer term data are required to characterise the risk of ADA/NAb persistence.

It is noted that rates of anti-drug antibody development in the 3 formulation comparison studies in healthy volunteers (and in particular studies PKM14161 and PKM14271) were higher than those seen in the Phase II and III clinical trials.

## **2.4.5. Conclusions on clinical pharmacology**

The pharmacokinetic profile of dupilumab has been adequately characterised. Based on the PK-PD data presented in the dossier, the proposed posology of 300 mg Q2W, following a 600 mg loading dose has been agreed.

## **2.5. Clinical efficacy**

The development program of dupilumab in atopic dermatitis consisted of eleven studies (10 double-blind placebo-controlled studies plus 1 OLE study) with a treatment period of  $\geq 4$  weeks. A total of over 2500 patients with AD contributed data for efficacy analysis, including patients randomized in the 2 phase 3, placebo-controlled, 16-week monotherapy studies SOLO 1 R668-AD-1334 (671 patients) and SOLO 2 R668-AD-1416 (708 patients), and in the phase 3, placebo-controlled study CHRONOS R668-AD-1224 of 52-week concomitant treatment with TCS (740 patients).

### **2.5.1. Dose response study**

R668-AD-1021 was a phase 2b, 32-week, multicenter, double-blind, randomized, placebo-controlled, dose-ranging study to assess the dose-response profile of SC doses of dupilumab.

The study consisted of a 16-week treatment period, during which patients were treated with dupilumab (100 mg Q4W, 300 mg Q4W, 200 mg Q2W, 300 mg Q2W, or 300 mg QW) or placebo, and a 16-week follow-up period. All patients received a loading dose on day 1 (600 mg for all 300 mg dose regimens and 400 mg for the 100 mg and 200 mg dose regimens). The target population was adults with moderate-to-severe AD that could not be adequately controlled with topical medications or for whom topical treatment was otherwise inadvisable (e.g., side effects or safety risks). Efficacy assessments included EASI, IGA of AD severity, pruritus scores (NRS, 4-point categorical scale, and 5-D pruritus scale), SCORAD, POEM, and GISS.

Medications (other than the study drug) and procedures that were used for the treatment of AD were considered rescue treatment. Patients who received rescue treatment were permanently discontinued from study drug.

A total of 380 patients were enrolled into the study and randomized. Baseline demographic as well as baseline disease characteristics, with respect to duration, extent, and severity of AD characteristics were similar among the treatment groups

The efficacy results showed that all dosing regimens improved AD severity scores compared to placebo. The results of the primary efficacy analysis show a dose-dependent, statistically significant reduction in EASI scores from baseline to week 16. The highest reductions in EASI were observed in the 300 mg Q2W (50.1%) and in the 300 mg QW (55.7%). The results from the secondary endpoints are in-line with the effects seen from the primary endpoint.



	Placebo	Dupilumab				
		100 mg Q4W	300 mg Q4W	200 mg Q2W	300 mg Q2W	300 mg QW
N	61	65	65	61	64	63
<b>Primary Endpoint</b>						
LS mean (SE) percent change in EASI from baseline at week 16	-18.1 (5.20)	-44.8*** (4.99)	-63.5*** (4.94)	-65.4*** (5.19)	-68.2*** (5.12)	-73.7*** (5.16)
<b>Secondary Endpoints</b>						
Proportion of patients achieving IGA 0 or 1 at week 16	1.6%	12.3%	21.5%	27.9%	29.7%	33.3%
Proportion of patients achieving IGA score reduction $\geq 2$ at week 16	9.8%	20.0%	35.4%	42.6%	46.9%	50.8%
LS mean (SE) percent change in peak weekly averaged pruritus NRS from baseline at week 16	5.15 (4.771)	-15.67 (4.491)	-32.63 (4.516)	-34.12 (4.721)	-40.06 (4.544)	-46.90 (4.608)
LS mean (SE) percent change in overall weekly averaged pruritus NRS from baseline at week 16,	-4.92 (4.492)	-24.11 (4.226)	-41.40 (4.249)	-43.29 (4.439)	-46.50 (4.277)	-53.20 (4.338)
Number of patients with weekly pruritus categorical scores at week 16:						
0	0	3.1%	7.7%	8.2%	3.1%	12.7%
1	23.0%	18.5%	40.0%	47.5%	53.1%	63.5%
2	21.3%	32.3%	27.7%	14.8%	21.9%	14.3%
3	23.0%	12.3%	6.2%	6.6%	4.7%	1.6%
Missing	32.8%	33.8%	18.5%	23.0%	17.2%	7.9%
Proportion of patients achieving EASI-50 at week 16	29.5%	44.6%	70.8%	62.3%	78.1%	82.5%
Proportion of patients achieving EASI-75 at week 16	11.5%	29.2%	49.2%	55.7%	53.1%	60.3%
Proportion of patients achieving EASI-90 at week 16	3.3%	15.4%	29.2%	31.1%	29.7%	36.5%
LS mean (SE) percent change in SCORAD from baseline at week 16	-13.8 (4.14)	-26.6 (3.98)	-48.8 (3.95)	-46.0 (4.12)	-51.2 (4.05)	-56.9 (4.12)
Proportion of patients achieving SCORAD-50 at week 16	19.7%	26.2%	55.4%	52.5%	59.4%	68.3%
Proportion of patients achieving SCORAD-75 at week 16	3.3%	7.7%	21.5%	16.4%	25.0%	23.8%
Proportion of patients achieving SCORAD-90 at week 16	0	3.1%	3.1%	4.9%	6.3%	6.3%
LS mean (SE) percent change in POEM from baseline at week 16	0.2 (4.61)	-14.2 (4.35)	-46.6 (4.33)	-49.2 (4.54)	-44.0 (4.44)	-57.3 (4.52)
LS mean (SE) changes in GISS cumulative score from baseline at week 16	-1.2 (0.38)	-2.3 (0.37)	-4.3 (0.37)	-3.9 (0.38)	-4.5 (0.37)	-4.6 (0.38)

## 2.5.2. Main studies

**Study R668-AD-1224:** A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate- to severe atopic dermatitis (Chronos)

### Methods

This was a 64-week (52-week treatment period plus 12-week follow-up), double-blind, randomized, placebo-controlled, parallel-group study to confirm the efficacy and safety of dupilumab administered concomitantly with TCS in adults with moderate-to-severe AD.

### Study Participants

The target population consisted of patients with moderate-to-severe AD that was not adequately controlled with medium to high potency TCS ( $\pm$ TCl, as appropriate).

### Key inclusion criteria:

1. Chronic AD (according to the American Academy of Dermatology Consensus Criteria, [Eichenfield 2014]), that was present for at least 3 years before the screening visit
2. Documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD medication(s)
  - a. Inadequate response represented 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 high potency ( $\pm$  TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for super-potent TCS), whichever was shorter.
  - b. Patients with documented systemic treatment for AD in the past 6 months were also considered as inadequate responders to topical treatments and were potentially eligible for treatment with dupilumab after appropriate washout.
  - c. Acceptable documentation included contemporaneous chart notes that recorded TCS with or without TCI prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician. If documentation was inadequate, potential patients were re-screened after such documentation was obtained (e.g., patients were shown to fail a 28-day course of mid-to-higher potency TCS [ $\pm$  TCI]).
3. IGA score  $\geq$  3 (on the 0 to 4 IGA scale, in which 3 was moderate and 4 was severe) at the screening and baseline visits
4.  $\geq$  10% lesional BSA of AD involvement in areas that could be treated with medium or higher potency TCS at the screening and baseline visits
5. EASI score  $\geq$  16 at the screening and baseline visits
6. Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity  $\geq$  3
7. Had applied a stable dose of a topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit.

The exclusion criteria were designed to ensure patients safety. Excluded were patients with active chronic or acute infections including HIV and hepatitis B and C, history of immunosuppression, presence of skin comorbidities, regular use of tanning beds, history of malignancies, active endoparasitic infections and other severe illnesses that could have affected the patient's participation in the study. Patients being unable to safely use TCS i.e. having important side effects of topical medication or  $\geq$  30% of the total lesional surface were located on areas of thin skin that cannot be safely treated with medium or higher potency TCS at the baseline visit, were excluded.

## **Treatments**

### **Investigational treatment:**

- Dupilumab 150 mg/mL vial: Each 5 mL vial contained 2.5 mL (150 mg/mL) with a withdrawable volume of 2.0 mL or 300 mg of study drug.
- Dupilumab 150 mg/mL prefilled syringe: Each 2.25 mL single-use, prefilled glass syringe with snap-off cap delivered 2.0 mL of a 150 mg/mL solution (300 mg) of study drug.

Treatment administered:



- QW subcutaneous (SC) injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 or
- Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 (with placebo on alternating weeks) or
- Placebo matching dupilumab was prepared in the same formulation: Matching QW SC injections of placebo (including doubling the amount of placebo on day 1 to match the loading dose)

### **Background Treatment**

All patients were required to apply emollients at least twice daily for at least the 7 consecutive days immediately before randomization and to continue throughout the study for 64 weeks. All types of emollients were permitted, but patients could not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients could have continued using stable doses of prescription emollients if initiated before the screening visit.

Starting on day 1 all patients were required to initiate treatment with TCS. A medium potency TCS was applied once daily to areas with active lesions. A low potency TCS was used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc.) or for areas where continued treatment with medium potency TCS was considered unsafe.

After lesions were under control (clear or almost clear), treatment was switched from medium potency to low potency TCS once daily for 7 days, then stopped. If lesions returned, treatment with medium potency TCS was reinstated, with the step-down approach described above upon lesion resolution. For lesions persisting or worsening under once daily treatment with medium potency TCS, patients were treated (rescued) with high or super-high potency TCS, unless higher potency TCS were considered unsafe. Rescue treatment with systemic therapy (systemic corticosteroids, systemic non-steroidal immunosuppressants) was also permitted after Week 2. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/immunomodulating drugs, study treatment was temporarily discontinued. After the treatment with these medications was completed, study treatment could be resumed, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

The patients were monitored for signs of local or systemic TCS toxicity and treatment was stepped down or stopped, as necessary.

Type and amount of the TCS and TCI used was determined by weighing the tube at each visit, which was recorded.

### ***Objectives***

#### **Primary Objective**

- The primary objective of the study was to demonstrate the efficacy of dupilumab administered concomitantly with TCS through week 16 in adult patients with moderate-to-severe AD compared to placebo administered concomitantly with TCS.

#### **Secondary Objectives**

The secondary objectives of the study were to:

- Evaluate the long-term efficacy of dupilumab when administered concomitantly with TCS for up to 52 weeks

- Evaluate the long-term safety of dupilumab when administered concomitantly with TCS for up to 52 weeks

### Research Objectives

The research objective was to assess the relationship between long-term exposure to dupilumab and potential biomarkers of AD and response to treatment.

### **Outcomes/endpoints**

The co-primary endpoints were proportion of patients with EASI-75 at week 16 and with both IGA 0 or 1 and a reduction of  $\geq 2$  points at week 16. Key secondary endpoints were the proportion of patients with improvement ( $\geq 4$  points) of weekly average of peak daily pruritus NRS from baseline to week 2, 4 and 16, reduction  $\geq 3$  points of weekly average of peak daily pruritus NRS from baseline to week 16, the percent change from baseline to week 16 in weekly average of peak daily pruritus NRS and EASI-75 and IGA 0 or 1 at week 52.

### **Sample size**

The sample size was chosen to allow for an adequate characterization of the long-term safety profile of dupilumab. With 300, 100, and 300 patients in the dupilumab 300 mg QW, dupilumab 300 mg Q2W, and placebo groups, respectively, there was about 99% power in both primary efficacy comparisons (dupilumab 300 mg QW vs placebo and dupilumab 300 mg Q2W vs. placebo, each comparison performed at  $\alpha = 0.025$ , 2-sided) to detect a difference of 29% between dupilumab and placebo regarding IGA response at week 16, assuming response rates of 38% (dupilumab) and 9% (placebo). This sample size also provides 99% power with regard to EASI-75 response in both comparisons assuming response rates at week 16 of 58% (dupilumab) and 15% (placebo). The assumptions were based on results from a phase 2 study, R668-AD-1117. To account for drop outs approximately 700 patients were planned to be enrolled.

### **Randomisation**

The subjects were randomized in a 3:1:3 ratio (dupilumab 300 mg QW: 300 mg Q2W : placebo). In all studies randomization was stratified by disease severity (IGA 3 vs IGA 4) and region (Asia Pacific, Eastern Europe, Western Europe, and North and South America).

In each study randomization was performed according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS).

### **Blinding (masking)**

The pivotal studies were double blind. With the exception of the IVRS/IWRS statistician (providing the randomization), the IDMC statistician and the IDMC members, and except for the provisions for emergency unblinding, all studies remained blinded until the pre-specified unblinding to conduct the primary analyses in each study.

### **Statistical methods**

In all studies data were described by means of statistical characteristics (continuous data: number of patients, mean, median, standard deviation, Q1, Q3, minimum, and maximum; categorical or ordinal

data: absolute and relative frequencies per category) stratified for treatment group and visit (if applicable).

For the 3 pivotal studies the primary efficacy analyses were performed on the full analysis set (FAS) of all patients randomized, as well as on the per protocol set (PPS) excluding patients with major protocol violations as a supporting analysis. The primary (null-) hypotheses of no difference between each of the dupilumab groups and placebo was tested by means of a Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity). For each comparison both co-primary endpoints (IGA response at week 16 and EASI-75 response at week 16) had to be statistically significant (at the 2.5%-level, 2-sided) in order to declare the corresponding dupilumab group superior to placebo. To account for missing values / intake of rescue medication, patients were counted as non-responder for the time points after withdrawal / first use of rescue medication.

Binary secondary efficacy endpoints were analysed using the same approach as that used for the analysis of the primary endpoints. If a patient had a missing value at a given week, they were counted as a non-responder for that week.

The continuous endpoints were analysed using multiple imputation (MI) with an analysis of covariance (ANCOVA) model. Patients' efficacy data after rescue treatment usage were set to missing first, and were then imputed by the MI method.

In addition to the method described above, various sensitivity analyses for the continuous endpoints for EASI and/or Pruritus NRS were conducted:

1. An analysis based on all observed data no matter if rescue treatment is used or data is collected after withdrawal using the MI method.
2. A mixed-effect model repeated measures (MMRM) analysis (initially planned as main analysis for continuous data for EU and Japan) including factors (fixed effects) for treatment, baseline strata, visit, baseline value, treatment-by-visit interaction, and baseline-by-visit interaction as covariates. An unstructured covariance matrix was used to model the within-patient errors. Efficacy data were set to missing after rescue treatment. The MMRM model was to be implemented for two sets of analyses separately:
  - a. Endpoints at week 16 by including data up to week 16
  - b. Endpoints at week 52 by including all data up to week 52
3. An ANCOVA model, including the treatment group, the baseline value and the randomization strata where efficacy data were set to missing after use of rescue medication. The post-baseline LOCF method was then to be used to impute missing values.
4. An ANCOVA model, including the treatment group, the baseline value and the randomization strata where efficacy data were set to missing after use of rescue medication. The post-baseline worst-observed-case-forward (WOCF) method was then to be used to impute missing values.
5. An ANCOVA model, including study, the treatment group, the baseline value and the randomization strata based on all observed value regardless rescue medication used. No imputation method was to be applied for the sensitivity analysis.

To control for multiplicity regarding the testing of secondary endpoints only if both co-primary endpoints were significant, the secondary endpoints were to be tested following the hierarchical testing procedure with a pre-specified order, i.e. inferential conclusions about secondary endpoints required statistical significance at the 0.025 significance level (2-sided) of the prior ones.



14.0% (44/315) of patients in the placebo + TCS group, 13.2% (14/106) of patients in the dupilumab 300 mg Q2W + TCS group, and 12.5% (40/319) of patients in the dupilumab 300 mg QW + TCS group had at least 1 major protocol deviation. 28 of the 30 major protocol violations involved the use of rescue treatment in the form of high potency TCS during the first 2 weeks of the trial, when rescue treatment was prohibited per protocol. 2 protocol violations involved the use of expired laboratory sampling kits. Other types of protocol deviations were in the categories 'Procedure not performed', 'Inadequate informed consent administration' and 'dosing noncompliance'. The primary efficacy endpoints were evaluated as a supportive analysis in the PPS, which excluded patients with major protocol violations deemed to potentially impact the assessment of efficacy.

## Baseline data

Demographic and baseline characteristics were similar among the treatment groups. Most patients were White (66.2%) or Asian (27.2%), with a mean age of  $37.1 \pm 13.46$  years. 60.3% of patients were men, and 39.7% were women. The mean (SD) duration of AD, the mean EASI score and the mean IGA score were similar between the treatment groups. 28.0% of patients had a history of prior cyclosporine treatment. 52.8% of patients had received systemic therapy for their AD, which included systemic corticosteroids (34.2%) and systemic nonsteroidal immunosuppressants (33.6%). Prior medication use was generally similar among all treatment groups.

## Baseline Disease Characteristics

The proportion of patients diagnosed with AD within specified age ranges was generally balanced between the placebo and dupilumab groups, with the majority ( $\geq 50\%$ ) of patients in the placebo and dupilumab groups diagnosed before the age of 5 years old.

The mean duration of AD was similar between the placebo (27.5 years), dupilumab 300 mg Q2W (30.1 years), and dupilumab 300 mg QW (27.9 years) groups.

The mean EASI score was  $32.6 \pm 12.9$  for patients in the placebo group,  $33.6 \pm 13.3$  for patients in the dupilumab 300 mg Q2W group, and  $32.1 \pm 12.8$  for patients in the dupilumab 300 mg QW group. The mean IGA score was  $3.5 \pm 0.5$  for all treatment groups, and scores of 3 and 4 were evenly split. The mean peak weekly averaged pruritus NRS was  $7.3 \pm 1.8$  for patients in the placebo group,  $7.4 \pm 1.7$  for patients in the dupilumab 300 mg Q2W group, and  $7.1 \pm 1.9$  for patients in the dupilumab 300 mg QW group. The mean duration of AD was similar between groups, with  $27.5 \pm 14.3$  years in the placebo + TCS arm,  $30.1 \pm 15.5$  years in the 300 mg Q2W + TCS arm, and  $27.9 \pm 14.5$  years in the 300 mg QW + TCS arm. Overall, 25.7% of patients had a history of prior systemic cyclosporine treatment.

## Numbers analysed

All 740 patients randomized were included in the SAF and the FAS.

The FAS included all randomized patients and was analysed based on the treatment allocated by the IVRS/IWRS. A total of 30 randomized patients were excluded from the PPS because of major violations of efficacy-related entry criteria (4 patients), they received  $< 80\%$  or  $> 120\%$  of scheduled doses (21 patients), or site closure (5 patients).

## Outcomes and estimation

### Co-primary endpoints

The Co-Primary Endpoints of study R668-AD-1224 show a significant higher effect of dupilumab 300 mg QW and Q2W each in combination with TCS on the severity of AD compared to placebo + TCS.

- The proportion of patients with IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16 was higher in the dupilumab 300 mg Q2W +TCS (38.7%) and dupilumab 300 mg QW (39.2%) groups than in the placebo + TCS group (12.4%).

### Primary Analysis of Proportion of Patients Achieving IGA 0 or 1 and a Reduction of $\geq 2$ Points from Baseline at Week 16, Patient Considered as Non-Responder After Rescue Treatment Use - FAS

	Placebo + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving an IGA Score of 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16, n (%)	39 (12.4)	41 (38.7)	125 (39.2)
Difference (%) (95% CI) <sup>a</sup>		26.3(16.34, 36.26)	26.8(20.33, 33.28)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment used were set to missing. Patients with missing IGA scores at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Source: Post-text Table 6.1.1.1/1

- Also for the other co-primary endpoint a higher efficacy was demonstrated in both dupilumab groups. 68.9% achieved an EASI-75 at week 16 in the dupilumab 300 mg Q2W, followed by 63.9% in the dupilumab 300 mg QW and 23.2% in the placebo group. The comparisons were statistically significant ( $p < 0.0001$  for each).

### Primary Analysis of Proportion of Patients Achieving EASI-75 at Week 16, Patient Considered as Non-Responder after Rescue Treatment Use – FAS

	Placebo + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving EASI-75 at week 16, n (%)	73 (23.2)	73 (68.9)	204 (63.9)
Difference (%) (95% CI) <sup>a</sup>		45.7 (35.72, 55.66)	40.8 (33.74, 47.81)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing EASI score at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Source: Post-text Table 6.2.1.1/1



## Key secondary endpoints

The results of the key secondary endpoints are consistent with the results from the primary endpoints.

- 58.8% of patients achieved a reduction of  $\geq 4$  points from baseline in weekly average of peak daily Pruritus NRS score at week 16 in the dupilumab 300 mg Q2W + TCS, 50.8% dupilumab 300 mg QW + TCS and 19.7% in the placebo + TCS group.
- 

### Primary Analysis of Proportion of Patients Achieving a Reduction of $\geq 4$ Points from Baseline in Weekly Average of Peak Daily Pruritus NRS at Week 16, Patient Considered as Non-Responder after Rescue Treatment Use – FAS

	Placebo + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving a peak daily Pruritus NRS score reduction of $\geq 4$ at week 16 from baseline, n/N1 (%)	59/299 (19.7)	60/102 (58.8)	150/295 (50.8)
Difference (%) (95% CI) <sup>a</sup>		39.1 (28.53, 49.65)	31.1 (23.84, 38.39)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Analysis was performed for patients with baseline peak pruritus NRS  $\geq 4$ . N1 stands for number of patients with baseline NRS score  $\geq 4$ . Values after first rescue treatment use were set to missing. Patients with missing peak NRS at week 16 were considered as a non-responder.

a Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

b P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Source: [Post-text Table 6.2.12.1/1](#)

- Similar effect was shown for reduction of  $\geq 3$  points from baseline in weekly average of peak daily Pruritus NRS score at week 16 where 65.7% in the dupilumab 300 mg Q2W + TCS 62.5% in the dupilumab 300 mg QW + TCS and 27.8% in the placebo + TCS group achieved this value.

### Primary Analysis of Proportion of Patients Achieving a Reduction of $\geq 3$ Points from Baseline in Weekly Average of Peak Daily Pruritus NRS at Week 16, Patient Considered as Non-Responder after Rescue Treatment Use – FAS

	Placebo + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving a peak daily Pruritus NRS score reduction of $\geq 3$ at week 16 from baseline, n/N1 (%)	85/306 (27.8)	69/105 (65.7)	193/309 (62.5)
Difference (%) (95% CI) <sup>a</sup>		37.9 (27.56, 48.31)	34.7 (27.31, 42.05)
P-value <sup>b</sup>		<0.0001	<0.0001

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

a Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

b P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Source: [Post-text Table 6.2.16.1/1](#)

- The proportion of patients with IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 52 was significantly higher in the dupilumab 300 mg Q2W + TCS (36%) and dupilumab 300 mg QW + TCS (40%) groups than the placebo + TCS group (12.5%). Both comparisons were statistically significant ( $p < 0.0001$  for each).

Proportion of Patients Achieving IGA 0 or 1 and a Reduction of  $\geq 2$  Points from Baseline at Week 52, Patient Considered as Non-Responder after Rescue Treatment Use – FAS Week 52

	Placebo QW + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving an IGA Score of 0 or 1 and a reduction from baseline of $\geq 2$ points at week 52, n (%)	39 (12.4)	37 (34.9)	119 (37.3)
Difference (%) (95% CI) <sup>a</sup>		22.5(12.75, 32.30)	24.9(18.49, 31.36)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment used were set to missing. Patients with missing IGA scores at week 52 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

IGA scoring is described in Section 3.5.3.1

Source: [Post-text Table 6.1.2.1/1a](#)

- Additionally the proportion of patients with EASI-75 at week 52 was significantly higher in the dupilumab 300 mg Q2W + TCS (65.2%) and dupilumab 300 mg QW + TCS (64.1%) groups than the placebo + TCS group (21.6%).

Proportion of Patients Achieving EASI-75 at Week 52, Patient Considered as Non-Responder after Rescue Treatment Use – FAS Week 52

	Placebo QW + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving EASI-75 at week 52 from baseline, n (%)	69 (21.9)	66 (62.3)	204 (63.9)
Difference (%) (95% CI) <sup>a</sup>		40.4(30.06, 50.66)	42.0(35.07, 49.02)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing EASI score at week 52 were considered as a non-responder.

<sup>a</sup> Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Scoring for the EASI is described in Section 3.5.3.2

Source: [Post-text Table 6.2.2.1/1a](#)



- Similarly a higher proportion of patients achieved a reduction of  $\geq 4$  points from baseline in weekly average of peak daily Pruritus NRS score at week 52 (51.2% in the dupilumab 300 mg Q2W + TCS, 39% dupilumab in the 300 mg QW + TCS and 12.9% in the placebo + TCS group).

