Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Dupilumab

Proprietary Product Name: Dupixent

Sponsor: Sanofi-Aventis Pty Ltd

First round report: 30 March 2017
Second round report: 26 August 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of common abbreviations 5

1. Submission details 9

1.1. Identifying information 9

1.2. Submission type 9

1.3. Drug class and therapeutic indication 9

1.4. Dosage forms and strengths 9

1.5. Dosage and administration 9

1.6. Proposed changes to the product documentation 10

2. Background 10

2.1. Information on the condition being treated 10

2.2. Current treatment options 10

2.3. Clinical rationale 11

2.4. Guidance 12

2.5. Evaluator's commentary on the background information 12

3. Contents of the clinical dossier 12

3.1. Scope of the clinical dossier 12

3.2. Paediatric data 13

3.3. Good clinical practice 13

3.4. Evaluator's commentary on the clinical dossier 13

4. Pharmacokinetics 13

4.1. Studies providing pharmacokinetic information 13

4.2. Summary of pharmacokinetics 14

4.3. Evaluator's overall conclusions on pharmacokinetics 20

5. Pharmacodynamics 20

5.1. Studies providing pharmacodynamic information 20

5.2. Summary of pharmacodynamics 21

5.3. Evaluator's overall conclusions on pharmacodynamics 30

6. Dosage selection for the pivotal studies 31

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies 31

6.2. Phase II dose finding studies 36

6.3. Phase III pivotal studies investigating more than one dose regimen 36

6.4. Evaluator's conclusions on dose finding for the pivotal studies 36

7. Clinical efficacy 36

7.1. Studies providing evaluable efficacy data 36

7.2. Pivotal or main efficacy studies 37
7.3. Other efficacy studies 64
7.4. Analyses performed across trials: pooled and meta analyses 71
7.5. Evaluator's conclusions on clinical efficacy 71
8. Clinical safety 72
8.1. Studies providing evaluable safety data 72
8.2. Studies that assessed safety as the sole primary outcome 73
8.3. Patient exposure 74
8.4. Adverse events 76
8.5. Evaluation of issues with possible regulatory impact 91
8.6. Other safety issues 99
8.7. Post marketing experience 99
8.8. Evaluator's overall conclusions on clinical safety 100
9. First round benefit-risk assessment 101
9.1. First round assessment of benefits 101
9.2. First round assessment of risks 101
9.3. First round assessment of benefit-risk balance 102
10. First round recommendation regarding authorisation 102
11. Clinical questions 102
11.1. Pharmacokinetics 102
11.2. Pharmacodynamics 102
11.3. Efficacy 102
11.4. Safety 103
12. First round evaluation errata 103
12.1. Minor editorial changes 103
12.2. Minor errors of fact 103
12.3. Significant errors of fact 103
13. Second round evaluation 103
13.1. Safety 107
14. Second round benefit-risk assessment 109
14.1. Second round assessment of benefits 109
14.2. Second round assessment of risks 109
14.3. Second round assessment of benefit-risk balance 109
15. Second round recommendation regarding authorisation 110
16. References 110

List of common abbreviations

Abbreviation	Meaning
AD	Atopic dermatitis
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BSA	Body surface area
BUN	Blood urea nitrogen
C_{ave}	Average plasma concentration
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CPK	Creatinine phosphokinase
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DAE	Discontinuation due to Adverse Event
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
FAS	Full Analysis Set
GCP	Good Clinical Practice

Abbreviation	Meaning
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
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IFMγ	Interferon-gamma
IGA	Investigator's Global Assessment
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IV	Intravenous
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model with Repeated Measures
NRS	Numerical Rating Scale

Abbreviation	Meaning
PARC	Pulmonary and activation-regulated chemokine
PCSV	Potentially clinically significant value
PK	Pharmacokinetic
POEM	Patient Oriented Eczema Measure
PT	Preferred Term
QOL	Quality of Life
QoLIAD	Quality of Life Index for Atopic Dermatitis
QW	Once weekly
Q2W	Once every two weeks
Q4W	Once every four weeks
RBC	Red blood cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SBA	Serum bactericidal antibody
SC	Subcutaneous
SOC	System Order Class
TARC	Thymus and activation-regulated chemokine
TCI	Topical calcineurin inhibitors
TCS	Topical corticosteroids
Tdap	Tetanus, diphtheria and pertussis
TEAE	Treatment-emergent adverse event
Th1	Type 1 helper T-cell
Th2	Type 2 helper T-cell
T_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal

Abbreviation	Meaning
WBC	White blood cell

1. Submission details

1.1. Identifying information

Submission number	PM-2016-04087-1-1
Sponsor	Sanofi-Aventis Pty Ltd
Trade name	Dupixent
Active substance	Dupilumab

1.2. Submission type

The submission is an application for a new chemical entity, dupilumab (Dupixent) 300 mg/2 mL; solution for injection, for subcutaneous administration.

1.3. Drug class and therapeutic indication

Dupilumab is a fully human monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture.

Dupilumab is an immunomodulating drug. Dupilumab inhibits interleukin-4 and interleukin-13 signalling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL 4Rα/γc), and both IL-4 and IL 13 signalling through the Type II receptor (IL-4Rα/IL-13Rα).

The proposed therapeutic indication is:

> *Dupixent is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.*
>
> *Dupixent can be used with or without topical therapy*

1.4. Dosage forms and strengths

- Dupixent (dupilumab) 300 mg/2 mL, solution for injection, pre-filled syringe
- Dupixent (dupilumab) 300 mg/2 mL, solution for injection, pre-filled syringe with needle.

1.5. Dosage and administration

The recommended dose of Dupilumab for adult patients is as follows:

> *Initial dose of 600 mg by subcutaneous injection (two 300 mg injections consecutively in different injection sites), followed by 300 mg given every other week.*

Dupixent (dupilumab) 300 mg/2 mL, solution for injection, is intended for subcutaneous administration.

1.6. Proposed changes to the product documentation

The Product Information is original to the present application.

2. Background

2.1. Information on the condition being treated

Atopic dermatitis (AD) is a chronic inflammatory condition of the skin. It is also known as eczema. It can occur at any age but is more common in children and may improve with age. It is characterised by dryness of the skin (xerosis), itching (pruritus) and in more severe conditions inflamed, red and weeping lesions.

The prevalence (95% CI) of atopic dermatitis in Australia is estimated to be 6.9% (5.6 to 8.3) (Plunckett, 1999). There was a similar prevalence in males compared to females: 5.7% compared to 8.1% respectively. Of atopic dermatitis in Australia, 82.8% was classified as mild, 14.6% as moderate and 2.6% as severe.

The condition has a high burden because of the itch and discomfort and is associated with sleep and mood disturbances. Broken skin is susceptible to infections, particularly with *Staphylococcus aureus* which may further exacerbate AD due to staphylococcal antigens.

Common comorbidities in patients with AD include allergic rhinitis, asthma, allergic rhinitis and food allergies. Hence, common co-medications include inhaled beta-agonists, inhaled steroids, inhaled anticholinergics, oral steroids and oral leukotriene antagonists.

In the Clinical Overview the sponsor summarises the pathophysiology of AD as:

> 'The pathophysiology of AD is influenced by genetics and environmental factors (including skin microbiome), and involves a complex interplay between antigens, skin barrier defects, and immune dysregulation, in which a polarized inflammatory response induced by the marked activation of the T helper type 2 (Th2) cell axis plays a central role (Gittler 2012). The skin lesions of AD are characterized by increased expression of pro-inflammatory Th2 cytokines, such as IL-4 and IL-13, and by skin infiltration of Th2 cells. The elevated immunoglobulin E (IgE) responses and eosinophilia observed in the majority of patients with AD reflects an increased expression of the Th2 cytokines IL-4 and IL-13 (Leung 1999). Reports of an IL-4 gene gain-of-function polymorphism being associated with an increased risk for AD further substantiate the role of this pathway in AD (Kawashima 1998). Type 2 helper T cell-associated cytokines regulate important barrier-related functions, such as epidermal cornification and production of antimicrobial proteins. These cytokines inhibit the production of major terminal differentiation proteins, such as loricrin, filaggrin, involucrin, and the antimicrobial proteins human beta defensin 2 and 3 (Howell 2007, Guttman-Yassky 2011a, and Guttman-Yassky 2011b). These proteins are involved in various aspects of epithelial function, including barrier function, and their inhibition is thought to be part of the pathophysiologic cascade that leads to the development of AD. The Th2 cytokines also act on keratinocytes and induce production of chemokines, including chemokine (C-C motif) ligand 17 (also known as thymus and activation-regulated chemokine [TARC]), and chemokine (C-C motif) ligand 26 (also known as eotaxin-3), which are chemo-attractants for Th2 cells and eosinophils; thus perpetuating the inflammatory response.'

2.2. Current treatment options

The current treatment options for atopic dermatitis are:

Topical treatments:

- Emollients
- Topical corticosteroids
- Topical calcineurin inhibitors: tacrolimus, pimecrolimus

Systemic treatments:

- Oral corticosteroids
- Ciclosporin
- Methotrexate
- Azathioprine

Adjunctive treatments:

- Antibiotics (anti-staphylococcal) are used for infected lesions
- Antivirals (acyclovir) are used for herpetic lesions
- Antihistamines for itch

Mild AD will usually be controlled with measures such as avoiding precipitants, use of emulsifying ointment instead of soap and liberal use of emollients. Occasional use of low potency topical steroids may be required. Moderate or severe AD will require the above measures plus high potency topical steroids and may require systemic treatments. All of the systemic treatments have a high risk of adverse event.

2.3. Clinical rationale

The sponsor provided the following rationale:

> *'Moderate-to-severe AD is a serious chronic inflammatory skin disease and is an under-recognized public health concern with a high disability burden. Clinical manifestations include intractable pruritus, xerosis, and extensive skin lesions, which can lead to significant psychological and sociological sequela and result in a condition that has a substantial negative impact on patients' day-to-day functioning and wellbeing.*
>
> *No currently available therapy provides complete remission or cure for affected patients. Management of AD includes patient education, optimal skin care practices, antihistamines (preferably first generation - sedating antihistamines), topical corticosteroids or approved therapies such as topical calcineurin inhibitors (e.g. tacrolimus), systemic corticosteroids, systemic calcineurin inhibitors (e.g. cyclosporine), phototherapy, and other off label treatments such as oral immune-suppressants (e.g. methotrexate and azathioprine).*
>
> *Effective therapies with an acceptable safety profile upon long-term use are currently not available to manage this serious and chronic condition. The currently available treatments for AD have important limitations including unsatisfactory effectiveness and important risks and side effects. These limitations result in a large number of patients with moderate-to-severe AD whose disease cannot be safely controlled by the existing therapies. Therefore, there exists a significant unmet medical need for a treatment that is safe and effective for long-term use.*
>
> *Dupilumab is a novel targeted immunoregulatory agent that selectively and simultaneously inhibits key disease drivers to achieve clinical benefit without the side effects commonly observed with existing nonselective systemic immunosuppressants.'*

2.4. Guidance

The following regulatory guidance applies to the present application:

- Note for guidance on population exposure: the extent of population exposure to assess clinical safety (CPMP/ICH/375/95).
- Committee for Medicinal Products for Human Use (CHMP) Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. EMA/CHMP/BMWP/86289/2010 (24 May 2012)

2.5. Evaluator's commentary on the background information

The sponsor has provided adequate rationale for the development of Dupixent (dupilumab). However, the sponsor has not provided adequate rationale for not performing comparator controlled studies. The sponsor acknowledges that systemic treatments are available for moderate to severe AD but dismisses these treatments because of their adverse effect profile without addressing their comparative efficacy and/or safety to dupilumab.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The development program for Dupixent in AD comprises:

- Six Phase I clinical pharmacology studies in healthy subjects
- Two Phase I clinical pharmacology studies in patients with AD
- Five Phase II studies in patients with AD
- Three Phase III efficacy and safety trials in patients with AD (pivotal)
- One Phase III long term safety (follow-on) study

The sponsor has provided four studies that were conducted in patient populations other that AD:

- Two Phase II studies in patients with asthma
- One long term follow-on study in patients with asthma
- One Phase II study in patients with nasal polyposis and sinusitis

The sponsors also provided evidence that the assays used in the development program had satisfactory performances and were suitable. The studies provided in support of the assays were:

- Study REGN668-AV-13074-VA-01V1: A validation study for an assay for functional dupilumab
- Study REGN668-AV-09095-VA-01V2: A validation study for an assay for functional dupilumab
- Study REG668-AV-09106-VA-01V2: A non-quantitative titre-based bridging immunoassay for anti-dupilumab antibodies read on a Meso Scale Discovery instrument
- Study REGN668-AV13112-VA-01V1: A validation study for a competitive ligand binding assay for detection of neutralising anti-dupilumab antibodies in human serum

- Study REG668-AV-13089-VA-01V2: A non-quantitative titre-based bridging immunoassay for anti-dupilumab antibodies read on a Meso Scale Discovery instrument; validated in patients with atopic dermatitis and asthma
- Study REG668-MX-15116-SR-01V1: was a study for screening and titre cut point determination for a dupilumab anti-drug antibody (ADA) assay (SOP PCL3400) using baseline serum samples from the atopic dermatitis (AD) study population
- Study AAV-LOR13577-PCL3400-R1: was an automated assay to perform the screening procedure developed in Study REG668-AV-13089-VA-01V2
- Study AAV-LOR13577-PCL3400-R2: was an automated assay to perform the confirmatory procedure developed in Study REG668-AV-13089-VA-01V2
- Study AAV-LOR13844-PCL3277-R1: was an automated assay for the analytical procedures described in Study REGN668-AV-13074-VA-01V1. Precision and accuracy were within acceptable limits

3.2. Paediatric data

No paediatric data are included in the submission.

The sponsor has an agreed Paediatric Investigation Plan for Europe.

In the US the sponsor has a partial waiver for the age groups preterm neonate to 5 months old. The sponsor has requested a deferral for all paediatric studies as they will not be completed at the time of the initial marketing application submission.

The following studies in children have been commenced and are ongoing:

- AD-1412: a Phase I study to evaluate the pharmacokinetics (PK), safety and preliminary efficacy of dupilumab in children 6-17 years of age with AD
- AD-1434: open label extension study in paediatric patients with AD.

3.3. Good clinical practice

The studies were stated to have been conducted according to, and appear to have adhered to, Good Clinical Practice.

3.4. Evaluator's commentary on the clinical dossier

The clinical dossier contains studies that support PK, PD, efficacy and safety in monotherapy and efficacy and safety in combination with topical corticosteroids (TCS). The dossier does not contain comparator controlled studies or studies in combination with topical calcineurin inhibitors (TCI) and/or other systemic treatments.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

The submitted pharmacokinetic (PK) studies are summarised in Table 1. There were no studies excluded from consideration.

Table 1: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	Study R668-AS-0907	*
		Study R668-HV-1108	*
		Study TDU12265	*
	Bioequivalence † - Single dose	Study PKM12350	*
		Study PKM14161	*
		Study PKM14271	*
PK in special populations	Target population § - Multi dose	Study R668-AD-0914	*
		Study R668-AD-1026	*
Population PK analyses	Target population §	Study REGN668-MX-16103	

* Indicates the primary PK aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

4.2. Summary of pharmacokinetics

4.2.1. Physicochemical characteristics of the active substance

Dupilumab is a fully human monoclonal antibody and is therefore a polypeptide. Dupixent is a covalent heterotetramer consisting of two disulphide-linked human heavy chains, each covalently linked through a disulphide bond to a human kappa light chain. There is a single N-linked glycosylation site in each heavy chain, located within the CH2 domain of the Fc constant region of the molecule. The Dupixent heavy chain has an immunoglobulin (Ig) $G4^P$ isotype constant region. $IgG4^P$ is an IgG4 constant region with a single amino acid substitution in the hinge region that recreates the IgG1 hinge sequence in order to stabilize IgG4 dimer formation. The variable domains of the heavy and light chains combine to form the IL-4Rα binding site within the antibody. Dupilumab has a molecular weight of approximately 147 kDa.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanism of absorption

Dupilumab is administered and absorbed from subcutaneous injection.

4.2.2.2. Bioavailability

Absolute bioavailability

Absolute bioavailability was determined in population PK studies as 64%.

Bioavailability relative to an oral solution or micronised suspension

Not applicable.

Bioequivalence of clinical trial and market formulations

In Study PKM12350 the bioavailability of two manufacturing processes and cell lines was compared: C2P1 and C1P2 (reference drug product); at a dose of 300 mg administered as a single subcutaneous injection in the left upper quadrant of the abdomen. The pharmacokinetic parameters for the two formulations were similar but not bioequivalent. Mean (SD) terminal half-life for the reference formulation was 131 (47.4) hours. The ratio (90% CI) C2P1/C1P2 for C_{max} was 1.10 (0.89 to 1.35), for AUC_{last} was 0.90 (0.71 to 1.16) and for AUC was 1.05 (0.86 to 1.29).

In Study PKM14161 the comparative bioequivalence study of two drug products (DP) of dupilumab was determined: DP1 (reference) and DP2 (test) administered as a 300 mg single dose by subcutaneous injection in the abdomen prior to breakfast. The PK parameters for the two treatments were similar, but the sample size was insufficient to demonstrate bioequivalence. The ratio (90% CI) DP2/DP1 for C_{max} was 0.96 (0.74 to 1.25) and for AUC_{last} was 0.98 (0.71 to 1.37) and for AUC was 1.05 (0.86 to 1.29).

In Study PKM14271 the comparative bioequivalence of two formulations of dupilumab was determined. Each treatment was administered as a 200 mg dose by subcutaneous injection. The PK parameters for the two treatments were similar, but the sample size was insufficient to demonstrate bioequivalence. The ratio (90% CI) DP2/DP1 for C_{max} was 1.03 (0.83 to 1.27) and for AUC_{last} was 1.06 (0.83 to 1.35).

Bioequivalence of different dosage forms and strengths

Not applicable.

Bioequivalence to relevant registered products

Not applicable.

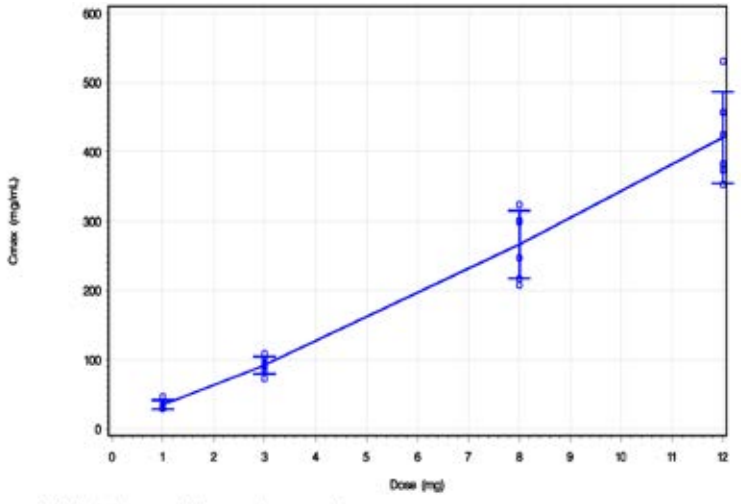
Influence of food

Not applicable.

Dose proportionality

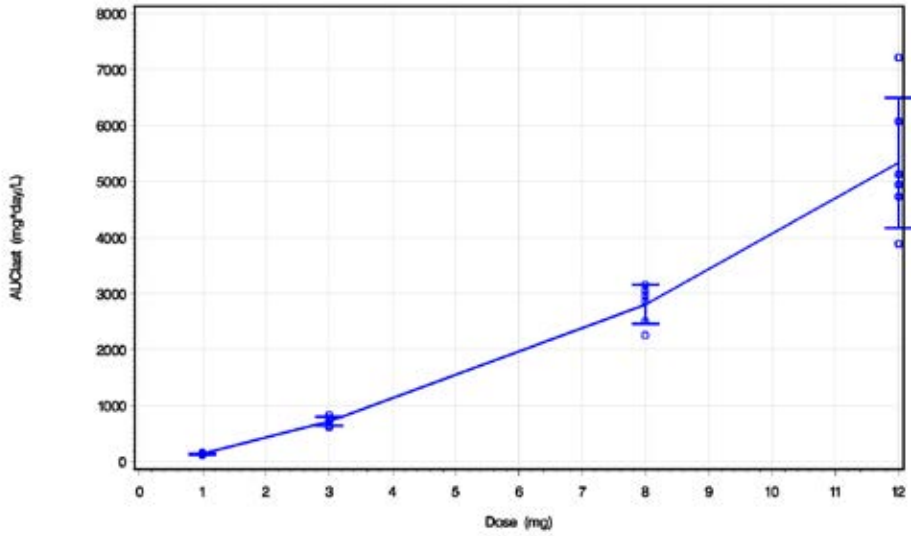
In Study R668-AS-0907 C_{max} was dose proportional in the range 1 to 12 mg/kg (Figure 1). AUC_{last} was greater than dose proportional (Figure 2). At the 300 mg SC dose level, mean (SD) C_{max}, was 32.4 (10.1) mg/L, AUC_{last} was 594 (190) day•mg/L, t_{max} was 5.69 (4.55) days and MRT_{last} was 12.6 (2.84) days.

Figure 1: Individual and Mean (SD) C_{max} versus Dose



Notes: One standard deviation around the mean is presented.

Figure 2: Individual and Mean (SD) AUC_{last} versus dose



Notes: One standard deviation around the mean is presented.

In Study TDU12265 in the dose range 75 to 600 mg, AUC was greater than dose proportional (Table 2). However C_{max} increased proportional to dose. CL/F decreased with increasing dose, and half-life increased. MRT increased with dose, and was 14.3 days at the 300 mg dose level.

In Study R668-AD-0914 in the dose range 75 to 300 mg, following multiple dosing (four doses, one week intervals), C_{max} was greater than dose proportional (see Table 3).

In Study R668-AD-1026 C_{max} was greater than dose proportional (see Table 4).

Table 2: Mean ± SD (geometric mean) [CV%] of serum functional SAR231893 PK parameters

	Serum functional SAR231893			
PK parameters	SAR231893 75mg	SAR231893 150mg	SAR231893 300mg	SAR231893 600mg
N	6	6	6	6
C_{max}	5.33 ± 1.50	10.4 ± 2.95	38.3 ± 15.3	70.1 ± 24.1
(mg/L)	(5.09) [28.2]	(10.1) [28.2]	(36.1) [40.1]	(66.8) [34.4]
C_{max}/Dose	0.0711 ± 0.0200	0.0696 ± 0.0197	0.128 ± 0.0512	0.117 ± 0.0402
(1/L)	(0.0679) [28.2]	(0.0672) [28.2]	(0.120) [40.1]	(0.111) [34.4]
t_{max}[a]	7.01	7.01	7.01	7.00
(day)	(3.00 - 7.03)	(3.00 - 7.03)	(6.99 - 10.00)	(3.00 - 7.02)
t_{last}[a]	17.02	24.03	42.00	52.51
(day)	(14.01 - 21.05)	(21.01 - 24.04)	(35.00 - 42.02)	(42.00 - 56.02)
AUC_{last}	59.2 ± 20.8	150 ± 41.3	700 ± 234	1780 ± 699
(mg•day/L)	(55.2) [35.2]	(146) [27.5]	(667) [33.5]	(1680) [39.3]
AUC_{last}/Dose	0.789 ± 0.278	0.999 ± 0.275	2.33 ± 0.782	2.96 ± 1.17
(day/L)	(0.736) [35.2]	(0.971) [27.5]	(2.22) [33.5]	(2.80) [39.3]
AUC	72.4 ± 10.6 [b]	155 ± 41.6	709 ± 231	1870 ± 852
(mg•day/L)	(71.9) [14.6]	(151) [26.8]	(677) [32.6]	(1740) [45.5]
V_{ss}/F	7.96 ± 0.673 [b]	10.7 ± 3.04	6.67 ± 2.34	6.60 ± 1.78
(L)	(7.94) [8.5]	(10.3) [28.4]	(6.32) [35.1]	(6.41) [26.9]
CL/F	1.05 ± 0.144 [b]	1.02 ± 0.238	0.464 ± 0.155	0.366 ± 0.126
(L/day)	(1.04) [13.7]	(0.993) [23.4]	(0.443) [33.5]	(0.344) [34.4]
$t_{1/2z}$	2.77 ± 0.567 [b]	3.18 ± 0.805	5.13 ± 1.42	8.77 ± 5.18
(day)	(2.73) [20.5]	(3.11) [25.3]	(4.96) [27.7]	(7.66) [59.1]
MRT	7.63 ± 0.624 [b]	10.5 ± 1.66	14.3 ± 0.801	19.2 ± 4.89
(day)	(7.61) [8.2]	(10.4) [15.8]	(14.3) [5.6]	(18.6) [25.5]

[a] Median (Min - Max), [b] N = 4 since terminal log-linear phase could not be determined in 2 subjects

Table 3: Summary of descriptive analysis of functional dupilumab and duration of exposures following 4 SC doses at 75 mg, 150 mg, or 300 mg of dupilumab, once weekly

Dose (mg)	Parameter (Unit)	N	Mean	SD	SE	CV%	Min	Median	Max	Range
75	C_{max} (mg/L)	8	11.4	8.86	3.13	77.7	3.42	8.57	29.1	25.7
	C_{last} (mg/L)	8	0.989	0.644	0.228	65.1	0.288	0.904	2.01	1.72
	t_{last} (day)	8	35.5	8.74	3.09	24.6	28.0	32.5	49.2	21.2
150	C_{max} (mg/L)	8	26.6	16.0	5.67	60.2	7.19	25.1	53.9	46.7
	C_{last} (mg/L)	8	4.10	6.67	2.36	163	0.104	1.70	20.2	20.1
	t_{last} (day)	8	40.6	14.4	5.10	35.6	22.0	38.5	63.0	41.0
300	C_{max} (mg/L)	8	94.8	11.1	3.91	11.7	82.2	91.6	112	29.8
	C_{last} (mg/L)	8	5.07	4.40	1.56	86.8	1.59	3.21	13.0	11.4
	t_{last} (day)	8	70.2	13.4	4.75	19.1	50.1	70.0	91.0	40.9

C_{last} = last measureable concentration; C_{max} = maximum concentration following the fourth (last) dose; CV = coefficient of variation; Max = Maximum; Min = Minimum; SD = standard deviation; SE = standard error; t_{last} = time of last measureable concentration in actual days ([actual date] = [date/time of event] – [date/time of the first dose])

Table 4: Summary of functional REGN668 drug concentrations and duration of exposures following 4 weekly 150 mg or 300 mg SC doses of REGN668

Dose (mg)	Parameter (Unit)	N	Mean	SD	SE	CV%	Min	Median	Max	Range
150	C_{max} (mg/L)[a]	12	39.2	16.1	4.64	41.1	5.63	47.1	53.2	47.6
	C_{last} (mg/L)	12	2.55	1.55	0.449	60.9	0.182	2.51	4.89	4.71
	t_{last} (day)[b]	12	53.5	13.7	3.96	25.6	27.8	55.0	70.0	42.2
300	C_{max} (mg/L)[a]	13	102	44.7	12.4	43.7	41.8	101	182	140
	C_{last} (mg/L)	13	7.80	9.72	2.70	125	1.68	3.57	32.7	31.0
	t_{last} (day)[b]	13	74.3	13.1	3.62	17.6	49.0	78.2	87.1	38.1

CV = coefficient of variation; SD = standard deviation; SE = standard error
a Maximum concentration of functional REGN668 following the fourth (last) dose.
b t_{last} = Mean time of last measurable concentration in actual days.

Bioavailability during multiple-dosing

Absolute bioavailability was determined in population PK studies as 64%.

Effect of administration timing

In Study R668-HV-1108 the PK parameters were similar for the fast and slow administrations (Table 5). However one subject in the slow infusion group had an unexpectedly low AUC_{last}.

Table 5: Summary of Non-Compartmental Pharmacokinetic Parameters and Descriptive Statistics of Functional REGN668 Following a Single 300 mg SC Dose Administered at 2 Different Rates to Subjects (Study R668-HV-1108)

Dose / Parameter / Units			n	Mean	SD	SE	CV%	Min	Median	Max
300 mg SC / Fast Injection	AUC_{last}	mg*Day/L	18	630	223	52.6	35.4	281	617	1003
	C_{max}	mg/L	18	34.4	10.3	2.43	29.9	19.8	33.7	58.5
	t_{max}	Days	18	6.25	4.42	1.04	70.6	2.95	4.97	20.0
	C_{last}	mg/L	18	2.65	1.56	0.367	58.8	0.283	2.48	5.30
	t_{last}	Days	18	34.9	9.42	2.22	27.0	21.0	34.5	49.0
300 mg SC / Slow Injection	AUC_{last}	mg*Day/L	18	530	233	55.0	44.0	31.4	607	795
	C_{max}	mg/L	18	35.0	14.3	3.37	40.9	7.59	35.5	55.9
	t_{max}	Days	18	5.19	2.08	0.491	40.2	2.90	6.91	7.23
	C_{last}	mg/L	18	4.62	6.23	1.47	135	0.0947	1.98	22.6
	t_{last}	Days	18	30.1	9.67	2.28	32.2	2.92	28.6	42.0

AUC = Total area under the serum drug concentration-time curve; C_{last} = Last measured serum drug concentration; C_{max} = Maximum serum drug concentration; CV = Coefficient of variation; Max = Maximum; Min = Minimum; n = Number of subjects; SD = Standard deviation; SE = Standard error; t_{last} = Time of last measurable serum drug concentration; t_{max} = Time after drug administration when maximum serum concentration is reached

4.2.2.3. Distribution

Volume of distribution

The population PK model estimated a central volume of distribution of 2.74 L and a peripheral volume of distribution of 1.86 L. Overall volume of distribution was 4.6 L (Study REGN668-MX-16103). Volume of distribution increased with body weight, and decreased with plasma albumin.

Plasma protein binding

The decrease in volume of distribution with increased plasma albumin most likely reflects displacement rather than binding.

Erythrocyte distribution

The dupilumab volume of distribution reflects the vascular compartment and there appears to be little erythrocyte distribution.

Tissue distribution

The dupilumab volume of distribution reflects the vascular compartment and there appears to be little tissue distribution.

4.2.2.4. Metabolism

Metabolism is thought to be by catabolism with recycling of individual amino acids.

4.2.2.5. Excretion

Routes and mechanisms of excretion

Clearance of dupilumab is presumed to be catabolism, in the same manner as similar monoclonal antibody drugs. The population PK modelling found the best fit for a combined, or parallel, linear and non-linear model for elimination. This is supported by AUC increasing more than proportional to dose. Elimination also increased with EASI score in the population PK model. The effect of ADA on elimination was also clinically significant: increase with a 17.8% increase in elimination rate constant

Mass balance studies

Not performed.

Renal clearance

Not applicable

4.2.2.6. Intra and inter individual variability of pharmacokinetics

In Study R688-AS-0907 at the 300 mg SC dose level the inter-individual variability, expressed as CV% for C_{max} was 31.1%, AUC_{last} was 32.1%, t_{max} was 80.0% and MRT_{last} was 22.5%.

In Study R668-HV-1108 for the fast injection group, the CV% for AUC_{all} was 35.4%, C_{max} was 29.9%, C_{last} was 58.8%, t_{last} was 27.0% and t_{max} was 70.6%.

4.2.3. Pharmacokinetics in the target population

The target population was studied in the population PK studies. These are discussed in Section 4.2.5.

4.2.4. Pharmacokinetics in special populations

4.2.4.1. Pharmacokinetics in subjects with impaired hepatic function

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of dupilumab.

4.2.4.2. Pharmacokinetics in subjects with impaired renal function

No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of dupilumab.

4.2.4.3. Pharmacokinetics according to age

Age did not significantly influence PK in the population PK studies, but there were few older patients in these studies.

4.2.4.4. Pharmacokinetics related to genetic factors

No clinical studies have been conducted to evaluate the effect of genetic factors on the pharmacokinetics of dupilumab.

4.2.4.5. Pharmacokinetics in other special population / with other population characteristic

No clinical studies have been completed in the paediatric or other special populations.

4.2.5. Population pharmacokinetics

4.2.5.1. PopPK analysis REGN668-MX-16103

In the population pharmacokinetic Study REGN668-MX-16103, the sponsor investigated the effects on PK of ADA and found a 17.8% increase in k_e. This translates to a 17.8% increase in clearance.

An increase in EASI score was associated with an increase in clearance. Volume of distribution decreased with increasing albumin concentrations. Dupilumab distribution was best described by a two compartment model, but the magnitudes of the two volumes of distribution were consistent with circulating blood volume and interstitial fluid.

4.2.6. Pharmacokinetic interactions

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied.

Interactions with other immunomodulatory agents have not been studied.

4.2.7. Clinical implications of *in vitro* findings

No clinical implications of in-vitro findings were apparent.

4.3. Evaluator's overall conclusions on pharmacokinetics

The basic pharmacokinetics of dupilumab have been adequately described by the sponsor in the Product Information document and have been adequately characterised. However, the sponsor has made the assumption that the elimination of dupilumab will be identical to that for other monoclonal antibody drugs. The sponsor has not confirmed this in mass balance studies.

The sponsor has studied the effect of ADA on PK. The effect of ADA on elimination was clinically significant and resulted in an increase of 17.8% in elimination rate constant. Greater disease severity, as measured by EASI score, also contributed to an increase in clearance.

Interactions between dupilumab and other immunomodulatory drugs have not been studied. Hence, combinations of these drugs should be contraindicated.

Dupilumab has the potential to be used extensively in the paediatric population. The PK in this population will need to be carefully characterised. Effects on vaccines will need further investigation.

There were few older patients in the PK studies. The effects of aging on the PK of dupilumab have not been adequately characterised.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Table 6: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on IgE and TARC	Study TDU12265	
		Study R668-AD-0914	

PD Topic	Subtopic	Study ID	*
		Study R668-AD-1026	
		Study R668-AD-1307	
Secondary Pharmacology	Effect on immune response	Study R668-AD-1314	
Population PD and PK-PD analyses	Target population	Study REGN668-MX-1602	

* Indicates the primary PD aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

There were no pharmacodynamic studies excluded from consideration.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Dupilumab inhibits interleukin-4 and interleukin-13 signalling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα).

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The sponsor examined effects of dupilumab on biomarkers of atopic disease including IgE, TARC and eosinophil count.

In Study TDU12265 in the dose range 75 to 600 mg there was no treatment effect on IgE concentrations. There were no apparent changes relative to placebo in the treatment groups (Figure 3). There was a decrease in TARC over time in the 300 and 600 mg treatment groups, but not in the 75 or 150 mg, with a more sustained decrease in the 300 mg group (Figure 4).

Figure 3: Summary plot of total IgE percent change from baseline from Day 1 to EOS – PD

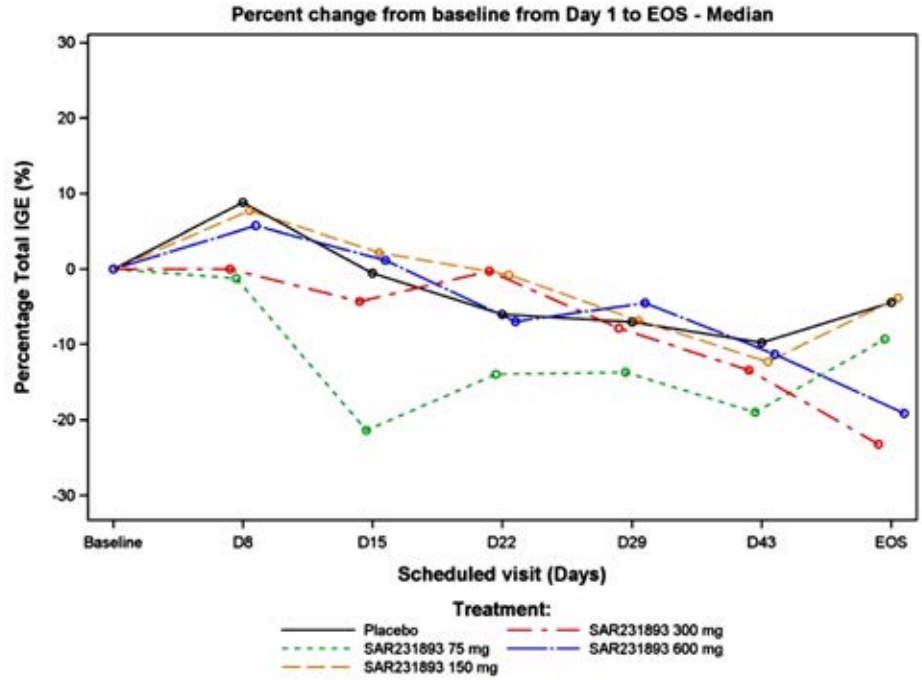
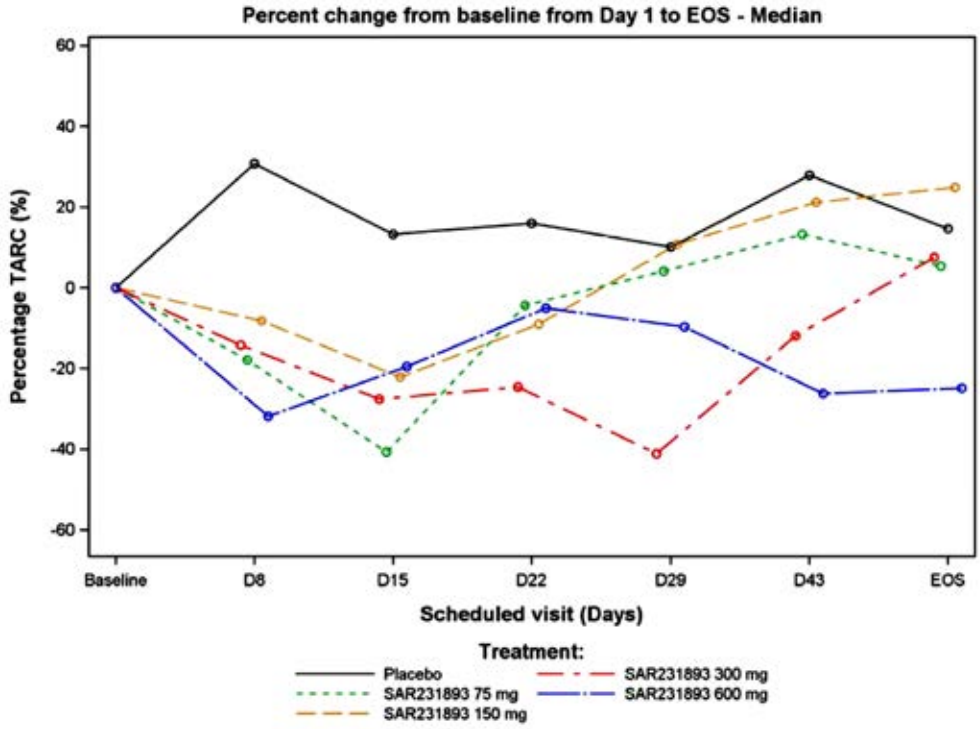


Figure 4: Summary plot TARC percent change from baseline from Day 1 to EOS - PD population



In Study R668-AD-0914 baseline measures of eosinophils, TARC, eotaxin-3 and total IgE did not correlate with treatment response. Total serum IgE decreased from baseline to a similar extent in the 150 and 300 mg groups but not in the 75 mg group (Figure 5). The decrease in TARC was dose dependent and greatest at the 300 mg dose level (Figure 6). Eosinophil count and eotaxin-3 concentrations did not correlate with treatment effect.

