EU-RISK MANAGEMENT PLAN FOR DUPIXENT® (DUPILUMAB)

Data Lock Point (DLP)	29-SEP-2023
RMP Version number	Version 10.3
Date of final sign-off	24-MAY-2024

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	This updated EU-RMP v10.3 is prepared in the context of the application for the new indication of COPD in adults.
Summary of significant changes in this RMP	Significant changes to each module in version 10.3[a] as compared to version 9.0: • Part I: Addition of new COPD indication. • Module II SI: Addition of epidemiological data for COPD. • Module II SII: Minor wording changes. • Module II SIII: Addition of COPD exposure data (EFC15804 and EFC15805 studies). Update of clinical trials exposure data for all indications. • Module II SIV: Addition of data relative to COPD. • Module II SV: Update of post-authorization exposure data. • Module II SVII: - Removal of "Conjunctivitis and keratitis related events in AD patients" from the list of important identified risks; - Update of risk tables with addition of COPD clinical studies data and update of post marketing data as of RMP DLP; - Missing information "Long-term safety in adult and paediatric patients" renamed "Long-term safety in paediatric patients". • Part III: Removal of completed studies R668-AD-1225 and LTS14424. Few changes to reflect current status for PEDISTAD study. • Module II SVIII, Part V and Part VI: Update for consistency with changes in other modules.

a Data for EFC15805 Study (DLP 29-Sep-2023) were added in RMP intermediate version 10.1 (as compared to intermediate version 10.0). The DLP of intermediate versions 10.0 and 10.1 was updated from 28-Mar-2023 to 29-Sep-2023 in intermediate version 10.2 to align with DLP of EFC15805 Study. RMP version 10.3 includes final indication wording agreed with EMA.

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disease; DLP: Data Lock Point; EMA: European Medicines Agency; EU: European Union; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	9.0
Approved with procedure	EMEA/H/C/004390/II/0060
Date of approval (opinion date)	26-Jan-2023 (CHMP positive opinion)

CHMP: Committee for Medicinal Products for Human Use; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Hadj Benzerdjeb[a], MD
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

TABLE OF CONTENTS

LIST OF TABLES

ABBREVIATIONS

ACE:	Angiotensin Converting Enzyme
AD:	Atopic Dermatitis
ADA:	Antidrug Antibody
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ALT:	Alanine Aminotransferase
ANA:	Anti-Nuclear Antibody
ATC:	Anatomical Therapeutic Chemical
BID:	Twice a Day
CD:	Clusters of Differentiation
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CMQ:	Customized MedDRA Query
CNS:	Central Nervous System
COPD:	Chronic Obstructive Pulmonary Disease
CRS:	Chronic Rhinosinusitis
CRSwNP:	Chronic Rhinosinusitis with Nasal Polyposis
CT:	Computed Tomography
C_{trough}:	Observed Minimum Concentration in Serum After a Dose During a Dosing Interval
CXCL8:	C-X-C Motif Chemokine Ligand 8
DALA:	Drug Abuse Liability Assessment
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
dsDNA:	Double Stranded Deoxyribonucleic Acid
EAACI:	European Academy of Allergy and Clinical Immunology
EASI:	Eczema Area and Severity Index
ECG:	Electrocardiogram
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EGPA:	Eosinophilic Granulomatosis with Polyangitis
EMA:	European Medicines Agency
EoE:	Eosinophilic Esophagitis
EPAR:	European Public Assessment Report
ePPND:	Enhanced Pre-/Postnatal Development
ESS:	Endoscopic Sinus Surgery
EU:	European Union
Fc:	Fragment Crystallizable
FDA:	Food and Drug Administration
FeNO:	Fraction of Exhaled Nitric Oxide
FESS:	Functional Endoscopic Sinus Surgery

FLG:	Filaggrin
GBD:	Global Burden of Disease
GD:	Gestation Day
GERD:	Gastroesophageal Reflux Disease
GOLD:	Global Initiative for Chronic Obstructive Lung Disease
GVP:	Good Pharmacovigilance Practices
HBcAb:	Hepatitis B Core Antibody
HBsAg:	Hepatitis B Surface Antigen
HBV-DNA:	Hepatitis B Virus Deoxyribonucleic Acid
hCG:	Human Chorionic Gonadotropin
HCP:	Healthcare Professional
HCV-RNA:	Hepatitis C Virus Ribonucleic Acid
HIV:	Human Immunodeficiency Virus
HLGT:	High Level Group Term
HR:	Hazard Ratio
HRQL:	Health-Related Quality of Life
hs-CRP:	High-Sensitivity C-Reactive Protein
IC_{90}:	Concentration of drug that inhibits viral replication by 90%
ICAR:	International Consensus Statement on Allergy and Rhinology: Rhinosinusitis
ICS:	Inhaled Corticosteroid
IFSI:	International Forum for the Study of Itch
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgG4:	Immunoglobulin G4
IHME:	Institute for Health Metrics and Evaluation
IL-13:	Interleukin-13
IL-13Rα:	Interleukin-13 Receptor Alpha
IL-17:	Interleukin-17
IL-18:	Interleukin-18
IL-1β:	Interleukin-1 Beta
IL-23:	Interleukin-23
IL-33:	Interleukin-33
IL-4:	Interleukin-4
IL-4Rα:	Interleukin-4 Receptor Alpha
IL-5:	Interleukin-5
IL-6:	Interleukin-6
IL-8:	Interleukin-8
IMP:	Investigational Medicinal Product
INCS:	Intranasal Corticosteroid
INN:	International Nonproprietary Name
IRR:	Incidence Rate Ratio
IV:	Intravenous
JAK:	Janus Kinase
LABA:	Long-Acting Beta Agonist
LAMA:	Long Acting Muscarinic Antagonist
LTT:	Long-Term Treatment
MA:	Marketing Authorization

mAb:	Monoclonal Antibody
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MART:	Maintenance and Reliever Therapy
MedDRA:	Medical Dictionary for Regulatory Activities
MOA:	Mechanism of Action
mRNA:	Messenger Ribonucleic Acid
MRSA:	Methicillin Resistant Staphylococcus Aureus
NMSC:	Non-Melanoma Skin Cancer
NOAEL:	No-Observed-Adverse-Effect Level
NOEL:	No-Observed-Effect Level
NP:	Nasal Polyposis
NSAID:	Nonsteroidal Anti-Inflammatory Drug
NSAID-ERD:	Nonsteroidal Anti-Inflammatory Drug-Exacerbated Respiratory Disease
OCS:	Oral Corticosteroid
OR:	Odds Ratio
PASS:	Post-Authorization Safety Study
PCSK9:	Proprotein Convertase Subtilisin/Kexin Type 9
PDE4:	Phosphodiesterase-4
PF:	Pre Filled
pH:	Potential of Hydrogen
PIL:	Patient Information Leaflet
PIP:	Pediatric Investigation Plan
PK:	Pharmacokinetic
PN:	Prurigo Nodularis
PPI:	Proton Pump Inhibitor
PRAC:	Pharmacovigilance Risk Assessment Committee
PSP:	Pediatric Study Plan
PSUR:	Periodic Safety Update Report
PT:	Preferred Term
PY:	Patient-Years
Q:	Quarter
Q2W:	Once Every Two Weeks
Q4W:	Once Every Four Weeks
Q8W:	Once Every Eight Weeks
QoL:	Quality of Life
QPPV:	Qualified Person Responsible for Pharmacovigilance
QW:	Once Every Week
REGN1103:	Mouse Surrogate Monoclonal Antibody
REGN646:	Monkey Surrogate Monoclonal Antibody
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SC:	Subcutaneous
SCS:	Systemic Corticosteroid
SIR:	Standardized Incidence Ratio
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query

SNRI:	Serotonin and Norepinephrine Reuptake Inhibitor
SOC:	System Organ Class
SU:	Sulphonyl Urea
TARC:	Thymus and Activation Related Chemokine
TB:	Tuberculosis
TCI:	Topical Calcineurin Inhibitor
TCS:	Topical Corticosteroid
TDAR:	T-cell Dependent Antibody Response
TEAE:	Treatment-Emergent Adverse Event
TH:	T Helper
Th1:	Type 1 Helper T Cell
Th2:	Type 2 Helper T Cell
TNF:	Tumour Necrosis Factor
TPO:	Thyroid Peroxidase
UI:	Uncertainty Interval
UK:	United Kingdom
ULN:	Upper Limit of Normal
US:	United States
UV:	Ultraviolet
UV-B:	Ultraviolet B
WHO:	World Health Organization
YLL:	Year of Life Lost

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Dupilumab
Pharmacotherapeutic group(s) (ATC Code)	Dermatologicals (D11AH05)
Marketing Authorization Holder	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	DUPIXENT
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Dupilumab is a fully human mAb that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit of the IL-4 and IL-13 receptor complexes.
	Summary of mode of action: Dupilumab inhibits IL-4 signaling via the type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the type II receptor (IL-4Rα/IL-13Rα).
	Important information about its composition: Fully human mAb produced in Chinese Hamster Ovary cells by recombinant DNA technology.
Hyperlink to the product information	Refer to e-CTD sequence for procedure for the new indication of COPD in adults, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	**Current**: **Atopic dermatitis** *Adults and adolescents* DUPIXENT is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy. *Children 6 months to 11 years of age* DUPIXENT is indicated for the treatment of severe AD in children 6 months to 11 years old who are candidates for systemic therapy. **Asthma** *Adults and adolescents* DUPIXENT is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1 (of SmPC), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

<table>
<tr><td></td><td><u>Children 6 to 11 years of age</u>
DUPIXENT is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1 (of SmPC), who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.
Chronic rhinosinusitis with nasal polyposis (CRSwNP):
DUPIXENT is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with SCSs and/or surgery do not provide adequate disease control.
Prurigo Nodularis (PN):
DUPIXENT is indicated for the treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy.
Eosinophilic Esophagitis (EoE):
DUPIXENT is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1 of SmPC).</td></tr>
<tr><td></td><td><u>Proposed</u>:
Chronic Obstructive Pulmonary Disease (COPD):
DUPIXENT is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate (see Section 5.1 of SmPC).</td></tr>
<tr><td>Dosage in the EEA</td><td><u>Current</u>:
Atopic Dermatitis
<u>Adults</u>
The recommended dose is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given Q2W administered as SC injection.
<u>Adolescents (12 to 17 years of age)</u>
The recommended dose of dupilumab for adolescent patients 12 to 17 years of age is specified in Table 5a.
Table 5a - Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with atopic dermatitis
<table>
<tr><th>Body weight of patient</th><th>Initial dose</th><th>Subsequent doses (Q2W)</th></tr>
<tr><td>less than 60 kg</td><td>400 mg (two 200 mg injections)</td><td>200 mg</td></tr>
<tr><td>60 kg or more</td><td>600 mg (two 300 mg injections)</td><td>300 mg</td></tr>
</table>
Q2W: Once Every Two Weeks.
<u>Children 6 to 11 years of age</u>
The recommended dose of dupilumab for children 6 to 11 years of age is specified in Table 5b.</td></tr>
</table>

Table 5b - Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses
15 kg to less than 60 kg	300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15	300 mg Q4W[a], starting 4 weeks after Day 15 dose
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

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

Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks.

Children 6 months to 5 years of age

The recommended dose of DUPIXENT for children 6 months to 5 years of age is specified in Table 5c.

Table 5c - Dose of dupilumab for subcutaneous administration in children 6 months to 5 years of age with atopic dermatitis

Body weight of patient	Initial dose	Subsequent doses
5 kg to less than 15 kg	200 mg (one 200 mg injection)	200 mg Q4W
15 kg to less than 30 kg	300 mg (one 300 mg injection)	300 mg Q4W

Q4W: Once Every Four Weeks.

Asthma

Adults and adolescents

The recommended dose of dupilumab for adult and adolescents patients (12 years of age and older) is:

- For patients with severe asthma and who are on OCSs or for patients with severe asthma and co-morbid moderate-to-severe AD or adults with co-morbid severe CRSwNP, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg Q2W administered as SC injection.
- For all other patients, an initial dose of 400 mg (two 200 mg injections), followed by 200 mg Q2W administered as SC injection.

Children 6 to 11 years of age

The recommended dose of dupilumab for paediatric patients 6 to 11 years of age is specified in Table 5d.

Table 5d - Dose of dupilumab for subcutaneous administration in children 6 to 11 years of age with asthma

Body weight of Patient	Initial dose
15 kg to less than 30 kg	300 mg Q4W
30 kg to less than 60 kg	200 mg Q2W or 300 mg Q4W
60 kg or more	200 mg Q2W

Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks.

For paediatric patients (6 to 11 years old) with asthma and co-morbid severe AD, as per approved indication, the recommended dose should be followed in Table 5b.

	Chronic rhinosinusitis with nasal polyposis (CRSwNP): The recommended dose of dupilumab for adult patients is an initial dose of 300 mg followed by 300 mg given Q2W. **Prurigo Nodularis (PN):** The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given Q2W. **Eosinophilic Esophagitis (EoE):** The recommended dose of dupilumab for patients 12 years of age and older is 300 mg given QW. Dupilumab 300 mg QW has not been studied in patients with EoE weighing less than 40 kg.
	<u>Proposed</u>: **COPD:** The recommended dose of dupilumab for adult patients is 300 mg given every other week.
Pharmaceutical form(s) and strength(s)	**<u>Current</u>:** Solution for injection Clear to slightly opalescent, colourless to pale yellow solution, which is free from visible particulates, with a pH of approximately 5.9. Each single-use PF syringe or pen contains 300 mg of dupilumab in 2 mL solution (150 mg/mL). Each single-use PF syringe or pen contains 200 mg of dupilumab in 1.14 mL solution (175 mg/mL).
	<u>Proposed</u>: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	No

AD: Atopic Dermatitis; ATC: Anatomical Therapeutic Chemical; CHMP: Committee for Medicinal Products for Human Use; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DNA: Deoxyribonucleic Acid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EoE: Eosinophilic Esophagitis; EU: European Union; FeNO: Fraction of Exhaled Nitric Oxide; ICS: Inhaled Corticosteroid; IL-4Rα: Interleukin-4 Receptor Alpha; IL-4: Interleukin-4; IL-13: Interleukin-13; IL-13Rα: Interleukin-13 Receptor Alpha; INN: International Nonproprietary Name; LABA: Long-Acting Beta Agonist; LAMA: Long Acting Muscarinic Antagonist; mAb: Monoclonal Antibody; OCS: Oral Corticosteroid; PF: Pre-Filled; pH: Potential of Hydrogen; PN: Prurigo Nodularis; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week; RMP: Risk Management Plan; SC: Subcutaneous; SCS: Systemic Corticosteroid; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

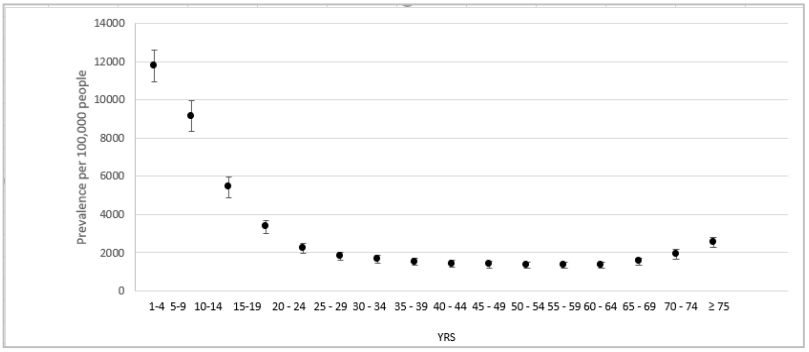
DUPIXENT is indicated:

- For the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy, and for the treatment of severe AD in children ≥6 months to 11 years old who are candidates for systemic therapy.
- As an add-on maintenance treatment for severe asthma with type 2 inflammation in patients ≥6 years of age.
- As an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with SCSs and/or surgery do not provide adequate disease control.
- For the treatment of adults with moderate to severe Prurigo Nodularis (PN) who are candidates for systemic therapy.
- For the treatment of Eosinophilic Esophagitis (EoE) in adults and adolescents ≥12 years of age, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy.
- As add-on maintenance treatment in adults for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

The epidemiology of AD in patients 6 months of age and older is summarized in the following table.

Table 6 - Epidemiology of atopic dermatitis in patients 6 months of age and older

Indication	Atopic Dermatitis in patients 6 months of age and older
Incidence	Data from the GBD Study 2019 indicate the incidence of AD in the EU as follows: [1] All ages: 331/100 000 PY; <20 years: 725/100 000 PY; ≥20 years: 229/100 000 PY.
Prevalence	Data from the GBD Study 2019 indicate the prevalence of AD in the EU as follows: [1] All ages: 2.75/100; <20 years: 6.81/100; ≥20 years: 1.69/100. The prevalence of AD varies globally. While the global prevalence of AD in young children aged 6 months - 6 years is estimated at 12%, variation around this summary estimate exists in European countries. For example, the prevalence of AD for children aged 6 months-6 years is estimated at 7% in Germany, while the estimates in Italy, Spain, France and the UK are in the range of 15-19%. [2] For children aged 6 years - 12 years, the global prevalence of AD is 13%, however within Europe, this varies from 9% in Germany to 15-20% in Italy, Spain, France and the UK. [2] For adolescents aged 12 years - 18 years, the global prevalence of AD is estimated at 14.8%, however within Europe, this varies from 9% in Germany to 14-20% in Italy, Spain, France and the UK. [2] Within Europe, the prevalence of AD in adults ranges from 2% in

Indication	Atopic Dermatitis in patients 6 months of age and older
	Switzerland to 18% in Estonia. [3] There are some data to indicate increasing prevalence of AD globally, particularly in Latin America, parts of Asia, Africa and Europe. [4, 5]
Demographics of the population in the authorized/proposed indication	**Age** The prevalence of atopic dermatitis is highest in children and young adolescents versus adults (see section above). [1] Prevalence tends to decrease with age, although a slight increase in prevalence can be seen in the oldest age groups eg, ≥65 years and driven by older men. [1, 6] **Figure 1 - Prevalence of atopic dermatitis in the EU by age. Data from the GBD Study 2019**  Source: Institute for Health Metrics and Evaluation (IHME). Used with permission. All rights reserved. **Gender** The prevalence of atopic dermatitis is higher in females than in males. This is true of those aged <20 years (8.07/100 versus 5.61/100) and those aged ≥20 years (2.06/100 versus 1.03/100). [1] **Race/ethnicity** In US studies, the prevalence of atopic dermatitis has been reported to be higher in children of African-American (19%) origin relative to Caucasian children (16%). Non-Hispanic black children are more likely to develop incident AD in early childhood and have persistent AD beyond mid-childhood in comparison to Caucasian children. [7, 8] Similarly, the prevalence of AD has been reported to be higher in black Caribbean children (16%) compared to white children (9%) in the UK. [9] **Risk factors** Genetic risk factors: Family history [10, 11] and mutations in the FLG gene. [12] Environmental risk factors: Climate inclusive of mixed evidence for high temperatures, high humidity, and UV radiation while consensus exists that high levels of precipitation are associated with AD [12, 13]; urban areas have been associated with higher prevalence of AD in contrast to rural or suburban areas [12, 14] the "hygiene hypothesis" for example decreased exposure to viral and bacterial pathogens and smaller family size. [15, 16]
Main existing treatment options	Basic therapy includes hydrating, TCS and TCI. Topical corticosteroids are the first-line anti-inflammatory treatment option in AD. The two TCIs, tacrolimus ointment and pimecrolimus cream, are licensed for children aged 2 years and above, and for adults. Off-label use of TCIs in children below 2 years of age is very common. Adjuvant therapy includes UV irradiation. [17, 18, 19] Systemic therapy is necessary if AD cannot be controlled sufficiently with appropriate topical treatments and UV light therapy. Systemic corticosteroids are rapidly effective, but their long-term use is associated with an unfavorable benefit-risk ratio. Until recently, rather broad-acting immunosuppressants, such as SCS, cyclosporine A, azathioprine,