Proportion of Patients Achieving a Reduction of  $\geq 4$  Points from Baseline in Weekly Average of Peak Daily Pruritus NRS at Week 52, Patient Considered Non-Responder after Rescue Treatment Use - FAS Week 52

	Placebo QW + TCS (N = 315)	Dupilumab + TCS	
		300 mg Q2W (N = 106)	300 mg QW (N = 319)
Patients achieving a Peak NRS Score Reduction of $\geq 4$ at week 52 from Baseline, n/N1 (%)	40/299 (13.4)	49/102 (48.0)	114/295 (38.6)
Difference vs. Placebo (%) (95% CI) <sup>a</sup>		34.7 (24.23, 45.10)	25.3 (18.50, 32.03)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Analyses were performed for patients with baseline peak pruritus NRS  $\geq 4$ . N1 stands for number of patients with baseline NRS score  $\geq 4$ . Values after first rescue treatment use were set to missing. Patients with missing peak NRS at week 52 were considered as a non-responder.

<sup>a</sup> Difference is dupilumab minus placebo. CI = Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA = 3 vs. IGA = 4).

Scoring for Pruritus NRS is described in Section 3.5.3.3

Source: Post-text Table 6.2.13.1/1a

The study report submitted as part of the MAA submission was considered the primary analysis for study R668-AD-1224 and included primary and secondary efficacy analyses at Week 16 for all randomized patients (n=740). The Week 52 efficacy analyses for patients who were randomized by 27 April 2015 and who would have completed the 52-week visit (n=623) and safety data from all treated patients whose data were available at the data cut-off date (27 April 2016) were also provided in this analysis. At the time of the data cut-off date, 101 patients – mostly from Japan/Korea – were still ongoing in the study. The final study presents the results (described above) based on the final database lock (16 December 2016) as an integrated analysis of all randomized patients. Both efficacy and safety analyses in this final report are entirely consistent with those in the primary analysis. However, as the integrated full analysis at week 52 (described below) was not controlled for multiplicity, data from the primary analysis is presented in section 5.1 of the SmPC.

**Clinical Response in Patients for whom Ciclosporin Treatment was Inadvisable**

In the CHRONO study, a subset of patients named subset 3 was defined to reflect the R668-AD-1424 population. This subset includes all patients who showed an inadequate efficacy response to oral ciclosporin, patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or because treatment with oral ciclosporin was otherwise medically inadvisable.

The data show that patients in subset 3 experienced clinically meaningful improvements in signs and symptoms of AD at week 16. Analyses of the data demonstrated that the proportion of patients who met the categorical endpoints in both dupilumab + TCS groups was greater than in the placebo + TCS group (nominal p-values <0.05 vs patients in subset 3 treated with placebo + TCS, Table below). Further, the percent reduction from baseline in peak pruritus NRS score was greater in both dupilumab

+ TCS groups than in the placebo + TCS group (nominal p-values <0.01 vs patients in subset 3 treated with placebo + TCS, Table below). The improvements in signs and symptoms of AD in patients from subset 3 were sustained at week 52.

R668-AD-1224 - Key Efficacy Parameters at Week 52 in Subset 3 (Ciclosporin Medically Inadvisable) versus Not Subset 3 – FAS

	Subset 3 (ciclosporin medically inadvisable)				Not Subset 3			
	Placebo + TCS	Dupilumab + TCS			Placebo + TCS	Dupilumab + TCS		
		300 mg Q2W	300 mg QW	Combined		300 mg Q2W	300 mg QW	Combined
N	59	21	46	67	205	68	224	292
Patients with IGA 0 or 1 and a reduction from baseline $\geq 2$ points at week 52, n (%) <sup>a</sup>	4 (6.8%)	8** (38.1%)	8 (17.4%)	16* (23.9%)	29 (14.1%)	24*** (35.3%)	100*** (44.6%)	124*** (42.5%)
Patients with EASI-75 at week 52, n (%) <sup>a</sup>	11 (18.6%)	11*** (52.4%)	23*** (50.0%)	34*** (50.7%)	46 (22.4%)	47*** (69.1%)	150*** (67.0%)	197*** (67.5%)
Patients with improvement in peak pruritus NRS ( $\geq 4$ point decrease) at week 52, n/N1 (%) <sup>ab</sup>	7/57 (12.3%)	9/21** (42.9%)	16/45** (35.6%)	25/66** (37.9%)	25/192 (13.0%)	35/65*** (53.8%)	81/204*** (39.7%)	116/269*** (43.1%)
Patients with improvement in peak pruritus NRS ( $\geq 3$ point decrease) at week 52, n/N1 (%) <sup>ac</sup>	8/58 (13.8)	9/21* (42.9)	19/45** (42.2)	28/66*** (42.4)	32/198 (16.2)	40/67*** (59.7)	93/216*** (43.1)	133/283*** (47.0)
LS mean % change (SE) from baseline in peak pruritus NRS score at week 52 <sup>d</sup>	-30.9 (6.47)	-54.8* (9.49)	-59.7** (5.62)	-58.3*** (4.90)	-31.9 (4.70)	-57.8** (7.36)	-55.7*** (3.78)	-56.2*** (3.48)

Subset 3 (ciclosporin medically inadvisable subset): Patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin, plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated according to the product prescribing information, or because treatment with oral ciclosporin was otherwise medically inadvisable.

Not subset 3 (remaining patients): Patients who did not meet the criteria for subset 3.

<sup>a</sup> Values after first rescue treatment use were set to missing. Patients with missing IGA, EASI or NRS scores at week 16 were considered non-responders.

<sup>b</sup> N1: Number of patients with baseline peak pruritus NRS score  $\geq 4$ .

<sup>c</sup> N1: Number of patients with baseline peak pruritus NRS score  $\geq 3$ .

<sup>d</sup> MI method with censoring after rescue treatment use.

Nominal p-value by Fisher's exact test for difference vs placebo of respective subset: \* <0.05 and  $\geq 0.01$ ; \*\* <0.01 and  $\geq 0.001$ ; \*\*\* <0.001.

TCS: Topical Corticosteroids

## Ancillary analyses

### Anti-Drug Antibody Analysis

The proportion of patients with a treatment-emergent positive response in the ADA assay was similar across treatment groups. Persistent ADA responses were observed in a higher proportion of patients in the placebo + TCS group. All treatment-emergent responses had titers that ranged in the low-to-moderate titer category. There were no high-titer (>10,000) ADA assay responses observed in any treatment group.

All samples positive in the ADA assay were further characterized for the presence of neutralizing antibodies. Two (0.7%) patients in the placebo + TCS group and 1 (1.0%) patient in the dupilumab 300 mg Q2W + TCS group were positive in the NAb assay.

### Study R668-AD-1334 (SOLO 1) and R668-AD-1416 (SOLO 2)

The studies Solo1 and Solo2 were confirmatory, monotherapy phase 3 studies, conducted in patients with moderate-to-severe AD whose disease was not adequately controlled with topical medications. These studies were identical and are therefore described together.

#### R668-AD-1334 (SOLO 1)

**A Phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.**

#### R668-AD-1416 (SOLO 2)

**A Phase 3 confirmatory study investigating the efficacy and safety of dupilumab monotherapy administered to adult patients with moderate to severe atopic dermatitis.**

## Methods

R668-AD-1334 (Solo1) and R668-AD-1416 (Solo2) were conducted as phase 3, multicenter, double-blind, randomized, placebo-controlled studies to confirm the efficacy and safety of SC dupilumab in adults with moderate-to-severe AD.

Both studies consisted of a screening period of 35 day, a 16-week treatment period, during which patients were treated with dupilumab (300 mg QW or 300 mg Q2W) or placebo, and a 12-week follow-up period (for patients not participating in the maintenance or OLE studies). Efficacy assessments included EASI, IGA of AD severity, pruritus NRS, BSA involvement with AD, SCORAD, GISS, DLQI, POEM, and HADS.

## Study Participants

The included patients were male or female, 18 years or older with a chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that had been present for at least 3 years before the screening visit. To define the severity of the AD the EASI score had to be  $\geq 16$  at the screening and baseline visits, the IGA score  $\geq 3$  (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits and  $\geq 10\%$  body surface area (BSA) must have been with AD involvement at the screening and baseline visits. Baseline Pruritus Numerical Rating Scale (NRS) needed to have an average score for maximum itch intensity  $\geq 3$ . Excluded were patients with active chronic or acute infections including HIV and hepatitis B and C, history of

immunosuppression, presence of skin comorbidities, regular use of tanning booths, history of malignancies, active endoparasitic infections and other severe illnesses that could have affected the patient's participation in the study.

## **Treatments**

Screening visits were scheduled within 35 days prior to randomization. During this period, treatments for AD were washed out, according to eligibility requirements. In addition, patients were required to apply moisturizers at least twice daily for at least 7 consecutive days immediately before randomization and continuing throughout the study. However, to allow for adequate assessment of skin dryness, moisturizers were not to be applied on the areas of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continued to meet all eligibility criteria at baseline underwent day 1/baseline assessments and were randomized in a 1:1:1 ratio to receive the following:

- QW subcutaneous (SC) injections of 300 mg dupilumab following a loading dose of 600 mg on day 1
- Q2W SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1
- or matching QW SC injections of placebo (including doubling the amount of placebo on day 1 to match the loading dose)

In order to maintain blinding, all patients received an injection each week from day 1 through week 15. Patients in the dupilumab 300 mg SC Q2W group received placebo on the weeks when dupilumab was not administered. Randomization was stratified by baseline disease severity (moderate [IGA 3] vs. severe [IGA 4]) and by region (Asia Pacific, East Europe, West Europe, and North and South America).

Following the initial dose, study treatment was administered weekly for the subsequent 15 weeks. Following the first 3 weekly injections patients had the option to self-administer study drug or have a caregiver administer study drug, after appropriate training, outside of the study site during the weeks in which no clinic visits were scheduled.

During the 16-week treatment period, patients had weekly study visits (some visits could be conducted by telephone). Safety laboratory tests, collection of samples for dupilumab concentrations and ADA, and clinical assessments were performed at specified clinic visits as noted in the Schedule of Events.

The end of treatment visit occurred at week 16, one week after the last dose of study drug. The primary endpoint was determined at week 16. Patients with IGA scores of 0 or 1 or Eczema Area and Severity Index (EASI)-75 at week 16 who had not received rescue treatment for AD were eligible to participate in a maintenance study. Patients who met eligibility criteria for the maintenance study but chose not to participate were potentially eligible to participate in an open label extension (OLE) study 36 weeks after completing the week 16 visit. Patients who did not meet eligibility criteria for the maintenance study were to undergo a variable follow-up period (between 4 and 12 weeks) and were eligible to participate in the OLE study when their IGA score was  $\geq 3$  or they reached week 28, whichever came first.

Patients could have received rescue treatment with an otherwise prohibited medication for treatment of intolerable AD symptoms during the study. Patients who received rescue treatment continued study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors could be used for rescue, but were reserved for problem areas only (e.g., face, neck, intertriginous and genital areas). Investigators attempted to limit rescue treatment to topical medications, and to escalate to systemic medications only if patients did not respond adequately after at least 7 days of topical treatment. If

disease severity or other medical considerations did not permit this gradual rescue approach, patients could be rescued directly with higher potency topical medications or with systemic treatments. If a patient received rescue treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive/ immunomodulating drugs, study treatment was temporarily discontinued. After the treatment with these medications was completed, study treatment could be resumed, but not sooner than 5 half-lives after the last dose of systemic rescue medication.

## **Objectives**

### **Primary Objective**

The primary objective of the study was to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

### **Secondary Objective**

The secondary objective of the study was to assess the safety of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe AD.

## **Outcomes/endpoints**

The co-primary endpoints were proportion of patients with EASI-75 at week 16 and with both IGA 0 or 1 and a reduction of  $\geq 2$  points at week 16. Key secondary endpoints were the proportion of patients with improvement (reduction  $\geq 4$  points) of weekly average of peak daily pruritus NRS from baseline to week 2, 4 and 16, reduction  $\geq 3$  points of weekly average of peak daily pruritus NRS from baseline to week 16, the percent change from baseline to week 16 in weekly average of peak daily pruritus NRS.

## **Sample size**

To detect a difference of 29% between dupilumab and placebo regarding IGA response (i.e. IGA score of 0 to 1) at week 16, assuming response rates of 38% (dupilumab) and 9% (placebo), 55 subjects per group were required in order to achieve 90% power ( $\alpha = 0.025$ , 2-sided). To ensure that sufficient safety information was collected, and to ensure that a sufficient number of responders would be available for inclusion in the maintenance study, the sample size was increased to 200 subjects per group, i.e. 600 subjects in total. With 200 subjects per group, the study would provide 99% power in both comparisons (dupilumab 300 mg QW vs. placebo treatment, and dupilumab 300 mg Q2W vs. placebo, each comparison performed at  $\alpha = 0.025$ , 2-sided). These numbers of patients would also provide 99% power to detect a difference of 43% in the proportions of patients achieving EASI-75 response at week 16, assuming that the proportions were 58% (dupilumab) and 15% (placebo).

## **Randomisation**

Subjects were randomized in a 1:1:1 ratio (dupilumab 300 mg QW: 300 mg Q2W : placebo). In all studies randomization was stratified by disease severity (IGA 3 vs IGA 4) and region (Asia Pacific, Eastern Europe, Western Europe, and North and South America).

In each study randomization was performed according to a central randomization scheme provided by an interactive voice response system (IVRS)/interactive web response system (IWRS).

## ***Blinding (masking)***

The pivotal studies were double blind. With the exception of the IVRS/IWRS statistician (providing the randomization), the IDMC statistician and the IDMC members, and except for the provisions for emergency unblinding, all studies remained blinded until the prespecified unblinding to conduct the primary analyses in each study.

## ***Statistical methods***

Statistical methods were as described for study R668-AD-1224.

## ***Results***

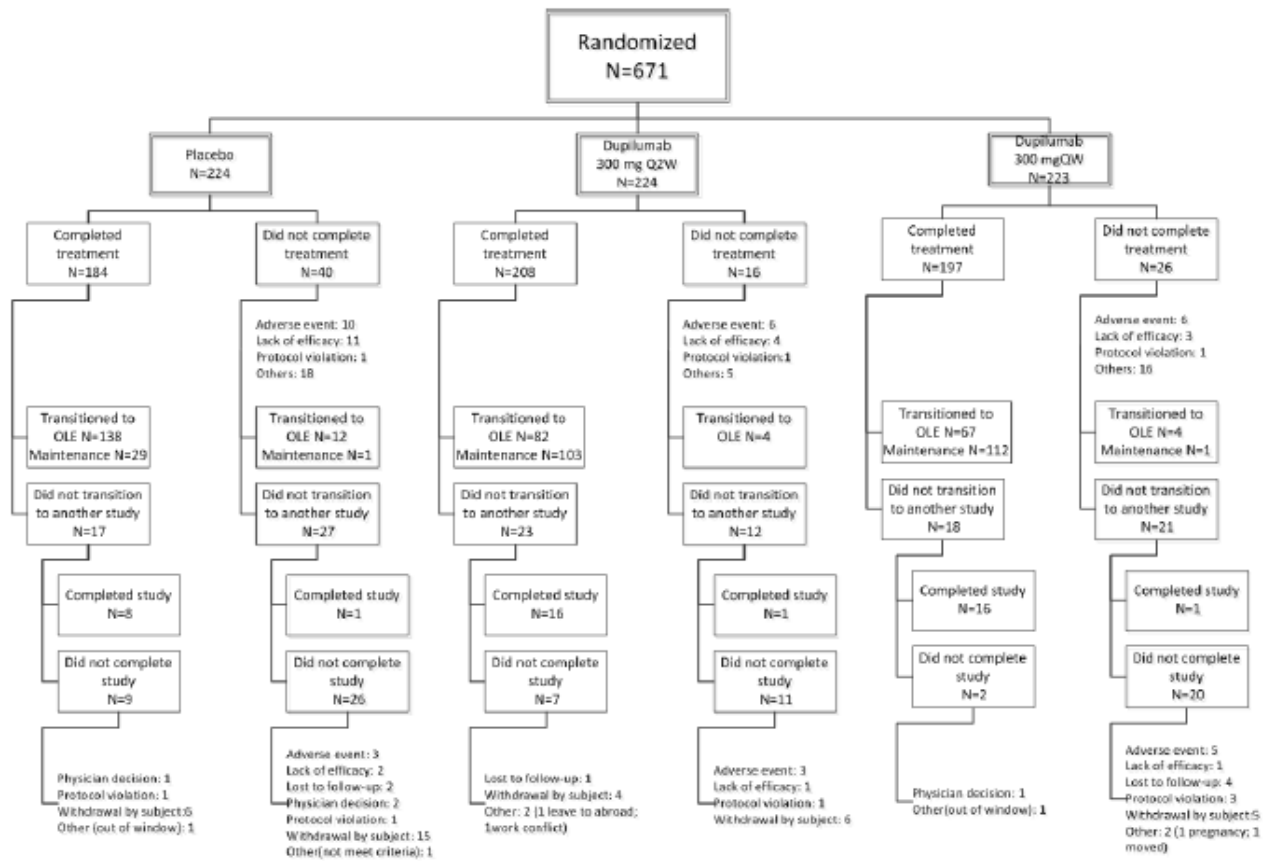
### **Participant flow**

#### **Study R668-AD-1334 (Solo1)**

A total of 917 patients were screened, of whom 671 were enrolled into the study and randomized (224 patients in the placebo group, 224 patients in the dupilumab 300 mg Q2W group, and 223 patients in the 300 mg QW group).

The proportion of patients who withdrew from study treatment was higher in the placebo group (17.9%) than in the dupilumab 300 mg Q2W group (7.1%) and dupilumab 300 mg QW group (11.7%). The 3 most frequently cited reasons for withdrawal from study treatment, which were reported for a greater proportion of placebo patients than dupilumab patients, were AEs (3.3% [22/671]), lack of efficacy (2.7%), and "other" (5.8%). The only other reason for withdrawal from study treatment (protocol violation) was reported for <1% of all patients.

A total of 553 of the 671 patients transitioned into either the maintenance study (246/671) or the OLE study (307/671). A total of 118 patients did not transition into another study: 43 (6.4%) patients completed the study (through week 28), and 75 (11.2%) patients withdrew from the study. A higher proportion of patients in the placebo group (15.6%) withdrew from the study than in the combined dupilumab groups (8.9%). The 2 most frequently reported reasons that patients withdrew from the study were "withdrawal by subject" (5.5%), which was reported for a higher proportion of patients in the placebo group than in the dupilumab groups, and AEs (1.6%), which were reported with similar frequency in the placebo and dupilumab groups. All other reasons were reported in ≤ 7 patients each in the study.

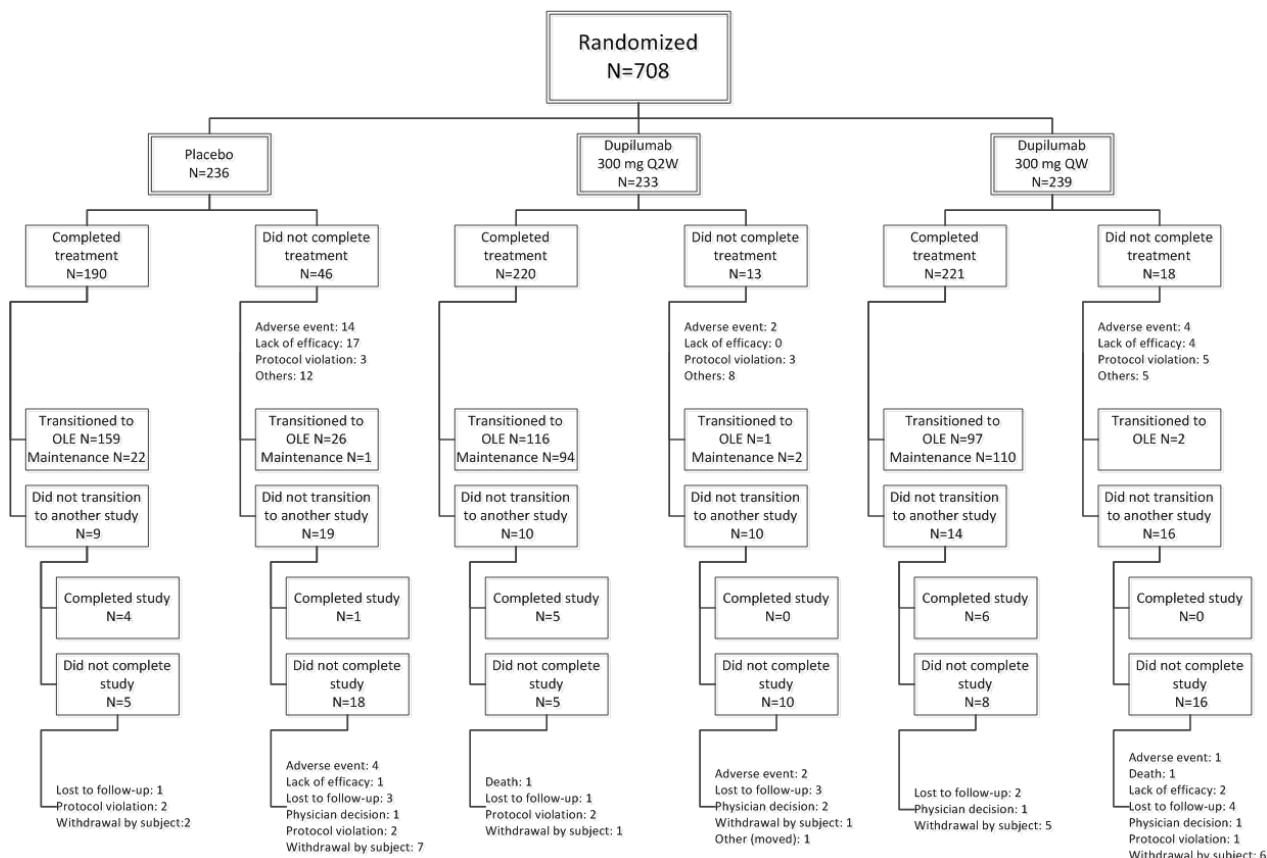


Source: Post-text Table 1.1.2/2 and Post-text Table 1.1.2/1.

### Study R668-AD-1416 (Solo2)

A total of 962 patients were screened, of whom 708 were enrolled into the study and randomized (236 patients in the placebo group, 233 patients in the dupilumab 300 mg Q2W group, and 239 patients in the 300 mg QW group).





The proportion of patients who withdrew from study treatment was higher in the placebo group (19.5% [46/236]) than in the dupilumab 300 mg Q2W group (5.6% [13/233]) and dupilumab 300 mg QW group (7.5% [18/239]). The 3 most frequently cited reasons for withdrawal from study treatment, which were reported for a greater proportion of placebo patients than dupilumab patients, were lack of efficacy (3.0% [21/708]), AEs (2.8% [20/708]), and “other” (3.5% [25/708]). The only other reason for withdrawal from study treatment (protocol violation) was reported for <2% of all patients.

A total of 630 of the 708 patients transitioned into either the maintenance study (229/708) or the OLE study (401/708). A total of 78 patients did not transition into another study: 16 (2.3%) patients completed the study (through week 28), and 62 (8.8%) patients withdrew from the study. A similar proportion of patients withdrew from the study in the placebo (9.7%) and combined dupilumab groups (8.3%). The 2 most frequently reported reasons that patients withdrew from the study were “withdrawal by subject” (3.2%) and lost to follow-up (2.0%), which were reported with similar frequency in the placebo and dupilumab groups. All other reasons were reported in ≤ 7 patients each in the study.

## Recruitment

### R668-AD-1334 (Solo1):

The first subject was enrolled on 28 October 2014.

The primary analysis data cut-off date was the 12 February 2016.

### R668-AD-1416 (Solo2):



The first subject enrolled on 03 December 2014.

The primary analysis data cut-off date was the 21 January 2016.

## Conduct of the study

There were 2 amendments to the study protocol of study R668-AD1334 and R668-AD-1416. 7.6% (17/224) of patients in the placebo group, 3.1% (7/224) of patients in the dupilumab 300 mg Q2W group, and 7.2% (16/223) of patients in the dupilumab 300 mg QW group had at least 1 major protocol deviation. The most common type of major protocol deviation was inadequate informed consent administration (4.0% of patients in the placebo group, 1.3% of patients in the dupilumab 300 mg Q2W group, and 3.6% of patients in the dupilumab 300 mg QW group). The incidence of each of the other major protocol deviation categories was low (<3% in any treatment group).

The amendments as well the number and types of protocol deviations were considered acceptable and unlikely to have impacted the results of the study.

## Baseline data

### R668-AD-1334 (Solo1)

58.1% of patients were men, and 41.9% were women. The mean weight, height, and BMI of all patients were  $76.6 \pm 17.99$  kg,  $169.8 \pm 10.16$  cm, and  $26.5 \pm 5.59$  kg/m<sup>2</sup>, and no differences were observed between treatment groups.

Overall, 42.6% of all patients were enrolled in the Americas, 29.2% in the Western European region, 17.9% in the Asia Pacific region, and 10.3% in the Eastern European region.

The highest proportion of patients was enrolled in the United States (35.5%). No patients were enrolled in South America.

Of the 671 patients randomized, 655 (97.6%) had an inadequate response to topical corticosteroid treatment, and 15 (2.2%) did not tolerate them: 5 patients had a history of significant skin atrophy, 4 patients had hypersensitivity reactions, 5 patients had systemic effects, and 3 patients could not tolerate topical corticosteroid treatment for "other" reasons.