Figure 5: Total Serum IgE: Median Percent Change

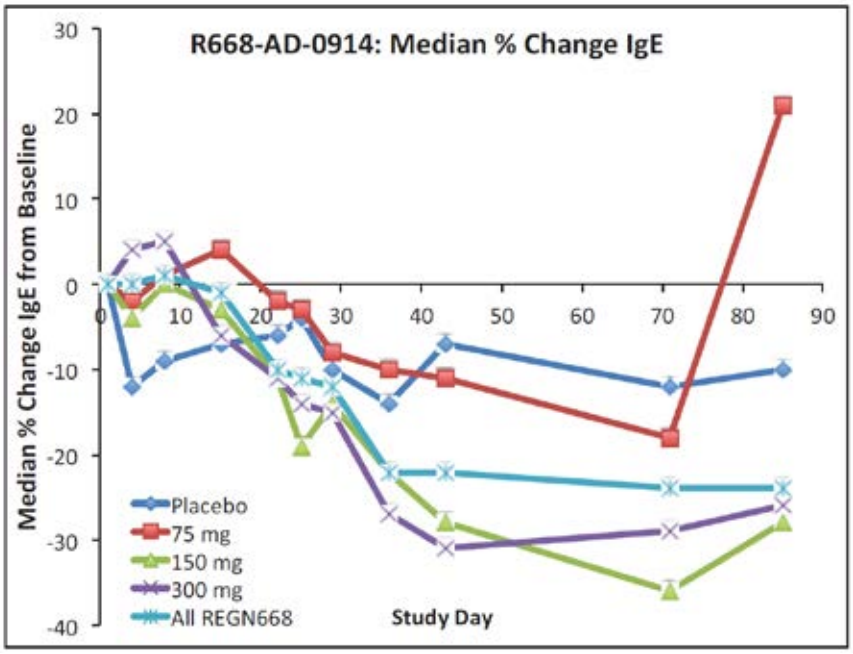
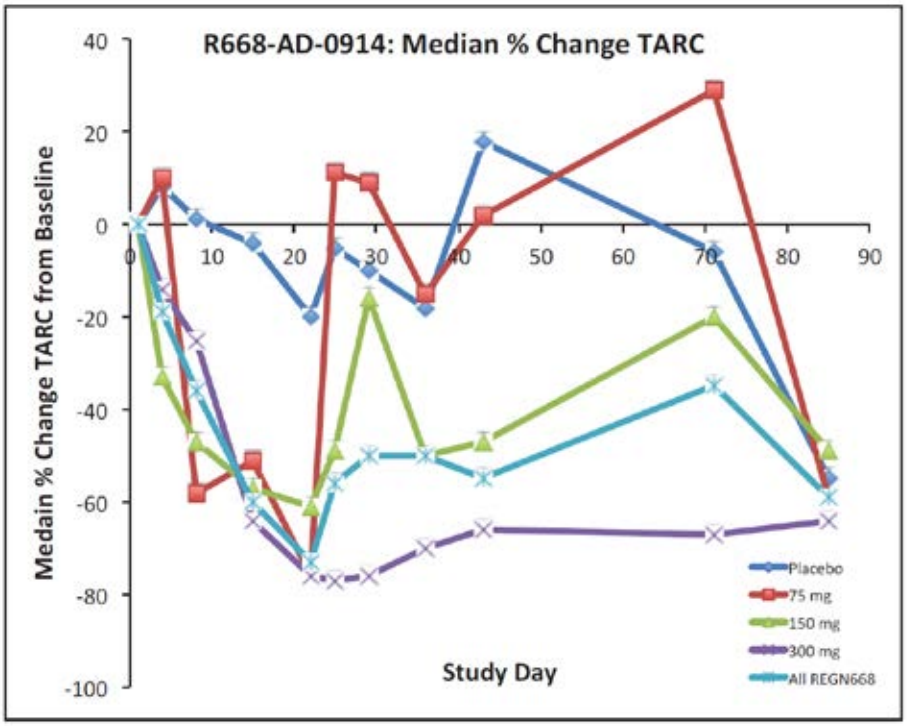


Figure 6: TARC: Median Percent Change



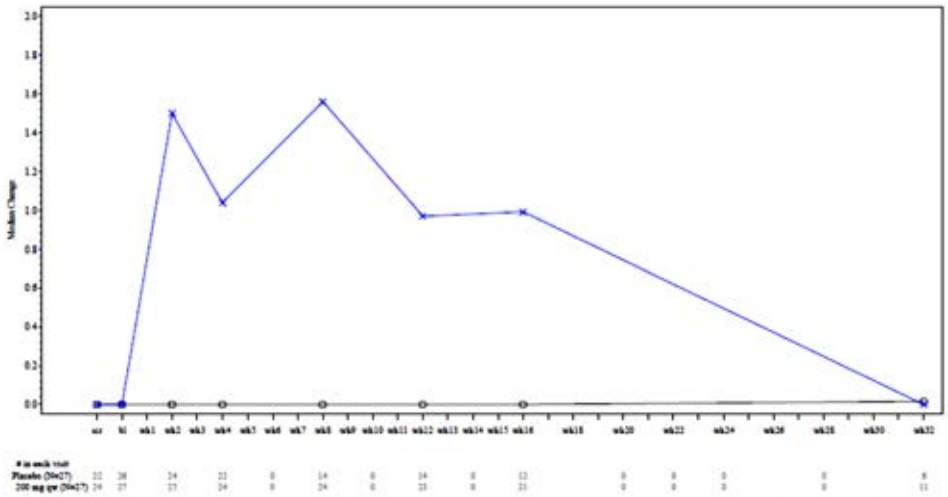
TARC levels were suppressed by dupilumab treatment. A trend for dose response was observed, with duration of suppression being longer with higher doses (150 mg and 300 mg)

In Study R668-AD-1026 which examined the 150 and 300 mg dose levels, at Day 29 peripheral eosinophils had changed by -29.9% in the 150 mg group, -34.6% in the 300 mg group and 13.1% in the placebo. At Day 29 TARC had changed by -79.9% in the 150 mg group, -70.9% in the 300 mg group and -22.7% in the placebo. Eotaxin-3 concentrations were below the lower limit of quantification for 74% of samples. At Day 29 there was little change in Total IgE but at Day 85 IgE changed by -16.8% in the 150 mg group, -23.9% in the 300 mg group and 41.7% in the placebo. Higher IgE, TARC and eosinophil measures at baseline correlated with greater

improvement in EASI score ($p < 0.05$). There was no association between Phadiatop and response.

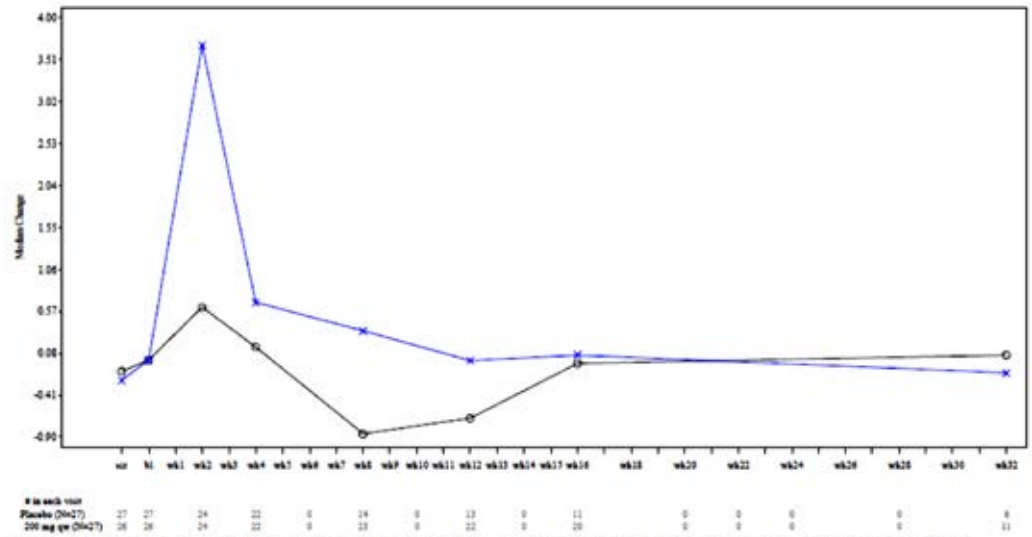
In Study R668-AD-1307 using a 200 mg weekly dose, for a 16 week treatment period, there were increases in IL-4 and IL-13 and decreases in TARC, periostin, PARC and IgE. Serum IL-4 concentrations increased in the dupilumab group during treatment and returned to baseline by 16 weeks after treatment (Figure 7). Serum IL-13 concentrations increased early in treatment but returned to baseline by Week 12 (Figure 8). Serum TARC decreased with treatment and remained decreased through to Week 32 (Figure 9). Serum periostin decreased relative from placebo from baseline through to Week 32 (Figure 10). Serum PARC decreased relative to placebo from baseline through to Week 32 (Figure 11). Eosinophil counts were similar for the two treatment groups. Total IgE decreased by 60% in the dupilumab group but remained the same in the placebo (Figure 12). There was a 60% decrease in Alder-Grey IgE in the dupilumab group (Figure 13). Neither baseline TARC nor total IgE correlated with EASI response. IgA, IgG subclasses and IgM did not change with treatment. Changes in skin permeability did not reflect treatment group. There were no apparent treatment effects on ANA. There were no significant changes in epidermal thickness compared to placebo.

Figure 7: Median Absolute Change (pg/mL) in Serum IL-4- SAF



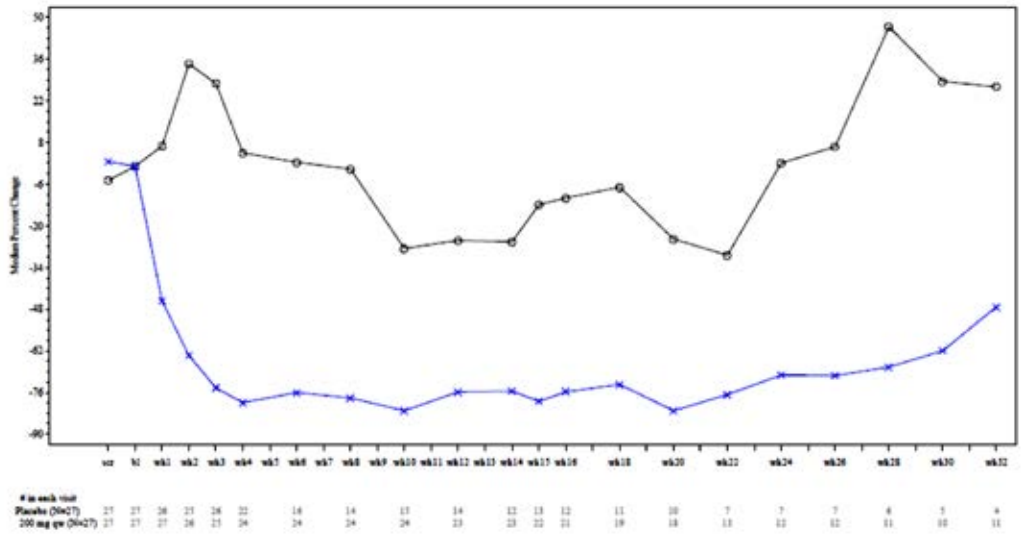
*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median changes from baseline in pg/mL are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 8: Median Absolute Change (pg/mL) in Serum IL-13- SAF



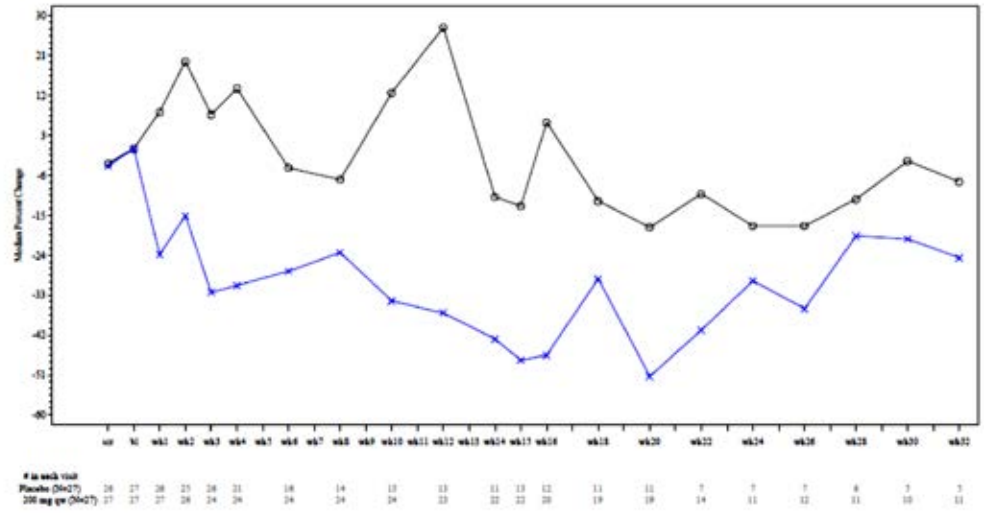
*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median changes from baseline in pg/mL are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 9: Median Percentage Change in Serum TARC-SAF



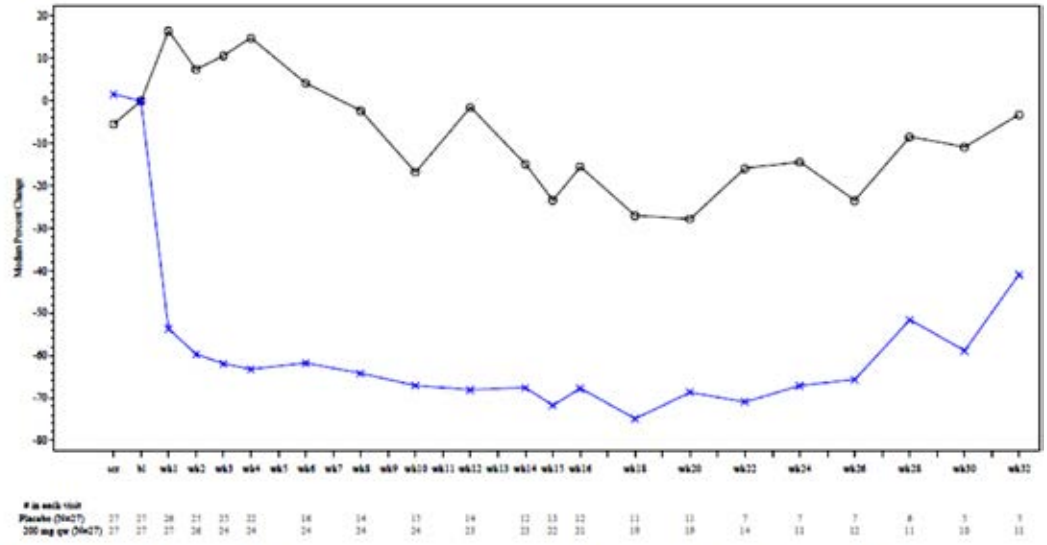
*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median percentage changes from baseline are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 10: Median Percentage Change in Serum Periostin- SAF



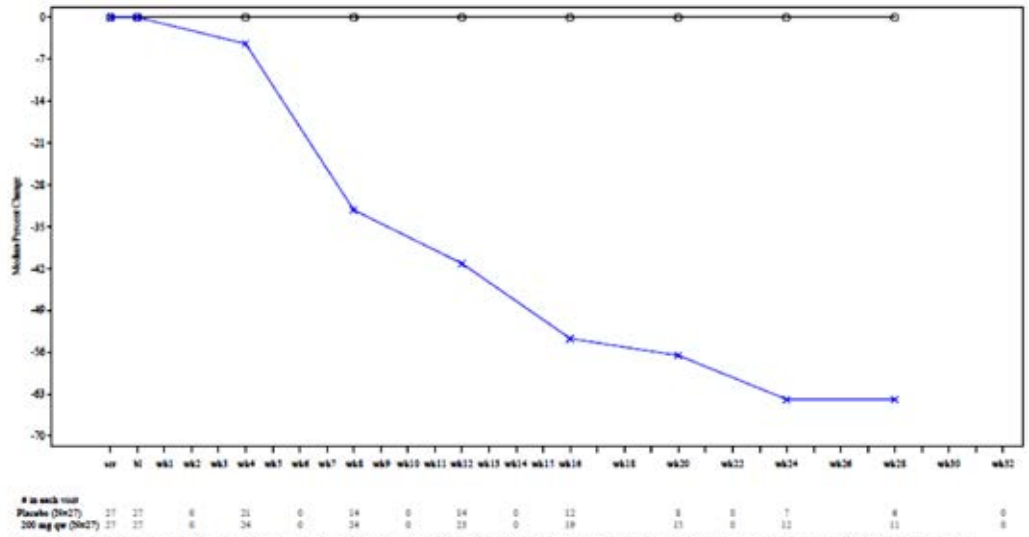
*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median percentage changes from baseline are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 11: Median Percentage Change in Serum PARC-SAF



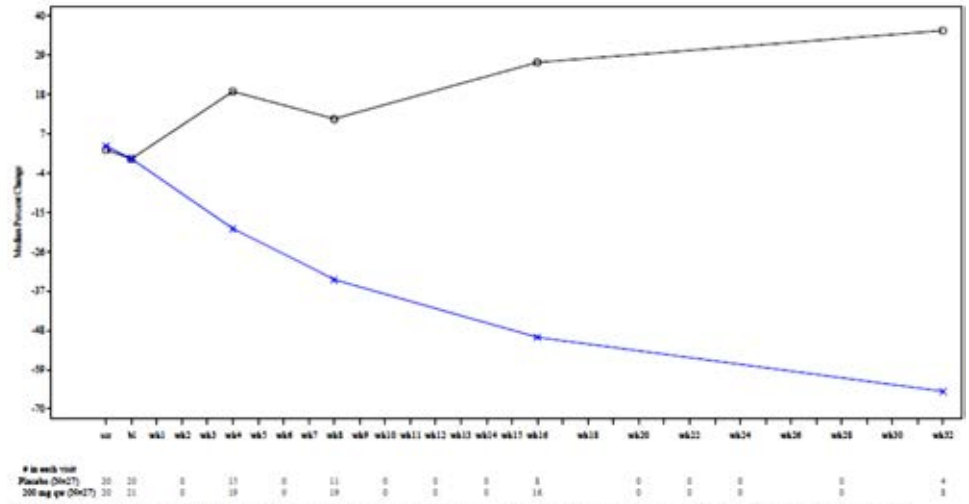
*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median percentage changes from baseline are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 12: Median Percentage Change Total IgE- SAF



*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median percentage changes from baseline are shown for the dupilumab group (blue line) and the placebo group (black line).

Figure 13: Median Percentage Change Alder Grey IgE- SAF



*Data were from the SAF, with values set to missing after first rescue medication use and no imputation of missing values
Median percentage changes from baseline are shown for the dupilumab group (blue line) and the placebo group (black line).

5.2.2.2. Secondary pharmacodynamic effects

In Study R668-AD-1314, a study of immunological response to vaccination, dupilumab did not have a significant effect on immunological response. The number (%) patients with a positive response (≥4 fold increase) to tetanus toxoid was 77 (83.7%) in the placebo group and 75 (83.3%) in the dupilumab, mean (95% CI) difference, dupilumab – placebo, -0.4 (-9.41 to 8.69) %. The mean (SD) % change from baseline was 3260.24 (6944.193) for the placebo group and 3159.89 (9230.999) for the dupilumab. The proportion of patients with a positive response (≥2 fold increase) at Week 16 in anti-tetanus IgG was 87 (94.6%) in the placebo group and 86 (95.6%) in the dupilumab, mean (95% CI) difference, dupilumab – placebo, 1.0 (-4.29 to 6.27) %. The proportion of patients with Menomune (immunity to *meningococci*) response (n SBA titre of ≥8 for serogroup C) was 80 (87.0%) in the placebo group and 78 (86.7%) in the dupilumab, mean (95% CI) difference, dupilumab – placebo, -0.3 (-8.54 to 7.96) %. The mean (SD) % change from baseline was 102655.978 (174936.5665) for the placebo group and 82503.371 (149051.9894) for the dupilumab, There was a significant decrease in IgE in the dupilumab group relative to placebo, but no significant change in IgA, IgG or IgM.

5.2.3. Time course of pharmacodynamic effects

In Study REGN668-MX-1602 maximum EASI response was at Day 84, maintained to Day 112 and was similar for 300 mg once weekly (QW) and fortnightly (Q2W) (Figure 14). The maximum response was an 80% reduction in EASI. Improvement in IGA increased over time up to the 112 day point (Figure 15). The once weekly and fortnightly regimens had similar response. The response plateaued at Day 140, with approximately 50% of patients achieving IGA of 0 or 1 with both regimens (Figure 16). There was improvement in pruritus to Day 84 that was similar for both treatment regimens (Figure 17).

Figure 14: Mean (±SE) Percent Change from Baseline in EASI versus Time by Dupilumab Dose Regimen or Placebo in Phase 3 Mono-therapy Studies (Studies R668-AD-1334 [SOLO 1] and R668-AD-1416 [SOLO 2

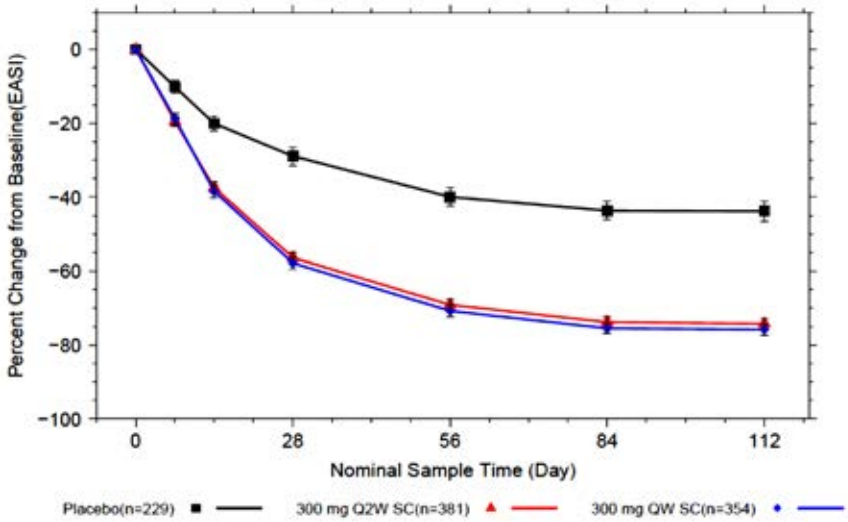


Figure 15: Proportion of AD Patients Achieving IGA 0-1 versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1334 and R668-AD-1416; SOLO studies)

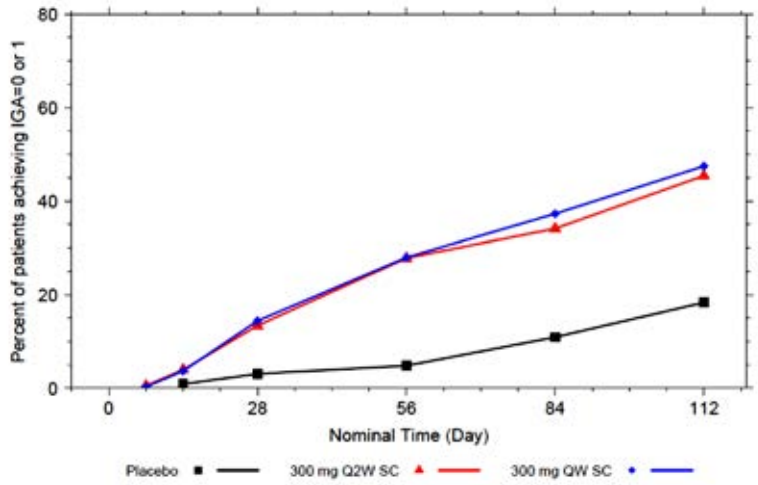


Figure 16: Proportion of AD Patients achieving IGA 0-1 versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1224: LTT study)

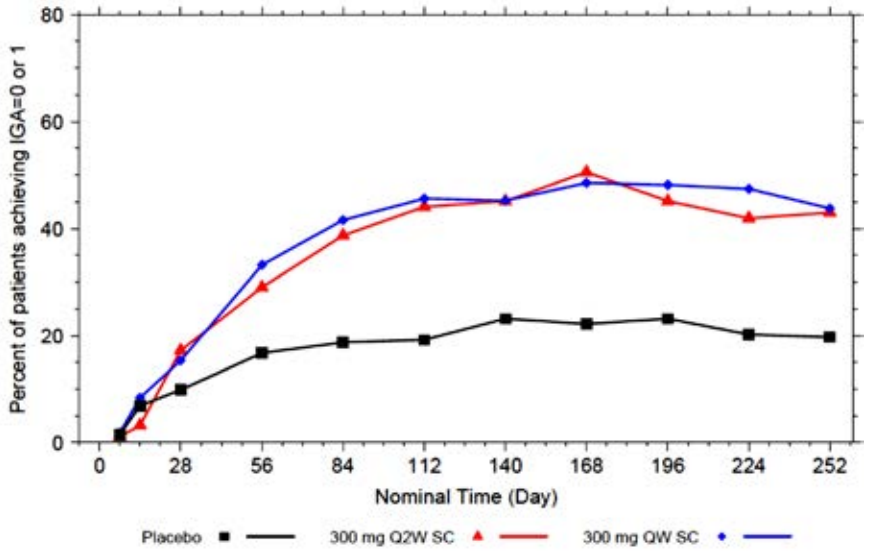
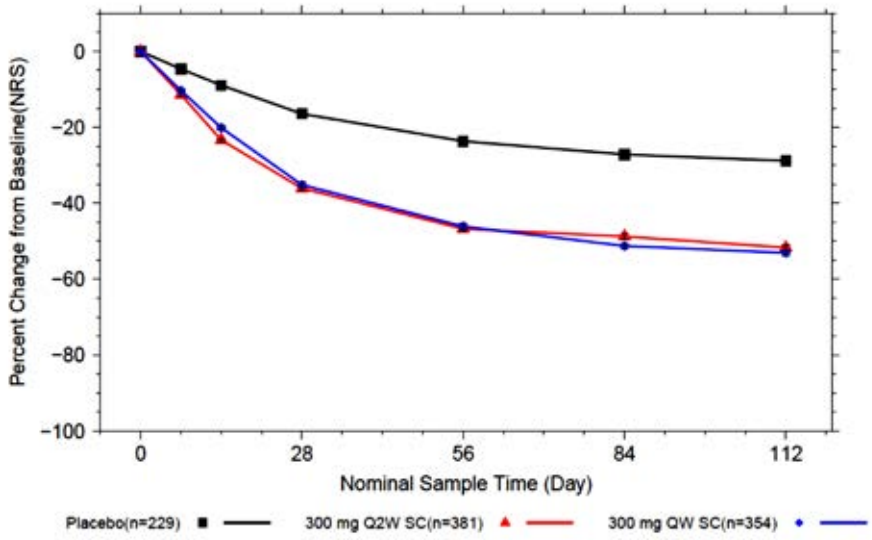


Figure 17: Mean (±SE) Percent Change from Baseline in Peak Pruritus NRS versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1334 and R668-AD-1416; SOLO studies)



5.2.4. Relationship between drug concentration and pharmacodynamic effects

Study REGN668-MX-1602 described the relationship between C_{trough} and EASI using an E_{max} model. Although ADA had an effect on the PK of dupilumab, there was no clinically significant effect on pharmacodynamics.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

In Study REGN668-MX-1602 for all of the outcome variables, patients with lower body weight had better response. However, exposure (C_{trough}) had a greater influence on outcome than weight (Table 7). The population PKPD model was not able to estimate inter-individual variability for the PD parameters because there was only one observation per patient. Body weight was the only significant covariate on response (Table 8).

Table 7: Inter-Quartile Comparison by Day 112 Dupilumab C_{trough} Concentrations and Body Weight on Selected Efficacy Response Variables (R668-AD-1334 and R668-AD-1416; SOLO studies)

Quartile	EASI (% change from baseline)		IGA 0-1 (Proportion of patients)		NRS (% change from baseline)	
	Quartile by body weight	Quartile by exposure	Quartile by body weight	Quartile by exposure	Quartile by body weight	Quartile by exposure
Q1	-76.2%	-69.5%	51.9%	37.1%	-54.3%	-49.4%
Q2	-76.4%	-73.1%	48.0%	45.5%	-52.2%	-52.4%
Q3	-76.5%	-78.2%	48.6%	51.1%	-53.3%	-53.6%
Q4	-70.7%	-80.6%	39.8%	56.6%	-49.6%	-54.1%
Q4-Q1	-5.5%	-11.1%	12.1%	19.5%	-4.7%	-4.7%
Q3-Q1	-0.3%	-8.7%	3.3%	14.0%	-1.0%	-4.2%

Table 8: The Final Model Parameter Estimates

Parameters	Estimate (Trough Conc)	%RSE	95% CI	Estimate (AUC_{0-112})	%RSE	95% CI
THETA						
GAMMA	1	---	---	1	---	---
EC50	30.96	139.41	[28.45, 362.95]	5770.82	55.17	[4760.8,76909]
E0	-40	-1.62	[-93.93, -0.49]	-40	-1.49	[-86.33, -0.31]
EMAX	-64.16	---	---	-71.92	---	---
IGA_BL_E0	-0.04	---	---	0	---	---
BMIBL_NOR_E0	0	---	---	0.4	---	---
NRS_BL_NOR_E0	0	---	---	0.04	---	---
PCC_NOR_E0	0	---	---	0.03	---	---
ALB_NOR_E0	0	---	---	-0.04	---	---
OMEGA						
EC50-EC50	1.49	---	---	5.16	---	---
E0-E0	2.07	---	---	3.6	---	---
SIGMA						
Proportional Error	5.38	---	---	10.36	---	---
Additional Error	0.11	---	---	0.11	---	---

5.2.6. Pharmacodynamic interactions

Dupilumab has not been studied in conjunction with live vaccines.

Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated patients (Study R668-AD-1314).

5.3. Evaluator's overall conclusions on pharmacodynamics

The basic pharmacodynamic relationships for dupilumab have been adequately characterised. The concentration response relationship has been adequately described. The effect of ADA on PD has been adequately studied.

The sponsor has not examined potential PD interactions between dupilumab and other immunomodulating agents. Other immunomodulatory agents should be contraindicated during treatment with dupilumab.

The effects of dupilumab on live vaccines have not been studied. Live vaccines should be contraindicated during treatment with dupilumab.

Pharmacodynamics in children have not been studied. There is potential for extensive use of dupilumab in the paediatric population. The PD relationships will need to be confirmed prior to

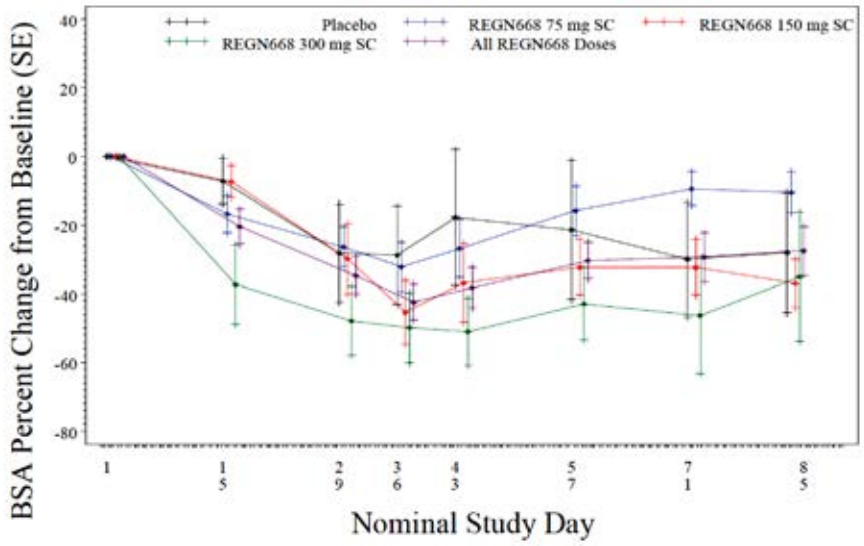
approval in the paediatric population. Further studies of the effects on vaccination will be required in the paediatric population.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

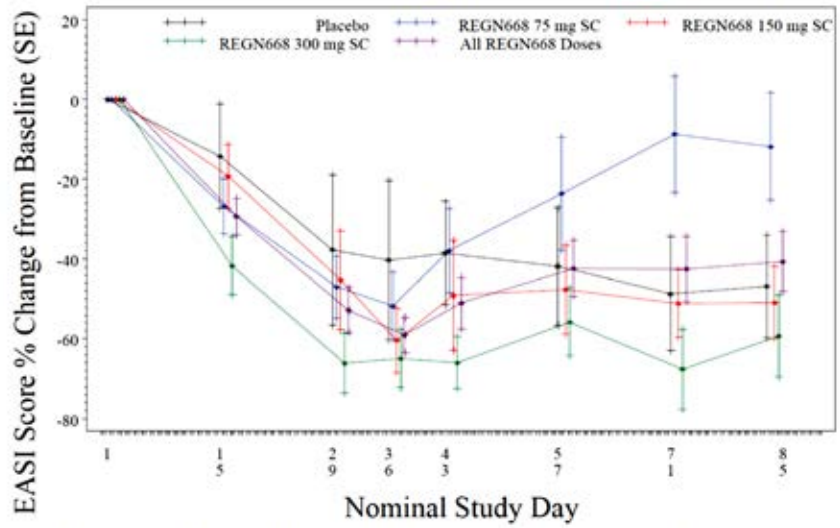
In Study R668-AD-0914 which investigated doses of 75 mg, 150 mg and 300 mg, there was a dose dependent increase in efficacy with the maximum response in the 300 mg group. There was a dose dependent decrease in BSA affected, with increasing effect to Week 4 (Figure 18). There was a dose dependent decrease in EASI, with increasing effect to Week 4 (Figure 19). The improvement in EASI was sustained in the 300 mg group up to Week 8. There was a dose dependent improvement in pruritus scale (Figure 20).