Indication	Atopic Dermatitis in patients 6 months of age and older
	mycophenolate mofetil, and methotrexate, were the only systemic treatment options for difficult-to-treat AD. The most commonly used anti-inflammatory drug in Europe was cyclosporine A, followed by SCS and azathioprine. The most recently approved class of therapies are topical crisaborole (licensed in the US but not in the EU), dupilumab and JAK inhibitors. Dupilumab is the first biologic approved for AD; in the EU, it is indicated for the treatment of moderate-to-severe AD in adults and adolescents 12 years and older who are candidates for systemic therapy. DUPIXENT is also indicated for the treatment of severe AD in children 6 to 11 years old who are candidates for systemic therapy. In the US, dupilumab is indicated for the treatment of patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Baricitinib (JAK inhibitor) and tralokinumab (anti IL-13 mAB) are both indicated in the EU for the treatment of moderate to severe AD in adult patients who are candidates for systemic therapy. Upadacitinib is approved in the EU for the treatment of moderate-to-severe AD in adolescents 12 years of age and older. In the US, tralokinumab and upadacitinib are both indicated for the treatment of moderate-to-severe AD for adults whose disease is not well controlled with topical prescription therapies or when those therapies are not advisable; upadacitinib is also approved in the US for the treatment of moderate-to-severe AD in adolescents 12 years of age and older. Other biologicals targeting key pathways in the atopic immune response, as well as other JAK inhibitors, are among emerging treatment options. Systemic treatment for children with AD: The anatomical and pathophysiological peculiarities of children, such as an incomplete skin barrier, a higher surface-to-body weight ratio, a less experienced immune system "together with the fact that many drugs effective for AD are not licensed for them" result in special considerations and treatment rules for young AD patients, especially for those aged 2 years and younger. Systemic treatment for children is administered on an individual patient basis in severe cases only, and there is no consented standard treatment for the substances or the duration. Cyclosporine A is frequently used and very effective for AD in both children and adults. Cyclosporine A has a narrow therapeutic index and requires close monitoring of blood pressure and renal function. Cyclosporine A is approved for systemic treatment of AD in adults in most European countries and may be used off-label for children. There is evidence that azathioprine is effective and safe for the treatment of AD for duration up to 5 years. However, drug survival is mainly limited due to side-effects. Azathioprine may be used in children. Methotrexate is about equally effective as azathioprine and cyclosporine A in adults and children. Recently, low-dose methotrexate was shown to have a good safety profile in children [20, 21], even for long-term treatment [22] and an effectiveness comparable to Cyclosporine A. [23]
Natural history of the indicated condition in the untreated population including mortality and morbidity	Because the incidence and prevalence of atopic dermatitis peaks in childhood, it has traditionally been thought of as a resolving childhood disease. However, it is now understood that atopic dermatitis has several heterogenous trajectories inclusive of early transient disease to relapsing remitting atopic dermatitis to chronic persistent dermatitis to long periods of remission followed by recurrence. [24, 25] Active dermatitis beyond childhood is common, inclusive of newly incident disease and recurrent disease since childhood. [4, 26] When compared to healthy controls, adult patients with atopic dermatitis have a poorer QoL. [27] Children with AD often go on to develop food allergy, allergic rhinitis and are also at increased risk of asthma, all as part of the "atopic march". [28] Patients with atopic dermatitis have a higher rate of serious cutaneous infections (eg, eczema herpeticum),

<table>
<tr><td>Indication</td><td colspan="4">Atopic Dermatitis in patients 6 months of age and older</td></tr>
<tr><td></td><td colspan="4">respiratory, multiorgan and systemic infections than patients without atopic dermatitis. [29] Additionally, some evidence exists to suggest that patients with atopic dermatitis have a higher risk of cardiovascular disease and autoimmune diseases than patients without atopic dermatitis. [29, 30, 31]
Mortality due to infectious disease, genito-urinary causes and cardiovascular causes is higher in adult patients with atopic dermatitis versus no atopic dermatitis. [32, 33]</td></tr>
<tr><td>Important co-morbidities</td><td colspan="4"><table>
<tr><th>Co-morbidities</th><th>Common co-medication in the general population</th><th>Specific treatment notes relating to children/adolescents</th></tr>
<tr><td>Asthma [34, 35]</td><td>See Table 7</td><td>Use of ICS-LABA in children <4 years old is not recommended due to insufficient data on its efficacy and safety. [36]</td></tr>
<tr><td>Allergic rhinitis [37]</td><td>Intranasal corticosteroids, antihistamines, leukotriene receptor antagonists, ipratropium bromide (intranasal), cromolyn sodium (intranasal).
Decongestants: pseudoephidrine, phenylephrine hydrochloride and oxymetazoline [38, 39]</td><td>Decongestants are not recommended for children <12 years. [40]</td></tr>
<tr><td>Attention deficit/hyperactivity disorder [41, 42]</td><td>Stimulants: methylphenidate and amphetamine
Non-stimulants: Atomoxetine, guanfacine [43, 44]</td><td></td></tr>
<tr><td>Urticaria [37]</td><td>Antihistamines and Oral corticosteroids given as symptomatic/rescue treatment in acute events.
Second line agents may include omalizumab, cyclosporin A, leukotriene receptor antagonists, mycophenolate mofetil, tacrolimus [45, 46]</td><td>Second line agents may include leukotriene receptor antagonists (montelukast) and omalizumab [45]</td></tr>
<tr><td>Food allergies [36]</td><td>Epinephrine is given for severe anaphylactic cases.[47]</td><td></td></tr>
<tr><td>Depression/anxiety and sleep disorders [41]</td><td>Selective serotonin reuptake inhibitors, dual serotonin and norepinephrine reuptake inhibitors, tricyclic anti-depressants, monoamine oxidase inhibitors, α2-antagonists, melatonergic agent agomelatine.
Anxiolytics (anti-anxiety agents), benzodiazepines, barbiturates, hypnotics. [50]</td><td>Fluoxetine in children and adolescents. [48, 49]</td></tr>
</table></td></tr>
</table>

Indication	Atopic Dermatitis in patients 6 months of age and older		
	Cutaneous infections and other infections (bacterial/viral/fungal) [29]	Topical antiseptics/antibiotics/anti-fungals or anti-viral preparations. Systemic antibiotic, antiviral and antifungal-agents.	

ICS: Inhaled Corticosteroid; LABA: Long-Acting Beta-Agonist.

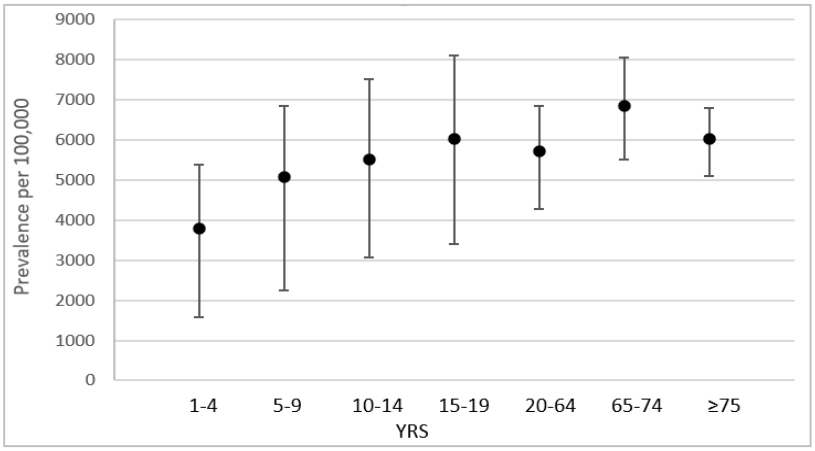
Notes: Common co-medications in the general population are outlined above. Where special treatment scenarios exist for children outside of those medicines highlighted in the general population column, these are flagged in the "specific treatment notes relating to children/adolescents" column.

AD: Atopic Dermatitis; EU: European Union; FLG: Filaggrin; GBD: Global Burden of Disease; ICS: Inhaled Corticosteroid; IHME: Institute for Health Metrics and Evaluation; JAK: Janus Kinase; LABA: Long-Acting Beta-Agonist; mAb: Monoclonal Antibody; PY: Patient-Years; QoL: Quality of Life; SCS: Systemic Corticosteroid; TCI: Topical Calcineurin Inhibitor; TCS: Topical Corticosteroid; UK: United Kingdom; US: United States; UV: Ultraviolet.

The epidemiology of asthma in patients 6 years of age and older is summarized in the following table.

Table 7 - Epidemiology of asthma in patients 6 years of age and older

Indication	Asthma in patients 6 years of age and older
Incidence	Data from the GBD Study 2019 in the EU indicate incidence as follows: [1] Asthma: All ages: 428/100 000 PY; 5 to 19 years: 813/100 000 PY; ≥20 years: 297/100 000 PY. Uncontrolled Asthma: All ages: 100/100 000 PY; 5 to 19 years: 190/100 000 PY; ≥20 years: 69/100 000 PY.
Prevalence	Data from the GBD Study 2019 in the European Union indicate prevalence as follows: [1] Asthma: All ages: 5852/100 000 PY; 5 to 19 years: 5746/100 000 PY; ≥20 years: 6043/100 000 PY. Uncontrolled Asthma: All ages: 1364/100 000 PY; 5 to 19 years: 1339/100 000 PY; ≥20 years: 1409/100 000 PY. The prevalence of asthma varies globally, and within Europe. Globally, higher rates (approximately 5.3%) have been observed in high-income English-speaking countries; European examples of such countries include the UK and Ireland. Lower rates (approximately 3.5%) have been observed in countries such as Italy and Greece, in addition to Eastern European countries. [51, 52] The exact prevalence of severe asthma is difficult to ascertain due to varying case definitions for severity, and how it is measured, along with how it is reported. Nonetheless, severe asthma is expected to be present in 2-5% of children with asthma in European countries. [53] In adults, 4-6% of those with asthma are estimated to have severe asthma. [54]

Indication	Asthma in patients 6 years of age and older
Demographics	**Age** The overall prevalence of asthma is slightly higher in children (<18 years) at 9.4% than in adults at 8.2% of the general population in Europe. [55] Figure 2 demonstrates the variation of prevalence according to age. **Figure 2 - Prevalence of asthma in the EU by age. Data from the GBD Study 2019**  Source: Institute for Health Metrics and Evaluation (IHME). Used with permission. All rights reserved. **Gender** In childhood, asthma is more common in boys than girls up until early adolescence. After that, the pattern reverses so that prevalence becomes higher in adult women than in adult men. [51] **Race/Ethnicity** In a meta-analysis of seven UK studies, it was found that prevalence of childhood asthma (5-15 years) ranged from 10.6% (95% CI: 4.6-16.7) in white children, to 15.0% (95% CI:3.5-26.5) in black children, to 7.6% (95% CI: 3.77-11.4) in South Asian children. For both children and adults combined, the risk of admission to hospitals for asthma was larger in South Asian people (OR 2.9, 95% CI: 2.4-3.4) and black people (OR 2.1, 95% CI:1.8-2.5) compared to white people. [56] Asthma hospitalization rates have been found to be higher in Pakistani and Indian populations in Scotland (IRR ranging from IRR 1.34, 95% CI: 1.16-1.54 to IRR1.59, 95% CI: 1.30-1.94), relative to a white Scottish population. In contrast, hospitalization rates for asthma were lower in a Chinese population, relative to a white Scottish population (IRR ranging from 0.49, 95% CI 0.39-0.61 to 0.62, 95% CI: 0.41-0.94). [57] **Risk factors for childhood asthma** Prenatal risk factors: parental asthma [58] and maternal smoking [59] Post-natal risk factors: hospitalization for respiratory syncytial virus in early life, [60] exposure to inhaled and food allergens (eg, house dust mite, pet allergens, cow's milk allergen, cigarette smoke), [61] household mould and dampness [62], traffic related air pollution (particularly nitrous oxide), [63] exposure to tobacco smoke, [64] overweight/obesity. [60] **Risk factors for adult asthma** Obesity; [65] Smoking/secondhand smoke; [66, 67] Occupational risk eg, nursing and cleaning, occupational exposures such as exposure to fire, mixed cleaning products or chemical spills; [68] Rhinitis. [69]

Indication	Asthma in patients 6 years of age and older
Main existing treatment options	Current treatment options are outlined in Global Initiative for Asthma guidelines and include a step-wise approach to utilizing asthma controller therapies as well as as-needed reliever therapy. The controller of choice is inhaled corticosteroids with or without long-acting beta agonists and other options include daily leukotriene receptor antagonists or tiotropium. Reliever therapies including short acting beta-2-agonists, or MART such as ICS-Formoterol. In certain regions, add-on biologic therapy is available for certain patients with asthma, including the anti-IgE therapy, omalizumab, as well as the anti-Il5 therapies, benralizumab or mepolizumab. Oral corticosteroids are used to treat acute respiratory exacerbations, and in rare instances for children are used as maintenance therapy to control disease. Inhaled corticosteroids can improve symptoms and reduce overall risk related to asthma, but have potential side effects related to immune suppression, including oral thrush and activity on the hypothalamic-pituitary-adrenal axis, including reduced linear growth. These same side effects can be seen with the use of OCSs. Given the potential for side effects, the lowest effective dose is recommended.
Natural History of the Disease	The natural history of asthma is variable, and this variability is likely underpinned by a range of genetic influences. [70] The role of environmental risk factors such as viruses, bacteria and allergens in genetically predisposed individuals, is yet to be fully elucidated, but it is known that the gene-environment association does contribute to the development, severity and persistence of asthma. [70] **Children** Most cases of chronic asthma develop in children of preschool age. [71, 72, 73] Wheeze is associated with asthma, however wheeze in young children is common and does not necessarily predict progression to asthma. [74] For most children, wheezing before the age of 3 years resolves itself. [74] A proportion of those children who wheeze before 6 years have persistence of symptoms and will have clinical asthma. [75] This group is characterized by the presence of atopy and severe symptoms at younger ages.[74, 75] Three out of four school-age asthma patients will have outgrown asthma by mid adulthood. [70] **Adults** Asthma can newly occur in adults, however new onset asthma in adulthood may be undiagnosed childhood asthma. Risk factors for adult-onset asthma include: female sex, smoking history, history of allergy and history of impaired lung function. [76] **Type 2 asthma** Asthma can be divided into two distinct molecular phenotypes, based on the level of Th2 inflammation. “Th2 high” asthma is corticosteroid responsive; however, as noted above, some patients do not achieve the goals of asthma management despite administration of corticosteroids with or without additional controller agents. [77] T-helper type 2 asthma is mediated by cytokines, including IL-4, IL-5, and IL-13. Biomarkers for the type 2 phenotype, including measurement of peripheral blood eosinophils or exhaled nitric oxide, are widely available. [78] Consequences of untreated asthma Approximately 20-60% of severe or persistent asthma is uncontrolled. [79, 80, 81] The consequences of uncontrolled asthma or poorly controlled asthma include adverse health events such as increased exacerbations, unscheduled urgent care visits, hospitalization for asthma and sleep disturbances. [80, 82] Daily activities such as attendance at school or work and levels of physical activity are also affected, leading to reduced quality of life. [80, 82] **Mortality** Asthma exacerbations can be fatal. [36] Amongst the total population, respiratory diseases, inclusive of asthma, are the third most common cause of death. The mortality rate for asthma is 1-1.4/100 000 EU inhabitants based on Eurostat 2018 data. [83, 84] Globally, 10.5 million YLL were attributed to asthma related premature death in 2016, which is 26% lower

<table>
<tr><td>Indication</td><td>Asthma in patients 6 years of age and older</td></tr>
<tr><td></td><td>compared to 2006. As such, asthma ranked 23rd in 2016 among leading causes of premature mortality (YLL). 85
Patients with asthma have an increased risk of death in comparison to patients without asthma, ranging from a 10% increased risk to a two-fold increase in risk. 86, 87, 88, 89 The risk of mortality is particularly high after a severe exacerbation. 87 The main causes of death in those with asthma are malignancies, cardiovascular disease and infections. 90</td></tr>
<tr><td>Co-morbidities</td><td>
<table>
<tr><th>Co-morbidities</th><th>Common co-medications in the general population</th><th>Specific treatment notes relating to children/adolescents</th></tr>
<tr><td>Atopic Dermatitis 35</td><td>Refer to Table 6</td><td></td></tr>
<tr><td>Allergic Rhinitis 91, 92, 93</td><td>Intranasal corticosteroids, antihistamines, leukotriene receptor antagonists,
ipratropium bromide (intranasal), cromolyn Sodium (intranasal).
Decongestants: pseudoephidrine, phenylephrine hydrochloride and oxymetazoline 38, 39</td><td>Decongestants are not recommended for children <12 years. 40</td></tr>
<tr><td>Chronic Rhinitis 93</td><td>Nasal or OCSs, Nasal or oral antihistamines, anti-cholinergic (Ipratropium bromide), capsaicin 94, 95</td><td></td></tr>
<tr><td>Nasal Polyposis 91, 96</td><td>Refer to Table 8</td><td></td></tr>
<tr><td>Food Allergy 97</td><td>Epinephrine is administered in severe anaphylaxis due to food allergy. 46</td><td></td></tr>
<tr><td>Eosinophilic Esophagitis 98</td><td>Proton pump inhibitors and topical corticosteroids 99</td><td></td></tr>
<tr><td>Respiratory infections 100</td><td>Pneumococcal vaccine
Antibiotics - penicillins, macrolides, etc</td><td></td></tr>
<tr><td>Anxiety/Depression 101</td><td>Selective serotonin reuptake inhibitors, Dual SNRIs, Tricyclic anti-depressants, Monoamine Oxidase Inhibitors, α2-antagonists, Agomelatine, Tianeptine, anxiolytics (anti-anxiety agents), benzodiazepines, barbiturates, hypnotics. 50</td><td>Fluoxetine in children and adolescents. 48, 49</td></tr>
<tr><td>Cardiovascular disease in adults 96, 102</td><td>Antihypertensives inclusive of ACE-inhibitor/angiotensin receptor blocker, beta-blockers, calcium channel blockers and aldosterone antagonists.
Nitrates, digoxin, anticoagulants, antiplatelets, thrombolytics, lipid lowering drugs. 103, 104, 105</td><td></td></tr>
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Indication	Asthma in patients 6 years of age and older		
	Gastroesophageal reflux disease [96]	Proton pump inhibitors: Omeprazole, lansoprazole, pantoprazole, rabeprazole Histamine-2 blockers: ranitidine, famotidine, nizatidine [106]	
	Obesity [107]	Orlistat, Naltrexone/Bupropion, Liraglutide [108]	Orlistat is not indicated for the treatment of obesity in children. [109] Naltrexone/Bupropion is not indicated in people <18 years. [110] Liraglutide is indicated for obesity in people aged ≥12 years.
	Sleep apnea [111, 112]	Medications are not recommended as the primary treatment for sleep apnea.	
	ACE: Angiotensin Converting Enzyme; OCS: Oral Corticosteroid; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor.		

Notes: Common co-medications in the general population are outlined above. Where special treatment scenarios exist for children outside of those medicines highlighted in the general population column, these are flagged in the "specific treatment notes relating to children/adolescents" column.

ACE: Angiotensin Converting Enzyme; CI: Confidence Interval; EU: European Union; GBD: Global Burden of Disease; ICS: Inhaled Corticosteroid; IHME: Institute for Health Metrics and Evaluation; IgE: Immunoglobulin E; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-13: Interleukin-13; IRR: Incidence Rate Ratio; MART: Maintenance and Reliever Therapy; OCS: Oral Corticosteroid; OR: Odds Ratio; PY: Patient-Years; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; Th2: Type 2 Helper T Cell; UK: United Kingdom: YLL: Year of Life Lost.

The epidemiology of CRSwNP is summarized in the following table.

Table 8 - Epidemiology of chronic rhinosinusitis with nasal polyposis in patients 18 years of age and older

Indication	Chronic rhinosinusitis with nasal polyposis in patients 18 years of age and older
Incidence	Data for the incidence of CRSwNP are scarce. The incidence of CRSwNP is estimated at 83/100 000 person-years, from US data. [113, 114] In a European setting, the incidence of symptomatic nasal polyposis has been estimated at 63/100 000 person-years. [115] Globally, the prevalence of CRSwNP varies from 1-4% of the general population. In European settings, data from France (≥18 years) and Sweden (≥20 years) were consistent in estimating prevalence of nasal polyposis at 2.1% (95% CI: 1.8-2.4) and 2.7% (95% CI: 1.9-3.5) respectively. [116, 117]
Prevalence	In Finland, the prevalence of nasal polyposis was estimated at 4.3% (95% CI: 2.8-5.8) of the population aged 18-65 years. [118] In South Korea, the prevalence of CRSwNP has been ranges from 0.5-2.5% of the general population. [114, 119] In the US, 1.1% of the general population is estimated to have prevalent CRSwNP. [120]
Demographics	Age Chronic rhinosinusitis with nasal polyposis is a disease of middle age, with incident cases typically occurring in those aged ≥45 years. [113] Prevalence increases with age; those aged

Indication	Chronic rhinosinusitis with nasal polyposis in patients 18 years of age and older
	≥65 years have the highest prevalence of CRSwNP compared to other age groups. [114, 116, 117, 121] Gender Chronic rhinosinusitis with nasal polyposis is more common in men than women with 60-70% of cases occurring in men. [115, 117, 121] However, women report more severe CRSwNP than men and report lower quality of life scores than men. [122, 123] Race/ethnicity There are no data on race/ethnicity specifically for CRSwNP. However, data from the National Health Interview Survey in the US demonstrate a lower reported prevalence of CRS among Asian (7%) and Hispanic (8.6%) populations compared to African American (13.3%) and Caucasian populations (13%). [124] There is some evidence to suggest that the extent of eosinophilia in CRSwNP varies by ethnicity. [125] Risk factors Family history; [126, 127] Male gender; [126] Asthma. [126]
Main existing treatment options	The key goal of CRSwNP management includes reduction in nasal polyp size, improvement of symptoms such as nasal congestion/obstruction, sense of smell, and prevention of polyp recurrence. [128, 129, 130, 131,132] Clinical guidelines generally recommend a disease severity-specific treatment course that includes nasal saline irrigation and topical/local nasal steroids for all severity levels, short courses of OCSs for moderate and/or severe disease, and surgery (polypectomy, FESS) if medical management is unsuccessful. [130] Biologics are recommended as treatment options for CRSwNP patients with disease that is refractory to surgery and first line therapies. Three biologics are currently approved for the treatment of CRSwNP: Anti-IL-4Rα (dupilumab), anti-IgE (omalizumab) and anti-IL-5 (mepolizumab). Dupilumab was the first biologic to be indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. [133] Omalizumab is indicated as an add-on therapy with INCS for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INCS does not provide adequate disease control. [46] Mepolizumab is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. [134] Intranasal corticosteroids have demonstrated improvement in symptoms, polyps size, polyps recurrence, and nasal airflow against placebo. However, nasal steroids do not improve the sense of smell, a cardinal symptom of CRSwNP. [135] Their effect, as measured by CT scan, in improving sinus disease is limited. [136] Side effects of topical steroids are generally mild and include epistaxis, dry nose, nasal irritation, headache, and cough. Corticosteroid nasal drops are more effective than sprays because of their enhanced distribution within the sinus cavities but are associated with a higher risk for hypothalamic-pituitary-adrenal axis suppression, limiting long-term use. [136] Systemic corticosteroids are more effective than nasal steroids, and maximal treatment effects with SCS are usually noted after 2 weeks of treatment, but the duration of these effects is short lived. Longer-term or frequent use of corticosteroids for CRSwNP is not recommended due to risk of significant side effects with longer dose and duration of treatment. [129] Adverse events associated with SCS are well documented and most commonly include adrenal suppression and bone loss (ie, osteopenia, osteoporosis). [137] Other more common AEs are gastric upset, glucose intolerance, cataracts, and weight gain. [138] An evidence-based risk analysis of OCS