### R668-AD-1416 (Solo2)

57.6% of the enrolled patients were men, and 42.4% were women. The mean weight, height, and BMI of all patients were  $77.1 \pm 18.95$  kg,  $170.4 \pm 9.75$  cm, and  $26.5 \pm 5.85$  kg/m<sup>2</sup>, respectively, and no differences were observed between treatment groups.

48.9% of all patients were enrolled in the Americas, 23.0% in the Western European region, 16.1% in the Eastern European region, and 12.0% in the Asia Pacific region. The highest proportion of patients was enrolled in the United States (33.6%).

Of the 708 patients randomized, 696 (98.3%) had an inadequate response to topical corticosteroid treatment, and 12 (1.7%) did not tolerate them: 7 patients had significant skin atrophy, 4 patients had hypersensitivity reactions, 2 patients had systemic effects, and 3 patients could not tolerate topical corticosteroid treatment for "other" reasons.

## **Baseline Disease Characteristics**

### **R668-AD-1334 (Solo1)**

The proportion of patients diagnosed with AD within specified age ranges was generally balanced between the placebo and dupilumab groups, with the majority ( $\geq 50\%$ ) of patients in the placebo and dupilumab groups diagnosed before the age of 5 years old.

The mean duration of AD was similar between the placebo (29.5 years), dupilumab 300 mg Q2W (28.5 years), and dupilumab 300 mg QW (27.9 years) groups.

The mean EASI score was  $34.5 \pm 14.47$  for patients in the placebo group,  $33.0 \pm 13.57$  for patients in the dupilumab 300 mg Q2W group, and  $33.2 \pm 13.98$  for patients in the dupilumab 300 mg QW group. The mean IGA score was  $3.5 \pm 0.5$  for all treatment groups, and scores of 3 and 4 were evenly split. The mean peak weekly averaged pruritus NRS was  $7.4 \pm 1.77$  for patients in the placebo group,  $7.2 \pm 1.89$  for patients in the dupilumab 300 mg Q2W group, and  $7.2 \pm 2.06$  for patients in the dupilumab 300 mg QW group, and most patients ( $>60\%$ ) had a baseline peak NRS  $\geq 7$ . The majority of patients in each treatment group reported a Patient Global Assessment of Disease Status of poor (1) ( $>37\%$ ) or fair (2) ( $>33\%$ ). The proportion of patients who ranked their status as very good (4) or excellent (5) was  $<5\%$  and  $<2\%$ , respectively, in each group. Overall, 28.8% of patients had a history of prior systemic cyclosporine treatment. More than half of these patients had used cyclosporine for longer than 12 weeks (64.8%). The most common reason for discontinuing cyclosporine for all treatment groups was inadequate efficacy (46.6%).

Overall, 63.4% of patients did not have a history of prior cyclosporine treatment. The most common stated reason for not using cyclosporine, apart from "other", was that the risk of important side effects was generally too high (12.0%).

### **R668-AD-1416 (Solo2)**

The majority ( $\geq 52\%$ ) of patients in the placebo and dupilumab groups diagnosed before the age of 5 years old. More patients in the dupilumab 300 mg Q2W group (10.3%) were diagnosed with AD between the age of 20 and 29 years old than the dupilumab 300 mg QW group (5.4%) or the placebo group (5.1%).

The mean duration of AD was similar between the placebo (28.2 years), dupilumab 300 mg Q2W (27.2 years), and dupilumab 300 mg QW (27.4 years) groups.

The mean EASI score was  $33.6 \pm 14.31$  for patients in the placebo group,  $31.8 \pm 13.08$  for patients in the dupilumab 300 mg Q2W group, and  $31.9 \pm 12.70$  for patients in the dupilumab 300 mg QW group. The mean IGA score was  $3.5 \pm 0.5$  for all treatment groups, and scores of 3 and 4 were evenly split. The mean peak weekly averaged pruritus NRS was  $7.5 \pm 1.85$  for patients in the placebo group,  $7.6 \pm 1.60$  for patients in the dupilumab 300 mg Q2W group, and  $7.5 \pm 1.81$  for patients in the dupilumab 300 mg QW group, and most patients ( $>69\%$ ) had a baseline peak NRS  $\geq 7$ . The majority of patients in each treatment group reported a Patient Global Assessment of disease status of poor (1) ( $>40\%$ ) or fair (2) ( $>28\%$ ). The proportion of patients who ranked their status as very good (4) or excellent (5) was  $<5\%$  and  $<2\%$ , respectively, in each group.

33.1% of patients had a history of prior cyclosporine treatment. Approximately half of these patients had used cyclosporine for longer than 12 weeks (51.7%). The most common reason for discontinuing cyclosporine for all treatment groups was inadequate efficacy (43.2%). Overall, 58.1% of patients did not have a history of prior cyclosporine treatment. The most common stated reason for not using cyclosporine was that the risk of important side effects was generally too high (12.4%).

## **Medical history**

### **R668-AD-1334 (Solo1)**

All patients had at least 1 medical history finding using the general questionnaire.  $\geq 10\%$  of patients in any treatment group were Dermatitis Atopic, Asthma, Rhinitis Allergic, Seasonal Allergy, Food Allergy, Allergy to Animal, House Dust Allergy, Conjunctivitis Allergic, Depression, and Hypertension were reported. Based on the specific atopic disease questionnaire, the proportion of patients with a family history of atopic/allergic conditions was similar between treatment groups.

The proportion of patients with a family history of atopic/allergic conditions was similar between treatment groups. The most common atopic/allergic condition in patient family history was AD (40.5% in the placebo group, 46.7% in the dupilumab 300 mg Q2W group, and 38.5% in the dupilumab 300 mg QW group).

All patients had a current history of AD (100%). The next most common ( $\geq 50\%$  of all patients) atopic/allergic condition was other allergies (59.5%). The proportion of patients with a current history of atopic/allergic conditions was similar between treatment groups for each condition.

Less than 10% of patients in any treatment group had a currently resolved atopic/allergic condition. The most common currently resolved atopic/allergic condition was asthma, which was reported for 8.6% of patients in the placebo group, 9.6% of patients in the dupilumab 300 mg Q2W group, and 6.9% of patients in the dupilumab 300 mg QW group.

25.5% of all patients indicated a current history of allergic conjunctivitis.

### **R668-AD-1416 (Solo2)**

All but 1 patient in the placebo group had at least 1 medical history finding using the general questionnaire with  $\geq 10\%$  of patients in any treatment group reporting Dermatitis Atopic, Asthma, Rhinitis Allergic, Food Allergy, Seasonal Allergy, Conjunctivitis Allergic, Depression, and Hypertension.

The proportion of patients with a family history of atopic/allergic conditions was similar between treatment groups. The most common atopic/allergic condition in patient family history was AD (38.0% in the placebo group, 41.5% in the dupilumab 300 mg Q2W group, and 41.4% in the dupilumab 300 mg QW group).

99.6% had a current history of AD, all patients randomized meeting the eligibility criteria for AD duration and severity. The proportion of patients with a current history of atopic/allergic conditions was similar between treatment groups for each condition.

27.3% of all patients indicated a current history of allergic conjunctivitis. The most common currently resolved atopic/allergic condition was asthma, which was reported for a lower proportion of patients in the dupilumab 300 mg Q2W group (3.8%) than the dupilumab 300 mg QW (7.6%) and placebo (7.7%) groups.

## **Numbers analysed**

In Solo1, 671 patients randomized, 669 were included in the SAF, and 671 patients were included in the FAS. Patients in the SAF were analysed as treated. A total of 25 randomized patients were excluded from the PPS because of major violations of efficacy-related entry criteria or a closed site or because they received  $<80\%$  or  $>120\%$  of scheduled doses or were randomized but not treated.

In Solo2, 708 patients were randomized. 707 were included in the SAF, and 708 patients were included in the FAS. Patients in the SAF were analysed as treated. A total of 28 randomized patients were excluded from the PPS because they received  $<80\%$  or  $>120\%$  of scheduled doses or were

randomized but not treated or because of major violations of efficacy-related entry criteria or potentially unreliable data because of site closure due to GCP violations.

## Outcomes and estimation

### Study R668-AD-1334 (Solo1)

The co-primary endpoints show significant higher response rates of dupilumab 300 mg QW and Q2W compared to placebo. The proportion of patients with IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16 was significantly higher in the dupilumab 300 mg Q2W (37.9%) and dupilumab 300 mg QW (37.2%) groups than the placebo group (10.3%).

- **Proportion of Patients with IGA 0 or 1 and a Reduction from Baseline of  $\geq 2$  Points at Week 16; R668-AD-1334 (Solo1)**

	Placebo (N=224)	Dupilumab	
		300 mg Q2W (N=224)	300 mg QW (N=223)
Patients achieving an IGA Score of 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16, n (%)	23 (10.3)	85 (37.9)	83 (37.2)
Difference (%) (95% CI) <sup>a</sup>		27.7 (20.18, 35.17)	27.0 (19.47, 34.44)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing IGA scores at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI=Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA=3 vs. IGA=4).

Source: Post-text Table 6.1.1.1/1

51.3% of patients achieved an EASI-75 at week 16 in the dupilumab 300 mg Q2W, followed by 52.5% in the dupilumab 300 mg QW and 14.7% in the placebo group.

	Placebo (N=224)	Dupilumab	
		300 mg Q2W (N=224)	300 mg QW (N=223)
Patients achieving EASI-75 at week 16, n (%)	33 (14.7)	115 (51.3)	117 (52.5)
Difference (%) (95% CI) <sup>a</sup>		36.6 (28.58, 44.63)	37.7 (29.70, 45.77)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing EASI score at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI=Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA=3 vs. IGA=4).

Source: Post-text Table 6.2.1.1/1

The key secondary endpoints also show a higher efficacy in both dupilumab groups compared to placebo.

- The proportion of patients achieving a reduction of  $\geq 4$  points from baseline in weekly average of peak daily pruritus NRS score at week 16 was significantly higher in the dupilumab 300 mg Q2W (40.8%) and dupilumab 300 mg QW (40.3%) groups than the placebo group (12.3%).
- The proportion of patients achieving a reduction of  $\geq 3$  points from baseline in weekly average of peak daily pruritus NRS score at week 16 was significantly higher in the dupilumab 300 mg Q2W (46.8%) and dupilumab 300 mg QW (51.7%) groups than the placebo group (17.2%).
- A significant decrease in weekly average of peak daily pruritus NRS score from baseline to week 16 was observed in the dupilumab 300 mg Q2W group (least squares [LS] mean [SE] vs baseline, -51.0% [2.50%]) and dupilumab 300 mg QW group (LS mean [SE] vs baseline, -48.9% [2.60%]) compared with the placebo group (LS mean [SE] vs baseline, -26.1% [3.02%]).
- The proportion of patients achieving a reduction of  $\geq 4$  points from baseline in weekly average of peak daily pruritus NRS score at week 4 was significantly higher in the dupilumab 300 mg Q2W (16.0%) and dupilumab 300 mg QW (23.4%) groups than the placebo group (6.1%).

### R668-AD-1416 (Solo2)

The proportion of patients with IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16 was significantly higher in the dupilumab 300 mg Q2W (36.1%) and dupilumab 300 mg QW (36.4%) groups than the placebo group (8.5%).

#### Proportion of Patients Achieving IGA 0 to 1 and a Reduction of $\geq 2$ Points from Baseline at Week 16, Patient Considered Non-Responder after Rescue Treatment Use – FAS

	Placebo (N=236)	Dupilumab	
		300 mg Q2W (N=233)	300 mg QW (N=239)
Patients achieving an IGA Score of 0 or 1 and a reduction from baseline of $\geq 2$ points, n (%)	20 (8.5)	84 (36.1)	87 (36.4)
Difference (%) (95% CI) <sup>a</sup>		27.6 (20.46, 34.69)	27.9 (20.87, 34.99)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing IGA scores at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI=Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA=3 vs. IGA=4).

Source: Post-text Table 6.1.1.1/1

44.2% of patients achieved an EASI-75 at week 16 in the dupilumab 300 mg Q2W, followed by 48.1% in the dupilumab 300 mg QW and 11.9% in the placebo group.

	Placebo (N=236)	Dupilumab	
		300 mg Q2W (N=233)	300 mg QW (N=239)
Patients achieving EASI-75 at week 16 from baseline, n (%)	28 (11.9)	103 (44.2)	115 (48.1)
Difference (%) (95% CI) <sup>a</sup>		32.3 (24.75, 39.94)	36.3 (28.69, 43.81)
P-value <sup>b</sup>		<0.0001	<0.0001

Note: Values after first rescue treatment use were set to missing. Patients with missing EASI score at week 16 were considered non-responders.

<sup>a</sup> Difference is dupilumab minus placebo. CI=Confidence interval, calculated using normal approximation.

<sup>b</sup> P-values were derived by the Cochran-Mantel-Haenszel test stratified by region and baseline disease severity (IGA=3 vs. IGA=4).

Source: Post-text Table 6.2.1.1/1

The key secondary endpoints also show a higher efficacy in both dupilumab groups compared to placebo.

- 36.0% of patients achieved a reduction of  $\geq 4$  points from baseline in weekly average of peak daily pruritus NRS score at week 16 in the dupilumab 300 mg Q2W, followed by 39.0% in the dupilumab 300 mg QW and 9.5% in the placebo group.
- The proportion of patients achieving a reduction of  $\geq 3$  points from baseline in weekly average of peak daily pruritus NRS score at week 16 was also higher in the dupilumab 300 mg Q2W (50.6%) and dupilumab 300 mg QW (49.1%) groups than the placebo group (12.8%).
- The observed decrease in weekly average of peak daily pruritus NRS score from baseline to week 16 was higher in the dupilumab 300 mg Q2W group (LS mean [SE] vs baseline, -44.3% [2.28%]) and dupilumab 300 mg QW group (least squares [LS] mean [SE] vs baseline, -48.3% [2.35%]) compared with the placebo group (LS mean [SE] vs baseline, -15.4% [2.98%]).
- 22.7% of patients achieved a reduction of  $\geq 4$  points from baseline in weekly average of peak daily pruritus NRS score at week 4 in the dupilumab 300 mg Q2W, 27.6% dupilumab 300 mg QW (27.6%) and 6.3% in the placebo group.

## Ancillary analyses

### Anti-Drug Antibody Analysis

#### R668-AD-1334 (Solo1)

A higher proportion of patients with treatment-emergent responses in the ADA assay was observed in the dupilumab 300 mg Q2W (6.8% [15/222]) and dupilumab 300 mg QW (2.9% [6/206]) group than the placebo group (1.0% [2/209]).

Persistent ADA assay responses were observed for 1 patient each in the dupilumab treatment groups. The remaining patients had an indeterminate response in the assay (with a positive result in the ADA assay at only the last time point analysed): 12 (5.4%) patients in the dupilumab 300 mg Q2W group, 5 (2.4%) patients in the dupilumab 300 mg QW group, and 2 (1.0%) patients in the placebo group.

#### R668-AD-1416 (Solo2)

A slightly higher proportion of patients with treatment-emergent ADA assay responses was observed in the dupilumab 300 mg Q2W group (8.0% [18/225]) compared to the placebo (1.8% [4/218]) and dupilumab 300 mg QW (2.7% [6/223]) groups.

## Summary of main studies

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

**Table 1. Summary of Efficacy for trial R668-AD-1224**

<b>Title:</b> A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of Dupilumab in adult patients with moderate- to- severe atopic dermatitis (Chronos)			
Study identifier	R668-AD-1224		
Design	randomized, double-blind, placebo-controlled parallel group design		
	Duration of main phase:	52 weeks	
	Duration of Run-in phase:	Day -35 to -1	
	Duration of Extension phase:	not applicable	
Hypothesis	Superiority		
Treatments groups	Dupilumab 300 Q2W	Dupilumab 300 mg Q2W+TCS N= 106	
	Dupilumab 300 QW	Dupilumab 300 mg QW+TCS N= 319	
	Placebo	Placebo QW+TCS N= 315	
Endpoints and definitions	Co-Primary endpoints	IGA 0 or 1 and reduction $\geq$ 2 points	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq$ 2 points at week 16
		Easi-75	Proportion of patients achieving 75% improvement in EASI at week 16
	Key Secondary endpoints	Pruritus NRS reduction $\geq$ 4 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus Numeric Rating Scale (NRS) $\geq$ 4 from baseline to week 16
		Pruritus NRS reduction $\geq$ 3 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus NRS $\geq$ 3 from baseline to week 16
		Change Pruritus NRS to week 16	Percent change from baseline to week 16 in weekly average of peak daily Pruritus NRS
	Secondary endpoints	IGA 0 or 1 and reduction $\geq$ 2 points	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq$ 2 points at week 52
		Easi-75	Proportion of patients achieving 75% improvement in EASI at week 52
	Database lock	27 April 2016	
<b><u>Results and Analysis</u></b>			
<b>Analysis description</b>	<b>Primary Analysis (16 weeks)</b>		
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 300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	106	319	315
	IGA 0 or 1 and $\geq 2$ Points reduction at Week 16	41 (38.7%)	125 (39.2%)	39 (12.4%)
	95%-CI (%)	(29.96, 48.19)	(33.99, 44.64)	(9.19, 16.48)
	EASI-75 at Week 16	73 (68.9%)	204 (63.9%)	73 (23.2%)
	95%-CI (%)	(59.52, 6.89)	(58.54, 69.02)	(18.86, 28.14)
Effect estimate per comparison	Co-Primary endpoint IGA 0 or 1 and $\geq 2$ Points reduction	Comparison groups	Dupilumab 300 Q2W vs Placebo	
		P-value	<0.0001	
	Co-Primary endpoint EASI-75	Comparison groups	Dupilumab 300 Q2W vs Placebo	
		P-value	<0.0001	
<b>Analysis description</b>	<b>Secondary analysis</b>			
Descriptive statistics and estimate variability	Treatment group	Dupilumab 300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	106	319	315
	Pruritus NRS reduction $\geq 4$ at week 16	60/102 (58.8%)	150/295 (50.8%)	59/299 (19.7%)
	95%-CI (%)	(49.12, 67.88)	(45.17, 56.50)	(15.62, 24.62)
	Pruritus NRS reduction $\geq 3$ at week 16	69/105 (65.7%)	193/309 (62.5%)	85/306 (27.8%)
	95%-CI (%)	(56.23, 74.09)	(56.94, 67.67)	(23.06, 33.05)
	Change Pruritus NRS to week 16, mean (SD) 95%-CI (%)	-30.9% (30.08) (-36.63, -25.17)	-57.4 (27.71) (-60.44, -54.36)	-56.9% (36.58) (-60.94, -52.86)
Effect estimate per comparison	Pruritus NRS reduction $\geq 4$ at week 16	Comparison groups	Dupilumab 300 Q2W vs. Placebo	
		P-value	< 0.0001	
	Pruritus NRS reduction $\geq 3$ at week 16	Comparison groups	Dupilumab 300 Q2W vs. Placebo	
		P-value	< 0.0001	
	Change Pruritus NRS to week 16	Comparison groups	Dupilumab 300 Q2W vs. Placebo	
		P-value	< 0.0001	



**Table 2. Summary of efficacy for trial R668-AD-1334**

<b>Title:</b> A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS				
Study identifier	R668-AD-1334			
Design	randomized, double-blind, placebo-controlled parallel group design			
	Duration of main phase:	16 weeks		
	Duration of Run-in phase:	Day -35 to -1		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority			
Treatments groups	Dupilumab 300 Q2W	Dupilumab 300 mg Q2W N=224		
	Dupilumab 300 QW	Dupilumab 300 mg QW N=223		
	Placebo	Placebo QW N=224		
Endpoints and definitions	Co-Primary endpoints	IGA 0 or 1 and reduction $\geq$ 2 points	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq$ 2 points at week 16	
		Easi-75	Proportion of patients achieving 75% improvement in EASI at week 16	
	Key Secondary endpoints	Pruritus NRS reduction $\geq$ 4 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus Numeric Rating Scale (NRS) $\geq$ 4 from baseline to week 16	
		Pruritus NRS reduction $\geq$ 3 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus NRS $\geq$ 3 from baseline to week 16	
		Change Pruritus NRS to week 16	Percent change from baseline to week 16 in weekly average of peak daily Pruritus NRS	
	Database lock	12 February 2016		
<b><u>Results and Analysis</u></b>				
<b>Analysis description</b>	<b>Primary Analysis</b>			
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 300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	224	223	224
	IGA 0 or 1 and $\geq$ 2 Points reduction	85 (37.9%)	83 (37.2%)	23 (10.3%)

	95%-CI (%)	(31.85, 44.45)	(31.14, 43.73)	(6.94, 14.94)
	EASI-75	115 (51.3%)	117 (52.5%)	33 (14.7%)
	95%-CI (%)	(44.83, 57.81)	(45.93, 58.92)	(10.69, 19.97)
Effect estimate per comparison	Co-Primary endpoint IGA 0 or 1 and $\geq 2$ Points reduction	Comparison groups	Dupilumab 300Q2W vs Placebo	
		P-value	<0.0001	
	Co-Primary endpoint EASI-75	Comparison groups	Dupilumab 300Q2W vs Placebo	
		P-value	<0.0001	
<b>Analysis description</b>	<b>Secondary analysis</b>			
Descriptive statistics and estimate variability	Treatment group	Dupilumab300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	224	223	224
	< Pruritus NRS reduction $\geq 4$ at week 16	87/213 (40.8%)	81/201 (40.3%)	26/212 (12.3%)
	95%-CI (%)	(34.46, 47.55)	(33.76, 47.20)	(8.51, 17.36)
	Pruritus NRS reduction $\geq 3$ at week 16	103/220 (46.8%)	109/211 (51.7%)	38/221 (17.2%)
	95%-CI (%)	(40.34, 53.41)	(44.95, 58.31)	(12.79, 22.72)
	Change Pruritus NRS to week 16, mean (SD) 95%-CI	-51.1 (28.81) (-54.87, -47.33)	-49.0 (33.45) (-53.39, 44.61)	-26.8 (28.38) (-30.52, 23.08)
Effect estimate per comparison	Pruritus NRS reduction $\geq 4$ at week 16	Comparison groups	Dupilumab 300 Q2W vs Placebo	
		P-value	<0.0001	
	Pruritus NRS reduction $\geq 3$ at week 16	Comparison groups	Dupilumab 300 Q2W vs Placebo	
		P-value	<0.0001	
	Change Pruritus NRS to week 16	Comparison groups	Dupilumab 300 Q2W vs Placebo	
		P-value	<0.0001	

**Table 3. Summary of efficacy for trial R668-AD-1416**

**Title:** A PHASE 3 CONFIRMATORY STUDY INVESTIGATING THE EFFICACY AND SAFETY OF DUPILUMAB MONOTHERAPY ADMINISTERED TO ADULT PATIENTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Study identifier	R668-AD-1416			
Design	randomized, double-blind, placebo-controlled parallel group design			
	Duration of main phase:	16 weeks		
	Duration of Run-in phase:	Day -35 to -1		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority			
Treatments groups	Dupilumab 300 Q2W	Dupilumab 300 mg Q2W N=233		
	Dupilumab 300 QW	Dupilumab 300 mg QW N=239		
	Placebo	Placebo QW N=236		
Endpoints and definitions	Co-Primary endpoints	IGA 0 or 1 and reduction $\geq$ 2 points	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq$ 2 points at week 16	
		Easi-75	Proportion of patients achieving 75% improvement in EASI at week 16	
	Key Secondary endpoints	Pruritus NRS reduction $\geq$ 4 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus Numeric Rating Scale (NRS) $\geq$ 4 from baseline to week 16	
		Pruritus NRS reduction $\geq$ 3 at week 16	Proportion of patients with improvement of weekly average of peak daily Pruritus NRS $\geq$ 3 from baseline to week 16	
		Change Pruritus NRS to week 16	Percent change from baseline to week 16 in weekly average of peak daily Pruritus NRS	
	Database lock	21 January 2016		
<b><u>Results and Analysis</u></b>				
<b>Analysis description</b>	<b>Primary Analysis</b>			
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 300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	233	239	236
	IGA 0 or 1 and $\geq$ 2 Points reduction	84 (36.1%)	87 (36.4%)	20 (8.5%)
	95%-CI (%)	(30.16, 42.40)	(30.56, 42.67)	(5.55, 12.73)
	EASI-75	103 (44.2%)	115 (48.1%)	28 (11.9%)

	95%-CI (%)	(37.97, 50.63)	(41.86, 54.43)	(8.34, 16.61)
Effect estimate per comparison	Co-Primary endpoint IGA 0 or 1 and $\geq 2$ Points reduction	Comparison groups	Dupilumab 300Q2W vs Placebo	
		P-value	<0.0001	
	Co-Primary endpoint EASI-75	Comparison groups	Dupilumab 300Q2W vs Placebo	
		P-value	<0.0001	
<b>Analysis description</b>	<b>Secondary analysis</b>			
Descriptive statistics and estimate variability	Treatment group	Dupilumab300 Q2W	Dupilumab 300 QW	Placebo
	Number of subject	233	239	236
	< Pruritus NRS reduction $\geq 4$ at week 16	81/225 (36.0%)	89/228 (39.0%)	21/221 (9.5%)
	95%-CI (%)	(30.01, 42.46)	(32.93, 45.50)	(6.30, 14.09)
	Pruritus NRS reduction $\geq 3$ at week 16	117/231 (50.6%)	115/234 (49.1%)	29/226 (12.8%)
	95%-CI (%)			
	Percent Change Pruritus NRS to week 16, mean (SD) 95%-CI	-47.2 (28.50) (-50.86, -43.54)	-50.9 (30.56) (-54.77, -47.03)	-18.1(27.66) (-21.63, -14.57)
Effect estimate per comparison	Pruritus NRS reduction $\geq 4$ at week 16	Comparison groups	Dupilumab 300 mQ2W vs placebo	
		P-value	<0.0001	
	Pruritus NRS reduction $\geq 3$ at week 16	Comparison groups	Dupilumab 300 mQ2W vs placebo	
		P-value	<0.0001	
	Change Pruritus NRS to week 16	Comparison groups	Dupilumab 300 mQ2W vs placebo	
		P-value	<0.0001	

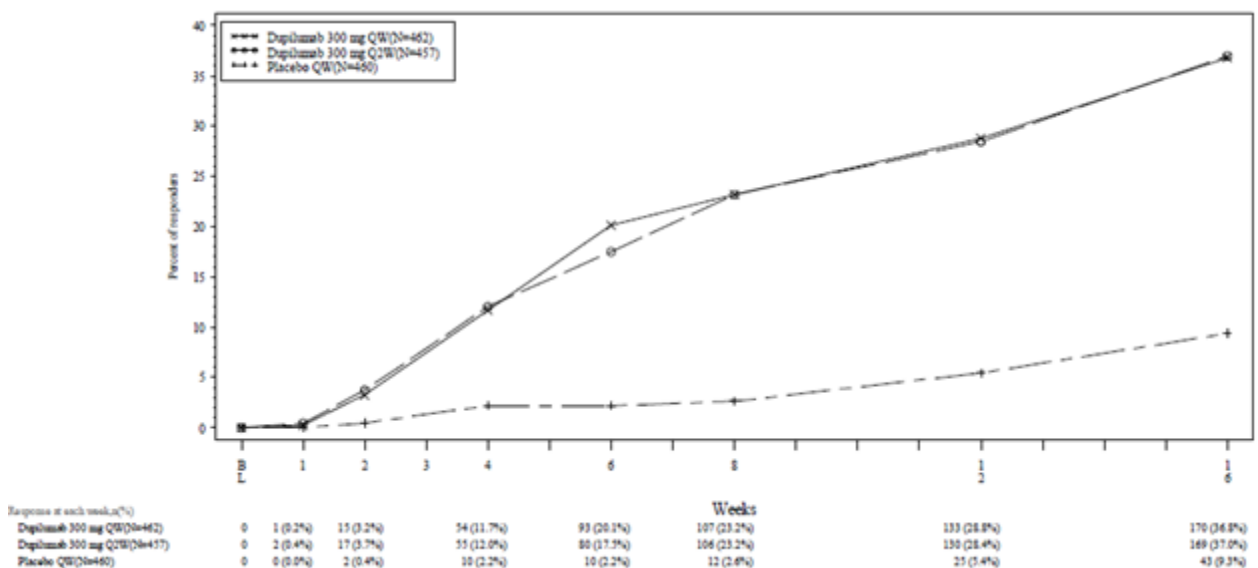
## Analysis performed across trials

The data from the identical 2 pivotal phase 3 studies R668-AD-1334 (Solo1) and R668-AD-1416 (Solo2) were pooled. The results show superiority of both dupilumab doses compared to placebo. The difference between both dosing regimens is very small.