Figure 18: Mean BSA Percent Change from Baseline vs. Study Day – LOCF (SAF)



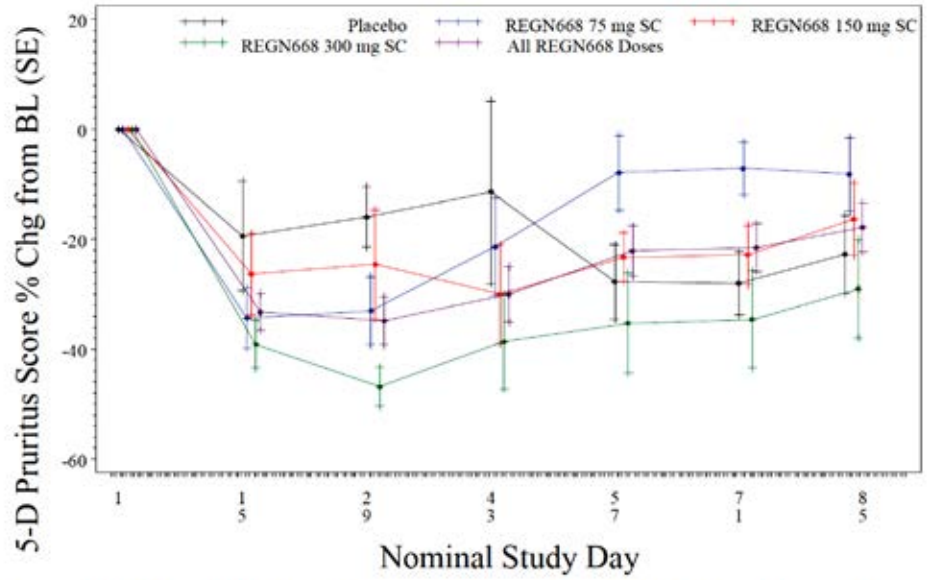
Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

Figure 19: Mean EASI Score Percent Change from Baseline vs. Study Day – LOCF (SAF)



Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

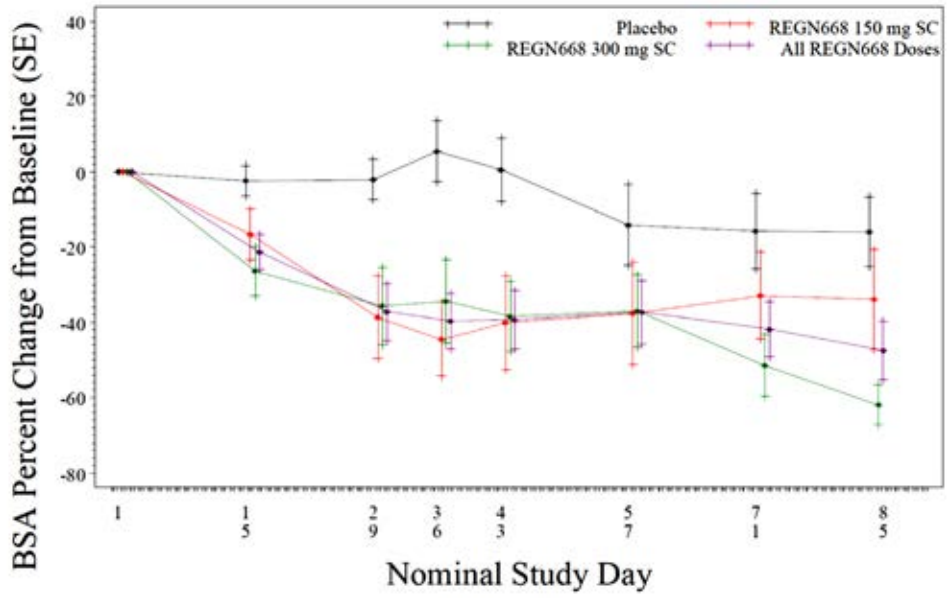
Figure 20: Mean 5-D Pruritus Score Percent Change from Baseline vs. Study Day - LOCF (SAF)



Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

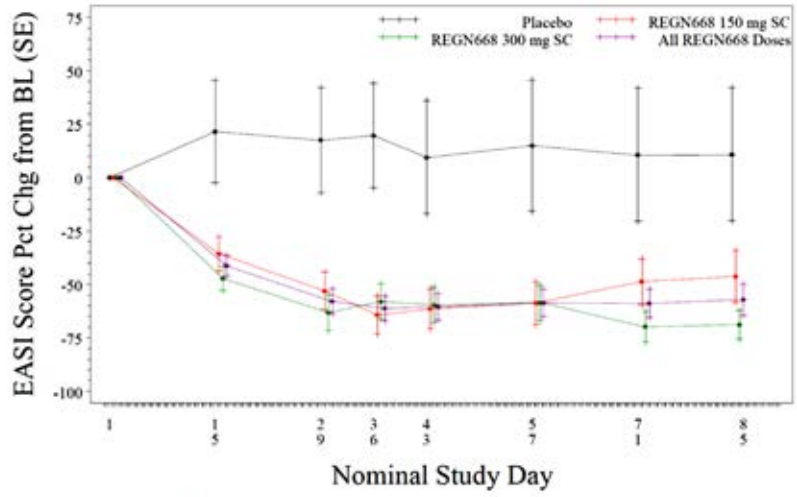
In Study R668-AD-1026 the 150 mg dose level was compared to 300 mg with weekly SC injections for 4 weeks. An IGA score of 0 or 1 at Day 29 was achieved by three (21.4%) patients in the 150 mg group, two (15.4%) in the 300 mg and none in the placebo. There was a similar, and clinically significant decrease in %BSA affected in the 150 and 300 mg treatment groups (Figure 21). There was a similar and clinically significant decrease in EASI score in the 150 and 300 mg treatment groups (Figure 22). A 50% decrease in EASI score was achieved by eight (57.1%) subjects in the 150 mg group, ten (76.9%) in the 300 mg and none in the placebo. There was a similar and clinically significant decrease in SCORAD in the 150 and 300 mg treatment groups (Figure 23). There was a similar and clinically significant decrease in 5-D Pruritus scare in the 150 and 300 mg treatment groups (Figure 24). NRS score improved in both treatment groups relative to placebo but there appeared to be greater improvement in the 300 mg group (Figure 25).

Figure 21: Mean BSA Percent Change from Baseline vs. Study Day – LOCF



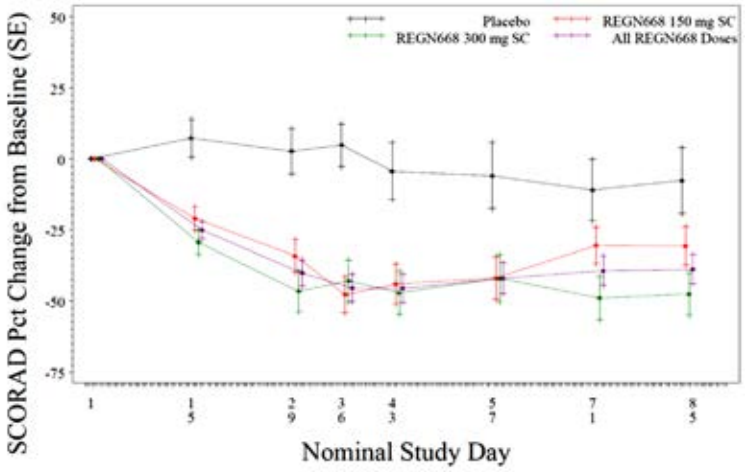
Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

Figure 22: Mean EASI Score Percent Change from Baseline vs. Study Day –LOCF



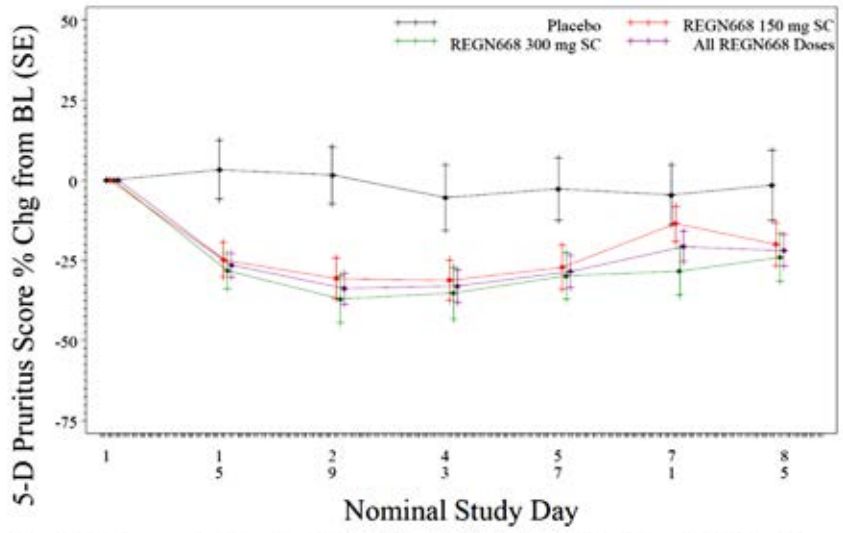
Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

Figure 23: Mean SCORAD Score Percent Change from Baseline vs. Study Day –LOCF



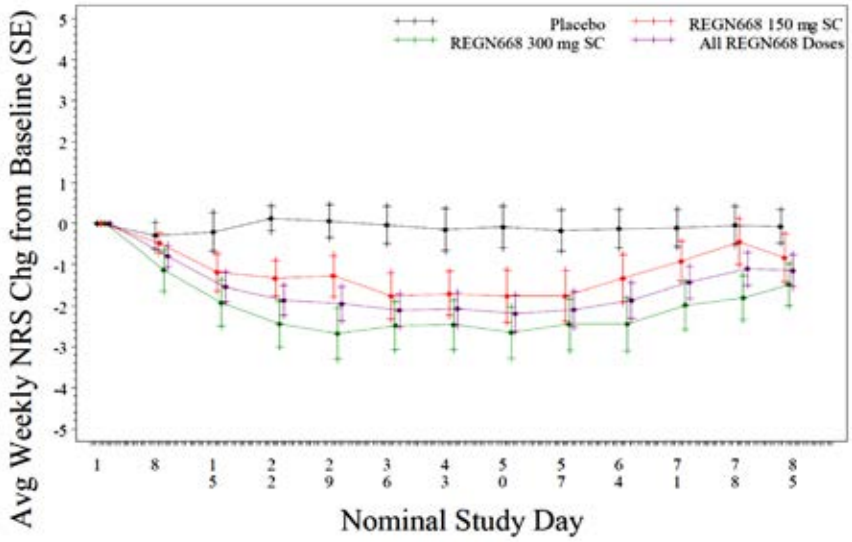
Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

Figure 24: Mean 5-D Pruritus Score Percent Change from Baseline vs. Study Day – LOCF



Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

Figure 25: Mean Average Weekly NRS Score Change from Baseline vs. Study Day – LOCF



Note: Study drug was administered at day 1/baseline, day 8/week 1, day 15/week 2, and day 22/week 3.

In Study REGN668-MX-1602 maximum EASI response was at Day 84, maintained to Day 112 and was similar for 300 mg once weekly and fortnightly (Figure 26). The maximum response was an 80% reduction in EASI. Improvement in IGA increased over time up to the 112 day point (Figure 27). The once weekly and fortnightly regimens had similar response. The response plateaued at Day 140, with approximately 50% of patients achieving IGA of 0 or 1 with both regimens (Figure 28). There was improvement in pruritus to Day 84 that was similar for both treatment regimens (Figure 29).

Figure 26: Mean (±SE) Percent Change from Baseline in EASI versus Time by Dupilumab Dose Regimen or Placebo in Phase 3 Mono-therapy Studies (Studies R668-AD-1334 [SOLO 1] and R668-AD-1416 [SOLO 2])

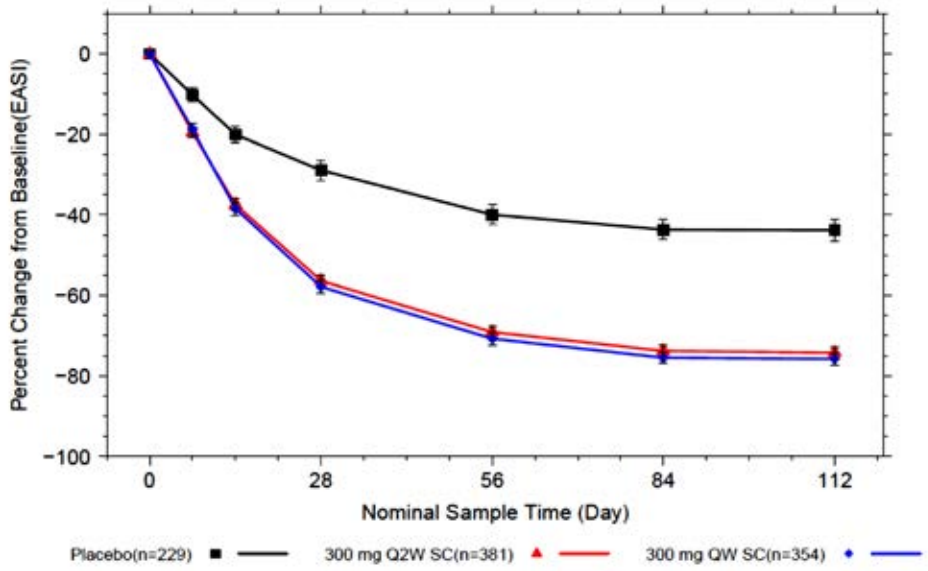


Figure 27: Proportion of AD Patients Achieving IGA 0-1 versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1334 and R668-AD-1416; SOLO studies)

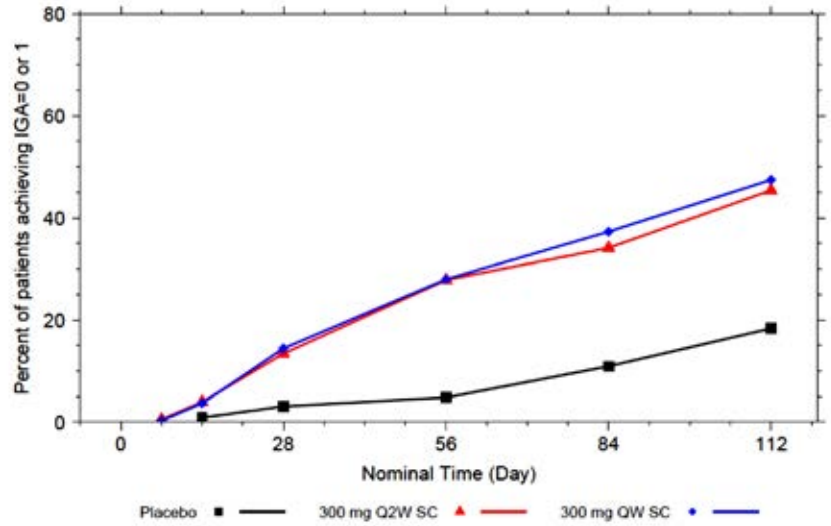


Figure 28: Proportion of AD Patients achieving IGA 0-1 versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1224: LTT study)

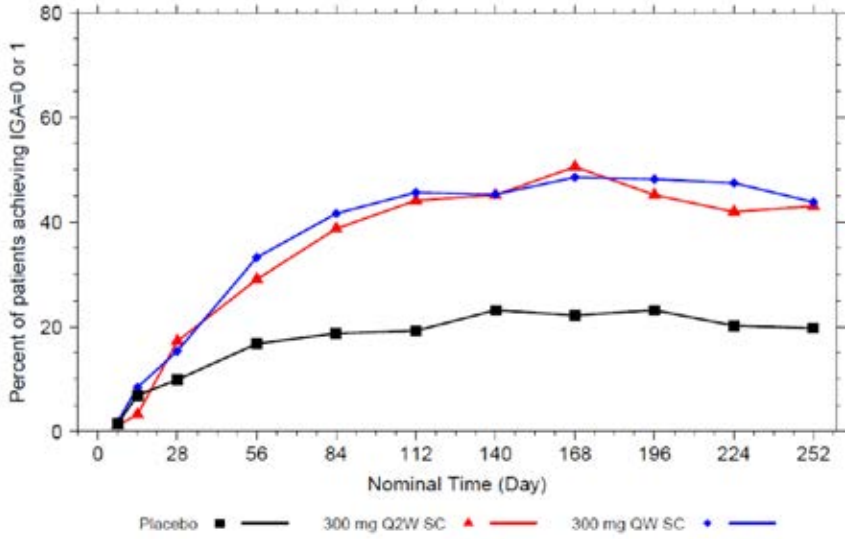
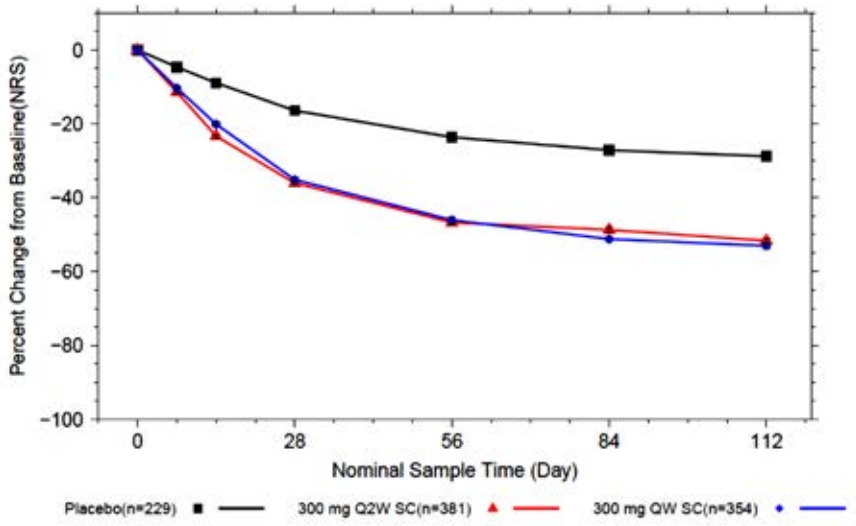


Figure 29: Mean (±SE) Percent Change from Baseline in Peak Pruritus NRS versus Time by Dupilumab Dose Regimen or Placebo (R668-AD-1334 and R668-AD-1416; SOLO studies)



6.2. Phase II dose finding studies

Study R668-AD-1021 examined the dose range 100 mg Q4W to 300 mg QW and found the greatest efficacy was with the 300 mg QW and 300 mg Q2W dose levels.

6.3. Phase III pivotal studies investigating more than one dose regimen

Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 examined two dose levels as monotherapy: 300 mg QW and 300 mg Q2W, both following a 600 mg bolus dose. There was no apparent, or significant, difference between the two dose levels for IGA, EASI or pruritus scores. Time to response was also similar for the two dosing regimens.

Study CHRONOS R668-AD-1224 examined two dose levels combined with TCS: 300 mg QW and 300 mg Q2W following a 600 mg bolus dose. There was no apparent, or significant, difference between the two dose levels for IGA, EASI or pruritus scores. Time to response was also similar for the two dosing regimens.

6.4. Evaluator's conclusions on dose finding for the pivotal studies

The sponsor examined a sufficient range of doses in Phase I and Phase II in order to select the dose regimens used in the Phase III studies. The Phase III studies confirmed a final dose recommendation of 600 mg as a bolus followed by 300 mg Q2W.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

There were three pivotal studies of dupilumab in AD:

- Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 examined two dose levels as monotherapy: 300 mg QW and 300 mg Q2W, both following a 600 mg bolus dose.

- Study CHRONOS R668-AD-1224 examined two dose levels combined with TCS: 300 mg QW and 300 mg Q2W following a 600 mg bolus dose.

There were four supportive studies:

- Three phase two controlled trials: Study R668-AD-1021, Study R668-AD-1117 and Study R668-AD-1121
- One long-term follow-on study: Study R668-AD-1225

7.2. Pivotal or main efficacy studies

7.2.1. Study SOLO 1 R668-AD-1334

7.2.1.1. Study design, objectives, locations and dates

Study SOLO 1 R668-AD-1334 was a randomised, double blind, parallel group, placebo controlled trial of dupilumab as monotherapy in patients with AD. The study was conducted at 138 sites in ten countries from October 2014 to February 2016.

7.2.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Male or female, 18 years or older
- Chronic AD, (according to American Academy of Dermatology Consensus Criteria from Eichenfield 2014 [Figure 30]), that had been present for at least 3 years before the screening visit

Figure 30: Diagnostic criteria for AD (from Eichenfield 2014)

Box 1. Features to be considered in the diagnosis of patients with atopic dermatitis

ESSENTIAL FEATURES—Must be present:
- Pruritus
- Eczema (acute, subacute, chronic)
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

Patterns include:

1. *Facial, neck, and extensor involvement in infants and children*
2. *Current or previous flexural lesions in any age group*
3. *Sparing of the groin and axillary regions*

IMPORTANT FEATURES—Seen in most cases, adding support to the diagnosis:
- Early age of onset
- Atopy
  - Personal and/or family history
  - Immunoglobulin E reactivity
- Xerosis

ASSOCIATED FEATURES—These clinical associations help to suggest the diagnosis of atopic dermatitis but are too nonspecific to be used for defining or detecting atopic dermatitis for research and epidemiologic studies:
- Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (eg, perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo lesions

EXCLUSIONARY CONDITIONS—It should be noted that a diagnosis of atopic dermatitis depends on excluding conditions, such as:
- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Adapted from Eichenfield et al.[24] Used with permission of the American Academy of Dermatology.

- EASI score ≥16 at the screening and baseline visits
- IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits
- ≥10% body surface area (BSA) with AD involvement at the screening and baseline visits
- Baseline Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity ≥ 3
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable (e.g. because of important side effects or safety risks):
  - Inadequate response was defined as failure to achieve and maintain remission or a low disease activity state (comparable to IGA 0=clear to 2=mild) despite treatment with a daily regimen of TCS of medium to higher potency (±TCI as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information (for example, 14 days for super-potent TCS), whichever was shorter.

  - 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.
  - Important side effects or safety risks were those that outweighed the potential treatment benefits and included intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects, as assessed by the investigator or by the patient's treating physician
- Applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit

The exclusion criteria included:

- Participation in a prior dupilumab clinical study
- Having used any of the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, was likely to require such treatment(s) during the first 4 weeks of study treatment:
  - Immunosuppressive/immunomodulating drugs (for example, systemic corticosteroids, cyclosporine, mycophenolate-mofetil [MMF], interferon gamma, Janus kinase [JAK] inhibitors, azathioprine [AZA], methotrexate [MTX], etc.)
  - Phototherapy for AD
- Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 1 week before the baseline visit
- Treatment with biologics as follows:
  - Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever was longer
  - Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever was longer
- Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients could continue using stable doses of such moisturizers if initiated before the screening visit)
- Regular use (more than 2 visits per week) of a tanning booth/parlour within 4 weeks of the baseline visit
- Planned or anticipated use of any prohibited medications and procedures during study treatment:
  - Treatment with a live (attenuated) vaccine Any
  - Treatment with immunomodulating biologics
  - Treatment with an investigational drug (other than dupilumab)
  - TCI could be administered during the study only if required for AD rescue. TCIs were used during the study, study treatment could continue as planned
  - Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (for example, cyclosporine, MTX, MMF, AZA, etc.)
- Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or

superficial skin infections within 1 week before the baseline visit. NOTE: patients could be rescreened after infection resolved

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (for example, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive with HBsAg, hepatitis B core antibody (HBcAb), or hepatitis C antibody
- At baseline, presence of any conditions listed as criteria for study drug discontinuation
  - Anaphylactic reaction or other severe systemic reaction to study drug injection
  - Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin
  - Evidence of pregnancy
  - Any infection that is opportunistic, such as active TB and other infections whose nature or course may suggest an immuno-compromised status
  - Severe laboratory abnormalities: Neutrophil count $\leq 0.5 \times 10^3/\mu L$, platelet count $\leq 50 \times 10^3/\mu L$, ALT and/or AST values >3xULN with total bilirubin >2xULN (unless elevated bilirubin is related to confirmed Gilbert's Syndrome)
  - Confirmed AST and/or ALT >5xULN (for more than 2 weeks)
- Presence of skin comorbidities that could interfere with study assessments
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment had ruled out active infection before randomization
- Severe concomitant illness(es) that, in the investigator's judgment, could have adversely affected the patient's participation in the study. Examples included, but were not limited to, patients with short life expectancy, patients with uncontrolled diabetes (haemoglobin A1c $\geq$ 9%), patients with cardiovascular conditions (for example, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (for example, patients on dialysis), hepato-biliary conditions (for example, Child-Pugh class B or C), neurological conditions (for example, demyelinating diseases), active major autoimmune diseases (for example, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases
- Planned or anticipated major surgical procedure during the patient's participation in this study
- Pregnant or breastfeeding women, or women who planned to become pregnant or breastfeed during the study
- Women unwilling to use adequate birth control, if of reproductive potential and sexually active

7.2.1.3. Study treatments

The study treatments were:

1. Dupilumab 600 mg (loading dose), followed by 300 mg once weekly (QW)
2. Dupilumab 600 mg (loading dose), followed by 300 mg every second week (Q2W)
3. Placebo

Treatments were administered subcutaneously. The same site was not injected for two consecutive weeks.

All patients were required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization and to continue throughout the study. For AD, permitted medications and procedures included basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anaesthetics, topical and systemic antihistamines, and topical and systemic anti-infective medications for any duration.

Treatments that were prohibited were the same as for the exclusion criteria:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- TCS or TCI could be administered during the study only if required for AD rescue. If TCS and/or TCIs were used during the study, study treatment could continue as planned
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (for example, cyclosporine, MTX, MMF, AZA, etc.)

7.2.1.4. Efficacy variables and outcomes

There were different primary efficacy outcome measures for the US / US reference market countries and for the EU / Japan. The primary efficacy outcome measure for the US and the US reference market countries was:

- The proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16. The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe).

For the European Union (EU) and EU reference market countries and Japan, the co-primary endpoints were:

- The proportion of patients with EASI[1]-75 (≥75% improvement from baseline) at Week 16.
- The proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16

The key secondary endpoints were:

- The proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16 (only for US and US reference market countries)
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 16.
- The proportion of patients with improvement (reduction ≥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
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 4

[1] Eczema Area and Severity Index

- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 2

Other secondary efficacy endpoints were:

- The change from baseline to Week 16 in weekly average of peak daily pruritus NRS
- The percent change in EASI score from baseline to Week 16
- The proportion of patients with EASI-50 (≥50% improvement from baseline) at Week 16
- The proportion of patients with EASI-90 (≥90% improvement from baseline) at Week 16
- The change from baseline to Week 16 in percent BSA involvement with AD
- The percent change from baseline to Week 16 in the SCORAD
- The change from baseline to Week 16 in the DLQI
- The change from baseline to Week 16 in the POEM
- The change from baseline to Week 16 in the HADS
- The percent change from baseline to Week 16 in the GISS (erythema, infiltration/ papulation, excoriations, lichenification)
- The percent change from baseline to Week 2 in weekly average of peak daily pruritus NRS
- The change from baseline to Week 16 in the Asthma Control Questionnaire, 5-item version (ACQ-5)
- The change from baseline to Week 16 in the Sinonasal Outcomes Test (SNOT-22) (total score and sub-scales)
- The change and percent change from baseline to Week 16 in the EQ-5D
- The proportion of patients who responded 'absence of pruritus' or 'mild pruritus' in the pruritus categorical scale at Week 16. The pruritus categorical scale was scored as: 0: absence of pruritus; 1: mild pruritus (occasional slight itching/scratching); 2: moderate pruritus (constant or intermittent itching/scratching that does not disturb sleep); and 3: severe pruritus (bothersome itching/scratching that disturbs sleep).
- The proportion of patients who responded 'very good' or 'excellent' in the Patient Global Assessment of Disease Status at Week 16
- The proportion of patients who responded 'very good' or 'excellent' in the Patient Global Assessment of Treatment Effect at Week 16
- The proportion of patients who achieved reduction of IGA score by ≥2 points from baseline to Week 16
- The proportion of patients who achieved reduction of IGA score by ≥3 points from baseline to Week 16
- Sick leave/missed school days assessment (number of days and proportion of patients)

The safety outcome measures included: incidence of skin infection TEAEs requiring systemic treatment from baseline through Week 16, SAEs, TEAEs leading to treatment discontinuation, clinical laboratory tests, vital signs, physical examination, ECGs and ADA.

The following biomarkers were evaluated: TARC, total IgE, antigen-specific IgE and hs-CRP.

7.2.1.5. Randomisation and blinding methods

Patients were randomised 1:1:1 by IVRS/IWRS. Blinding was maintained by using a placebo with identical appearance to active treatment, and all patients received weekly injections.

7.2.1.6. Analysis populations

The efficacy analysis was based on the full analysis set (FAS) which included all randomised patients. The safety analysis set (SAF) included all randomised patients who received any study drug, and was analysed as treated.

7.2.1.7. Sample size

The sample size was more than sufficient for determining efficacy because of the need for a sufficient number of patients to demonstrate safety. To detect a difference of 29% between dupilumab and placebo treatment in the proportion of patients who achieved an IGA score of 0 to 1 at Week 16, assuming that the proportions were 38% and 9% for dupilumab and placebo, respectively, the number of patients required for 90% power was 55 per group. To ensure that a sufficient number of responders would be available for inclusion in the maintenance study, the sample size was increased to 600 in total, 200 in each treatment group.

7.2.1.8. Statistical methods

The Cochran-Mantel-Haenszel test adjusted by randomization strata (region, disease severity) was used for the proportion of patients with IGA 0 or 1 at Week 16 or the proportion of patients with EASI-75 at Week 16.

Continuous outcome measures were analysed using ANCOVA, with treatment, randomisation strata (region, disease severity) and baseline measure included in the model.

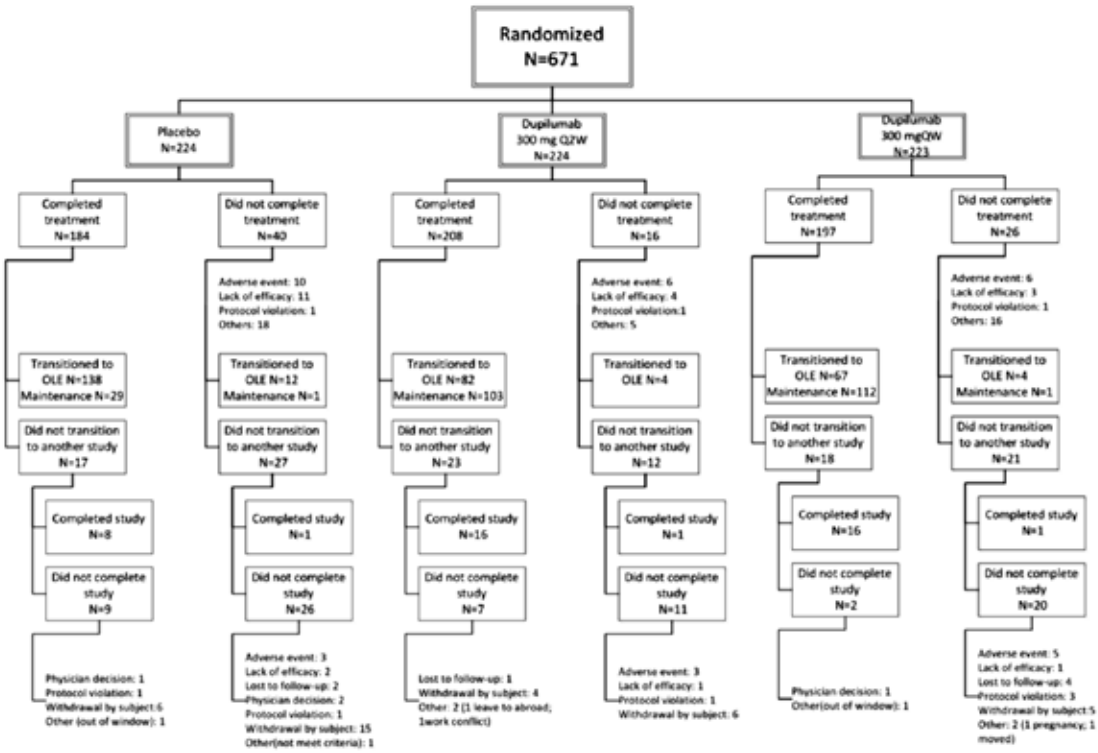
Where imputation was used, the LOCF method was used for missing observations, and where a patient withdrew from the study they were counted as a non-responder for subsequent time-points.

Multiplicity was addressed by using a hierarchical approach to hypothesis testing. For each dose regimen, an intersection-union method was applied to the co-primary endpoints, which required statistical significance of both co-primary endpoints at the 2-sided 0.025 level, followed by a hierarchical testing procedure of secondary endpoints with a pre-specified order, that is, inferential conclusions about successive secondary endpoints required statistical significance at the 0.025 significance level of the prior one.

7.2.1.9. Participant flow

A total of 917 patients were screened, and 671 were randomised: 224 to placebo, 224 to dupilumab Q2W and 223 to dupilumab QW. There were 184 (82.1%) patients in the placebo group, 208 (92.9%) in the Q2W and 197 (88.3%) in the QW who completed the study. In total 11 (1.6%) subjects withdrew because of adverse event. Participant flow is summarised in Figure 31.

Figure 31: Schematic of Patient Disposition – All Randomized Patients



7.2.1.10. Major protocol violations/deviations

There were major protocol deviations in 17 (7.6%) patients in the placebo group, seven (3.1%) in the Q2W and 16 (7.2%) in the QW. The commonest major protocol deviation was inadequate informed consent administration.

7.2.1.11. Baseline data

There were 390 (58.1%) males, 281 (41.9%) females and the age range was 18 to 85 years. The treatment groups were similar in demographic characteristics. There were 32 (4.8%) patients aged ≥65 years. Nearly all the patients had an unsatisfactory response to topical corticosteroid treatment: 655 (97.6%). The treatment groups were similar in baseline outcome measure scores. The treatment groups were similar in previous medical history. The treatment groups were similar in history of previous atopic disease and asthma. A higher proportion of patients in the placebo group required rescue treatment: 116 (51.3%) in the placebo group, 47 (21.0%) in the Q2W and 52 (23.3%) in the QW. Mean (SD) adherence to study treatment was 98.01 (7.564) % for placebo, 98.53 (6.200) for Q2W and 98.68 (4.766) for QW.

7.2.1.12. Results for the primary efficacy outcome

- The proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 was 23 (10.5%) patients for placebo, 85 (37.9%) for Q2W and 83 (37.2%) for QW. The difference (95% CI) in % dupilumab – placebo was 27.7 (20.18 to 35.17) %, p <0.0001, for Q2W and 27.0 (19.47 to 34.44) %, p <0.0001, for QW.
- The proportion of patients with EASI-75 at Week 16 was 33 (14.7%) patients for placebo, 115 (51.3%) for Q2W and 117 (52.5%) for QW. The difference (95% CI) in % dupilumab – placebo was 36.6 (28.58 to 44.63) %, p <0.0001, for Q2W and 37.7 (29.70 to 45.77) %, p <0.0001, for QW.

Subgroup analysis did not identify any significant difference between subgroups in response.

7.2.1.13. Results for other efficacy outcomes

- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 16 was 26 (12.3%) patients for placebo, 87 (40.8%) for Q2W and 81 (40.3%) for QW. The difference (95% CI) in % dupilumab – placebo was 28.6 (20.64 to 36.52) %, p <0.0001, for Q2W and 28.0 (19.94 to 36.13) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction ≥3 points) of weekly average of peak daily pruritus NRS from baseline to Week 16 was 38 (17.2%) patients for placebo, 103 (46.8%) for Q2W and 109 (51.7%) for QW. The difference (95% CI) in % dupilumab – placebo was 29.6 (21.36 to 37.88) %, p <0.0001, for Q2W and 34.5 (26.08 to 42.84) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS was -26.8 (28.38) for placebo, -51.1 (28.81) for Q2W and -49.0 (33.45) for QW. The LS mean difference (95% CI) dupilumab – placebo was -24.9 (-32.26 to -17.52) for Q2W and -22.8 (-30.33 to -15.33) for QW.
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 4 was 13 (6.1%) patients for placebo, 34 (16.0%) for Q2W and 47 (23.4%) for QW. The difference (95% CI) in % dupilumab – placebo was 9.8 (3.95 to 15.71) %, p = 0.0012, for Q2W and 17.3 (10.57 to 23.93) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 2 was seven (3.3%) patients for placebo, 20 (9.4%) for Q2W and 19 (9.5%) for QW. The difference (95% CI) in % dupilumab – placebo was 6.1 (1.49 to 10.68) %, p = 0.0097, for Q2W and 6.2 (1.45 to 10.86) %, p = 0.0094, for QW.
- The mean (SD) change from baseline to Week 16 in weekly average of peak daily pruritus NRS was -2.13 (2.044) for placebo, -3.78 (2.325) for Q2W and -3.72 (2.186) for QW. The LS mean difference (95% CI) dupilumab – placebo was -1.75 (-2.236 to -1.260), p <0.0001 for Q2W and -1.69 (-2.189 to -1.186) for QW.
- The mean (SD) percent change in EASI score from baseline to Week 16 was -39.5 (33.66) for placebo, -73.9 (26.28) for Q2W and -73.8 (26.41) for QW. The LS mean difference (95% CI) dupilumab – placebo was -34.6 (-42.35 to -26.88), p <0.0001, for Q2W and -34.4 (-42.17 to -26.56), p <0.0001, for QW.
- The proportion of patients with EASI-50 (≥50% improvement from baseline) at Week 16 was 55 (24.6%) patients for placebo, 154 (68.8%) for Q2W and 136 (61.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 44.2 (35.91 to 52.84) %, p <0.0001, for Q2W and 36.4 (27.90 to 44.96) %, p <0.0001, for QW.
- The proportion of patients with EASI-90 (≥90% improvement from baseline) at Week 16 was 17 (7.6%) patients for placebo, 80 (35.7%) for Q2W and 74 (33.2%) for QW. The difference (95% CI) in % dupilumab – placebo was 28.1 (20.96 to 35.29) %, p <0.0001, for Q2W and 25.6 (18.51 to 32.68) %, p <0.0001, for QW.
- The change from baseline to Week 16 in percent BSA involvement with AD was -17.20 (17.381) for placebo, -33.72 (19.619) for Q2W and -35.42 (19.926) for QW. The LS mean difference (95% CI) dupilumab – placebo was -17.92 (-22.487 to -13.353), p <0.0001, for Q2W and -18.89 (-23.125 to -14.650), p <0.0001, for QW.
- The percent change from baseline to Week 16 in the SCORAD was -28.9 (24.25) % for placebo, -57.2 (24.03) % for Q2W and -57.0 (24.27) % for QW. The LS mean difference (95%

CI) dupilumab – placebo was -28.7 (-35.79 to -21.54) %, p <0.0001, for Q2W and -28.0 (-35.09 to -20.87) %, p <0.0001, for QW.

