



Australian Government  
Department of Health  
Therapeutic Goods Administration

# Australian Public Assessment Report for Dupilumab

Proprietary Product Name: Dupixent

Sponsor: Sanofi-Aventis Australia Pty Ltd

**June 2018**

**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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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# Contents

<b>Common abbreviations</b>	<b>5</b>
<b>I. Introduction to product submission</b>	<b>8</b>
Submission details	8
Product background	8
Regulatory status	9
Product Information	10
<b>II. Registration timeline</b>	<b>10</b>
<b>III. Quality findings</b>	<b>11</b>
Drug substance (active ingredient)	11
Drug product	11
Quality summary and conclusions	12
<b>IV. Nonclinical findings</b>	<b>12</b>
Introduction	12
Pharmacology	12
Pharmacokinetics	14
Toxicology	14
Nonclinical summary and conclusions	17
<b>V. Clinical findings</b>	<b>18</b>
Introduction	18
Pharmacokinetics	20
Pharmacodynamics	21
Dosage selection for the pivotal studies	21
Efficacy	22
Safety	23
First round benefit-risk assessment	26
First round assessment of benefits	26
First round assessment of risks	27
First round assessment of benefit-risk balance	27
First round recommendation regarding authorisation	27
Second round evaluation of clinical data submitted in response to questions	27
Second round benefit-risk assessment	28
Second round assessment of benefits	28
Second round assessment of risks	28
Second round assessment of benefit-risk balance	28
<b>VI. Pharmacovigilance findings</b>	<b>29</b>

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Risk management plan _____	29
<b>VII. Overall conclusion and risk/benefit assessment _____</b>	<b>31</b>
Quality _____	31
Nonclinical _____	31
Clinical _____	31
Risk management plan _____	40
Risk-benefit analysis _____	40
Outcome _____	47
<b>Attachment 1. Product Information _____</b>	<b>48</b>
<b>Attachment 2. Extract from the Clinical Evaluation Report _____</b>	<b>48</b>

## 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
GISS	Global Individual Signs Score

Abbreviation	Meaning
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
IFM $\gamma$	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
PARC	Pulmonary and Activation-Regulated Chemokine
PCSV	Potentially Clinically Significant Value

Abbreviation	Meaning
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 <sub>max</sub>	Time to maximum plasma concentration
ULN	Upper limit of normal
WBC	White blood cell

# I. Introduction to product submission

## Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	22 January 2018
<i>Date of entry onto ARTG</i>	24 January 2018
<i>Active ingredient:</i>	Dupilumab
<i>Product name:</i>	Dupixent
<i>Sponsor's name and address:</i>	Sanofi-Aventis Australia Pty Ltd 12-24 Talavera Road, Macquarie Park NSW 2113
<i>Dose form:</i>	Solution for Injection
<i>Strength:</i>	300 mg/2 mL solution
<i>Container:</i>	Pre-filled syringe with needle shield
<i>Pack size:</i>	2 per carton
<i>Approved therapeutic use:</i>	<i>Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for chronic systemic therapy. Dupixent is not intended for episodic use.</i>
<i>Route of administration:</i>	Subcutaneous (SC)
<i>Dosage:</i>	The recommended dose of dupilumab for adult patients is as follows: <ul style="list-style-type: none"><li>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.</li></ul>
<i>ARTG numbers:</i>	283127 and 282981

## Product background

This AusPAR describes the application by the sponsor to register a new biological entity, dupilumab (Dupixent), for the treatment of adult patients with moderate to severe atopic dermatitis with the following indications:

*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.*

It has thus been proposed as a second line treatment for adults with moderate to severe atopic dermatitis (AD). Use is proposed to be restricted to patients with an inadequate



response to topical prescription therapies or when those therapies are not advisable. It is proposed that it may be used concomitantly with topical treatments.

The recommended clinical treatment regimen involves an 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. For more details on dosage and administration see PI (Attachment 1).

Dupixent is a fully human monoclonal antibody that inhibits interleukin subtypes 4 and 13 (IL-4 and IL-13) signalling by specifically binding to the IL-4R $\alpha$  subunit of the IL-4 and IL-13 receptor complex. IL-4 and IL-13 are key type 2 cytokines involved in inflammatory response in atopic dermatitis. Dupilumab does not exhibit Fc<sup>1</sup>-mediated cytotoxicity.

Dupilumab is produced by recombinant deoxyribonucleic acid (DNA) technology in Chinese hamster ovary (CHO) cell suspension culture. This would be the first biological therapy for the treatment of AD. Apart from management of aggravating factors current treatments include: emollients, topical corticosteroids and calcineurin inhibitors, and systemic corticosteroids, cyclosporin, methotrexate (off label) and azathioprine (off label).

As noted by the sponsor, effective therapies with an acceptable safety profile on long-term use are currently not always able to adequately control moderate to severe AD. The currently available treatments 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. Moderate to severe AD is more frequent in children than in adults and a development program to assess safety and efficacy of dupilumab in children is ongoing. So far that studies associated with that program appear to be limited to children aged from 6 years.

Atopic skin is particularly susceptible to bacterial infection (for example, staphylococci, streptococci) and viral infection (herpes simplex virus, molluscum contagiosum virus, human papilloma virus (warts)) which also requires management.

Dupilumab is also in clinical development for the treatment of asthma, with Phase III studies in progress, and for the treatment of nasal polyposis and eosinophilic esophagitis.

## **Regulatory status**

This is an application to register a new chemical entity in Australia.

The application for Dupixent has been submitted and approved in the United States of America (USA); and the European Union (EU) under the Centralised Procedure. The Rapporteur in the EU was Germany and the Co-Rapporteur was Ireland.

A summary of the current regulatory status is provided in Table 1 below.

The dossiers submitted in the EU and the USA are essentially the same as that submitted in Australia. The sponsor had proposed an alternative weekly dosing regimen in the USA for patients with an inadequate response to dosing every second week however the Delegate notes that the approved US PI does not include weekly dosing. Dupilumab was designated a 'breakthrough therapy' for the treatment of moderate to severe AD by the US Food and Drug Administration (FDA).

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<sup>1</sup> The Fc region of an antibody mediates its serum half-life and effector functions, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cell phagocytosis (ADCP).

**Table 1: International regulatory status**

Country	Submission Date	Status (pending; approved; deferred; withdrawn; rejected)
EU	7 November 2016	Approved (26 September 2017)
USA	29 July 2016	Approved (28 March 2017)
Canada	15 December 2016	Review Ongoing
Switzerland	14 September 2017	Review Ongoing

## Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

## II. Registration timeline

**Table 2: Registration timeline for Submission PM-2016-04087-1-1**

Description	Date
Submission dossier accepted and 1st round evaluation commenced	3 January 2017
First round evaluation completed	30 June 2017
Sponsor provides responses on questions raised in the first round evaluation	31 July 2017
Second round evaluation completed	6 October 2017
Request for Advisory Committee advice and/or Delegate's Overview	26 October 2017
Sponsor's response to Delegate's Overview	14 November 2017
Advisory Committee meeting	December 2017
Registration decision	22 January 2018
Entry onto ARTG	24 January 2018
Number of TGA working days from commencement of evaluation to registration decision*	242

\*Statutory timeframe: 255 working days.

### III. Quality findings

#### Drug substance (active ingredient)

Dupilumab is the active ingredient of Dupixent.

Dupilumab is produced by recombinant DNA technology CHO cell suspension culture. Dupilumab is not currently listed on the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) but given it is a monoclonal antibody for human use, it is likely to meet the criteria for listing in Schedule 4 (Prescription only Medicine).

#### Structure

Dupilumab is a covalent hetero-tetramer 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) G4P isotype constant region. IgG4P is an IgG4 constant region with a single amino acid substitution in the hinge region that recreates the IgG1 hinge sequence in order to stabilise IgG4 dimer formation. The variable domains of the heavy and light chains combine to form the IL-4R $\alpha$  binding site within the antibody.

Dupilumab has a molecular weight of approximately 149 kDa.

#### Specifications

All analytical procedures are validated.

There are no issues pertaining to specifications.

#### Stability

Real time stability data support the storage of:

- Drug substance at  $-30\pm 10^{\circ}\text{C}$  for 24 months, protected from light,
- Formulated drug substance at  $-30\pm 10^{\circ}\text{C}$  for 24 months, protected from light.

All stability studies are carried out in accordance with the relevant International Conference on Harmonisation (ICH) Technical Requirements for Pharmaceuticals for Human Use guidelines on stability.

#### Drug product

Dupilumab is supplied as a sterile, preservative free, clear to slightly opalescent, colourless to pale yellow solution for SC injection which is free from visible particulates.

Each pre-filled syringe is designed to deliver 300 mg dupilumab in 2 mL (150 mg/mL solution).

Dupilumab is provided as a single dose in a 2.25 mL siliconised clear Type 1 glass pre-filled syringe with a fixed, 27 gauge 0.5 inch, thin wall stainless steel staked needle. The needle cap is not made with natural rubber latex.

#### Specifications

All analytical procedures are validated.

## Quality summary and conclusions

There are no objections on quality grounds to the approval of Dupixent.

### Summary of outstanding issues

Sponsor must obtain Good Manufacturing Practice (GMP) clearances before a decision is made on this submission.

### Proposed conditions of registration for delegate

Batch release testing and compliance with Certified Product Details (CPD)

1. It is a condition of registration that all batches of Dupixent imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Dupixent imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

## IV. Nonclinical findings

### Introduction

The overall quality of the nonclinical dossier was high, with the package of studies in general accordance with relevant TGA adopted guidelines, including ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. All pivotal safety-related studies were conducted according to Good Laboratory practice (GLP).

### Pharmacology

#### Primary pharmacology

IL-4R $\alpha$ , the target for dupilumab, is a component of two heterodimeric receptor complexes that mediate IL-4 signalling; the type I receptor, composed of IL-4R $\alpha$  and the common cytokine receptor  $\gamma$  chain ( $\gamma$ c); and the type II receptor, composed of IL-4R $\alpha$  and IL-13R $\alpha$ 1. IL-4 signals through both of these receptors, whereas IL-13 signals only through the type II receptor. IL-13 also binds to the IL-13R $\alpha$ 2 chain, which does not contain a transmembrane signalling domain and may act as a decoy receptor. By binding to IL-4R $\alpha$ , dupilumab is intended to inhibit both IL-4 and IL-13 signal transduction, which appear to be key cytokines mediating the inflammatory response leading to atopic dermatitis, among others.