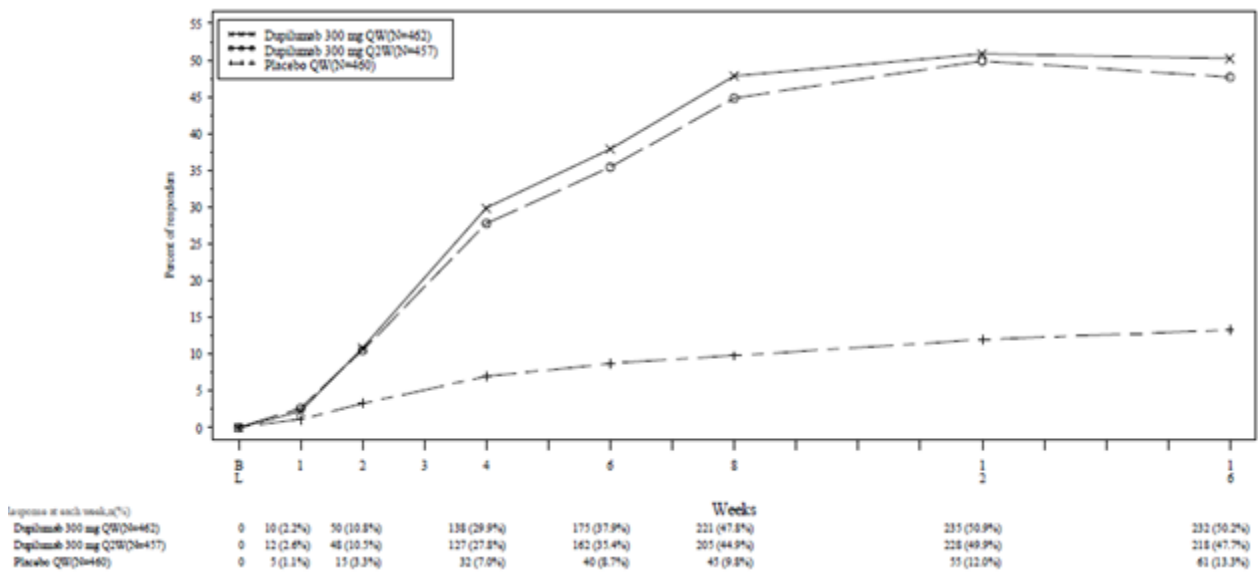
Primary Analysis of Proportion of Patients Achieving both IGA 0 or 1 and a Reduction of  $\geq 2$  Points from Baseline at Week 16, Patient considered non-responder after rescue treatment Use (Full Analysis Set).

Study	Treatment	Patients achieving an IGA Score of 0 or 1 and a reduction from baseline of $\geq 2$ points,		
		n (%)	Difference vs. Placebo (%) (95% CI) [1]	P-value vs. placebo [2]
R668-AD-1334	Dupilumab 300 mg QW (N=223)	83 (37.2)	27.0 (19.47, 34.44)	<0.0001
	Dupilumab 300 mg Q2W (N=224)	85 (37.9)	27.7 (20.18, 35.17)	<0.0001
	Placebo QW (N=224)	23 (10.3)		
R668-AD-1416	Dupilumab 300 mg QW (N=239)	87 (36.4)	27.9 (20.87, 34.99)	<0.0001
	Dupilumab 300 mg Q2W (N=233)	84 (36.1)	27.6 (20.46, 34.69)	<0.0001
	Placebo QW (N=236)	20 (8.5)		
Pooled Analysis	Dupilumab 300 mg QW (N=462)	170 (36.8)	27.4 (22.31, 32.59)	<0.0001
	Dupilumab 300 mg Q2W (N=457)	169 (37.0)	27.6 (22.47, 32.80)	<0.0001
	Placebo QW (N=460)	43 (9.3)		

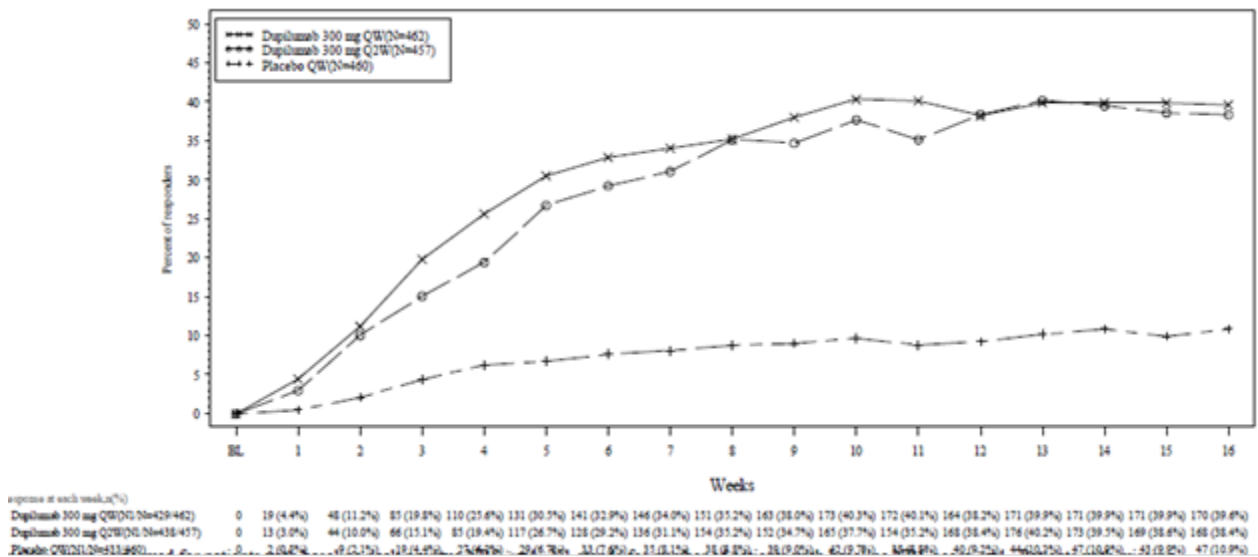
Primary analysis of percentage of patients achieving IGA 0 or 1 and a reduction of  $\geq 2$  points from baseline to week 16, Censoring after Rescue Treatment Use



Primary analysis of percentage of patients Achieving EASI-75 (>=75% Improvement from Baseline) from baseline to week 16



Primary analysis of percentage of patients achieving a reduction of >= 4 points in weekly average of peak daily pruritus NRS from baseline to week 16. Censoring after Rescue Treatment Use



Pooled subgroup analyses were performed on the integrated efficacy dataset. These analyses e.g. by age, sex, race, weight and prior systemic therapies were planned to be performed for the primary and key secondary efficacy endpoints.

Subgroup Analysis of Proportion of Patients Achieving EASI-75 (>=75% Improvement from Baseline) at Week 16 by BMI, Patient considered non-responder after rescue treatment use (Full Analysis Set)

**BMI : 15-<25**

Study	Treatment	Patients achieving EASI-75 at Week 16 from baseline, n (%)	Difference vs. Placebo (%) (95% CI) [1]
Pooled Analysis	Dupilumab 300 mg QW (N=211)	107 (50.7)	39.9 (31.04, 48.32)
	Dupilumab 300 mg Q2W (N=206)	96 (46.6)	35.8 (26.78, 44.43)
	Placebo QW (N=223)	24 (10.8)	

**BMI : 25-<30**

Pooled Analysis	Dupilumab 300 mg QW (N=146)	74 (50.7)	38.0 (26.79, 48.43)
	Dupilumab 300 mg Q2W (N=161)	72 (44.7)	32.0 (20.93, 42.58)
	Placebo QW (N=134)	17 (12.7)	

**BMI : >=30**

Of special interest are the three subsets of patients with various history of ciclosporin therapy defined at baseline. Subset 1 included patients who showed an inadequate efficacy response to oral ciclosporin. Subset 2 included patients who showed an inadequate efficacy response or were intolerant to oral ciclosporin. Subset 3 included all patients in subset 2 plus patients who did not receive prior oral ciclosporin treatment because ciclosporin was contraindicated or otherwise medically inadvisable. The analyses of 3 the subsets indicated that these patients had slight more severe AD (e.g., mean baseline EASI score of approximately 36 in patients in subset 3 vs approximately 32 in patients not in subset 3 of Efficacy Pool 1). Nevertheless, both dupilumab dose regimens consistently resulted in clinically meaningful improvements in signs and symptoms of AD across all 3 patient subsets.

**Clinical studies in special populations**

Use of dupilumab in elderly was quite limited as AD mainly affects younger patients.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials (AD-1334, AD-1416,)	23	9	1
AD- 1224	27 > 65 Years		
Non Controlled trials AD-1225	51 (3.4%)	9 (0.6%)	2 (0.1%)

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### ***Supportive studies***

**R668-AD-0914** and **R668-AD-1026** were phase 1b, 12-week, multicenter, double-blind, randomized, placebo-controlled, multiple ascending dose studies conducted to assess the safety and PK profile of SC treatment with dupilumab in adult patients with moderate-to-severe AD. Exploratory objectives in both studies included an assessment of the clinical effect of dupilumab. In both studies, the percent decrease in EASI score over the treatment period was greater in the dupilumab groups than in the placebo group, with the greatest decrease seen in the 300 mg group.

**R668-AD-1121** was a phase 2a, 11-week, multicenter, double-blind, randomized, placebo-controlled study to assess the safety and efficacy (exploratory) of SC dupilumab administered concomitantly with TCS in adult patients with moderate-to-severe AD. Exploratory efficacy assessments included EASI, IGA of AD severity, pruritus NRS, and SCORAD. Higher decreases from baseline in IGA, EASI, pruritus NRS, and SCORAD scores were observed in the dupilumab + TCS group than the placebo + TCS group.

**R668-AD-1117** was a phase 2a, 28-week, multicenter, double-blind, randomized, placebo-controlled, proof-of-concept study to assess the efficacy, safety and tolerability, and pharmacodynamics of SC dupilumab treatment in adults with moderate-to-severe AD. The primary efficacy endpoint was the mean percent reduction in EASI score from baseline to week 12 and was statistically significantly larger in the dupilumab group than in the placebo group. Results from the secondary efficacy analyses also demonstrated a greater reduction in AD severity in the dupilumab group than the placebo group.

**R668-AD-1307** was a phase 2, 32-week, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy, safety, concentration of functional dupilumab in serum over time, and immunogenicity of SC dupilumab treatment in adults with moderate-to-severe AD that could not be adequately controlled with topical medications or for whom topical treatment was medically inadvisable.

**R668-AD-1314** was a phase 2, 32-week, multicenter, double-blind, randomized, placebo-controlled study conducted in the USA to assess T-cell-dependent and T-cell-independent immunization responses, respectively, to tetanus toxoid adsorbed Adacel® (Tdap) and Menomune (meningococcal polysaccharide) vaccinations in adults with moderate-to-severe AD, who were treated with SC dupilumab. Improvements were seen for absolute and percent changes in peak pruritus NRS, BSA involvement with AD, GISS and POEM scores from baseline to week 16, in the proportions of patients achieving IGA scores of 0 or 1, IGA score reductions  $\geq 2$  and patients achieving 50% and 75% reductions in EASI scores at week 16.

**R668-AD-1225** is a phase 3, multicenter, open-label, extension study to assess the long-term safety and efficacy of repeat doses of dupilumab in adults with moderate-to-severe AD.

This study is currently ongoing. At the time of data cut-off, no patients had completed treatment or had completed the study. At week 16 37.8% and at week 52 56.0% had an IGA score of 0 or 1, respectively (at baseline 4.6%). At week 16 and week 52, 75.0% and 87.1% of patients achieved EASI-75 relative to baseline of the parent study.

#### **R668-AD-1424 (Café Study)**

This was a 32-week phase 3 double-blind, randomized, placebo-controlled, parallel group study to confirm the efficacy, safety, and tolerability of dupilumab administered in adults with severe Atopic Dermatitis for whom CSA had either not demonstrated adequate efficacy, had unacceptable side



effects or for whom initiating CSA was not medically advisable. The results of this study were requested due to the patient population of this study and introduction of final manufacturing process.

The primary endpoint EASI 75 at week 16 was statistically significantly higher in the treated patients versus placebo. The many secondary endpoints which included IGA 0-1 response, PRURITIS, SCORAD, POEM and DLQI were statistically significantly better with dupilumab therapy. Onset of action was rapid, with divergence between dupilumab + TCS and placebo + TCS apparent as early as week 2 for many endpoints. Multiple sensitivity analyses using all observed data confirmed the results of the primary analysis, demonstrating that these outcomes were not driven by the analytic method of categorizing patients who used rescue treatment as non-responders, even though rescue was more common in the placebo + TCS group.

### Results of the primary and secondary endpoints in CAFE study

	Placebo + TCS	Dupilumab 300 mg Q2W + TCS	Dupilumab 300 mg QW+TCS
<b>Patients randomised</b>	108	107	110
EASI-75, % responders	29.6 %	62.6 %	59.1 %
EASI, LS mean % change from baseline (+/- SE)	-46.6 (2.76)	-79.8 (2.59)	-78.2 (2.55)
Pruritus NRS, LS mean % change from baseline (+/- SE)	-25.4 % (3.39)	-53.9 % (3.14)	-51.7 % (3.09)
SCORAD, LS mean % change from baseline (+/- SE)	-29.5 % (2.55)	-62.4 % (2.48)	-58.3 % (2.45)
DLQI, LS mean change from baseline (SE)	-4.5 (0.49)	-9.5 (0.46)	-8.8 (0.45)

(all p values < 0.0001)

### R668-AD-1415 (SOLO-CONTINUE Study)

R668-AD-1415 was a phase 3, randomized, double-blind, placebo-controlled study enrolling only the subset of patients who achieved high-level clinical response [IGA(0,1) or EASI-75] after 16-week treatment in one of the initial-treatment (parent) studies (SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416). SOLO-CONTINUE compared the ability of increased dosing intervals to maintain the high level of response achieved after 166 weeks of dupilumab mono-therapy in the SOLO studies.

SOLO-CONTINUE consisted of a 36-week treatment period, during which patients received dupilumab 300 mg QW, Q2W, Q4W, Q8W, or placebo from day 1 (ie, week 16 in the parent studies), and a 12-week follow-up period. The co-primary endpoints were i, the mean change between baseline and week 36 in percent change in EASI Score from parent study baseline, and ii, percent of patients with EASI-75 at week 36 for patients with EASI-75 at baseline. Patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300 mg Q2W or 300 mg QW) showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner.

### 2.5.3. Discussion on clinical efficacy

#### ***Design and conduct of clinical studies***

A total of over 2500 patients with AD contributed data for efficacy analysis, including patients randomized in the pivotal phase 3 studies. The phase 3 development program of dupilumab in patients with moderate to severe atopic dermatitis consists of 3 pivotal studies with 2 replicate 16 weeks

monotherapy studies (SOLO 1 R668-AD-1334 and SOLO 2 R688-AD-1416) and a 52-week long-term treatment study of dupilumab with concomitant use of topical medications (CHRONOS R668-AD-1224).

Two different subcutaneous (SC) dupilumab dosing regimens were evaluated in the phase 3 studies, 300 mg Q2W and 300 mg QW, each with a loading dose of 600 mg on day 1. These doses were selected based on the results of the phase 2b dose ranging study (R668-AD-1021) with the 300 mg QW and 300 mg Q2W regimens demonstrating the highest efficacy.

Study R668-AD-1224 (Chronos) consisted of a 35 days long screening phase, including wash out of treatments for AD, a 52-week treatment phase and a 12 week follow up period. At baseline 740 patients were randomized in a 3:1:3 ratio to receive dupilumab 300 mg SC QW or Q2W, following the loading dose on day 1, or matching placebo. All patients also received TCS using a standardized predefined regimen. Randomization was stratified by baseline disease severity and by region. The end of treatment period visit occurred at week 52, 1 week after the last dose of study drug. Follow-up visits occurred week 64 (EOS).

Dupilumab as monotherapy was studied in the pivotal 16-week studies R668-AD-1334 (SOLO 1) and R668-AD-1416 (SOLO 2). The design of both studies was identical. The studies consisted of a 35 day screening phase, a 16 week treatment phase and a 12 week safety follow up. In R668-AD-1334 671 patients and in R668-AD-1416 708 patients were randomized in a 1:1:1 ratio to receive SC 300 mg dupilumab QW, 300 mg dupilumab Q2W (each with the loading dose of 600 mg) or matching placebo. The design of the studies is considered adequate to assess short term efficacy.

The eligibility criteria were adequate for the inclusion of patients with moderate to severe atopic dermatitis and comparable across the clinical studies with little modifications for study R669-AD-1224 (Chronos) pertaining to patients being able to safely use TCS, due to the design of the study. The demographic and baseline disease characteristics were similar among the treatment groups across the studies and the mean baseline values for all AD assessments were consistent with moderate-to-severe AD. No meaningful imbalances were identified.

Patients were 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 (e.g., because of important potential side effects from TCS).

In the monotherapy studies, patients could have received rescue treatment with an otherwise prohibited medication for treatment of intolerable AD symptoms during the study. In both studies, the proportion of patients who required rescue treatment in the dupilumab 300 mg Q2W group was similar to the 300 mg QW group (15-23% for dupilumab versus 51-52% placebo). The most commonly used rescue medications in both monotherapy studies were topical corticosteroids. A smaller proportion of patients were rescued with systemic medications than topical medications.

The co-primary endpoints were proportion of patients with EASI-75 at week 16 and IGA 0 or 1 and a reduction of  $\geq 2$  points at week 16. This is considered adequate to evaluate improvement in atopic dermatitis. Key secondary endpoints were the proportion of patients with improvement (reduction  $\geq 4$  points or  $\geq 3$  points) of weekly average of peak daily pruritus NRS from baseline to week 2, 4, 16, and the percent change from baseline to week 16. The endpoints were similar for all three pivotal studies.

Study R668-AD-1424 was a supplementary 32-week phase 3 double-blind, randomized, placebo-controlled, parallel group study to confirm the efficacy, safety, and tolerability of dupilumab in a specific sub set of adults with severe Atopic Dermatitis for whom CSA had either not demonstrated adequate efficacy, or had unacceptable side effects, or for whom initiating CSA was not medically advisable.

The report is based on the results of the primary analysis of efficacy, which included data up to the cut-off date of 5 January 2017. A total of 325 patients were enrolled and randomized 1:1:1 to receive placebo, dupilumab 300 mg Q2W + TCS, or dupilumab 300 mg QW + TCS for 16 weeks (108 patients in the placebo + TCS group, 107 patients in the dupilumab 300 mg Q2W + TCS group, and 110 patients in the 300 mg QW + TCS group). Patients selected in this study were males and females of 18 years of age or older with severe AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014] with EASI score  $\geq 20$ , IGA score  $\geq 3$  and BSA  $\geq 10\%$ ), whose disease could not be adequately controlled with TCS, who were not adequately controlled with or were intolerant to oral CSA, or for whom CSA treatment was deemed not medically advisable by a physician.

Study R668-AD-1415 was a study conducted in a subset of patients who achieved high-level clinical response (IGA(0,1) or EASI-75) after 16-week treatment in one of the initial-treatment (parent) studies (SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416). Its purpose was to assess efficacy and safety of continuation of the dupilumab dose regimens (300 mg Q2W or QW) administered in the initial treatment studies compared with dose frequency reductions (to Q4W or Q8W) and dose withdrawal (discontinue dupilumab to receive placebo).

### ***Efficacy data and additional analyses***

A serial gatekeeping procedure with alpha split between the 2 dose regimens was used to test the primary and key secondary endpoints while controlling for multiplicity in each of the phase 3 studies. The co-primary efficacy endpoints were met in all phase 3 studies and show a statistically significant higher efficacy ( $p < 0.0001$ ) for both dupilumab doses compared to placebo in combination with TCS or as monotherapy. Hierarchical testing was applied to the key and other secondary endpoints at a 2-sided significance level of 0.025 for the comparison between each dupilumab dose regimen and placebo.

The Co-Primary Endpoints of study R668-AD-1224 show a significant higher effect of dupilumab 300 mg QW and Q2W each in combination with TCS on the severity of AD compared to placebo + TCS. The Secondary efficacy Endpoints support the effects seen in the Co-Primary Endpoints. The difference in clinical efficacy was small between both dupilumab doses.

In the 2 replicate 16-week studies R668-AD-1334 (Solo1) and -1416 (Solo2) both dupilumab dosing regimens show superiority to placebo in the key efficacy measurements. The secondary efficacy endpoints support the effects seen in the Co-Primary Endpoints and show a significant reduction in the Weekly Average of Peak Daily Pruritus NRS at several timepoints. Additionally the high amount of other efficacy endpoints that were assessed support the favourable efficacy of dupilumab compared to placebo.

The data from the identical 2 pivotal phase 3 studies were pooled in Efficacy Pool1. The analyses show the superiority of both dupilumab doses to placebo with respect to the co-primary and key secondary endpoints.

Additionally pooled subgroup analyses were performed on the integrated efficacy dataset of Efficacy Pool 1. Of special interest is the Ciclosporin subgroup analysis. 3 subsets of patients for whom treatment with oral Ciclosporin was medically inadvisable show that both dupilumab dose regimens resulted in clinically meaningful improvements in signs and symptoms of AD across all 3 patient subsets in Efficacy Pool 1, with similar findings observed in R668-AD-1224.

The trials were not powered to detect differences between the active arms however no difference in efficacy can be seen between dupilumab given Q2W or QW which is similar to the monotherapy trials. It can also be seen in the week 16 data that the IGA response is slightly higher with the combination of

dupilumab+ TCS VS dupilumab alone, however the placebo response is higher in study AD 1224 as patients were on TCS, but the differences from placebo are similar, therefore the effects are additive only.

For both dose regimens in the three studies, the difference in the proportion of patients who met the endpoint EASI 75 at week 16 compared to placebo was clinically meaningful and statistically significant ( $P < 0.0001$ ). The differences in the proportion of patients who met the endpoint compared to placebo and the associated 95% CIs suggested there was no meaningful difference in the response rate of the 300 mg QW regimen over the 300 mg Q2W regimen in either study.