- The mean (SD) change from baseline to Week 16 in the DLQI was -5.6 (5.86) for placebo, -9.0 (6.61) for Q2W and -8.8 (6.79) for QW. The LS mean difference (95% CI) dupilumab – placebo was -4.0 (-5.16 to -2.80), p <0.0001, for Q2W and -3.7 (-4.87 to -2.49), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in the POEM was -5.3 (5.89) for placebo, -11.5 (7.07) for Q2W and -11.3 (6.36) for QW. The LS mean difference (95% CI) dupilumab – placebo was -6.5 (-8.02 to -5.01), p <0.0001, for Q2W and -5.9 (-7.44 to -4.32), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in the HADS total score was -2.7 (4.40) for placebo, -4.8 (5.50) for Q2W and -4.9 (5.36) for QW. The LS mean difference (95% CI) dupilumab – placebo was -2.2 (-3.44 to -0.95), p = 0.0006, for Q2W and -2.2 (-3.46 to -1.03), p = 0.0003, for QW.
- The mean (SD) percent change from baseline to Week 16 in the GISS (erythema, infiltration/papulation, excoriations, lichenification) was -26.2 (25.70) % for placebo, -52.5 (27.33) % for Q2W and -51.1 (26.58) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -27.0 (-35.04 to -18.91) %, p <0.0001, for Q2W and -25.6 (-33.06 to -18.12) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 2 in weekly average of peak daily pruritus NRS was -4.2 (22.77) % for placebo, -20.4 (21.40) % for Q2W and -18.9 (28.40) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -16.5 (-21.08 to -11.90), p <0.0001, for Q2W and -15.1 (-19.62 to -10.50), p <0.0001, for QW.
- There was no significant difference between the treatment groups in the change from baseline to Week 16 in the Asthma Control Questionnaire, 5-item version (ACQ-5): mean (SD) -0.29 (0.629) for placebo, -0.06 (0.657) for Q2W and -0.26 (0.731) for QW.
- There was no significant difference between the treatment groups in the change from baseline to Week 16 in the Sinonasal Outcomes Test (SNOT-22) (total score and sub-scales): mean (SD) -8.67 (14.116) for placebo, -10.31 (15.803) for Q2W and -13.90 (17.759) for QW.
- The mean (SD) change from baseline to Week 16 in the EQ-5D Index Utility Score was 0.1590 (0.27152) for placebo, 0.2337 (0.28825) for Q2W and 0.2142 (0.27599) for QW. The LS mean difference (95% CI) dupilumab – placebo was 0.1083 (0.06523 to 0.15136), p <0.0001, for Q2W and 0.0832 (0.03884 to 0.12757), p = 0.0003, for QW.
- The mean (SD) change from baseline to Week 16 in the EQ-5D VAS Score was 8.1 (19.08) for placebo, 19.1 (23.29) for Q2W and 15.7 (24.83) for QW. The LS mean difference (95% CI) dupilumab – placebo was 12.5 (8.22 to 16.73), p <0.0001, for Q2W and 8.4 (4.05 to 12.79), p = 0.0002, for QW.
- The proportion of patients who responded 'absence of pruritus' or 'mild pruritus' in the pruritus categorical scale at Week 16 was 41 (18.3%) patients for placebo, 116 (51.8%) for Q2W and 120 (53.8%) for QW. The difference (95% CI) in % dupilumab – placebo was 33.5 (25.21 to 41.76) %, p <0.0001, for Q2W and 35.5 (27.23 to 43.78) %, p <0.0001, for QW.
- The proportion of patients who responded 'very good' or 'excellent' in the Patient Global Assessment of Disease Status at Week 16 was 25 (11.2%) patients for placebo, 85 (37.9%) for Q2W and 79 (35.4%) for QW. The difference (95% CI) in % dupilumab – placebo was 26.8 (19.21 to 34.36) %, p <0.0001, for Q2W and 24.3 (16.75 to 31.78) %, p <0.0001, for QW.

- The proportion of patients who achieved reduction of IGA score by ≥2 points from baseline to Week 16 was 27 (12.1%) patients for placebo, 104 (46.4%) for Q2W and 100 (44.8%) for QW. The difference (95% CI) in % dupilumab – placebo was 34.4 (26.58 to 42.17) %, p <0.0001, for Q2W and 32.8 (24.99 to 40.59) %, p <0.0001, for QW.
- The proportion of patients who achieved reduction of IGA score by ≥3 points from baseline to Week 16 was 11 (4.9%) patients for placebo, 35 (15.6%) for Q2W and 37 (16.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 10.7 (5.18 to 16.25) %, p <0.0001, for Q2W and 11.7 (6.04 to 17.32) %, p <0.0001, for QW.
- The mean (SD) sick leave/missed school days for full-time was 1.81 (6.868) days for placebo, 0.52 (1.873) days for Q2W and 0.66 (3.197) days for QW.
- The mean (SD) sick leave/missed school days for part-time was 4.89 (18.241) days for placebo, 0.14 (0.601) days for Q2W and 0.10 (0.519) days for QW.

With regard to biomarkers:

- The median % change from baseline to Week 16 in TARC was -75.35% for QW, -77.93% for Q2W and -5.86 for placebo.
- The median % change from baseline to Week 16 in serum IgE was -44.62% for QW, -43.91% for Q2W and 4.53% for placebo.
- Decreases from baseline were observed for the dupilumab treatment groups compared with placebo during the treatment period in IgEs elicited against all allergen panels tested, including *Candida albicans, Dermatophagoides farinae,* staphylococcal enterotoxin A, cat dander, and *Pityrosporum (Malassezia)*.
- There was no significant difference between the groups in hsCRP, ANA, anti-double stranded DNA or anti-thyroid peroxidase.

7.2.1.14. Evaluator commentary

Study SOLO 1 R668-AD-1334 was appropriately designed and conducted as a pivotal study. The randomisation was robust and blinding was maintainable. The outcome measures were objective and able to demonstrate clear differences in disease severity. There were multiple valid outcome measures which assessed disease response, symptomatology and quality of life. The statistical analysis was appropriate and the study was sufficiently powered.

The study was appropriate to the proposed indication. The inclusion and exclusion criteria ensured a study population of patients *with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.* In this case the study examined dupilumab as a monotherapy.

The study showed clear superiority (clinically and statistically significant) in comparison to placebo for both dupilumab Q2W and QW. Efficacy was similar for Q2W and QW, i.e. there was no benefit for QW over Q2W. Superiority was also demonstrated for quality of life measures in addition to disease severity and symptomatology measures.

7.2.2. Study SOLO 2 R668-AD-1416

7.2.2.1. Study design, objectives, locations and dates

Study SOLO 2 R668-AD-1416 was a randomised, double blind, parallel group, placebo controlled trial of dupilumab as monotherapy in patients with moderate to severe AD. The study was conducted at 136 sites in ten countries from December 2014 to January 2016. There was a 16 week treatment period and a 12-week follow-up period. The study was a replicate of Study SOLO 1 R668-AD-1334.

7.2.2.2. Inclusion and exclusion criteria

As per Study SOLO 1 R668-AD-1334.

7.2.2.3. Study treatments

As per Study SOLO 1 R668-AD-1334.

7.2.2.4. Efficacy variables and outcomes

As per Study SOLO 1 R668-AD-1334.

7.2.2.5. Randomisation and blinding methods

As per Study SOLO 1 R668-AD-1334.

7.2.2.6. Analysis populations

As per Study SOLO 1 R668-AD-1334.

7.2.2.7. Sample size

As per Study SOLO 1 R668-AD-1334.

7.2.2.8. Statistical methods

As per Study SOLO 1 R668-AD-1334.

7.2.2.9. Participant flow

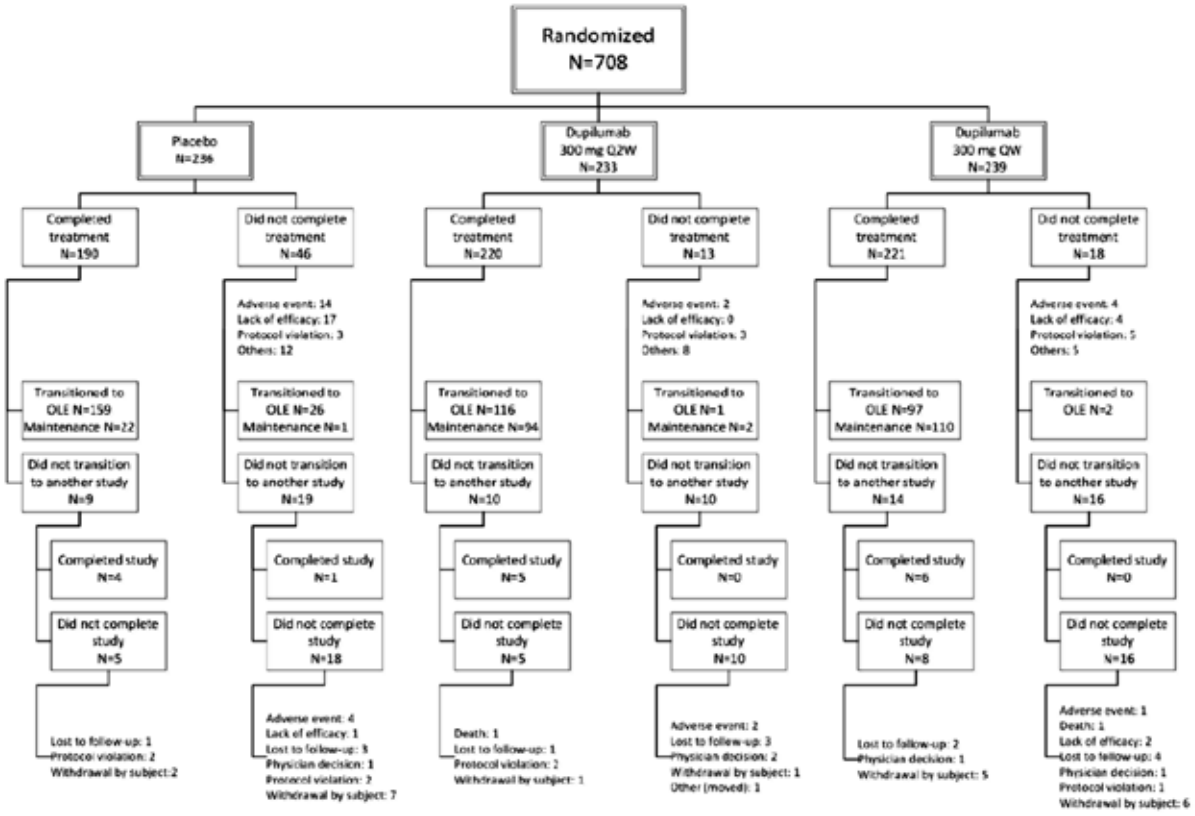
A total of 962 patients were screened, and 708 were randomised: 236 to placebo, 233 to dupilumab Q2W and 239 to dupilumab QW (Table 9). There were 190 (80.5%) patients in the placebo group, 220 (94.4%) in the Q2W and 221 (92.5%) in the QW who completed the study. In total 20 (2.8%) subjects withdrew because of an adverse event. Participant flow is summarised in Figure 32.

Table 9: Summary of Patient Accountability and Study Disposition – All Randomized Patients

		Dupilumab			
	Placebo (N=236)	300 mg Q2W (N=233)	300 mg QW (N=239)	Combined (N=472)	Total (N=708)
Patients who received study drug, n (%)	235 (99.6%)	233 (100%)	239 (100%)	472 (100%)	707 (99.9%)
Patients randomized but not treated, n (%)	1 (0.4%)	0	0	0	1 (0.1%)
Patients who completed study treatment, n (%)					
Yes	190 (80.5%)	220 (94.4%)	221 (92.5%)	441 (93.4%)	631 (89.1%)
No	46 (19.5%)	13 (5.6%)	18 (7.5%)	31 (6.6%)	77 (10.9%)
Adverse event	14 (5.9%)	2 (0.9%)	4 (1.7%)	6 (1.3%)	20 (2.8%)
Lack of efficacy	17 (7.2%)	0	4 (1.7%)	4 (0.8%)	21 (3.0%)
Protocol violation	3 (1.3%)	3 (1.3%)	5 (2.1%)	8 (1.7%)	11 (1.6%)
Other[a]	12 (5.1%)	8 (3.4%)	5 (2.1%)	13 (2.8%)	25 (3.5%)
Patients who transitioned into another study, n (%)					
Yes	208 (88.1%)	213 (91.4%)	209 (87.4%)	422 (89.4%)	630 (89.0%)
Open-label extension	185 (78.4%)	117 (50.2%)	99 (41.4%)	216 (45.8%)	401 (56.6%)
R668-AD-1415 maintenance study	23 (9.7%)	96 (41.2%)	110 (46.0%)	206 (43.6%)	229 (32.3%)
No	28 (11.9%)	20 (8.6%)	30 (12.6%)	50 (10.6%)	78 (11.0%)
Patients who completed week 28 (end of study)	5 (2.1%)	5 (2.1%)	6 (2.5%)	11 (2.3%)	16 (2.3%)
Patients who did not complete the study	23 (9.7%)	15 (6.4%)	24 (10.0%)	39 (8.3%)	62 (8.8%)
Adverse event	4 (1.7%)	2 (0.9%)	1 (0.4%)	3 (0.6%)	7 (1.0%)
Death	0	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (0.3%)
Lack of efficacy	1 (0.4%)	0	2 (0.8%)	2 (0.4%)	3 (0.4%)
Lost to follow-up	4 (1.7%)	4 (1.7%)	6 (2.5%)	10 (2.1%)	14 (2.0%)
Physician decision	1 (0.4%)	2 (0.9%)	2 (0.8%)	4 (0.8%)	5 (0.7%)
Protocol violation	4 (1.7%)	2 (0.9%)	1 (0.4%)	3 (0.6%)	7 (1.0%)
Withdrawal by subject	9 (3.8%)	3 (1.3%)	11 (4.6%)	14 (3.0%)	23 (3.2%)
Other[b]	0	1 (0.4%)	0	1 (0.2%)	1 (0.1%)

Percentages are based on the number of randomized patients.
[a] Other reasons were withdrawal of consent, death, lost to follow-up, missed last injection, rescue medication, and other.
[b] Other reason was the patient moved for work reasons.

Figure 32: Schematic of Patient Disposition – All Randomized Patients



7.2.2.10. Major protocol violations/deviations

There were major protocol deviations in 15 (6.4%) patients in the placebo group, 22 (9.4%) in the Q2W and 18 (7.5%) in the QW. The commonest major protocol deviation was 'Personnel not qualified and/or designated to perform study related activities'.

7.2.2.11. Baseline data

There were 408 (57.6%) males, 300 (42.4%) females and the age range was 18 to 88 years. The treatment groups were similar in demographic characteristics. There were 32 (4.5%) patients aged ≥65 years. Nearly all the patients had an unsatisfactory response to topical corticosteroid treatment: 696 (98.3%). The treatment groups were similar disease severity and in baseline outcome measure scores. The treatment groups were similar in previous medical history. The treatment groups were similar in history of previous atopic disease and asthma. A higher proportion of patients in the placebo group required rescue treatment: 123 (52.1%) in the placebo group, 35 (15.0%) in the Q2W and 49 (20.5%) in the QW. Mean (SD) adherence to study treatment was 98.03 (7.215) % for placebo, 98.88 (3.827) for Q2W and 99.17 (3.306) for QW.

7.2.2.12. Results for the primary efficacy outcome

- The proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 was 20 (8.5%) patients for placebo, 84 (36.1%) for Q2W and 87 (36.4%) for QW. The difference (95% CI) in % dupilumab – placebo was 27.6 (20.46 to 34.69) %, p <0.0001, for Q2W and 27.9 (20.87 to 34.99) %, p <0.0001, for QW.
- The proportion of patients with EASI-75 at Week 16 was 28 (11.9%) patients for placebo, 103 (44.2%) for Q2W and 115 (48.1%) for QW. The difference (95% CI) in % dupilumab – placebo was 32.3 (24.75 to 39.94) %, p <0.0001, for Q2W and 36.3 (28.69 to 43.81) %, p <0.0001, for QW.

Subgroup analysis did not identify any significant difference between subgroups in response.

7.2.2.13. Results for other efficacy outcomes

- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 16 was 21 (9.5%) patients for placebo, 81 (36.0%) for Q2W and 89 (39.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 26.5 (19.13 to 33.87) %, p <0.0001, for Q2W and 29.5 (22.11 to 36.95) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction ≥3 points) of weekly average of peak daily pruritus NRS from baseline to Week 16 was 29 (12.8%) patients for placebo, 117 (50.6%) for Q2W and 115 (49.1%) for QW. The difference (95% CI) in % dupilumab – placebo was 37.8 (30.03 to 45.60) %, p <0.0001, for Q2W and 36.3 (28.56 to 44.06) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 16 in weekly average of peak daily pruritus NRS was -18.1 (27.66) for placebo, -47.2 (28.50) for Q2W and -50.9 (30.56) for QW. The LS mean difference (95% CI) dupilumab – placebo was -28.9 (-36.04 to -21.83) for Q2W and -32.8 (-40.20 to -25.49) for QW.
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 4 was 14 (6.3%) patients for placebo, 51 (22.7%) for Q2W and 63 (27.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 16.3 (9.99 to 22.68) %, p <0.0001, for Q2W and 21.3 (14.66 to 27.93) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction ≥4 points) of weekly average of peak daily pruritus NRS from baseline to Week 2 was two (0.9%) patients for placebo, 24 (10.7%) for Q2W and 29 (12.7%) for QW. The difference (95% CI) in % dupilumab – placebo was 9.8 (5.54 to 13.98) %, p <0.0001, for Q2W and 11.8 (7.31 to 16.32) %, p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in weekly average of peak daily pruritus NRS was -1.41 (1.973) for placebo, -3.56 (2.258) for Q2W and -3.87 (2.426) for QW. The LS mean difference (95% CI) dupilumab – placebo was -2.10 (-2.605 to -1.587), p <0.0001 for Q2W and -2.47 (-2.605 to -1.587). p <0.0001, for QW.
- The mean (SD) percent change in EASI score from baseline to Week 16 was -33.7 (33.45) for placebo, -69.6 (27.84) for Q2W and -71.6 (27.08) for QW. The LS mean difference (95% CI) dupilumab – placebo was -36.2 (-43.46 to -28.86), p <0.0001, for Q2W and -38.2 (-45.55 to -30.88), p <0.0001, for QW.
- The proportion of patients with EASI-50 (≥50% improvement from baseline) at Week 16 was 52 (22.0%) patients for placebo, 152 (65.2%) for Q2W and 146 (61.1%) for QW. The difference (95% CI) in % dupilumab – placebo was 43.2 (35.12 to 51.29) %, p <0.0001, for Q2W and 39.1 (30.92 to 47.19) %, p <0.0001, for QW.
- The proportion of patients with EASI-90 (≥90% improvement from baseline) at Week 16 was 17 (7.2%) patients for placebo, 70 (30.0%) for Q2W and 73 (30.5%) for QW. The difference (95% CI) in % dupilumab – placebo was 22.8 (16.09 to 29.59) %, p <0.0001, for Q2W and 23.3 (16.63 to 30.05) %, p <0.0001, for QW.
- The change from baseline to Week 16 in percent BSA involvement with AD was -14.48 (17.810) for placebo, -31.69 (19.614) for Q2W and -32.97 (20.400) for QW. The LS mean difference (95% CI) dupilumab – placebo was -17.99 (-22.062 to -13.927), p <0.0001, for Q2W and -19.51 (-23.491 to -15.529), p <0.0001, for QW.
- The mean percent change (SD) from baseline to Week 16 in the SCORAD was -22.7 (25.48) % for placebo, -53.5 (25.23) % for Q2W and -56.0 (25.53) % for QW. The LS mean difference

(95% CI) dupilumab – placebo was -31.4 (-37.36 to -25.40) %, p <0.0001, for Q2W and -33.8 (-39.75 to -27.80) %, p <0.0001, for QW.

- The mean (SD) change from baseline to Week 16 in the DLQI was -40 (5.75) for placebo, -9.7 (6.20) for Q2W and -10.3 (6.75) for QW. The LS mean difference (95% CI) dupilumab – placebo was -5.7 (-6.86 to -4.47), p <0.0001, for Q2W and -5.9 (-7.10 to -4.72), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in the POEM was -3.8 (6.07) for placebo, -10.7 (6.89) for Q2W and -11.7 (7.13) for QW. The LS mean difference (95% CI) dupilumab – placebo was -7.0 (-8.36 to -5.571), p <0.0001, for Q2W and -8.0 (-9.36 to -6.64), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in the HADS total score was -1.0 (4.44) for placebo, -5.2 (5.42) for Q2W and -6.2 (6.01) for QW. The LS mean difference (95% CI) dupilumab – placebo was -4.2 (-5.34 to -3.09), p <0.0001, for Q2W and -4.9 (-6.04 to -3.81), p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 16 in the GISS (erythema, infiltration/ papulation, excoriations, lichenification) was -20.3 (25.03) % for placebo, -47.5 (27.00) % for Q2W and -48.4 (27.29) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -27.7 (-33.73 to -21.70) %, p <0.0001, for Q2W and -28.9 (-35.03 to -22.74) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 2 in weekly average of peak daily pruritus NRS was -6.3 (21.91) % for placebo, -24.1 (21.22) % for Q2W and -21.2 (24.96) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -17.7 (-21.96 to -13.53), p <0.0001, for Q2W and -15.0 (-19.16 to -10.78), p <0.0001, for QW.
- There was no significant difference between the treatment groups in the change from baseline to Week 16 in the Asthma Control Questionnaire, 5-item version (ACQ-5): mean (SD) -0.09 (0.721) for placebo, -0.24 (0.715) for Q2W and -0.31 (0.708) for QW.
- There was a significant improvement in the dupilumab groups compared to placebo in the change from baseline to Week 16 in the Sinonasal Outcomes Test (SNOT-22) (total score and sub-scales): mean (SD) -3.47 (16.291) for placebo, -10.02 (15.630) for Q2W and -13.28 (15.778) for QW. The LS mean difference (95% CI) dupilumab – placebo was -7.76 (-13.515 to -2.000), p = 0.0086, for Q2W and -8.97 (-14.676 to -3.255), p = 0.0023, for QW.
- The mean (SD) change from baseline to Week 16 in the EQ-5D Index Utility Score was 0.0720 (0.28118) for placebo, 0.2375 (0.30308) for Q2W and 0.2825 (0.32847) for QW. The LS mean difference (95% CI) dupilumab – placebo was 0.1669 (0.12329 to 0.21043), p <0.0001, for Q2W and 0.1864 (0.14208 to 0.23069), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in the EQ-5D VAS Score was 4.4 (19.06) for placebo, 16.3 (22.48) for Q2W and 21.0 (23.18) for QW. The LS mean difference (95% CI) dupilumab – placebo was 10.9 (7.00 to 14.85), p <0.0001, for Q2W and 14.7 (10.63 to 18.76), p <0.0001, for QW.
- The proportion of patients who responded 'absence of pruritus' or 'mild pruritus' in the pruritus categorical scale at Week 16 was 48 (20.3%) patients for placebo, 121 (51.9%) for Q2W and 128 (53.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 31.6 (23.37 to 39.81) %, p <0.0001, for Q2W and 33.2 (25.07 to 41.36) %, p <0.0001, for QW.
- The proportion of patients who responded 'very good' or 'excellent' in the Patient Global Assessment of Disease Status at Week 16 was 28 (11.9%) patients for placebo, 89 (38.2%) for Q2W and 90 (37.7%) for QW. The difference (95% CI) in % dupilumab – placebo was 26.3 (18.85 to 33.81) %, p <0.0001, for Q2W and 25.8 (18.39 to 33.19) %, p <0.0001, for QW.

- The proportion of patients who responded 'very good' or 'excellent' in the Patient Global Assessment of Treatment Effect at Week 16 was 19 (8.1%) patients for placebo, 101 (43.3%) for Q2W and 105 (43.9%) for QW. The difference (95% CI) in % dupilumab – placebo was 35.3 (28.05 to 42.55) %, p <0.0001, for Q2W and 35.9 (28.70 to 43.07) %, p <0.0001, for QW.
- The proportion of patients who achieved reduction of IGA score by ≥2 points from baseline to Week 16 was 28 (12.1%) patients for placebo, 104 (44.6%) for Q2W and 104 (43.5%) for QW. The difference (95% CI) in % dupilumab – placebo was 32.8 (25.17 to 40.37) %, p <0.0001, for Q2W and 31.7 (24.13 to 39.17) %, p <0.0001, for QW.
- The proportion of patients who achieved reduction of IGA score by ≥3 points from baseline to Week 16 was three (1.3%) patients for placebo, 39 (16.7%) for Q2W and 42 (17.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 15.5 (10.47 to 20.47) %, p <0.0001, for Q2W and 16.3 (11.27 to 21.33) %, p <0.0001, for QW.
- The mean (SD) sick leave/missed school days for full-time was 2.62 (7.360) days for placebo, 1.22 (6.353) days for Q2W and 1.94 (8.910) days for QW.
- The mean (SD) sick leave/missed school days for part-time was 4.28 (8.001) days for placebo, 0.46 (1.623) days for Q2W and 0.50 (1.867) days for QW.

With regard to biomarkers:

- The median % change from baseline to Week 16 in TARC was -78.71% for QW, -80.31% for Q2W and -8.56 for placebo.
- The median % change from baseline to Week 16 in serum IgE was -45.29% for QW, -45.44% for Q2W and 12.12% for placebo.
- Decreases from baseline were observed for the dupilumab treatment groups compared with placebo during the treatment period in IgEs elicited against all allergen panels tested, including *Candida albicans, Dermatophagoides farinae,* staphylococcal enterotoxin A, cat dander, and *Pityrosporum (Malassezia)*.

There was no significant difference between the groups in hsCRP, ANA, anti-double stranded DNA or anti-thyroid peroxidase.

7.2.2.14. Evaluator commentary

Study SOLO 2 R668-AD-1416 was a replicate of Study SOLO 1 R668-AD-1334. The study confirmed all the major findings of Study SOLO 1 R668-AD-1334 with similar effect sizes.

7.2.3. Study CHRONOS 1 R668-AD-1224

7.2.3.1. Study design, objectives, locations and dates

Study CHRONOS R668-AD-1224 was a randomised, double blind, parallel group, placebo controlled trial of dupilumab when administered concomitantly with topical corticosteroids (TCS) in patients with AD for up to 52 weeks. The study was conducted at 162 sites in 14 countries. The sponsor has provided an interim report for the cutoff date of 27 April 2016. The treatment phase was for 52 weeks with a 12-week follow-up phase.

7.2.3.2. Inclusion and exclusion criteria

The inclusion criteria were the same as for Study SOLO 1 R668-AD-1334, with the exception that patients who could not tolerate topical treatments or for whom they were contraindicated were excluded from the study.

The exclusion criteria were similar to Study SOLO 1 R668-AD-1334 with the following important additional exclusion criteria:

- Important side effects of topical medication (for example, intolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or the patient's treating physician
- At the baseline visit ≥30% of the total lesional surface located on areas of thin skin that could not be safely treated with medium or higher potency TCS (for example, face, neck, intertriginous areas, genital areas, areas of skin atrophy)

7.2.3.3. Study treatments

The study treatments were:

1. Dupilumab 600 mg (loading dose), followed by 300 mg once weekly (QW)
2. Dupilumab 600 mg (loading dose), followed by 300 mg every second week (Q2W)
3. Placebo

Treatments were administered subcutaneously. The same site was not injected for two consecutive weeks. Patients had the option to self-administer study drug outside the study site during weeks in which no clinic visit was scheduled.

All patients also received medium potency TCS which was applied once daily to active areas, with step-down to low potency TCS. Patients were recommended triamcinolone acetonide 0.1% cream or fluocinolone acetonide 0.025% ointment for medium potency, and hydrocortisone 1% cream for low potency. If rescue with TCS was needed, it was recommended that patients use mometasone 0.1% ointment for high potency and either betamethasone dipropionate 0.05% optimized ointment or clobetasol propionate 0.05% cream for super high potency TCS.

All patients were required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization and to continue throughout the study. For AD, permitted medications and procedures included basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anaesthetics, topical and systemic antihistamines, and topical and systemic anti-infective medications for any duration.

Treatments that were prohibited were the same as for the exclusion criteria:

- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics
- Treatment with wet wraps
- Any other medications for AD that could have interfered with efficacy outcomes or affected the evaluation for AD severity.

7.2.3.4. Efficacy variables and outcomes

The primary efficacy endpoints were the same as for Study SOLO 1 R668=AD-1334 and Study SOLO 2 R668-AD-1416. The key secondary endpoints were:

- Proportion of patients with EASI-75 response (reduction of EASI score by ≥75% from baseline) at Week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 16
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥3 from baseline to Week 16
- Proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at week 52
- Proportion of patients with EASI-75 response at week 52

- Percent change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 52
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥3 from baseline to Week 52
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 24
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 4
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 2

Other secondary efficacy endpoints were:

- Change from baseline to Week 16 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to Week 16
- Change from baseline to Week 16 in percent BSA
- Percent change in SCORAD from baseline to Week 16
- Change from baseline to Week 16 in DLQI
- Change from baseline to Week 16 in POEM
- Change from baseline to Week 16 in HADS
- Percent change from baseline to Week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Proportion of topical AD medication-free day on-treatment period (week 52)
- Percent change from baseline to Week 2 in weekly average of peak daily Pruritus NRS
- Percent change in EASI score from baseline to Week 52
- Change from baseline to Week 52 in percent BSA
- Percent change in SCORAD from baseline to Week 52
- Percent change from baseline to Week 52 in GISS (erythema, infiltration/papulation, excoriations, lichenification)
- Change from baseline to Week 52 in DLQI
- Change from baseline to Week 52 in POEM
- Change from baseline to Week 52 in HADS
- Incidence rate of flares through week 52
- Change in Asthma Control Questionnaire 5-item version (ACQ-5) score from baseline to Week 16
- Change in Sinonasal Outcome Test-22 (SNOT-22) score from baseline to Week 16
- Change in ACQ-5 score from baseline to Week 52
- Change in SNOT-22 score from baseline to Week 52

- Proportion of patients with skin infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections, high-level term [HLT] = Herpes viral infections) from baseline through week 52
- Incidence of skin infection TEAEs (excluding herpetic infections, HLT = Herpes viral infections) from baseline through week 52
- Proportion of patients with skin infection TEAEs (excluding herpetic infections, HLT = Herpes viral infections) requiring systemic treatment from baseline through week 52
- Incidence of skin infection TEAEs (excluding herpetic infections, HLT = Herpes viral infections) requiring systemic treatment from baseline through week 52

Exploratory efficacy outcome measures were:

- Percentage of patients with IGA 0 to 1 at Week 16 and maintaining IGA 0 to 1 on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52
- Percentage of patients with IGA 0 to 1 at Week 16 and maintaining IGA 0 to 2 on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52)
- Percentage of patients achieving EASI-75 response (reduction of EASI score by at least 75% from baseline) at Week 16, and maintaining EASI-50 response on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52)
- Proportion of well-controlled weeks
- Additional endpoints based on POEM, EQ-5D, patient global assessment of disease, atopic keratoconjunctivitis (AKC), and sick leave/missed school days
- Time to first relapse (for example, IGA >2) for IGA 0 to 1 responders at week 52 during the off-treatment period

Up to Week 12 the schedule of study events was the same as for Study SOLO 1 R668-AD-1334.

7.2.3.5. Randomisation and blinding methods

Randomisation was by IVRS/IWRS in the ratio 3:1:3 for QW: Q2W: placebo. Randomisation was stratified by baseline disease severity and by region. Blinding was maintained by identical placebo so that all patients received a weekly injection.

7.2.3.6. Analysis populations

The FAS included all randomised patients. The SAF included all randomised patients who received any study drug and was analysed as-treated.

7.2.3.7. Sample size

The final sample size was determined by the safety evaluation because the number required to for efficacy was less. To demonstrate efficacy, it was estimated that with 300, 100, and 300 patients in the dupilumab 300 mg QW, dupilumab 300 mg Q2W, and placebo groups, respectively, the study could provide 99% power in both comparisons (between dupilumab 300 mg QW and placebo treatment, and between dupilumab 300 mg Q2W and placebo treatment) to detect a difference of 29% between dupilumab and placebo treatment in the percentage of patients who achieved an IGA score 0 to 1 at Week 16, assuming that the percentages were 38% and 9% for dupilumab and placebo, respectively. The same numbers of patients could also provide 99% power in both comparisons assuming that the percentages of patients achieving EASI-75 responder at Week 16 were 58% and 15% for dupilumab and placebo, respectively.

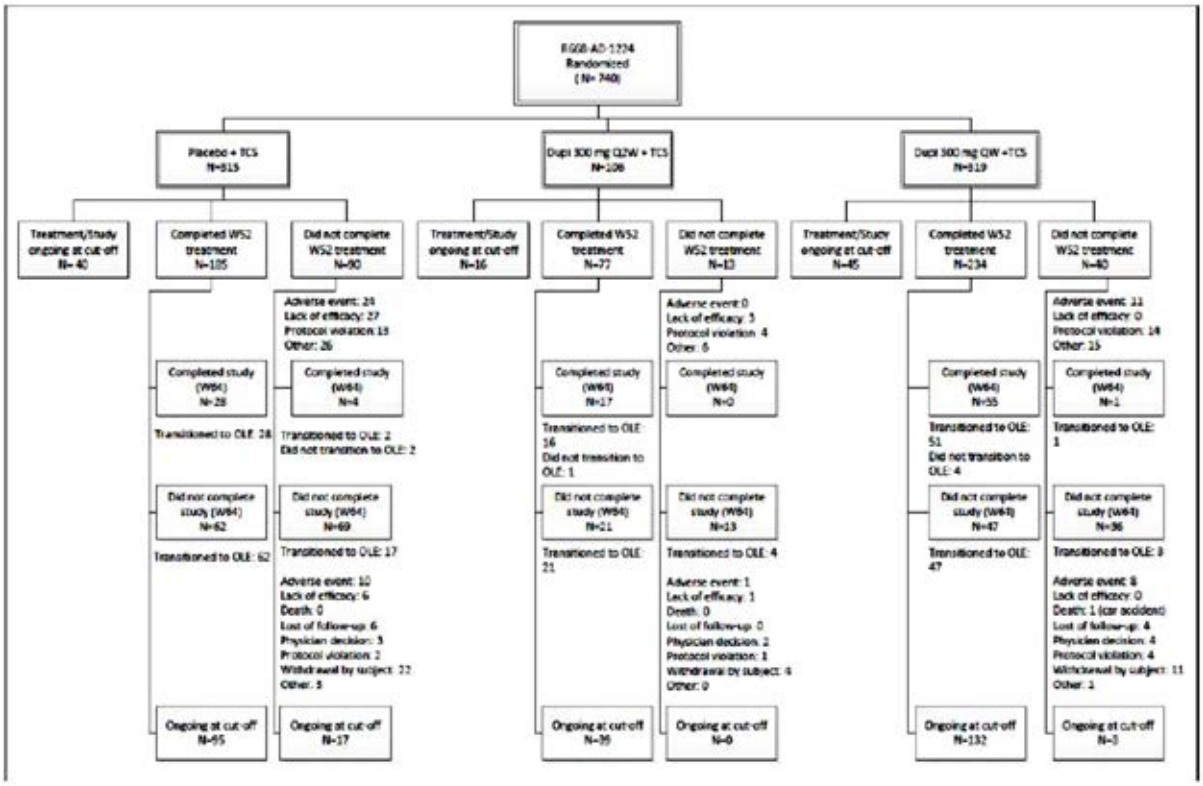
7.2.3.8. Statistical methods

The statistical methods were the same as for Study SOLO 1 R668-AD-1334.

7.2.3.9. Participant flow

There were 957 patients screened and 740 were randomised: 315 to placebo, 106 to dupilumab Q2W and 319 to dupilumab QW. The majority of the patients were still participating in the study at the cutoff date.[2] There were 95 (30.2%) patients in the placebo group, 39 (36.8%) in the Q2W and 132 (41.4%) in the QW who completed 52 weeks. In total 19 (2.6%) subjects withdrew because of adverse event. Participant flow is summarised in Figure 33.

Figure 33: Schematic of Patient Disposition – All Randomized Patients



Abbreviations: AE, adverse event; EOS, end of study; Q2W, every 2 weeks; QW, weekly; TCS, topical corticosteroids.

7.2.3.10. Major protocol violations/deviations

There were major protocol deviations in 44 (14.0%) patients in the placebo group, 14 (13.2%) in the Q2W and 40 (12.5%) in the QW. The commonest major protocol deviation was 'procedure not performed'.

7.2.3.11. Baseline data

There were 446 (60.3%) males, 294 (39.7%) females and the age range was 18 to 81 years. There were 27 (3.6%) patients aged ≥65 years. There were 41 (55.5%) patients treated in Australia. The treatment groups were similar in demographic characteristics. The treatment groups were similar in baseline disease characteristics and outcome measures. Medical history was similar for the three treatment groups. Allergic / atopic disease history was similar for the three treatment groups. A higher proportion of patients in the placebo group required rescue treatment in the initial 16-week treatment period: 120 (38.1%) in the placebo group, 12 (10.9%) in the Q2W and 34 (10.8%) in the QW. A higher proportion of patients in the placebo group required rescue treatment in the 52-week treatment period: 164 (52.1%) in the placebo group, 18 (16.4%) in the Q2W and 55 (17.5%) in the QW. Mean (SD) adherence to study treatment was 96.86 (7.702) % for placebo, 96.89 (6.307) for Q2W and 97.93 (4.878) for QW.