Dupilumab was shown to bind to human IL-4R $\alpha$  with high affinity (equilibrium dissociation constant (KD) for the monomeric form, 33 pM). Binding studies with IL-4R $\alpha$  from laboratory animal species showed that dupilumab has only very weak affinity for monkey IL-4R $\alpha$  (KD for cynomolgus monkey, 832 nM) and does not recognise mouse IL-4R $\alpha$ . Accordingly, surrogate monoclonal antibodies against mouse and monkey IL-4R $\alpha$  were generated and used in the nonclinical program. The mouse surrogate antibody (designated REGN1103) displayed a KD of 87 pM against mouse IL-4R $\alpha$ , and the monkey surrogate antibody (REGN646) displayed a KD of 2.5 nM against cynomolgus monkey

IL-4R $\alpha$ ; their affinities are 2.6 times (mouse) and 76 times (monkey) lower than that of dupilumab for human IL-4R $\alpha$ .

In vitro cell-based experiments demonstrated binding by dupilumab to IL-4R $\alpha$  on the surface of human lymphocytes, and functional inhibition of IL-4- and IL-13-mediated signalling in primary human B lymphocytes and cell lines expressing human IL-4R $\alpha$  (for example, inhibition of IL-4-induced upregulation of CD23 expression by B lymphocytes). In whole human blood, dupilumab inhibited IL-4 and IL-13-stimulated secretion of thymus and activation regulated chemokine/chemokine C C motif ligand 17 (TARC/CCL17; a clinical biomarker of atopic dermatitis) with subnanomolar potency (50% inhibition at 0.24 to 0.52 nM and 0.26 to 0.27 nM). In similar experiments using cynomolgus monkey whole blood, the monkey surrogate antibody inhibited IL-4 and IL-13-stimulated TARC/CCL17 secretion with respective 50% inhibitory concentration (IC<sub>50</sub>) values of 38 and 51 nM (that is, approximately 73 to 190 times more weakly than seen with dupilumab in human blood). Functional activity of the mouse surrogate antibody was shown in vitro as inhibition of IL-4- and IL-13-induced proliferation of mouse T and B cell lines, respectively.

The activity of dupilumab in vivo was investigated in transgenic mice that were engineered to express human IL-4R $\alpha$  as well as human IL-4 (as mouse IL-4 no longer activates the receptor). Treatment with dupilumab significantly inhibited the increases in total serum IgE and circulating allergen-specific IgG1, pulmonary infiltration of activated eosinophils, and bronchial epithelial goblet cell metaplasia induced by house dust mite exposure. The mouse surrogate antibody was shown to produce similar effects in wildtype mice exposed to house dust mite allergen. The efficacy of dupilumab (or a surrogate antibody) was not investigated in a nonclinical model of atopic dermatitis.

### **Secondary pharmacodynamics and cross-reactivity**

Dupilumab is an IgG4 antibody. In vitro cell-based assays for antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) show no detectable Fc effector function activity for dupilumab.

Immunohistochemical studies examining cross-reactivity involving a suitably comprehensive panel of tissues revealed no specific staining for dupilumab or the monkey surrogate antibody in any human or cynomolgus monkey tissue, respectively. Binding to positive control samples was demonstrated.

### **Safety pharmacology**

Specialised safety pharmacology studies were not conducted. Instead, some safety pharmacology endpoints were incorporated into the general repeat-dose toxicity studies, conducted with species-specific surrogate antibodies. In monkeys, the surrogate antibody had no effect on blood pressure or ECG parameters; the highest serum concentration of the monkey surrogate antibody at the time of examination was 4246  $\mu$ g/mL (with dosing at 100 mg/kg/week SC in the 13 week study). Other than body temperature (which was unaffected), functional indices to investigate potential adverse effects on the central nervous system (CNS) and respiratory function were not measured; this is not in accordance with the guideline ICH S7A Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals. In any case, while the extent of the examination was not ideal, there were no clinical signs observed in treated mice or monkeys to indicate adverse effects on CNS or respiratory function.

## Pharmacokinetics

Single-dose pharmacokinetic studies were performed with dupilumab in rats and cynomolgus monkeys by the SC and IV routes. Peak plasma concentration ( $C_{max}$ ) and overall (area under the concentration versus time curve (AUC)) exposure were approximately dose-proportional in both species but noting that target binding in these species is negligible or absent. As expected for an antibody, half-life was long (approximately 6 days in rats and 16 days in monkeys) and the volume of distribution was low, consistent with confinement to the systemic circulation.

The mouse and monkey surrogate antibodies showed non-linear pharmacokinetics in their respective species, with greater than dose-proportional exposure seen, consistent with the operation of saturable target-mediated clearance mechanisms. Accumulation with repeat weekly dosing was seen in both species. In monkeys, serum half-life increased significantly with dose, volume of distribution was low (approximately 40 mL/kg; indicating restriction to the vascular compartment) and bioavailability by the SC route was high (approximately 72%); these pharmacokinetic parameters were not determined for mice (although a half-life in excess of the one week dosing interval is apparent from the observed accumulation). Showing similarities to the surrogate antibodies in their respective species, dupilumab was determined to have 64% bioavailability by the SC route in humans, display a long half-life that gave rise to accumulation with repeat dosing (every two weeks (Q2W)), a low volume of distribution (4.6 L) and non-linear (greater than dose-proportional) pharmacokinetics.

No distribution, metabolism, excretion or pharmacokinetic interaction studies were submitted (acceptable in accordance with the ICH S6(R1) guideline for a protein drug).<sup>2</sup>

## Toxicology

### Acute toxicity

Single-dose toxicity studies were not conducted with dupilumab or surrogate antibodies. No acute treatment-related findings were noted with the mouse and monkey surrogate antibodies in repeat-dose toxicity studies, which involved SC (both species) or IV (monkey only; 30 min infusion) administration of doses up to 100 mg/kg.

### Repeat-dose toxicity

Due to the species specificity of dupilumab, no repeat-dose toxicity study was performed with dupilumab itself; surrogate IgG4 antibodies against mouse and monkey IL-4R $\alpha$  were used instead.

The pivotal repeat-dose toxicity study was conducted in cynomolgus monkeys, and involved once weekly dosing at up to 100 mg/kg SC or 25 mg/kg IV for 6 months. The study was appropriately designed and conducted. The cynomolgus monkey is an appropriate species on pharmacodynamic and pharmacokinetic grounds; the absence of a pivotal study in a second (non-rodent species) is in accordance with ICH S6(R1).<sup>Error!</sup> Bookmark not defined. Group size was appropriate. The duration of the study is sufficient to support chronic use in humans. The clinical route (SC) was tested. A higher dosing frequency in animals (once weekly) compared to patients (once every two weeks) was employed, and was of value.

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<sup>2</sup> ICH S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

Shorter studies were conducted in mice (up to 200 mg/kg/week SC for 5 weeks; but featuring only limited histopathological examination) and cynomolgus monkeys (up to 100 mg/kg IV for 5 weeks and 100 mg/kg SC for 13 weeks).

Anti-drug antibodies were commonly seen to develop in treated monkeys but are not considered to affect the validity of the studies. While the presence of anti-drug antibodies frequently acted to reduce drug exposure, this was not the case at the highest dose level (100 mg/kg). Immunogenicity in animals is not predictive of immunogenicity in humans.

### Major findings and relative exposure

The mouse and monkey surrogate antibodies were well tolerated in their respective species. Treatment-related findings were limited to minimal to moderate perivascular immune cell recruitment at SC injection sites in the pivotal 6 month study in monkeys (seen at both dose levels tested, 25 and 100 mg/kg), which is not considered adverse per se. The pivotal study establishes a No observable adverse effect level (NOAEL) of 100 mg/kg/week SC (and 25 mg/kg/week IV) in monkeys for the surrogate antibody.

Given that the study used a surrogate antibody with different target affinity, a direct comparison of animal: human serum AUC to gauge relative exposure at the NOAEL is inappropriate. Considering the 76 fold lower target affinity of the monkey surrogate antibody compared to dupilumab, a serum AUC<sub>0-7d</sub> of 790667 µg·h/mL in monkeys at 100 mg/kg/week SC (week 26), a serum AUC<sub>0-14d</sub> of 31327 µg·h/mL for patients at steady-state under the proposed treatment regimen (300 mg Q2W after a loading dose of 600 mg), and adjusting for twice as frequent dosing in animals compared to humans, relative exposure at the NOAEL in monkeys is seen to be approximately two thirds of the clinical exposure. However, serum concentrations of the monkey surrogate antibody in the 100 mg/kg/week dose group were well in excess of the 90% inhibitory concentration (IC<sub>90</sub>) concentration for inhibition of IL-4 induced TARC/ CCL17 secretion in monkey whole blood observed in vitro at all time points in the study, with the serum trough concentration after the first dose more than approximately 12 times the IC<sub>90</sub> and the trough concentrations measured later in the study (Weeks 5, 13 and 26) between 39 and 52 times the IC<sub>90</sub>. As such, continued saturation of IL-4Rα in the monkeys is likely. Despite the apparent subclinical exposure ratio based on potency-adjusted AUC at the highest dose tested, the selection of the high-dose level in the pivotal study is considered appropriate given the high specificity of the agent, all toxicity is expected to be pharmacologically mediated, and with target binding apparently saturated, the use of higher doses would not have revealed any additional relevant toxicity.

### Genotoxicity

No genotoxicity studies were submitted. This is in accordance with ICH S6(R1), with a large protein like dupilumab not expected to interact with DNA or other chromosomal material.