Supportive analysis using data from the PPS yielded comparable results to the FAS for both studies and supported the same conclusions as those generated from the FAS. Sensitivity analyses showed that the results of the primary efficacy endpoint were not driven by the method of handling missing data. In both studies, the results of all pre-specified sensitivity analyses were consistent with the primary analysis.

Inclusion of other secondary efficacy endpoints allowed an assessment of different perspectives of the treatment response. Analysis of these endpoints at week 16 showed that dupilumab monotherapy and with TCS resulted in statistically significantly larger reductions from baseline in EASI, SCORAD, BSA involvement with AD, and GISS cumulative score compared to placebo. These findings provide further evidence for improvements in both objective and subjective assessments of AD in dupilumab-treated patients.

Further, dupilumab monotherapy or in combination with TCS resulted in statistically significantly greater reductions from baseline compared to placebo for POEM, DLQI and HADS, indicating improvements in patient-reported symptoms, HRQL, and symptoms of anxiety and depression.

Dupilumab demonstrated a consistent effect for the co primary endpoints on the proportion of patients who achieved both IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16 across all subgroups assessed and for EASI 75 response including age, weight, race, baseline disease severity, and previous use of systemic medications for AD, as shown by treatment-by-subgroup interaction testing.

Longer term efficacy was examined in study R688-AD-1224. Statistically significant results are seen in IGA response 0 or 1 with continued treatment at 52 weeks in patients who achieved an IGA 0 or 1 at 16 weeks in both regimens. The proportion of patients with EASI-75 at week 52 was significantly higher in both dupilumab groups.

In Study R668-AD-1424 (Café Study) including patients with a documented history of intolerance or inadequate response to previous treatment with CSA, or for whom treatment with CSA is medically inadvisable, both dose regimens of dupilumab + TCS significantly improved the extent and severity of AD. The overall baseline disease and previous therapy used were similar between the groups. Most patients were White (96.3%), male (61.2%) and the mean weight, height, and BMI of all patients were 75.8 ( $\pm 16.96$ ) kg, 172.5 ( $\pm 10.01$ ) cm, and 25.3 ( $\pm 4.63$ ) kg/m<sup>2</sup>.

The primary endpoint EASI 75 at week 16 was statistically significantly higher in the treated patients versus placebo. The many secondary endpoints which included IGA 0-1 response, PRURITIS, SCORAD, POEM and DLQI were statistically significantly better with dupilumab therapy. Onset of action was rapid, with divergence between dupilumab + TCS and placebo + TCS apparent as early as week 2 for many endpoints. The study was adequately powered for the primary analysis.

Multiple sensitivity analyses using all observed data confirmed the results of the primary analysis, demonstrating that these outcomes were not driven by the analytic method of categorizing patients who used rescue treatment as non-responders, even though rescue was more common in the placebo

+ TCS group. The applicant stated that the PPS analysis was not conducted as it was not different from the FAS.

Exposure in terms of the number of doses of study treatment and treatment duration was similar in the Café study compared to Study Drug Exposure for Subset 3 Patients in the Pooled R668-AD-1334 and R668-AD-1416 analysis (ref table 77 of summary of Clinical safety)

Of note, the commercial formulation was introduced in June 2016. This study was ongoing between 28 Jan 2016 and 28 Dec 2016. Of the 325 patients enrolled in the study, 48 patients received the previous clinical formulation only and 27 patients received the commercial formulation only.

The duration of the study was rather short as the endpoints measured efficacy at 16 weeks however the trial adds additional support for use in patients with AD who cannot tolerate or do not respond to CsA therapy and confirms results from the CAFÉ -like population subset in the CHRONOS study (R668-AD-1224) that demonstrated efficacy in this patient population at both Weeks 16 and 52.

In study R668-AD-1415 (SOLO-CONTINUE), a study conducted in a subset of patients who achieved high-level clinical response (IGA(0,1) or EASI-75) after 16-week treatment in one of the initial-treatment (parent) studies (SOLO 1 R668-AD-1334 and SOLO 2 R668-AD-1416), patients who continued on the same dose regimen received in the SOLO 1 and SOLO 2 studies (300 mg Q2W or 300 mg QW) showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner.

#### **2.5.4. Conclusions on the clinical efficacy**

The superiority to placebo was demonstrated for both dupilumab doses as monotherapy or in combination with TCS in AD patients who are insufficiently controlled with topical therapies alone. No significant additional benefit was observed with weekly dosing versus Q2W dosing (300 mg s.c) in the overall population. Therefore, the CHMP endorsed the proposed dose of 300 mg every other week (Q2W) with a loading dose of 600 mg on day 1.

### **2.6. Clinical safety**

#### ***Patient exposure***

Safety data from 17 studies (data cut-off date of 31 May 2016) was evaluated in this submission. 2526 AD patients were exposed to dupilumab in 11 studies (10 placebo-controlled studies and 1 OLE study, excluding healthy volunteers) with a treatment period of  $\geq 4$  weeks. The duration of exposure for adult patients with AD who have been treated with dupilumab is as follows:

- at least 1 year (364 days) for 739 patients (total duration any dupilumab dose): 645 patients with 300 mg weekly (QW) and 58 patients with 300 mg every 2 weeks (Q2W)
- at least 1.5 years (546 days) for 309 patients (total duration any dupilumab dose): 91 patients with 300 mg QW
- at least 2 years (728 days) for 160 patients (total duration any dupilumab dose)

The safety data from these studies have been integrated into 3 pools, the Primary Safety Pool, the Supportive Safety Pool, and the Exposure Pool. The first 2 pools provide a comprehensive evaluation of dupilumab as monotherapy. The Exposure Pool provides a comprehensive evaluation of the overall extent of exposure to dupilumab in patients with AD.

	Total	Exposed to Dupilumab
Overall from 17 phase 1 to 3 studies in healthy subjects and patients with AD (including studies in the Exposure Pool plus 6 studies in healthy subjects) [Figure 1]	3200	2728
Exposure Pool (including 11 phase 1 to 3 studies in patients with AD with a treatment period of $\geq 4$ weeks: R668-AD-0914, R668-AD-1026, R668-AD-1121, R668-AD-1117, R668-AD-1021, R668-AD-1307, R668-AD-1314, SOLO 1 R668-AD-1334, SOLO 2 R668-AD-1416, CHRONOS R668-AD-1224, R668-AD-1225) [Module 5.3.5.3 Pool 4 Table 1.1.1/1 and Table 5.2.2/1]		
Received at least 1 dose	2978	2526
Cumulative treatment duration $\geq 1$ year ( $\geq 364$ days)	NA	739
Cumulative treatment duration $\geq 18$ months ( $\geq 546$ days)	NA	309
Cumulative treatment duration $\geq 24$ months ( $\geq 728$ days)	NA	160
Supportive Safety Pool (including 6 monotherapy studies in patients with AD with a treatment period of 12 to 16 weeks: R668-AD-1117, R668-AD-1021, R668-AD-1307, R668-AD-1314, R668-AD-1334, SOLO 2 R668-AD-1416) [Module 5.3.5.3 Pool 3 Table 4.1.1/1]	2047 <sup>a</sup>	1352 <sup>a</sup>
Primary Safety Pool (including 3 studies of 16-week monotherapy in patients with AD: SOLO 1 R668-AD-1334, SOLO 2 R668-AD-1416, and R668-AD-1021) [Module 5.3.5.3 Pool 2 Table 4.1.1/1]	1564	1047

CHRONOS R668-AD-1224 (long-term [52-week] concomitant treatment with TCS) [Module 5.3.5.1 R668-AD-1224 Post-text Table 5.2.1/1 and Table 5.2.1/2]		
Received at least 1 dose	740	425
Cumulative treatment exposure $\geq 16$ weeks	682	400
Cumulative treatment exposure $\geq 52$ weeks	394	254
R668-AD-1225 (long-term OLE study) [Module 5.3.5.2 R668-AD-1225 Post-text Table 5.2.1/2]		
Received at least 1 dose	1491	1491
Cumulative treatment exposure $\geq 52$ weeks	404	404
Cumulative treatment exposure $\geq 76$ weeks	277	277
Cumulative treatment exposure $\geq 100$ weeks	63	63

<sup>a</sup>. Includes patients exposed to  $\geq 300$  mg Monthly Total Dose.

Note: For the pooled count, patients participated in more than 1 study is counted only once.

NA = not available

## Adverse events

### Primary Safety Pool - R668-AD-1334, R668-AD-1416, and R668-AD-1021 (16-Week Monotherapy)

Approximately 69% of patients experienced a TEAE. The proportion of patients who experienced a TEAE during the 16-week treatment period was similar between the dupilumab 300 mg Q2W and 300 mg QW groups and the placebo group. The proportion of patients with treatment-emergent SAEs was lower in the dupilumab 300 mg Q2W and 300 mg QW groups than in the placebo group (2.5% and 2.1% versus 5.0%).

The proportion of patients with severe TEAEs was lower in the dupilumab 300 mg Q2W and 300 mg QW groups than in the placebo group (3.8% and 4.1% versus 8.3%).

Table: Overview of Treatment-Emergent Adverse Events –16-Week Treatment Period - Primary Safety Pool



	Placebo QW (N=517)	Dupilumab		
		300 mg Q2W (N=529)	300 mg QW (N=518)	Combined (N=1047)
Any TEAE	359 (69.4)	366 (69.2)	357 (68.9)	723 (69.1)
Any drug related TEAE <sup>a</sup>	104 (20.1)	146 (27.6)	158 (30.5)	304 (29.0)
Any TEAE causing discontinuation of study drug permanently	10 (1.9)	10 (1.9)	8 (1.5)	18 (1.7)
Maximum intensity for any TEAE, n(%)				
Mild	143 (27.7)	197 (37.2)	191 (36.9)	388 (37.1)
Moderate	173 (33.5)	149 (28.2)	145 (28.0)	294 (28.1)
Severe	43 (8.3)	20 (3.8)	21 (4.1)	41 (3.9)
Any death	0	0	1 (0.2)	1 (<0.1)
Any TE SAE	26 (5.0)	13 (2.5)	11 (2.1)	24 (2.3)
Any drug related TE SAE	3 (0.6)	2 (0.4)	2 (0.4)	4 (0.4)
Any TE SAE causing Discontinuation of study drug permanently	7 (1.4)	4 (0.8)	2 (0.4)	6 (0.6)

a. Relatedness to study drug as assessed by the investigator

Source: Module 5.3.5.3 Integrated Analysis Pool 2 Table 7.1.2.1/1

### R668-AD-1224 (Dupilumab plus Concomitant TCS): 16-Week Data

For the purpose of comparison with 16-week monotherapy data, 16-week treatment data from the long-term study R668-AD-1224 (dupilumab+ TCS) were evaluated. Overall, the TEAE results during the first 16 weeks of treatment in the R668-AD-1224 study were consistent with those observed for the 16-week treatment period in the Primary Safety Pool. The proportion of patients who had treatment-emergent SAEs was similar among the Q2W+TCS (0.9%) and dupilumab 300 mg QW+TCS (2.5%) groups. A higher proportion of patients in the placebo + TCS group had TEAEs leading to permanent discontinuation of study drug (4.8%) than the dupilumab 300 mg.

The trend in TEAEs were generally the same as observed for the monotherapy Primary Safety Pool, with the notable exception of a higher incidence of Conjunctivitis Allergic across all treatment groups, including placebo, compared to the incidence in the monotherapy population. There was also a lower incidence of Dermatitis Atopic across all treatment groups compared to the incidence in the monotherapy Primary Safety Pool.

	Placebo QW + TCS (N=315)	Dupilumab		
		300 mg Q2W + TCS (N=110)	300 mg QW + TCS (N=315)	Combined + TCS (N=425)
Any TEAE	214 (67.9%)	81 (73.6%)	227 (72.1%)	308 (72.5%)
Any TEAE causing discontinuation of study drug permanently	15 (4.8%)	1 (0.9%)	8 (2.5%)	9 (2.1%)
Maximum intensity for any TEAE, n(%)				
Mild	93 (29.5%)	45 (40.9%)	124 (39.4%)	169 (39.8%)
Moderate	110 (34.9%)	32 (29.1%)	94 (29.8%)	126 (29.6%)
Severe	11 (3.5%)	4 (3.6%)	9 (2.9%)	13 (3.1%)
Any death	0	0	0	0
Any TE SAE	6 (1.9%)	3 (2.7%)	4 (1.3%)	7 (1.6%)
Any TE SAE causing Discontinuation of study drug permanently	1 (0.3%)	0	3 (1.0%)	3 (0.7%)

Source: Module 5.3.5.3 R668-AD-1224 Post-text Table 7.1.2.1/1

### R668-AD-1224 (Dupilumab plus Concomitant TCS): 52-Week Data

The TEAE results for the 52-week treatment period were generally similar to the results observed for the 16-week treatment period except for a higher crude (unadjusted) incidence of AEs. The overall pattern of TEAEs during the 52-week treatment period in the R668-AD-1224 study was consistent with that observed for the first 16-weeks of treatment. A higher proportion of patients in the placebo + TCS group had treatment-emergent SAEs (5.1%) compared to the dupilumab 300 mg Q2W + TCS (3.6%)



and dupilumab 300 mg QW + TCS (2.9%) groups, and TEAEs leading to permanent discontinuation of study drug (7.6%) compared to the dupilumab 300 mg Q2W + TCS (1.8%) and dupilumab 300 mg QW + TCS (2.9%) groups.

There was no clear evidence of an overall dose dependent increase in TEAEs across the Dupilumab 300mg Q2W and QW doses except for injection site reaction (ISR). This was apparent across all analyses. At week 52 there was a trend toward a higher incidence of TEAE in the Q2W treated group for TEAEs herpes simplex, blepharitis and dry eye. In the QW dose group oral herpes conjunctivitis bacterial, conjunctivitis allergic, blepharitis and injection site reaction occurred more commonly compared with the QW2 regime.

### Number of Patients with Treatment-Emergent Adverse Events ≥2% in any Treatment Group by Primary System Organ Class and Preferred Term – 52-Week Treatment Period – R668-AD-1224 – Primary Safety Pool

Primary System Organ Class Preferred Term	Dupilumab							
	Placebo QW + TCS (N=315) nP/PY (nP/100 PY)	Placebo QW + TCS (N=315) nP/PY (nP/100 PY)	300 mg Q2W + TCS (N=110) nP/PY (nP/100 PY)	300 mg Q2W + TCS (N=110) nP/PY (nP/100 PY)	300 mg QW + TCS (N=315) nP/PY (nP/100 PY)	300 mg QW + TCS (N=315) nP/PY (nP/100 PY)	Combined + TCS (N=425) nP/PY (nP/100 PY)	Combined + TCS (N=425) nP/PY (nP/100 PY)
Number of patients with at least 1 such Event, n (%)	266 (84.4%)	266/82.8 (321.380)	97 (88.2%)	97/25.3 (383.683)	261 (82.9%)	261/80.8 (322.891)	358 (84.2%)	358/106.1 (337.374)
Infections and infestations	182 (57.8%)	182/168.4 (108.080)	63 (57.3%)	63/62.1 (101.503)	166 (52.7%)	166/176.0 (94.331)	229 (53.9%)	229/238.0 (96.201)
Nasopharyngitis	61 (19.4%)	61/246.0 (24.796)	25 (22.7%)	25/85.5 (29.227)	60 (19.0%)	60/253.5 (23.671)	85 (20.0%)	85/339.0 (25.073)
Upper respiratory tract infection	32 (10.2%)	32/260.8 (12.272)	11 (10.0%)	11/92.5 (11.887)	43 (13.7%)	43/265.9 (16.174)	54 (12.7%)	54/358.4 (15.067)
Sinusitis	9 (2.9%)	9/276.5 (3.255)	2 (1.8%)	2/100.0 (1.999)	18 (5.7%)	18/280.0 (6.428)	20 (4.7%)	20/380.1 (5.262)
Oral herpes	9 (2.9%)	9/276.1 (3.259)	4 (3.6%)	4/97.6 (4.097)	15 (4.8%)	15/283.2 (5.297)	19 (4.5%)	19/380.8 (4.989)
Urinary tract infection	13 (4.1%)	13/275.0 (4.728)	2 (1.8%)	2/99.6 (2.007)	14 (4.4%)	14/286.3 (4.890)	16 (3.8%)	16/385.9 (4.146)
Influenza	17 (5.4%)	17/272.4 (6.240)	4 (3.6%)	4/98.5 (4.059)	9 (2.9%)	9/288.0 (3.125)	13 (3.1%)	13/386.5 (3.363)
Viral upper respiratory tract infection	9 (2.9%)	9/275.0 (3.273)	3 (2.7%)	3/98.3 (3.053)	9 (2.9%)	9/285.0 (3.158)	12 (2.8%)	12/383.3 (3.131)
Conjunctivitis bacterial	5 (1.6%)	5/278.0 (1.799)	2 (1.8%)	2/99.4 (2.011)	9 (2.9%)	9/285.9 (3.148)	11 (2.6%)	11/385.3 (2.855)
Gastroenteritis	9 (2.9%)	9/274.5 (3.279)	4 (3.6%)	4/98.8 (4.047)	4 (1.3%)	4/289.6 (1.381)	8 (1.9%)	8/388.4 (2.060)
Herpes simplex	2 (0.6%)	2/279.6 (0.715)	3 (2.7%)	3/98.9 (3.034)	5 (1.6%)	5/289.0 (1.730)	8 (1.9%)	8/387.9 (2.062)
Pharyngitis	8 (2.5%)	8/277.8 (2.880)	3 (2.7%)	3/100.1 (2.998)	5 (1.6%)	5/289.0 (1.730)	8 (1.9%)	8/389.1 (2.056)
Rhinitis	4 (1.3%)	4/278.4 (1.437)	1 (0.9%)	1/99.4 (1.006)	7 (2.2%)	7/287.2 (2.437)	8 (1.9%)	8/386.7 (2.069)
Folliculitis	7 (2.2%)	7/275.6 (2.540)	2 (1.8%)	2/99.0 (2.019)	4 (1.3%)	4/289.5 (1.381)	6 (1.4%)	6/388.6 (1.544)
Impetigo	10 (3.2%)	10/276.0 (3.624)	1 (0.9%)	1/100.2 (0.998)	4 (1.3%)	4/289.8 (1.380)	5 (1.2%)	5/390.0 (1.282)
Skin infection	7 (2.2%)	7/274.3 (2.552)	0	0/100.4 (0.000)	1 (0.3%)	1/291.1 (0.344)	1 (0.2%)	1/391.5 (0.255)
Eye disorders	46 (14.6%)	46/255.8 (17.985)	34 (30.9%)	34/77.9 (43.629)	102 (32.4%)	102/227.4 (44.853)	136 (32.0%)	136/305.3 (44.541)
Conjunctivitis allergic	19 (6.0%)	19/268.9 (7.065)	13 (11.8%)	13/92.7 (14.031)	53 (16.8%)	53/262.4 (20.199)	66 (15.5%)	66/355.0 (18.590)
Eye pruritus	4 (1.3%)	4/277.8 (1.440)	4 (3.6%)	4/98.6 (4.055)	14 (4.4%)	14/282.7 (4.953)	18 (4.2%)	18/381.3 (4.720)
Blepharitis	3 (1.0%)	3/278.7 (1.076)	6 (5.5%)	6/96.9 (6.194)	11 (3.5%)	11/284.0 (3.874)	17 (4.0%)	17/380.8 (4.464)
Dry eye	4 (1.3%)	4/279.0 (1.434)	3 (2.7%)	3/98.1 (3.059)	6 (1.9%)	6/287.9 (2.084)	9 (2.1%)	9/385.9 (2.332)
Skin and subcutaneous tissue disorders	167 (53.0%)	167/173.1 (96.500)	31 (28.2%)	31/81.0 (38.267)	103 (32.7%)	103/224.7 (45.838)	134 (31.5%)	134/305.7 (43.831)
Dermatitis atopic	144 (45.7%)	144/196.3 (73.367)	20 (18.2%)	20/88.4 (22.612)	52 (16.5%)	52/260.5 (19.960)	72 (16.9%)	72/349.0 (20.632)
Erythema	3 (1.0%)	3/278.4 (1.078)	1 (0.9%)	1/99.4 (1.006)	11 (3.5%)	11/286.3 (3.842)	12 (2.8%)	12/385.7 (3.111)
Acne	7 (2.2%)	7/274.8 (2.547)	0	0/100.4 (0.000)	7 (2.2%)	7/287.2 (2.437)	7 (1.6%)	7/387.6 (1.806)

		Dupilumab							
Primary System Organ Class	Preferred Term	Placebo QW + TCS	Placebo QW + TCS	300 mg Q2W + TCS	300 mg Q2W + TCS	300 mg QW + TCS	300 mg QW + TCS	Combined + TCS	
		(N=315)	(N=315)	(N=110)	(N=110)	(N=315)	(N=315)	(N=425)	
		nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	
	Pruritus	8 (2.5%)	8/275.1 (2.908)	1 (0.9%)	1/99.5 (1.005)	5 (1.6%)	5/289.2 (1.729)	6 (1.4%)	6/388.7 (1.544)
	Urticaria	10 (3.2%)	10/273.5 (3.656)	1 (0.9%)	1/99.5 (1.005)	3 (1.0%)	3/290.0 (1.034)	4 (0.9%)	4/389.5 (1.027)
	General disorders and administration site conditions	50 (15.9%)	50/246.1 (20.315)	29 (26.4%)	29/80.0 (36.243)	81 (25.7%)	81/230.1 (35.197)	110 (25.9%)	110/310.2 (35.466)
	Injection site reaction	24 (7.6%)	24/261.3 (9.185)	16 (14.5%)	16/89.2 (17.942)	60 (19.0%)	60/245.4 (24.446)	76 (17.9%)	76/334.6 (22.713)
	Fatigue	10 (3.2%)	10/274.2 (3.647)	1 (0.9%)	1/99.4 (1.006)	11 (3.5%)	11/285.6 (3.851)	12 (2.8%)	12/385.0 (3.117)
	Pyrexia	6 (1.9%)	6/277.6 (2.162)	4 (3.6%)	4/97.9 (4.086)	7 (2.2%)	7/288.7 (2.425)	11 (2.6%)	11/386.5 (2.846)
	Gastrointestinal disorders	58 (18.4%)	58/243.0 (23.863)	15 (13.6%)	15/89.9 (16.685)	51 (16.2%)	51/262.4 (19.439)	66 (15.5%)	66/352.3 (18.736)
	Diarrhoea	13 (4.1%)	13/272.5 (4.770)	1 (0.9%)	1/99.8 (1.002)	12 (3.8%)	12/284.7 (4.215)	13 (3.1%)	13/384.5 (3.381)
	Nausea	12 (3.8%)	12/272.1 (4.410)	2 (1.8%)	2/98.9 (2.022)	9 (2.9%)	9/285.9 (3.148)	11 (2.6%)	11/384.8 (2.858)
	Abdominal pain	4 (1.3%)	4/278.4 (1.437)	0	0/100.4 (0.000)	7 (2.2%)	7/289.0 (2.422)	7 (1.6%)	7/389.4 (1.798)
	Toothache	8 (2.5%)	8/276.0 (2.899)	1 (0.9%)	1/99.6 (1.004)	3 (1.0%)	3/290.0 (1.034)	4 (0.9%)	4/389.6 (1.027)
	Musculoskeletal and connective tissue disorders	49 (15.6%)	49/250.4 (19.565)	17 (15.5%)	17/90.6 (18.757)	44 (14.0%)	44/264.6 (16.630)	61 (14.4%)	61/355.2 (17.172)
	Arthralgia	15 (4.8%)	15/270.4 (5.547)	5 (4.5%)	5/97.7 (5.120)	10 (3.2%)	10/286.3 (3.493)	15 (3.5%)	15/384.0 (3.907)
	Back pain	11 (3.5%)	11/273.3 (4.025)	2 (1.8%)	2/99.1 (2.017)	6 (1.9%)	6/288.3 (2.074)	8 (1.9%)	8/388.5 (2.059)
	Pain in extremity	2 (0.6%)	2/279.4 (0.716)	0	0/100.4 (0.000)	8 (2.5%)	8/286.9 (2.788)	8 (1.9%)	8/387.3 (2.066)
	Osteoarthritis	3 (1.0%)	3/280.0 (1.071)	3 (2.7%)	3/99.2 (3.023)	2 (0.6%)	2/290.5 (0.689)	5 (1.2%)	5/389.7 (1.283)
	Muscle spasms	7 (2.2%)	7/276.2 (2.535)	0	0/100.4 (0.000)	1 (0.3%)	1/291.6 (0.343)	1 (0.2%)	1/392.0 (0.255)
	Respiratory, thoracic and mediastinal disorders	53 (16.8%)	53/248.2 (21.354)	13 (11.8%)	13/91.6 (14.196)	45 (14.3%)	45/265.6 (16.944)	58 (13.6%)	58/357.2 (16.239)
	Cough	8 (2.5%)	8/275.3 (2.906)	3 (2.7%)	3/98.1 (3.059)	10 (3.2%)	10/285.1 (3.507)	13 (3.1%)	13/383.2 (3.392)
	Oropharyngeal pain	12 (3.8%)	12/273.1 (4.395)	3 (2.7%)	3/98.8 (3.038)	10 (3.2%)	10/287.0 (3.484)	13 (3.1%)	13/385.8 (3.370)
	Asthma	19 (6.0%)	19/269.1 (7.061)	5 (4.5%)	5/97.1 (5.152)	2 (0.6%)	2/291.1 (0.687)	7 (1.6%)	7/388.2 (1.803)
	Nervous system disorders	38 (12.1%)	38/254.4 (14.935)	10 (9.1%)	10/92.6 (10.796)	38 (12.1%)	38/264.5 (14.366)	48 (11.3%)	48/357.1 (13.440)
	Headache	19 (6.0%)	19/266.9 (7.120)	5 (4.5%)	5/96.3 (5.192)	24 (7.6%)	24/273.4 (8.779)	29 (6.8%)	29/369.7 (7.845)
	Injury, poisoning and procedural complications	43 (13.7%)	43/252.7 (17.017)	10 (9.1%)	10/94.3 (10.608)	32 (10.2%)	32/271.4 (11.790)	42 (9.9%)	42/365.7 (11.485)
	Ligament sprain	3 (1.0%)	3/279.0 (1.075)	3 (2.7%)	3/98.1 (3.057)	6 (1.9%)	6/288.3 (2.081)	9 (2.1%)	9/386.4 (2.329)
	Sunburn	7 (2.2%)	7/275.3 (2.543)	0	0/100.4 (0.000)	2 (0.6%)	2/290.2 (0.689)	2 (0.5%)	2/390.6 (0.512)
	Investigations	37 (11.7%)	37/259.2 (14.273)	12 (10.9%)	12/91.7 (13.085)	30 (9.5%)	30/269.4 (11.136)	42 (9.9%)	42/361.1 (11.631)
	Blood creatine phosphokinase increased	9 (2.9%)	9/275.4 (3.268)	3 (2.7%)	3/98.3 (3.052)	11 (3.5%)	11/284.2 (3.870)	14 (3.3%)	14/382.5 (3.660)