[2] Data from 623 patients were available for primary analysis at Week 52 and 101 patients were still in the treatment period.

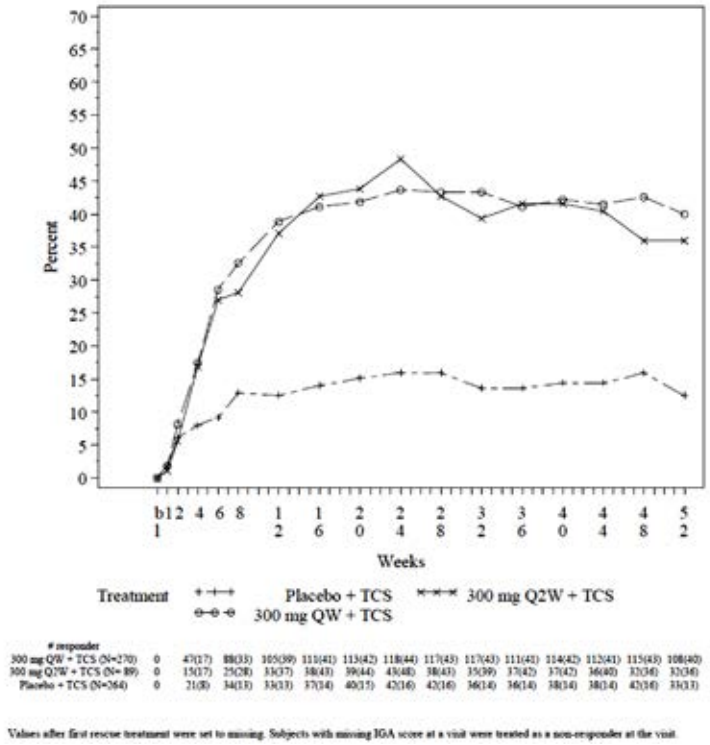
7.2.3.12. Results for the primary efficacy outcome

- The proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 was 39 (12.4%) patients for placebo, 41 (38.7%) for Q2W and 125 (39.2%) for QW. The difference (95% CI) in % dupilumab – placebo was 26.3 (16.34 to 36.26) %, p <0.0001, for Q2W and 26.8 (20.33 to 33.28) %, p <0.0001, for QW.
- The proportion of patients with EASI-75 at Week 16 was 73 (23.2%) patients for placebo, 73 (68.9%) for Q2W and 204 (63.9%) for QW. The difference (95% CI) in % dupilumab – placebo was 45.7 (35.72 to 55.66) %, p <0.0001, for Q2W and 40.8 (33.74 to 47.81) %, p <0.0001, for QW.

Subgroup analysis did not identify any significant difference between subgroups in response.

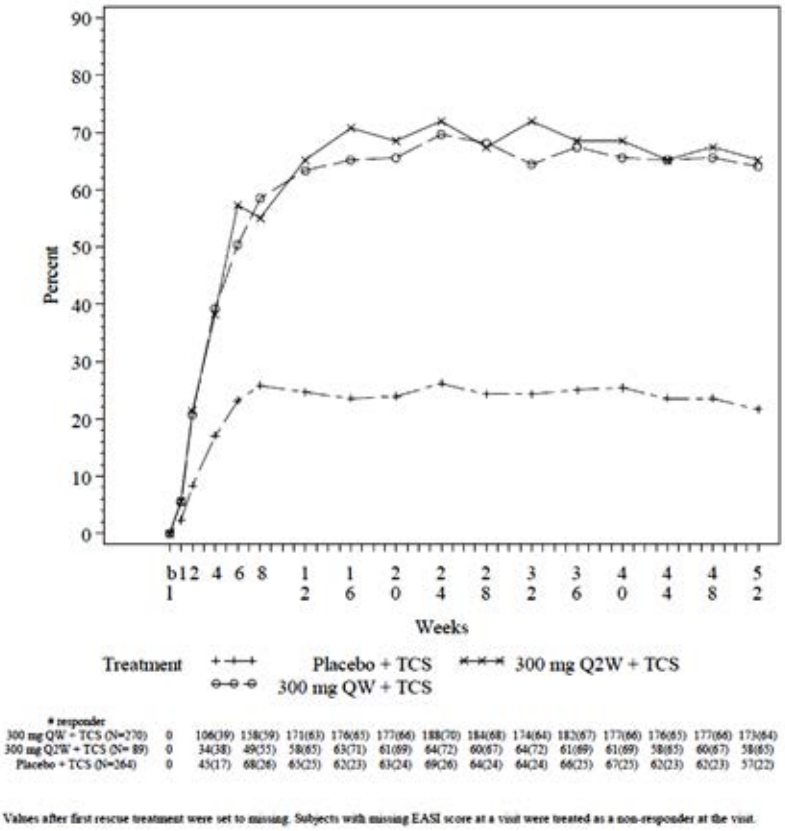
The improvements in the proportion of patients with IGA 0 or 1 were apparent from Week 8 and persisted to Week 52 (Figure 34).

Figure 34: Proportion of Patients Achieving IGA 0 to 1 and a Reduction of ≥2 Points from Baseline through Week 52, Patient Considered as Non-Responder after Rescue Treatment Use – FAS Week 52



The improvements in the proportion of patients with EASI-75 were apparent from Week 8 and persisted to Week 52 (Figure 35).

Figure 35: Proportion of Patients Achieving EASI-75 from Baseline through Week 52, Patient Considered as Non-Responder after Rescue Treatment Use – FAS Week 52



Values after first rescue treatment were set to missing. Subjects with missing EASI score at a visit were treated as a non-responder at the visit.

7.2.3.13. Results for other efficacy outcomes

- The proportion of patients with IGA 0 or 1 and a reduction from baseline of ≥2 points at week 52 was 33 (12.5%) patients for placebo, 32 (36.0%) for Q2W and 108 (40.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 23.5 (12.72 to 34.19) %, p <0.0001, for Q2W and 27.5 (20.42 to 34.58) %, p <0.0001, for QW.
- The percentage of patients with IGA 0 to 1 at Week 16 and maintaining IGA 0 to 1 on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52 was 20 (7.6%) patients for placebo, 22 (24.7%) for Q2W and 80 (29.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 17.1 (7.63 to 26.66) %, p <0.0001, for Q2W and 22.1 (15.74 to 28.37) %, p <0.0001, for QW.
- The percentage of patients with IGA 0 to 1 at Week 16 and maintaining IGA 0 to 2 on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52) was 27 (10.2%) patients for placebo, 35 (39.3%) for Q2W and 100 (37.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 29.1 (18.31 to 39.89) %, p <0.0001, for Q2W and 26.8 (19.99 to 33.63) %, p <0.0001, for QW.
- The proportion of patients with EASI-75 response at week 52 was 57 (21.6%) patients for placebo, 58 (65.2%) for Q2W and 173 (64.1%) for QW. The difference (95% CI) in % dupilumab – placebo was 46.3 (32.50 to 54.65) %, p <0.0001, for Q2W and 42.5 (34.91 to 50.06) %, p <0.0001, for QW.
- The mean (SD) percent change in EASI score from baseline to Week 16 was -48.9 (33.78) for placebo, -81.1 (20.30) for Q2W and -82.0 (19.73) for QW. The LS mean difference (95% CI) dupilumab – placebo was -32.1 (-46.37 to -17.82) for Q2W and -33.1 (-46.98 to -19.24) for QW.

- The mean (SD) percent change in EASI score from baseline to Week 52 was -61.1 (26.71) for placebo, -85.3 (16.40) for Q2W and -87.9 (17.12) for QW. The LS mean difference (95% CI) dupilumab – placebo was -24.0 (-38.85 to -9.14) for Q2W and -26.9 (-41.25 to -12.51) for QW.
- The percentage of patients achieving EASI-75 response (reduction of EASI score by at least 75% from baseline) at Week 16, and maintaining EASI-50 response on at least 6 of the 9 subsequent Q4W visits (from visits at weeks 20, 24, 28, 32, 36, 40, 44, 48, and week 52) was 47 (17.8%) patients for placebo, 59 (66.3%) for Q2W and 161 (59.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 48.5 (37.64 to 59.34) %, p <0.0001, for Q2W and 41.8 (34.37 to 49.28) %, p <0.0001, for QW.
- Proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 16 was 59 (19.7%) patients for placebo, 60 (58.8%) for Q2W and 150 (50.8%) for QW. The difference (95% CI) in % dupilumab – placebo was 39.1 (28.53 to 49.65) %, p <0.0001, for Q2W and 31.1 (23.84 to 38.39) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥3 from baseline to Week 16 was 85 (27.8%) patients for placebo, 69 (65.7%) for Q2W and 193 (62.5%) for QW. The difference (95% CI) in % dupilumab – placebo was 37.9 (27.56 to 48.31) %, p <0.0001, for Q2W and 34.7 (27.31 to 42.05) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 16 in weekly average of peak daily Pruritus NRS was -30.9 (30.08) for placebo, -57.4 (27.71) for Q2W and -56.9 (36.58) for QW. The LS mean difference (95% CI) dupilumab – placebo was -26.2 (-35.04 to -17.43) for Q2W and -26.8 (-32.83 to -20.73) for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 52 was 32 (12.9%) patients for placebo, 44 (51.2%) for Q2W and 97 (39.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 38.3 (26.97 to 49.66) %, p <0.0001, for Q2W and 26.1 (18.76 to 33.45) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥3 from baseline to Week 52 was 40 (15.6%) patients for placebo, 49 (55.7%) for Q2W and 112 (42.9%) for QW. The difference (95% CI) in % dupilumab – placebo was 40.1 (28.76 to 51.35) %, p <0.0001, for Q2W and 27.3 (19.81 to 34.76) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 24 was 48 (16.1%) patients for placebo, 55 (53.9%) for Q2W and 129 (43.7%) for QW. The difference (95% CI) in % dupilumab – placebo was 37.9 (27.34 to 48.40) %, p <0.0001, for Q2W and 27.7 (20.65 to 34.70) %, p <0.0001, for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 4 was 49 (16.4%) patients for placebo, 38 (37.3%) for Q2W and 80 (27.1%) for QW. The difference (95% CI) in % dupilumab – placebo was 20.9 (10.59 to 31.15) %, p <0.0001, for Q2W and 10.7 (4.15 to 17.31) %, p = 0.0021, for QW.
- The proportion of patients with improvement (reduction) of weekly average of peak daily Pruritus NRS ≥4 from baseline to Week 2 was 24 (8.0%) patients for placebo, 18 (17.6%) for Q2W and 40 (13.6%) for QW. The difference (95% CI) in % dupilumab – placebo was 9.6 (1.61 to 17.63) %, p = 0.0062, for Q2W and 5.5 (0.56 to 10.51) %, p = 0.0344 for QW.

- The mean (SD) change from baseline to Week 16 in weekly average of peak daily Pruritus NRS was -2.45 (2.203) for placebo, -4.30 (2.192) for Q2W and -4.23 (2.328) for QW. The LS mean difference (95% CI) dupilumab – placebo was -1.81 (-2.297 to -1.322), p <0.0001, for Q2W and –1.91 (-2.266 to -1.550), p <0.0001, for QW.
- The mean (SD) percent change from baseline to Week 2 in weekly average of peak daily Pruritus NRS was -20.1 (22.48) for placebo, -27.7 (22.47) for Q2W and -25.8 (31.80) for QW. The LS mean difference (95% CI) dupilumab – placebo was -7.6 (-13.57 to -1.56), p = 0.0136, for Q2W and –6.0 (-10.26 to -1.73), p = 0.0059, for QW.
- The mean (SD) change from baseline to Week 16 in percent BSA was -22.89 (19.006) % for placebo, -42.72 (20.384) % for Q2W and -38.93 (19.585) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -18.38 (-22.583 to -14.187) %, p <0.0001, for Q2W and –17.58 (-20.626 to -14.528) %, p <0.0001, for QW.
- The mean (SD) change from baseline to Week 52 in percent BSA was -30.43 (19.643) % for placebo, -42.31 (19.755) % for Q2W and -42.77 (20.780) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -14.34 (-18.550 to -10.123) %, p <0.0001, for Q2W and –14.26 (-17.709 to -10.817) %, p <0.0001, for QW.
- The mean (SD) percent change in SCORAD from baseline to Week 16 was -36.5 (25.56) % for placebo, -64.6 (19.38) % for Q2W and -66.2 (19.77) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -27.7 (-33.46 to -21.90) %, p <0.0001, for Q2W and –29.7 (-33.88 to -25.49) %, p <0.0001, for QW.
- The mean (SD) percent change in SCORAD from baseline to Week 52 was -47.7 (22.78) % for placebo, -70.7 (17.12) % for Q2W and -70.7 (18.29) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -22.4 (-29.44 to -15.31) %, p <0.0001, for Q2W and –23.1 (-28.32 to -17.86) %, p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in DLQI was -6.0 (6.33) for placebo, -10.0 (7.33) for Q2W and -10.8 (6.71) for QW. The LS mean difference (95% CI) dupilumab – placebo was -4.2 (-5.31 to -3.02), p <0.0001, for Q2W and –4.9 (-5.82 to -4.08), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 52 in DLQI was -7.4 (6.23) for placebo, -11.5 (7.07) for Q2W and -11.1 (7.00) for QW. The LS mean difference (95% CI) dupilumab – placebo was -4.2 (-5.54 to -2.94), p <0.0001, for Q2W and –3.9 (-4.89 to -2.99), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in POEM was -5.4 (6.68) for placebo, -13.0 (6.92) for Q2W and -13.1 (7.13) for QW. The LS mean difference (95% CI) dupilumab – placebo was -7.4 (-8.85 to -5.93), p <0.0001, for Q2W and –7.6 (-8.70 to -6.57), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 52 in POEM was -7.0 (6.51) for placebo, -14.5 (6.66) for Q2W and -13.4 (7.16) for QW. The LS mean difference (95% CI) dupilumab – placebo was -7.2 (-9.02 to -5.35), p <0.0001, for Q2W and –6.2 (-7.59 to -4.79), p <0.0001, for QW.
- The mean (SD) change from baseline to Week 16 in HADS was -4.0 (5.57) for placebo, -5.1 (7.46) for Q2W and -5.5 (5.95) for QW. The LS mean difference (95% CI) dupilumab – placebo was -1.0 (-2.27 to 0.37), p = 0.1596, for Q2W and –1.4 (-2.40 to -0.45), p = 0.0042, for QW.
- The mean (SD) change from baseline to Week 52 in HADS was -4.1 (5.96) for placebo, -6.0 (7.02) for Q2W and -6.2 (6.46) for QW. The LS mean difference (95% CI) dupilumab – placebo was -1.7 (-3.28 to -0.13), p = 0.0337, for Q2W and –2.0 (-3.21 to -0.84), p = 0.0008, for QW.

- The mean (SD) percent change from baseline to Week 16 in GISS (erythema, infiltration/papulation, excoriations, lichenification) was -33.1 (26.32) % for placebo, -55.7 (23.68) % for Q2W and -59.9 (22.42) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -22.2 (-28.43 to -15.87) %, p <0.0001, for Q2W and –26.0 (-30.86 to -21.14) %, p <0.0001, for QW.
- The mean (SD) percent change from baseline to week 58 in GISS (erythema, infiltration/papulation, excoriations, lichenification) was -41.2 (24.82) % for placebo, -63.9 (22.44) % for Q2W and -65.0 (22.01) % for QW. The LS mean difference (95% CI) dupilumab – placebo was -21.9 (-29.35 to -14.55) %, p <0.0001, for Q2W and –23.6 (-29.89 to -17.22) %, p <0.0001, for QW.
- The mean (SD) change in Asthma Control Questionnaire 5-item version (ACQ-5) score from baseline to Week 16 was -0.14 (0.911) for placebo, -0.20 (0.868) for Q2W and -0.36 (0.919) for QW. The LS mean difference (95% CI) dupilumab – placebo was -0.07 (-0.354 to 0.208), p = 0.6093, for Q2W and –0.24 (-0.448 to -0.032), p = 0.0239, for QW.
- The mean (SD) change in ACQ-5 score from baseline to Week 52 was -0.11 (0.768) for placebo, -0.22 (0.746) for Q2W and -0.38 (0.866) for QW. The LS mean difference (95% CI) dupilumab – placebo was -0.11 (-0.457 to 0.238), p = 0.5351, for Q2W and –0.30 (-0.568 to -0.032), p = 0.0287, for QW.
- The mean (SD) change in Sinonasal Outcome Test-22 (SNOT-22) score from baseline to Week 16 was -3.02 (11.632) for placebo, -4.81 (14.442) for Q2W and -11.20 (16.275) for QW. The LS mean difference (95% CI) dupilumab – placebo was -1.61 (-7.271 to 4.044), p = 0.5750, for Q2W and –5.62 (-10.392 to -0.853), p = 0.0211, for QW.
- The mean (SD) change in SNOT-22 score from baseline to Week 52 was -2.41 (17.302) for placebo, -7.08 (18.096) for Q2W and -13.84 (20.012) for QW. The LS mean difference (95% CI) dupilumab – placebo was -4.01 (-14.360 to 6.343), p = 0.4454, for Q2W and –6.99 (-15.321 to -1.351), p = 0.0999, for QW.
- The incidence rate (95% CI) of flares through week 52 was 0.77 (0.633 to 0.929) flares per patient-year in the placebo group, 0.19 (0.119 to 0.319) flares per patient-year in the Q2W and 0.17 (0.126, 0.233) flares per patient-year in the QW. The relative risk (95% CI) for flares was 0.25 (0.150 to 0.430), p <0.0001, for Q2W and 0.22 (0.157 to 0.319), p <0.0001, for QW.
- The proportion of patients with skin infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections, high-level term [HLT] = Herpes viral infections) from baseline through week 52 was 56 (17.8%) patients for placebo, 12 (10.9%) for Q2W and 26 (8.3%) for QW. The difference (95% CI) in % dupilumab – placebo was -6.9 (-14.06 to 0.33) %, p= 0.925, for Q2W and -9.5 (-14.73 to -4.32) %, p = 0.0004, for QW.
- The incidence rate (95% CI) of skin infection TEAEs (excluding herpetic infections, HLT = Herpes viral infections) from baseline through week 52 was 0.260 (0.1948 to 0.3480) per patient-year in the placebo group, 0.135 (0.0749 to 0.2447) per patient-year in the Q2W and 0.089 (0.0586, 0.1348) per patient-year in the QW. The relative risk (95% CI) for flares was 0.520 (0.2729 to 0.9904), p = 0.0467, for Q2W and 0.341 (0.2096 to 0.5560), p <0.0001, for QW.
- The proportion of patients with skin infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections, high-level term [HLT] = Herpes viral infections) requiring systemic treatment from baseline through week 52 was 30 (9.58%) patients for placebo, six (5.5%) for Q2W and 12 (3.8%) for QW. The difference (95% CI) in % dupilumab – placebo was -4.1 (-9.41 to 1.27) %, p= 0.1854, for Q2W and -5.7 (-9.58 to -1.84) %, p = 0.0041, for QW.

- The incidence rate (95% CI) of skin infection TEAEs (excluding herpetic infections, HLT = Herpes viral infections) requiring systemic treatment from baseline through week 52 was 0.127 (0.0821 to 0.1955) per patient-year in the placebo group, 0.056 (0.0226 to 0.1366) per patient-year in the Q2W and 0.034 (0.0176, 0.0651) per patient-year in the QW. The relative risk (95% CI) for flares was 0.439 (0.1675 to 1.1483), p = 0.0933, for Q2W and 0.267 (0.1287 to 0.5556), p = 0.0004, for QW.
- The mean (SD) proportion of topical AD medication-free day on-treatment period (week 52) was 10.5 (23.68) for placebo, 16.6 (30.08) for Q2W and 22.5 (33.69) for QW. The comparison dupilumab to placebo was p = 0.0677 for Q2W and p <0.0001 for QW.
- The proportion of well-controlled weeks on-treatment period (week 52) was 121 (65.4) for placebo, 63 (84.0) for Q2W and 174 (83.7) for QW. The comparison dupilumab to placebo was p = 0.0035 for Q2W and p <0.0001 for QW.
- The mean (SD) change in EQ-5D Index Utility Score from baseline at Week 16 was 0.1701 (0.28201) for placebo, 0.2168 (0.26894) for Q2W and 0.2545 (0.28842) for QW. The LS mean difference (95% CI) dupilumab – placebo was 0.0602 (0.01743 to 0.10299), p = 0.0058, for Q2W and 0.0926 (0.06129 to 0.12391), p <0.0001, for QW.
- The mean (SD) change in EQ-5D VAS Score from baseline at Week 16 was 9.7 (19.74) for placebo, 19.6 (22.08) for Q2W and 22.2 (22.92) for QW. The LS mean difference (95% CI) dupilumab – placebo was 10.9 (6.92 to 14.80), p <0.0001, for Q2W and 12.1 (9.20 to 14.99), p <0.0001, for QW.
- The proportion of patients who responded 'absence of pruritus' at Week 16 was 103 (32.7%) patients for placebo, 70 (66.0%) for Q2W and 220 (69.0%) for QW. The difference (95% CI) in % dupilumab – placebo was 33.3 (22.94 to 43.74) %, p<0.0001, for Q2W and 36.3 (29.01 to 43.52) %, p <0.0001, for QW.
- The proportion of patients who responded 'very good' or 'excellent' at Week 16 in the Patient Global Assessment of disease status was 49 (15.6%) patients for placebo, 53 (50.0%) for Q2W and 175 (54.9%) for QW. The difference (95% CI) in % dupilumab – placebo was 34.4 (24.12 to 44.77) %, p<0.0001, for Q2W and 39.3 (32.53 to 46.07) %, p <0.0001, for QW.
- The proportion of patients who responded 'very good' or 'excellent' at Week 16 in the Patient Global Assessment of treatment effect was 52 (16.5%) patients for placebo, 61 (57.5%) for Q2W and 184 (57.7%) for QW. The difference (95% CI) in % dupilumab – placebo was 41.0 (30.78 to 51.30) %, p<0.0001, for Q2W and 41.2 (34.38 to 47.97) %, p <0.0001, for QW.
- The mean (SD) sick leave/missed school days for full-time was 2.28 (9.699) days for placebo, 0.43 (2.454) days for Q2W and 0.63 (3.192) days for QW.
- The mean (SD) sick leave/missed school days for part-time was 2.35 (6.845) days for placebo, 0.98 (2.857) days for Q2W and 0.71 (2.957) days for QW.

With regard to biomarkers:

- The median % change from baseline to Week 52 in TARC was -88.19 % for QW, -81.50 % for Q2W and -34.14 % for placebo.
- The median % change from baseline to Week 16 in serum IgE was -74.75% for QW, -73.88 % for Q2W and 0.00 % for placebo.
- The median % change from baseline to Week 16 in hs-CRP -37.84 % for QW, -31.93 % for Q2W and -16.67 % for placebo.

- The median % change from baseline to Week 52 in hs-CRP -35.47 % for QW, -24.56 % for Q2W and -13.56 % for placebo.
- Decreases from baseline were observed for the dupilumab treatment groups compared with placebo during the treatment period in IgEs elicited against most allergen panels tested, including staphylococcal enterotoxin A, staphylococcal enterotoxin B, grass allergen panels and tree allergen panels.

There was no significant difference between the groups in ANA, anti-double stranded DNA or anti-thyroid peroxidase.

7.2.3.14. Evaluator commentary

Study CHRONOS R668-AD-1224 was similar in design to Study SOLO 1 R668-AD-1334, but was of much longer duration and used TCS as concomitant treatment. The primary efficacy outcome measures were the same.

The study was appropriate to the proposed indication. The inclusion and exclusion criteria ensured a study population of patients *with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies* but excluded patients for whom *those therapies are not advisable.* In this case, the study examined dupilumab as concomitant treatment with TCS.

The study showed clear superiority (clinically and statistically significant) in comparison to placebo for both dupilumab Q2W and QW when used concomitantly with TCS. Efficacy was similar for Q2W and QW, i.e. there was no benefit for QW over Q2W. Superiority was also demonstrated for quality of life measures in addition to disease severity and symptomatology measures.

However, there was no demonstration of efficacy for dupilumab Q2W in the treatment of asthma or sinusitis.

7.3. Other efficacy studies

7.3.1. Study R668-AD-1021

Study R668-AD-1021 was a randomised, double-blind, dose ranging study of dupilumab in patients with moderate to severe AD. The study was conducted at 91 sites in seven countries from May 2013 to September 2014. The study included male or females, 18 years or older, with chronic AD, EASI score ≥12, IGA score ≥3, ≥10% BSA of AD involvement and inadequate response to outpatient treatment with topical medications, or for whom topical treatments are otherwise inadvisable. The study treatments were:

1. Dupilumab 400 mg loading dose, then 100 mg Q4W
2. Dupilumab 600 mg loading dose, then 300 mg Q4W
3. Dupilumab 400 mg loading dose, then 200 mg Q2W
4. Dupilumab 600 mg loading dose, then 300 mg Q2W
5. Dupilumab 600 mg loading dose, then 300 mg QW
6. Placebo

Patients were required to apply stable doses of a topical emollient (moisturizer) twice daily for at least 7 days before the baseline visit and at least 7 days after the baseline visit. The primary efficacy outcome measure was the change in EASI to Week 16. Secondary efficacy outcome measures were IGA, pruritus scores, SCORAD, POEM and GISS. There were 452 patients screened and 380 were randomised: 65 to 100 mg Q4W, 65 to 300 mg Q4W, 62 to 200 mg Q2W,

64 to 300 mg Q2W, 63 to 300 mg QW and 61 to placebo. There were 234 (61.7%) males, 145 (38.3%) females and the age range was 18 to 75 years.

All active treatment were superior to placebo, but the greatest efficacy by the primary efficacy outcome measure was in the 300 mg QW and 300 mg Q2W groups (Table 10). This was supported by the change in IGA scores (Table 11), change in pruritus scores (Table 12), change in SCORAD score (Table 13), and change in POEM score (Table 14). The largest reduction in GISS was seen with the 300 mg Q2W dose level.

Table 10: Percent Change in EASI Score from Baseline to Week 16 – FAS (LOCF)

		Dupilumab				
	Placebo QW (N=61)	100 mg Q4W (N=65)	300 mg Q4W (N=65)	200 mg Q2W (N=61)	300 mg Q2W (N=64)	300 mg QW (N=63)
Baseline						
n	61	65	65	61	64	63
Mean (SD)	32.9 (13.77)	32.2 (13.49)	29.4 (11.48)	32.9 (15.50)	33.8 (14.52)	30.1 (11.23)
Median	31	28	25	28	34	28
Min : Max	15 : 67	16 : 70	16 : 57	16 : 69	11 : 72	16 : 72
Week 16						
n	61	64	65	60	63	61
Mean (SD)	25.6 (18.32)	17.4 (15.28)	9.8 (11.16)	10.9 (12.41)	10.7 (12.89)	7.2 (8.83)
Median	19	14	6	6	6	5
Min : Max	3 : 69	0 : 57	0 : 56	0 : 52	0 : 52	0 : 54
% Change from Baseline to Week 16						
n	61	64	65	60	63	61
Mean (SD)	-20.2 (46.15)	-46.7 (41.96)	-64.9 (37.21)	-67.4 (31.97)	-70.5 (35.09)	-75.5 (26.86)
Median	-20	-55	-75	-80	-78	-82
Min : Max	-92 : 107	-100 : 59	-100 : 66	-100 : 26	-100 : 106	-100 : 44
LS Mean (SE)	-18.1 (5.20)	-44.8 (4.99)	-63.5 (4.94)	-65.4 (5.19)	-68.2 (5.12)	-73.7 (5.16)
LS Mean Difference vs. Placebo (SE)		-26.8 (6.65)	-45.4 (6.66)	-47.4 (6.76)	-50.1 (6.67)	-55.7 (6.74)
95% C.I.		(-39.8, -13.7)	(-58.5, -32.3)	(-60.6, -34.1)	(-63.3, -37.0)	(-68.9, -42.4)
P-value*		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

* P-values were derived from ANCOVA model, which includes treatment, baseline, region, and baseline IGA strata. Values after first rescue medication use were set to missing. Missing values were imputed by LOCF.

Table 11: Number of Patients Achieving an IGA Score of 0 or 1 at Week 16 FAS (All Observed Values with Censoring after Rescue Medication Use – Missing Treated as a Non-Responder)

		Dupilumab				
	Placebo QW (N=61)	100 mg Q4W (N=65)	300 mg Q4W (N=65)	200 mg Q2W (N=61)	300 mg Q2W (N=64)	300 mg QW (N=63)
Week 16						
Number and proportion of patients achieving an IGA Score of 0 or 1	1 (1.6%)	8 (12.3%)	14 (21.5%)	17 (27.9%)	19 (29.7%)	21 (33.3%)
95% CI	(0.04, 8.80)	(5.47, 22.82)	(12.31, 33.49)	(17.15, 40.83)	(18.91, 42.42)	(21.95, 46.34)
Difference vs. Placebo		10.7	19.9	26.2	28.0	31.7
(95% CI)		(2.07, 19.27)	(9.41, 30.39)	(14.54, 37.92)	(16.41, 39.69)	(19.63, 43.76)
P-value vs. placebo *		0.0242	0.0004	<0.0001	<0.0001	<0.0001

* P-values were derived by CMH stratified by region and baseline IGA strata.
Values after first rescue medication use were set to missing. Patients with missing IGA score at week 16 were treated as a non-responder.

Table 12: Percent Change from Baseline in Peak Weekly Averaged Pruritus NRS Scores at Week 16 FAS (LOCF)

		Dupilumab				
	Placebo QW (N=61)	100 mg Q4W (N=65)	300 mg Q4W (N=65)	200 mg Q2W (N=61)	300 mg Q2W (N=64)	300 mg QW (N=63)
Baseline						
n	58	64	63	59	63	62
Mean (SD)	6.34 (1.832)	6.71 (1.882)	6.84 (1.853)	6.98 (2.315)	6.74 (2.072)	6.54 (1.540)
Median	6.3	6.8	7.0	7.1	7.1	6.6
Min : Max	2.0 : 9.8	1.7 : 9.7	2.6 : 10.0	0.0 : 10.0	1.7 : 10.0	2.0 : 10.0
Week 16						
n	61	65	64	61	64	63
Mean (SD)	6.05 (2.312)	5.26 (2.465)	3.99 (2.449)	4.21 (2.763)	3.64 (2.388)	3.07 (2.148)
Median	6.2	5.4	4.0	3.8	3.1	3.0
Min : Max	1.1 : 10.0	0.0 : 10.0	0.0 : 9.1	0.0 : 10.0	0.0 : 10.0	0.0 : 8.8
% Change from Baseline to Week 16						
n	58	64	63	58	63	62
Mean (SD)	-0.43 (38.423)	-21.47 (32.952)	-38.69 (38.366)	-40.60 (33.073)	-46.22 (31.964)	-52.85 (31.368)
Median	-4.3	-22.3	-40.0	-40.4	-45.4	-52.3
Min : Max	-82.6 : 116.7	-100.0 : 50.0	-100.0 : 113.3	-100.0 : 61.5	-100.0 : 31.8	-100.0 : 20.7
LS Mean (SE)	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 Difference vs. Placebo (SE)		-20.81 (6.108)	-37.77 (6.140)	-39.27 (6.284)	-45.21 (6.131)	-52.05 (6.144)
95% C.I.		(-32.82, -8.80)	(-49.85, -25.70)	(-51.63, -26.91)	(-57.27, -33.15)	(-64.13, -39.97)
P-value*		0.0007	<0.0001	<0.0001	<0.0001	<0.0001

* P-values were derived from ANCOVA model, which includes treatment, baseline, region, and baseline IGA strata. Values after first rescue medication use were set to missing. Missing values were imputed by LOCF.

Table 13: Percent Change in SCORAD Score from Baseline to Week 16 FAS (LOCF)

		Dupilumab				
	Placebo QW (N=61)	100 mg Q4W (N=65)	300 mg Q4W (N=65)	200 mg Q2W (N=61)	300 mg Q2W (N=64)	300 mg QW (N=63)
Baseline						
n	61	65	65	61	64	63
Mean (SD)	67.1 (13.63)	68.2 (15.01)	67.2 (12.28)	68.3 (13.99)	68.5 (12.59)	65.0 (12.24)
Median	65	66	65	67	69	65
Min : Max	36 : 97	33 : 101	41 : 91	40 : 97	42 : 95	42 : 93
Week 16						
n	60	64	65	60	63	61
Mean (SD)	54.7 (22.15)	48.1 (24.77)	32.6 (19.49)	35.4 (22.76)	31.7 (20.59)	26.1 (17.09)
Median	53	51	29	30	30	24
Min : Max	13 : 99	0 : 101	0 : 86	0 : 92	0 : 90	0 : 89
% Change from Baseline to Week 16						
n	60	64	65	60	63	61
Mean (SD)	-16.6 (32.48)	-29.3 (32.78)	-51.3 (27.72)	-48.8 (30.43)	-54.1 (28.88)	-59.4 (25.57)
Median	-12	-21	-56	-53	-56	-64
Min : Max	-85 : 79	-100 : 25	-100 : 32	-100 : 30	-100 : 25	-100 : 28
LS Mean (SE)	-13.8 (4.14)	-26.6 (3.98)	-48.8 (3.95)	-46.0 (4.12)	-51.2 (4.05)	-56.9 (4.12)
LS Mean Difference vs. Placebo (SE)		-12.8 (5.34)	-35.0 (5.31)	-32.2 (5.42)	-37.4 (5.35)	-43.1 (5.40)
95% C.I.		(-23.3, -2.3)	(-45.4, -24.6)	(-42.9, -21.6)	(-47.9, -26.9)	(-53.7, -32.5)
P-value*		0.0172	<0.0001	<0.0001	<0.0001	<0.0001

* P-values were derived from ANCOVA model, which includes treatment, baseline, region, and baseline IGA strata. Values after first rescue medication use were set to missing. Missing values were imputed by LOCF.

Table 14: Percent Change in POEM Score from Baseline to Week 16 – FAS (LOCF)

		Dupilumab				
	Placebo QW (N=61)	100 mg Q4W (N=65)	300 mg Q4W (N=65)	200 mg Q2W (N=61)	300 mg Q2W (N=64)	300 mg QW (N=63)
Baseline						
n	61	65	65	61	64	63
Mean (SD)	20.3 (5.33)	21.3 (5.55)	20.4 (5.69)	21.7 (5.65)	20.7 (6.35)	20.7 (5.73)
Median	20	22	21	23	23	21
Min : Max	6 : 28	10 : 28	5 : 28	5 : 28	6 : 28	7 : 28
Week 16						
n	59	64	65	59	63	61
Mean (SD)	18.6 (6.68)	17.0 (7.29)	10.0 (7.45)	10.1 (8.17)	10.2 (6.87)	7.9 (5.09)
Median	19	17	9	7	10	6
Min : Max	1 : 28	0 : 28	0 : 25	0 : 28	0 : 24	0 : 20
% Change from Baseline to Week 16						
n	59	64	65	59	63	61
Mean (SD)	-4.5 (32.44)	-18.9 (33.22)	-50.6 (36.57)	-54.3 (33.28)	-48.5 (37.02)	-62.0 (22.58)
Median	0	-16	-57	-63	-50	-68
Min : Max	-96 : 63	-100 : 60	-100 : 43	-100 : 18	-100 : 100	-100 : 0
LS Mean (SE)	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 Difference vs. Placebo (SE)		-14.4 (5.88)	-46.8 (5.85)	-49.4 (6.00)	-44.2 (5.89)	-57.5 (5.93)
95% C.I.		(-26.0, -2.9)	(-58.3, -35.3)	(-61.2, -37.6)	(-55.8, -32.6)	(-69.1, -45.8)
P-value*		0.0144	<0.0001	<0.0001	<0.0001	<0.0001

* P-values were derived from ANCOVA model, which includes treatment, baseline, region, and baseline IGA strata. Values after first rescue medication use were set to missing. Missing values were imputed by LOCF.

7.3.2. Study R668-AD-1117

Study R668-AD-1117 was a randomised, double-blind, placebo controlled Phase II study of repeat doses of dupilumab in patients with moderate to severe AD. The study was conducted at 25 sites in Europe from April 2012 to June 2013. The study included males or females, 18 years or older, with chronic AD, EASI score ≥16, IGA score ≥3, ≥10% BSA of AD involvement and inadequate response to a stable (≥1 month) regimen of TCS or TCI. The study treatments were:

1. Dupilumab 300 mg QW for 12 weeks
2. Placebo

The primary efficacy outcome measure was change in EASI from baseline. Secondary efficacy outcome measures were: IGA, %BSA, SCORAD, pruritus NRS and QoLIAD.

A total of 153 patients were screened and 109 were randomised: 55 to dupilumab and 54 to placebo. There were 41 (74.5%) subjects in the dupilumab group and 24 (44.4%) in the placebo who completed the study. The mean % change in EASI from baseline to Week 12 was -74.0% in the dupilumab group and -23.3% in the placebo, p <0.0001. The secondary efficacy outcome measures supported the primary analysis (Table 15).