### Carcinogenicity

Carcinogenicity studies were not conducted. This is acceptable under ICH S6(R1);<sup>Error!</sup> Bookmark not defined. given the absence of cause for concern from the general repeat-dose toxicity studies (for example, proliferative lesions) and based on consideration of the role of the targeted pathway, with published literature identifying no plausible mechanistic/target-related link between IL-4Rα inhibition and increased cancer risk (rather, the IL-4Rα pathway is predominantly pro-tumorigenic and inhibition of this pathway is likely to reduce the risk for tumour promotion and proliferation if anything).

## Reproductive toxicity

Reproductive toxicity was evaluated in a fertility study in mice and in an enhanced pre/postnatal development study in cynomolgus monkeys, involving once weekly SC administration of species-specific surrogate antibodies. Adequate animal numbers were used, and dose selection and the timing/duration of treatment and monitoring were appropriate.

No adverse effects on male or female fertility were observed in mice up to the highest dose level tested (200 mg/kg/week of the surrogate antibody), associated with a potency-adjusted animal: human exposure multiple of 12 (based on 2.6 fold lower target affinity for the mouse surrogate antibody compared with dupilumab, a mean serum AUC<sub>0-7d</sub> of 491500 µg·h/mL in mice, a clinical

AUC<sub>0-14d</sub> of 31327 µg·h/mL at steady-state under the proposed dosing regimen, and accounting for twice as frequent dosing in animals as compared to humans).

In monkeys, no adverse effects were observed in the offspring of animals that were treated with the surrogate antibody from the beginning of organogenesis (approximately Gestation Day 20) through to parturition. Infants were monitored from birth to 6 months of age. Parameters assessed included embryofetal survival, malformations, growth, functional development and immunology. The highest dose level tested (100 mg/kg/week) is associated with a potency-adjusted animal: human exposure multiple of 0.4 (calculated as above, using an animal AUC<sub>0-7d</sub> value of 443306 µg·h/mL), but saturation of the maternal target is expected to have been achieved based on trough concentrations measured in serum being approximately 10 to 28 times higher than the IC<sub>90</sub> concentration for inhibition of IL-4 induced TARC/ CCL17 secretion determined in vitro in monkey whole blood. The monkey surrogate antibody was detected in the serum of infants, consistent with placental transfer of an IgG antibody. Excretion of the surrogate antibody in milk was not investigated (and even if it did occur, actual oral absorption from breast milk would be expected to be minimal).

IL-4Rα knockout mice are viable and display no overt phenotypic abnormalities, supporting that the target for dupilumab is not critical for development.

## Pregnancy classification

The sponsor has proposed Pregnancy Category B1.<sup>3</sup> This category is considered appropriate based on the absence of adverse effects on embryofetal development observed in monkeys, and considering information on the role of the pharmacological target in development from knockout mice.

## Local tolerance

The sponsor did not conduct local tolerance studies with dupilumab. SC administration was well tolerated locally in the general repeat-dose toxicity studies in animals. The pivotal study identified some possible local irritation potential of the vehicle, which was minor in nature, as well as perivascular immune cell recruitment. However, these studies used formulations with a different excipient profile compared to Dupixent (lacking arginine hydrochloride and/or with lower concentrations of histidine and acetate), and the highest strength of the active ingredient administered to animals (25 mg/mL antibody) is far below that in the clinical formulation (that is, 150 mg/mL).

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<sup>3</sup> Pregnancy Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.



## Immunotoxicity

Immunotoxicity was not apparent in mice or monkeys treated with the surrogate antibodies. This was assessed via haematology and histopathological examination of lymphoid tissues in all studies and from specialised endpoints (lymphocyte subpopulations, T-cell dependent antibody response, serum total IgE, IgG and IgM concentration, and plasma IL-4 concentration) included in the pivotal 6 month study and the enhanced pre/postnatal development study in monkeys.

## Paediatric use

Dupilixent is not proposed for paediatric use. No specific juvenile animal studies were conducted, although the general repeat-dose toxicity program did include monkeys that were pre-pubescent at the time of dosing initiation, and toxicity to developing systems was not seen.

## Nonclinical summary and conclusions

- The nonclinical submission contained an adequate set of studies investigating pharmacology, pharmacokinetics and toxicity, conducted in general accordance with the relevant TGA adopted guideline applicable to biotechnology derived pharmaceuticals.<sup>3</sup> The overall quality of the nonclinical package was high. All pivotal safety-related studies were GLP compliant.
- In vitro studies established that dupilumab binds to human IL-4R $\alpha$  with picomolar affinity, but recognises the target in monkeys only poorly and does not bind to mouse IL-4R $\alpha$ , necessitating the use of surrogate anti IL-4R $\alpha$  antibodies in much of the nonclinical program. Dupilumab, and the surrogate antibodies, were shown to inhibit IL-4 and IL-13 mediated signalling in vitro in experiments using human, mouse or monkey cells. Of particular note, dupilumab inhibited IL-4 and IL-13 stimulated secretion of TARC/CCL17 (a clinical biomarker of atopic dermatitis) with subnanomolar potency in human whole blood.
- In vivo, dupilumab showed efficacy in a model of allergen-induced lung inflammation in transgenic mice (expressing human IL-4R $\alpha$  and human IL-4), as did the mouse surrogate antibody in treated wildtype mice.
- Efficacy in an animal model of atopic dermatitis was not investigated, but the in vivo models that were used are recognised to share some features of that condition. Together with the in vitro pharmacology data, they offer support for use of dupilumab for the proposed indication.
- Dupilumab lacks antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) activity, and showed no cross-reactivity against a comprehensive panel of human tissues. Examination of safety pharmacology identified no effects on cardiovascular, respiratory or CNS function.
- Pharmacokinetic studies with dupilumab and surrogate antibodies revealed a typical profile for an antibody: non-linear pharmacokinetics consistent with saturable target-mediated clearance, a long serum half-life giving rise to accumulation with repeat dosing, and a low volume of distribution indicative of confinement to the vascular compartment.
- Repeat-dose toxicity studies were performed with surrogate antibodies in mice (up to 5 weeks) and cynomolgus monkeys (up to 6 months). No target organs for toxicity were identified, with treatment-related findings limited to perivascular immune cell recruitment at SC injection sites in the pivotal monkey study. Serum concentrations of

the surrogate antibody at the NOAEL in monkeys were such that continuous saturation of IL-4R $\alpha$  throughout the study is expected to have been achieved.

- Genotoxicity and carcinogenicity studies were not conducted, in line with ICH S6(R1).<sup>2</sup>
- Fertility was unaffected in male and female mice and no adverse effects on fetal and postnatal development were observed in monkeys in reproductive toxicity studies conducted with surrogate anti IL-4R $\alpha$  antibodies. Placement in Pregnancy Category B1, as the sponsor proposes, is supported.<sup>3</sup>
- The local tolerability of dupilumab/Dupilumab is not assessable from the nonclinical data submitted. This aspect of safety will rely on clinical data only.
- After the first round evaluation, the sponsor was requested to revise the draft PI document. The updated PI, provided for the second round evaluation, is now considered to be acceptable from a nonclinical perspective.
- There are no nonclinical objections to the registration of Dupixent for the proposed indication.

## V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

### Introduction

#### 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 sequelae 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 (for example, tacrolimus), systemic corticosteroids, systemic calcineurin inhibitors (for example, cyclosporine), phototherapy, and other off label treatments such as oral immune-suppressants (for example, 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.*

**Guidance**

The following regulatory clinical 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).

**Contents of the clinical dossier*****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 than 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 sponsor also provided evidence that the assays used in the development program had satisfactory performance and were suitable. Details of the studies provided in support of the assays are given in Attachment 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:

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

**Good clinical practice**

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

## Pharmacokinetics

### Studies providing pharmacokinetic data

The submitted pharmacokinetic (PK) studies are summarised in Table 3. There were no studies excluded from consideration.

**Table 3: Submitted pharmacokinetic studies**

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

\* Indicates the primary PK aim of the study.

### Evaluator's conclusions on pharmacokinetics

The basic pharmacokinetics of dupilumab has been adequately described by the sponsor in the draft PI 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 the 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 Eczema Area and Severity Index (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.

## Pharmacodynamics

### Studies providing pharmacodynamic data

Table 4 summarises the pharmacodynamic (PD) studies submitted.

**Table 4: Submitted pharmacodynamic studies**

PD Topic	Subtopic	Study ID
<b>Primary Pharmacology</b>	Effect on IgE and TARC	Study TDU12265
		Study R668-AD-0914
		Study R668-AD-1026
		Study R668-AD-1307
<b>Secondary Pharmacology</b>	Effect on immune response	Study R668-AD-1314
<b>Population PD and PK-PD analyses</b>	Target population	Study REGN668-MX-1602

There were no PD studies excluded from consideration.

### Evaluator's 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 has 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.

### Dosage selection 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.

For further details see Attachment 2.

## Efficacy

### Studies providing 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 topical corticosteroids (TCS): 300 mg QW and 300 mg Q2W, both after a 600 mg bolus dose.

There were four supportive studies:

- 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.

### Evaluator's conclusions on 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.

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## Safety

### Studies providing safety data

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

### *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.

### *Studies evaluable for safety only*

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

- Study ACT11457
- Study DRI12544
- Study LTS12551
- Study ACT12340

For further details of these see Attachment 2.

### 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  $\geq 65$  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  $\geq 112$  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  $\geq 65$  years, and 19 aged  $\geq 75$  years. There were no patients aged  $< 18$  years.

### *Dose finding studies*

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  $\geq 52$  weeks, 266 for  $\geq 76$  weeks and 51 for  $\geq 100$  weeks.

***Studies for other indications***

In Study ACT11457 there were 52 patients with eosinophilic asthma treated with dupilumab 300 mg once a week (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 5: Exposure to dupilumab and comparators in clinical studies**

Study type/ Indication	Controlled studies				Uncontrolled studies	Total Dupilumab
	Dupilumab	Placebo	*Control A	*Control B	Dupilumab	
<b>Clinical pharmacology</b>						
<b>Dose finding</b>	175	140				175
<b>Indication: AD</b>						
<b>Pivotal/Main</b>	1345	771				1345
<b>Other</b>	394	125			1491	1885
<b>TOTAL</b>						<b>3,405 #</b>

\* Control = Comparator; # double counts as it included follow-on study

### Safety issues with the potential for major regulatory impact

For details on safety issues please see *Evaluation of issues with possible regulatory impact* in Attachment 2 and *Evaluator's conclusions on clinical safety* below.