		Dupilumab							
Primary System Organ Class	Preferred Term	Placebo QW + TCS	Placebo QW + TCS	300 mg Q2W + TCS	300 mg Q2W + TCS	300 mg QW + TCS	300 mg QW + TCS	Combined + TCS	
		(N=315)	(N=315)	(N=110)	(N=110)	(N=315)	(N=315)	(N=425)	
		nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	nP/100 PY	
	Blood lactate dehydrogenase increased	5 (1.6%)	5/276.4 (1.809)	4 (3.6%)	4/97.1 (4.120)	1 (0.3%)	1/290.9 (0.344)	5 (1.2%)	5/388.0 (1.289)
	Immune system disorders	12 (3.8%)	12/272.7 (4.401)	5 (4.5%)	5/97.6 (5.121)	19 (6.0%)	19/278.0 (6.835)	24 (5.6%)	24/375.6 (6.389)
	Seasonal allergy	6 (1.9%)	6/276.7 (2.169)	2 (1.8%)	2/99.1 (2.017)	9 (2.9%)	9/285.5 (3.153)	11 (2.6%)	11/384.6 (2.860)
	Psychiatric disorders	18 (5.7%)	18/271.3 (6.636)	9 (8.2%)	9/96.9 (9.288)	11 (3.5%)	11/286.5 (3.839)	20 (4.7%)	20/383.4 (5.217)
	Anxiety	2 (0.6%)	2/279.7 (0.715)	3 (2.7%)	3/99.0 (3.030)	3 (1.0%)	3/290.6 (1.032)	6 (1.4%)	6/389.6 (1.540)

Note: MedDRA Version 18.0

Source: Module 5.3.5.1 R668-AD-1224 Post-text Tables 7.5.1.2/4 and 7.5.1.2/6

## Treatment-Emergent Treatment-Related Adverse Events (TEAE)

### Primary Safety Pool - R668-AD-1334, R668-AD-1416 and R668-AD-1021 (16-Week Monotherapy)

The proportion of patients with treatment-related TEAEs (relatedness assessed by the investigator) during the 16-week treatment period was higher for patients in the dupilumab 300 mg Q2W (27.6% [146/529]) and dupilumab 300 mg QW (30.5% [158/518]) groups than for patients in the placebo group (20.1% [104/517]).

The General Disorders and Administration Site Conditions SOC had the highest proportion of patients with treatment-related TEAEs. A higher proportion of patients in the dupilumab 300 mg Q2W (12.5% [66/529]) and dupilumab 300 mg QW (15.1% [78/518]) groups reported TEAEs from this SOC compared to patients in the placebo group (6.8% [35/517]). A single PT, ISR, was responsible for this increased incidence in all treatment groups, as expected for an injectable biologic medicinal product.

The Infections and Infestations SOC had the second highest proportion of patients with treatment-related TEAEs. A similar proportion of patients in the dupilumab groups and the placebo group reported these TEAEs.

The most common treatment-related TEAEs ( $\geq 1\%$  in any treatment group) that occurred with a higher frequency in either dupilumab treatment groups ( $\geq 1\%$  higher in either dupilumab treatment groups) than the placebo group were as follows:

- Injection Site Reaction: The incidence was higher in both dupilumab groups compared to placebo, with a higher incidence in the 300 mg QW group. These treatment-related TEAEs accounted for the majority of all reported ISR.
- Headache: 2.5% (13/529) in the dupilumab 300 mg Q2W group, 2.5% (13/518) in the dupilumab 300 mg QW group, and 1.4% (7/517) in the placebo group.
- Conjunctivitis (Infections and Infestations SOC): 1.3% (7/529) in the dupilumab 300 mg Q2W group and 1.5% (8/518) in the dupilumab 300 mg QW group, and 0% in the placebo group.
- Eosinophilia: 1.3% (7/529) in the dupilumab 300 mg Q2W group, 0.2% (1/518) in the dupilumab 300 mg QW group, and 0.2% (1/517) in the placebo group.

The treatment-related TEAE ( $\geq 1\%$  in any treatment group) that occurred with a higher frequency in the placebo group was dermatitis atopic (typically reported as worsening or exacerbation): 3.2% (17/529) in the dupilumab 300 mg Q2W group, 1.9% (10/5118) in the dupilumab 300 mg QW group, and 4.3% (22/517) in the placebo group.

In patients treated with dupilumab as monotherapy over 16 weeks, > 10% of participants reported at least 1 event in Infections and infestations, Skin and subcutaneous tissue disorders, General disorders and administration site conditions, Nervous system disorders SOCs.

In the dupilumab groups the following TEAEs were the most commonly reported: injection site reaction (ISR), Nasopharyngitis, Headache, Upper Respiratory Tract Infection, Conjunctivitis, Oral Herpes, Herpes Simplex, Diarrhoea, Conjunctivitis Allergic, Conjunctivitis Bacterial, Blepharitis, Dry Eye, Fatigue, Nausea, Arthralgia, Myalgia, Alopecia, Rash, Injection Site Erythema, Cough, Oropharyngeal Pain, Blood CPK Increased, Eosinophilia, Hypertension and Pain in Extremity. The majority of cases were mild to moderate in severity.

In the Infections and infestation SOC the percentage of patients who experienced at least 1 TEAE was similar across all treatment groups (dupilumab 300mg Q2W 33% dupilumab QW 34%: placebo 31%). Within the SOC there was some difference in reporting rates noted. There were higher rates of sinusitis, oral herpes, conjunctivitis bacterial, herpes simplex, URTI and nasopharyngitis in the dupilumab group compared with placebo. There was higher incidence of conjunctivitis and herpes simplex, oral herpes cases in the dupilumab treated groups in both the primary safety pool and the supportive safety pool. Folliculitis, impetigo and skin infections occurred more frequently in the placebo group. The majority of these events were mild to moderate in severity, resolved during the treatment period and did not lead to study medication discontinuation.

In the eye disorders SOC there was an increased incidence of allergic conjunctivitis, blepharitis and dry eye in both the primary safety pool and the supportive safety pool. This was against a high background history of eye disorders (23% patients had a history of allergic conjunctivitis). The majority were mild to moderate in severity and resolved with treatment. However, 20% of cases had not resolved during the study period. There were no serious cases.

**Number of Patients with Treatment-Emergent Adverse Events  $\geq 1\%$  in any Treatment Group by Primary System Organ Class and Preferred Term – 16-Week Treatment Period – Primary**

Primary System Organ Class Preferred Term MedDRA Version 18.0	Dupilumab			
	Placebo QW (N=517)	300 mg Q2W (N=529)	300 mg QW (N=518)	Combined (N=1047)
Number of patients with at least 1 such Event, n (%)	359 (69.4)	366 (69.2)	357 (68.9)	723 (69.1)
Infections and infestations	167 (32.3)	175 (33.1)	177 (34.2)	352 (33.6)
Nasopharyngitis	52 (10.1)	55 (10.4)	58 (11.2)	113 (10.8)
Upper respiratory tract infection	15 (2.9)	18 (3.4)	24 (4.6)	42 (4.0)
Conjunctivitis	3 (0.6)	21 (4.0)	20 (3.9)	41 (3.9)
Oral herpes	8 (1.5)	20 (3.8)	13 (2.5)	33 (3.2)
Conjunctivitis bacterial	2 (0.4)	7 (1.3)	8 (1.5)	15 (1.4)
Herpes simplex	4 (0.8)	9 (1.7)	4 (0.8)	13 (1.2)
Folliculitis	10 (1.9)	4 (0.8)	8 (1.5)	12 (1.1)
Bronchitis	6 (1.2)	5 (0.9)	4 (0.8)	9 (0.9)
Urinary tract infection	9 (1.7)	7 (1.3)	2 (0.4)	9 (0.9)
Impetigo	8 (1.5)	5 (0.9)	3 (0.6)	8 (0.8)
Skin infection	7 (1.4)	5 (0.9)	2 (0.4)	7 (0.7)
Sinusitis	6 (1.2)	2 (0.4)	2 (0.4)	4 (0.4)
Skin and subcutaneous tissue disorders	187 (36.2)	109 (20.6)	102 (19.7)	211 (20.2)
Dermatitis atopic	158 (30.6)	70 (13.2)	62 (12.0)	132 (12.6)
Alopecia	4 (0.8)	3 (0.6)	9 (1.7)	12 (1.1)
Rash	2 (0.4)	6 (1.1)	2 (0.4)	8 (0.8)
Pruritus	10 (1.9)	1 (0.2)	6 (1.2)	7 (0.7)
Pruritus generalised	6 (1.2)	1 (0.2)	3 (0.6)	4 (0.4)
General disorders and administration site conditions	59 (11.4)	85 (16.1)	100 (19.3)	185 (17.7)
Injection site reaction	28 (5.4)	51 (9.6)	72 (13.9)	123 (11.7)
Fatigue	7 (1.4)	12 (2.3)	9 (1.7)	21 (2.0)
Injection site erythema	2 (0.4)	6 (1.1)	7 (1.4)	13 (1.2)
Pyrexia	6 (1.2)	6 (1.1)	5 (1.0)	11 (1.1)
Nervous system disorders	49 (9.5)	67 (12.7)	58 (11.2)	125 (11.9)
Headache	26 (5.0)	45 (8.5)	41 (7.9)	86 (8.2)
Dizziness	12 (2.3)	6 (1.1)	5 (1.0)	11 (1.1)
Musculoskeletal and connective tissue disorders	32 (6.2)	52 (9.8)	41 (7.9)	93 (8.9)
Back pain	12 (2.3)	9 (1.7)	12 (2.3)	21 (2.0)
Arthralgia	9 (1.7)	15 (2.8)	4 (0.8)	19 (1.8)
Pain in extremity	5 (1.0)	7 (1.3)	4 (0.8)	11 (1.1)
Myalgia	2 (0.4)	6 (1.1)	3 (0.6)	9 (0.9)
Gastrointestinal disorders	34 (6.6)	46 (8.7)	44 (8.5)	90 (8.6)
Diarrhoea	9 (1.7)	18 (3.4)	10 (1.9)	28 (2.7)
Nausea	5 (1.0)	10 (1.9)	11 (2.1)	21 (2.0)
Eye disorders	15 (2.9)	33 (6.2)	42 (8.1)	75 (7.2)
Conjunctivitis allergic	5 (1.0)	16 (3.0)	12 (2.3)	28 (2.7)
Elephantitis	1 (0.2)	2 (0.4)	6 (1.2)	8 (0.8)
Dry eye	0	1 (0.2)	6 (1.2)	7 (0.7)
Respiratory, thoracic and mediastinal disorders	31 (6.0)	37 (7.0)	33 (6.4)	70 (6.7)
Cough	4 (0.8)	10 (1.9)	7 (1.4)	17 (1.6)
Oropharyngeal pain	5 (1.0)	8 (1.5)	9 (1.7)	17 (1.6)
Asthma	8 (1.5)	7 (1.3)	1 (0.2)	8 (0.8)
Investigations	21 (4.1)	28 (5.3)	23 (4.4)	51 (4.9)
Blood creatine phosphokinase increased	9 (1.7)	10 (1.9)	5 (1.0)	15 (1.4)
Blood and lymphatic system disorders	21 (4.1)	19 (3.6)	9 (1.7)	28 (2.7)
Lymphadenopathy	8 (1.5)	7 (1.3)	5 (1.0)	12 (1.1)
Eosinophilia	2 (0.4)	9 (1.7)	1 (0.2)	10 (1.0)
Vascular disorders	10 (1.9)	14 (2.6)	10 (1.9)	24 (2.3)
Hypertension	6 (1.2)	9 (1.7)	5 (1.0)	14 (1.3)
Psychiatric disorders	24 (4.6)	11 (2.1)	10 (1.9)	21 (2.0)

**R668-AD-1224 (Dupilumab plus Concomitant TCS): 52-Week Data**

The results for the treatment-related TEAEs during the 52-week treatment period were generally similar to the results observed for the first 16-weeks of treatment described above. The trends in the SOCs and PTs with TEAEs were generally the same.

**Immunogenicity**

As with all monoclonal antibodies, dupilumab has the potential to elicit an ADA response. Accordingly, serum samples were collected in all dupilumab clinical studies for immunogenicity assessments using validated ADA assays.



Immunogenicity assay results were reported as ADA positive or negative. Positive immunoreactivity results in the ADA assay were summarized according to the current ADA definitions as pre-existing, treatment-boostered, or treatment-emergent. Treatment-emergent responses were further characterized as persistent, indeterminate, or transient. In the phase 3 studies, samples that were positive in the ADA assay were further characterized for neutralizing activity.

In all the studies of dupilumab in AD patients, 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 approximately 7%.

Immunogenicity of dupilumab generally varied inversely with dupilumab dose regimen, with the incidence of treatment-emergent ADA-positive response observed to decrease with greater dupilumab doses in all studies. Most patients who had a positive response in the ADA assay had titers that were low (<1000). Some patients exhibited moderate titers ( $\geq 1,000$  to  $\leq 10,000$ ), and only a few patients had high titer (>10,000). Of those patients with treatment-emergent positive response in the ADA assay, only a small proportion of patients were found to have a persistent ADA-positive response (<1% of all dupilumab-treated patients sampled in the Primary Safety Pool). Even among patients treated with dupilumab over a 52-week period, persistent treatment-emergent ADA-positive response was observed in <2% of patients.

As the overall number of patients who experienced a treatment-emergent or treatment-boostered assay response was small, no clear conclusions can be drawn regarding the clinical relevance of any differences in the incidence of TEAEs between ADA-positive and ADA-negative patients.

There were 2 patients with high ADA titer, one of whom had a Serum Sickness-Like Reaction and the other had Serum Sickness.

## ***Serious adverse events and deaths***

### **Deaths**

There were 6 deaths that occurred in the dupilumab AD studies as of 31 May 2017, none of which was assessed as related to study drug. There were 4 additional deaths that occurred in patients with known exposure to dupilumab in the asthma program, two of which were assessed as related to dupilumab. One of these occurred in a smoker who died from metastatic lung cancer and the other in a patient with history of chronic gastritis who died from adenocarcinoma of stomach.

### **Other Serious Adverse Events**

#### Primary Safety Pool

In the primary safety pool, 5% in the placebo group, 2.5% in the dupilumab 300 mg Q2W and 2.1% in the dupilumab 300 mg QW groups had an SAE during the 16-week monotherapy treatment period. In the long term combination study (Dupilumab + TCS): 16-Week Data, 1.9% in the placebo + TCS group, 2.7% in the dupilumab 300 mg Q2W + TCS group and 1.3% for patients in the dupilumab 300 mg QW + TCS reported SAEs. During the 52-week treatment period 5.1% in the placebo QW + TCS group, 3.6% for patients in the dupilumab 300 mg Q2W + TCS, and 2.9% in the dupilumab 300 mg QW + TCS group reported SAEs.

The PTs for treatment-emergent SAEs reported for  $\geq 2$  patients in any treatment group in the monotherapy studies either occurred only in the placebo group (Sepsis, Suicide Ideation, and Acute Kidney Injury), or occurred at a higher frequency in the placebo group than in the dupilumab groups

(Dermatitis Atopic). All other SAEs occurred in 1 patient. In the Infections and Infestations SOC, the proportion of patients with a treatment-emergent SAE was 0.2% in the dupilumab Q2W treated group, 0.8% in the dupilumab QW group and was 1% in the placebo group. There were no discernible trends at the SOC and PT levels for the remaining SAEs in the dupilumab treated populations. Three cases of myocardial infarction (two reported as acute) were reported in the dupilumab treatment groups in the monotherapy studies. The proportion of patients discontinuing from their study due to SAEs was slightly lower in the dupilumab group compared to placebo (dupilumab 300mg Q2W 0.8% dupilumab QW 0.4%: placebo 1.4%).

In the long term combination study, the results for the SAEs for the first 16-weeks and 52 of treatment were generally similar to the results observed for the Primary Safety Pool. At week 52 in the Infections and Infestations SOC, the proportion of patients with an SAE was 0.9% in the dupilumab 300mg Q2W +TCS treated group, 0 % in the dupilumab 300mg QW +TCS group and 0.6% in the placebo group. In the dupilumab +TCS group (combined) four cases of squamous cell carcinoma were reported.

### **Laboratory findings**

The dupilumab groups, both as monotherapy and with concomitant TCS, showed a trend toward modestly greater mean decrease from baseline in platelets and neutrophils than did the placebo group from baseline to week 16 with a similar trend extending through week 52. The changes in these 2 hematology parameters appeared to be due to patients with high values at baseline decreasing to normal, observed with dupilumab but not with placebo treatment. Of note, a proportion of patients had high baseline values in platelet and neutrophil counts and many of these patients shifted to normal values by the end of the treatment period. The incidences of Thrombocytopenia and Platelet Count Decreased TEAEs were low overall and there did not appear to be any clinical consequence of this modest decrease in platelet count. The modest decrease in neutrophil count was not associated with an increased incidence of Infections and Infestations.

The dupilumab monotherapy groups had a transient increase from baseline in eosinophils, and the mean increase from baseline was modestly greater in the dupilumab groups than in the placebo group at all post-baseline assessments to week 16 with a similar trend extending through week 52. A high proportion of patients had high eosinophil levels at baseline, with more patients in the placebo group shifting to normal values by the end of treatment, compared with patients in the dupilumab groups.

Lactate dehydrogenase levels clearly showed a progressive and greater decrease from baseline in the dupilumab treatment groups than in the placebo treatment group from baseline to week 16, with a similar trend extending through week 52. Consistent with this result, greater proportions of the dupilumab groups showed a shift in LDH levels from high to normal. Given the direct correlation between LDH levels with AD disease activity and severity reported from other studies, the greater decrease in LDH in the dupilumab group, compared with the placebo group, may be related to the greater efficacy of dupilumab in decreasing AD severity. The eDISH analyses found no evidence of drug-induced liver toxicity in any patient.

### **Vital Signs**

There were no trends in mean or median changes and no differences in mean or median changes from baseline between the dupilumab and placebo groups in diastolic blood pressure, respiratory rate, or heart rate in any of the conducted studies. There were no clinically meaningful trends in mean and median change from baseline, shifts from baseline, and incidence of PCSVs in heart rate, QTcB, QTcF in the Primary and Supportive Safety Pools, as well as the R668-AD- 1224 and R668-AD-1225 studies.

## ***Safety in special populations***

### **Treatment-Emergent Adverse events by Gender**

#### **Primary Safety Pool - R668-AD-1334, R668-AD1416, and R668-AD-1021 (16-Week Monotherapy)**

During the treatment period, in the placebo group, male patients had a higher incidence of Dermatitis Atopic (exacerbation) than did females (34.6% [100/289] versus 25.4% [58/228]). This may be due to a higher proportion of males than females in the combined dupilumab group (~60% males versus ~40% females). Females in both the placebo and dupilumab groups appeared to be more prone than males to having ISR, with the difference more pronounced in the dupilumab group patients (18.1% [75/415] females versus 7.6% [48/632] males, combined dupilumab). In both the placebo and dupilumab groups, female patients had a higher incidence of headache, with a greater difference seen in the dupilumab group patients (11.1% [46/415] versus 6.3% [40/632], combined dupilumab).

#### **R668-AD-1224 (Dupilumab plus Concomitant TCS): 52-Week Data**

The incidence of ISRs for the 52-week period was higher in females than in males for the combined dupilumab + TCS group and the placebo + TCS. Similarly to results for the 16-week treatment period, the incidence of Headache was higher only in males in the dupilumab 300mg QW + TCS dose group (7.1% [18/253]) than in the placebo + TCS group (2.6% [5/193]). Conversely, in females, the incidence of Headache was lower in the combined dupilumab + TCS group (6.4% [11/172]) than in the placebo + TCS group (11.5% [14/122]).

Consistent with results for the first 16 weeks, a higher incidence of Nasopharyngitis in the dupilumab 300 mg Q2W + TCS group (23.8% [15/63]) than in the placebo + TCS group (18.7% [36/193]) was noted only in males. The incidence of Eye Pruritus was higher in females than in males in both the combined dupilumab + TCS group (7.0% [12/172] females versus 2.4% [6/253]) males and the placebo + TCS group (3.3% [4/122] females versus 0% [0/193] males).

### **Treatment-Emergent Adverse events by Age**

#### Elderly Patients

Of the 1777 patients treated with dupilumab  $\geq$ 300 mg total monthly dose in the 6 placebo-controlled studies with a study treatment period of  $\geq$ 12 weeks in Pool 3 and patients treated with dupilumab in CHRONOS R668-AD-1224, 71 patients were  $\geq$ 65 years of age at study entry.

Of the 1472 patients treated with dupilumab 300 mg Q2W or QW in the 4 placebo-controlled studies with a study treatment period of  $\geq$ 16 weeks, a total of 67 were  $\geq$ 65 years at study entry. Subgroup analysis by age ( $\geq$ 18 to  $<$ 40;  $\geq$ 40 to  $<$ 65;  $\geq$ 65) on the co-primary and key secondary efficacy endpoints showed no treatment-age group interaction for the dupilumab monotherapy as well as for dupilumab + TCS concomitant. Results of the subgroup analysis by age on TEAEs did not reveal any clinically meaningful differences for the age subgroups.

Comparison was not made for patients in the  $>$ 65 year age subgroup, as there were too few patients in to make meaningful comparisons with other age subgroups.

#### Pediatric Patients

Safety and efficacy in pediatric patients have not been established.



## Treatment-Emergent Adverse Events by Bodyweight

### Primary Safety Pool - R668-AD-1334, R668-AD-1416, and R668-AD-1021 (16-Week Monotherapy)

Patients in the placebo group with <70 kg body weight at baseline had a higher incidence of Dermatitis Atopic (35.7% [74/207]) than patients with  $\geq$ 70 kg to <100 kg (27.2% [69/254]) or with  $\geq$ 100 kg (26.8% [15/56]) body weight; the incidence of Dermatitis Atopic decreased in the dupilumab groups, though it remained slightly higher in the 70 kg subgroup, compared with those of the other 2 baseline body weight.

### R668-AD-1224 (Dupilumab plus Concomitant TCS): 52-Week Data

Results of comparison of frequency of TEAEs between patients with body weight of <70 kg and patients with body weight of  $\geq$ 70 to <100 kg for the 52-week treatment period were consistent with results of the 16-week treatment period.

### Patients with Other Atopic Diseases

The development of dupilumab for the treatment of asthma, nasal polyposis, and eosinophil esophagitis is ongoing, with 2 studies completed and 4 studies ongoing in the asthma program, 1 study in nasal polyposis completed, and 1 study in eosinophil esophagitis ongoing. Safety data from the 2 completed studies in asthma, 1 ongoing open-label extension study in asthma as of the data cutoff of 31 January 2016, and the completed study in nasal polyposis revealed no new safety signal that is different from the AD program. It is noted that the higher incidence of conjunctivitis and Oral Herpes with dupilumab treatment in the AD program was not observed in data from the asthma and nasal polyposis programs. The SUSARs from the ongoing studies up through 31 May 2016 did not reveal any new safety pattern or signal.