Table 15: Overview of the efficacy results

	Placebo N=54	Dupilumab N=55
Primary Endpoint		
Mean percentage change in EASI from baseline at week12	-23.3%	-74.0%*
Secondary endpoints		
IGA 0 or 1 responder rate at week 12	7.4%	40.0%*
EASI 50 responder rate at week 12	35.2%	85.5%*
Mean change in EASI from baseline to week 12	-6.4	-19.9*
Mean change in IGA score from baseline to week 12	-0.6	-1.9*
Mean percent change in IGA score from baseline to week 12	-14.7%	-49.5%*
Mean change in AD affected BSA (%) from baseline to week 12	-9.0	-27.4*
Mean change in SCORAD from baseline to week 12	-9.8	-35.0*
Mean change in Pruritus NRS from baseline to week 12	-0.9	-3.5*
Mean change in 5-D Pruritus from baseline to week 12	-1.9	-7.4*
Exploratory Endpoints		
Mean change in QoLIAD from baseline to week 12	-1.1	-6.8*
Proportion of patients with IGA reduction ≥2 from baseline to week 12	30.8%	74.5%**
Proportion of patients with IGA reduction ≥3 from baseline to week 12	15.4%	29.8%***

Results were based on LOCF analysis.
*P-values for treatment group comparison <0.0001.
**P-value for treatment group comparison = 0.0003
***P-value for treatment group comparison =0.1799

7.3.3. Study R668-AD-1121

Study R668-AD-1121 was a Phase II, randomised, double-blind, parallel group, placebo controlled study to assess the safety of dupilumab administered concomitantly with TCS in patients with moderate to severe AD. The study was conducted at 14 sites in Europe from July 2012 to December 2012. The study included adults aged 18 years or older with chronic, moderate-to-severe AD, for whom treatment with a potent topical corticosteroid was indicated. The study treatments were:

1. Dupilumab 300 mg QW for four weeks
2. Placebo

All patients received concomitant, open-label potent TCS for up to 28 days. The efficacy outcome measures were EASI, IGA, NRS and SCORAD. There were 31 patients randomised: 21 to dupilumab and ten to placebo. All 31 patients completed the study. There were 18 (58.1%) females, 13 (41.9%) males and the age range was 19 to 66 years. The most frequently used potent (group III) dermatological corticosteroid medications were mometasone furoate, for 10 (47.6%) patients in the 300 mg QW group and five (50.0%) in the placebo group; and methylprednisolone aceponate for eight (38.1%) patients in the 300 mg QW group and six (60.0%) in the placebo.

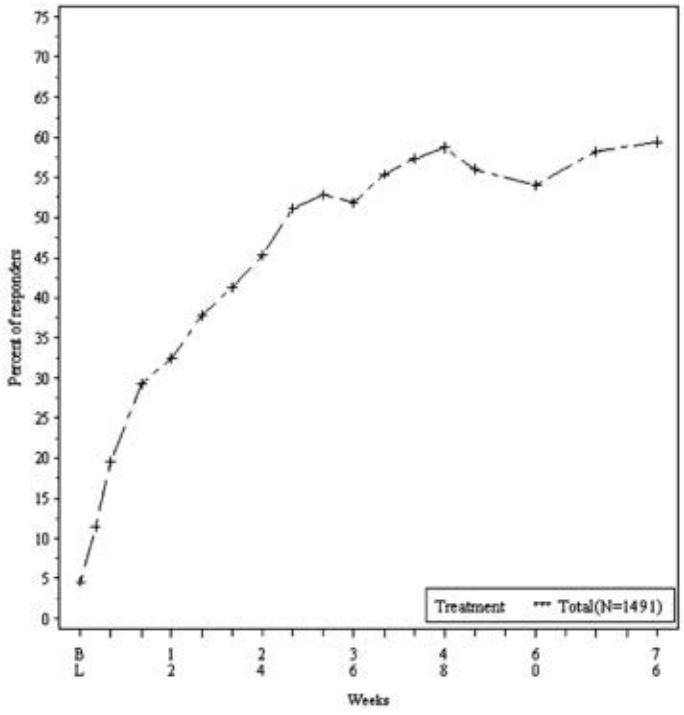
At Week 4, the mean (SD) change in IGA score from baseline was -1.6 (0.86) in the 300 mg QW group and -1.1 (1.12) in the placebo. The mean (SD) change in EASI score from baseline was -16.9 (8.06) in the 300 mg QW group and -9.7 (8.42) in the placebo. The mean (SD) change in pruritus NRS score from baseline was -4.6 (2.01) in the 300 mg QW group and -1.6 (2.40) in the placebo. The mean (SD) % change in SCORAD score from baseline was -40.0 (33.91) % in the 300 mg QW group and -59.8 (18.35) % in the placebo.

7.3.4. Study R668-AD-1225

Study R668-AD-1225 was an open-label, long term follow-on study of dupilumab 300 mg QW in patients with moderate to severe AD. An interim report was provided because the study is ongoing. The study included subjects who had completed Study R668-AD-1334 or Study R668-AD-1416, or who had completed screening for these studies after recruitment had closed. The study treatment was 300 mg QW for all subjects, with a 600 mg loading bolus dose for patients who had not received dupilumab in the preceding 4 weeks. The efficacy outcomes were

secondary and were: proportion of patients with IGA 1 or 0; and EASI-75. There were 1587 patients screened, 1492 were enrolled and 1491 received treatment. There were 606 patients who were dupilumab naïve and 850 who had previously been treated with dupilumab. A total of 106 (7.1%) subjects were withdrawn from treatment. There were 894 (60.0%) males, 597 (40.0%) females and the age range was 18 to 89 years. There were 400 (26.8%) patients treated for ≥52 weeks, 266 (17.8%) for ≥76 weeks and 51 (3.4%) for ≥100 weeks. Over time, approximately 60% of patients achieved IGA response of 0 or 1, and this was maintained to Week 76 of treatment (Figure 36). Over time, approximately 90% of patients achieved EASI-75, and this was maintained to Week 76 of treatment (Figure 37). Up to 60% of patients achieved a reduction in IGA ≥2. Over time, there was a mean reduction in EASI score of up to 85% and this was maintained to Week 76 of treatment (Figure 38). Over time, there was a mean reduction in pruritus score of up to 55% and this was maintained to Week 76 of treatment (Figure 39).

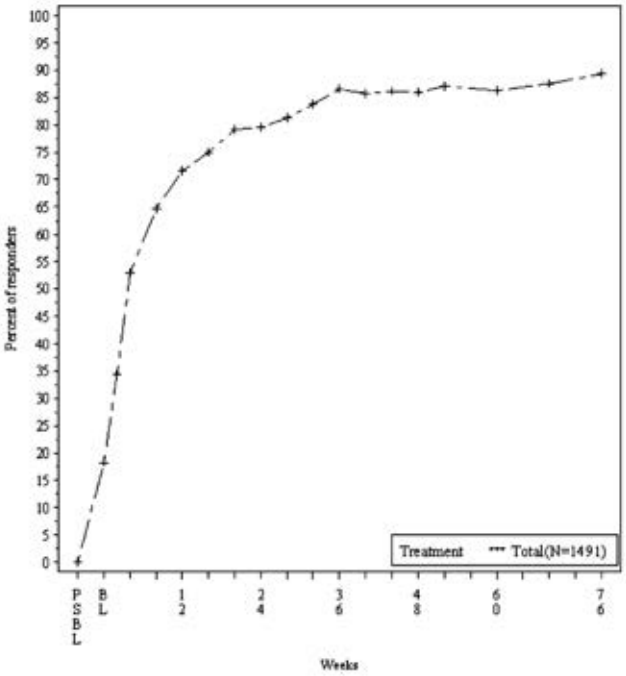
Figure 36: Percentage of Patients Achieving IGA Responder Rate (0 or 1) by Visit – SAF



# at each visit							
Total	1491	1278	759	536	436	357	271

Abbreviations: BL, baseline; IGA, Investigator's Global Assessment; SAF, safety analysis set

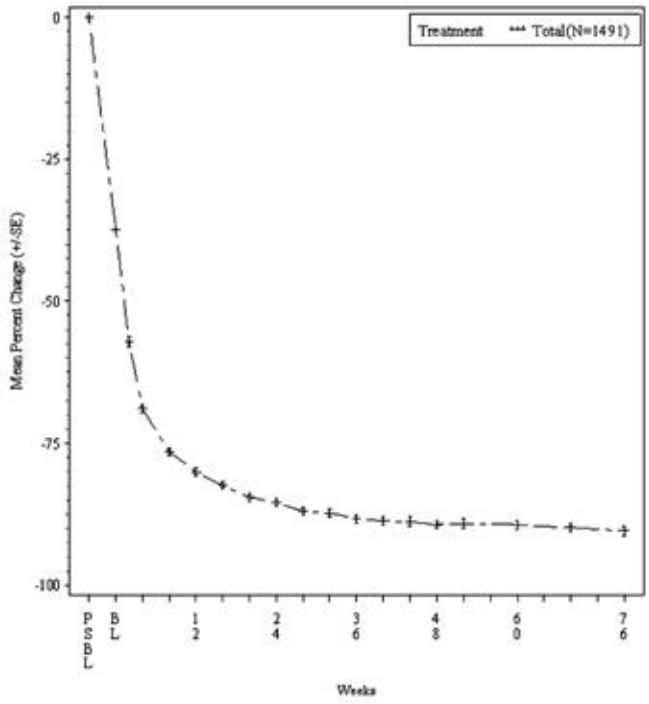
Figure 37: Percentage of Patients Achieving an EASI-75 Relative to Baseline of Parent Study by Visit – SAF



# at each visit							
Total	1460	1254	758	536	436	357	271

Abbreviations: BL, baseline; EASI, Eczema area and severity index; PSBL, parent study baseline; SAF, safety analysis set

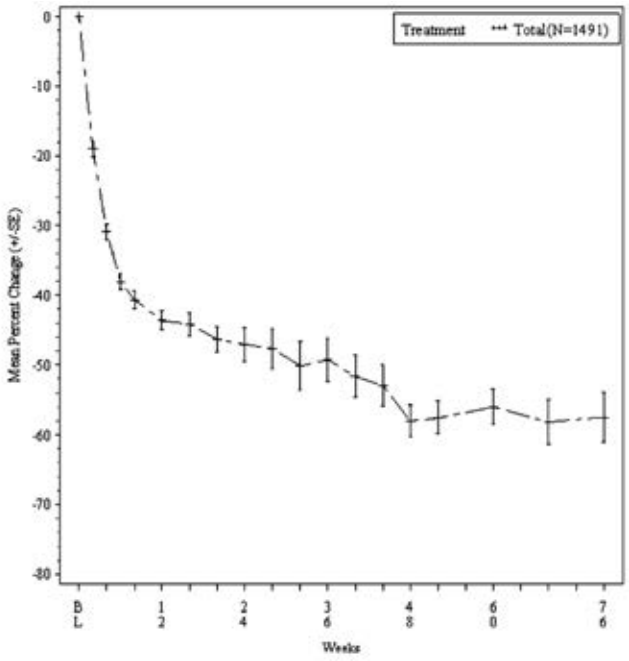
Figure 38: Mean Percent Change (±SE) in EASI Score from Baseline of the Parent Study – SAF



# at each visit							
Total	1460	1254	758	536	436	357	271

Abbreviations: BL, baseline; EASI, eczema area severity index; PSBL, parent study baseline; SAF, safety analysis population; SE, standard error

Figure 39: Mean Percent Change (+/-SE) in Pruritus NRS from Baseline of Current Study – SAF



# at each visit							
Total	1119	755	394	244	183	150	95

Abbreviations: BL, baseline; NRS, numerical rating score; SE, standard error

7.3.5. Evaluator commentary on 'Other efficacy studies'

Study R668-AD-1021 was useful to demonstrate the optimal dosing strategy for dupilumab. This helped determine the dose used in the pivotal studies.

Study R668-AD-1117 was a proof of concept study which served its purpose in development but contributes little to the overall demonstration of efficacy. The dose regimen used was more frequent than that proposed by the sponsor.

Study R668-AD-1121 was of insufficient duration to determine efficacy because the treatment duration was only 4 weeks. The dose frequency was greater than the proposed recommended regimen.

Study R668-AD-1225 demonstrated that efficacy can be maintained for 76 weeks of treatment.

7.4. Analyses performed across trials: pooled and meta analyses

An Integrated Summary of Efficacy was included in the dossier. The analyses did not contribute any addition findings for efficacy.

7.5. Evaluator's conclusions on clinical efficacy

The sponsor has demonstrated efficacy for the proposed indication. Efficacy was demonstrated for moderate to severe AD as monotherapy for up to 16 weeks in Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416. Efficacy was demonstrated for moderate to severe AD in combination with TCS for up to one year in Study CHRONOS R668-AD-1224. The demonstration of efficacy was convincing, and was clinically and statistically significant.

The efficacy measures were well developed and validated. Responder analyses were performed. The measures included symptomatology, particularly itch, and patient reported outcomes. These measures were relevant to patients. The sponsor also demonstrated improvement in quality of life scores.

The presentation of the statistical analysis was unnecessarily complex. There were multiple analyses of the same data, which made it appear that there were more outcome measures performed. However, the primary outcome measures were clearly defined and presented. The approach used for hypothesis testing in the statistical analysis was appropriate.

The sponsor did not perform comparator controlled studies. This means that dupilumab has not been compared with usual care for moderate to severe AD. The sponsor mentions the usual treatment for moderate to severe AD (systemic corticosteroids or immunomodulatory agents such as ciclosporine) in the clinical rationale, but does not provide adequate justification for not performing comparator controlled trials.

The clinical trials did not explore co-medication with immunomodulatory drugs. Hence, it is unknown whether there might be additive effects for co-medication, or no added benefit. In the absence of this data, the benefit risk for co-medication cannot be determined. These drug combinations should be contraindicated.

AD is a chronic disease, often starting in infancy. It is to be expected that patients would be treated with dupilumab for extended periods, perhaps for decades. Hence, the studies that have been performed are of relatively short duration. The sponsor has supported efficacy for up to 18 months but this is insufficient in comparison with the potential duration of treatment.

8. Clinical safety

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.1.2. Pivotal and/or main efficacy studies

There were three pivotal efficacy studies of dupilumab in AD:

- Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 examined two dose levels as monotherapy: 300 mg QW and 300 mg Q2W, both following a 600 mg bolus dose.
- Study CHRONOS R668-AD-1224 examined two dose levels combined with TCS: 300 mg QW and 300 mg Q2W following a 600 mg bolus dose.

8.1.3. Other studies

8.1.3.1. Other efficacy studies

There were four supportive studies of efficacy:

- Three Phase II controlled trials: Study R668-AD-1021, Study R668-AD-1117 and Study R668-AD-1121
- One long-term follow-on study: Study R668-AD-1225

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

There were ten dose finding and pharmacology studies: Study PKM12350, Study PKM14161, Study PKM14271, Study R668-AS-0907, Study R668-HV-1108, Study TDU12265, Study R668-AD-0914 and Study R668-AD-1026, Study R668-AD-1307 and Study R668-AD-1314.

8.1.3.3. Studies evaluable for safety only

There were four studies conducted for other indications that were evaluable for safety only:

Study ACT11457

Study ACT11457 was a randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy, safety, and tolerability of dupilumab 300 mg administered subcutaneously (SC) QW for 12 weeks in patients with persistent moderate to severe eosinophilic asthma who were partially controlled/uncontrolled by inhaled corticosteroid (ICS) plus long-acting beta-2 agonist (LABA) therapy. The study was conducted at 28 sites in the US from March 2011 to October 2012. The study included 104 patients: 52 dupilumab and 52 placebo patients. There were 24 patients who discontinued, most due to an asthma exacerbation. There were 52 (50%) males, 52 (50%) females and the age range was 18 to 65 years. The efficacy results indicated that dupilumab was protective against asthma exacerbation when ICS and LABA were withdrawn.

Study DRI12544

Study DRI12544 was a randomised, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate to severe uncontrolled asthma. The study was conducted at 174 centres in 15 countries from June 2013 to April 2015. Patients were randomised using a 1:1:1:1:1 ratio for dupilumab 300 mg Q2W with a 600 mg loading dose, 200 mg Q2W with a 400 mg loading dose, 300 mg Q4W with a 600 mg loading dose, 200 mg Q4W with a 400 mg loading dose, or placebo. Treatment duration was 24 weeks. There were 776 patients randomised and 769 received treatment. There were 490 (63.1%) females, 286 (36.9%) males and the age range was 18 to 87 years. There were 74 (9.5%) patients aged ≥65 years. All of the active treatment groups were superior to placebo, with the greatest improvement in FEV1 in the 200 mg Q2W group: LS mean increases compared with placebo were 0.10 L for 200 mg Q4W ($p = 0.0304$), 0.12 L for 300 mg Q4W ($p = 0.0048$), 0.20 L for 200 mg Q2W ($p < 0.0001$), and 0.16 L for 300 mg Q2W ($p = 0.0002$).

Study LTS12551

Study LTS12551 was an open label extension that included patients who had previously participated in a study of dupilumab in patients with asthma (Study DRI12544, Study PDY14192, Study EFC13579, and Study EFC13691). The study was conducted at 137 sites in 15 countries from August 2014, and is ongoing. The study treatment was dupilumab 300 mg Q2W as add-on therapy to inhaled corticosteroids and long-acting beta-agonists. The intended duration of treatment is 96 weeks. The report submitted in the application was an interim report. At the time of reporting, 532 patients were included in the study and all were from Study DRI12544. There were 328 (61.7%) females, 204 (38.3%) males and the age range was 18 to 80 years.

Study ACT12340

Study ACT12340 was a randomized, double-blind, Phase 2, placebo controlled, two arm study to evaluate dupilumab in patients with bilateral nasal polyposis and chronic symptoms of sinusitis. The study was conducted at 14 sites in Europe and the US from August 2013 to November 2014. The study treatment was a loading dose of 600 mg followed by 300 mg QW for 16 weeks. The study included 60 patients: 30 in the dupilumab group and 30 in the placebo. There were 34 (56.7%) males, 26 (43.3%) females and the age range was 25 to 64 years. Dupilumab demonstrated an improvement in bilateral endoscopic nasal polyp score and improved airflow compared to placebo.

8.2. Studies that assessed safety as the sole primary outcome

There were no pivotal studies that assessed safety as the sole primary outcome.

8.3. Patient exposure

There were 2526 patients exposed to dupilumab in the development program; 739 for one year and 160 for two years. There were 1468 males and 1058 females. There were 95 patients aged ≥65 years. Of the exposed patients, 1737 were White, 513 were Asian, 184 were Black or African American and 48 were other. There were 1035 patients exposed to placebo. There were 1418 patients exposed to dupilumab for ≥112 days,

In addition to exposure in studies of AD:

- 774 patients have been exposed in asthma studies, 414 for 1 year and 200 for 18 months.
- 60 patients have been exposed in studies of nasal polyposis for up to 16 weeks

In the Integrated Summary of Safety, for studies as monotherapy, there were 1564 patients included in the safety analysis set, with 529 exposed to dupilumab 300 mg Q2W, 518 to 300 mg QW and 517 to placebo. There were 68 (4.3%) subjects aged ≥65 years, and 19 aged ≥75 years. There were no patients aged <18 years.

Dose finding:

In Study R668-AD-0914 there were 24 patients exposed to four doses of dupilumab in the dose range 75 to 300 mg over 1 month, and six to placebo. Eight patients were exposed to the 300 mg dose level.

In Study R668-AD-1026 there were 27 patients exposed to four doses of dupilumab, 14 to 150 mg and 13 to 300mg, and ten to placebo, over 4 weeks.

In Study R668-AD-1307 there were 27 patients exposed to a loading dose of 400 mg followed by 200 mg weekly for 15 weeks; and 27 were exposed to placebo.

In Study R668-AD-1314 there were 97 patients exposed to a loading dose of 600 mg followed by 300 mg once weekly for 15 weeks; and 97 were exposed to placebo.

Pivotal Studies

In Study SOLO 1 R668-AD-1334 there were 229 subjects exposed to a 600 mg loading dose followed by 300 mg once weekly for 15 weeks, 218 exposed to a 600 mg loading dose followed by 300 mg every second week for 15 weeks and 222 to placebo.

In Study SOLO 2 R668-AD-1416 there were 237 subjects exposed to a 600 mg loading dose followed by 300 mg once weekly for 15 weeks, 236 exposed to a 600 mg loading dose followed by 300 mg every second week for 15 weeks and 234 to placebo.

In Study CHRONOS R668-AD-1224, as concomitant treatment with TCS, there were 315 patients exposed to a 600 mg loading dose followed by 300 mg once weekly, 110 exposed to a 600 mg loading dose followed by 300 mg every second week and 315 to placebo. There were 297 patients exposed to 300 mg once weekly for 16 weeks, 110 exposed to 300 mg every second week for 16 weeks and 278 to placebo. There were 147 patients exposed to 300 mg once weekly for 52 weeks, 43 exposed to 300 mg every second week for 52 weeks and 107 to placebo for 52 weeks.

Other efficacy studies:

In Study R668-AD-1021 there were 65 patients exposed to 100 mg Q4W, 65 to 300 mg Q4W, 62 to 200 mg Q2W, 64 to 300 mg Q2W, 63 to 300 mg QW and 61 to placebo; for up to 16 weeks.

In Study R668-AD-1117 there were 55 patients exposed to 300 mg QW for 12 weeks and 54 exposed to placebo.

In Study R668-AD-1121 there were 21 patients exposed to 300 mg QW for four weeks and ten exposed to placebo.

In Study R668-AD-1225 there were 1491 patients treated with dupilumab 300 mg QW for up to 2 years. There were 400 patients treated for ≥52 weeks, 266 for ≥76 weeks and 51 for ≥100 weeks.

Studies for other indications:

In Study ACT11457 there were 52 patients with eosinophilic asthma treated with dupilumab 300 mg QW and 52 with placebo for up to 12 weeks.

In Study DRI12544 there were 156 patients exposed to dupilumab 300 mg Q2W with a 600 mg loading dose, 148 exposed to 200 mg Q2W with a 400 mg loading dose, 157 exposed to 300 mg Q4W with a 600 mg loading dose, 158 exposed to 200 mg Q4W with a 400 mg loading dose, and 158 exposed to placebo; for up to 24 weeks.

In Study LTS12551 there were 532 patients with asthma exposed to dupilumab 300 mg Q2W: 317 for >48 weeks and 32 for >72 weeks.

In Study ACT12340 there were 30 patients with nasal polyposis and sinusitis treated with dupilumab 300 mg QW for 16 weeks, and 30 with placebo.

Table 16: Exposure to dupilumab and comparators in clinical studies

Study type/ Indication	Controlled studies				Uncontrolled studies	Total D
	D	PBO	*Con A	*Con B	D	
Clinical pharmacology						
Dose finding	175	140				175
Indication: AD						
Pivotal/Main	1345	771				1345
Other	394	125			1491	1885
TOTAL						3,405 #

* Control = Comparator, # double counts as it included follow-on study; PBO=placebo; D=Dupilumab' Con A=control A; Con B=control B

Table 17: Exposure to dupilumab in clinical studies according to dose and duration

Study type/ Indication	Proposed dose range				Proposed maximum dose			
	≥ 3 mo	≥ 6 mo	≥ 12 mo	Any	≥ 3 mo	≥ 6 mo	≥ 12 mo	Any
Clinical pharmacology								

Study type/ Indication	Proposed dose range				Proposed maximum dose			
	≥ 3 mo	≥ 6 mo	≥ 12 mo	Any	≥ 3 mo	≥ 6 mo	≥ 12 mo	Any
Dose finding	124			175	97			118
Indication 1								
Placebo controlled	611	98	58	632	611			632
TOTAL	735	98	58	807	708			750

mo=months; Any=any duration

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Integrated safety analyses

In the ISS for studies as monotherapy, TEAEs were reported in 366 (69.2%) subjects in the Q2W group, 357 (68.9%) in the QW and 359 (69.4%) in the placebo. TEAEs are discussed by study in the following sections.

8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.1.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 TEAEs were reported in 151 (69.3%) patients in the QW group, 171 (74.7%) in the Q2W and 148 (66.7%) in the placebo. The commonest TEAE was injection site reaction: 41 (18.8%) patients in the QW group, 19 (8.3%) in the Q2W and 13 (5.9%) in the placebo (Table 18). In the follow-up period, TEAEs were reported in 16 (16.5%) patients in the QW group, 20 (17.4%) in the Q2W and 30 (17.8%) in the placebo.

In Study SOLO 2 R668-AD-1416 TEAEs were reported in 159 (67.1%) patients in the QW group, 156 (66.1%) in the Q2W and 172 (73.5%) in the placebo. Other than AD itself, the commonest TEAE was injection site reaction: 31 (13.1%) patients in the QW group, 32 (13.6%) in the Q2W and 15 (6.4%) in the placebo (Table 19). In the follow-up period, TEAEs were reported in 20 (18.3%) patients in the QW group, 25 (19.1%) in the Q2W and 31 (16.0%) in the placebo. Adverse events of special interest were more common with placebo than with dupilumab (Table 20).

In Study CHRONOS R668-AD-1224 TEAEs were reported in 273 (86.7%) patients in the QW group, 100 (90.9%) in the Q2W and 268 (85.1%) in the placebo. The commonest TEAEs in all treatment groups were nasopharyngitis and URTI (Table 21). Allergic conjunctivitis was more common with dupilumab: 53 (15.5%) patients in the QW group, 13 (11.8%) in the Q2W and 19 (6.0%) in the placebo. Narrow conjunctivitis was more common in the dupilumab groups: 61 (19.4%) patients in the QW group, 15 (13.6%) in the Q2W and 25 (7.9%) in the placebo. Broad conjunctivitis was more common in the dupilumab groups: 88 (27.9%) patients in the QW group, 26 (23.6%) in the Q2W and 33 (10.5%) in the placebo. AESIs were reported in eight (2.5%) patients in the QW group, four (3.6%) in the Q2W and 23 (7.3%) in the placebo (Table 22).

Table 18: Summary of Treatment-Emergent Adverse Events Reported by ≥2% of Patients in any Treatment Group by SOC and PT during the 16-Week Treatment Period – SAF

Primary System Organ Class Preferred term	Placebo (N=222)	Dupilumab 300 mg Q2W (N=229)	Dupilumab 300 mg QW (N=218)	Dupilumab Combined (N=447)
Number of patients with at least 1 such event, n (%)	145 (65.3%)	167 (72.9%)	150 (68.8%)	317 (70.9%)
Infections and infestations	63 (28.4%)	80 (34.9%)	74 (33.9%)	154 (34.5%)
Nasopharyngitis	17 (7.7%)	22 (9.6%)	25 (11.5%)	47 (10.5%)
Conjunctivitis	2 (0.9%)	11 (4.8%)	7 (3.2%)	18 (4.0%)
Upper respiratory tract infection	5 (2.3%)	6 (2.6%)	11 (5.0%)	17 (3.8%)
Oral herpes	4 (1.8%)	9 (3.9%)	4 (1.8%)	13 (2.9%)
Herpes simplex	3 (1.4%)	7 (3.1%)	2 (0.9%)	9 (2.0%)
General disorders and administration site conditions	20 (9.0%)	39 (17.0%)	50 (22.9%)	89 (19.9%)
Injection site reaction	13 (5.9%)	19 (8.3%)	41 (18.8%)	60 (13.4%)
Fatigue	1 (0.5%)	5 (2.2%)	2 (0.9%)	7 (1.6%)
Skin and subcutaneous tissue disorders	78 (35.1%)	47 (20.5%)	34 (15.6%)	81 (18.1%)
Dermatitis atopic	67 (30.2%)	30 (13.1%)	21 (9.6%)	51 (11.4%)
Pruritus	5 (2.3%)	0	1 (0.5%)	1 (0.2%)
Nervous system disorders	20 (9.0%)	30 (13.1%)	13 (6.0%)	43 (9.6%)
Headache	13 (5.9%)	21 (9.2%)	11 (5.0%)	32 (7.2%)
Eye disorders	4 (1.8%)	18 (7.9%)	19 (8.7%)	37 (8.3%)
Conjunctivitis allergic	2 (0.9%)	12 (5.2%)	7 (3.2%)	19 (4.3%)
Gastrointestinal disorders	9 (4.1%)	21 (9.2%)	16 (7.3%)	37 (8.3%)
Diarrhoea	4 (1.8%)	7 (3.1%)	7 (3.2%)	14 (3.1%)
Nausea	1 (0.5%)	5 (2.2%)	2 (0.9%)	7 (1.6%)
Musculoskeletal and connective tissue disorders	13 (5.9%)	19 (8.3%)	17 (7.8%)	36 (8.1%)
Arthralgia	3 (1.4%)	6 (2.6%)	1 (0.5%)	7 (1.6%)
Back pain	4 (1.8%)	2 (0.9%)	5 (2.3%)	7 (1.6%)
Investigations	9 (4.1%)	13 (5.7%)	11 (5.0%)	24 (5.4%)
Blood creatine phosphokinase increased	4 (1.8%)	5 (2.2%)	2 (0.9%)	7 (1.6%)

Note: Adverse events were coded according to MedDRA version 18.0.

Table 19: Summary of Treatment-Emergent Adverse Events Reported by ≥2% of Patients in any Treatment Group during the 16-Week Treatment Period by SOC and PT – SAF

Primary System Organ Class Preferred term	Placebo (N=234)	Dupilumab 300 mg Q2W (N=236)	Dupilumab 300 mg QW (N=237)	Dupilumab Combined (N=473)
Number of patients with at least 1 such event, n (%)	168 (71.8%)	154 (65.3%)	157 (66.2%)	311 (65.8%)
Infections and infestations	76 (32.5%)	65 (27.5%)	68 (28.7%)	133 (28.1%)
Nasopharyngitis	22 (9.4%)	20 (8.5%)	20 (8.4%)	40 (8.5%)
Conjunctivitis	1 (0.4%)	9 (3.8%)	9 (3.8%)	18 (3.8%)
Oral herpes	4 (1.7%)	8 (3.4%)	9 (3.8%)	17 (3.6%)
Upper respiratory tract infection	5 (2.1%)	7 (3.0%)	9 (3.8%)	16 (3.4%)
Skin infection	5 (2.1%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Skin and subcutaneous tissue disorders	93 (39.7%)	49 (20.8%)	60 (25.3%)	109 (23.0%)
Dermatitis atopic	81 (34.6%)	32 (13.6%)	38 (16.0%)	70 (14.8%)
Alopecia	3 (1.3%)	1 (0.4%)	7 (3.0%)	8 (1.7%)
Pruritus generalised	5 (2.1%)	1 (0.4%)	3 (1.3%)	4 (0.8%)
General disorders and administration site conditions	32 (13.7%)	41 (17.4%)	41 (17.3%)	82 (17.3%)
Injection site reaction	15 (6.4%)	32 (13.6%)	31 (13.1%)	63 (13.3%)
Fatigue	3 (1.3%)	6 (2.5%)	5 (2.1%)	11 (2.3%)
Nervous system disorders	23 (9.8%)	29 (12.3%)	36 (15.2%)	65 (13.7%)
Headache	11 (4.7%)	19 (8.1%)	22 (9.3%)	41 (8.7%)
Dizziness	6 (2.6%)	3 (1.3%)	4 (1.7%)	7 (1.5%)
Gastrointestinal disorders	18 (7.7%)	22 (9.3%)	21 (8.9%)	43 (9.1%)
Diarrhoea	3 (1.3%)	9 (3.8%)	3 (1.3%)	12 (2.5%)
Nausea	3 (1.3%)	5 (2.1%)	7 (3.0%)	12 (2.5%)
Musculoskeletal and connective tissue disorders	15 (6.4%)	27 (11.4%)	16 (6.8%)	43 (9.1%)
Back pain	5 (2.1%)	7 (3.0%)	5 (2.1%)	12 (2.5%)
Arthralgia	6 (2.6%)	6 (2.5%)	2 (0.8%)	8 (1.7%)
Respiratory, thoracic and mediastinal disorders	16 (6.8%)	17 (7.2%)	13 (5.5%)	30 (6.3%)
Oropharyngeal pain	4 (1.7%)	5 (2.1%)	4 (1.7%)	9 (1.9%)
Psychiatric disorders	17 (7.3%)	6 (2.5%)	6 (2.5%)	12 (2.5%)
Depression	5 (2.1%)	0	0	0
Vascular disorders	6 (2.6%)	7 (3.0%)	4 (1.7%)	11 (2.3%)
Hypertension	4 (1.7%)	5 (2.1%)	2 (0.8%)	7 (1.5%)

Note: Adverse events were coded according to MedDRA version 18.0.

Table 20: Summary of Treatment-Emergent Adverse Events of Special Interest (AESI) by AESI Category, High Level Term, and Preferred Term – SAF

AESI category		Dupilumab		
High Level Term	Placebo	300 mg Q2W	300 mg QW	Combined
Preferred Term	(N=234)	(N=236)	(N=237)	(N=473)
Number of patients with at least 1 such event, n (%)	8 (3.4%)	3 (1.3%)	1 (0.4%)	4 (0.8%)
Any opportunistic infection	2 (0.9%)	2 (0.8%)	0	2 (0.4%)
Herpes viral infections	2 (0.9%)	2 (0.8%)	0	2 (0.4%)
Eczema herpeticum	1 (0.4%)	2 (0.8%)	0	2 (0.4%)
Herpes zoster	1 (0.4%)	0	0	0
Any severe infection	4 (1.7%)	1 (0.4%)	0	1 (0.2%)
Bacterial infections NEC	3 (1.3%)	1 (0.4%)	0	1 (0.2%)
Conjunctivitis bacterial	0	1 (0.4%)	0	1 (0.2%)
Endocarditis bacterial	1 (0.4%)	0	0	0
Folliculitis	2 (0.9%)	0	0	0
Sepsis, bacteraemia, viraemia and fungaemia NEC	2 (0.9%)	0	0	0
Sepsis	2 (0.9%)	0	0	0
Septic embolus	1 (0.4%)	0	0	0
Suicidal behavior	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Suicidal and self-injurious behaviour	1 (0.4%)	0	1 (0.4%)	1 (0.2%)
Completed suicide	0	0	1 (0.4%)	1 (0.2%)
Suicidal ideation	1 (0.4%)	0	0	0
Suicide attempt	1 (0.4%)	0	0	0
Acute allergic reactions	1 (0.4%)	0	0	0
Allergies to foods, food additives, drugs and other chemicals	1 (0.4%)	0	0	0
Drug hypersensitivity	1 (0.4%)	0	0	0

Note: Adverse events were coded according to MedDRA version 18.0.