### Post-marketing data

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

### Risk management plan

The Risk Management Plan (RMP) 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

### Evaluator's conclusions on clinical safety

The overall rates of treatment emergent adverse events (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 serious adverse events (SAEs) appeared to be more common with placebo than dupilumab. There was no pattern to the SAEs that would indicate an identifiable risk.

Discontinuation due to Adverse Event (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 drug induced liver injury (DILI) attributed to Bactrim.

Several patients treated with dupilumab were reported with elevated creatinine phosphokinase (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.

## First round benefit-risk assessment

### First round assessment of benefits

The following table summarises the first round clinical benefit assessment:

**Table 6: First round assessment of benefits**

Indication	
Benefits	Strengths and Uncertainties
<p>Dupilumab has superior efficacy to placebo as monotherapy in patients with moderate to severe AD.</p> <p>Dupilumab has superior efficacy to placebo in patients with moderate to severe AD who are receiving concomitant topical corticosteroids</p> <p>The efficacy of dupilumab appears to be maintained for up to 18 months.</p>	<p>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.</p> <p>The duration of efficacy that has been demonstrated is relatively short for a drug that might be used as long-term treatment.</p> <p>Efficacy has not been compared to currently used treatments for moderate to severe AD such as topical and/or systemic immunomodulatory agents.</p>

## First round assessment of risks

The following table summarises the first round clinical risk assessment

**Table 7: First round clinical benefit assessment**

Risks	Strengths and Uncertainties
<p>Dupilumab has a similar rate of adverse effects to placebo.</p> <p>Dupilumab has a higher rate of injection site reactions than placebo.</p> <p>Dupilumab has a higher rate of conjunctivitis than placebo.</p>	<p>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.</p> <p>There appears to be a higher rate of elevated CPK with dupilumab. The risks of rhabdomyolysis have not been fully addressed.</p> <p>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.</p> <p>Interactions with live vaccines have not been addressed.</p> <p>Interactions with topical and/or systemic immunomodulatory drugs have not been addressed.</p>

## 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.

## First round recommendation regarding authorisation

The clinical 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.

## Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to Clinical questions raised and the TGA's evaluation of these responses please see Attachment 2.

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## Second round benefit-risk assessment

### 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.

### 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 the first round.

### Second round assessment of benefit-risk balance

Overall, dupilumab has a favourable risk benefit profile. The clinical 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), and so on.
- 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 hepatitis B virus antigen (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 PI.

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

The application to authorise dupilumab (Dupixent) 300 mg/2 mL; solution for injection, for SC 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 clinical evaluator would have no objection to authorisation of dupilumab (Dupixent) 300 mg/2 mL; solution for injection, for SC administration if the sponsor takes the following actions to improve the risk-benefit balance and in order to address residual safety concerns. The clinical evaluator recommends that the PI 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, MMF, interferon gamma, JAK inhibitors, AZA, MTX and so forth.
- 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 HIV infection or positive HIV serology.
- Positive with HBsAg, 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.

## VI. Pharmacovigilance findings

### Risk management plan

- The sponsor has submitted EU-RMP version 1.0 (dated 21 October 2016; data lock point (DLP) 27 April 2016) and Australian Specific Annex (ASA) version 1.0 (dated 30 November 2016) in support of this application. The sponsor has submitted the updated EU-RMP version 1.1 dated 11 May 2017 DLP 27 April 2016 with ASA version 1.1 dated July 2017 with its response to the TGA's request for further information.
- The updated Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8 below (highlighted parts are updates to the EU-RMP version 1.1).

**Table 8: Sponsor's summary of ongoing safety concerns**

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
<b>Important identified risks</b>	Systemic hypersensitivity (including events associated with immunogenicity)	Ü	-	Ü	-
<b>Important potential risks</b>	None	-	-	-	-
<b>Missing information</b>	Use in paediatric AD patients < 18 years of age	Ü	Ü	Ü	-
	Use in pregnant and lactating women	Ü	Ü	Ü	-
	Long term safety	Ü	Ü	Ü	-
	Effects on live vaccine safety	Ü	-	Ü	-

R = routine; A = additional.

- Routine and additional pharmacovigilance are proposed for Dupixent. Additional activities include studies on paediatric use and drug interactions, dedicated clinical assessments of conjunctivitis, and a pregnancy registry study. There is Australian involvement proposed in the conjunctivitis activity.
- Only routine risk minimisation is proposed for Dupixent, which includes detailed Instructions for Use (IFU) to be included in packaging.

### Outstanding recommendations following second round evaluation

1. This is an outstanding recommendation from the first round RMP evaluation report. The clinical evaluator has considered the sponsor's response to the recommendations regarding the safety specification of the RMP in the second round clinical evaluation report and recommended that 'rhabdomyolysis' is listed as an important potential risk. The RMP evaluator supports the clinical evaluator's recommendation. The sponsor should add rhabdomyolysis as an important potential risk in the ASA.

### Wording proposed for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

No suggested wording could be provided at this stage as there is still outstanding RMP issue with this submission.

## VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

### Quality

There are no objections on quality grounds to the approval of Dupixent.

The evaluator has noted GMP clearance for multiple manufacturing sites require finalisation prior to approval of this product.

See also Quality findings above.

### Nonclinical

There are no nonclinical objections to the registration of Dupixent for the proposed indication.

The local tolerability of dupilumab/Dupixent is not assessable from the nonclinical data submitted. This aspect of safety will rely on clinical data only.

For further details see Nonclinical findings summary above.

### Clinical

The clinical evaluator has recommended approval of dupilumab for the proposed indications, subject to revision of the PI and RMP.

### Pharmacology

Four drug substance production processes (C1P1, C1P2, C2P1, and C2P2) were used to produce dupilumab for clinical studies. Studies assessing bioequivalence (BE) for these changes were examined in the biological evaluation. The sponsor has claimed that the drug product produced with the C1P2 and C2P1 cell lines were shown to be clinically comparable, it was sufficient to demonstrate that the to be marketed C2P2 drug product was analytically and biochemically comparable to the C2P1 drug product to also conclude clinical comparability between these drug products. Ongoing Phase III studies have been transitioned to the drug product manufactured using the C2P2 process.

The following was based on results from a Population PK (Pop PK) analysis developed from 13 Phase I and Phase II studies, plus data up to at least Week 16 from all patients in the 2 pivotal Phase III studies and approximately 97% of patients in the long term treatment (LTT) Study R668-AD-1224 with week 52 data.

Dupilumab is administered and absorbed from SC injection. Absolute bioavailability was determined in population PK studies as 64%.

$C_{max}$  was dose proportional in the range 1 to 12 mg/kg. After a single SC administration of 75 to 600 mg dupilumab, the median time to  $C_{max}$  ( $T_{max}$ ) was 3 to 7 days in healthy subjects. When administered with the proposed dose regimen of a loading dose of 600 mg followed every two weeks with 300 mg the Pop PK analysis determined steady state concentrations to be achieved after 10 weeks in a typical patient. Mean steady state trough concentration was 74 mg/L. With weekly dosing of 300 mg after the loading dose Pop PK

analysis determined steady state concentrations to be achieved after 13 weeks in a typical patient with mean steady state trough concentration was 189 mg/L.

The Pop PK model estimated a central volume of distribution of 2.74 L and a peripheral volume of distribution of 1.86 L. The dupilumab volume of distribution reflects the vascular compartment and there appears to be little tissue distribution. Metabolism is thought to be by catabolism with recycling of individual amino acids.

Clearance is nonlinear with increases with dose resulting in a greater than proportional increase in AUC for SC doses between 75 mg and 600 mg. The effect of ADA on elimination was clinically significant with a 17.8% increase in the elimination rate constant but this was based on a small number of subjects. Drug exposure reduced with increasing body weight.

PK interaction studies, including studies with live vaccines and studies in special populations have not been performed.

Dupilumab inhibits IL-4 and IL-13 signalling by specifically binding to the IL-4R $\alpha$  subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signalling via the type I receptor (IL-4R $\alpha$ / $\gamma$ c), and both IL-4 and IL-13 signalling through the type II receptor (IL-4R $\alpha$ /IL-13R $\alpha$ ). TARC is an IL-4 and IL-13 induced chemokine known to be elevated in the serum of AD patients. The sponsor examined effects of dupilumab on IgE and TARC in a single dose ascending study levels of 32 healthy Japanese subjects. There was no treatment effect on IgE concentrations. There was a decrease in TARC over time in the 300 and 600 mg treatment groups but not in the 75 or 150 mg. The decline in concentration of TARC in the presence of dupilumab confirms the reduction of type 2 inflammatory responses associated with dupilumab as a consequence of reduced signalling through IL-4R $\alpha$ . Multiple dose studies described in Attachment 2 generally supported reductions in IgE, TARC and increases in IL4 and IL13 with various doses of dupilumab.

In Study R668-AD-1314, subjects received vaccination with a tetanus toxoid and a meningococcal polysaccharide vaccine at Week 12 of treatment with either dupilumab or placebo. Tetanus was chosen as a representative of a T cell dependent vaccine because a protective level for anti-tetanus antibodies has been established. Menomune vaccine (meningococcal polysaccharide) was selected as a vaccine that selectively stimulates a T cell independent immune response because the meningococcal vaccine has been previously administered to patients with AD being treated with a potential immunosuppressive agent.<sup>4</sup> Dupilumab did not have a significant effect on immunological response. Immunological responses with live vaccines have not been assessed.

Dose-finding was assessed in Study R668-AD-1021, described in Attachment 2. That study showed an increasing response with increasing doses up to the highest exposure of 300 mg weekly though this study was not designed to allow for statistical comparisons of efficacy between doses.