### Use in Pregnancy and Lactation

Pregnant or breastfeeding women, or women who planned to become pregnant or breastfeed during the study period were excluded from the studies. A review of cases reported in the pharmacovigilance database (covering all investigational indications) as of the data cutoff date of 27 April 2016 revealed a total of 23 pregnancies in patients treated with dupilumab and 17 pregnancies in partners of male patients exposed to dupilumab. The 23 pregnancies in study patients treated with dupilumab have led to 7 live births giving 8 healthy babies (1 birth with twins), 2 induced (elective) abortions, and 6 spontaneous abortions, with 5 pregnancies ongoing and 3 pregnancies lost to follow-up. Of the 6 study patients with spontaneous abortion, 2 patients had 1 or more factors known to increase the risk of spontaneous abortion (elevated parathyroid hormone, clotting disorders, and a history of infertility). The 17 partner pregnancies of male study patients have led to 5 live births giving 5 healthy babies, 1 induced (elective) abortion, and 2 spontaneous abortions, with 8 pregnancies ongoing and 1 lost to follow-up.

### Ciclosporin Subgroups

Analysis of the safety of dupilumab in AD patients who are not adequately controlled with or were intolerant to oral ciclosporin, or for whom oral ciclosporin was not medically advisable (for conciseness referred to as the ciclosporin intolerant group) was compared with that of patients who did not meet these criteria.

The incidence of TEAEs was slightly higher in the ciclosporin intolerant subset than in the remainder of the patients for overall TEAEs, severe TEAEs, TEAEs leading to permanent discontinuation of study drug, and treatment-emergent SAEs, but not for TEAEs assessed by the investigator as related to study treatment. Within the ciclosporin intolerant subset, the TEAE incidences were lower in the combined dupilumab group than in the placebo group with for overall TEAEs, severe TEAEs, and treatment-emergent SAEs. In the ciclosporin intolerant subgroup 17.4% of dupilumab-treated patients compared with 44.8% placebo-treated patients reported worsening of Atopic Dermatitis. Injection Site Reaction and Headache were higher for dupilumab (12.4% vs 5.7% vs and 8.0% vs 4.6%, respectively) than for placebo.

In the R668-AD-1224 study, at week 16 dupilumab+TCS treated patients who were intolerant of ciclosporin had a higher incidence of TEAEs in the Eye Disorders SOC, which consisted largely of Conjunctivitis Allergic and Blepharitis. The incidence was also higher in the combined dupilumab + TCS group than in the placebo + TCS group for both the Conjunctivitis Allergic and Blepharitis PTs over the 52-week duration of the study.

### **Adverse Events of Special Interest (AESI)**

AESIs were prospectively identified in the dupilumab clinical program except for the AESI of Conjunctivitis, which was identified following the analysis of the SOLO studies. The prospectively identified AESIs were considered based on the pharmacologic properties of dupilumab and its mechanism of action, conditions associated with or diagnosed in patients with AD, or the fact that dupilumab is a protein biologic that is administered SC.

The following is a list of all the events included and analyzed as AESIs:

- Anaphylactic reactions
- Acute allergic reactions requiring treatment
- Mycosis fungoides or cutaneous T-cell dyscrasias
- Any severe infection
- Any infection requiring treatment with parenteral antibiotics
- Any infection requiring treatment with oral antibiotics/anti-viral/anti-fungal for longer than 2 weeks
- Any clinical endoparasitosis
- Any opportunistic infection
- Severe ISRs lasting longer than 24 hours
- Suicidal behavior (suicidal ideation, suicidal behavior, depression suicidal, suicide attempt and completed suicide)
- Conjunctivitis (post-hoc analysis)

### **Primary Safety Pool - R668-AD-1334, R668-AD-1416, and R668-AD-1021 (16-Week Monotherapy)**

The proportion of patients who had at least 1 AESI during the 16-week treatment period was low across treatment groups (approximately 4.0%), and was lower for patients in the dupilumab 300 mg Q2W and 300 mg QW groups (approximately 2% and 1%) than the placebo group (approximately 4%). The proportion of patients who had at least 1 serious AESI during the 16-week treatment period was low overall (approximately 1%), and was lower in the dupilumab 300 mg Q2W (0.2% [1/529]) and dupilumab 300 mg QW (0.4% [2/518]) groups than the placebo group (1.2% [6/517]).

The proportion of patients with at least 1 AESI or serious AESI, and the profile of AESIs and serious AESIs during the entire study period was similar to that observed for the 16-week treatment period and for the follow-up period.

The exposure-adjusted patient and event incidence of AESIs showed similar trends as the crude patient incidence of AESIs. The mean time to first occurrence of any AESI during the 16-week treatment period was similar between all treatment groups (range: 104.6 [ $\pm$ 25.57] days in placebo group to 108.5 [ $\pm$ 19.34] days in the 300 mg Q2W group. The HRs with 95% CI were 0.577 (0.282 - 1.180) in dupilumab 300 mg Q2W and 0.246 (0.092 - 0.655) in the 300 mg QW groups.

The cumulative incidence of any AESI during the 16-week treatment period was lower over time in the dupilumab treatment groups compared to the placebo group.

Of the patients who reported any event of this conjunctivitis category, only 1 patient in the dupilumab 300 mg QW group discontinued study treatment due to the event. Of the 103 conjunctivitis TEAEs reported during the treatment period in dupilumab-treated patients in the Primary Safety Pool, 78.6% of the events resolved or were resolving during the treatment period.

**Table 1.** Treatment-Emergent AESIs - Primary Safety Pool – 16-Week Monotherapy

<b>Primary Safety Pool - R668-AD-1334, R668-AD-1416, and R668-AD-1021 (16-Week Monotherapy)</b>			
	Placebo (%)	Dupilumab 300 mg Q2W (%)	Dupilumab 300 mg QW (%)
Acute allergic reaction	0.6	0.6	0.2
Opportunistic infection	1.0	0.8	0.4
Severe infection	1.7	0.9	0.2
Suicidal behavior	0.6	0	0.2
Conjunctivitis	2.1	9.3	7.9

**R668-AD-1224 (Dupilumab plus Concomitant TCS): 52-Week Data**

The overall AESI results for the 52-week treatment period were generally similar to the results observed for the 16-week treatment period described above, except for a higher overall rate of reporting of AESIs, consistent with the longer treatment period. The proportion of patients who had at least 1 AESI during the 52-week treatment period was lower for patients in the dupilumab 300 mg Q2W + TCS group (3.6%) and 300 mg QW + TCS group (2.5%) than the placebo + TCS group (7.0%).

The trends in the individual AESIs were generally the same as observed for the first 16-week of treatment. There were no new safety signals for AESIs detected with LTT during the 52-week treatment period.

**Table 2.** Treatment-Emergent AESIs - CHRONOS R668-AD-1224 (52-Week Data)

<b>CHRONOS R668-AD-1224 (52-Week Data)</b>			
	Placebo + TCS (%)	Dupilumab 300 mg Q2W + TCS (%)	Dupilumab 300 mg QW + TCS (%)
Acute allergic reaction	0.3	0	0
Opportunistic infection	3.5	1.8	0.3
Infection requiring treatment with parenteral antibiotic	1.0	0.9	1.3
Infection requiring treatment with oral antibiotic/anti-	1.9	0.9	0.6

viral/anti-fungal for longer than 2 weeks:			
Severe infection	1.6	0	0.3
Suicidal behavior <sup>1</sup>	-	-	-
Conjunctivitis	7.9	13.6	19.4
Clinical endoparasitosis	0	0	0.3
Mycosis fungoides	0.3	0	0

### Acute allergic reactions and anaphylaxis

In the primary safety pool acute allergic reactions requiring treatment occurred in 0.6% of the dupilumab 300mg Q2W group, 0.2% of the dupilumab QW group and 0.6% of the placebo group. A similar picture was seen in the supportive safety pool and the long-term safety data from the combination dupilumab +TCS study. A higher proportion of patients in the dupilumab Q2W group than the dupilumab QW group reported these reactions. Average time to onset was between 107-110 days across the treatment groups. Most events of Acute Allergic Reactions requiring treatment had clear precipitating agents responsible for the reactions. In the long term combination study at week 52 acute allergic reaction requiring treatment were reported in 0.3% (1/315) for placebo + TCS, and 0% for both dupilumab 300 mg Q2W + TCS and 300 mg Q2W + TCS.

A review of events of urticaria from the Safety Pools, as well as the R668-AD-1224 LTT and R668-AD-1225 OLE studies indicated that incidence of these events was not increased with dupilumab treatment. No cases of anaphylactic reactions were identified in the primary safety pool or the LTT safety study (dupilumab +TCS). There was one case in the supportive safety pool and 3 cases in the OLE all attributable to food allergies. In the OLE study there was one case of systemic allergic reaction following four doses of study treatment that resulted in study drug discontinuation.

There was no indication that dupilumab treatment increased the overall occurrence of acute allergic reactions requiring treatment or anaphylactic reactions.

### Mycosis Fungoides or Cutaneous T-Cell Dyscrasias

No cases of mycosis fungoides were reported in the primary safety pool. In the long-term combination study at 52 week Mycosis fungoides or other forms of cutaneous T cell lymphoma was reported for 1 patient (0.3%) on placebo + TCS, and 0 patients (0%) on either dupilumab group: 300 mg Q2W + TCS or 300 mg QW + TCS.

However overall a total of four cases of mycosis fungoides were identified across the supportive safety pool and the long term combination dupilumab +TCS study R668-AD-1224 and the OLE study. Two cases occurred during treatment with dupilumab 300mg. One case occurred in the placebo group. One case was misdiagnosed. None of the cases were considered by the investigator to be related to study drug.

### Infection

In the primary safety pool any severe infections were reported in 1.7% for placebo, 0.9% for dupilumab 300 mg Q2W, and 0.2% for dupilumab 300 mg QW. Any opportunistic infection were reported in 1% for placebo, 0.8% for dupilumab 300 mg Q2W, and 0.4% for dupilumab 300 mg QW treated patients. Infection requiring treatment with parenteral antibiotic was reported for 0.7% for placebo, 1% for dupilumab 300 mg Q2W, and 1.9% for dupilumab 300 mg QW groups. No infection

requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks or cases of clinical endoparasitosis was reported for this safety population.

In the long term combination therapy study at 52 weeks, infection requiring treatment with parenteral antibiotic were reported for 1.0% for placebo + TCS, 0.9% for dupilumab 300 mg Q2W + TCS, and 1.3% for dupilumab 300 mg QW + TCS groups. Infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks was reported for 1.9% for placebo + TCS, 0.9% for dupilumab 300 mg Q2W+ TCS, and 0.6% for dupilumab 300 mg QW + TCS groups. Opportunistic infection was reported in 3.5% for placebo + TCS, 1.8% (2/110) for dupilumab 300 mg Q2W + TCS, and 0.3% for dupilumab 300 mg QW + TCS groups. Severe infection was reported for 1.6% for placebo + TCS, 0% for dupilumab 300 mg Q2W + TCS, and 0.3% for dupilumab 300 mg QW + TCS treated patients. Clinical endoparasitosis was reported in 0% for placebo + TCS, 0% for dupilumab 300 mg Q2W + TCS, and 0.3% for dupilumab 300 mg QW + TCS

In all categories of infection AESI the incidence of infection was very low and was generally higher in placebo group compared to the dupilumab treated population. The only opportunistic infections identified in the Primary Safety Pool were Herpes Viral Infections (Eczema Herpeticum and Herpes Zoster). The incidence of these opportunistic infections during the treatment period was either higher in the placebo group (Herpes Zoster) or similar between the dupilumab groups and the placebo group (Eczema Herpeticum). All opportunistic Herpes Viral Infections resolved by the end of the study. In the long term combination study all the events were consistent with Herpes Viral Infections as described for the Primary and Supportive Safety Pools except for 1 event of Cytomegalovirus Infection reported in the placebo + TCS group. The incidence of Eczema Herpeticum was highest in the placebo group (1.9%).

One case of Clinical Endoparasitosis (based on serology) was reported for 1 patient in the dupilumab 300 mg QW + TCS study: 16-Week Data analysis. Overall there was no evidence of increased serious infections in the dupilumab treated populations.

In the R668-AD-1225 OLE study, the incidence of opportunistic infections was 1.7% , 0.4% for patients requiring i.v antibiotics, 0.9% for severe infection and 1% for infection requiring oral treatment >2 weeks

### **Injection Site Reactions**

No TEAEs met the criteria for this AESI category (Severe ISR lasting longer than 24 hours in the Primary Safety Pool or the Supportive Safety Pool or the R668-AD-1224 LTT study). In the R668-AD-1225 OLE study, 1 patient developed a severe ISR. The events were assessed as a non-serious AESI and TEAE leading to study drug discontinuation. The events were considered to be related to the study drug and improved or stopped after stopping the study drug.

### **Suicidal Behaviour**

In the Primary Safety Pool, AESIs for Suicidal Behaviour were reported during the treatment period for no patients in the dupilumab 300 mg Q2W group, 0.2% of patients in the dupilumab 300 mg QW group, and 0.6% of patients in the placebo group. One case of Completed Suicide in the dupilumab 300 mg QW group is 1 of the deaths reported for the Primary Safety Pool. The death was not considered to be treatment-related. An additional event for Suicidal Behaviour was identified in the Supportive Safety Pool (study R668-AD-1021). The patient experienced suicidal ideation on study day 178 during the follow-up period. The event resolved and was not considered related to study medication. There were no additional events of suicidal behaviour in the Supportive Safety Pool, the R668-AD-1224 LTT safety study, or the R668-AD-1225 OLE study

### **Conjunctivitis and selected eye-related TEAEs**

An ad-hoc analyses were performed on a grouped MedDRA PTs consistent with conjunctivitis, including PTs of conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, and atopic Keratoconjunctivitis. Eye disorders were reported for 2.1% of the placebo group, 9.3% of dupilumab 300 mg Q2W group, and 7.9% of the dupilumab 300mg QW. In the long term dupilumab +TCS combination study at 52 week 7.9% for placebo + TCS, 13.6% for dupilumab 300 mg Q2W + TCS, and 19.4%) for dupilumab 300 mg QW reported eye disorders.

Conjunctivitis and eye disorders (dry eye, eye pruritus, and blepharitis) were observed more commonly in the dupilumab groups than the placebo group in all safety pools and long term combination and open label studies. Most cases were mild to moderate in severity and resolved with local treatment. (approx. 80% in the monotherapy studies and 90% in the combination therapy studies). However 10-20% did not resolve. Two patients discontinued study treatment due to conjunctivitis across all studies. Although a number of these events were classified as infectious in origin, microbiological confirmation was not conducted. A significant proportion of patients who developed these events had a background history of conjunctivitis, longer history of AD and higher baseline disease activity. Increased report of eye disorders was not seen in the phase 2b study for dupilumab in asthma.

### **Malignancy**

The overall malignancy related incidence of TEAEs was 1.2% in the placebo group, 1.3% in the dupilumab 300mg Q2W group and 1.4% in the dupilumab QW group in the primary safety pool. In study R668-AD-1224 (Dupilumab plus Concomitant TCS): at the 16-week data analysis, 1.3%, 0.9%, and 1.3% in the placebo, dupilumab 300 mg Q2W + TCS, and 300 mg QW + TCS groups, respectively reported TEAEs in the Neoplasm SOC. The corresponding rates for the 52-week treatment period were 3.2%, 4.5%, and 2.2%. The most commonly reported TEAES were benign lesions. Two serious reports in patients treated with dupilumab QW and Q2W respectively (Hodgkin Lymphoma and Lipoma) were both considered not to be related to study drug. Three additional SAEs were identified in the supportive safety pool analysis, Mycosis Fungoides and Squamous Cell Carcinoma in the dupilumab group, and Malignant Melanoma in-situ in the placebo group. None of these were considered related to study drug. Four serious cases of squamous cell carcinoma (2 skin, 1 tongue and 1 not otherwise specified) were reported during the 52 wk. treatment period ,3 in the Dupilumab +TCS 300mg QW group and 1 in the Dupilumab +TCS 300mg Q2W group.

In the open label extension study R668-AD-1225 the overall incidence of TEAEs was 2.4% in the Neoplasm SOC. (1.5% dupilumab naïve, 4.2% retreated group, 2% interrupted treatment, 5% continuous treatment. Skin papilloma was the commonest TEAE (0.9%). There were four cases of basal cell carcinoma (0.3%) and squamous cell carcinoma (0.3%).

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

Because dupilumab is a monoclonal antibody, it is not anticipated to directly interact with cytochrome P450 enzymes, other drug metabolizing enzymes, or drug transporters; thus, no typical drug-drug interactions via these mechanisms is expected. However, limited *in vitro* data suggest that IL-4 and IL-13 affect the expression (and potentially the activities) of some cytochrome P450 isoforms. Therefore, it is possible that dupilumab, by inhibiting IL-4 and IL-13 signaling, may indirectly influence the expression of these cytochrome P450 isoforms. Consequently, an open-label, drug-drug interaction study (R668-AD-1433) was designed to examine the effects of dupilumab on the PK of selected cytochrome P450 substrates in adult patients with moderate-to-severe AD. This study was completed and did not indicate clinically relevant effects of dupilumab on CYP1A2, CYP3A, CYP2C19, CYP2D6, or CYP2C9 activity.



During the dupilumab development program, investigators were advised to monitor patients who used concomitant drugs with narrow therapeutic indexes and that were metabolized by cytochrome enzymes. No AEs related to a drug-drug interaction were reported.

### ***Discontinuation due to adverse events***

In the Primary Safety Pool, the proportion of patients who had at least 1 TEAE leading to permanent study drug discontinuation was low overall and comparable across the treatment groups, 1.9% (10/517) in the placebo group, 1.9% (10/529) in the dupilumab 300 mg Q2W group, and 1.5% (8/518) in the dupilumab 300 mg QW group. Dermatitis Atopic was the only PT with an incidence  $\geq 1\%$  in any group: 1.0% (5/517) for placebo, 1.3% (7/529) for dupilumab 300 mg Q2W, and 0.4% (2/518) for dupilumab 300 mg QW. Largely similar findings were seen in the Supportive Safety Pool.

In the 52-week treatment period of the R668-AD-1224 study, the proportion of patients who had at least 1 TEAE leading to permanent study drug discontinuation was lower in the dupilumab 300 mg Q2W + TCS group (1.8% [2/110]) and the dupilumab 300 mg QW + TCS group (2.9% [9/315]) than in the placebo + TCS group (7.6% [24/315]). The most common SOC accounting for permanent treatment discontinuation was in the Skin Disorders SOC, with a higher incidence in the placebo group (5.1% [16/315]) than in the dupilumab 300 mg Q2W group (1.8% [2/110]), and the dupilumab 300 mg QW group (0.3% [1/315]), with most of the events being Dermatitis Atopic. The SOCs or PT that had  $\geq 2$  patients in the dupilumab group experiencing TEAEs leading to permanent study drug discontinuation were Eye Disorder SOC (with 1 event each of Allergic Keratitis, Cystoid Macular Edema, and Eye Pruritus, all reported in the 300 mg QW group) and Injection Site Reactions (2 patients in the 300 mg QW group). Infections and Infestations events leading to discontinuation occurred in 3 placebo patients and none in the dupilumab groups.

### ***Safety Data from R668-AD1415 and R668-AD1424***

The safety data of these studies have not been included as of the cut-off of the 31<sup>st</sup> May 2017.

#### **R668-AD-1415**

Dupilumab was well tolerated in this study. The majority of patients reported TEAEs that were mild to moderate in intensity. The incidence of severe TEAEs was less than 6% in any treatment group and was similar across the treatment groups. One death occurred in the dupilumab 300 mg Q4W group as a result of Gun Shot Wound (a homicide event). Treatment-emergent SAEs were reported by <5% of patients across all treatment groups. No dose-response trend was observed. There was no anaphylaxis or other systemic hypersensitivity reactions to dupilumab. There appeared to be a reverse dose-response trend in the incidence of TEAEs leading to temporary discontinuation of the study treatment, with the highest incidence in the placebo group (12.2%) and the lowest in the dupilumab 300 mg Q2W/QW group (3.6%). An inverse dose-response trend was observed in the incidence of overall TEAEs, which was largely driven by exacerbation of AD and skin infections. There was no apparent safety advantage for the lower dupilumab dose regimens (300 mg Q4W and Q8W). The incidences of conjunctivitis and herpes viral infections were similar between placebo and dupilumab regimen groups. The incidence of skin infections in placebo was higher than dupilumab regimen groups.

#### **R668-AD-1424**

Both dose regimens of dupilumab were well tolerated in this study with an acceptable safety profile, generally comparable with that observed in placebo-treated patients. No new safety signals related to



dupilumab treatment were identified, and no dose-dependent trends were observed.

There were no deaths. A similar proportion of patients in the placebo + TCS group (1.9%) and in the dupilumab + TCS groups had SAEs (1.9% in the dupilumab 300 mg Q2W + TCS group and 1.8% in the dupilumab 300 mg QW + TCS group). No SAEs were considered related to dupilumab treatment. The proportion of patients with TEAEs leading to permanent discontinuation of study drug was generally low and comparable across treatment groups. A lower proportion of patients in the in the combined dupilumab + TCS treatment group (3.7%) had severe TEAEs compared to patients in the placebo + TCS group (9.3%).

The incidence of infections was 45.8% in the dupilumab 300 mg Q2W + TCS group, 42.7% in the dupilumab 300 mg QW + TCS group, and 40.7% in the placebo + TCS group. The most common PTs in the SOC of Infections and Infestations were Nasopharyngitis, Conjunctivitis (of unspecified etiology) and Oral Herpes, all of which occurred with higher frequency in dupilumab-treated patients. While there was a higher incidence of localized, Muco-cutaneous Herpes Infections in dupilumab-treated patients, more serious forms of herpes infections such as Eczema Herpeticum, Ophthalmic Herpes Simplex and Ophthalmic Herpes Zoster occurred only in the placebo + TCS group. Of the localized herpes infections, none was severe and all but 1 had recovered/resolved by the end of treatment visit. Conjunctivitis events were more common in dupilumab treated patients than placebo treated patients. The majority of events had recovered/resolved by the end of treatment visit. No patients discontinued the trial due an AE of Conjunctivitis, and all but 2 patients continued into the OLE trial.

### ***Post marketing experience***

Not applicable

#### **2.6.1. Discussion on clinical safety**

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

A total of 2825 clinical trial subjects have received at least one dose of dupilumab across a range of diseases including atopic dermatitis, asthma and nasal polyposis with chronic sinusitis during 26 clinical studies (6 HV, 16 AD, 3 Asthma, 1 Nasal Polyposis). Overall, 1929 subjects with moderate to severe AD have received at least one dose of dupilumab and 1908 of these received dupilumab 300 mg SC, either as part of a randomized placebo-controlled or the open-label extension study. The absolute numbers and percentages of the AEs have been reported. For longer treatment periods, exposure adjusted incidence rates were calculated as well. This is important, because the exposure to dupilumab varied with time, in particular studies where patients were treated in a previous study prior to enrollment and the overall exposure to dupilumab was greater than with placebo.

The size of the safety database and degree of patient exposure for dupilumab to support this application is largely considered sufficient. The numbers of patients with long term exposure to dupilumab 300mg Q2W dose, the intended dose for inclusion in the SmPC, are quite low. However, the ICH E1 safety exposure requirements of >1500 patients exposed, 300 to 600 for 6 months, > 100 for 1 year are well exceeded. There is one ongoing open-label extension study (1225) that will provide further data on long-term safety. The final report of this study should be submitted when available.

In general, a similar frequency of patients of monotherapy placebo and verum groups showed treatment-emergent AEs with most AEs occurred in SOCs Infections and Infestations, Skin and Subcutaneous Tissue Disorders and General Disorders/Administration Site Conditions. Concerning the treatment-related TEAEs, the treatment groups had a higher frequency than the placebo group. The General Disorders and Administration Site Conditions SOC had the highest AE proportion, followed by

Infections and Infestations SOC. Besides, ISR, Headache, Conjunctivitis, Eosinophilia were identified as important treatment-related TEAEs. No differences in AE pattern were seen between monotherapy and dupilumab+topical treatment (TCI/TCS). Baseline demographic characteristics were balanced apart from gender.

Of the 3 cases of TESAE observed in the SSP, only the Serum Sickness-like Reaction was considered by the investigator to be caused by study drug and lead to treatment discontinuation. It was moderate in severity and fully resolved.

A case of severe Serum Sickness happened during the R668-AD-1225 OLE study which was attributed to the study drug and lead to treatment discontinuation. The symptoms occurred after a latency of 12 days from the most recent and second drug administration. With the responses to the Day 120 LoQ the applicant proposed to rephrase the already existing important identified risk of "Systemic hypersensitivity" to "Systemic hypersensitivity (including events associated with immunogenicity)" which is endorsed

The major difference between the safety profile for the monotherapy treatment and the combination therapy safety profiles at both 16 and 52 weeks is an increase in the eye disorder reports. A higher incidence of eye-disorders (conjunctivitis, blepharitis and dry eye), was seen in dupilumab treated patients compared to placebo in both the monotherapy and combination therapy studies. Patients who developed eye disorders were older, had longer duration of AD, had higher disease activity at baseline, had a baseline history of eye disorders and were more likely to have been treated previously with immunosuppressants. Although the majority of cases were mild to moderate in severity and responded to treatment with topical preparations a significant proportion (10-20%) hadn't resolved. The long-term effect of this chronic conjunctivitis is unknown. The aetiology of these cases has not been adequately determined. Higher frequency of treatment emergent conjunctivitis in dupilumab-treated patients than placebo-treated patients was observed in AD studies, but not in asthma or NP studies, suggesting that moderate-severe AD may be a risk factor for this event. As outlined by the applicant, there are clear gaps in the knowledge related to conjunctivitis related events. Inclusion of Conjunctivitis related events as missing information is supported. Until further information is available, patients treated with dupilumab who develop conjunctivitis should undergo ophthalmological examination and appropriate warning has been included in SmPC section 4.4.