<table>
<tr><th>Indication</th><th>Chronic rhinosinusitis with nasal polyposis in patients 18 years of age and older</th></tr>
<tr><td></td><td>use in CRSwNP found that a breakeven threshold favored surgery over medical therapy when CRSwNP patients required OCSs more than once every 2 years. [139] Thus, in the ICAR [129] OCSs are recommended only in the short-term management of CRSwNP.
Antibiotics may be useful in treating infectious exacerbations of CRSwNP, but evidence is highly limited. [140]
When intranasal corticosteroids or short courses of SCS or other treatments (eg, antihistamines, topical or systemic antibiotics) fail or are contraindicated, surgical treatment is typically the next step. In patients with both CRSwNP and NSAID-ERD, ESS is the treatment of choice for nasal polyps removal.
Recurrence of nasal polyps following surgery is common. Recurrence rates among patients with severe disease are as high as 60 to 78% and the need for revision surgery is higher in patients with increased eosinophil counts, IL-5 and IgE levels in nasal tissue measured in baseline biopsy specimens. [141, 142, 143] Multiple surgeries are not infrequent in this population. [142] Surgical treatment often has only limited effects on olfactory sensation despite satisfactory resolution of other complaints. Common complications of sinus surgery, such as perioperative bleeding, postoperative infection, and synechiae in the nose, are typically minor. [135, 138] However, life-threatening major complications, including hemorrhage and orbital and intracranial complications, have been reported. Results from a US-based meta-analysis show that major complication rates associated with conventional surgeries are slightly less than those associated with ESS, with the majority being cerebral spinal fluid leaks (0.9% versus 1.3%). [130]</td></tr>
<tr><td>Natural history of disease</td><td>Chronic rhinosinusitis with nasal polyposis, characterized by type II inflammation, manifests as severe and recurrent disease. [144] Various aetiologies have been suggested inclusive of hereditary factors, systemic and local allergy, and infection. [145]
The genetics of CRSwNP are poorly understood, and to date, no genetic mutation has been definitively associated with the disease. Nonetheless, there is evidence to suggest a genetic predisposition given that first degree relatives of people with CRSwNP have four times (HR = 4.1, 95% CI: 1.8-9.4) the risk of developing CRSwNP. [146]
Chronic rhinosinusitis has a marked impact on quality of life in domains such as bodily pain, general health and social functioning. Indeed, CRS has been demonstrated to have a greater impact on social functioning than other chronic diseases such as angina or chronic heart failure. [147] Comorbid depressive illness is associated with poorer HRQL than CRS without depressive illness. [148]
Chronic rhinosinusitis with nasal polyposis is associated with several comorbidities inclusive of allergic rhinitis, asthma, gastroesophageal reflux disease and sleep apnea. [113, 149] The association between CRSwNP and asthma is perhaps the best studied: CRSwNP occurs in 7% of those with asthma (in comparison to 1-4% of the general population), whereas up to 48% of patients with CRSwNP have comorbid asthma. [150, 151] Chronic rhinosinusitis without nasal polyposis with comorbid asthma is associated with more severe sinonasal symptoms and worse quality of life. Similarly, asthma with comorbid CRSwNP tends to be difficult to control and exacerbation prone. [144, 152]
Chronic rhinosinusitis with nasal polyposis has been associated with an increased risk of mortality relative to polyp negative CRS patents (HR = 1.4, 95% CI: 1.1-1.8). [153]</td></tr>
<tr><td>Co-morbidities</td><td>
<table>
<tr><th>Co-morbidities</th><th>Co-medications</th></tr>
<tr><td>Asthma [113, 149]</td><td>Refer to Table 7</td></tr>
<tr><td>Atopic Dermatitis [113]</td><td>Refer to Table 6</td></tr>
<tr><td>Allergic Rhinitis [114]</td><td>Intranasal corticosteroids,
antihistamines, leukotriene receptor antagonists,</td></tr>
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</td></tr>
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Indication	Chronic rhinosinusitis with nasal polyposis in patients 18 years of age and older	
		ipratropium bromide (intranasal), cromolyn Sodium (intranasal). Decongestants: pseudoephidrine, phenylephrine hydrochloride and oxymetazoline [38, 39]
	Aspirin/NSAID-ERD [154]	See nasal polyposis main existing treatment options and common co-medications for asthma
	Chronic Obstructive Pulmonary Disease [155]	Short-acting beta 2 agonists, Long-acting beta 2 agonists, anti-cholinergics (short and long acting), methylxanthines, phosphodiesterase 4 inhibitors, mucolytic agents [156]
	Esophageal Reflux Disease [113, 157]	Proton pump inhibitors: omeprazole, lansoprazole, pantoprazole, rabeprazole Histamine-2 blockers: ranitidine, famotidine, nizatidine [106]
	Respiratory infections (upper and lower) [158]	Pneumococal vaccine Antibiotics - penicillins, macrolides, etc

NSAID-ERD: Nonsteroidal Anti-Inflammatory Drug-Exacerbated Respiratory Disease.

AE: Adverse Event; CI: Confidence Interval; CRS: Chronic Rhinosinusitis; CRSwNP: Chronic Rhinosinusitis without Nasal Polyposis; CT: Computed Tomography; ESS: Endoscopic Sinus Surgery; FESS: Functional Endoscopic Sinus Surgery; HR: Hazard Ratio; HRQL: Health-Related Quality of Life; ICAR: International Consensus Statement on Allergy and Rhinology: Rhinosinusitis; IgE: Immunoglobulin E; IL-4Rα: Interleukin-4 Receptor Alpha; IL-5: Interleukin-5; INCS: Intranasal Corticosteroid; NSAID-ERD: Nonsteroidal Anti-Inflammatory Drug-Exacerbated Respiratory Disease; OCS: Oral Corticosteroid; SCS: Systemic Corticosteroid; US: United States.

The epidemiology of Prurigo Nodularis in adults is summarized in the following table.

Table 9 - Epidemiology of Prurigo Nodularis in adults

Indication	Prurigo Nodularis in adults
Incidence	Data on the incidence of PN are sparse. It has been estimated that the annual incidence of PN is 0.02% in a general population, based on German data. [159]
Prevalence	Globally, the prevalence of PN ranges from 6/100 000 people (Poland) to 72/100 000 people (US) to 111/100 000 people (Germany). [159,160,161]
Demographics	Age The disease occurs in all age groups, however, it rarely occurs in children and is more common in the fifth and sixth decades of life. [159,160, 161, 162, 163, 164] Gender The prevalence of PN is slightly higher in females than in males, with 50-60% of cases occurring in women. [159,160, 161, 162, 163] Ethnicity In the US, African American patients were 3.4 times more likely to have PN than white patients (OR 3.4; 95% CI 2.9-3.9). [165]
Main existing treatment options	There are no FDA approved therapies for the treatment of PN, and EMA approved therapies are limited to a few specific topical corticosteroids. Before starting symptomatic topical and/or systemic therapy, PN patients should undergo a careful diagnostic evaluation, as well as treatment for any underlying disease. It is important to establish an individual therapy regimen for PN patients. It is thus advised to follow a multimodal approach including general strategies to control pruritus, treatment of

Indication	Prurigo Nodularis in adults
	concomitant, potentially pruritogenic diseases and therapy of pruriginous lesions. As PN has inflammatory and neuropathic elements, patients are often treated with more than one therapy to address several aspects of the disease. The IFSI-guideline on chronic prurigo from 2020 by Stander et al recommends the use of emollients as supportive care. [166] The choice of a topical agent should consider the eventual presence of erosions, scratch lesions, superinfection, and crusts, and may include anti-inflammatory and anti-infectious substances. Medium to high-potency TCS and TCI are often used initially. While there is a mechanistic rationale for their use, no rigorous clinical studies confirming their efficacy were identified. While occasionally effective, especially when used under occlusion, long term use of TCS is not recommended because of the risk of irreversible skin atrophy, dyspigmentation, acneiform eruptions, and risks associated with systemic absorption (eg, hypothalamic pituitary axis effects, etc,). To limit the risk of adverse effects, topical corticosteroid preparations can be used only as short-term or intermittent therapy, which in many cases fails to optimally control PN signs and symptoms. For thicker lesions, corticosteroids are also administered intralesionally. Lesional cryotherapy is another available topical treatment; case reports indicate temporary relief. Cryotherapy and intralesional steroid injections, while often effective, are limited to treatment of a few lesions due to procedure-associated pain. Antihistamines and antileukotrienes are occasionally used; their efficacy, however, is not supported by well conducted, randomized clinical trials and is rated low by patients. Phototherapy, in particular narrowband UVB, can be added in patients not responding to topical pharmacotherapy, except in those who are concurrently treated with topical calcineurin inhibitors and substances with photosensitizing effects. Oral immunosuppressants such as methotrexate and cyclosporine have been used off-label with some success as reported in case reports and retrospective data collection. [167] Use of cyclosporine in PN is limited by commonly recognized toxicities including hypertension, impaired renal and hepatic function, and potential for increased susceptibility to infections and cancer, particularly skin cancer, due to decreased cancer immunosurveillance. Methotrexate has well established toxicities, in particular, myelosuppression and hepatotoxicity. In addition, the broad immunosuppression caused by all these drugs carries an increased risk of developing serious bacterial, fungal, viral, and mycobacterial infections. The IFSI-guideline recommend that the dosage of the immunosuppressants should be tapered off as soon as possible upon healing of lesions. Further studies to evaluate the efficacy and safety of methotrexate and cyclosporine in PN are needed. Healthcare providers are advised to always consider contraindications, and monitor AEs and lab values. Neuromodulatory agents such as gabapentin and anti-inflammatory agents such as thalidomide have been used in PN with varying degrees of success, but have also considerable adverse effects. Gabapentin and pregabalin are recommended in the IFSI guideline for treatment of PN. Thalidomide is only recommended in very exceptional cases of PN that are refractory to safer therapies, and used by physicians who have experience with the drug. Adverse effects of thalidomide include peripheral neuropathies, sedation, dizziness and teratogenicity, while adverse effects of gabapentin and pregabalin include headache, sedation and dizziness. Opioid modulators, neurokinin 1 receptor antagonists, antidepressants, topical capsaicin and psychosomatic therapy are also being used in treating PN. A step-wise approach to treatment of PN is generally recommended starting with topical therapies and escalating to systemic therapies when topicals are inadequate or inadvisable. Overall, despite the use of multiple treatments, many patients with PN remain uncontrolled, and some of the available therapies are associated with potential serious adverse reactions. Importantly, all systemic treatments used are off-label. Given the lack

<table>
<tr><th>Indication</th><th>Prurigo Nodularis in adults</th></tr>
<tr><td></td><td>of targeted treatments and the suboptimal efficacy associated with currently available therapies, there remains a significant unmet need in patients with PN.</td></tr>
<tr><td>Natural history of disease</td><td>The pathogenesis of PN remains unclear, although is thought to involve both immune and neural dysregulation. 168
Prurigo Nodularis lesions can start in areas of normal or dry skin, although atopic dermatitis may be present and may be an initiating factor also. Due to pruritus, continual scratching will cause dome shaped lesions to occur. Prurigo Nodularis can occur sporadically, or continuously, and can increase with clothing irritation or sweat. Lesions that are repeatedly scratched can become excoriated and are at risk of secondary infection. The condition is associated with physical and psychological morbidity and is difficult to treat. 169
Prurigo Nodularis is associated with several comorbidities inclusive of mental health, dermatological, endocrine, cardiovascular and renal disorders, in addition to HIV and malignancy. Chronic itch experienced in some of these conditions, eg, AD, Hodgkin's lymphoma and end stage renal disease, can further exacerbate the itch-scratch cycle. 161, 162 Patients with PN have a reduced quality of life in comparison to healthy controls stemming from: itch, sleep disturbance, visibility of skin lesions, bleeding, impact on everyday activities, psychological consequences, and pain. 161, 162, 163, 170</td></tr>
<tr><td>Co-morbidities</td><td>
<table>
<tr><th>Co-morbidities</th><th>Co-medications</th></tr>
<tr><td>Dermatologic/allergic</td><td></td></tr>
<tr><td>Atopic Dermatitis</td><td>Refer to Table 6</td></tr>
<tr><td>Psoriasis 161</td><td>Topical - TCSs, emollients, calcipotriene/calcitriol, coal tar, tazarotene, tacrolimus/pimeocrolimus, UV-B phototherapy.
Systemic - Methotrexate, cyclosporin, adalimumab, etanercept, infliximab, apremilast, brodalumab, certolizumab pegol, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab. 171</td></tr>
<tr><td>Asthma 161</td><td>Refer to Table 7</td></tr>
<tr><td>Mental Health</td><td></td></tr>
<tr><td>Depression, Anxiety 161, 162, 172</td><td>Selective serotonin reuptake inhibitors, Dual SNRIs, Tricyclic anti-depressants, Irreversible non-selective monoamine oxidase inhibitors, α2 antagonists, Agomelatine, Tianeptine.
anxiolytics (anti-anxiety agents), benzodiazepines, barbiturates, hypnotics. 50, 173</td></tr>
<tr><td>Infections</td><td></td></tr>
<tr><td>HIV 162</td><td>Nucleos(t)ide reverse transcriptase inhibitors - Lamivudine, Abacavir, Tenofovir, Emtricitabine, Zidovudine; Non-nucleos(t)ide reverse transcriptase inhibitors - doravirine, rilpivirine, efavirenz, etravirine, nevirapine;
Integrase strand transfer inhibitors - olutegravir, raltegravir, elvitegravir, bictagravir; Protease inhibitors - atazanavir, darunavir, lopinavir; Protease inhibitor boosting agents: ritonavir, cobicistat;
Fusion Inhibitor - enfuvirtide;</td></tr>
</table>
</td></tr>
</table>

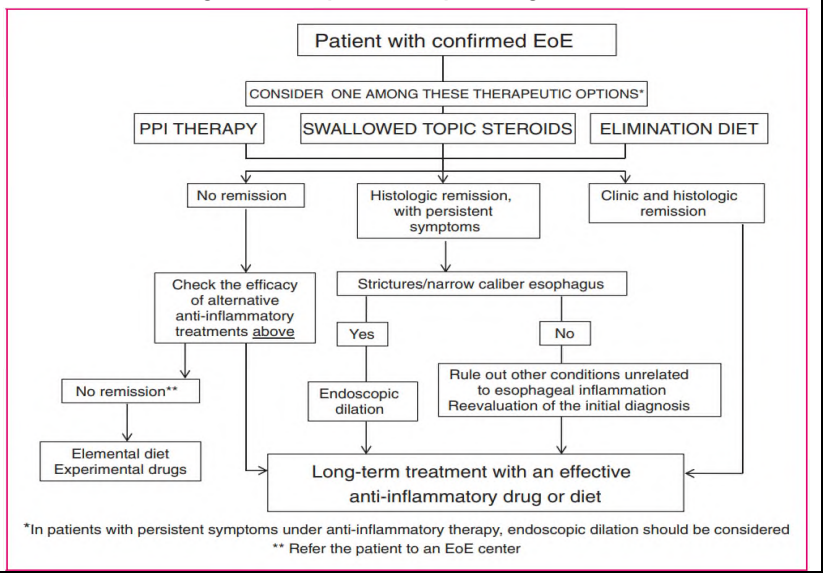
Indication	Prurigo Nodularis in adults	
		C-C chemokine receptor type 5inhibitor - maraviroc; CD4 directed post attachment. HIV1 inhibitor - Ibalizumab. [174]
	Autoimmune	
	Celiac disease [161]	Gluten avoidance.
	Inflammatory Bowel Disease (Crohn's disease, Ulcerative Colitis) [161, 165]	Ulcerative Colitis - 5-acetyl salicylic acid, oral prednisolone, topically acting oral budesonide methotrexate, and beclomethasone dipropionate, mesalazine, thiopurine, vedolizumab, tofacitinib, infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, ustekinumab, methotrexate, ciclosporin. Crohn's disease - Ileal release budesonide, oral prednisolone, anti-TNF therapy, methotrexate, mesalazine, vedolizumab, ustekinumab, azathioprine or mercaptopurine, adalimumab, proton pump inhibitors.
	Diabetes Mellitus Type I [162]	Insulin
	Endocrine	
	Diabetes Mellitus Type II [162]	Metformin, SUs, α-glucosidase inhibitors, thia-zolidinediones, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon-like peptide-1 receptor agonists and insulin. [175]
	Other systemic illnesses	
	Chronic Kidney disease[162]	Anti-hypertensives - ACE inhibitor or angiotensin II receptor blocker. [176]
	Heart Failure [159,161,165]	Angiotensin converting enzyme inhibitor, angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonists, dapagliflozin, empagliflozin, sacubitril, valsartan. [177]
	Cardiovascular/cerebrovascular disease [161, 165]	Anti-hypertensives, lipid lowering drugs (statins, ezetimibe), anti-platelet agents
	Chronic Obstructive Pulmonary Disease [159, 161, 165]	Short-acting beta 2-agonists, long-acting beta 2-agonists, anti-cholinergics (short and long-acting), theophylline, inhaled/oral steroids, phosphodiesterase-4 inhibitors, mucolytic agents [156]

ACE: Angiotensin Converting Enzyme; CD: Clusters of Differentiation; HIV: Human Immunodeficiency Virus; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; SU: Sulfonyl Urea; TCS: Topical Corticosteroid; TNF: Tumor Necrosis Factor; UV-B: Ultraviolet B.

ACE: Angiotensin Converting Enzyme; AD: Atopic Dermatitis; AE: Adverse Event; CD: Clusters of Differentiation; CI: Confidence Interval; EMA: European Medicines Agency; FDA: Food and Drug Administration; HIV: Human Immunodeficiency Virus; ICS: Inhaled Corticosteroid; IFSI: International Forum for the Study of Itch; IL-13: Interleukin-13; OR: Odds Ratio; PN: Prurigo Nodularis; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; SU: Sulfonyl Urea; TCI: Topical Calcineurin Inhibitor; TCS: Topical Corticosteroid; TNF: Tumor Necrosis Factor; US: United States; UV-B: Ultraviolet B.

The epidemiology of EoE in adults and adolescents 12 years and older is summarized in the following table.