Analysis of the efficacy responses of patients from 2 Phase III monotherapy studies showed that the time course of the efficacy response, as measured by mean percent changes from baseline in Eczema Area and Severity Index (EASI), mean percent change from baseline in peak Pruritus Numerical Rating Scale (NRS) score, and the percentage of patients achieving Investigator's Global Assessment (IGA) score of 0 or 1, was similar between the 2 dupilumab treatment regimens (300 mg Q2W and 300 mg QW) despite an approximately 2.4 fold difference in the trough concentration of dupilumab. This finding

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<sup>4</sup> Hofman T1, Cranswick N, Kuna P, Boznanski A, Latos T, Gold M, Murrell DF, Gebauer K, Behre U, Machura E, Olafsson J, Szalai Z; International Tacrolimus Ointment Study Group. Tacrolimus ointment does not affect the immediate response to vaccination, the generation of immune memory, or humoral and cell-mediated immunity in children. Arch Dis Child. 2006 Nov;91(11):905-10.



suggests that the clinical benefit achieved with the 300 mg Q2W dose regimen is maximal or near maximal for most patients.

### **Efficacy**

The Phase III program consisted of 2 replicate, randomised, double blind, placebo controlled, confirmatory monotherapy studies (Study SOLO 1 R668-AD-1334 and Study SOLO 2 R688-AD-1416) designed with a 16 week treatment period, a 52 week long term treatment study of dupilumab with concomitant use of topical medications (Study CHRONOS R668-AD-1224) and an open-label extension study (Study OLE R668-AD-1225). The Phase II dose-finding study 1021 allowed some assessment of time to relapse after cessation to treatment.

Studies 1334 and 1416 are considered pivotal. Major inclusion criteria were:

- adult subjects with chronic AD present for at least 3 years;
- an EASI score of  $\geq 16$ . EASI is a validated measure of severity and extent of AD. Scores range from 0 to 72 with the highest score indicating worse severity of AD;
- Investigator's Global Assessment (IGA) score  $\geq 3$  (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits;
- $\geq 10\%$  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  $\geq 3$ ;
- documented inadequate response to treatment with topical medications or for whom topical treatments were otherwise medically inadvisable.

Major exclusion criteria were:

- use of immunosuppressive/immunomodulating drugs within 4 weeks of baseline visit or the likely requirement for such treatment (for example, systemic corticosteroids, cyclosporine, MMF, interferon gamma, JAK inhibitors, AZA, MTX and so on) or phototherapy for AD;
- treatment with TCS or topical calcineurin inhibitors (TCI) in the 1 week before the baseline visit;
- use of rituximab within the prior 6 months or other biological products within 5 half-lives or 16 weeks (whichever was longer) prior to the baseline visit;
- active infection;
- known or suspected history of immunosuppression.

Patients were randomised 1:1:1 to receive one of the following treatments:

1. Dupilumab 600 mg, followed by 300 mg QW
2. Dupilumab 600 mg, followed by 300 mg Q2W
3. Placebo

Treatments were administered SC. The same site was not injected for two consecutive weeks. Patients who received rescue treatment continued study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors could be used for rescue, but were reserved for problem areas only, for example, face, neck, intertriginous and genital areas and so on. If possible, investigators attempted to limit rescue treatment to topical medications, and to escalate to systemic medications only if patients did not

respond adequately after at least 7 days of topical treatment. Emollients were to be applied at least twice daily during the study.

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 US reference market countries was the proportion of patients with Investigator Global Assessment (IGA) 0 or 1 (on a 5 point scale) and a reduction from Baseline of  $\geq 2$  points at Week 16. For the EU and EU reference market countries and Japan, the co-primary endpoints were:

- The proportion of patients with EASI-75 ( $\geq 75\%$  improvement from Baseline) at Week 16; and
- the proportion of patients with IGA 0 or 1 (on a 5 point scale) and a reduction from Baseline of  $\geq 2$  points at Week 16.
- Secondary endpoints are listed in Attachment 2.

The Cochran-Mantel-Haenszel test adjusted by randomisation 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 analysis of co-variance (ANCOVA), with treatment, randomisation strata (region, disease severity) and baseline measure included in the model. Where imputation was used, the last observation carried forward (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.

*Study 1334:* A total of 671 patients were randomised. Baseline demographic data and disease characteristics are discussed in Attachment 2. There were 390 (58.1%) males and 281 (41.9%) females. Mean age was 39.5 years, 67.1% were White, mean weight was 76.6 kg, mean (SD) EASI score was 33.6 (14.00) and mean (SD) IGA score was 3.5 (0.50). Rescue treatment was given to 116 (51.3%) patients in the placebo group, 47 (21.0%) in the Q2W and 52 (23.3%) in the QW.

Both the US and EU primary endpoints were statistically significant, favouring dupilumab. The proportion of patients with IGA 0 or 1 (on a 5 point scale) and a reduction from Baseline of  $\geq 2$  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. The primary and key secondary endpoints as listed below were all clinically and statistically significantly in favour of dupilumab.

**Table 9: Primary and key secondary endpoints**

Placebo N=224		Dupilu mab 300 mg Q2W N = 224	Dupilu mab 300 mg QW N = 223
<i>Primary/Co-primary Endpoints</i>			
Proportion of patients with IGA 0 or 1 and a reduction from baseline of $\geq 2$ points at Week 16	10.3 %	37.9%*	37.2% *
Proportion of patients with EASI-75 at Week 16	14.7 %	51.3%*	52.5% *
<i>Key Secondary Endpoints</i>			
Proportion of patients with improvement (reduction $\geq 4$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 16	12.3 %	40.8%*	40.3% *
Proportion of patients with improvement (reduction $\geq 3$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 16	17.2 %	46.8%*	51.7% *
Least squares mean percent change from Baseline to Week 16 in weekly average of peak daily pruritus NRS	- 26.1 %	-51.0%*	- 48.9% *
Proportion of patients with improvement (reduction $\geq 4$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 4	6.1 %	16.0%*	23.4% *

\*=statistically significant

Reductions in pruritus were also seen in both active treatment groups.

*Study 1416:* A total of 708 patients were randomised. Baseline demographic data and disease characteristics are shown Attachment 2. In that study there were 408 (57.6%) males and 300 (42.4%) females. Mean age was 37.1 years, 69.1% were White, mean weight was 77.1 kg, mean (SD) EASI score was 32.4 (13.39) and mean (SD) IGA score was 3.5 (0.50). ). Rescue treatment was given to 123(52.1%) patients in the placebo group, 35 (15.0%) in the Q2W and 49 (20.5%) in the QW.

The proportion of patients with IGA 0 or 1 (on a 5 point scale) and a reduction from Baseline of  $\geq 2$  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. The primary and key secondary endpoints as listed below were all statistically significantly in favour of dupilumab.

Efficacy results are summarised below and show very significant clinical improvements in all measures.

**Table 10: Efficacy results**

	Placebo	Dupiluma b 300 mg Q2W	Dupilum ab 300 mg QW
	N = 236	N = 233	N = 239
<b>Primary/Co-primary Endpoints</b>			
Proportion of patients with IGA 0 or 1 and a reduction from Baseline of $\geq 2$ points at Week 16	8.5%	36.1%*	36.4%*
Proportion of patients with EASI-75 at Week 16	11.9%	44.2%*	48.1%*
<b>Key Secondary Endpoints</b>			
Proportion of patients with improvement (reduction $\geq 4$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 16	9.5%	36.0%*	39.0%*
Proportion of patients with improvement (reduction $\geq 3$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 16	12.8%	50.6%*	49.1%*
Least squares mean percent change from Baseline to Week 16 in weekly average of peak daily pruritus NRS	-15.4%	-44.3%*	-48.3%*
Proportion of patients with improvement (reduction $\geq 4$ points) of weekly average of peak daily pruritus NRS from Baseline to Week 4	6.3%	22.7%*	27.6%*

Reductions in pruritus were also seen in both active treatment groups.

In both studies approximately 27% more patients given dupilumab achieved complete or near complete resolution of their AD signs and symptoms and around 32 to 38% more achieved at least a 75% improvement from baseline in EASI score. There was little difference in efficacy between the QW and Q2W dose regimens of dupilumab.

Study 1224 was a randomised, double blind, parallel group, placebo controlled trial of dupilumab when administered concomitantly with TCS in patients with AD for up to 52 weeks with a 12 week follow-up period. The study report in the submission presented results of the primary analysis which included the Week 16 primary and Week 2, Week 4, Week 16 and Week 24 secondary endpoints for all 740 randomised patients. Week 52 efficacy endpoints were presented for 623 patients; 264 patients in the placebo + TCS group, 89 patients in the dupilumab 300 mg Q2W + TCS group, and 270 patients in the dupilumab 300 mg QW + TCS group).

Patients were randomised 3:1:3 to placebo + TCS, dupilumab 300 mgQ2W + TCS, or dupilumab 300 mg QW + TCS respectively.

The inclusion and exclusion criteria were similar to those of the monotherapy 16 week studies with the additional exclusion criteria of side effects of TCS treatment and presence of  $\geq 30\%$  of affected skin in areas of thin skin that could not be safely treated with medium or higher potency TCS (for example, face, neck and genital areas).

As in the monotherapy studies subjects were randomised 1:1:1 to receive one of the following treatments:

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

Dupilumab was administered as in the monotherapy studies and emollient use twice daily was also required in all treatment groups. 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% optimised ointment or clobetasol propionate 0.05% cream for super high potency TCS.

The primary efficacy endpoints were the same as for the monotherapy studies. Various secondary endpoints were determined from baseline to Week 52 and were not available at the time of submission.