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

Circulating eosinophils were transiently increased in the dupilumab treatment groups without any difference as to the dosing scheme. The increase was moderate and returned to baseline after week 16. Based on the data provided, the Applicant identified this TEAE as an ADR and this is fully endorsed.

Currently there is only a limited amount of safety data for elderly patients and the Applicant has stated that the number of elderly patients enrolled in the AD studies was too small to make meaningful comparisons with the general adult population data. This might be caused by the fact that incidence and prevalence of AD declines in the course of lifetime. Therefore, 'Safety in patients aged 65 years and above' has been included in the RMP as 'Missing information'.

The spontaneous abortion rate registered during the dupilumab studies does not seem to exceed the general rate (26% vs. ~30%). However, dedicated studies analysing the effect of dupilumab on pregnancies and their outcomes are hitherto missing. So far, no adverse effects on pregnancy or on the baby could be determined. The same applies to breastfeeding.

Opportunistic infections were rare in general and patients of the dupilumab treatment groups showed lower incidences than the placebo groups apart from local HSV infections which seem as in general linked to AD and not to be caused by the dupilumab treatment. Results of the CHRONOS and OLE

study were consistent. After due analysis, it appears that allergic reactions are infrequent, mostly mild to moderate and manageable by supportive care apart from Injection site reactions which were listed as ADR.

The number of subjects experiencing AEs leading to withdrawal in both the placebo-controlled and OLE studies was low. Especially in the LTT study CHRONOS the treatment discontinuation was lower than in the placebo groups.

No clinically significant differences in the AE- or SAE-profiles or -rates were observed in dupilumab patients for whom ciclosporin treatment is inadvisable. This analysis included patients from the pivotal and long term studies who didn't respond to ciclosporin, who could not tolerate ciclosporin or for whom post ciclosporin was medically inadvisable.

The incidence and pattern of TEAEs was broadly comparable between patients for whom ciclosporin was medically inadvisable and patient who were not included in this subset. Of note there were higher rates of exacerbation of atopic dermatitis, including cases that were severe and requiring discontinuation of study drug and higher rates of allergic conjunctivitis and blepharitis that increased over the duration of the 52 week study in the population for whom ciclosporin was medically inadvisable. The safety profile treatment with a dupilumab dose regimen of 300 mg Q2W or 300 mg QW is broadly similar. For AD patients with a history of inadequate response to topical therapies for whom CSA treatment is medically inadvisable, there is a high unmet medical need. In this patient population, the safety profile following treatment with a dupilumab dose regimen of 300 mg Q2W or 300 mg QW, was broadly similar to the subset 3 analysis (subgroup of AD patients not adequately controlled with, intolerant of oral ciclosporin, or for whom oral ciclosporin was not medically advisable in the pooled pivotal studies and the dupilumab +TCS long term study). Considering these patients are the most severe treatment resistant subgroup these data suggest that dupilumab is well tolerated.

Overall rates of ADA in the monotherapy studies and combination therapy studies were low and appear to be transient. In general titre levels were low. Of note, two cases (1 each of serum sickness type reaction/serum sickness) were reported for 2 dupilumab treated patients with high antibody titres. The onset of reaction in both cases was approximately around 2 weeks of starting study treatment. Currently Dupilumab is contraindicated in patients who have a known hypersensitivity to it, or to any of its excipients. Section 4.4 with cross reference to 4.8 warns that dupilumab should be discontinued immediately if a patient develops a systemic hypersensitivity reaction. The warnings regarding serum sickness were additionally revised to state that these reactions occurred within the first few weeks of treatment with dupilumab. Further data on the incidence of ADAs and their relation to safety from follow-up studies lasting over 1 year should be provided for review when available.

### **2.6.2. Conclusions on the clinical safety**

Based on the presented and available data, dupilumab has been found to have an acceptable safety profile. With regard to TEAE profile, no meaningful qualitative and quantitative differences were seen as to short-term and long-term treatment as well as to the dose regimen.

As questions still remain on the long term safety, ongoing open-label extension studies are being undertaken that will provide further data.

## 2.7. Risk Management Plan

### Safety concerns

<b>Important identified risks</b>	Systemic hypersensitivity (including events associated with immunogenicity)
<b>Important potential risks</b>	Malignancy
<b>Missing information</b>	Use in pediatric AD patients <18 years of age Use in pregnant and lactating women Conjunctivitis related events Long-term safety Dupilumab effect on live vaccine safety

AD: Atopic Dermatitis.

### Pharmacovigilance plan

<b>Study/activity Type, title and category (1-3)</b>	<b>Objectives</b>	<b>Safety concerns addressed</b>	<b>Status</b>	<b>Date for submission of interim or final reports</b>
Pregnancy registry (Cat. 3) (R668-AD-1639)	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes in exposed pregnancies compared to disease-matched and healthy unexposed pregnancies.	Effects of dupilumab exposure during pregnancy on the pregnancy and infant outcomes	Not started	Final report: 8 years following product launch in North America or following protocol approval by FDA
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (R668-AD-1225) (LTS14041) (Cat. 3)	To assess the long term safety, efficacy, PK, and immunogenicity of REGN668 in patients with moderate to severe AD.  To measure the incidence and risk of malignancies in patients who have long-term exposure (up to 5 years) to dupilumab	Long term safety of dupilumab and Malignancy (Ophthalmology sub study: additional information on conjunctivitis related events)	Ongoing	Final report: May 2022
An single-arm extension study to assess the long-term safety of dupilumab in patients ≥6 to <18 years of age with AD (LTS1434)	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long term safety of dupilumab in pediatric patients with AD	Ongoing	Final report: 1Q 2020

<b>Study/activity Type, title and category (1-3)</b>	<b>Objectives</b>	<b>Safety concerns addressed</b>	<b>Status</b>	<b>Date for submission of interim or final reports</b>
(R668-AD-1434) (Cat. 3)				
A randomized, double blind, placebo controlled study to investigate the efficacy and safety of dupilumab in patients 12 to <18 years of age, with moderate to severe AD (EFC1526) (R668-AD-1526) (Cat. 3)	To demonstrate the efficacy of dupilumab in patients $\geq 12$ years to <18 years of age with moderate-to-severe AD.	Safety of dupilumab in patients 12 to <18 years of age, with moderate to severe AD	Ongoing	Final report: 4Q 2019
A phase 2/3 study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged $\geq 6$ months to <6 years with severe atopic dermatitis (R668-AD-1539) (Cat. 3)	To characterize the safety and PK of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age; demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS	Safety in children <6 years of age with severe AD	Ongoing	Final report 3Q 2019
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients, $\geq 6$ years to <12 years of age, with severe atopic dermatitis (R668-AD-1652) (Cat. 3)	To demonstrate the safety and efficacy of dupilumab administered concomitantly with TCS in patients, $\geq 6$ years to <12 years of age, with severe AD.	Safety in children $\geq 6$ years to <12 years of age, with severe AD	Planned	Final report 1Q 2019
Pregnancy Outcomes Database Study (Cat. 3) (R668-AD-1760)	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to	Effects of dupilumab exposure during pregnancy on the pregnancy and infant outcomes	Planned	Final report will be submitted once available

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
dupilumab).				

AD: Atopic Dermatitis; PK: Pharmacokinetics; CYP: Cytochrome P450; qw: Once a Week; q2w: Once Every Two Weeks; DLP: Data Lock Point; TCS: Topical Corticosteroid; FDA: Food and Drug Administration.

### **Risk minimisation measures**

Safety concern	Routine risk minimization activities	Additional risk minimization activities
<b>Important identified risks</b>		
Systemic hypersensitivity (including events associated with immunogenicity)	SmPC section 4.3 Contraindications, section 4.4 Special warnings and precautions for use, section 4.8 Undesirable effects	None
<b>Important potential risks</b>		
Malignancy	None	None
<b>Missing information</b>		
Use in pediatric AD patients <18 years of age	SmPC section 4.2 Posology and method of administration, section 5.2 Pharmacokinetic profile	None
Use in pregnant and lactating women	SmPC section 4.6 Fertility, pregnancy and lactation, section 5.3 Preclinical safety data	None
Conjunctivitis related events	SmPC section 4.4 Special warnings and precautions for use, section 4.8 Undesirable effects	None
Long-term safety	None	None
Dupilumab effect on live vaccine safety	SmPC section 4.5 Interaction with other medicinal products and other forms of interactions	None

AD: Atopic Dermatitis; SmPC: Summary of Product Characteristics.

### **Conclusion**

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

## **2.8. Pharmacovigilance**

### **Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

## ***Periodic Safety Update Reports submission requirements***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

### ***2.9. New Active Substance***

The applicant declared that dupilumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers dupilumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

### ***2.10. Product information***

#### **2.10.1. User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

#### **2.10.2. Additional monitoring**

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

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

## **3. Benefit-Risk Balance**

### ***3.1. Therapeutic Context***

#### **3.1.1. Disease or condition**

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



### 3.1.2. Available therapies and unmet medical need

Among the main goals in treating AD are the reduction of skin inflammation and the alleviation of symptoms, particularly pruritus.

Atopic dermatitis is treated primarily with topical corticosteroids (TCS). However, continuous long-term application of TCS, particularly TCS products with higher potency, is not recommended, because of the risk of skin atrophy, dyspigmentation, acneiform eruptions and risks associated with systemic absorption and subsequent HPA axis suppression. Topical calcineurin inhibitors (TCI) such as tacrolimus and pimecrolimus, are generally safe and effective as continuous short-term treatments or intermittent long-term treatment. Concerns over the potential increased risk of skin malignancies and lymphomas associated with TCI use has prompted regulatory authorities to require, in their prescribing information, a warning regarding long-term safety. Treatment guidelines currently recommend TCI as second-line therapy and typically restrict TCI to “problem areas” that cannot be treated with TCS (eg, face, genital, intertriginous areas, or areas of skin atrophy).

The majority of patients with mild AD respond well to topical therapy. However, patients with moderate-to-severe AD often do not achieve adequate control with acceptable doses of topical medications and frequently require systemic therapy.

Systemic therapy is indicated in patients who do not respond adequately to topical therapies or for whom topical therapy is inadvisable. Currently available systemic therapies include nonselective immunosuppressants such as systemic corticosteroids, which are associated with severe toxicity and side effects (eg, glaucoma, edema, weight gain, increased blood pressure, and mood swings with short term use; cataracts, increased blood sugar, osteoporosis, thinning of the skin, increased risk of infections, and effects on growth in children with long term use). Because of these safety drawbacks, most guidelines recommend systemic corticosteroids only for short term treatment of AD. Patients' AD often rebounds once treatment is stopped, particularly after discontinuing systemic glucocorticoids.

Other nonselective immunosuppressive drugs are being used in AD, off-label, with variable results. These drugs have well established toxicity profiles (eg, myelosuppression and hepatotoxicity for methotrexate, leucopenia for azathioprine, etc.) that make it difficult for use in managing a chronic, life-long disease such as AD. In addition, the broad immunosuppressive effects of these drugs are associated with an increased risk of developing serious bacterial, fungal, viral, and mycobacterial infections.

Ciclosporin A, a potent, oral, non-selective immunosuppressant originally developed for prevention of organ transplant rejection, is currently approved in many countries of the EU to treat severe AD, particularly AD that is refractory to topical treatment. The use of Ciclosporin A in AD is limited by commonly recognized toxicities, including hypertension, impaired renal and hepatic function, and the potential for greater susceptibility to infections and cancer, particularly to skin cancer. The use of ciclosporin A requires intensive safety monitoring, especially of renal and liver function. Because of the high toxicity of ciclosporin A, its approved use in AD is limited to treatment of only severe cases, with a maximum duration of 1 year. Other limitations of ciclosporin A treatment include its interactions with other commonly used medicines, which can potentially affect their metabolism and efficacy.

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

### 3.1.3. Main clinical studies

This application was supported by data from 13 studies in adult patients with AD, ranging from phase 1b to phase 3, with the clinical efficacy almost entirely based on the results of the pivotal phase 3

studies. The majority of the studies evaluated dupilumab as a monotherapy in adult patients who were candidates for systemic therapy.

In the pivotal phase 3 studies standard efficacy variables for AD were used as key endpoints to assess efficacy of dupilumab. Efficacy assessments included direct measurements of the extent and severity of AD signs and symptoms, the impact of AD disease symptoms on quality of life, and anxiety and depression scores. Physician and patients reported efficacy evaluations were used (e.g. EASI-75, IGA 0 or 1, Pruritus NRS, DLQI, HADS) at different timepoints during the studies.

The phase 3 studies and the treatment groups in the phase 2b study that were studied in phase 3 (placebo, 300 mg weekly [QW], and 300 mg every 2 weeks [Q2W]) have been pooled to provide a more comprehensive and precise assessment of the safety of dupilumab as monotherapy. Two phase 3 studies provide information on dupilumab when administered concomitantly with topical medications (TCS with or without TCI, as applicable; referred to as + TCS in the summary), since TCS represent the mainstay of pharmacological treatment for AD and many patients may ultimately use dupilumab with concomitant topical treatments. These are the long-term treatment study R668-AD-1224 (LTT), which provides placebo-controlled safety information on dupilumab when administered as concomitant treatment with TCS, and the open-label extension study R668-AD-1225 (OLE) where patients had the option of using dupilumab concomitantly with topical treatments. These 2 studies also provide information on long-term safety. Study R668-AD-1224 provides 52-week randomized control data on the use of dupilumab + TCS versus placebo + TCS. The OLE study includes patients from phase 2 and phase 3 studies and allows evaluation of the safety of continued LTT as well as re-treatment with dupilumab after treatment discontinuation.

### **3.2. Favourable effects**

Over 2000 patients were enrolled in the pivotal phase 3 studies. The analyses of the key efficacy results of all studies show a significant higher reduction in severity and symptoms of atopic dermatitis compared to placebo. Standard efficacy variables for AD were used to assess efficacy of dupilumab i.e. IGA 0 or 1 with  $\geq 2$  points reduction and EASI-75 as co-primary and Pruritus NRS at different time points as key secondary endpoints.

In study R668-AD-1224 the dupilumab 300 mg Q2W + TCS group 68.9% of the patients achieved EASI-75 at week 16, followed by the dupilumab 300 mg QW + TCS group with 63.9% and 23.2% of the patients on placebo + TCS. The results of the other co-primary endpoint show that 38.7% in the dupilumab 300 mg Q2W + TCS, 39.2% dupilumab 300 mg QW + TCS and 12.4% placebo + TCS group achieved an IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16. Both comparisons were statistically significant ( $p < 0.0001$  for each). At week 52 the proportion of patients with EASI-75 at week 52 was still significantly higher in the dupilumab 300 mg Q2W + TCS (62.3%) and dupilumab 300 mg QW + TCS (63.9%) groups than the placebo + TCS group (21.69%).

In the identical studies R669-AD-1334 and -1416 the proportion of patients with EASI-75 at week 16 was higher in the dupilumab 300 mg Q2W (51.3% and 44.2%) followed by dupilumab 300 mg QW (52.5% and 48.1%) groups and the placebo groups (14.7% and 11.9%). The proportion of patients with IGA 0 or 1 and a reduction from baseline of  $\geq 2$  points at week 16 was significantly higher in the dupilumab 300 mg Q2W (37.9% and 36.1%) and dupilumab 300 mg QW (37.2% and 36.4%) groups compared to the placebo groups (10.3% and 8.5%). The comparisons were statistically significant ( $p < 0.0001$  for each).

The applicant submitted the results from the supplementary studies R668-AD-1424 and R668-AD-1415 in specific subsets, demonstrating clinically relevant efficacy and safety information of both dupilumab doses. R668-AD-1424 was conducted in patients with severe atopic dermatitis for whom CSA had

either not demonstrated adequate efficacy, had unacceptable side effects or for whom initiating CSA was not medically advisable. They represent a population that is difficult to treat and for which there is an unmet medical need as there are limited treatment options. Efficacy has been demonstrated on the EASI-75 response at 16 weeks and for all of the key secondary objective and symptomatic endpoints.

Study R668-AD-1415 enrolled patients who had completed 16 weeks of mono-therapy. In this study, patients who continued on the same dose regimen received in the parent AD-1334 and AD-1416 studies (300 mg Q2W or 300 mg QW), showed the optimal effect in maintaining clinical response while efficacy for other dose regimens diminished in a dose-dependent manner. A trend for increased treatment-emergent ADA positivity with increased dosing intervals was observed.

Onset of action was rapid in all studies, with divergence between dupilumab + TCS and placebo + TCS apparent as early as week 2 for many endpoints.

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

In none of the pivotal studies an active comparator was used. In the earlier Scientific Advice the CHMP recommended the use of an approved systemic treatment (Ciclosporin) for AD. However, this was not done as a study with Ciclosporin as active comparator was problematic with regards to adequate sample size, adequate design and blinding.

### **3.4. *Unfavourable effects***

A higher incidence of Conjunctivitis was observed in the dupilumab groups compared to the placebo group in both the Primary and Supportive Safety Pools. Patients who developed eye disorders were older, had longer duration of AD, had higher disease activity at baseline, had a baseline history of eye disorders and were more likely to have been treated previously with immunosuppressants. Conjunctivitis has therefore been listed as ADRs as well as Conjunctivitis Allergic, Blepharitis, and Dry Eye, based on the association with dupilumab treatment. The majority of cases were mild to moderate in severity and were self-limiting. However, approximately 10-20% had not resolved by the end of the study. The long term effect of chronic conjunctivitis in these patients is unknown. The aetiology of these cases has not been adequately determined. Conjunctivitis related events have there been included as missing information in the RMP which is endorsed.

The incidence of Oral Herpes during the treatment periods in the Primary and Supportive Safety Pools was higher in the dupilumab groups compared to the placebo group. However, the long term data show an only slightly higher rate of oral herpes in the dupilumab Q2W group compared to placebo.

The frequency of Eosinophilia during the 16-week treatment period in the Primary Safety Pool was higher in the dupilumab 300 mg Q2W group (1.7%), and similar between the 300 mg QW group (0.2%) and placebo group (0.4%). However, Eosinophilia was reported at a similar incidence in the dupilumab group (1.0%) and in the placebo group (0.7%) in the Supportive Safety Pool. Evaluation of laboratory data indicates that a Transient Eosinophilia was seen with dupilumab treatment in a minority of patients. Although the precise mechanism is unknown, Eosinophilia is considered as an ADR.

Dupilumab use was associated with ISRs at a higher incidence than placebo in both the Primary and Supportive Safety Pools. There were no events of severe ISRs in both Pools. Based on the association with dupilumab use, ISRs are considered an ADR.

The incidence of Acute Allergic Reactions was similar across all treatment groups in the Primary

Safety Pool and different dose groups, respectively. Most of these reactions were skin-related. There was a serious event of Serum sickness-Like Illness described in a patient treated with dupilumab in the Supportive Safety Pool and one serious event of serum sickness in study R668-AD-1225. Both these events were associated with high titers ADA There was one non-serious serum sickness case observed in study R668-AD-1424. There were 3 events of Anaphylaxis in the R668-AD-1225 OLE study and none were assessed as related to dupilumab treatment.

### 3.5. Uncertainties and limitations about unfavourable effects

Long-term safety experience is limited. Based on the currently available data, on review of adverse events of special interest, there was no apparent increased risk of malignancy, infections, or serious cardiac, vascular, thromboembolic and ischaemic events. The overall risk of systemic allergic and non-allergic reactions with dupilumab and the immunogenic potential of dupilumab appear low. However, this will be further explored and confirmed in the ongoing open-label extension trial to further characterise the long-term safety of treatment.

Currently there is only a limited amount of safety data for special populations as pregnant and lactating women, children and patients with organ impairment. Further data will be collected in the post-marketing setting.

Animal studies do not indicate reproductive toxicity. However, data from use of dupilumab is too limited to draw any conclusions on potential embryofetal harms.

### 3.6. Effects Table

**Table 4.** Effects Table for dupilumab

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
<b>Favourable Effects</b>						
EASI 75	Proportion of subjects achieving 75% improvement at week 16	Fracti on	Dupilumab 300mg Q2W Solo1: 51.3% Solo2: 44.2%  Chronos (+TCS): 68.9%  300mg QW Solo1: 52.5% Solo2: 48.1%  Chronos (+TCS): 63.9%	Placebo  Solo1:14.7% Solo2:11.9%  Chronos (+TCS) 23.2%	Both doses are superior to placebo without or in combination with TCS (Chronos-study)	Clinical AR

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
IGA 0/1 and $\geq 2$ Points	Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq 2$ points at week 16	Fraction	Dupilumab 300mg Q2W Solo1: 37.9% Solo2: 36.1%  Chronos (+TCS): 38.7%  300mg QW Solo1: 37.2% Solo2: 36.4%  Chronos (+TCS): 39.2%	Placebo  Solo1: 10.3% Solo2: 8.5%  Chronos (+TCS) 12.4%		
Key secondary endpoint	Reduction in the Weekly Average of Peak Daily Pruritus NRS at several timepoints					
<b>Unfavourable Effects</b>						
Immune system disorders	Hypersensitivity , Serum Sickness	Number	Dupilumab 300 mg QW R668-AD-1225 (OLE)		Single case	Clinical AR
	Hypersensitivity , Serum Sickness-like Reaction	Number	Dupilumab 300 mg QW R668-AD-1314 (OLE)		Single case	Clinical AR
General disorders	ISR	Fraction	Dupilumab 300mg Q2W PSP: 9.6%  300mg QW PSP: 13.9%  300mg Q2W +TCS (LTT): 10.0%  300mg QW +TCS (LTT): 15.9%	Placebo PSP: 5.4%  Placebo: 5.7%	Incidence keeps increasing with longer treatment duration	Clinical AR

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Blood and lymphatic system disorders	Eosinophilia	Fracti on	Dupilumab 300mg Q2W PSP: 1.7%	Placebo PSP: 0.4%	Transient	Clinical AR
			300mg QW PSP: 0.2%			
			300mg Q2W +TCS (LTT): 0.9%	Placebo: 0%		
			300mg QW +TCS (LTT): 0.3%			
Infections and Infestations	Conjunctivitis	Fracti on	Dupilumab 300mg Q2W PSP: 3.0%	Placebo PSP: 1.0%	Post-hoc analysis	Clinical AR
			300mg QW PSP: 2.3%			
			300mg Q2W +TCS (LTT): 6.4%	Placebo: 3.2%		
			300mg QW +TCS (LTT): 7.0%			
	Oral herpes	Fracti on	Dupilumab 300mg Q2W PSP: 3.8%	Placebo 1.5%		Clinical AR
			300mg QW PSP: 2.5%			
			300mg Q2W +TCS (LTT): 2.7%	Placebo: 1.6%		
			300mg QW +TCS (LTT): 2.5%			

### 3.7. Benefit-risk assessment and discussion

#### 3.7.1. Importance of favourable and unfavourable effects

Atopic dermatitis is a chronic or chronically relapsing inflammatory skin disease characterized by pruritus, xerosis, and eczematous lesions. Especially pruritus and skin infections which are a major complication in AD compromise health and lower the quality of life and, in the worst case, can result in psychic comorbidities as anxiety and depression. To date, limited treatment options are available. Local therapies often relieve typical symptoms for the duration of their application. Atopic dermatitis is treated primarily with topical corticosteroids. However, continuous long-term application of TCS, particularly TCS products with higher potency, is not recommended, because of side effects as skin

atrophy and others. The majority of patients with mild AD respond well to topical therapy. However, patients with moderate-to-severe AD often do not achieve adequate control with acceptable doses of topical medications and frequently require systemic therapy. Systemic therapy is indicated in patients who do not respond adequately to topical therapies or for whom topical therapy is inadvisable. Currently available systemic therapies include nonselective immunosuppressants such as systemic corticosteroids, which are associated with severe toxicity and side effects.

The overall safety profile of dupilumab is mainly characterised by minor adverse reactions (upper respiratory tract infections, conjunctivitis and local injection site reactions which were in general mild, self-limiting and manageable). Its immunogenicity and allergic potential is low. In addition, the burden of biweekly subcutaneous injections is likely to be considered low by the patient against the background that no systemic and efficacious therapy is in place to date. The safety profile of the both dose regimens did not significantly differ. Further long-term data will be collected to substantiate the safety profile which hitherto seems to be acceptable.

### **3.7.2. Balance of benefits and risks**

Efficacy of dupilumab in the treatment of AD has been demonstrated and the safety profile has been found to be favourable.

The risks of dupilumab have been found to be low and manageable and a reduction in illness severity and exacerbations is considered to exceed them. The B/R in adult patients with moderate to severe atopic dermatitis is positive.

### **3.8. Conclusions**

The overall B/R of Dupixent (dupilumab) is positive.

## **4. Recommendations**

### ***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Dupixent (dupilumab) is favourable in the following indication:

Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

### ***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)



## ***Other conditions and requirements of the marketing authorisation***

### **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

#### **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

### ***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.

### ***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that dupilumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.