Table 21: Number of Patients with Treatment-Emergent Adverse Events ≥2% during the 52-Week Period by Primary System Organ Class and Preferred Term – SAF

Primary System Organ Class Preferred term	Placebo + TCS (N = 315)	Dupilumab + TCS 300 mg Q2W (N = 110)	Dupilumab + TCS 300 mg QW (N = 315)	Dupilumab + TCS Combined (N = 425)
Number of patients with at least 1 such event, n (%)	266 (84.4%)	97 (88.2%)	261 (82.9%)	358 (84.2%)
Infections and infestations	182 (57.8%)	63 (57.3%)	166 (52.7%)	229 (53.9%)
Nasopharyngitis	61 (19.4%)	25 (22.7%)	60 (19.0%)	85 (20.0%)
Upper respiratory tract infection	32 (10.2%)	11 (10.0%)	43 (13.7%)	54 (12.7%)
Sinusitis	9 (2.9%)	2 (1.8%)	18 (5.7%)	20 (4.7%)
Oral herpes	9 (2.9%)	4 (3.6%)	15 (4.8%)	19 (4.5%)
Urinary tract infection	13 (4.1%)	2 (1.8%)	14 (4.4%)	16 (3.8%)
Influenza	17 (5.4%)	4 (3.6%)	9 (2.9%)	13 (3.1%)
Viral upper respiratory tract infection	9 (2.9%)	3 (2.7%)	9 (2.9%)	12 (2.8%)
Conjunctivitis bacterial	5 (1.6%)	2 (1.8%)	9 (2.9%)	11 (2.6%)
Gastroenteritis	9 (2.9%)	4 (3.6%)	4 (1.3%)	8 (1.9%)
Herpes simplex	2 (0.6%)	3 (2.7%)	5 (1.6%)	8 (1.9%)
Pharyngitis	8 (2.5%)	3 (2.7%)	5 (1.6%)	8 (1.9%)
Rhinitis	4 (1.3%)	1 (0.9%)	7 (2.2%)	8 (1.9%)
Folliculitis	7 (2.2%)	2 (1.8%)	4 (1.3%)	6 (1.4%)
Impetigo	10 (3.2%)	1 (0.9%)	4 (1.3%)	5 (1.2%)
Skin infection	7 (2.2%)	0	1 (0.3%)	1 (0.2%)
Eye disorders	46 (14.6%)	34 (30.9%)	102 (32.4%)	136 (32.0%)
Conjunctivitis allergic	19 (6.0%)	13 (11.8%)	53 (16.8%)	66 (15.5%)
Eye pruritus	4 (1.3%)	4 (3.6%)	14 (4.4%)	18 (4.2%)
Blepharitis	3 (1.0%)	6 (5.5%)	11 (3.5%)	17 (4.0%)
Dry eye	4 (1.3%)	3 (2.7%)	6 (1.9%)	9 (2.1%)
Skin and subcutaneous tissue disorders	167 (53.0%)	31 (28.2%)	103 (32.7%)	134 (31.5%)
Dermatitis atopic	144 (45.7%)	20 (18.2%)	52 (16.5%)	72 (16.9%)
Erythema	3 (1.0%)	1 (0.9%)	11 (3.5%)	12 (2.8%)
Acne	7 (2.2%)	0	7 (2.2%)	7 (1.6%)
Pruritus	8 (2.5%)	1 (0.9%)	5 (1.6%)	6 (1.4%)
Urticaria	10 (3.2%)	1 (0.9%)	3 (1.0%)	4 (0.9%)
General disorders and administration site conditions	50 (15.9%)	29 (26.4%)	81 (25.7%)	110 (25.9%)
Injection site reaction	24 (7.6%)	16 (14.5%)	60 (19.0%)	76 (17.9%)
Fatigue	10 (3.2%)	1 (0.9%)	11 (3.5%)	12 (2.8%)
Pyrexia	6 (1.9%)	4 (3.6%)	7 (2.2%)	11 (2.6%)

Table 21 (cont): Number of Patients with Treatment-Emergent Adverse Events ≥2% during the 52-Week Period by Primary System Organ Class and Preferred Term – SAF

Primary System Organ Class Preferred term	Placebo + TCS (N = 315)	Dupilumab + TCS 300 mg Q2W (N = 110)	 300 mg QW (N = 315)	 Combined (N = 425)
Gastrointestinal disorders	58 (18.4%)	15 (13.6%)	51 (16.2%)	66 (15.5%)
Diarrhoea	13 (4.1%)	1 (0.9%)	12 (3.8%)	13 (3.1%)
Nausea	12 (3.8%)	2 (1.8%)	9 (2.9%)	11 (2.6%)
Abdominal pain	4 (1.3%)	0	7 (2.2%)	7 (1.6%)
Toothache	8 (2.5%)	1 (0.9%)	3 (1.0%)	4 (0.9%)
Musculoskeletal and connective tissue disorders	49 (15.6%)	17 (15.5%)	44 (14.0%)	61 (14.4%)
Arthralgia	15 (4.8%)	5 (4.5%)	10 (3.2%)	15 (3.5%)
Back pain	11 (3.5%)	2 (1.8%)	6 (1.9%)	8 (1.9%)
Pain in extremity	2 (0.6%)	0	8 (2.5%)	8 (1.9%)
Osteoarthritis	3 (1.0%)	3 (2.7%)	2 (0.6%)	5 (1.2%)
Muscle spasms	7 (2.2%)	0	1 (0.3%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	53 (16.8%)	13 (11.8%)	45 (14.3%)	58 (13.6%)
Cough	8 (2.5%)	3 (2.7%)	10 (3.2%)	13 (3.1%)
Oropharyngeal pain	12 (3.8%)	3 (2.7%)	10 (3.2%)	13 (3.1%)
Asthma	19 (6.0%)	5 (4.5%)	2 (0.6%)	7 (1.6%)
Nervous system disorders	38 (12.1%)	10 (9.1%)	38 (12.1%)	48 (11.3%)
Headache	19 (6.0%)	5 (4.5%)	24 (7.6%)	29 (6.8%)
Injury, poisoning and procedural complications	43 (13.7%)	10 (9.1%)	32 (10.2%)	42 (9.9%)
Ligament sprain	3 (1.0%)	3 (2.7%)	6 (1.9%)	9 (2.1%)
Sunburn	7 (2.2%)	0	2 (0.6%)	2 (0.5%)
Investigations	37 (11.7%)	12 (10.9%)	30 (9.5%)	42 (9.9%)
Blood creatine phosphokinase increased	9 (2.9%)	3 (2.7%)	11 (3.5%)	14 (3.3%)
Blood lactate dehydrogenase increased	5 (1.6%)	4 (3.6%)	1 (0.3%)	5 (1.2%)
Immune system disorders	12 (3.8%)	5 (4.5%)	19 (6.0%)	24 (5.6%)
Seasonal allergy	6 (1.9%)	2 (1.8%)	9 (2.9%)	11 (2.6%)
Psychiatric disorders	18 (5.7%)	9 (8.2%)	11 (3.5%)	20 (4.7%)
Anxiety	2 (0.6%)	3 (2.7%)	3 (1.0%)	6 (1.4%)

Abbreviations: Q2W, every 2 weeks; QW, weekly; TCS, topical corticosteroids.
Note: Adverse events were coded according to MedDRA version 18.0.

Table 22: Number of Patients with Treatment-Emergent Adverse Events of Special Interest during the 52-Week Treatment Period by AESI Category, High Level Term, and Preferred Term – SAF

AESI category		Dupilumab + TCS		
High Level Term	Placebo + TCS	300 mg Q2W	300 mg QW	Combined
Preferred Term	(N = 315)	(N = 110)	(N = 315)	(N = 425)
Number of patients with at least 1 such event, n (%)	23 (7.3%)	4 (3.6%)	8 (2.5%)	12 (2.8%)
Any infection requiring treatment with parenteral antibiotic	3 (1.0%)	1 (0.9%)	4 (1.3%)	5 (1.2%)
Bacterial infections NEC	1 (0.3%)	1 (0.9%)	0	1 (0.2%)
Superinfection bacterial	0	1 (0.9%)	0	1 (0.2%)
Cellulitis	1 (0.3%)	0	0	0
Dental and oral soft tissue infections	0	0	1 (0.3%)	1 (0.2%)
Tooth abscess	0	0	1 (0.3%)	1 (0.2%)
Lower respiratory tract and lung infections	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Bronchitis	0	0	1 (0.3%)	1 (0.2%)
Pneumonia	1 (0.3%)	0	0	0
Skin structures and soft tissue infections	0	0	1 (0.3%)	1 (0.2%)
Subcutaneous abscess	0	0	1 (0.3%)	1 (0.2%)
Upper respiratory tract infections	0	0	1 (0.3%)	1 (0.2%)
Upper respiratory tract infection	0	0	1 (0.3%)	1 (0.2%)
Abdominal and gastrointestinal infections	1 (0.3%)	0	0	0
Gastroenteritis	1 (0.3%)	0	0	0
Influenza viral infections	1 (0.3%)	0	0	0
Influenza	1 (0.3%)	0	0	0
Any infection requiring treatment with oral antibiotic/anti-viral/anti-fungal for longer than 2 weeks	6 (1.9%)	1 (0.9%)	2 (0.6%)	3 (0.7%)
Bacterial infections NEC	2 (0.6%)	0	1 (0.3%)	1 (0.2%)
Skin bacterial infection	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Folliculitis	1 (0.3%)	0	0	0
Skin structures and soft tissue infections	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Subcutaneous abscess	0	0	1 (0.3%)	1 (0.2%)
Dermatitis infected	1 (0.3%)	0	0	0
Upper respiratory tract infections	0	1 (0.9%)	0	1 (0.2%)
Sinusitis	0	1 (0.9%)	0	1 (0.2%)
Borrelial infections	1 (0.3%)	0	0	0
Erythema migrans	1 (0.3%)	0	0	0
Herpes viral infections	2 (0.6%)	0	0	0
Eczema herpeticum	1 (0.3%)	0	0	0

8.4.1.4. Other studies

Other efficacy studies

In Study R668-AD-1021 TEAEs were reported in 53 (81.5%) patients exposed to 100 mg Q4W, 56 (86.2%) to 300 mg Q4W, 46 (75.4%) to 200 mg Q2W, 50 (78.1%) to 300 mg Q2W, 53 (84.1%) to 300 mg QW and 49 (80.3%) to placebo. Nasopharyngitis and headache were the commonest TEAEs.

In Study R668-AD-1117 TEAEs were reported in 43 (78.2%) patients in the 300 mg QW group and 44 (81.5%) in the placebo. The commonest TEAE was nasopharyngitis.

In Study R668-AD-1121 TEAEs were reported in 12 (57.1%) patients in the dupilumab 300 mg QW group and seven (70%) in the placebo. The most common TEAE was nasopharyngitis.

In Study R668-AD-1225 TEAEs were reported in 1054 (70.7%) patients at a rate of 278.960 patients per 100 patient years. The commonest TEAE was nasopharyngitis in 306 (20.5%)

patients. Overall there were 67 (4.5%) patients with AESI, including 25 (1.7%) with opportunistic infection. Narrow conjunctivitis was reported in 160 (10.7%) patients and broad conjunctivitis in 197 (13.2%).

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 TEAEs were reported in 20 (83.3%) subjects in the dupilumab groups and five (83.3%) in the placebo. The rate of TEAEs was highest in the 75 mg group: eight (100%) patients. The most common TEAE was headache: three (12.5%) subjects in the dupilumab groups.

In Study R668-AD-1026 TEAEs were reported in nine (90.0%) patients in the placebo group, twelve (85.7%) in the 150 mg and twelve (92.3%) in the 300 mg. The most commonly reported TEAE was nasopharyngitis in two (20.0%) patients in the placebo group, four (28.6%) in the 150 mg and five (38.5%) in the 300 mg.

In Study R668-AD-1307 TEAEs were reported in 24 (88.9%) subjects in the dupilumab group and 23 (85.2%) in the placebo. The most common TEAEs were nasopharyngitis and upper respiratory tract infection.

In Study R668-AD-1314 TEAEs were reported in 54 (55.7%) patients in the dupilumab group and 60 (61.9%) in the placebo. URTI was reported for eleven (11.3%) patients in the dupilumab group and 14 (14.4%) in the placebo. Atopic dermatitis was reported as a TEAE in one (1.0%) subjects in the dupilumab group and eleven (11.3%) in the placebo.

Studies evaluable for safety only

In Study ACT11457 TEAEs were reported in 42 (80.8%) patients in the dupilumab group and 40 (76.9%) in the placebo. Nasopharyngitis was reported in 13.5% patients in the dupilumab group and 3.8% in the placebo. Injection site reaction was reported in 9.6% patients in the dupilumab group and none in the placebo.

In Study DRI12544 TEAEs were reported in 121 (77.6%) patients in the dupilumab 300 mg Q2W group, 119 (80.4%) in the 200 mg Q2W, 130 (82.8%) in the 300 mg Q4W, 113 (75.3%) in the 200 mg Q4W and 118 (74.7%) in the placebo. Administration site reactions were reported in 18.1% patients.

In Study LTS12551 there were 390 (73.3%) patients with TEAEs. There were 89 (16.7%) subjects with nasopharyngitis. Injection site erythema was reported in 68 (12.8%) subjects, injection site pruritus in 25 (4.7%) and injection site pain in 16 (3.0%).

In Study ACT12340 TEAEs were reported in 30 (100%) patients in the dupilumab group and 25 (83.3%) in the placebo.

8.4.2. Treatment related adverse events (adverse drug reactions)

8.4.2.1. Integrated safety analyses

In the ISS for studies as monotherapy, treatment related TEAEs were reported in 146 (27.6%) subjects in the Q2W group, 158 (30.5%) in the QW and 104 (20.1%) in the placebo. Treatment related TEAEs are discussed by study in the following sections.

8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.2.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 treatment related TEAEs were reported in 68 (31.2%) patients in the QW group, 67 (29.3%) in the Q2W and 42 (18.9%) in the placebo. Injection site reaction was more common with dupilumab: 37 (17.0%) patients in the QW group, 17 (7.4%) in the Q2W and 13 (5.9%) in the placebo.

In Study SOLO 2 R668-AD-1416 treatment related TEAEs were reported in 66 (27.8%) patients in the QW group, 65 (27.5%) in the Q2W and 49 (20.9%) in the placebo. Injection site reaction was more common with dupilumab: 27 (11.4%) patients in the QW group, 29 (12.3%) in the Q2W and 12 (5.1%) in the placebo.

In Study CHRONOS R668-AD-1224 treatment-related TEAEs were reported in 86 (27.3%) patients in the QW group, 28 (25.5%) in the Q2W and 67 (21.3%) in the placebo. Injection site reaction was more common with dupilumab: 46 (15.6%) patients in the QW group, 10 (9.1%) in the Q2W and 15 (4.8%) in the placebo.

8.4.2.4. Other studies

Other efficacy studies

In Study R668-AD-1021 treatment related TEAEs were reported in 22 (33.8%) patients exposed to 100 mg Q4W, 16 (24.6%) to 300 mg Q4W, 16 (26.2%) to 200 mg Q2W, 19 (29.7%) to 300 mg Q2W, 24 (38.1%) to 300 mg QW and 15 (24.6%) to placebo. Injection site reactions were reported in 6.9% of the dupilumab groups.

In Study R668-AD-1117 treatment related TEAEs were reported in 24 (43.6%) patients in the 300 mg QW group and 18 (33.3%) in the placebo. Injection site induration was reported in five (9.1%) patients in the 300 mg QW group and three (5.6%) in the placebo.

In Study R668-AD-1121 treatment related TEAEs were reported in six (28.6%) patients in the dupilumab 300 mg QW group and four (40%) in the placebo.

In Study R668-AD-1225 treatment related TEAEs were reported in 408 (27.4%) patients at a rate of 50.794 patients per 100 patient years. Conjunctivitis was reported in 35 (2.3%), injection site reaction in 75 (5.0%) and injection site erythema in 35 (2.3%).

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 treatment related TEAEs were reported in ten (33.3%) subjects in the dupilumab groups and three (50.0%) in the placebo.

In Study R668-AD-1026 treatment related TEAEs were reported in four (40.0%) patients in the placebo group, four (28.6%) in the 150 mg and seven (53.8%) in the 300 mg.

In Study R668-AD-1307 treatment related TEAEs were reported in nine (33.3%) subjects in the dupilumab group and seven (25.9%) in the placebo.

In Study R668-AD-1314 treatment related TEAEs were reported in 18 (18.6%) patients in the dupilumab group and 10 (10.3%) in the placebo. General and administration site conditions were more common in the dupilumab group: 13 (13.4%) patients compared with three (3.1%) in the placebo.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Integrated safety analyses

In the ISS for studies as monotherapy, there was one death in the QW group. SAEs were reported in 13 (2.5%) subjects in the Q2W group, 11 (2.1%) in the QW and 26 (5.0%) in the placebo. SAEs are discussed by study in the following sections.

8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable

8.4.3.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 there were no deaths. SAEs were reported in two (0.9%) patients in the QW group, seven (3.1%) in the Q2W and 12 (5.4%) in the placebo (Table 23).

In Study SOLO 2 R668-AD-1416 there was one death in the QW group (completed suicide), one in the Q2W group (hypoxic ischaemic encephalopathy / asthma / respiratory failure) and none in the placebo. SAEs were reported in nine (3.8%) patients in the QW group, six (2.5%) in the Q2W and 16 (6.8%) in the placebo (Table 24).

In Study CHRONOS R668-AD-1224 there was one death in the QW group (car accident). SAEs were reported in ten (3.2%) patients in the QW group, four (3.6%) in the Q2W and 20 (6.3%) in the placebo (Table 25). There was no apparent pattern to the SAEs.

Table 23: Summary of Serious Treatment-Emergent Adverse Events during the 16-Week Treatment Period by SOC and PT – SAF

		Dupilumab		
Primary System Organ Class Preferred term	Placebo (N=222)	300 mg Q2W (N=229)	300 mg QW (N=218)	Combined (N=447)
Number of patients with at least 1 SAE, n (%)	11 (5.0%)	7 (3.1%)	2 (0.9%)	9 (2.0%)
Cardiac disorders	1 (0.5%)	1 (0.4%)	1 (0.5%)	2 (0.4%)
Acute myocardial infarction	0	1 (0.4%)	0	1 (0.2%)
Myocardial infarction	0	0	1 (0.5%)	1 (0.2%)
Coronary artery disease	1 (0.5%)	0	0	0
Infections and infestations	2 (0.9%)	1 (0.4%)	1 (0.5%)	2 (0.4%)
Abscess sweat gland	0	1 (0.4%)	0	1 (0.2%)
Kidney infection	0	0	1 (0.5%)	1 (0.2%)
Mastitis	1 (0.5%)	0	0	0
Urinary tract infection bacterial	1 (0.5%)	0	0	0
Skin and subcutaneous tissue disorders	3 (1.4%)	2 (0.9%)	0	2 (0.4%)
Dermatitis atopic	3 (1.4%)	2 (0.9%)	0	2 (0.4%)
Injury, poisoning and procedural complications	0	1 (0.4%)	0	1 (0.2%)
Clavicle fracture	0	1 (0.4%)	0	1 (0.2%)
Laceration	0	1 (0.4%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4%)	0	1 (0.2%)
Lipoma	0	1 (0.4%)	0	1 (0.2%)
Renal and urinary disorders	0	0	1 (0.5%)	1 (0.2%)
Nephrolithiasis	0	0	1 (0.5%)	1 (0.2%)
Surgical and medical procedures	0	1 (0.4%)	0	1 (0.2%)
Limb operation	0	1 (0.4%)	0	1 (0.2%)
Blood and lymphatic system disorders	1 (0.5%)	0	0	0
Anaemia	1 (0.5%)	0	0	0
Metabolism and nutrition disorders	1 (0.5%)	0	0	0
Hyperglycaemia	1 (0.5%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.5%)	0	0	0
Intervertebral disc protrusion	1 (0.5%)	0	0	0
Psychiatric disorders	3 (1.4%)	0	0	0
Depression	1 (0.5%)	0	0	0
Suicidal ideation	2 (0.9%)	0	0	0
Vascular disorders	1 (0.5%)	0	0	0
Aortic stenosis	1 (0.5%)	0	0	0

Note: Adverse events were coded according to MedDRA version 18.0.

Table 24: Summary of Serious Treatment-Emergent Adverse Events during the 16-Week Treatment Period by SOC and PT – SAF

Primary System Organ Class Preferred term	Placebo (N=234)	Dupilumab 300 mg Q2W (N=236)	 300 mg QW (N=237)	 Combined (N=473)
Number of patients with at least 1 such event, n (%)	13 (5.6%)	4 (1.7%)	8 (3.4%)	12 (2.5%)
Gastrointestinal disorders	0	0	2 (0.8%)	2 (0.4%)
Abdominal pain	0	0	1 (0.4%)	1 (0.2%)
Colonic pseudo-obstruction	0	0	1 (0.4%)	1 (0.2%)
Infections and infestations	3 (1.3%)	0	2 (0.8%)	2 (0.4%)
Cellulitis	0	0	1 (0.4%)	1 (0.2%)
Erysipelas	0	0	1 (0.4%)	1 (0.2%)
Endocarditis bacterial	1 (0.4%)	0	0	0
Sepsis	2 (0.9%)	0	0	0
Septic embolus	1 (0.4%)	0	0	0
Skin infection	1 (0.4%)	0	0	0
Injury, poisoning and procedural complications	1 (0.4%)	2 (0.8%)	0	2 (0.4%)
Fall	0	1 (0.4%)	0	1 (0.2%)
Radius fracture	0	1 (0.4%)	0	1 (0.2%)
Concussion	1 (0.4%)	0	0	0
Ligament sprain	1 (0.4%)	0	0	0
Nervous system disorders	1 (0.4%)	2 (0.8%)	0	2 (0.4%)
Headache	0	1 (0.4%)	0	1 (0.2%)
Subarachnoid haemorrhage	0	1 (0.4%)	0	1 (0.2%)
Cerebrovascular accident	1 (0.4%)	0	0	0
Psychiatric disorders	3 (1.3%)	0	2 (0.8%)	2 (0.4%)
Completed suicide	0	0	1 (0.4%)	1 (0.2%)
Delirium	0	0	1 (0.4%)	1 (0.2%)
Confusional state	1 (0.4%)	0	0	0
Psychotic disorder	1 (0.4%)	0	0	0
Suicidal ideation	1 (0.4%)	0	0	0
Skin and subcutaneous tissue disorders	5 (2.1%)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Dermatitis atopic	5 (2.1%)	0	1 (0.4%)	1 (0.2%)
Dermatitis exfoliative	0	1 (0.4%)	0	1 (0.2%)
Cardiac disorders	0	0	1 (0.4%)	1 (0.2%)
Acute myocardial infarction	0	0	1 (0.4%)	1 (0.2%)
Cardiac failure congestive	0	0	1 (0.4%)	1 (0.2%)

Table 24 cont: Summary of Serious Treatment-Emergent Adverse Events During the 16-Week Treatment Period by SOC and PT – SAF

Primary System Organ Class Preferred term	Placebo (N=234)	Dupilumab 300 mg Q2W (N=236)	 300 mg QW (N=237)	 Combined (N=473)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.4%)	1 (0.2%)
Hodgkin's disease	0	0	1 (0.4%)	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	0	0	1 (0.4%)	1 (0.2%)
Abortion spontaneous	0	0	1 (0.4%)	1 (0.2%)
Blood and lymphatic system disorders	1 (0.4%)	0	0	0
Thrombocytopenia	1 (0.4%)	0	0	0
Eye disorders	1 (0.4%)	0	0	0
Angle closure glaucoma	1 (0.4%)	0	0	0
Metabolism and nutrition disorders	1 (0.4%)	0	0	0
Failure to thrive	1 (0.4%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.4%)	0	0	0
Bursitis	1 (0.4%)	0	0	0
Renal and urinary disorders	2 (0.9%)	0	0	0
Acute kidney injury	2 (0.9%)	0	0	0

Note: Adverse events were coded according to MedDRA version 18.0.
Note: At each level of patient summarization, a patient was counted once if the patient reported one or more events.

Table 25: Number of Patients with Serious Treatment-Emergent Adverse Events during the 52-Week Period by Primary System Organ Class and Preferred Term – SAF

Primary System Organ Class Preferred term	Placebo + TCS (N = 315)	Dupilumab + TCS 300 mg Q2W (N = 110)	 300 mg QW (N = 315)	 Combined (N = 425)
Number of patients with at least 1 such event, n (%)	16 (5.1%)	4 (3.6%)	9 (2.9%)	13 (3.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.3%)	1 (0.9%)	3 (1.0%)	4 (0.9%)
Squamous cell carcinoma of skin	0	1 (0.9%)	1 (0.3%)	2 (0.5%)
Squamous cell carcinoma	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Squamous cell carcinoma of the tongue	0	0	1 (0.3%)	1 (0.2%)
Cervix carcinoma	1 (0.3%)	0	0	0
Penile squamous cell carcinoma	1 (0.3%)	0	0	0
Uterine leiomyoma	1 (0.3%)	0	0	0
Skin and subcutaneous tissue disorders	2 (0.6%)	1 (0.9%)	2 (0.6%)	3 (0.7%)
Dermatitis atopic	1 (0.3%)	1 (0.9%)	1 (0.3%)	2 (0.5%)
Rash maculo-papular	0	0	1 (0.3%)	1 (0.2%)
Urticaria	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	3 (1.0%)	0	2 (0.6%)	2 (0.5%)
Road traffic accident	0	0	1 (0.3%)	1 (0.2%)
Spinal compression fracture	0	0	1 (0.3%)	1 (0.2%)
Clavicle fracture	1 (0.3%)	0	0	0
Concussion	1 (0.3%)	0	0	0
Contusion	1 (0.3%)	0	0	0
Limb traumatic amputation	1 (0.3%)	0	0	0
Eye disorders	1 (0.3%)	0	1 (0.3%)	1 (0.2%)
Cystoid macular oedema	0	0	1 (0.3%)	1 (0.2%)
Cataract	1 (0.3%)	0	0	0
Glaucoma	1 (0.3%)	0	0	0
Hepatobiliary disorders	0	0	1 (0.3%)	1 (0.2%)
Cholelithiasis	0	0	1 (0.3%)	1 (0.2%)
Infections and infestations	2 (0.6%)	1 (0.9%)	0	1 (0.2%)
Superinfection bacterial	0	1 (0.9%)	0	1 (0.2%)
Bronchitis	1 (0.3%)	0	0	0
Eczema herpeticum	1 (0.3%)	0	0	0
Pneumonia	1 (0.3%)	0	0	0
Nervous system disorders	2 (0.6%)	1 (0.9%)	0	1 (0.2%)
Cerebral infarction	0	1 (0.9%)	0	1 (0.2%)

Table 25 cont: Number of Patients with Serious Treatment-Emergent Adverse Events During the 52-Week Period by Primary System Organ Class and Preferred Term – SAF

Primary System Organ Class Preferred term	Placebo + TCS (N = 315)	Dupilumab + TCS 300 mg Q2W (N = 110)	 300 mg QW (N = 315)	 Combined (N = 425)
Carotid artery stenosis	1 (0.3%)	0	0	0
Cerebrovascular accident	1 (0.3%)	0	0	0
Psychiatric disorders	0	1 (0.9%)	0	1 (0.2%)
Anxiety	0	1 (0.9%)	0	1 (0.2%)
Gastrointestinal disorders	1 (0.3%)	0	0	0
Pancreatitis	1 (0.3%)	0	0	0
General disorders and administration site conditions	1 (0.3%)	0	0	0
Soft tissue inflammation	1 (0.3%)	0	0	0
Investigations	1 (0.3%)	0	0	0
Liver function test abnormal	1 (0.3%)	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	0	0	0
Pseudarthrosis	1 (0.3%)	0	0	0

Note: Adverse events were coded according to MedDRA version 18.0.
At each level of summarization, a patient is counted once if the patient reported one or more events.

8.4.3.4. Other studies

Other efficacy studies

In Study R668-AD-1021 there were no deaths. SAEs were reported in five (7.7%) patients exposed to 100 mg Q4W, three (4.6%) to 300 mg Q4W, one (1.6%) to 200 mg Q2W, two (3.1%) to 300 mg Q2W, one (1.6%) to 300 mg QW and four (6.6%) to placebo. One patient in the 200 mg Q2W group was reported with anaphylactic shock.

In Study R668-AD-1117 there were no deaths. SAEs were reported in one (1.8%) patients in the 300 mg QW group (right orbital fracture) and seven (13.0%) in the placebo.

In Study R668-AD-1121 there were no deaths. One SAE was reported in the placebo group and none in the dupilumab.

In Study R668-AD-1225 there were no deaths. SAEs were reported in 74 (5.0%) patients at a rate of 7.346 patients per 100 patient years. There was no apparent pattern to the SAEs.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 there were no deaths. There was one SAE in one subject in the 150 mg group: elevated CPK.

In Study R668-AD-1026 there were no deaths. One SAE was reported in the placebo group.

In Study R668-AD-1307 there were no deaths. SAEs were reported in no subjects in the dupilumab group and three (11.1%) in the placebo.

In Study R668-AD-1314 there were no deaths. SAEs were reported in three (3.1%) patients in the dupilumab group (serum sickness-like reaction/ injection site reaction / urticarial / wheezing, squamous cell carcinoma, mycosis fungoides) and none in the placebo.

Studies evaluable for safety only

In Study ACT11457 there were no deaths. SAEs were reported in one (1.9%) patient in the dupilumab group (bipolar disorder) and three (5.8%) in the placebo.

In Study DRI12544 there were two deaths in the 300 mg Q4W group (acute cardiovascular failure, metastatic gastric cancer). SAEs were reported in 13 (8.3%) patients in the dupilumab

300 mg Q2W group, ten (6.8%) in the 200 mg Q2W, 16 (10.2%) in the 300 mg Q4W, six (4.0%) in the 200 mg Q4W and nine (5.7%) in the placebo. Asthma was reported as an SAE in 1.6% patients.

In Study LTS12551 there was one death (metastatic lung cancer). There were 28 (5.3%) patients with SAEs. Pneumonia was reported in five (0.9%) patients.

In Study ACT12340 there were no deaths. SAEs were reported in two (6.7%) patients in the dupilumab group (herpes zoster, arrhythmia/ pain in extremity/ hypoaesthesia/ mono-neuropathy) and four (13.3%) in the placebo.

8.4.4. Discontinuations due to adverse events

8.4.4.1. Integrated safety analyses

In the ISS for studies as monotherapy, discontinuation due to adverse event (DAE) was reported for ten (1.9%) subjects in the Q2W group, eight (1.5%) in the QW and ten (1.9%) in the placebo. DAEs are discussed by study in the following sections.

8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.4.4.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 DAE was reported for four (1.8%) patients in the QW group, four (1.7%) in the Q2W and two (0.9%) in the placebo. There was no apparent pattern to the DAEs.

In Study SOLO 2 R668-AD-1416 DAEs was reported for three (1.3%) patients in the QW group (spontaneous abortion, lethargy / diarrhoea, Hodgkin's disease), two (0.8%) in the Q2W (atopic dermatitis, eczema impetiginous) and five (2.1%) in the placebo.

In Study CHRONOS R668-AD-1224 DAE was reported for nine (2.9%) patients in the QW group, three (2.7%) in the Q2W and 25 (7.9%) in the placebo. There were 14 (4.4%) patients in the placebo group who discontinued because of atopic dermatitis.

8.4.4.4. Other studies

Other efficacy studies

In Study R668-AD-1021 DAE was reported in ten (15.4%) patients exposed to 100 mg Q4W, three (4.6%) to 300 mg Q4W, three (4.9%) to 200 mg Q2W, four (6.3%) to 300 mg Q2W, one (1.6%) to 300 mg QW and three (4.9%) to placebo. There was no apparent pattern to the DAEs.

In Study R668-AD-1117 DAEs (from study treatment) were reported in one (1.8%) patients in the 300 mg QW group (right orbital fracture) and seven (13.0%) in the placebo.

In Study R668-AD-1121 one patient was reported with DAE in the placebo group and none in the dupilumab.

In Study R668-AD-1225 DAE was reported for 27 (1.8%) patients at a rate of 2.603 patients per 100 patient years. Three (0.2%) patients discontinued because of conjunctivitis.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 no patient was withdrawn from the study or from study treatment because of an AE.

In Study R668-AD-1026 one patient in the placebo group withdrew due to an AE.

In Study R668-AD-1307 discontinuation from study treatment due to TEAE was reported in three (11.1%) subjects in the dupilumab group (elevated ALT, worsening of atopic dermatitis [2]), and four (14.8%) in the placebo.

In Study R668-AD-1314 DAE was reported for five (5.2%) patients in the dupilumab group (serum sickness-like reaction/ injection site reaction / urticarial / wheezing, mycosis fungoides, photosensitivity reaction, dizziness/ fatigue, conjunctivitis)) and none in the placebo.

Studies evaluable for safety only

In Study ACT11457 DAE was reported for three (5.8%) patients in the dupilumab group (bipolar disorder, wheezing, angioedema) and three (5.8%) in the placebo (URTI, psoriasis, asthma exacerbation).

In Study DRI12544 DAE was reported for four (2.6%) patients in the dupilumab 300 mg Q2W group, six (4.1%) in the 200 mg Q2W, ten (6.4%) in the 300 mg Q4W, seven (4.7%) in the 200 mg Q4W and five (3.2%) in the placebo. General and administration site disorders resulted in discontinuation in two (1.3%) patients in the dupilumab 300 mg Q2W group, two (1.4%) in the 200 mg Q2W, two (1.3%) in the 300 mg Q4W, one (0.7%) in the 200 mg Q4W and none in the placebo.

In Study LTS12551 there were 16 (3.0%) patients with DAE. No individual term was reported in more than one subject. Three (0.6%) patients discontinued due to infections.

In Study ACT12340 DAE was reported in two (6.7%) patients in the dupilumab group (constipation, injection site reaction) and five (16.7%) in the placebo.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

8.5.1.1. Integrated safety analyses

Not applicable.

8.5.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.1.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334, Study SOLO 2 R668-AD-1416 and Study CHRONOS R668-AD-1224 there was a decrease in mean serum LDH concentration in the dupilumab groups.

In Study CHRONOS R668-AD-1224 elevated ALT was reported in four (1.3%) patients in the QW group, one (0.9%) in the Q2W and four (1.3%) in the placebo. Elevated AST was reported in three (0.9%) patients in the QW group, one (0.9%) in the Q2W and five (1.6%) in the placebo.

8.5.1.4. Other studies

Other efficacy studies

In Study R668-AD-1021 one patient in the 300 mg Q4W group had elevated ALT.

In Study R668-AD-1117 there was a decrease in LDH with treatment in the 300 mg QW group.

In Study R668-AD-1121 there were no clinically significant abnormalities in hepatic function.

In Study R668-AD-1225 one patient developed hepatic cirrhosis that was not considered to be related to treatment. One patient developed drug induced liver injury that was attributed to bactrim.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 and Study R668-AD-1026 there were no clinically significant changes in hepatic function.

In Study R668-AD-1307 one patient in each treatment group had elevated ALT.

In Study R668-AD-1314 no patients in the dupilumab group and three (3.1%) in the placebo elevated ALT. No patients in the dupilumab group and three (3.1%) in the placebo elevated AST.

Studies evaluable for safety only

In Study DRI12544 two patients in the dupilumab 200 mg Q2W group developed elevated ALT leading to discontinuation.

8.5.2. Renal function and renal toxicity

8.5.2.1. Integrated safety analyses

Not applicable.

8.5.2.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.2.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 there were no between group differences in renal function.

In Study CHRONOS R668-AD-1224 a ≥30% and <100% change from baseline in serum creatinine was reported in 25 (8.1%) patients in the QW group, 14 (12.8%) in the Q2W and 35 (11.1%) in the placebo.

8.5.2.4. Other studies

Other efficacy studies

In Study R668-AD-1021 there were no clinically significant abnormalities in renal function.

In Study R668-AD-1117 one patient in the placebo group was reported with renal failure.

In Study R668-AD-1121 there were no clinically significant abnormalities in renal function.

In Study R668-AD-1225 there were 104 (7.4%) patients with a ≥30% and <100% change from baseline in serum creatinine.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-091) and Study R668-AD-1026 there were no clinically significant changes in renal function.

In Study R668-AD-1307 four patients in each treatment group had an increase in serum creatinine from baseline.

In Study R668-AD-1314 three (3.1%) patients in the dupilumab group and eleven (11.3%) in the placebo had ≥30% and <100% change from baseline in serum creatinine.

Studies evaluable for safety only

In Study ACT11457 one patient in the dupilumab group had serum creatinine increased ≥100% from baseline.

8.5.3. Other clinical chemistry

8.5.3.1. Integrated safety analyses

Not applicable.

8.5.3.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.3.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 there were no clinically significant between group differences in other clinical chemistry.

8.5.3.4. Other studies

Other efficacy studies

In Study R668-AD-1021 there were no clinically significant abnormalities in other chemistry.

In Study R668-AD-1117 five (9.1%) patients in the 300 mg QW group were reported with CPK >3xULN.

In Study R668-AD-1121 and In Study R668-AD-1225 there were no clinically significant abnormalities in other clinical chemistry.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 there was on subject in the 150 mg group with elevated CPK.

Study R668-AD-1026 there were no clinically significant changes in other clinical chemistry.

Studies evaluable for safety only

In Study ACT11457 four (7.7%) patients in the dupilumab group and one (1.9%) in the placebo had elevated CPK.

In Study DRI12544 one patient in the dupilumab 300 mg Q4W group developed elevated CPK and rhabdomyolysis leading to discontinuation.

8.5.4. Haematology and haematological toxicity

8.5.4.1. Integrated safety analyses

Not applicable.

8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.4.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 there was a decrease in mean platelet count over the study. The greatest decrease in mean platelet count over the study was 6.6 $x10^9$/L for Q2W at Week 4 and 9.5 $x10^9$/L for QW at Week 16. More patients in the dupilumab groups had a shift in eosinophils from normal to high: at Week 23 (15.0%) patients in the QW group, 17 (10.3%) in the Q2W and eight (5.2%) in the placebo.

In Study SOLO 2 R668-AD-1416 there was a decrease in mean platelet count over the study. The greatest decrease in mean platelet count over the study was 8.5 $x10^9$/L for Q2W at Week 12 and 12.7 $x10^9$/L for QW at Week 16, and 3.9 $x10^9$/L for placebo at Week 16. More patients in the dupilumab group QW had a shift in eosinophils from normal to high at Week 16: 23 (14.6%) patients in the QW group, 15 (8.8%) in the Q2W and 12 (7.2%) in the placebo. One patient in the Q2W group had a TEAE of neutropenia.

In Study CHRONOS R668-AD-1224 one patient in the dupilumab groups was reported with thrombocytopenia. More patients in the dupilumab group QW had a shift in eosinophils from normal to high at Week 52: 17 (9.7%) patients in the QW group, nine (18.4%) in the Q2W and ten (7.0%) in the placebo.

8.5.4.4. Other studies

Other efficacy studies

In Study R668-AD-1021 and Study R668-AD-1117 there were no clinically significant abnormalities in haematology.

In Study R668-AD-1121 one patient in the dupilumab 300 mg QW group was reported with neutropenia.

In Study R668-AD-1225 there was a mean (SD) decrease in platelet count from baseline to Week 48 of 15.9 (43.65) $x10^9$/L. One patient was reported with a TEAE of thrombocytopenia.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-HV-1108 there were four subjects with neutropenia: two in the fast administration group and two in the slow administration group.

In Study R668-AD-0914 and Study R668-AD-1026 there were no clinically significant changes in haematology.

In Study R668-AD-1314 there was a trend for increasing eosinophils in the dupilumab group (19 [25%] patients) but no other trends in haematology parameters.

Studies evaluable for safety only

In Study ACT11457 one patient in the dupilumab group had decreased neutrophils.

In Study DRI12544 one patient in the dupilumab 300 mg Q2W group developed hypereosinophilia leading to discontinuation.

8.5.5. Other laboratory tests

No between-group differences in other laboratory tests were identified.

8.5.6. Electrocardiograph findings and cardiovascular safety

8.5.6.1. Integrated safety analyses

Not applicable.

8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.6.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 and Study SOLO 2 R668-AD-1416 there were no clinically significant changes in ECGs.

In Study CHRONOS R668-AD-1224 an increase in QTcB from baseline of 30 to60 ms was observed in 20 (6.6%) patients in the QW group, 11 (10.4%) in the Q2W and 21 (7.0%) in the placebo.

8.5.6.4. Other studies

Other efficacy studies

In Study R668-AD-1021 there were no between group differences in ECG changes.

In Study R668-AD-1117 there was an increase in QTcF of 30 to 60 ms in three (5.8%) subjects in the 300 mg QW group and one (2.1%) in the placebo. There were no clinically significant ECG changes.