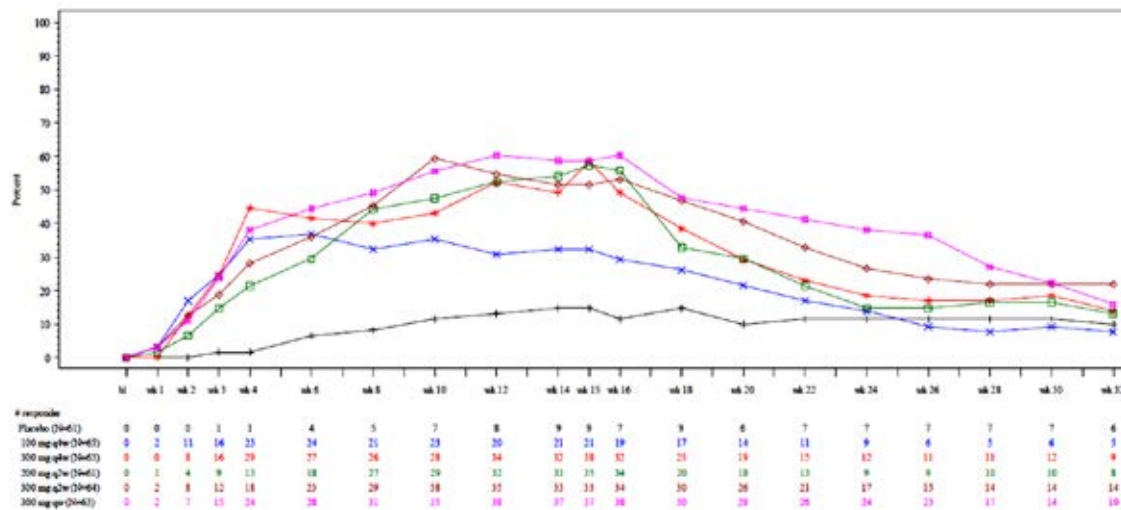
A total of 740 patients were randomised. Baseline demographic data and disease characteristics are shown in Attachment 2. There were 446 (60.3%) males and 294 (39.7%) females. Mean age was 37.1 years, 66.2% were White, mean weight was 74.5 kg, mean (SD) EASI score was 32.5 (12.90) and mean (SD) IGA score was 3.5 (0.50). Rescue treatment was given to 120(38.1%) patients in the placebo group, 12 (10.9%) in the Q2W and 34 (10.8%) in the QW.

This study allowed an assessment of time to onset of effect. Attachment 2 shows efficacy endpoints over time to Week 52. Although 623/740 (84%) of patients had completed 52 weeks of treatment the Week 52 efficacy endpoints were all statistically significant, favouring dupilumab. These figures also show an onset of effect commencing around Week 2 and stabilising at around Weeks 8 to 12 after commencement of treatment.

While a 12 week follow-up period after discontinuation of treatment was planned for this study the results were not included in the study report.

Study 1021 allowed an assessment of AD severity on cessation of treatment. This was a dose-finding Phase IIa study described in Attachment 2. The primary efficacy measures were at Week 16. There was an additional 16 week follow-up period in which the effect of treatment discontinuation on AD signs and symptoms could be assessed. During the 16 week follow-up period (Weeks 17 to 32) at the end of the 16 week monotherapy treatment period, there was an apparent gradual return of AD symptomatology, though this was based on limited patient numbers and mean measures of AD signs symptoms did not return to Baseline during the follow-up period (Figure 1 below).

**Figure 1: Study 1021 Percentage of patients with an EASI-75 response up to Week 32 (FAS)**



Similarly there are very limited data on the effect of re-treatment after cessation of treatment. Effects of retreatment with dupilumab on efficacy parameters were evaluated in the open label extension (OLE) Study R668-AD-1225. Efficacy data were evaluated from patients who had a treatment gap of > 13 weeks between the last dose of dupilumab in the parent study and the first dose of dupilumab in that OLE study. Those results suggested a response similar to initial treatment however as the study in which efficacy was re-assessed was open label and uncontrolled no firm conclusions regarding the extent of response on re-treatment can be made.

Study 1225 was an open label extension study with efficacy outcomes secondary to safety. After the 600 mg loading dose dupilumab was given 300 mg weekly. This study showed that for that dose regimen for continuing patients there was a mean reduction in EASI score of up to 85% maintained to Week 76 of treatment. There was a mean reduction in pruritus score of up to 55% and this was maintained to Week 76 of treatment.

## Safety

A total of 2526 patients were exposed to dupilumab in the development program; 739 for one year and 160 for two years. There were 1468 males and 1058 females. Of these 95 patients were aged  $\geq 65$  years. Most patients with exposure to dupilumab for  $\geq 12$  months received 300 mg QW (n = 645) rather than the proposed dose of 300 mg Q2W (n = 58). There were 6 deaths in the development program, none were attributed to dupilumab. Causes of death were hypoxic ischemic encephalopathy in a patient with asthma, suicide, car accident, acute CV failure, gastric cancer and lung cancer.

The primary safety analysis was of the 3 monotherapy to 16 week studies (Studies 1021, 1334 and 1416). In those studies TEAEs were reported in 366 (69.2%) patients in the Q2W group, 357 (68.9%) in the QW and 359 (69.4%) in the placebo. AEs considered to be treatment related in these studies were reported in 146 (27.6%) subjects in the Q2W group, 158 (30.5%) in the QW and 104 (20.1%) in the placebo. There was one death in the QW group. SAEs were reported in 13 (2.5%) patients in the Q2W group, 11 (2.1%) in the QW and 26 (5.0%) in the placebo. Discontinuation primarily due to adverse event (DAE) was reported for ten (1.9%) patients in the Q2W group, eight (1.5%) in the QW group and ten (1.9%) in the placebo group.

Attachment 2 details TEAEs reported by  $\geq 2\%$  of patients in any treatment group during the 16 week treatment period. The most frequently reported events were in the System Organ Class: infections and infestations. Conjunctivitis was reported in 3.8% of patients

given dupilumab cf. 0.4% given placebo. There was no other infection or infestation with a higher incidence in the active treatment groups. Atopic dermatitis was reported in 34.6% of patients given placebo as compared to 13-16% in patients given dupilumab.

Injection site reactions occurred in 6.4% of patients given placebo as compared to around 13% for patients given dupilumab. TEAE of special interest are also summarised in Attachment 2. Of particular note, the incidence of any severe infection was lower in the dupilumab groups than in the placebo group (1.7% placebo compared to 0.2% combined dupilumab). Likewise opportunistic infections were not more frequent in patients given either dose of dupilumab (0.9% placebo compared to 0.4% combined dupilumab).

Longer term safety data are available from Study 1224 where all patients also received TCS. Safety data from this study are incomplete as not all patients have completed 52 weeks of treatment.

The mean duration of exposure was shorter in the placebo + TCS group (296.4 days) than in the dupilumab 300 mg Q2W + TCS (322.4 days) and dupilumab 300 mg QW + TCS (330.4 days) groups. Similarly, the duration of observation was shorter in the placebo + TCS group (355.2 days) than in the dupilumab 300 mg Q2W + TCS (370.0 days) and 300 mg QW + TCS (376.1 days) groups. The results for the treatment related TEAEs during the 52 week treatment period were generally similar to the results observed for the first 16 weeks of treatment.

While there was no separate tabulation of malignancies for Study 1224, these reports were listed in the publically available FDA Safety Evaluation;<sup>5</sup>

- Placebo: keratoacanthoma, squamous cell carcinoma (site unspecified), cervix carcinoma (2 reports), mycosis fungoides, and penile squamous cell carcinoma
- Dupilumab 300 Q2W + TCS: squamous cell carcinoma of skin
- Dupilumab 300 QW + TCS: basal cell carcinoma, squamous cell carcinoma of the tongue, squamous cell carcinoma (site unspecified) (1224 study report)

Dupilumab was associated with small mean reductions in platelets and neutrophils and in LDH but these were not clinically significant.

Immunogenicity is discussed in Attachment 2 on a study by study basis. In the combined Phase III monotherapy (Studies 1334 and 1416) approximately 13.6% (61/447) and 7.2% (31/429) of patients had anti-drug antibodies to dupilumab following 16 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the patients who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 18% (11/61) and 13% (4/31), respectively, had neutralising antibodies. In the 52 week study with concomitant TCS (Study 1224) approximately 9.5% (10/105) and 10.7% (33/308) of patients had anti-drug antibodies to dupilumab following 52 weeks of treatment with dupilumab Q2W and QW dosing regimens, respectively. Of the patients who developed anti-drug antibodies to dupilumab while receiving Q2W and QW dosing regimen, approximately 10% (11/10) and 0% (0/33), respectively, had neutralising antibodies. In that study there were also 39 patients given placebo who developed ADA to dupilumab and of these 2/39 had neutralising antibodies to dupilumab.

The presence of ADA was associated with reduced serum dupilumab concentrations.

The relationship between positive ADA and TEAE was evaluated and while no conclusions were drawn it was noted that 2 patients with high ADA titre developed a serum sickness like reaction, and serum sickness respectively.

<sup>5</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2017/761055Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761055Orig1s000MedR.pdf)

## Risk management plan

The sponsor submitted EU-RMP version 1.0 (dated 21 October 2016; DLP 27 April 2016) and ASA version 1.0 (dated 30 November 2016) in support of this application. The sponsor has submitted the updated EU-RMP version 1.1 dated 11 May 2017, DLP 27 April 2016 with ASA version 1.1 dated July 2017 with its post-first round response.

The updated Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised above in Table 8.

Routine and additional pharmacovigilance are proposed for Dupixent. Additional activities include studies on paediatric use and drug interactions, dedicated clinical assessments of conjunctivitis, and a pregnancy registry study. There is Australian involvement proposed in the conjunctivitis activity. Thus only routine risk minimisation has been proposed for Dupixent.

There was a minor outstanding issue regarding the content of the Safety Specification. Both the clinical evaluator and RMP evaluator have recommended that rhabdomyolysis be listed as an important potential risk.

## Risk-benefit analysis

### Delegate's considerations

Dupilumab showed highly clinically and statistically significant efficacy results across the AD efficacy studies. In the monotherapy studies approximately 27% more patients given dupilumab achieved complete or near complete resolution of their AD signs and symptoms and around 32 to 38% more achieved at least a 75% improvement from Baseline in EASI score. A benefit became apparent as soon as 2 weeks after the first dose of dupilumab, stabilised at around Weeks 8 to 12 and was persistent while treatment continued.