Table 10 - Epidemiology of Eosinophilic Esophagitis in adults and adolescents 12 years and older

Indication	Eosinophilic Esophagitis in adults and adolescents 12 years and older
Incidence	Globally, the incidence of EoE in adults ranges from 7.2-8.5/100 000 person-years. Globally the incidence of EoE in children is reported to be 6.6/100 000 person-years. There is no variation in incidence between the US and Europe. [178, 179]
Prevalence	Globally, the prevalence of EoE in adults is 42.4/100 000 people. Some geographical variation has been reported for the prevalence of EoE in adults, however it is likely that this is due to differences in epidemiological methods versus a true difference. Globally the prevalence of EoE in children (<16 years) is reported to be 53.4/100 000 people. There is no variation in prevalence of EoE in children between the US and Europe. [178, 179]
Demographics	**Age** Eosinophilic Esophagitis can occur throughout the lifespan, however most cases occur in children, in adolescents and in adults <50 years. [179] **Gender** Males are up to 3.5 times more likely to have EoE than females (range OR 2.22 95% CI 2-2.46 to OR 3.49, 95% CI 2.52-4.83). [178, 180, 181] **Ethnicity** Eosinophilic Esophagitis is approximately two times (range OR 1.90, 95% CI 1.26-2.85 to range OR: 2.00 95% CI: 1.86-2.14) more likely to be reported in a Caucasian population relative to other ethnicities eg, African-Americans or Asian. [181, 182]
Main existing treatment options	Below is an overview of consensus guidelines from the United European Gastroenterology, The European Society of Pediatric Gastroenterology, Hepatology and Nutrition, the EAACI, and the European Society of Eosinophilic Oesophagitis [99]; guidance from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters. [182] Additional JORVEZA® (budesonide orodispersible tablet) clinical data is also included. [179] The example below is the proposed therapeutic algorithm from the United European Gastroenterology. [99] **Figure 3 - Proposed therapeutic algorithm** [99] 

Indication	Eosinophilic Esophagitis in adults and adolescents 12 years and older
	Proton Pump Inhibitors: • A meta-analysis showed PPI therapy induces histological remission (defined by <15 eos/hpf) in up to 50% and symptomatic improvement in 60.8% of cases. [99, 183] • Up to 80% of patients maintained histological remission for 1 year while on PPIs in clinical trials. [99] • The recommended PPIs doses in adults are omeprazole 20-40 mg twice daily or equivalent; in children, 1-2 mg/kg or equivalent. [99] Topical corticosteroids: In the EU, JORVEZA (budesonide orodispersible tablet) is the only swallowed topical steroid formulation approved for use in patients with EoE aged 18 years and older: • JORVEZA 1 mg BID was studied in patients with active EoE and was able to induce clinic-pathological remission (defined as both peak of <16 eosinophils/mm^2 high power field in esophageal biopsies and no or only minimal symptoms of dysphagia or pain during swallowing) in significantly more patients than placebo (57.6% versus 0% at week 6). • JORVEZA was studied in patients with EoE in clinic-pathological remission. Significantly more patients in the budesonide groups (0.5 mg BID = 73.5%; 1 mg BID = 75.0%) were free of treatment failure compared to placebo (4.4%) at week 48. • Fungal infections in the mouth, pharynx and esophagus were the most frequently observed adverse reactions in JORVEZA clinical studies (total number of infections at 26.9%). Diet Adaptation: Elemental diet: • There is a limited place for elemental diet in EoE. Elemental diet induces histologic remission in up to 90% EoE patients. There is limited information regarding symptom relief. [99] • Potential harms include interference with development of oral motor skills in children, social isolation, the need for a gastrostomy tube, costs of elemental formula, burden of repeated endoscopies during food re-introduction [183], and lack of adherence in adult patients. [99] Elimination Diet: • Six food, four food, and two food empiric group elimination diets induce histologic remission (approximately 75%, approximately 50%, approximately 40% respectively). [99] Dilation: [178] • Esophageal dilation is a mechanical widening of the esophagus which typically needs to be repeated to maintain remission of symptoms • A systematic review reported symptom improvement in 87% of patients who underwent esophageal dilation. [183, 185] • There is no associated histologic improvement in eosinophilia with dilation. • The most commonly reported AE was chest discomfort or pain. • Post dilation, the pooled rate of perforation was 0.4%, hospitalization - 1.2%, and significant gastrointestinal hemorrhage - 0.1%
Natural history of disease	Eosinophilic Esophagitis is a chronic, progressive disease that is thought to start in childhood, and can go undetected until adulthood. [180] Family history studies along with a predominance of EoE amongst males indicate the influence of genetic-environment interactions in the development of EoE. [186] Early life environmental risk factors include exposure to antibiotics, cesarean section and pre-term delivery. [181, 182] EoE is thought to be mediated by Th2, induced primarily by food allergens. [183, 184] Both IL-5 and IL-13

<table>
<tr><th>Indication</th><th>Eosinophilic Esophagitis in adults and adolescents 12 years and older</th></tr>
<tr><td></td><td>have been suggested to be involved. [184] For example, IL-5 null mice do not develop EoE in allergen-induced models to the same extent that wild-type mice do. [187] In biopsy specimens from patients with EoE, IL-13 has been found to be overexpressed. [188]
Eosinophilic Esophagitis does not typically resolve. The disease progresses with age and may develop fibrostenotic features. [175, 179] This explains the differences in clinical presentations between children and adults. [175] For example, children may experience difficulty feeding, vomiting and failure to thrive, whereas adult symptoms include dysphagia, heartburn, food impaction and upper abdominal pain that will continue without treatment or recur on discontinuation of treatment. [179, 189]
Patients with EoE report reduced health related quality of life scores, especially in severe disease. Specifically, this stems from concerns about eating, dysphagia, impact on social relationships and concerns about effective treatments. [190] Patients with EoE do not appear to have an increased risk of mortality in comparison with their siblings and the general population. [191]</td></tr>
<tr><td>Co-morbidities</td><td>
<table>
<tr><th>Co-morbidities</th><th>Co-medications</th></tr>
<tr><td>Food Allergy [192]</td><td>Epinephrine for anaphylaxis</td></tr>
<tr><td>Food-pollen allergy [193, 194]</td><td>Epinephrine for anaphylaxis</td></tr>
<tr><td>Atopic Dermatitis [98]</td><td>Refer to Table 6</td></tr>
<tr><td>Asthma [98]</td><td>Refer to Table 7</td></tr>
<tr><td>Allergic Rhinitis (Hay Fever) [98]</td><td>Treatment for ≥12 years of age:
Intranasal corticosteroids: fluticasone, budesonide, beclomethasone dipropionate, mometasone.
Antihistamine: oral fexofenadine, loratadine, desloratadine, levocetirizine, cetirizine; intranasal-azelastine, olopatadine, levocabastine
Leukotriene Receptor Antagonists: Montelukast, Zafirlukast and Pranlukast
Bronchodilators: Ipratropium bromide (intranasal)
Cromones: Cromolyn Sodium (intranasal)
Decongestants: Pseudoephidrine, phenylephrine hydrochloride and oxymetazoline. [38, 39, 223, 224]</td></tr>
</table>
</td></tr>
</table>

AE: Adverse Event; BID: Twice a Day; CI: Confidence Interval; EAACI: European Academy of Allergy and Clinical Immunology; EoE: Eosinophilic Esophagitis; EU: European Union; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-13: Interleukin-13; OR: Odds Ratio; PPI: Proton Pump Inhibitor; Th2: Type 2 Helper T Cell; US: United States.

The epidemiology of COPD is summarized in the following table.

Table 11 - Epidemiology of Chronic Obstructive Pulmonary Disease in adults

<table>
<tr><th>Indication</th><th>Chronic Obstructive Pulmonary Disease in adults</th></tr>
<tr><td>Incidence</td><td>Data from the GBD Study 2019 indicate the incidence of COPD in the European region to be 305 per 100 000 person-years, 95% UI: 290.8 to 318.5.
Geographical variation in incidence is provided in Table 11a.
Table 11a - Global COPD incidence (per 100 000 person years) from the GBD study, 2019[a]
<table>
<tr><th>Location</th><th>Incidence</th><th>95%UI</th></tr>
<tr><td>Global</td><td>209.6</td><td>196.8 to 222.6</td></tr>
</table>
</td></tr>
</table>

Indication	Chronic Obstructive Pulmonary Disease in adults

United States	403.2	381.0 to 422.5
Asia	219.0	203.8 to 234.8
European Region	305.0	290.8 to 318.5

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COPD: Chronic Obstructive Pulmonary Disease; GBD: Global Burden of Disease; IHME: Institute for Health Metrics and Evaluation; UI: Uncertainty Interval.

Prevalence

Data from the GBD Study 2019 indicate the prevalence of COPD in the European region to be 4434 per 100 000, 95% UI: 4239 to 4646.

Geographical variation in prevalence is provided in Table 11b, using data also from the GBD study 2019.

Table 11b - Global COPD prevalence (per 100 000) from the GBD study, 2019[a]

Location	Prevalence	95% UI
Global	2744.3	2590.3 to 2909.2
United States	6143.1	5867.1 to 6382.5
Asia	2657.0	2482.3 to 2838.8
European Region	4434.1	4238.8 to 4645.6

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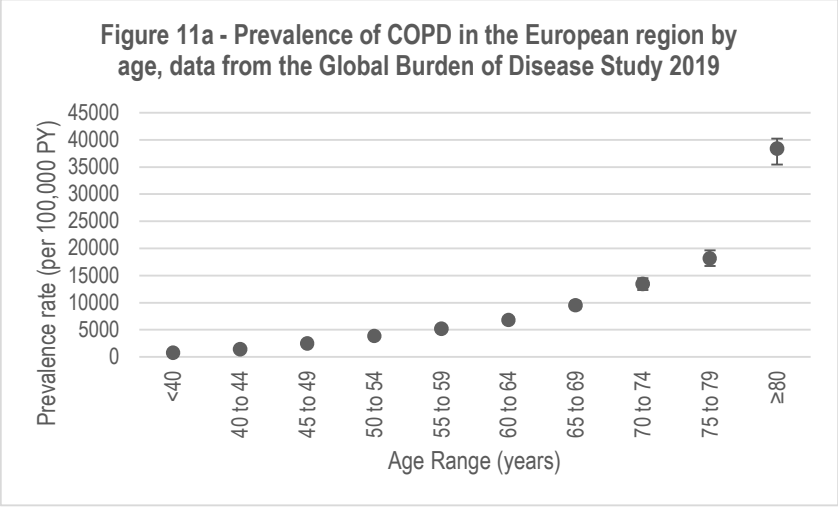
COPD: Chronic Obstructive Pulmonary Disease; GBD: Global Burden of Disease; IHME: Institute for Health Metrics and Evaluation; UI: Uncertainty Interval.

Demographics

Age

Chronic Obstructive Pulmonary Disease is most commonly diagnosed after age ≥45 years. [195] Prevalence increases with increasing age, as shown in Figure 11a which uses European prevalence data by age from the GBD study 2019.

Figure 11a - Prevalence of COPD in the European region by age, data from the Global Burden of Disease Study 2019

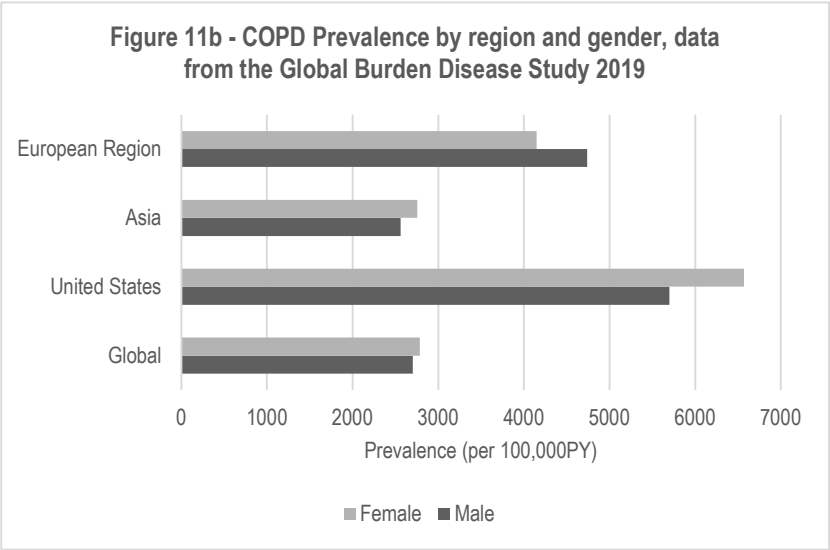


Source: Institute for Health Metrics and Evaluation (IHME). Used with permission. All rights reserved.

Gender

In the European region, the prevalence of COPD is higher in males (4737 per 100 000) than in females (4147 per 100 000).

Of note, the trend is reversed in the US with higher prevalence of COPD in females (6572 per 100 000) than in males (5700 per 100 000) [Figure 11b].

Indication	Chronic Obstructive Pulmonary Disease in adults
	Figure 11b - COPD Prevalence by region and gender, data from the Global Burden Disease Study 2019  Source: Institute for Health Metrics and Evaluation (IHME). Used with permission. All rights reserved. **Race/Ethnicity** In a cross-sectional study of 358 614 patients across 47 practices in London, it was found that Black individuals had less than half the odds (adjusted OR: 0.44; CI: 0.39-0.51) of being diagnosed with COPD compared to white individuals after considering age, sex, smoking, social deprivation, and practice clustering. *196* Data from the US demonstrate that this could be due to underdiagnosis as opposed to a genetic difference. In a cohort of patients with respiratory evidence of COPD, Black patients had a higher odd of undiagnosed COPD versus non-hispanic White patients, with odds ratios of underdiagnosis ranging from OR 1.5 to 3.75 depending on increasing levels of airway obstruction. *197*
Main existing treatment options	The GOLD [Report] is updated every year and serves as the strategy document for the diagnosis, management, and prevention of COPD. The information below is from 2023 strategic document. In the 2023 GOLD Report, initial pharmacological treatment is based on the number and severity of exacerbations as well as symptoms scores. Treatment is then revisited for symptoms and exacerbations, and patients are assessed for correct inhaler technique and adherence as well as non-pharmacological approaches such as pulmonary rehabilitation, oxygen use and vaccination. The GOLD strategy document details recommendations on what should be done if a patient experiences dyspnea and exacerbations on current therapy, which should be guided by eosinophils. The majority of medications for COPD are inhalers that work locally in the lung. The treatment algorithm is below and recommends starting with a LABA or LAMA initially for Group A based on severity and using dual bronchodilator therapy with LABA + LAMA based on Group B and Group D. Therapy is added based on control of exacerbations and symptoms, as well as eosinophil levels. Inhaled corticosteroids (ICS) have shown to have the greatest likelihood of treatment benefit in patients with eosinophils >300 cells/uL. ICS should not be used in patients with eosinophils <100 cells/uL. There are oral medications (ie, roflumilast and azithromycin) also approved that work systemically that are added to triple inhaler therapy regimen. Roflumilast is a PDE4 inhibitor that has many adverse effects such as gastrointestinal and psychiatric symptoms (ie, anxiety, depression, insomnia, suicidal thoughts). Azithromycin is an antibiotic that is recommended in former smokers who require additional therapy beyond triple therapy (LABA + LAMA + ICS). Adverse events associated with azithromycin include tinnitus, hearing loss, gastrointestinal symptoms and antibacterial resistance. *198, 199, 200* Biologics for COPD are being studied as an add on to triple inhaler therapy (LABA + LAMA + ICS). To date, there are no approved biologics for the treatment of COPD. Oral corticosteroids are

Indication	Chronic Obstructive Pulmonary Disease in adults
	recommended in COPD for short-term use to treat acute respiratory exacerbations, as longer courses of oral corticosteroids have shown to increase risk of pneumonia and are associated with increased mortality.

Figure 11c – Initial Pharmacological Treatment

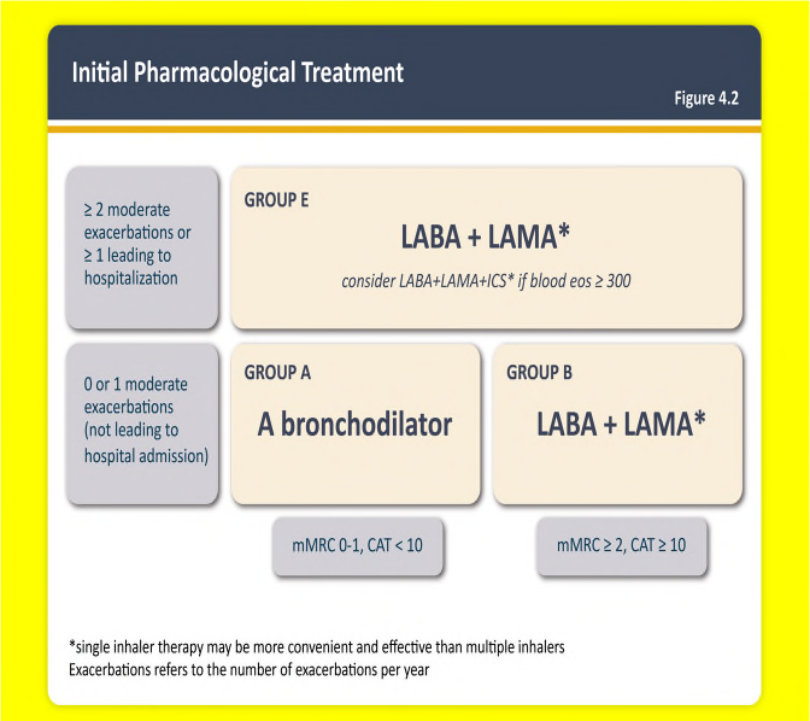
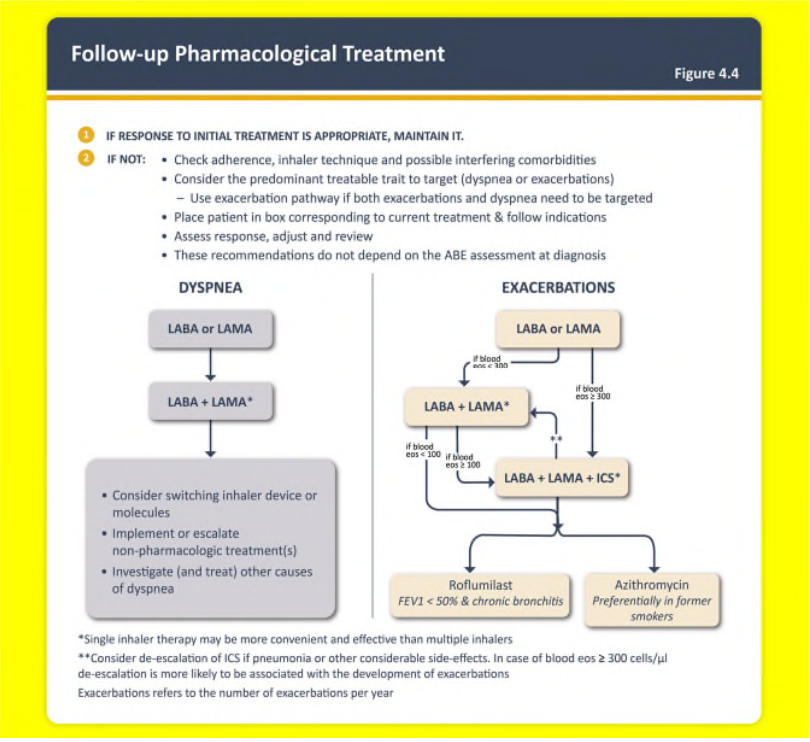
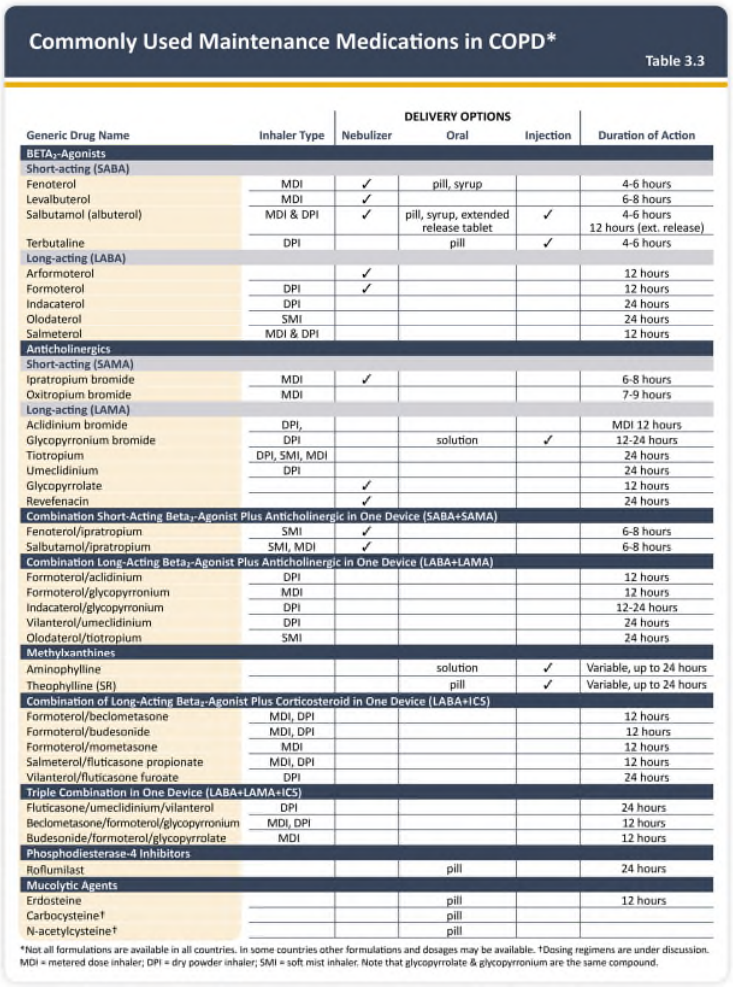


Figure 11d – Follow-up Pharmacological Treatment



Indication	Chronic Obstructive Pulmonary Disease in adults
	Figure 11e – Commonly Used Maintenance Medications in COPD 
Natural History of the disease	The 2023 GOLD Report defines COPD as "a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction." [201] The most common risk factors for development of COPD are tobacco smoking, increasing age, exposure to air pollutants including the domestic use of biomass fuels, occupational exposure and also general environmental pollution, familial history, asthma, and childhood respiratory infections. [202] Tobacco smoking is considered the most important risk factor for development of COPD, with approximately 15-45% of all smokers going on to develop the disease. [202,203] All smokers have some inflammation in their lungs, however those with COPD have an enhanced response to inhalation of cigarette smoke. [204] This amplified response may result in mucous hypersecretion (chronic bronchitis), tissue destruction (emphysema), and disruption of normal repair and defense mechanisms causing small airway inflammation and fibrosis (bronchiolitis). [204] The inflammatory response is mediated by macrophages, neutrophils and T-lymphocytes. Exacerbations can be characterized by the presence of increasing numbers of eosinophils. [204] There is evidence to support the involvement of both Th1 and Th2 pathways in the development of COPD, and consequently the following cytokines and chemokines may be involved in the pathology of

Commonly Used Maintenance Medications in COPD*

Table 3.3

Generic Drug Name	Inhaler Type	DELIVERY OPTIONS: Nebulizer	Oral	Injection	Duration of Action
BETA$_2$-Agonists					
Short-acting (SABA)					
Fenoterol	MDI	✓	pill, syrup		4-6 hours
Levalbuterol	MDI	✓			6-8 hours
Salbutamol (albuterol)	MDI & DPI	✓	pill, syrup, extended release tablet	✓	4-6 hours 12 hours (ext. release)
Terbutaline	DPI		pill	✓	4-6 hours
Long-acting (LABA)					
Arformoterol		✓			12 hours
Formoterol	DPI	✓			12 hours
Indacaterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
Anticholinergics					
Short-acting (SAMA)					
Ipratropium bromide	MDI	✓			6-8 hours
Oxitropium bromide	MDI				7-9 hours
Long-acting (LAMA)					
Aclidinium bromide	DPI,				MDI 12 hours
Glycopyrronium bromide	DPI		solution	✓	12-24 hours
Tiotropium	DPI, SMI, MDI				24 hours
Umeclidinium	DPI				24 hours
Glycopyrrolate		✓			12 hours
Revefenacin		✓			24 hours
Combination Short-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (SABA+SAMA)					
Fenoterol/ipratropium	SMI	✓			6-8 hours
Salbutamol/ipratropium	SMI, MDI	✓			6-8 hours
Combination Long-Acting Beta$_2$-Agonist Plus Anticholinergic in One Device (LABA+LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/glycopyrronium	MDI				12 hours
Indacaterol/glycopyrronium	DPI				12-24 hours
Vilanterol/umeclidinium	DPI				24 hours
Olodaterol/tiotropium	SMI				24 hours
Methylxanthines					
Aminophylline			solution	✓	Variable, up to 24 hours
Theophylline (SR)			pill	✓	Variable, up to 24 hours
Combination of Long-Acting Beta$_2$-Agonist Plus Corticosteroid in One Device (LABA+ICS)					
Formoterol/beclometasone	MDI, DPI				12 hours
Formoterol/budesonide	MDI, DPI				12 hours
Formoterol/mometasone	MDI				12 hours
Salmeterol/fluticasone propionate	MDI, DPI				12 hours
Vilanterol/fluticasone furoate	DPI				24 hours
Triple Combination in One Device (LABA+LAMA+ICS)					
Fluticasone/umeclidinium/vilanterol	DPI				24 hours
Beclometasone/formoterol/glycopyrronium	MDI, DPI				12 hours
Budesonide/formoterol/glycopyrrolate	MDI				12 hours
Phosphodiesterase-4 Inhibitors					
Roflumilast			pill		24 hours
Mucolytic Agents					
Erdosteine			pill		12 hours
Carbocysteine†			pill		
N-acetylcysteine†			pill		

*Not all formulations are available in all countries. In some countries other formulations and dosages may be available. †Dosing regimens are under discussion.
MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = soft mist inhaler. Note that glycopyrrolate & glycopyrronium are the same compound.