In Study R668-AD-1121 there was an increase in QTcF of 30 to 60 ms in three (14.3%) subjects in the 300 mg QW group and one (10.0%) in the placebo. There was an increase in QTcB of 30 to 60 ms in three (14.3%) subjects in the 300 mg QW group and one (10.0%) in the placebo.

In Study R668-AD-1225 one patient had an increase in QTcF and QTcB which was related to right bundle branch block that was no attributed to study treatment.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914 and Study R668-AD-1026 there were no ECG changes.

In Study R668-AD-1307 and Study R668-AD-1314 there were no between group differences in ECG changes.

Studies evaluable for safety only

In Study ACT11457 there were no clinically significant changes in ECGs.

8.5.7. Vital signs and clinical examination findings

8.5.7.1. Integrated safety analyses

Not applicable.

8.5.7.2. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.7.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334, Study SOLO 2 R668-AD-1416 and Study CHRONOS R668-AD-1224 there were no clinically significant between group differences in vital signs.

8.5.7.4. Other studies

Other efficacy studies

In Study R668-AD-1021 there were no between group differences in vital signs.

In Study R668-AD-1117 there was a decrease in mean pulse rate, but still within normal limits, in the 300 mg QW group.

In Study R668-AD-1121 there were no between group differences in vital signs.

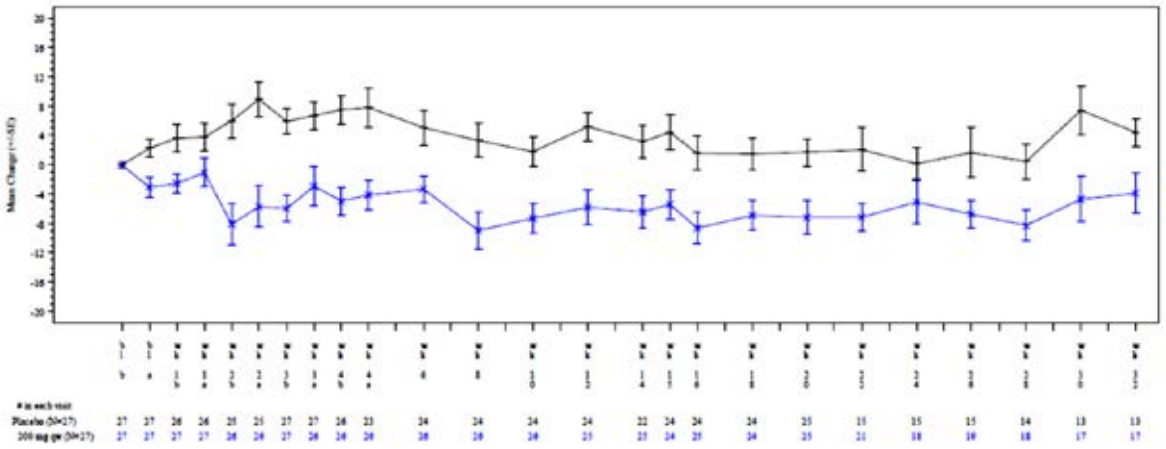
In Study R668-AD-1225 there were 46 (3.1%) patients with SBP >160 mmHg and an increase from baseline ≥20 mmHg.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-AD-0914, Study R668-AD-1026 and Study R668-AD-1314 there were no clinically significant changes in vital signs.

In Study R668-AD-1307 there was a decrease in SBP in the dupilumab group of 8.6 mmHg at Week 16, but not in the placebo group (Figure 40). Five (18.5%) patients in the dupilumab group and one (3.7%) in the placebo had a SBP ≤95 mmHg and decrease from baseline ≥20 mmHg.

Figure 40: Change in Mean Systolic Blood Pressure from Baseline-SAF Population



b- pre injection time point; a-1 hour post injection time point

Studies evaluable for safety only

In Study ACT11457 there were no clinically significant changes in vital signs.

8.5.8. Immunogenicity and immunological events

8.5.8.1. Integrated safety analyses

Not applicable.

8.5.8.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.8.3. Pivotal and/or main efficacy studies

In Study SOLO 1 R668-AD-1334 treatment emergent ADAs were reported in six (2.7%) patients in the QW group, 15 (6.8%) in the Q2W and two (1.0%) in the placebo. Two patients in the QW group had high titres. Injection site reaction was more common in patients with ADA: in the Q2W group 26.7% of patients with ADA and 18.8% of patients without ADA.

In Study SOLO 2 R668-AD-1416 treatment emergent ADAs were reported in six (2.7%) patients in the QW group, 18 (8.0%) in the Q2W and four (1.8%) in the placebo. Injection site reaction was not more common in patients with ADA: in the Q2W group 6.9% of patients with ADA and 15.3% of patients without ADA.

In Study CHRONOS R668-AD-1224 treatment emergent ADAs were reported in 14 (4.5%) patients in the QW group, six (5.7%) in the Q2W and 20 (6.6%) in the placebo.

8.5.8.4. Other studies

Other efficacy studies

In Study R668-AD-1021 one patient in the 200 mg Q2W group was reported with anaphylactic shock. At Week 16 ADA were reported in 15 (23.1%) patients exposed to 100 mg Q4W, nine (13.8%) to 300 mg Q4W, nine (14.8%) to 200 mg Q2W, seven (10.9%) to 300 mg Q2W, four (6.35%) to 300 mg QW and one (1.6%) to placebo.

In Study R668-AD-1117 treatment emergent ADA were reported in four (7.3%) patients in the 300 mg QW group and none in the placebo. One of the titres in the dupilumab group was high.

In Study R668-AD-1121 treatment emergent ADA were reported in three (10.0%) patients treated with 300 mg QW for 4 weeks, and none in the placebo group.

In Study R668-AD-1225 treatment emergent ADA were reported in 23 (2.8%) patients.

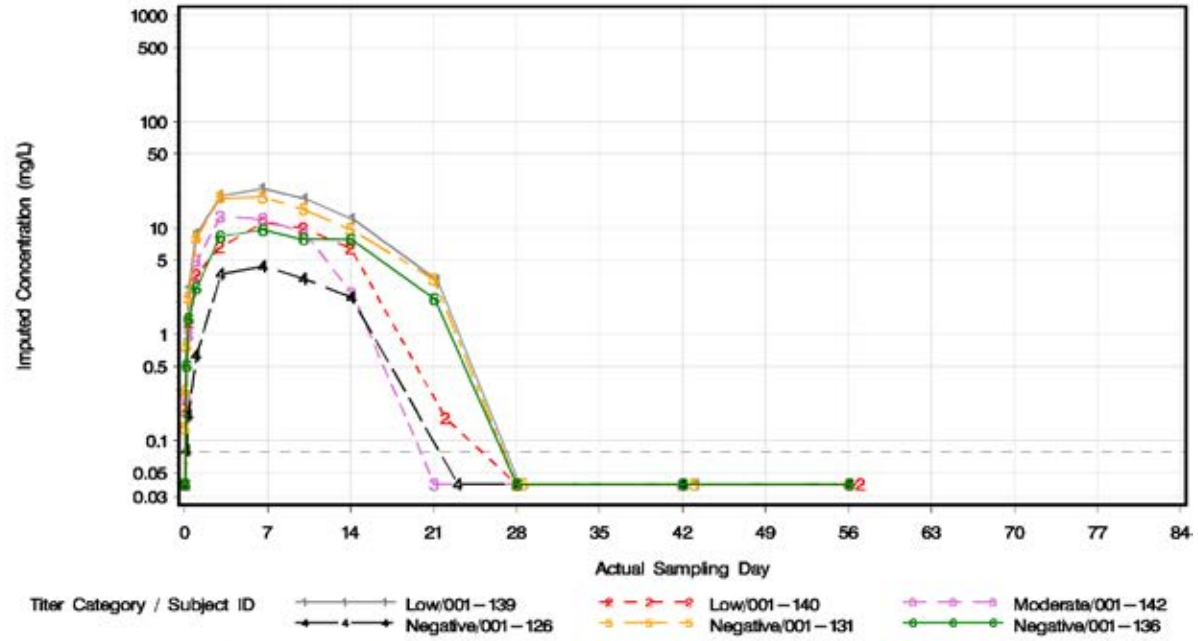
Studies with evaluable safety data: dose finding and pharmacology

In Study PKM14161 at end of study 11 (57.9%) subjects in the DP2 group and 14 (73.7%) in the DP1 had developed anti-dupilumab antibodies (ADA). No subjects had a high titre response. No specific pattern of AEs was identified with the antibody response.

In Study PKM14271 there were ten (52.6%) subjects on DP1 and five (26.3%) on DP2 positive for ADA. One subject positive for ADA had a hypersensitivity reaction (rhinitis) which was not considered to be related to treatment.

In Study R688-AS-0907 which examined the dose range 1 to 12 mg/kg IV and 150 to 300 mg SC, no subjects were positive for ADA at baseline and no placebo subjects developed ADA. Positive ADA titres were observed in nine subjects: eight were low and one was moderate. There were three, two, none and none subjects positive for ADA in the 1, 3, 8 and 12 mg/kg IV dose groups respectively, and three and one in the 150 and 300 mg SC dose group respectively. Concentrations of functional dupilumab may have been influenced by ADA titres. In the 150 mm SC group, the subject with moderate ADA titres had the smallest t_{last} for functional dupilumab (Figure 41). The rate of developing ADA did not increase with dose.

Figure 41: Individual Log-scaled Concentrations of Functional REGN668 vs. Nominal Day By Dose and Binding ADA Titre Category - Dose of 150 mg SC



Note: Concentrations below the lower limit of quantification (LLOQ) are imputed as LLOQ/2. Placebo subjects are excluded.

In Study R668-HV-1108 ADA were developed by seven (38.9%) subjects in the fast administration group and six (33.3%) in the slow administration (Table 26). Overall two (5.56%) had moderate titres.

Table 26: Number of Subjects Classified by ADA Category Following a Single 300 mg SC Dose Administered at 2 Different Rates (Study R668-HV-1108)

Max Titer	300 mg SC / Fast Injection		300 mg SC / Slow Injection		Overall	
	n	%	n	%	n	%
Negative	11	61.1	12	66.7	23	63.9
Low (<1000)	6	33.3	5	27.8	11	30.6
Moderate (≥1000 to ≤10000)	1	5.56	1	5.56	2	5.56
High (>10000)	0	0	0	0	0	0
Overall	18	100	18	100	36	100

ADA = Anti-drug antibodies; N = Number of subjects; SC = Subcutaneous

In Study R668-AD-0914 ADA were detected in ten (33.3%) subjects in the dupilumab groups, and none in the placebo. Development of ADA was not dose related. ADA were detected in six (75%) patients in the 75 mg group, four (50.0%) in the 150 mg and none in the 300 mg. One patient in the 75 mg group had high titres.

In Study R668-AD-1026 ADA were detected in seven (18.9%) subjects in the dupilumab groups, and none in the placebo. Development of ADA was not dose related. ADA were detected in five (35.7%) patients in the 150 mg and two (15.4%) in the 300 mg. One patient in the 150 mg group had moderate titres.

In Study R668-AD-1307 treatment emergent AD were reported in eight (29.6%) patients in the dupilumab group and one (3.7%) in the placebo.

In Study R668-AD-1314 one patient in the dupilumab group had a serum sickness-like reaction which followed on from an episode of injection site reaction, urticarial and wheezing. The patient was positive for ADA. Treatment emergent ADA were detected in 28 (28.9%) patients in the dupilumab group and five (5.2%) in the placebo.

In the population pharmacokinetic study REGN668-MX-16103 the sponsor investigated the effects on PK of ADA and found a 17.8% increase in k_e. This translates to a 17.8% increase in clearance. However, in the population PKPD Study REGN668-MX-1602 ADA did not significantly affect response.

Studies evaluable for safety only

In Study DRI12544 one patient in the 300 mg Q2W group was reported with anaphylaxis to grapes four months after last administration of study drug. Treatment emergent ADA were reported for 37 (23.9%) patients in the dupilumab 300 mg Q2W group, 38 (25.7%) in the 200 mg Q2W, 51 (32.5%) in the 300 mg Q4W, 64 (43.2%) in the 200 mg Q4W and 19 (12.0%) in the placebo.

8.5.9. Serious skin reactions

8.5.9.1. Integrated safety analyses

In Study DRI12544 severe or serious infections were reported in seven (4.5%) patients in the dupilumab 300 mg Q2W group, two (1.4%) in the 200 mg Q2W, three (1.9%) in the 300 mg Q4W, one (0.7%) in the 200 mg Q4W and two (1.3%) in the placebo.

8.5.10. Injection site reactions

8.5.10.1. Integrated safety analyses

Not applicable.

8.5.10.2. Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.5.10.3. Pivotal and/or main efficacy studies

Discussed in Section 8.4.1.

8.5.10.4. Other studies

Other efficacy studies

Discussed in Section 8.4.1.

Studies with evaluable safety data: dose finding and pharmacology

In Study R668-HV-1108 there was good tolerability for both fast and slow administration techniques. Erythema and induration were greater with slow administration but there was more tenderness and itch with fast administration (Table 27).

Table 27: Assessment of Injection Site Reactions (SAF)

	Dupilumab 300 mg/2 mL	
	Fast Injection (N=18)	Slow Injection (N=18)
Subjects with ISR	16 (88.9%)	17 (94.4%)
Subjects with Objective ISR Findings	8 (44.4%)	15 (83.3%)
Subjects with Injection Site Erythema	2 (11.1%)	11 (61.1%)
Subjects with Injection Site Edema	0	0
Subjects with Injection Site Induration	7 (38.9%)	12 (66.7%)
Subjects with Subjective ISR Findings	13 (72.2%)	10 (55.6%)
Subjects with Injection Site Tenderness	13 (72.2%)	7 (38.9%)
Subjects with Injection Site Itching	12 (66.7%)	9 (50.0%)

Studies evaluable for safety only

Discussed in Section 8.4.1 above.

8.6. Other safety issues

8.6.1. Safety in special populations

Children, pregnancy and lactation were not addressed in the development program.

8.6.2. Safety related to drug-drug interactions and other interactions

There was no effect of dupilumab on the immune response to tetanus toxoid or meningococcal C antigen.

8.7. Post marketing experience

8.7.1. Post-Marketing Data

No post-marketing experience is available as dupilumab has never been marketed in any country.

8.7.2. Risk Management Plan

The Risk Management Plan states the following risks:

Important Identified Risks:

· Systemic hypersensitivity

Important Potential Risks:

· No important potential risks were identified

Missing Information:

- Use in paediatric AD patients <18 years of age
- Use in pregnant and lactating women
- Drug-drug interactions
- Conjunctivitis
- Helminthic infections

8.8. Evaluator's overall conclusions on clinical safety

The overall rates of TEAEs were similar for dupilumab and placebo. The rates of TEAEs did not increase with exposure to dupilumab, either by dose or time. Injection site reactions, narrow conjunctivitis and broad conjunctivitis were reported more frequently with dupilumab than placebo.

The most common treatment related TEAE was injection site reaction, occurring in up to 17% of patients in a dupilumab group. The other significant treatment related TEAE was conjunctivitis, occurring in up to 2.3%.

There were six deaths in the development program. None of the deaths were attributed to dupilumab.

Overall SAEs appeared to be more common with placebo than dupilumab. There was no pattern to the SAEs that would indicate an identifiable risk.

DAE occurred at a similar rate in dupilumab and placebo groups. The rate of DAE did not increase with exposure, either by dose or time. There was no pattern to the DAEs that would indicate an identifiable risk.

The rate of liver and renal injury was similar for dupilumab and placebo. There was one patient with DILI attributed to Bactrim.

Several patients treated with dupilumab were reported with elevated CPK and one was reported with rhabdomyolysis.

Neutropenia and thrombocytopenia were reported in patients treated with dupilumab. These events do not appear to have been clinically significant.

The development program did not address the following issues:

- Interactions with live vaccines.
- Long-term safety beyond 18 months. Hence, long term effects on immunity or neoplasia have not been discounted.
- Interactions with topical and/or systemic immunomodulatory drugs

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Indication	
Benefits	**Strengths and Uncertainties**
Dupilumab has superior efficacy to placebo as monotherapy in patients with moderate to severe AD. *Dupilumab has superior efficacy to placebo in patients with moderate to severe AD who are receiving concomitant topical corticosteroids* *The efficacy of dupilumab appears to be maintained for up to 18 months.*	*Efficacy was demonstrated using investigator measures, patient reported outcomes and quality of life scores. The margin of efficacy was convincing and was clinically and statistically significant.* *The duration of efficacy that has been demonstrated is relatively short for a drug that might be used as long-term treatment.* *Efficacy has not been compared to currently used treatments for moderate to severe AD such as topical and/or systemic immunomodulatory agents.*

9.2. First round assessment of risks

Risks	Strengths and Uncertainties
Dupilumab has a similar rate of adverse effects to placebo. *Dupilumab has a higher rate of injection site reactions than placebo.* *Dupilumab has a higher rate of conjunctivitis than placebo.*	*There is good evidence of a favourable safety profile for up to 18 months of treatment. However, long-term effects on immunity and neoplasia have not been addressed.* *There appears to be a higher rate of elevated CPK with dupilumab. The risks of rhabdomyolysis have not been fully addressed.* *There are higher rates of neutropenia and thrombocytopenia with dupilumab that do not appear to be clinically significant. The implications for monitoring have not been addressed.* *Interactions with live vaccines have not been addressed.* *Interactions with topical and/or systemic immunomodulatory drugs have not been addressed.*

9.3. First round assessment of benefit-risk balance

Dupilumab appears to have a favourable risk benefit profile. However, there are a number of uncertainties that need to be addressed before the risk benefit profile can be determined. These are:

- The possible risk of rhabdomyolysis and need for monitoring CPK
- The need for monitoring of neutrophil and platelet counts
- Long term safety beyond 18 months of treatment

10. First round recommendation regarding authorisation

The evaluator recommends deferring the decision to authorise dupilumab (Dupixent) 300 mg/2 mL; solution for injection. In the opinion of the evaluator the following safety issues should be resolved prior to authorisation:

- The possible risk of rhabdomyolysis and need for monitoring CPK
- The need for monitoring of neutrophil and platelet counts
- Long term safety beyond 18 months of treatment

11. Clinical questions

11.1. Pharmacokinetics

1. Does the sponsor have data examining the potential PK interactions between dupilumab and other immunomodulating agents?
2. Does the sponsor intend to study the PK of dupilumab in infants and young children?
3. Does the sponsor intend to study the PK of dupilumab in older patients?

11.2. Pharmacodynamics

4. Does the sponsor have data examining the potential PD interactions between dupilumab and other immunomodulating agents?
5. Does the sponsor have data examining the potential effects of dupilumab on live vaccines?
6. Does the sponsor intend to study the PD of dupilumab in infants and children?
7. Does the sponsor intend to study the effects of dupilumab on vaccinations in infants and children?

11.3. Efficacy

8. Does the sponsor have evidence of efficacy for dupilumab in AD in comparison with systemic corticosteroids and/or immunomodulatory agents such as ciclosporine, azathioprine and/or methotrexate?
9. Does the sponsor have data for efficacy in combination with immunomodulatory drugs, either topical or systemic?
10. Does the sponsor have evidence of efficacy beyond 18 months?

11. How does the sponsor intend to monitor the effect of long-term use on the development, and titres, of neutralising ADA?
12. How does the sponsor intend to monitor the potential effect of increasing titres of ADA with long term use on efficacy?

11.4. Safety

13. Has the sponsor performed an analysis of the rates of elevated CPK and rhabdomyolysis? Is the risk of either elevated CPK or rhabdomyolysis increased with dupilumab?
14. Neutropenia and thrombocytopenia were reported in patients treated with dupilumab. Has the sponsor developed recommendations for monitoring haematology in patients treated with dupilumab?
15. The prohibited drugs during the pivotal studies were:
    - Treatment with a live (attenuated) vaccine
    - Treatment with immunomodulating biologics
    - TCI could be administered during the study only if required for AD rescue
    - Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (for example, ciclosporine, MTX, MMF, AZA, etc.)

    Does the sponsor have any evidence of safety in combination with these treatments?
16. Does the sponsor have any evidence of safety in combination with live vaccines?
17. Does the sponsor have any evidence of long-term safety beyond 18 months?
18. Does the sponsor intend to monitor long term effects on immunity or neoplasia?

12. First round evaluation errata

12.1. Minor editorial changes

There were no minor editorial changes.

12.2. Minor errors of fact

There were no minor errors of fact.

12.3. Significant errors of fact

There were no significant errors of fact.

13. Second round evaluation

The sponsor has made the following responses to the clinical questions:

1. Does the sponsor have data examining the potential PK interactions between dupilumab and other immunomodulating agents?

Sponsor's response:

The sponsor states*: 'No specific interaction studies with immunomodulating agents have been performed.'* The sponsor also states that the submitted data, with regard to systemic corticosteroids and calcineurin inhibitors, indicate 'effects of dupilumab on AD are unlikely to modulate the pharmacokinetics of drugs metabolized by CYP3A, CYP2C9, CYP2C19, CYP1A2 or CYP2D6 in these patients'.

Evaluator's comments:

The sponsor's response is satisfactory. In the opinion of the Evaluator there are unlikely to be any drug-drug interactions with dupilumab at the level of drug metabolising enzymes or transporters. Pharmacokinetic interactions with other antibody based treatments have not been studied but are unlikely to affect the PK of dupilumab.

2. Does the sponsor intend to study the PK of dupilumab in infants and young children?

Sponsor's response:

The sponsor states: *'There are 2 ongoing pediatric studies: open-label-extension study (R668-AD-1434) and study R668-AD-1526 (12 to <18 years of age, phase 3). Additional studies are planned to start late this year, R668-AD-1652 (6 to <12 years of age, phase 3) and R668-AD-1539 (6 months to < 6 years of age, phase 2/3).*'

Evaluator's comment:

The sponsor's response is not satisfactory because the sponsor has not stated whether PK data will be collected and analysed as part of these planned studies. The response would be satisfactory if the sponsor intends to measure dupilumab concentrations and conduct an appropriately designed population pharmacokinetic study.

3. Does the sponsor intend to study the PK of dupilumab in older patients?

Sponsor's response:

The sponsor states *'No additional study of dupilumab in older patients is planned.'* The sponsor has provided post-hoc estimates for exposure parameters that indicate no significant difference in patients that were ≥65 years.

Evaluator's comment:

The sponsor's response is ambiguous because post-hoc estimates can be generated from covariate and dosing data using a population pharmacokinetic model in the absence of PK data. Hence the sponsor's response does not actually indicate the number of patients who have contributed PK data. It appears that there were approximately 106 patients between the ages of 62 and 88 years in Study REGN668-MX-16103. In the opinion of the Evaluator this sample size would be adequate to provide acceptable estimates of the exposure parameters in older patients.

4. Does the sponsor have data examining the potential PD interactions between dupilumab and other immunomodulating agents?

Sponsor's response:

The sponsor states '*No formal PD interaction studies have been performed*.' The sponsor argues that because there was no interaction between dupilumab and corticosteroids no other interactions with immunomodulatory agents would be expected.

Evaluator's comments:

The evaluator does not agree with the sponsor's rationale. There are a number of mechanisms by which immunomodulatory agents can act and interactions with dupilumab are plausible. In the opinion of the Evaluator, in the absence of data supporting concomitant use,

immunomodulatory agents other than corticosteroids should be contraindicated during treatment with dupilumab.

5. Does the sponsor have data examining the potential effects of dupilumab on live vaccines?

Sponsor's response:

The sponsor states *'The use of live vaccines in patients with AD being treated with dupilumab has not been systematically studied.'* The sponsor argues that the antibody response to live vaccines would be not impaired with the use of dupilumab '*since individuals capable of mounting an immune response to non-live vaccines should be able to do so against live vaccines'.*

Evaluator's comments:

The sponsor's response is not satisfactory. Currently the effects of live vaccines during treatment with dupilumab are unknown. If the sponsor's argument is correct then there would be no barrier to the sponsor studying these effects. It would be important to know the effects of live vaccines prior to use in young children, an age group where vaccination with live vaccines is part of routine healthcare. In the opinion of the Evaluator, in the absence of data supporting concomitant use, live vaccines should be contraindicated during treatment with dupilumab. The sponsor should commit to studying the effects of live vaccines as part of their Paediatric Investigation Plan and Risk Management Plan.

6. Does the sponsor intend to study the PD of dupilumab in infants and children?

Sponsor's response:

The sponsor states that *'A separate clinical development program is currently underway to support use in infants and young children'.*

Evaluator's comments:

The sponsor's response is not satisfactory because the sponsor has not stated whether PD data will be collected and analysed as part of these planned studies. The response would be satisfactory if the sponsor intends to measure dupilumab PD variables and conduct an appropriately designed population pharmacokinetic-pharmacodynamic study.

7. Does the sponsor intend to study the effects of dupilumab on vaccinations in infants and children?

Sponsor's response:

The sponsor states that a sub-study, part of an open label study, will evaluate 'the response to protein and glycoprotein vaccinations will be assessed in the age-group 6 months-<18 yrs. old.'

Evaluator's comments:

The sponsor's response is not satisfactory. The sponsor does not state whether response to live vaccines will be evaluated. In response to the question '*Does the Sponsor have data examining the potential effects of dupilumab on live vaccines?'* the sponsor argues that '*individuals capable of mounting an immune response to non-live vaccines should be able to do so against live vaccines*'. If the sponsor's argument is correct then there would be no barrier to the sponsor studying these effects. It would be important to know the effects of live vaccines prior to use in young children, an age group where vaccination with live vaccines is part of routine healthcare. In the opinion of the Evaluator, in the absence of data supporting concomitant use, live vaccines should be contraindicated during treatment with dupilumab. The sponsor should commit to studying the effects of live vaccines as part of their Paediatric Investigation Plan and Risk Management Plan.

8. Does the sponsor have evidence of efficacy for dupilumab in AD in comparison with systemic corticosteroids and/or immunomodulatory agents such as ciclosporine, azathioprine and/or methotrexate?

Sponsor's response:

The sponsor states that *'The sponsor has not performed a direct head to head comparison study to CSA given the logistical difficulties of designing a properly blinded study'.*

Evaluator's comments:

The sponsor's response is satisfactory. The lack of data supporting efficacy compared to usual second-line treatments would normally indicate dupilumab should be a third-line treatment. However, the safety profile of dupilumab appears to be better than current second-line agents. In the opinion of the Evaluator, it is appropriate that the indication for dupilumab should be as a second-line agent.

9. Does the sponsor have data for efficacy in combination with immunomodulatory drugs, either topical or systemic?

Sponsor's response:

The sponsor states *'In all Phase 3 dupilumab trials, use of systemic immunomodulating biologics was prohibited during the treatment period. Patients could receive systemic corticosteroids and systemic non-steroidal immunosuppressive drugs as rescue therapy if medically necessary to control intolerable AD symptoms'.*

Evaluator's comments:

The sponsor's response is satisfactory. In the opinion of the Evaluator, in the absence of data supporting concomitant use, concomitant use of immunomodulatory agents other than corticosteroids should be contraindicated during treatment with dupilumab.

10. Does the sponsor have evidence of efficacy beyond 18 months?

Sponsor's response:

The sponsor states *'the application contains data from the open label extension study (R668-AD-1225), in which over 300 patients were exposed to dupilumab for > 18 months and 160 were exposed to dupilumab for ≥24 months. The analysis of the data from this study demonstrated a markedly positive benefit/risk ratio in dupilumab treated patients, with rapid, robust, and sustained efficacy, and with a safety profile generally consistent with placebo-treated patients (Module 2.7.4 Section 1.1.5.10)'.*

Evaluator's comments:

The sponsor's response is satisfactory. Response appears to be maintained for up to 24 months.

11. How does the sponsor intend to monitor the effect of long-term use on the development, and titres, of neutralising ADA?

Sponsor's response:

The sponsor states that *in Study R668-AD-1225 ADA and NAb will be monitored for up to 3 years.*

Evaluator's comments:

The sponsor's response is satisfactory. The Evaluator recommends that the sponsor considers monitoring for a longer period based upon the results over 3 years from Study R688-AD-1225.

12. How does the sponsor intend to monitor the potential effect of increasing titres of ADA with long term use on efficacy?

Sponsor's response:

The sponsor intends monitor safety and ADA titres in Study R688-AD-1225.

Evaluator's comments:

The sponsor's response is satisfactory. The evaluator recommends the sponsor undertake an analysis of the effect of ADA and NAbs on efficacy and submit this analysis to the TGA.

13.1. Safety

13. Has the sponsor performed an analysis of the rates of elevated CPK and rhabdomyolysis? Is the risk of either elevated CPK or rhabdomyolysis increased with dupilumab?

Sponsor's response:

The sponsor states *'There was no meaningful difference in the incidence of rhabdomyolysis in the combined dupilumab treatment group (0.2% [2 of 1047]; non-serious) than the placebo group (0% [0 of 517]) in the Primary Safety Pool'. The sponsor also argues that the although the rates of elevated CPK were slightly elevated in the dupilumab groups compared to placebo in the 16-week monotherapy studies and the 52-week concomitant TCS study, there was no dose-response effect. With regard to myalgia, the sponsor refers to the Integrated Summary of Safety, which in the Safety Analysis Set reports mild myalgia in one (0.2%) patient in the placebo group and five (0.5%) in the dupilumab and moderate myalgia in one (0.2%) patient in the placebo group and four (0.4%) in the dupilumab.*

Evaluator's comments:

The sponsor's response is not satisfactory. In the opinion of the evaluator there is a difference between statistically significant and clinically meaningful. The incidence of rhabdomyolysis in the dupilumab group was 0.2% (i.e. 1 in 500) which although not statistically significant is still clinically meaningful. The rate of myalgia in the dupilumab group was double that of the placebo, which supports rather than contradicts a signal of rhabdomyolysis. To place this risk in context, the incidence of myopathy with simvastatin is reported as approximately 0.03%, 0.08% and 0.61% at 20, 40 and 80 mg/day, respectively. The Evaluator recommends that rhabdomyolysis should be included in the Safety Specification as an important potential risk. In addition, the sponsor should analyse whether there are associated factors in patients with rhabdomyolysis, such as overactivity, increasing age or co-medications.

14. Neutropenia and thrombocytopenia were reported in patients treated with dupilumab. Has the sponsor developed recommendations for monitoring haematology in patients treated with dupilumab?

Sponsor's response:

The sponsor states *'given the absence of any clinically relevant changes in haematological parameters and clinically associated adverse events, the sponsor does not propose haematological monitoring in patients treated with dupilumab'.*

Evaluator's comments:

The sponsor's response is satisfactory. In the opinion of the Evaluator, neutropenia and thrombocytopenia are not currently identified as risks with dupilumab. Hence recommendations for routine monitoring are not appropriate at the present time. However, the sponsor should consider neutropenia and thrombocytopenia in the pharmacovigilance plan for dupilumab.

15. The prohibited drugs during the pivotal studies were:

- ***Treatment with a live (attenuated) vaccine***

- ***Treatment with immunomodulating biologics***
- ***TCI could be administered during the study only if required for AD rescue***
- ***Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (for example, ciclosporine, MTX, MMF, AZA, etc.)***

Does the sponsor have any evidence of safety in combination with these treatments?

Sponsor's response:

In the sponsor's response there was no indication that the sponsor has evidence of safety in combination with these treatments, except for TCI. In Study R688-AD1224 there were 13 (11.8%) patients in the 200 mg Q2W group and 35 (11.1%) in the 300 mg QW treated with TCI.

Evaluator's comments:

The sponsor's response is not satisfactory. The sponsor has limited safety data for treatments that could be administered concomitantly with dupilumab. The sponsor describes dupilumab as a 'novel targeted immunoregulatory agent' and there are no similar drugs that enable prediction of interactions with other immunomodulatory agents or live vaccines. In the opinion of the Evaluator, these treatments, with the exception of TCI, should be contraindicated during treatment with dupilumab.

16. Does the sponsor have any evidence of safety in combination with live vaccines?

Sponsor's response:

The sponsor has not provided evidence of safety in combination with live vaccines. The sponsor refers to the response to the question: Does the Sponsor have data examining the potential effects of dupilumab on live vaccines?

Evaluator's comments:

The sponsor's response is not satisfactory. The sponsor does not state whether safety in combination with live vaccines will be evaluated. In response to the question *Does the Sponsor have data examining the potential effects of dupilumab on live vaccines*? the sponsor argues that 'individuals capable of mounting an immune response to non-live vaccines should be able to do so against live vaccines'. If the sponsor's argument is correct then there would be no barrier to the sponsor studying these effects. It would be important to know the effects of live vaccines prior to use in young children, an age group where vaccination with live vaccines is part of routine healthcare. In the opinion of the Evaluator, in the absence of data supporting the safety of concomitant use, live vaccines should be contraindicated during treatment with dupilumab. The sponsor should commit to studying the effects of live vaccines as part of their Paediatric Investigation Plan and Risk Management Plan.

17. Does the sponsor have any evidence of long-term safety beyond 18 months?

Sponsor's response:

The sponsor states *'Long term safety data is being collected. Please refer to the description of Open Label Extension Study R668-AD-1225 in the response provided to question 1.4.6'. The sponsor intends to follow-up patients for up to 3 years in Study R668-AD-1225.*

Evaluator's comments:

The sponsor's response is satisfactory.

18. Does the sponsor intend to monitor long term effects on immunity or neoplasia?

Sponsor's response:

The sponsor states '*The sponsor has recently amended the ongoing open-label extension study R668-AD-1225, to include 'malignancies' as an AE of special interest*'. The sponsor will collect data for up to 3 years in Study R668-AD-1225.

Evaluator's comments:

The sponsor's response is satisfactory.

14. Second round benefit-risk assessment

14.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of dupilumab (Dupixent) 300 mg/2 mL; solution for injection, in the proposed usage are unchanged from those identified in the First round evaluation.

14.2. Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of dupilumab (Dupixent) 300 mg/2 mL; solution for injection, in the proposed usage are unchanged from those identified in First round evaluation.

14.3. Second round assessment of benefit-risk balance

Overall, dupilumab has a favourable risk benefit profile. The Evaluator has some residual safety concerns with regard to use of dupilumab in the following circumstances:

- Treatment with any of the following treatments within 4 weeks, and during treatment with dupilumab:
  - Immunosuppressive/immunomodulating drugs including ciclosporine, mycophenolate-mofetil [MMF], interferon gamma, Janus kinase [JAK] inhibitors, azathioprine [AZA], methotrexate [MTX], etc.)
- Treatment with cell-depleting agents including rituximab within 6 months, or until lymphocyte count returns to normal,
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (for example, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections
- History of human immunodeficiency virus (HIV) infection or positive HIV serology
- Positive with HBsAg, hepatitis B core antibody (HBcAb), or hepatitis C antibody
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment had ruled out active infection
- Treatment with a live (attenuated) vaccine

- Treatment with immunomodulating biologics

The risk-benefit profile would be improved if they were listed as contraindications or if sufficient warnings were present in the Product Information.

In addition, in the opinion of the evaluator the development data indicate that rhabdomyolysis is an Important Potential Risk that has not been addressed in the RMP.

15. Second round recommendation regarding authorisation

The application to authorise dupilumab (Dupixent) 300 mg/2 mL; solution for injection, for subcutaneous administration should be rejected because of the risk of concurrent administration with immunomodulating agents and/or live vaccines (combinations that have not been investigated during the development program).

The evaluator would have no objection to authorisation of dupilumab (Dupixent) 300 mg/2 mL; solution for injection, for subcutaneous administration if the sponsor takes the following actions to improve the risk-benefit balance and in order to address residual safety concerns. The Evaluator recommends that the Product Information lists the following conditions as contraindications, or alternatively includes sufficient warning statements:

- Treatment with any of the following treatments within 4 weeks, and during treatment with dupilumab:
  - Immunosuppressive/immunomodulating drugs including ciclosporine, mycophenolate-mofetil [MMF], interferon gamma, Janus kinase [JAK] inhibitors, azathioprine [AZA], methotrexate [MTX], etc.)
- Treatment with cell-depleting agents including rituximab within 6 months, or until lymphocyte count returns to normal,
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (for example, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections
- History of human immunodeficiency virus (HIV) infection or positive HIV serology
- Positive with HBsAg, hepatitis B core antibody (HBcAb), or hepatitis C antibody
- Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment had ruled out active infection
- Treatment with a live (attenuated) vaccine
- Treatment with immunomodulating biologics

16. References

Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012 Dec;130(6):1344-54.

Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part I: clinical and pathologic concepts. The Journal of allergy and clinical immunology. 2011a May;127(5):1110-8. PubMed PMID: 21388665.

Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis--part II: immune cell subsets and therapeutic concepts. The Journal of allergy and clinical immunology. 2011b Jun;127(6):1420-32. PubMed PMID: 21419481.

Howell MD. The role of human beta defensins and cathelicidins in atopic dermatitis. Current opinion in allergy and clinical immunology. 2007 Oct;7(5):413-7. PubMed PMID: 17873581.

Kawashima T, Noguchi E, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, et al. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. J Med Genet. 1998 Jun;35(6):502-4. PubMed PMID: 9643293.

Leung DY. Pathogenesis of atopic dermatitis. The Journal of allergy and clinical immunology. 1999 Sep;104(3 Pt 2):S99-108. PubMed PMID: 10482860.

Plunkett A1, Merlin K, Gill D, Zuo Y, Jolley D, Marks R. The frequency of common nonmalignant skin conditions in adults in central Victoria, Australia.Int J Dermatol. 1999 Dec;38(12):901-8.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au