While the use of TCS with dupilumab was examined there appeared to be little additional clinical benefit compared with dupilumab alone in patients with moderate to severe AD. This observation relies on cross study comparison of the placebo group responses in the monotherapy and with those in the concomitant TCS study.

None of the efficacy and safety studies showed a clinically significant difference in efficacy between QW and Q2W dosing of dupilumab. No statistical comparison of efficacy for these two dose regimens was made and the sponsor is not pursuing weekly dosing.

Recurrence of the signs and symptoms of AD on cessation of treatment at the end of the 12 month treatment period were to be assessed in Study 1224 however the results were not included in the interim report submitted. The sponsor is requested to submit those results with their Pre-Advisory Committee on Medicines (ACM) response. The limited data from the dose-finding study suggests that ongoing treatment will be required to maintain peak clinical response. An indication of the proportion of patients who may not require ongoing treatment is not available from the data submitted. Similarly the extent of efficacy on re-treatment with dupilumab has not been adequately examined.

Overall the safety profile of dupilumab appears very reassuring with no increases in any type of infection seen so far, though this is based on a relatively small number of patients assessed for treatment of a generally non-life threatening illness. That lack of information should be considered with the known side effects of alternative treatments such as cyclosporin. Cyclosporin is associated with hypertension and impaired renal and hepatic function. It may also result in increased susceptibility to infections and decreased cancer immunosurveillance.



The sponsor responded to the clinical and RMP evaluators request that rhabdomyolysis be included as an important potential risk of dupilumab. The sponsor responded to this request and has satisfied the evaluator that 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. Similarly there was no consistent dose response for increases in creatinine kinase seen in the active treatment groups. The sponsor attributed these small, asymptomatic increases to increased participation in physical activity.

### **Summary of issues**

Safety and efficacy in paediatric patients, the population group with the greatest need for additional therapy for AD have not been established.

It is not clear whether vaccination with live vaccine should be contraindicated given the lack of effect of vaccination with T cell dependent and T cell independent non-live vaccines seen in Study R668-AD-1314.

There are very limited long term safety data. Given this it is not clear whether initial use should be limited to third line treatment for patients who are unable to use TCS or with inadequate response to TCS and who are also unable to take cyclosporine.

The extent of need and optimal dosing regimen for long term maintenance has not been adequately examined.

### **Proposed action**

The Delegate had no reason to say, at this time, that the application for Dupixent (dupilumab) should not be approved for registration subject to negotiation of the conditions for registration, including the PI and agreement to submit further studies.

### **Request for ACPM advice**

The committee is requested to provide advice on the following specific issues:

1. Should approval be conditional on the sponsor agreeing to undertake studies of dupilumab in infants and children with moderate to severe AD? The Delegate notes that studies currently underway in the paediatric population are limited to children of at least 6 years of age and a study is planned for children aged from 6 months.
2. Does the committee consider that the limited long term efficacy and safety data support use as third line treatment, after TCS and cyclosporin or as a second line treatment for patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable?
3. While it is clear that there is a mean reduction in effect when treatment with dupilumab is ceased it is not clear whether all patients require ongoing treatment and whether it is appropriate to cease treatment and observe patients for recurrence of AD signs and symptoms. Does the committee consider it appropriate to state this, or a similar phrase in the PI?
4. If issue 3 is agreed, does the committee consider that approval should be conditional on submission of further investigation of maintenance treatment requirements, including the efficacy results for the 12 week follow-up period at the end of Study 1225 (a 52 week active treatment study)?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

## Sponsor response

The sponsor's comments on the issues for which the advice of the ACM is sought, as outlined in the Delegate's Overview above, are presented below.

- 1. *Should approval be conditional on the sponsor agreeing to undertake studies of dupilumab in infants and children with moderate to severe AD? I note that studies currently underway in the paediatric population are limited to children of at least 6 years of age and a study is planned for children aged from 6 months.***

The comprehensive pediatric development program for dupilumab includes patients ranging from 6 months to less than 18 years of age. A waiver has been granted in the EU and USA for infants less than 6 months old on the grounds that dupilumab is likely to be unsafe in this age group. A revised Pediatric Investigation Plan (PIP) was approved in April 2017 and the current date for completion of the plan is December 2020. A copy of the latest PIP is provided with this response for the convenience of the ACM.

The ASA of the AU-RMP includes use in paediatric patients < 18 years as missing information to align with the EU RMP. The paediatric studies referenced in the ASA align with those in the approved PIP and the ASA includes a commitment for these to be submitted to the TGA as the reports become available.

Since the RMP and subsequent updated versions will be included as a condition of registration the sponsor does not consider that a specific condition relating to pediatric development is necessary.

- 2. *Does the Committee consider that the limited long-term efficacy and safety data support use as third line treatment, after TCS and cyclosporin or as a second line treatment for patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable?***

Moderate to severe atopic dermatitis is a disease with a high disability burden which is frequently associated with important comorbid conditions that add to the burden of disease. 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 major impact on patients' day to day functioning and well-being. Effective therapies with an acceptable long term safety profile are currently not available to manage this serious and chronic condition.

Current treatment options include topical corticosteroids and cyclosporin. Due to the risk of adverse effects associated with steroid treatment, such as skin atrophy, the use of topical corticosteroids is limited, while steroid phobia is often the cause of poor adherence to treatment, resulting in ineffective management of the disease. In Australia, cyclosporin is approved for treatment of severe atopic dermatitis only when other treatment is ineffective or inappropriate.

As noted by the Delegate, use of cyclosporin in AD is associated with commonly recognised toxicities including hypertension, impaired renal and hepatic function and may also result in increased susceptibility to infections and decreased cancer immunosurveillance. These toxicities require close monitoring and can limit the duration of therapy. The available long term safety data for cyclosporin, referenced in the Australian PI, is limited to 98 patients treated for 12 months.

Recommended assessments include regular full blood count, renal function and electrolytes, liver biochemistry, fasting lipids and blood pressure.

Long term efficacy of cyclosporin in atopic dermatitis has not been established, and data suggest relapses usually occurs following treatment cessation.<sup>6</sup> Furthermore, when cyclosporin is utilised, the discontinuation rate is high. In a report from one experienced Dutch referral centre, 234 out of 267 cyclosporin-treated patients discontinued treatment. The median duration of treatment was 258 days. Only 29% of 234 patients discontinued treatment because their disease was under control. The remainder discontinued due to adverse effects and/or lack of efficacy.<sup>7</sup>

Since existing therapies have inconsistent effects on disease control over time and can themselves cause undesirable topical and systemic adverse effects, the availability of a safe and effective treatment for moderate to severe AD remains a significant unmet need.

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 non-selective systemic immunosuppressants. The sponsor believes that the efficacy and safety profile of dupilumab support the positioning of it as a second line treatment for patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

In contrast to the limited evidence available for cyclosporin, long term data from the ongoing extension Study AD-1225 continues to support the safety profile of dupilumab. As of 3 November 2017, 2136 patients have been exposed to a dose of 300 mg QW for more than one year; 673 patients for more than two years; and 279 patients for more than three years. Thus far, no new safety signals have emerged. Nor have any new safety signals been observed in post-marketing safety reports and other ongoing clinical programs for asthma and nasal polyposis indications.

Further support for the use of dupilumab as second line therapy after failure on topical therapy (that is, first line systemic treatment) is provided by a recent published extensive review of the available literature by a multi-disciplinary group of AD experts comprised of 8 dermatologists, 2 allergists, and a patient advocacy group representative, who reached the following consensus: *'Given the strong evidence for the efficacy and safety of dupilumab in adults with moderate-to-severe AD and the significant safety concerns associated with conventional systemic therapies, the SC recommends dupilumab for first-line systemic treatment in adults with chronic moderate-to-severe AD who are uncontrolled with topical therapies.'*<sup>8</sup>

Dupilumab has already been approved for the second line treatment of moderate to severe AD by the FDA and in the EU. The proposed indication for Australia is consistent with the approved labelling in both the USA and the EU:

*USPI:*

*Dupilumab is an interleukin-4 receptor alpha antagonist 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. Dupilumab can be used with or without topical corticosteroids.*

*SmPC:*

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<sup>6</sup> Lee SS, Tan AWH, Giam YC, Cyclosporin in the treatment of severe Atopic Dermatitis, A Retrospective Study, National Skin Center, Singapore, May 2004

<sup>7</sup> Van der Schaft J, Politiek K, Van den Reek JMPA, Christoffers WA, Kievit W, de Jong EMGJ, et al. Drug survival for ciclosporin A in a long term daily practice cohort of adult patients with atopic dermatitis. Br J dermatol. 2015

<sup>8</sup> Boguniewicz M et al. Expert Perspectives on Management of Moderate-to-Severe Atopic Dermatitis: A Multidisciplinary Consensus Addressing Current and Emergent Therapies. J Allergy Clin Immunol Pract. 2017

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

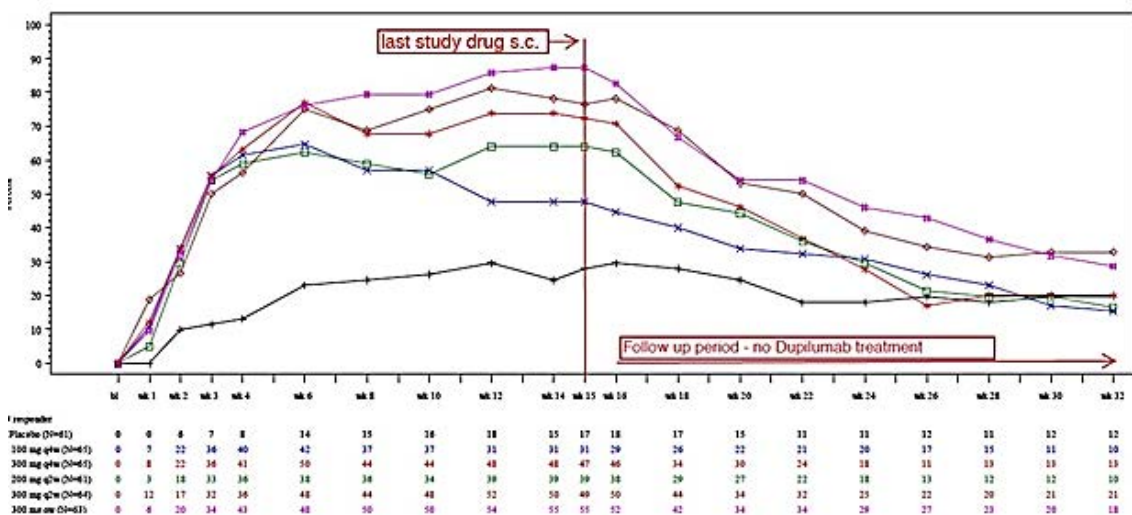
In summary, Dupixent provides an important treatment option that addresses a current unmet medical need to reduce the burden of disease for patients with moderate to severe AD. The sponsor considers Australian prescribers and patients should have the same access to innovative therapies as available in other major jurisdictions. Compared to the limited data and long term safety concerns with cyclosporin, the robust demonstration of safety and efficacy in the intended treatment population supports the approval of Dupixent for use as second line therapy, ensuring patients receive an effective therapy to manage a serious and chronic condition.