<table>
<tr><th>Indication</th><th>Chronic Obstructive Pulmonary Disease in adults</th></tr>
<tr><td></td><td>COPD: TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8 (CXCL8), IL-13, IL-17, IL-18, IL-23, IL-33, and thymic stromal lymphopoietin, as well as growth factors such as transforming growth factor-β. [205]

Recent clinical trial evidence supports the involvement of IL-4 and IL-13 in the Th2 pathway. [206] IL-4 and IL-13 increase FeNO levels and promote eosinophil and Th2 inflammatory cell infiltrates into the lung. These infiltrates are believed to be involved in pathologic processes in COPD, including airway hyperreactivity, impairment of epithelial barrier function, fibrosis, and airway remodeling; lung-function decline; goblet-cell hyperplasia; mucociliary dysfunction; and mucus hypersecretion. [201, 207, 208]

Survival and Mortality

The overall 5-year survival for COPD patients is between 46% and 89% depending on severity of the disease. [209] In 2020, the WHO stated that COPD is the third leading cause of death worldwide. [210] For men in the European region, the mortality rate from COPD is 14/100 000, while it is 6.4/100 000 for women. [211]</td></tr>
<tr><td>Comorbidities/Comedications</td><td>Table 11c - Comorbidities of COPD in the general population, and associated medications
<table>
<tr><th>Comorbidities</th><th>Common co-medications in the general population</th></tr>
<tr><td>Hypertension (high blood pressure) [212]</td><td>Antihypertensive medications: ACE inhibitors, angiotensin receptor blocker, beta-blockers, calcium channel blockers, or diuretics [213]</td></tr>
<tr><td>Asthma [212]</td><td>Refer to Table 7</td></tr>
<tr><td>Coronary artery disease [212]</td><td>Short and long-acting nitrates, calcium channel blockers, beta-blockers, anti-platelet agents, anti-coagulant agents, cardiovascular diseases reduction as appropriate eg, ACE-inhibitor/angiotensin receptor blocker, lipid lowering therapy, [214]</td></tr>
<tr><td>Chronic heart failure [212]</td><td>Angiotensin converting enzyme inhibitor, angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonists, dapagliflozin, empagliflozin, sacubitril, valsartan. [177]</td></tr>
<tr><td>Arrhythmia [212] or atrial fibrillation</td><td>Anti-arrhythmic drugs eg, flecainide or amiodarone, beta-blockers, calcium channel blockers [215]
Vitamin K antagonists: warfarin
Non-vitamin K antagonists: eg, abixaban, dabigatran, edoxaban, rivaroxaban
Anti-platelet agent: aspirin [216]
Treatment of other cardiovascular risk factors eg, hypertension, diabetes as appropriate [216]</td></tr>
<tr><td>Peripheral arterial disease [212]</td><td>Anti-thrombotic therapy, lipid lowering therapy, anti-hypertensive therapy [217]</td></tr>
<tr><td>GERD [212]</td><td>Proton pump inhibitors
H2-receptor antagonists [218]</td></tr>
<tr><td>Osteoporosis or osteoarthritis [212]</td><td>Calcium/Vitamin d supplements, bisphosphonates, denosumab, hormone replacement therapy, raloxifene and strontium ranelate teriparatide, romosozumab [219]
Oral/topical NSAID, opioids, duloxetine, glucosamine/chondroitin, tramadol, acetaminophen/paracetamol, vitamin D, intra-articular corticosteroid [220]</td></tr>
<tr><td>Depression/anxiety [212]</td><td>Selective serotonin reuptake inhibitors, Dual SNRIs, Tricyclic anti-depressants, Irreversible non-selective monoamine oxidase inhibitors, α2 antagonists, Agomelatine, Tianeptine.</td></tr>
</table></td></tr>
</table>

Indication	Chronic Obstructive Pulmonary Disease in adults	
		anxiolytics (anti-anxiety agents), benzodiazepines, barbiturates, hypnotics. [50, 173]
	Diabetes [212]	Insulin
	Hyperlipidemia	Statins, ezetimibe, fibrates, nicotinic acid, PCSK9 inhibitors, n-3 fatty acids [221]
	Chronic Kidney Disease [212]	Anti-hypertensives - ACE inhibitor or Angiotensin II receptor blocker [176]
	Obesity [212]	Orlistat, Naltrexone/Bupropion, Liraglutide [108]

ACE: Angiotensin Converting Enzyme; COPD: Chronic Obstructive Pulmonary Disease; GERD: Gastroesophageal Reflux Disease; NSAID: Non-Steroidal Anti-Inflammatory Drug; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors.

ACE: Angiotensin Converting Enzyme; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CXCL8: C-X-C Motif Chemokine Ligand 8; FeNO: Fraction of Exhaled Nitric Oxide; GBD: Global Burden of Disease; GERD: Gastroesophageal Reflux Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled Corticosteroids; IHME: Institute for Health Metrics and Evaluation; IL-1β: Interleukin-1 Beta; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-13: Interleukin-13; IL-17: Interleukin-17; IL-18: Interleukin-18; IL-23: Interleukin-23; IL-33: Interleukin-33; LABA: Long-Acting Beta-Agonist; LAMA: Long Acting Muscarinic Antagonist; NSAID: Non-Steroidal Anti-Inflammatory Drug; OR: Odds Ratio; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; PDE4: Phosphodiesterase-4; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors; Th1: Type 1 Helper T Cell; Th2: Type 2 Helper T Cell; TNF: Tumor Necrosis Factor; UI: Uncertainty Interval; US: United States; WHO: World Health Organization.

RISK MANAGEMENT PLAN – PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key non-clinical findings

This section presents a summary of non-clinical safety data for dupilumab. Because dupilumab does not bind to mouse IL-4Rα and has very low affinity for monkey IL-4Rα, the non-clinical testing strategy included the development and use of surrogate antibodies, mouse surrogate monoclonal antibody (REGN1103) and monkey surrogate monoclonal antibody (REGN646), against mouse and cynomolgus monkey IL-4Rα, respectively. The results of these studies provided data to guide the administration of dupilumab in initial clinical studies. The non-clinical safety profile of dupilumab, was evaluated in the following in vivo and ex vivo studies using surrogate antibodies REGN1103 and REGN646:

- Exploratory repeat-dose general toxicology study with REGN1103 up to 5-weeks duration using the SC route in adult CD-1 mice;
- Repeat-dose general toxicology studies with REGN646 up to 6-months duration using the intravenous (IV) or SC route in cynomolgus monkeys;
- A combined male/female fertility study with REGN1103 using the SC route in adult CD-1 mice;
- An enhanced pre-/post-natal development (ePPND) toxicology study with REGN646 in cynomolgus monkeys using the SC route;
- An in vitro tissue cross-reactivity study in human and cynomolgus monkey tissues with biotinylated dupilumab and REGN646.

REGN646- and REGN1103-related findings are described below and in Table 12.

The doses administered in the toxicology studies with surrogate antibodies provided substantially higher observed minimum concentration in serum after a dose during a dosing interval (C_{trough}) levels in vivo, relative to the concentration of drug that inhibits viral replication by 90% (IC_{90}) values determined using ex vivo in cell-based assays, confirming target saturation.

REGN1103 was well tolerated in a repeat-dose general toxicology study in mice at 200 mg/kg/week, the highest dose evaluated. REGN646 was well tolerated in repeat-dose general toxicology studies in cynomolgus monkeys following either IV administration of 100 mg/kg/week for 5 weeks and 25 mg/kg/week for 26 weeks or SC administration of 100 mg/kg/week up to 26 weeks in duration. The highest doses administered in the mouse and monkey studies, 200 mg/kg/week SC and 100 mg/kg/week SC, respectively, were the no-observed-adverse-effect levels (NOAEL).

Safety pharmacology endpoints for the central nervous system (CNS), cardiovascular system, or respiratory system were evaluated as part of the toxicology studies conducted in cynomolgus monkeys in which REGN646 was administered at doses of 25 mg/kg/week IV or up to 100 mg/kg/week SC for 26 weeks. No REGN646-related effects were observed in these organ systems in the repeat-dose studies.

The potential effects of IL-4Rα inhibition on fertility and early embryonic development were studied in CD-1 mice using REGN1103 (mouse surrogate). Potential effects of IL-4Rα inhibition on embryo-fetal and postnatal development were studied in monkeys using REGN646 (monkey surrogate). Inhibition of IL-4Rα did not impair fertility in male or female mice administered REGN1103; NOAEL for fertility and early embryonic effects was 200 mg/kg/week, the highest dose evaluated. No REGN646-related teratogenic or pre/postnatal developmental effects were observed in pregnant monkeys administered up to 100 mg/kg/week SC from gestation day (GD) 20 to natural birth (approximately GD160-GD165). The overall rate of embryo-fetal loss was 5 of 20 (25%) in the vehicle group and 13 of 38 (34.2%) in both REGN646 groups (25 mg/kg/week: 10 of 20 [50%]; 100 mg/kg/week: 3 of 18 [16.7%]). These data are consistent with published data generated in monkeys administered soluble IL-4R, a result that was not evident when studied in mice. [225]

Because the observed incidence of embryo-fetal loss in the current study remained within the range of historical control data from the testing facility, it is considered incidental and unrelated to REGN646 exposure. Serum REGN646 trough levels measured in animals that received 25 or 100 mg/kg/week were 5.4 and 27.5-fold greater, respectively, than the ex vivo IC_{90} for REGN646-mediated inhibition of human IL-4-stimulated thymus and activation related chemokine (TARC) secretion in cynomolgus whole blood (80.3 µg/mL IC_{90} for 0.5 nM human IL-4-stimulated TARC secretion). The fact that REGN646 trough concentrations at both dose levels were significantly greater than the IC_{90} for inhibition of TARC secretion measured ex vivo in cynomolgus whole blood assays provides evidence of target saturation at both dose levels allowing for the fetal incidence data to be pooled. The overall combined incidence of fetal loss at target saturating dose levels was within the historical range of incidence observed in control animals during 17 ePPND studies of similar design conducted at the testing facility between 2008 and 2014 (6.7-38.9%). These losses were therefore considered incidental and not related to test article. Additionally, no test article-related effects were noted in the infant monkeys from the treated females when evaluated up to 6 months after birth.

In an immunohistochemical tissue cross-reactivity study with biotinylated dupilumab and REGN646, the staining pattern of biotinylated dupilumab in human tissues was very similar to that noted for biotinylated REGN646 in cynomolgus monkey tissues. No test article-specific staining was observed to any normal human or cynomolgus monkey tissues evaluated.

Based on a carcinogenicity risk assessment, which evaluated the weight-of-evidence from the animal toxicology studies and the literature assessment of the IL-4/IL-13 receptor pharmacology, dupilumab does not appear to increase the risk of cancer. After review of the marketing authorization holder's (MAHs) risk assessment, the carcinogenic risk was considered sufficiently characterized by the EMA and US FDA. No specific non-clinical studies to assess carcinogenicity were required.

There was no evidence in animal toxicology or pharmacology studies to suggest a dependence potential or abuse liability for dupilumab or its surrogates. The rationale for not performing drug abuse and liability assessment (DALA) studies was supported by the absence of behavioral and anatomic pathology effects in the CNS in any of the toxicology studies. The US FDA has concurred with the Sponsor's position that no additional non-clinical DALA studies are needed.

The key non-clinical findings are presented in the following table.

Table 12 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity Repeat-Dose Toxicity No test article related changes observed in repeat-dose toxicity studies up to 5 weeks (mouse) or 6 months (monkey) in duration. The highest dose evaluated in each study (mouse: 200 mg/kg/week SC; monkey: 100 mg/kg/week IV, 100 mg/kg/week SC) was considered the NOAEL.	The margin of safety for the highest dose tested in humans (300 mg dupilumab SC dose per week) is high. For a 70 kg adult subject, this corresponds to 4.3 mg dupilumab/kg/week, which is 23 times lower than the NOAEL dose in monkey.
Reproductive and Developmental Toxicity Fertility: There were no REGN1103-related effects on male and female reproductive parameters (mating, fertility, and pregnancy) in mice. The highest dose administered, 200 mg/kg/week SC, was NOEL.	Preclinical findings did not raise concern for impairment of fertility by dupilumab in humans.
Embryo-fetal and Developmental toxicity: In an ePPND toxicology study in cynomolgus monkeys, REGN646 was administered SC at doses up to 100 mg/kg/week to pregnant monkeys from GD20 through natural delivery (approximately GD160-GD165). Maternal toxicity endpoints before and after delivery were assessed. Monitoring of offspring for approximately 6 months after delivery was performed. Administration of REGN646 did not cause any embryo-fetal effects or effects on gestation length. The incidences of embryo-fetal loss and stillbirths in the control (5/20 [25%]) and REGN646 groups (25 mg/kg/week: 10/20 [50%]; 100 mg/kg/week: 3/18 [17%]) were similar to the historical control incidence reported by the testing facility (7-39%). Therefore, it was concluded that REGN646 did not affect either maintenance of pregnancy or natural delivery. The fact that administration of the surrogate IL-4 antibody, REGN646, did not have a dramatic impact on embryo-fetal loss suggests that the anti-inflammatory bias known to exist during the later stages of gestation may be mediated by factors other than (or, in addition to) IL-4Rα signaling, and that disruption of such signaling is not, by itself, sufficient to induce adverse outcomes during pregnancy. Serum REGN646 trough concentrations measured in animals administered 25 or 100 mg/kg/week during the ePPND study were 5.4- and 27.5-fold greater, respectively, than the ex vivo IC_{90} for REGN646-mediated inhibition of IL-4-stimulated TARC secretion, measured in the presence of a constant concentration of 0.5 nM IL-4. Therefore, these dosages were considered sufficient to fully saturate the IL-4Rα receptors in vivo. No REGN646-related effects in infants were noted up to 6 months after birth in the following parameters: clinical observations, body weight, or in parameters of functional or morphological development including skeletal findings, coagulation, serum chemistry, immunophenotyping of peripheral blood lymphocytes, TDAR, organ weights,	Lack of effect of surrogate antibody for dupilumab on maintenance of pregnancy or natural delivery in cynomolgus monkeys is relevant to testing of dupilumab in humans.

Key Safety Findings	Relevance to human usage
macroscopic observations, and microscopic evaluations. Infants in the high dose group were exposed to REGN646 up to 90 days post birth. The maternal and infant NOAEL was 100 mg/kg/week SC, the highest dose evaluated.	
Carcinogenicity A carcinogenicity risk assessment was performed. Based on the weight-of-evidence from the animal toxicology studies and the literature assessment of the IL-4Rα/IL-4/IL-13 pathway, the data supported the conclusion that chronic administration of REGN646 does not pose an increased risk of cancer. After review of the Sponsor's risk assessment, the carcinogenic risk was considered sufficiently characterized by the EMA and the US FDA. No specific non-clinical studies were requested to assess the carcinogenic potential of REGN646.	Preclinical finding that the monkey and mouse surrogate antibodies for dupilumab do not pose an increased risk of cancer is relevant to human use as some immunomodulating drugs in the market, especially those inhibiting TH1 and TH17 cytokines or that are broadly immunosuppressive like cyclosporine, are associated with higher risk of cancers. These preclinical findings are consistent with findings from dupilumab trials which showed no increase in incidence in malignancy in dupilumab treated patients relative to placebo treated patients.
Safety pharmacology No evidence of REGN646-related cardiovascular, CNS, respiratory or gastrointestinal changes in a 6-month repeat-dose studies in cynomolgus monkeys.	Pre-clinical studies did not show evidence that treatment with dupilumab increased injury to heart, lung, CNS and gastrointestinal tract. Completed clinical studies also did not suggest that dupilumab treatment was associated with an increase in the incidence of immune-mediated disorders in the brain, lung and gastrointestinal tract.
Other toxicity related information or data Drug Abuse and Liability Assessment Based on a review of data from non-clinical and available clinical studies, as well as an evaluation of dupilumab's MOA, there was no evidence of CNS activity or signs suggestive of drug abuse.	Due to the large size of dupilumab (molecular weight of 147 kDA), negligible concentrations of dupilumab are expected in cerebrospinal fluid, limiting its potential for abuse liability. [226]

AD: Atopic Dermatitis; CNS: Central Nervous System; C_{trough}: Observed Minimum Concentration in Serum After a Dose During a Dosing Interval; DLP: Data Lock Point; EMA: European Medicines Agency; ePPND: Enhanced Pre-/Postnatal Development; FDA: Food and Drug Administration; GD: Gestational Day; IC_{90}: Concentration of drug that inhibits viral replication by 90%; IL-4: Interleukin-4; IL-4Rα: Interleukin 4 Receptor Alpha; IL-13: Interleukin-13; IV: Intravenous; MOA: Mechanism of Action; NOAEL: No-Observed-Adverse-Effect-Level; NOEL: No-Observed-Effect Level; REGN646: Monkey Surrogate Monoclonal Antibody; REGN1103: Mouse Surrogate Monoclonal Antibody; RMP: Risk Management Plan; SC: Subcutaneous; TDAR: T-cell Dependent Antibody Response; TH: T Helper; US: United States.

Safety Findings in Special Populations

A Pediatric Study Plan (PSP) and Pediatric Investigation Plan (PIP) for AD have been agreed with FDA and EMA, respectively. No additional non-clinical studies are required by the FDA and EMA. The available non-clinical safety package supports all dupilumab indications.

Conclusion of the module:

Based on the absence of key safety findings, data from non-clinical studies did not result in the identification of important risks or missing information.

RISK MANAGEMENT PLAN – PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Clinical trial exposure

This section includes summary information on the clinical trial exposure. The data are being pooled across the current approved/under review indications of PN, AD, asthma, CRSwNP, EoE[1] and COPD as well as presented separately by indication.

The data are stratified for relevant categories, including:

- Duration of exposure
- Age group and gender
- Dose
- Ethnic origin and race

Duration of exposure

A total of 9958 patients were exposed to dupilumab in 48 completed/unblinded EoE, COPD, PN, AD, asthma and CRSwNP studies (3 studies in EoE, 2 studies in COPD, 2 studies in PN, 27 studies in AD, 10 in asthma and 4 in CRSwNP). Of these, 6831 and 3237 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively.

The data cut-off date (last patient last visit) for R668-EE-1877 part A is 28 April 2022, for part B is 17 January 2023. The data cut-off date for EFC15804 is 08 February 2023, and for EFC15805 is 29 September 2023. For R668-AD-1434, EFC16823, LTS14424, and LPS16872, the data cut-off date is 28 March 2023. All other studies are completed as of 28 March 2023.

Table 13 - Duration of exposure – EoE[1] + COPD+ Atopic Dermatitis + Asthma + CRSwNP + PN

Duration of exposure	Persons	Person-years[a]
Any	9958	
≥4 weeks	9822	
≥12 weeks	9545	16 071.5
≥16 weeks	9167	
≥24 weeks	8501	15 721.5
≥52 weeks	6831	14 581.7
≥76 weeks	4902	
≥104 weeks	3237	
≥130 weeks	1879	
≥156 weeks	979	
Total person-years		16 115.5

[1] Exposure data for EoE in patients 1 to 12 years of age have been included (subject to an ongoing submission).

Duration of exposure	Persons	Person-years[a]

EoE: Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A, part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324, R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022, for part B is 17-Jan-2023 (last patient last visit date).

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914, R668-AD-1021, R668-AD-1026, R668-AD-1117, R668-AD-1121, R668-AD-1224, R668-AD-1225, R668-AD-1307, R668-AD-1314, R668-AD-1334, R668-AD-1412, R668-AD-1415, R668-AD-1416, R668-AD-1424, R668-AD-1433, R668-AD-1607, R668-AD-1434, R668-AD-1526, R668-AD-1539 (part A and part B), R668-AD-1652, R668-AD-1924, EFC15116, LPS15497, LPS15991, LPS16763, LPS16764, and EFC16823.

Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study).

Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.

PN: Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

EoE and Atopic Dermatitis: Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7, 14, or 28 days for patients on QW, Q2W, or Q4W injection schedule, respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

COPD, PN, Asthma and CRSwNP: Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg, 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

A total of 436 adult and pediatric patients were exposed to dupilumab in the completed/unblinded EoE studies. Of these, 222 patients were exposed to dupilumab for at least 1 year.

Table 14 - Duration of exposure – Eosinophilic Esophagitis

Duration of exposure	Persons	Person-years[a]
Any	436	
≥4 weeks	436	
≥12 weeks	423	355.3
≥16 weeks	401	350.2
≥52 weeks	222	236.5
≥76 weeks	5	
≥104 weeks	2	
Total person-years		357.6

Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A, part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324, R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022, for part B is 17-Jan-2023 (last patient last visit date).

Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + 7).

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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A total of 938 adults were exposed to dupilumab in the completed/unblinded COPD studies. Of these, 687 patients were exposed to dupilumab for at least 1 year.

Table 15 - Duration of exposure – Chronic Obstructive Pulmonary Disease

Duration of exposure	Persons	Person-years[a]
Any	938	
≥4 weeks	929	
≥12 weeks	915	852.6
≥16 weeks	904	
≥24 weeks	872	837.0
≥52 weeks	687	687.9
Total person-years		854.7

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.

a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

A total of 4503 adult and pediatric patients were exposed to dupilumab in completed/unblinded AD studies including open label extension studies R668-AD-1434 and R668-AD-1225. Of these, 3295 and 1949 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively. Also, 777 patients were exposed to dupilumab for at least 3 years.

Table 16 - Duration of exposure – Atopic Dermatitis

Duration of exposure	Persons	Person-years[a]
Any	4503	
≥4 weeks	4420	
≥12 weeks	4271	8602.2
≥16 weeks	4027	8535.9
≥52 weeks	3295	8164.8
≥76 weeks	2836	
≥104 weeks	1949	
≥130 weeks	1258	
≥156 weeks	777	
Total person-years		8624.6

Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914,¬ R668-AD-1021,¬ R668-AD-1026,¬ R668-AD-1117,¬ R668-AD-1121,¬ R668-AD-1224,¬ R668-AD-1225,¬ R668-AD-1307,¬ R668-AD-1314,¬ R668-AD-1334,¬ R668-AD-1412,¬ R668-AD-1415,¬ R668-AD-1416,¬ R668-AD-1424,¬ R668-AD-1433,¬ R668-AD-1607,¬ R668-AD-1434,¬ R668-AD-1526,¬ R668-AD-1539 (part A and part B),¬ R668-AD-1652,¬ R668-AD-1924, EFC15116,¬ LPS15497,¬ LPS15991,¬ LPS16763,¬ LPS16764,¬ and EFC16823. Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

Duration of exposure	Persons	Person-years[a]

Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7,¬ 14,¬ or 28 days for patients on QW,¬ Q2W,¬ or Q4W injection schedule,¬ respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category
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Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

A total of 3434 adult and pediatric patients were exposed to dupilumab in completed/unblinded asthma studies including open label extension studies LTS12551, LPS15023 and LTS14424. Of these, 2392 and 1286 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively.

Table 17 - Duration of exposure – Asthma

Duration of exposure	Persons	Person-years[a]
Any	3434	
≥4 weeks	3394	
≥12 weeks	3302	5814.9
≥16 weeks	3229	
≥24 weeks	3075	5731.3
≥52 weeks	2392	5257.6
≥76 weeks	2061	
≥104 weeks	1286	
≥130 weeks	621	
≥156 weeks	202	
Total person-years		5830.6

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study). Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; QW: Once Every Week.

A total of 495 adult patients with CRSwNP were exposed to dupilumab in the completed/unblinded studies. 235 patients were exposed to dupilumab for at least 1 year.

Table 18 - Duration of exposure – CRSwNP

Duration of exposure	Persons	Person-years[a]
Any	495	
≥4 weeks	491	

Duration of exposure	Persons	Person-years[a]
≥12 weeks	485	377.4
≥16 weeks	457	
≥24 weeks	424	355.2
≥52 weeks	235	234.8
Total person-years		378.5

Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 7 for QW dosing and 14 for Q2W dosing regardless of intermittent discontinuations.

a Person-years calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

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CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; QW: Once Every Week; Q2W: Once Every Two Weeks.

A total of 152 adult patients were exposed to dupilumab in the two completed/unblinded phase 3 PN studies.

Table 19 - Duration of exposure – Prurigo Nodularis

Duration of exposure	Persons	Person-years[a]
Any	152	
≥4 weeks	152	
≥12 weeks	149	69.0
≥16 weeks	149	
≥24 weeks	137	63.7
Total person-years		69.4

Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.

a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

Exposure by age group and gender

Overall, a total of 5266 (52.9%) patients are male and 4692 (47.1%) patients are female. 229 (2.3%) patients are less than 6 years old, 898 (9.0%) between 6 and 11, 566 (5.6%) between 12 and 17 and 8265 (83.0%) are adults.

Table 20 - Exposure by age group (years) and gender – EoE + COPD + Atopic Dermatitis + Asthma + CRSwNP + PN

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
≥6 months to <2	24	3	42.9	9.5
2 to 5	128	74	251.1	131.6
6 to 11	530	368	996.6	773.5

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
12 to 17	338	228	445.8	334.6
18 to 64	3554	3530	6055.3	5636.7
65 to 74	551	418	644.1	554.6
75 to 84	139	69	148.3	85.5
≥85	2	2	3.0	2.5
Total	5266	4692	8587.1	7528.5

EoE: Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A, part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324, R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022, for part B is 17-Jan-2023 (last patient last visit date).

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is29-Sep-2023.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914, R668-AD-1021, R668-AD-1026, R668-AD-1117, R668-AD-1121, R668-AD-1224, R668-AD-1225, R668-AD-1307, R668-AD-1314, R668-AD-1334, R668-AD-1412, R668-AD-1415, R668-AD-1416, R668-AD-1424, R668-AD-1433, R668-AD-1607, R668-AD-1434, R668-AD-1526, R668-AD-1539 (part A and part B), R668-AD-1652, R668-AD-1924, EFC15116, LPS15497, LPS15991, LPS16763, LPS16764, and EFC16823.

Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study).

Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.

PN: Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

EoE and Atopic Dermatitis: Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7, 14, or 28 days for patients on QW, Q2W, or Q4W injection schedule, respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

COPD, PN, Asthma and CRSwNP: Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

A higher proportion of males (65.8%) than females (34.2%) were exposed to dupilumab in EoE studies. About half (54.8%) of exposed patients; ie, 239, were in the 18 to 64 year age range, while 98 (22.5%) were aged 12 to 17, and 2 (0.5%) were aged 65 and older.

Table 21 - Exposure by age group and gender – Eosinophilic Esophagitis

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
≤6	25	8	25.4	8.2
6 to 11	51	15	50.3	12.9
12 to 17	72	26	59.3	22.7
18 to 64	139	98	103.9	72.9
65 to 74		2		2.2
Total	287	149	238.8	118.8

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]

Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A,¬ part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324,¬ R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022,¬ for part B is 17-Jan-2023 (last patient last visit date).
Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + 7).
a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.
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A higher proportion of males (66.0%) than females (34.0%) were exposed to dupilumab in COPD studies. 387 (41.3%) patients were between 18 and 64, 435 (46.4%) between 65 and 74 and 116 (12.4%) were aged 75 and older.

Table 22 - Exposure by age group and gender – Chronic Obstructive Pulmonary Disease

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
18 to 64	242	145	226.7	132.8
65 to 74	288	147	257.7	133.0
75 to 84	89	27	80.5	24.0
Total	619	319	564.9	289.8

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.
Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.
a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.
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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

A higher proportion of males (57.3%) than females (42.7%) were exposed to dupilumab in AD studies. The majority (74.5%) of exposed patients were in the 18 to 64 year age range, while 196 (4.4%) were aged 6 months to 5 years old, 432 (9.6%) were aged 6 to 11, 365 (8.1%) were aged 12 to 17, and 153 (3.4%) were aged 65 and older.

Table 23 - Exposure by age group and gender – Atopic Dermatitis

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
<6	127	69	268.6	133.0
6 to 11	221	211	549.2	540.0
12 to 17	200	165	273.7	243.1
18 to 64	1934	1423	3882.6	2519.7
65 to 74	77	48	106.3	67.8
75 to 84	18	6	21.7	13.4
≥85	2	2	3.0	2.5
Total	2579	1924	5105.2	3519.4

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]

Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914,¬ R668-AD-1021,¬ R668-AD-1026,¬ R668-AD-1117,¬ R668-AD-1121,¬ R668-AD-1224,¬ R668-AD-1225,¬ R668-AD-1307,¬ R668-AD-1314,¬ R668-AD-1334,¬ R668-AD-1412,¬ R668-AD-1415,¬ R668-AD-1416,¬ R668-AD-1424,¬ R668-AD-1433,¬ R668-AD-1607,¬ R668-AD-1434,¬ R668-AD-1526,¬ R668-AD-1539 (part A and part B),¬ R668-AD-1652,¬ R668-AD-1924 EFC15116,¬ LPS15497,¬ LPS15991,¬ LPS16763,¬ LPS16764,¬ and EFC16823. Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7,¬ 14,¬ or 28 days for patients on QW,¬ Q2W,¬ or Q4W injection schedule,¬ respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

A majority of patients (58.4%) exposed to dupilumab in asthma studies were female. Most exposed patients (75.1%) were in the 18 to 64 year age range, while 400 (11.6%) were aged 6 to 11, 103 (3.0%) were aged 12 to 17, and 353 (10.3%) were aged 65 and older.

Table 24 - Exposure by age group and gender – Asthma

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
6 to 11	258	142	397.1	220.6
12 to 17	66	37	112.9	68.8
18 to 64	950	1628	1635.5	2756.1
65 to 74	132	173	240.4	317.8
75 to 84	21	27	37.8	43.7
Total	1427	2007	2423.7	3407.0

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study). Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; QW: Once Every Week.

A majority of exposed patients (61.6%) in the CRSwNP program were male and 410 (82.8%) were in the range of 18 to 64 years.

Table 25 - Exposure by age group and gender – CRSwNP

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
18 to 64	255	155	190.8	117.9
65 to 74	43	30	34.6	25.9
75 to 84	7	5	6.4	2.9
Total	305	190	231.8	146.7

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]

Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.
Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 7 for QW dosing and 14 for Q2W dosing regardless of intermittent discontinuations.
a Person-years calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.
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CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; QW: Once Every Week.

The majority of patients (67.8%) exposed to dupilumab in PN studies were female. Most (75.7%) exposed patients were in the 18 to 64 year age range.

Table 26 - Exposure by age group and gender – Prurigo Nodularis

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
18 to 64	34	81	15.8	37.3
65 to 74	11	18	5.1	7.9
75 to 84	4	4	1.8	1.5
Total	49	103	22.7	46.7

Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.
Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.
a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.
PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

Exposure by dose

The authorized doses in adults for AD, CRSwNP and PN is 300 mg Q2W. The authorized doses for AD pediatric patients between 6 to 17 years old are 300 mg Q4W, 200 mg Q2W and 300 mg Q2W, for 6 months to 5 years of age is 200 mg Q4W and 300 mg Q4W.

The authorized doses for asthma adult and pediatric patients 12 years and older are 300 mg Q2W and 200 mg Q2W, for 6 to 11 years old are 100 Q2W, 200 mg Q2W and 300 mg Q4W. The authorized dose for EoE adult and pediatric patients 12 years and older is 300 mg QW.

Table 27 - Exposure by dose – EoE + COPD + Atopic Dermatitis + Asthma + CRSwNP + PN

Dose of exposure	Persons	Person-years[a]
Dupilumab 75 mg QW	8	0.6
Dupilumab 100 mg Q4W	65	17.1
Dupilumab 100 mg Q2W	171	140.6
Dupilumab 100 mg Q2W to 200 mg Q2W	16	15.8
Dupilumab 100 mg Q2W to 300 mg Q2W	14	13.9
Dupilumab 100 mg Q2W to 300 mg Q4W to 200 mg Q2W	1	1.0
Dupilumab 150 mg QW	22	1.6

Dose of exposure	Persons	Person-years[a]
Dupilumab 200 mg Q4W	185	84.4
Dupilumab 200 mg Q2W	1661	1365.7
Dupilumab 200 mg QW	336	120.3
Dupilumab 200/300 mg Q2W	529	873.5
Dupilumab 200/300 mg Q4W	854	737.4
Dupilumab 300 mg Q8W	84	56.0
Dupilumab 300 mg Q4W	609	260.8
Dupilumab 300 mg Q4W to 200 mg Q2W	1	1.0
Dupilumab 300 mg Q2W to 300 mg Q4W	148	144.5
Dupilumab 300 mg Q2W	5428	6367.4
Dupilumab 300 mg QW	3196	5748.2
Dupilumab 2 mg/kg SC	38	3.6
Dupilumab 4 mg/kg SC	39	3.7
Dupilumab 3 mg/kg	20	0.4
Dupilumab 6 mg/kg	20	0.4
Dupilumab 2 mg/kg QW	34	53.9
Dupilumab 3 mg/kg QW	17	28.2
Dupilumab 4 mg/kg QW	35	54.2
Dupilumab 6 mg/kg QW	18	19.6
Total	9958	16 113.7

EoE: Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A, part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324, R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022, for part B is 17-Jan-2023 (last patient last visit date).

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914, R668-AD-1021, R668-AD-1026, R668-AD-1117, R668-AD-1121, R668-AD-1224, R668-AD-1225, R668-AD-1307, R668-AD-1314, R668-AD-1334, R668-AD-1412, R668-AD-1415, R668-AD-1416, R668-AD-1424, R668-AD-1433, R668-AD-1607, R668-AD-1434, R668-AD-1526, R668-AD-1539 (part A and part B), R668-AD-1652, R668-AD-1924, EFC15116, LPS15497, LPS15991, LPS16763, LPS16764, and EFC16823.

Data cutoff date for R668-AD-1434 and EFC16823 are 28MAR2023; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study).

Data cutoff date for LTS14424 is 28MAR2023; all other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.

PN: Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

EoE and Atopic Dermatitis: Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7, 14, or 28 days for patients on QW, Q2W, or Q4W injection schedule, respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

COPD, PN, Asthma and CRSwNP: Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

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Dose of exposure	Persons	Person-years[a]

COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; Q8W: Once Every Eight Weeks; QW: Once Every Week; SC: Subcutaneous.

The most commonly studied dupilumab dose in EoE clinical trials was 300 mg QW (219 persons and 160.9 person-years).

Table 28 - Exposure by dose – Eosinophilic Esophagitis

Dose of exposure	Persons	Person-years[a]
Dupilumab 100 mg Q2W	9	5.3
Dupilumab 200 mg Q2W	48	39.9
Dupilumab 300 mg Q2W	146	122.6
Dupilumab 300 mg Q4W	27	23.3
Dupilumab 300 mg QW	219	160.9
Dupilumab 200 mg Q4W	6	5.5
Total	436	357.6

Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A,¬ part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324,¬ R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022,¬ for part B is 17-Jan-2023 (last patient last visit date).

Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + 7).

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category

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Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

The dose of dupilumab studied in the COPD clinical trials was 300 mg Q2W (938 persons, 854.7 person-years).

Table 29 - Exposure by dose – Chronic Obstructive Pulmonary Disease

Dose of exposure	Persons	Person-years[a]
Dupilumab 300 mg Q2W	938	854.7

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.

a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023_2/REPORT/PGM/cdc_exp_s_t.sas
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IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

The most commonly studied dupilumab doses in AD clinical trials were 300 mg QW (2895 persons and 5566.9 person-years).

Table 30 - Exposure by dose – Atopic Dermatitis

Dose of exposure	Persons	Person-years[a]
Dupilumab 2 mg/kg QW	34	53.9

Dose of exposure	Persons	Person-years[a]
Dupilumab 2 mg/kg SC	38	3.6
Dupilumab 3 mg/kg	20	0.4
Dupilumab 3 mg/kg QW	17	28.2
Dupilumab 4 mg/kg QW	35	54.2
Dupilumab 4 mg/kg SC	39	3.7
Dupilumab 6 mg/kg	20	0.4
Dupilumab 6 mg/kg QW	18	19.6
Dupilumab 75 mg QW	8	0.6
Dupilumab 100 mg Q2W	63	19.1
Dupilumab 100 mg Q4W	65	17.1
Dupilumab 150 mg QW	22	1.6
Dupilumab 200 mg Q2W	284	102.9
Dupilumab 200 mg QW	336	120.3
Dupilumab 200/300 mg Q2W[b]	529	873.5
Dupilumab 300 mg Q2W	1378	785.4
Dupilumab 300 mg Q4W	422	166.6
Dupilumab 300 mg Q8W	84	56.0
Dupilumab 300 mg QW	2895	5566.9
Dupilumab 200 mg Q4W	29	13.0
Dupilumab 200/300 mg Q4W	854	737.4
Total	4503	8624.6

Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914,¬ R668-AD-1021,¬ R668-AD-1026,¬ R668-AD-1117,¬ R668-AD-1121,¬ R668-AD-1224,¬ R668-AD-1225,¬ R668-AD-1307,¬ R668-AD-1314,¬ R668-AD-1334,¬ R668-AD-1412,¬ R668-AD-1415,¬ R668-AD-1416,¬ R668-AD-1424,¬ R668-AD-1433,¬ R668-AD-1607,¬ R668-AD-1434,¬ R668-AD-1526,¬ R668-AD-1539 (part A and part B),¬ R668-AD-1652,¬ R668-AD-1924 EFC15116,¬ LPS15497,¬ LPS15991,¬ LPS16763,¬ LPS16764,¬ and EFC16823. Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7,¬ 14,¬ or 28 days for patients on QW,¬ Q2W,¬ or Q4W injection schedule,¬ respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category

b These patients are from study R668-AD-1434. Patients weighing ≥60 kg received 300 mg Q2W dose; and patients weighing <60 kg received 200 mg Q2W dose. Hence a patient whose weight fluncated around 60 kg can receive 200 mg or 300 mg dose depending on weight.

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Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; Q8W: Once Every Eight Weeks; QW: Once Every Week; SC: Subcutaneous.

The most commonly studied dose in asthma clinical trials was 300 mg Q2W (2497 persons and 4310.0 person-years).

Table 31 - Exposure by dose – Asthma

Dose of exposure	Persons	Person-years[a]
Dupilumab 100 mg Q2W	99	116.2
Dupilumab 100 mg Q2W to 200 mg Q2W	16	15.8
Dupilumab 100 mg Q2W to 300 mg Q4W	14	13.9
Dupilumab 100 mg Q2W to 300 mg Q4W to 200 mg Q2W	1	1.0
Dupilumab 200 mg Q4W	150	65.9
Dupilumab 200 mg Q2W	1329	1222.9
Dupilumab 300 mg Q4W	160	70.9
Dupilumab 300 mg Q4W to 200 mg Q2W	1	1.0
Dupilumab 300 mg Q2W	2497	4310.0
Dupilumab 300 mg QW	52	11.4
Total	3434	5828.8

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study). Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_asthma_s_t_i.rtf (06JUL2023 3:13)

IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

The most commonly studied dose in CRSwNP clinical trials is 300 mg Q2W (317 persons, 225.2 person-years).

Table 32 - Exposure by dose – CRSwNP

Dose of exposure	Persons	Person-years[a]
Dupilumab 300 mg Q2W to 300 mg Q4W	148	144.5
Dupilumab 300 mg Q2W	317	225.2
Dupilumab 300 mg QW	30	8.9
Total	495	378.5

Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28MAR2023. All other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 7 for QW dosing and 14 for Q2W dosing regardless of intermittent discontinuations.

a Person-years calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_crswnp_s_t_i.rtf (06JUL2023 3:13)

CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; Once Every Four Weeks; QW: Once Every Week.

The dose of dupilumab studied in the PN clinical trials was 300 mg Q2W (152 persons, 69.4 person-years).

Table 33 - Exposure by dose – Prurigo Nodularis

Dose of exposure	Persons	Person-years[a]
Dupilumab 300 mg Q2W	152	69.4

Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.
Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.
a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.
PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_pn_s_t_i.rtf (06JUL2023 3:13)
IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

Exposure by ethnic origin and race

The majority of subjects exposed to dupilumab in the clinical trial program were non-Hispanic or Latino (8316 persons) and were Caucasian (7538 persons).