**3. While it is clear that there is a mean reduction in effect when treatment with dupilumab is ceased it is not clear whether all patients require ongoing treatment and whether it is appropriate to cease treatment and observe patients for recurrence of AD signs and symptoms. Does the Committee consider it appropriate to state this, or a similar phrase in the PI?**

Since AD is a chronic disease, the clinical development program was not designed to evaluate dupilumab for intermittent use. The sponsor believes that a recommendation for treatment discontinuation of patients whose AD is well controlled with Dupixent is not supported by the totality of the data.

In general, stopping treatment after 16 weeks results in relapse of AD approximately 16 to 20 weeks after stopping injections (300 mg/Q2W) in the majority of patients. Figure 2 illustrates this for the 16 week follow-up up period of the Phase IIb DRI Study AD-1021 (note: only very limited follow up data is available from Phase III studies, as patients rolled over in other long term studies prior to completing the follow up period of the respective parent study).

**Figure 2: Study AD-1021 Percentage of patients with EASI 50 response (to Week 32)**



Data on type 2 inflammation also indicate that 16 weeks is an insufficient duration to guide a decision on treatment withdrawal/change in dosing interval. Biomarker (for example, IgE) data from 52 week CHRONOS study demonstrate that, although the clinical condition may improve in some patients as early as within the first 16 weeks, the effect of dupilumab to correct the type 2 state requires longer treatment as evidenced by ongoing reductions (but not yet normalisation) in IgE at Week 52.

As outlined in the sponsor’s Clinical Summary, monotherapy maintenance Study R668-AD-1415 (SOLO CONTINUE) has been conducted as part of the development program to

evaluate a less frequent dose regimen (Q4W and Q8W). Study AD-1415 was ongoing at the time of submission.

Patients from SOLO 1 and SOLO 2 (Phase III confirmatory monotherapy studies) who achieved an excellent or very good clinical response (IGA = 0 or 1, or EASI-75) after 16 weeks of treatment were eligible to rollover into the maintenance study. The study also includes a placebo group, to allow an assessment of durability of effect off treatment, in a randomised withdrawal design.

The maintenance study results demonstrate that after 16 weeks of treatment, patients who continued on the same dose regimen received in the parent study (300 mg Q2W or QW) showed the optimal effect in maintaining clinical response, while efficacy for other dose regimens diminished in a dose-dependent manner. Furthermore, the incidence of ADA increased with the increases in dosing interval.

To ensure patients do not experience a recurrence of AD after ceasing dupilumab (the timing of which may hinge on dose and duration of previous dupilumab treatment) and to avoid the increased risk to develop ADA, the sponsor does not recommend a 'stop-observe (recurrence)-retreat' regimen for dupilumab for management of AD.

**4. *If issue 3 is agreed does the Committee consider that approval should be conditional on submission of further investigation of maintenance treatment requirements, including the efficacy results for the 12 week follow-up period at the end of Study 1225 (a 52 week active treatment study)?***

Based on the previous response above the sponsor does not agree with Issue 3. In reference to Study AD-1225 12 week follow up data, the sponsor considers these are inadequate to address the maintenance question, as firstly most patients directly continue with commercial drug after approval in the respective jurisdictions and secondly patients in Study 1225 are treated with 300 mg QW dose which is not the dose proposed for approval.

The sponsor acknowledges the interest in additional data on long term management of AD with Dupixent and is considering designs for further studies to investigate Dupilumab maintenance regimens. These studies will test the hypothesis as to whether treatment periods longer than 16 weeks can induce a durable response in AD patients, in particular in children, and if these patients can be predicted. As previously stated, in the absence of these data, intermittent treatment or 'stop-observe (recurrence)-retreat' regimen is not recommended.

**5. *Other: Use with live vaccines***

The Delegate commented that it is not clear whether vaccination with live vaccine should be contraindicated given the lack of effect of vaccination with T cell independent non-live vaccines seen in Study R668-AD-1314.

In Study R668-AD-1314, the immune response to tetanus, diphtheria, and pertussis (whooping cough) (Tdap) and meningococcal vaccines in dupilumab-treated patients was similar to that in patients who received placebo. By extension, the sponsor does not anticipate that the antibody response to live vaccines would be 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.

As previously noted the sponsor is not proposing to include a general rule on use with live vaccines but rather to leave the decision to the judgment of the treating physician. The treating physician is best placed to assess the level of immune competence of an individual patient, taking into account the effect of the flares of the underlying condition (atopic dermatitis) and other pharmacological treatments that the patient might be receiving.

### **Advisory Committee Considerations**

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Dupixent solution for injection, pre-filled syringe; with needle guard, containing 300 mg/2 mL of dupilumab to have an overall positive benefit-risk profile for the indication:

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

In making this recommendation the ACM expressed concern that:

- While Dupixent exhibited significant efficacy in clinical trials (approximately 50%), it was noted that there was a high drop-out rate (approximately 70%) in the clinical trial (CHRONOS) designed to assess long term efficacy and safety.
- AD is far more prevalent in children, a patient population not indicated for Dupixent. There is a risk of off label leakage into this patient group given the greater clinical need in this group.
- There were no data on concomitant administration of Dupixent with other immunomodulators.
- There were no data on the interaction of Dupixent with live vaccines.
- The comparative efficacy with current systemic treatments was not addressed.

### **Proposed conditions of registration**

The ACM agreed with the Delegate on the proposed conditions of registration and advised on the inclusion of the following:

- Restriction of prescribing by specialist dermatologists and immunologists.
- Negotiation of the Product Information and Consumer Medicine Information to the satisfaction of the TGA.

### **Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments**

The ACM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine information (CMI) and specifically advised on the inclusion of the following:

- A statement in the Precautions section stating that there are no data on the safety of Dupixent when co-administered with other systemic immunomodulators or with live vaccines.
- A statement in the Dosing and Administration section recommending that Dupixent be a third line agent following topical (first line) and currently available systemic (second line) agents with established long term safety profiles, due to a lack of safety data for Dupixent beyond 52 weeks of use.

### **Specific advice**

The ACM advised the following in response to the Delegate's specific questions on the submission:

The committee is requested to provide advice on the following specific issues:

1. *Should approval be conditional on the sponsor agreeing to undertake studies of dupilumab in infants and children with moderate to severe AD? I note that studies*

*currently underway in the paediatric population are limited to children of at least 6 years of age and a study is planned for children aged from 6 months.*

The ACM agreed that approval should be restricted to use in adults 18 years and older. Paediatric studies for Dupixent are on-going and should be submitted to the TGA when available. In addition to the studies already under way, the ACM recommended proactive pharmacovigilance studies in the paediatric population in Australia (such as drug utilisation studies to evaluate the extent and safety outcomes of potential off label uses in this population). The additional proactive pharmacovigilance measures should include vaccine safety (in the paediatric and adult population).

2. *Does the Committee consider that the limited long-term efficacy and safety data support use as third line treatment, after TCS and cyclosporin or as a second line treatment for patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable?*

Given the limited long-term efficacy and safety data and the availability of other steroid-sparing systemic treatments, the ACM supports the use of Dupixent as a third line agent following topical (first line) and currently available systemic (second line) agents.

3. *While it is clear that there is a mean reduction in effect when treatment with dupilumab is ceased it is not clear whether all patients require ongoing treatment and whether it is appropriate to cease treatment and observe patients for recurrence of AD signs and symptoms. Does the Committee consider it appropriate to state this, or a similar phrase in the PI?*

The ACM considers it appropriate to recommend cessation of treatment and clinical assessment following 16 weeks of therapy instead of routine continuation of treatment for responders since AD is commonly self-limiting (similar guidelines exist for omalizumab in the treatment of chronic spontaneous urticaria which is also commonly self-limiting).

4. *If issue 3 is agreed does the Committee consider that approval should be conditional on submission of further investigation of maintenance treatment requirements, including the efficacy results for the 12 week follow-up period at the end of Study 1225 (a 52 week active treatment study)?*

The ACM concluded that approval should *not* be conditional on submission of further investigation of maintenance treatment requirements since the maintenance treatment requirements in AD are highly variable due to the relapsing nature of the condition. There is insufficient evidence for routine continuation of therapy once a favourable treatment endpoint is achieved.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Dupixent (dupilumab) solution for injection, pre-filled syringe; solution for injection, pre-filled syringe with needle guard 300 mg/2 mL, indicated for:

*Dupixent is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for chronic systemic therapy. Dupixent is not intended for episodic use.*

### **Specific conditions of registration applying to these goods**

- Dupixent (dupilumab) is to be included in the Black Triangle Scheme. The PI and CMI for Dupixent must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Dupixent EU-Risk Management Plan (RMP) (version 1.4, dated 20 July 2017, data lock point 27 April 2016), with Australian Specific Annex (version 1.2, dated November 2017), included with submission PM-2016-04087-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

## **Attachment 1. Product Information**

The PI for Dupixent approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

## **Attachment 2. Extract from the Clinical Evaluation Report**



## **Therapeutic Goods Administration**

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