Table 34 - Exposure by ethnic origin and race – EoE + COPD + Atopic Dermatitis + Asthma + CRSwNP + PN

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	1564	2372.7
Non-Hispanic or Latino	8316	13 651.8
Not Reported	76	89.0
Unknown	2	2.0
Race		
Caucasian	7538	12 654.2
Black	549	757.0
Asian	1603	2320.9
Other	233	327.0
Not Reported	35	56.4
Total	9958	16 115.5

EoE: Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A, part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324, R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022, for part B is 17-Jan-2023 (last patient last visit date).
COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.
Atopic Dermatitis: Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914, R668-AD-1021, R668-AD-1026, R668-AD-1117, R668-AD-1121, R668-AD-1224, R668-AD-1225, R668-AD-1307, R668-AD-1314, R668-AD-1334, R668-AD-1412, R668-AD-1415, R668-AD-1416, R668-AD-1424, R668-AD-1433, R668-AD-1607, R668-AD-1434, R668-AD-1526, R668-AD-1539 (part A and part B), R668-AD-1652, R668-AD-1924, EFC15116, LPS15497, LPS15991, LPS16763, LPS16764, and EFC16823.
Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.
Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study).
Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.
CRSwNP: Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.
PN: Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

	Persons	Person-years[a]

EoE and Atopic Dermatitis: Duration of treatment for a patient in one study is calculated as (date of last study drug injection – date of first study drug injection + x days) where x is 7, 14, or 28 days for patients on QW, Q2W, or Q4W injection schedule, respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.
COPD, PN, Asthma and CRSwNP: Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days – first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.
a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.
PGM=PRODOPS/SAR231893/OVERALL/RMP_2023_2/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_all_v2_s_t_i.rtf (06FEB2024 4:19)
COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

Among 432 patients with reported ethnicity exposed to dupilumab in the EoE studies, 94.2% were non-Hispanic or Latino. Among 433 patients with reported race exposed to dupilumab in the EoE studies, 91.0% were Caucasian, 4.6% were Black and 1.6% were Asian.

Table 35 - Exposure by ethnic origin and race – Eosinophilic Esophagitis

	Persons	Person-years[a]
Ethnicity		
Hispanic Or Latino	25	21.0
Not Hispanic Or Latino	407	332.9
Not Reported	4	3.7
Race		
Caucasian	394	318.8
Black Or African American	20	18.6
Asian	7	7.1
Other	12	11.2
Not Reported	3	1.9
Total	436	357.6

Includes dupilumab exposed patients in phase 2 study: R668-EE-1324 and phase 3 studies R668-EE-1774 (part A,¬ part B and part C rolled over from part A and part B) and R668-EE-1877 (part A and part B). R668-EE-1324,¬ R668-EE-1774 are completed. Data cutoff date for R668-EE-1877 part A is 28-Apr-2022,¬ for part B is 17-Jan-2023 (last patient last visit date).
Duration of treatment for a patient in one study is calculated as (date of last study drug injection - date of first study drug injection + 7).
a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.
/sasdata/Data/Production/BDM/R668/R668-Inflammation/RMP/2023/202306/Programs/Generated/T_expo_re_over_Int_ee.sas (fan.xu 06JUL2023 08:57 SAS Win 9.4)

In the COPD studies, among 934 patients with reported ethnicity exposed to dupilumab, approximately 69.8% of patients were non-Hispanic or Latino, and among 936 patients with reported race exposed to dupilumab, most were Caucasian (87.1%).

Table 36 - Exposure by ethnic origin and race – Chronic Obstructive Pulmonary Disease

	Persons	Person-years[a]
Ethnicity		

	Persons	Person-years[a]
Hispanic or Latino	282	255.7
Non-Hispanic or Latino	652	595.0
Not Reported	3	3.0
Unknown	1	1.0
Race		
Caucasian	815	745.3
Black	7	5.7
Asian	74	67.6
Other	40	34.7
Not Reported	2	1.5
Total	938	854.7

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Data cutoff date for EFC15804 is 08-Feb-2023, and data cut-off date for EFC15805 is 29-Sep-2023.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days - first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.

a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023_2/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_copd_s_t_i.rtf (06FEB2024 4:19)

IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

Among 4434 patients with reported ethnicity exposed to dupilumab in the AD studies, 93.4% were non-Hispanic or Latino. Among 4474 patients with reported race exposed to dupilumab in the AD studies, 70.7% were Caucasian, 8.2% were Black and 18.8% were Asian.

Table 37 - Exposure by ethnic origin and race – Atopic Dermatitis

	Persons	Person-years[a]
Ethnicity		
Hispanic Or Latino	293	412.9
Not Hispanic Or Latino	4141	8129.4
Not Reported	69	82.3
Race		
Caucasian	3163	6393.5
Black Or African American	367	538.3
Asian	841	1479.6
American Indian Or Alaska Native	10	10.5
Other	93	150.1
Not Reported	29	52.6
Total	4503	8624.6

Includes dupilumab exposed patients in a total of 27 studies: R668-AD-0914,¬ R668-AD-1021,¬ R668-AD-1026,¬ R668-AD-1117,¬ R668-AD-1121,¬ R668-AD-1224,¬ R668-AD-1225,¬ R668-AD-1307,¬ R668-AD-1314,¬ R668-AD-1334,¬ R668-AD-1412,¬ R668-AD-1415,¬ R668-AD-1416,¬ R668-AD-1424,¬ R668-AD-1433,¬ R668-AD-1607,¬ R668-AD-1434,¬ R668-AD-1526,¬ R668-AD-1539 (part A and part B),¬ R668-AD-1652,¬ R668-AD-1924 EFC15116,¬ LPS15497,¬ LPS15991,¬ LPS16763,¬ LPS16764,¬ and EFC16823. Data cutoff date for R668-AD-1434 and EFC16823 are 28-Mar-2023; all other studies are completed.

	Persons	Person-years[a]

Duration of treatment for a patient in one study is calculated as (date of last study drug injection - date of first study drug injection + x days) where x is 7,¬ 14,¬ or 28 days for patients on QW,¬ Q2W,¬ or Q4W injection schedule,¬ respectively. The duration of treatment exposure to dupilumab dose for a patient who entered multiple studies was calculated as the sum of duration of treatment exposure to dupilumab in all individual studies.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category /sasdata/Data/Production/BDM/R668/R668-Inflammation/RMP/2023/202306/Programs/Generated/T_expo_re_over_Int_ad.sas (fan.xu SAS Win 9.4)

Q2W: Once Every Two Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

In asthma studies, among 3434 patients with reported ethnicity and race exposed to dupilumab, approximately 75.7% of patients were non-Hispanic or Latino, and most were Caucasian (77.8%).

Table 38 - Exposure by ethnic origin and race – Asthma

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	836	1576.1
Non-Hispanic or Latino	2598	4254.5
Race		
Caucasian	2671	4852.6
Black	137	184.0
Asian	565	687.3
Other	61	106.7
Total	3434	5830.6

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study). Data cutoff date for LTS14424 is 28-Mar-2023; all other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days - first IMP injection date)/7 where x is dosing dependent (eg. 7 for QW dosing and 14 for Q2W dosing) regardless of intermittent discontinuations, except for LTS12551 patients receiving dupilumab in DRI12544 where the protocol defined 16-week follow-up period is excluded.

a Person year for each category was calculated as the sum of duration of exposure in years for all patients in each category.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_asthma_s_t_i.rtf (06JUL2023 3:13)

IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; QW: Once Every Week.

In the CRSwNP studies, among 494 patients with reported ethnicity exposed to dupilumab, approximately 79.8% of patients exposed to dupilumab were non-Hispanic or Latino; among 494 patients with reported race exposed to dupilumab, most patients were Caucasian (83.6%).

Table 39 - Exposure by ethnic origin and race – CRSwNP

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	100	94.1
Non-Hispanic or Latino	394	283.5
Unknown	1	1.0
Race		
Caucasian	413	306.6
Black	7	5.2
Asian	62	54.9
Other	12	11.4
Not Reported	1	0.5
Total	495	378.5

Includes dupilumab exposed patients in a total of 4 studies: ACT12340, EFC14146, EFC14280, LPS16872. Data cutoff date for LPS16872 is 28-Mar-2023. All other studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days - first IMP injection date)/7 where x is 7 for QW dosing and 14 for Q2W dosing regardless of intermittent discontinuations.

a Person-years calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_crswnp_s_t_i.rtf (06JUL2023 3:13)

CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks; QW: Once Every Week.

In the PN studies, among 152 patients exposed to dupilumab, 81.6% were non-Hispanic or Latino, 53.9% were Caucasian, 7.2% were Black and 35.5% were Asian.

Table 40 - Exposure by ethnic origin and race – Prurigo Nodularis

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	28	13.0
Non-Hispanic or Latino	124	56.4
Race		
Caucasian	82	37.4
Black	11	5.2
Asian	54	24.5
Other	5	2.3
Total	152	69.4

Includes dupilumab exposed patients in phase 3 studies EFC16459 and EFC16460. Both studies are completed.

Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + x days - first IMP injection date)/7 where x is 14 for Q2W dosing regardless of intermittent discontinuations.

a Person year calculated as the sum of duration of exposure for all patients treated for at least the duration indicated.

PGM=PRODOPS/SAR231893/OVERALL/RMP_2023/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_pn_s_t_i.rtf (06JUL2023 3:13)

IMP: Investigational Medicinal Product; Q2W: Once Every Two Weeks.

Exposure in blinded studies in approved/under review indications

The number of patients enrolled in ongoing, blinded, clinical studies at the cut-off date of 28 March 2023 is presented below:

Asthma: approximately 400 patients exposed to dupilumab

- Seventy-three (73) adult patient were enrolled in blinded phase 4 study LPS15834 with approximately two thirds on dupilumab 300 mg Q2W.
- One hundred and ninety (190) adult patients were enrolled in blinded phase 4 study LPS16677 with approximately half on dupilumab 200 mg Q2W.
- Three hundred and eighteen (318) adult patients were enrolled in blinded phase 4 study LPS16676 with approximately two thirds on dupilumab 300 mg Q2W.
- Thirty-nine (39) adult patients were enrolled in blinded phase 4 study AS-1903 with approximately half on dupilumab 300 mg Q2W.

CRSwNP with comorbid asthma: approximately 72 patients exposed to dupilumab

- One hundred and forty-four (144) adult patients were enrolled in blinded phase 4 study LPS16747 with approximately half on dupilumab 300 mg Q2W.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 41 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patients with specific past or current medical history			
Atopic dermatitis, Asthma, EoE, PN, CRSwNP, and COPD studies: Known or suspected history of immunosuppression/immunodeficient states, including: • Established diagnosis of a primary immunodeficiency disorder (eg, Severe Combined Immunodeficiency, Wiskott Aldrich Syndrome, DiGeorge Syndrome, X-linked Agammaglobulinemia, Common Variable Immunodeficiency) • History of invasive opportunistic infections (eg, TB, non-tuberculous mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) or history of HIV infection/positive HIV 1/ 2 serology • Use of immunosuppressive or immunomodulating drugs within 5 half-lives before the baseline visit • or any condition that, in the opinion of the investigator, is likely to require immunosuppressive treatment during the first few weeks of study treatment (AD studies only). • Active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis or a history of incompletely treated	• Immunosuppressive or immunomodulating drugs could have confounded the evaluation of efficacy and safety endpoints. • It was not known at beginning of the development of dupilumab whether it might increase the risk of severe or serious infections.	No	In AD studies, there was no evidence to suggest that dupilumab had significant effect on host defense against microbial infections. The incidence of opportunistic infections and serious infections was lower in dupilumab groups than in placebo group. In AD-1224 with concomitant TCS ± TCI, the incidence of eczema herpeticum was significantly lower in the combined dupilumab group than the placebo group. In one of the asthma pivotal studies (Venture, EFC13691), in patients with OCS-dependent severe asthma, no increase in opportunistic infections was observed in dupilumab group versus placebo group. Dupilumab therapy in patients with CRSwNP on a background therapy with intranasal corticosteroids was not associated with increased risks of infections (bacterial, viral, opportunistic, or parasitic). There was no imbalance in the proportions of patients that reported TEAEs of oral herpes and herpes simplex infections. In the pivotal CRSwNP studies (EFC14146, EFC14280), OCSs were allowed as rescue therapy to be used on top of dupilumab for worsening CRSwNP with no increase in

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
tuberculosis unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the investigator and/or infectious disease specialist (for COPD study).			opportunistic infections in dupilumab group versus placebo group. Dupilumab therapy in patients with COPD on a standard of care therapy with inhaled corticosteroids was not associated with increased risk of infections including serious infections (bacterial, viral, opportunistic, or parasitic). As there was no significant immunosuppressive effect observed for dupilumab with concurrent use of immunosuppressive drugs and dupilumab use did not increase risk of opportunistic infections, use in patients with immunodeficiency is therefore not considered as missing information or a contraindication.
Atopic dermatitis and PN studies: Patients with active major autoimmune diseases. Asthma, EoE, CRSwNP, and COPD studies: Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc) or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.	The reason for excluding these conditions was that at the beginning of the program it was not known if IL-4Rα blockade in AD (or asthma) patients might increase the risk for certain non-type 2 immunity driven autoimmune disorders. Such conditions/ treatments may confound the ability to assess the data for potential effects of the investigational product and may interfere with assessment of the outcomes.	No	Data from clinical trials did not show evidence of increased autoimmunity to suggest a different safety profile for use of dupilumab in patients with autoimmune disorders. Adults: In phase 3 pivotal AD studies (AD-1334 and AD-1416), there were no meaningful changes in hs-CRP and autoantibodies (anti-dsDNA and anti-TPO and ANA) from baseline between dupilumab treatment group and placebo to suggest an effect of dupilumab on autoimmunity. In the AD-1307 study, mRNA data from skin biopsies showed that when dupilumab suppressed Th2 immune responses, Th1 responses were also down-regulated as inflammation decreased, adding further support that Th2 regulation by dupilumab does not increase Th1 inflammation and the risk of autoimmunity. In addition, there was no meaningful increase in

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			autoimmune diseases with dupilumab treatment in safety analysis set comprising of primary safety pool, AD-1224 (52 week) and AD-1424. The incidence of autoimmune disorders (HLGT) was 0.36% (6/1689) in dupilumab group versus 0.32% (3/940) in placebo group. Of the 1567 patients exposed to dupilumab in asthma pivotal pooled safety population (DRI12544 plus EFC13579), none reported treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders. Of the 440 patients exposed to dupilumab in CRSwNP pivotal pooled safety studies (EFC14146 plus EFC14280), none reported treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders. Of the 203 patients exposed to dupilumab in EoE pivotal pooled safety studies (Part A [placebo and 300 mg QW] and Part B [placebo, 300 mg Q2W, and 300 mg QW] of study EE-1774), none reported treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders. Of the 152 patients exposed to dupilumab in PN pivotal pooled safety studies (EFC16459 and EFC16460), no treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders were noted. Of the 938 patients exposed to dupilumab in COPD pivotal study (EFC15804 and EFC15805), treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders, were

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			similar and numerically low in both dupilumab and placebo groups.
Infections and infestations (AD, asthma, EoE, PN, CRSwNP, and COPD studies): • Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. (within 2 weeks for AD studies and 4 weeks for asthma and CRSwNP studies); • positive for HBsAg, HBcAb, or hepatitis C antibody Chronic Obstructive Pulmonary Disease: • Respiratory tract infection within 4 weeks prior to screening, or during the screening period. • Patients on macrolide (eg, azithromycin) therapy, unless on stable therapy for >12 months. Atopic dermatitis/asthma pediatric studies: • Exclusion criterion removed for superficial skin infections above. (Data from the phase 3 program in adults has shown that dupilumab actually reduces the risk of superficial skin infections)	These exclusion criteria were considered because immunomodulating drugs might potentially increase the risk of infections. It was not known at beginning of the development of dupilumab whether it might increase the risk of severe or serious infections.	No	There was no increased risk of serious infections in combined dupilumab group relative to placebo in completed Phase 3 AD studies, pivotal asthma studies, pivotal EoE, pivotal PN, pivotal COPD, and pivotal Phase 3 CRSwNP studies to suggest that use of dupilumab in patients with infections would constitute a safety concern.
Atopic dermatitis, asthma, EoE, PN, and CRSwNP studies: • Patients with high risk of parasite infection, such as residence within or recent travel (within 12 months before the baseline visit) to areas endemic for endoparasitoses. • Active endoparasitic infection Atopic dermatitis studies: History of clinical endoparasite infection within 12 months of the	The mammalian immune response against helminths is consistently of the type 2 (including Th2) phenotype, characterized by IgE antibody production, eosinophilia, mastocytosis and specific forms of fibrotic wound repair under the control of the cytokines IL-4, IL-5, and IL-13. *227, 228, 229, 230, 231, 232, 233,*	No	The MOA of dupilumab has the potential to increase the risk of helminthic infections. Patients with active helminthic infections or at high risk of developing helminthic infections were excluded from the dupilumab clinical trials out of caution. Enterobiasis is listed as an ADR in children 6-11 years old with asthma in section 4.8 Paediatric population of the SmPC.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
baseline visit, other than treated vaginal trichomoniasis. Chronic Obstructive Pulmonary Disease: • Diagnosed active parasitic infection (Helminthes), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.	[234, 235] Since dupilumab's MOA consists of suppressing the type 2 response (including Th2 response) by blocking IL-4 and IL-13 signaling, the risk of helminthic infections is considered a theoretical concern with dupilumab therapy.		
Atopic dermatitis adults, asthma, EoE, PN, CRSwNP and COPD studies: History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin. Atopic dermatitis/asthma pediatric studies: History of malignancy before the baseline visit.	Not possible to stratify for this factor and more informative to exclude this known confounder from the safety data to be able to more accurately assess the data for any unexpected risks	No	Available evidence from approximately 14 671 PYs of exposure in clinical studies does not support an increase the risk of malignancy with dupilumab. The clinical data corroborate preclinical data, indicating IL-4 and IL-13 actions via the IL-4Rα activation pathway to be predominantly pro-tumorigenic. As agreed with several regulatory Health Authorities (including EMA and FDA), no additional specific nonclinical studies, eg, no animal carcinogenicity studies, are needed. In AD, asthma, CRSwNP and COPD clinical trials, crude incidence rate of malignancy in dupilumab-treated patients was numerically lower than placebo patients.
Atopic dermatitis and asthma studies: Use of live attenuated vaccines within 12 weeks before baseline. CRSwNP, EoE, PN, asthma, atopic dermatitis pediatric studies, and COPD: Use of live attenuated vaccines within 4 weeks prior to screening and during study.	This exclusion criterion was included as a precautionary measure, as the effect of IL-4Rα inhibition and subsequent suppression of type 2 immunity on viral immunity/host defense is not known.	No	Dupilumab effect on live vaccine safety is not considered as missing information in the EU-RMP as there is no additional risk minimization measures or additional pharmacovigilance activities planned or required. Adequately addressed in section 4.5 of the SmPC.
Atopic dermatitis, asthma, EoE, CRSwNP, and COPD studies: Pregnant, lactating or breastfeeding women, or women planning to become pregnant or breastfeed during the study.	This exclusion criterion is commonly applied to clinical trials for drugs or biologics in development before the safety profile	Yes	Adequately addressed in section 4.6 of the SmPC.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	is established in non-pregnant patients.		
Atopic dermatitis pediatric, AD, asthma, EoE, CRSwNP and COPD studies: Female patients of childbearing potential and sexually active, who are unwilling to use adequate methods of contraception throughout the duration of the study (and for 120 days after the last dose of study drug in AD pediatric studies). Asthma pediatric studies: Female patients who have commenced menstruating at any time during the study and are either: • Found to have a positive urine pregnancy test, or • Sexually active, not using an established acceptable contraceptive method. Chronic Obstructive Pulmonary Disease: • Do not have a confirmed negative serum beta-hCG test at Visit 1 or negative urine pregnancy test at Visit 2.	This exclusion criterion is commonly applied to clinical trials for drugs or biologics in development before the safety profile is established in non-pregnant patients.	Yes	Not applicable
Atopic dermatitis adult studies, asthma, EoE, PN, CRSwNP and COPD studies: Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.	Patients with a history of hypersensitivity reactions to biologics are excluded for their own safety, since excipients for biologics may be similar, so hypersensitivity to these components may be shared across biologic therapies	No	This exclusion criterion does not meet the level of importance to be retained in missing information and was included because of methodological reasons. Adequately addressed in sections 4.3, 4.4 and 4.8 of the SmPC.
Asthma, EoE, PN and CRSwNP studies: Liver injury related criteria: • Clinically significant/active hepatobiliary disease or • Alanine aminotransferase >3 ULN • Hepato-biliary conditions (eg, Child-Pugh Class B or C)	Signs and symptoms associated with these conditions may confound the safety profile of dupilumab treated study participants	No	Dupilumab, as a mAb, is not expected to undergo significant hepatic elimination. No specific safety issue is expected in this population. Adequately addressed in sections 4.2 and 5.2 of the SmPC.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Atopic dermatitis and asthma studies: History of alcohol or drug abuse within 2 years before the screening visit, or evidence of such abuse as documented by a positive result in a laboratory test for alcohol and/or drug panel conducted at the screening visit. CRSwNP and PN studies: Known or suspected alcohol and/or drug abuse. Eosinophilic Esophagitis studies: History of alcohol or drug abuse within 6 months prior to screening.	Signs and symptoms associated with liver injury may confound the safety profile of dupilumab treated study participants	No	Dupilumab, as a mAb, is not expected to undergo significant hepatic elimination. No specific safety issue is expected in this population.
Eosinophilic Esophagitis study: • Other causes of esophageal eosinophilia or the following conditions: hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) • Active Helicobacter pylori infection • History of achalasia, Crohn's disease, ulcerative colitis, celiac disease, and prior esophageal surgery	Patients with other causes of esophageal eosinophilia were not considered as they were not the intended population for this study. Patients with active Helicobacter Pylori infection could have underlying GERD which is not considered as type 2 inflammatory condition. Further it is not the intended population for this study. The reason for excluding other gastrointestinal autoimmune condition is that these conditions can mimic findings of EoE but are not type 2 inflammatory conditions. Also, prior esophageal surgeries increase risk of complications during endoscopy.	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.
Chronic Obstructive Pulmonary Disease study: • Significant pulmonary disease other than COPD (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary	Patients with other significant pulmonary disease other than COPD were not considered as they were	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
hypertension, bronchiectasis, Churg-Strauss Syndrome, etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts. • Diagnosis of α-1 anti-trypsin deficiency.	not the intended population for this study. Patient with diagnosis of α-1 anti-trypsin deficiency could potentially lead to COPD however not manifested via Type 2 inflammation and thus is not the intended population.		
Prurigo Nodularis studies: • Presence of skin morbidities other than PN and mild AD. Conditions such as, but not limited to, the following: scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease. • Patients with a documented AD severity moderate to severe within 6 months before the screening visit, or documented diagnosis of moderate to severe AD from screening visit to randomization visit (eg, IGA AD of 3 or 4, EASI ≥16, SCORAD ≥25).	Such conditions may confound the ability to assess the data for potential effects of the investigational product and may interfere with assessment of the outcomes.	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.
Prurigo Nodularis studies: • Prurigo Nodularis secondary to medications (eg, opioids, ACE inhibitors). Prurigo Nodularis secondary to medical conditions such as neuropathy or psychiatric disease (eg, notalgia paresthetica, brachioradial pruritus, neurotic excoriations, obsessive compulsive disorder, delusions of parasitosis, etc).	Patients with prurigo nodularis secondary to medications and due to other medical conditions were not considered as they were not the intended population for this study.	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.
Prurigo Nodularis and COPD studies: • Severe renal conditions (eg, patients with uremia and/or on dialysis) - for PN only. • Participants with uncontrolled thyroid disease - for PN only.	These are severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
• Patients with cardiovascular conditions (eg, Class III or IV heart failure according to the New York Heart Association classification) • Clinically significant abnormal ECG at randomization that may affect the conduct of the study in the judgment of the investigator, prolonged QTc interval [male >450 msec, female >470 msec, Fredericia correction] - for COPD only. • Cor pulmonale, evidence of right cardiac failure - for COPD only. • Cardiac arrhythmias including paroxysmal (eg, intermittent) atrial fibrillation are excluded - for COPD only.	the patient's participation in the study.		
Exclusion criteria related to the active comparator and/or mandatory background therapies			
Adult AD and asthma patients requiring treatment with drugs associated with clinically significant QTc interval prolongation/Torsades de Pointes ventricular tachycardia.	Such treatments may confound the ability to assess the data for potential effects of the investigational product	No	No relevant mean changes from baseline were observed for QT intervals in AD and asthma studies.
Atopic dermatitis, asthma, CRSwNP, PN, EoE, and COPD patients with significant laboratory abnormalities before randomization			
Any relevant laboratory abnormalities at screening that, in the opinion of the investigator, might suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial were excluded. EFC13579 and EFC13691 (asthma), EFC14146 and EFC14280 (CRSwNP): Abnormal lab values at screening: • Creatine phosphokinase >10 ULN or • Platelets <100 000 cells/mm^3 or • Eosinophils >1500 cells/mm^3 <u>Atopic dermatitis pediatric studies 6 to <12 years</u>:	Patients with clinically significant laboratory abnormalities were excluded as they might have an unknown clinical disease. Inclusion of such patients might also confound the safety evaluation of dupilumab safety profile.	No	This exclusion criterion does not meet the level of importance to be retained in missing information and was included because of methodological reasons.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Presence of any 1 or more of the following abnormalities in laboratory test results at Screening: • Platelets $\leq$100 x 103/µL • Neutrophils <1.5 x 103/µL • Creatine phosphokinase >5 x ULN • Serum creatinine >1.5 x ULN <u>AD (6 months to 5 years)</u>: Platelets $\leq$100 x 10^3/µL Neutrophils $\leq$1.0 x 10^3/µL for patients <1 year of age; Neutrophils $\leq$1.5 x 10^3/µL for patients 1 year to <6 years of age • Eosinophils >5000/µL • Creatine phosphokinase >2.5 x ULN • Serum creatinine >1.5 x ULN <u>Asthma pediatric studies <12 years, PN, EoE, and COPD (at the time of screening)</u>: At any time: Patients with positive (or indeterminate) test for HBs-Ag; positive IgM HBc-Ab; positive total HBc-Ab confirmed by positive HBV-DNA; positive HCV-Ab confirmed by positive HVC RNA. <u>Eosinophilic Esophagitis studies</u>: Any of the following abnormal lab values at screening: • Platelets <100 x 103/µL • Neutrophils <1.5 x 103/µL • Estimated glomerular filtration rate <30 mL/min/1.7m^2 <u>Chronic Obstructive Pulmonary Disease</u>: Clinically significant laboratory tests at screening: • Alanine transaminase (ALT) >3 times upper limit of normal range (ULN). • Hemoglobin <10g /100 mL for male and <9g/ 100 mL for female. • Platelets <100 000/mm3.			

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
• Creatinine ≥150 µmol/L.			

ACE: Angiotensin Converting Enzyme; AD: Atopic Dermatitis; ADR: Adverse Drug Reaction; ALT: Alanine Aminotransferase; ANA: Anti-Nuclear Antibody; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; dsDNA: Double Stranded Deoxyribonucleic Acid; EASI: Eczema Area and Severity Index; ECG: Electrocardiogram; EGPA: Eosinophilic Granulomatosis with Polyangitis; EMA: European Medicines Agency; EoE: Eosinophilic Esophagitis; EU: European Union; FDA: Food and Drug Administration; GERD: Gastroesophageal Reflux Disease; GVP: Good Pharmacovigilance Practices; HBcAb: Hepatitis B Core Antibody; HBsAg: Hepatitis B Surface Antigen; HBV-DNA; Hepatitis B Virus Deoxyribonucleic Acid; hCG: Human Chorionic Gonadotropin; HCV-RNA; Hepatitis C Virus Ribonucleic Acid; HIV: Human Immunodeficiency Virus; HLGT: High Level Group Term; hs-CRP: High-Sensitivity C-Reactive Protein; ICS: Inhaled Corticosteroid; IgE: Immunoglobulin E; IL-4: Interleukin-4; IL-4Rα: Interleukin-4 Receptor Alpha; IL-5: Interleukin-5; IL-13: Interleukin-13; IMP: Investigational Medicinal Product; mAb: Monoclonal Antibody; MOA: Mechanism of Action; mRNA: Messenger Ribonucleic Acid; OCS: Oral Corticosteroid; PN: Prurigo Nodularis; PY: Patient-Years; Q2W: Once Every Two Weeks; QW: Once Every Week; RMP: Risk Management Plan; SC: Subcutaneous; SmPC: Summary of Product Characteristics; SOC: System Organ Class; TB: Tuberculosis; TCI: Topical Calcineurin Inhibitor; TCS: Topical Corticosteroid; TEAE: Treatment-Emergent Adverse Event; Th1: Type 1 Helper T Cell; Th2: Type 2 Helper T Cells; TPO: Thyroid Peroxidase; ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development programme is unlikely to detect certain types of adverse reactions such as: very rare adverse reactions, or adverse reactions with a long latency that is beyond study period. The clinical development programme can detect ADRs that are rare (≥1/10 000 to <1/1000) or more frequent.

A total of 9958 patients were exposed to dupilumab in completed/unblinded EoE[2] ,COPD, PN, AD, asthma and CRSwNP studies as per DLP specified in RMP Part II module SIII. A breakdown of exposure by indication is provided in the RMP Part II module SIII.

The probability to observe at least one occurrence of an AE in the dupilumab group is 95% if this event truly occurs in at least 0.04% of the population, meaning that AEs with a frequency greater than 1 in 2500 patients (ie, 0.04%) could be detected in the dupilumab treatment group.

Of the 9958 patients in completed/unblinded studies, 6831 and 3237 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively.

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
Which are rare ≥1/10 000 to <1/1000	As of the DLP, over 9900 patients have been exposed to dupilumab in the clinical program across several indications. Among completed/unblinded dupilumab studies, 938 adult patients were in the COPD program, 436 adult and pediatric patients were in the EoE program, 152 adult patients were in the PN program, 4503 adult and pediatric patients	Based on the number of patients exposed to dupilumab, adverse reactions with crude incidence rate of ≥01 in 2500 patients could be detected in the dupilumab group with at least 95% probability.

[2] Exposure data for EoE in patients 1 to 12 years of age have been included (subject to an ongoing submission).

Ability to detect adverse reactions	Limitation of trial programme	Discussions of implications for target population
	were in the AD program, 3434 adult and pediatric patients were in the asthma program, and 495 adult patients were in the CRSwNP program.	
Due to prolonged exposure	As of the DLP, the total number of patients across the unblinded/completed trials exposed to dupilumab for ≥52 weeks was 6831, with over 3237 exposed for 2 years or more. Since this long-term exposure is in uncontrolled open label studies in the asthma and AD indications, there are limitations due to the lack of a placebo control group.	Prolonged exposure is relevant as AD and asthma are chronic conditions and dupilumab may be used by some patients chronically. Safety information on patients treated with dupilumab for over 2 years has been adequately characterized following completion of long-term safety study LTS14041 [R668-AD-1225] conducted in adult patients. Thus, missing information topic "long-term safety in adult and pediatric patients" is renamed "long-term safety in pediatric patients".

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 42 - Exposure of special populations included or not in clinical trial development programmes[3]

Type of special population	Exposure
Pregnant women	As of the DLP of 28-Mar-2023, there were 84 pregnancies in completed and ongoing phase 2/3 placebo controlled or open label asthma, EoE, AD, and CRSwNP studies (4 in EoE [1 in dupilumab arm, 3 in placebo arm], 31 in asthma [26 in dupilumab arm and 5 in placebo arm], 48 in AD [41 in dupilumab arm; 7 in placebo arm]; and 1 in CRSwNP studies [1 subject in placebo arm]). No pregnancy cases were reported in PN and COPD studies.
Breastfeeding women	Breastfeeding women were not included in the clinical development program.
Patients with relevant comorbidities • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

[3] Exposure data for EoE in patients 1 to 12 years of age have been included in this table (subject to an upcoming submission).

Type of special population	Exposure
Populations with relevant different ethnic origin (Completed studies)	
Ethnicity	
Hispanic or Latino	AD: 293 (412.9 PY); asthma: 836 (1576.1 PY); CRSwNP: 100 (94.1 PY); EoE: 25 (21.0 PY); PN: 28 (13.0 PY); COPD: 282 (255.7 PY)
Non-Hispanic or Latino	AD: 4141 (8129.4 PY); asthma: 2598 (4254.5 PY); CRSwNP: 394 (283.7 PY); EoE: 407 (332.9 PY); PN: 124 (56.4 PY); COPD: 652 (595.0 PY)
Not reported/missing	AD: 69 (82.3 PY); CRSwNP: 1 (1.0 PY); EoE: 4 (3.7 PY); COPD 4 (4.0PY)
Race	
White / Caucasian	AD: 3163 (6293.5 PY); asthma: 2671 (4852.6 PY); CRSwNP: 413 (306.6 PY); EoE: 394 (318.8 PY); PN: 82 (37.4 PY); COPD: 815 (745.3 PY)
Black or African American	AD: 367 (538.3 PY) asthma 137 (184.0 PY); CRSwNP: 7 (5.2 PY); EoE: 20 (18.6 PY); PN: 11 (5.2 PY); COPD: 7 (5.7 PY)
Asian	AD: 841 (1479.6 PY); asthma: 565 (687.3 PY); CRSwNP: 62 (54.9 PY); EoE: 7 (7.1 PY); PN: 54 (24.5 PY); COPD: 74 (676 PY)
American Indian or Alaska Native	AD: 10 (10.5 PY)
Other	AD: 93 (150.1 PY); asthma: 61 (106.7 PY); CRSwNP: 12 (11.4 PY); EoE: 12 (11.2 PY); PN: 5 (2.3 PY); COPD: 40 (34.7 PY)
Not reported	AD: 29 (52.6 PY); CRSwNP: 1 (0.5 PY); EoE: 3 (1.9 PY); COPD: 2 (1.5 PY)
Subpopulations carrying known and relevant genetic polymorphisms	Not included in the clinical development program.
Children (Completed studies)	Both genders ≥6 months and ≤11 years: AD (608; 1490.8 PY), asthma (400; 617.7 PY), EoE (99; 96.8 PY), 0 (PN), 0 (COPD) and 0 (CRSwNP); • Males: ≥6 months and ≤11 years: AD (328; 817.8 PY), asthma (258; 397.1 PY); 0 (CRSwNP); EoE (76; 75.7 PY), 0 (PN), 0 (COPD). • Females: ≥6 months and ≤11 years: AD (280; 673.0 PY), asthma (142; 220.6 PY); 0 (CRSwNP); 0 (EoE), 0 (PN), 0 (COPD). Both genders ≥12 and ≤17: AD (365; 516.8 PY); asthma (103; 181.7 PY); EoE (98; 83.0 PY); 0 (CRSwNP); 0 (PN), 0 (COPD). • Males ≥12 and ≤17: AD (200; 273.7 PY); asthma (66; 112.9 PY); EoE (72; 59.3 PY); 0 (CRSwNP); 0 (PN); 0 (COPD) • Females ≥12 and ≤17: AD (165; 243.1 PY); asthma (37; 68.8 PY); EoE (26; 22.7 PY); 0 (CRSwNP); 0 (PN); 0 (COPD)
Other Elderly (>65)	Both genders: AD (153; 214.7 PY); asthma (353; 639.7 PY); CRSwNP (85; 69.8 PY); EoE (2; 2.2 PY); PN (37; 16.3); COPD (551; 495.2 PY)
Males (>65)	Males: AD (97; 131.0 PY); asthma (153; 278.2 PY); CRSwNP (50; 41.0 PY); EoE (0); PN (15; 6.9 PY); COPD (377; 338.2 PY)
Females (>65)	Females: AD (56; 83.7 PY); asthma (200; 361.5 PY), CRSwNP (35; 28.8 PY); EoE (2; 2.2 PY); PN (22; 9.4 PY); COPD (174; 157.0 PY)

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis; PY: Patient-Years.

Pregnant and breastfeeding women:

As of the DLP of 28 March 2023, there were 84 pregnancies in completed and ongoing phase 2/3 placebo controlled or open label asthma, EoE, AD, and CRSwNP studies (4 in EoE [1 in dupilumab arm, 3 in placebo arm], 31 in asthma [26 in dupilumab arm and 5 in placebo arm], 49 in AD [41 in dupilumab arm; 7 in placebo arm]; and 1 in CRSwNP studies [1 subject in placebo arm]). No pregnancy cases were reported in PN and COPD studies.

Among the 84 pregnancies in all dupilumab trials for AD, EoE, asthma, and CRSwNP, 49 pregnancies (*in 48 patients wherein 1 subject had twin pregnancy*) were from AD studies. Among these, 41 patients (*with 42 pregnancies as 1 of these patients had a twin pregnancy*) received dupilumab and 7 patients received placebo. The outcomes of the 7 AD placebo patients include 2 elective abortions, 2 normal live births, 1 spontaneous abortion, 1 unknown outcome, and 1 not reported. The outcomes of the 41 AD dupilumab exposed patients correspond to 42 outcomes including 24 normal live births, 6 spontaneous abortions, 3 elective abortions, 1 premature birth (with no fetal defect), 1 with unknown outcome, 1 not reported and 6 lost to follow-up. Of note, 1 dupilumab exposed patient had a twin pregnancy (live, normal birth of one twin and spontaneous abortion of the other).

Of the 84 pregnancies as of the DLP of 28 March 2023, 31 pregnancies were reported in the unblinded (DRI12544 and EFC13579) and open-label (LTS12551, LPS15023, EFC13691 and ACT11457) asthma studies. Of the 31 pregnancies reported in asthma studies, 5 pregnancies occurred in placebo patients in study EFC13579, of which three pregnancies resulted in live births of normal infants, 1 elective abortion and 1 ectopic pregnancy. Among the 26 pregnancies in dupilumab-treated patients, outcomes include 7 spontaneous abortions, 2 elective abortions, 14 full term live births, and 3 premature births. One woman in study EFC13579 delivered a baby with congenital anomaly of Turner's syndrome associated with bicuspid aortic valve. One woman in study LTS12551, who had been diagnosed with tuberculosis meningitis, delivered a live, very low birth weight infant at 23 weeks gestation via caesarian delivery; on the same day, the patient died and no information about the child's health status was reported. At the time of this report, there are no ongoing pregnancies in asthma patients who were exposed to dupilumab.

A total of four pregnancies were reported in EoE studies (R668-EE-1324 and R668-EE-1774). Of the 4 pregnancies, 1 occurred in a dupilumab-treated patient and 3 in patients on placebo. The pregnancy in the dupilumab-treated patient resulted in spontaneous abortion (assessed as not related to dupilumab by the investigator in view of patient medical history of cervical surgery due to cervical cancer) and among the pregnancies in the placebo patients, 1 patient reported spontaneous abortion and for other 2 patients outcome was unknown.

One pregnancy was reported in the CRSwNP safety pool (ACT12340, EFC14146 and EFC14280 studies). This pregnancy occurred in a placebo-exposed patient and the outcome was reported as normal live birth.

There are no safety data reported from clinical studies on the use of dupilumab in lactating/breastfeeding women.

Clinical data available concerning the use of dupilumab in pregnant women who experienced unplanned pregnancies while participating in clinical trials did not provide required safety information. Animal studies do not indicate direct or indirect harmful effects with respect to

reproductive toxicity (See Table 12). Due to the small number of pregnancies in patients exposed to dupilumab in the clinical studies, the current data are insufficient to adequately assess the pregnancy risks associated with dupilumab exposure.

No information is currently available regarding the presence of dupilumab in human milk, the effects of dupilumab on breastfed infants, or the effects of dupilumab on milk production. As an immunoglobulin G4 (IgG4) drug has been shown to transfer into the breast milk of lactating cynomolgus monkeys [236], dupilumab as a human IgG4 mAb is also expected to appear in the milk of lactating patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for dupilumab and any potential adverse effects on the breastfed infant due to dupilumab or to the underlying maternal condition.

Since there is a gap in knowledge about the safety of dupilumab in case of use in pregnant and breastfeeding women, the use of dupilumab in pregnant and lactating women is considered as missing information (see [RMP Part II module SVII]).

In order to acquire more data on any effects on dupilumab exposure during pregnancy, a pregnancy registry and a pregnancy outcome study are part of the pharmacovigilance plan (see [RMP Part III]).

Potential for use in paediatric patients not covered by the authorized indications (postmarketing data)

A cumulative search with a DLP of 28 March 2023 was performed in the Sanofi safety database for all ADRs with regards to off-label use in pediatric age groups not covered by approved indications respectively. It was noted that 62 reports were from pediatric patients aged <6 months old treated for AD; 208 cases reported use in pediatric patients aged <6 years treated for asthma; 66 cases reported the indication as CRSwNP in patients aged <18 years; 189 cases reported the indication as EoE in patients aged <12 year and 19 cases reported the indication as PN in patients aged <18 years. No pediatric patients were reported with a COPD indication. The cumulative exposure in marketed experience is estimated to be 1.2 million patients up to DLP of 31 March 2023.

AD pediatric patients (<6 months of age):

Among 62 postmarketing case reports, 55 were non-serious and 7 were serious. Among 7 serious cases, 5 neonates reported foetal exposure during pregnancy and one among them additionally had neonatal jaundice with outcome as recovered and another one had ventricular septal defect on day 2 (underwent surgical correction) with outcome as recovered. In the remaining 2 cases maternal exposure to dupilumab was unclear, wherein one patient, aged 69 days experienced food allergy (leading to burned and blistered mouth and gums) for which outcome was unknown. In the other patient, aged 3 months shoulder pain and pneumonia was reported, however no additional details were available.

The most frequently reported event is linked to the off-label use, in the SOC Injury, poisoning and procedural complications (N = 63 events; with off-label use [N = 23], Off label use of device [N = 13], and Product use issue [N = 12]. The next most frequently reported SOC was Skin and subcutaneous tissue disorders (N = 15) with the most commonly reported preferred term (PTs) being rash [N = 3], dermatitis atopic [N = 2], pruritis [N = 2], urticaria [N = 2]. The next most frequently reported SOC was General disorders and administration site conditions with the most commonly reported events being Injection Site Reactions (N = 5) which included PTs of Injection

site pain (N = 2), Injection site erythema (N = 1), Injection site reaction (N = 1) and Injection site bruising (N = 1). All these events of injection site reactions were consumer reports and were reported as non-serious, in 4 cases no action was taken with dupilumab and in 1 case action taken was unknown. The outcome was not recovered in 2 cases and unknown in 3 cases. Injection site reactions have been previously identified as ADRs in the clinical development program and do not represent a new safety concern.

No new safety concerns or pattern of events were identified upon review of these reports.

Asthma pediatric patients (<6 years of age)

Among 208 postmarketing case reports, 200 were non-serious and 8 were serious. Among these 8 serious cases, 4 were consumer reports; 3 were patient support program and 1 was a healthcare professional (HCP) report, all patients were between 4 to 6 years of age; outcome was recovered in 2 cases, not recovered in 2 cases and unknown in rest of the cases. In one of these 8 cases, a patient with a medical history of prior methicillin resistant staphylococcus aureus (MRSA) infection developed another episode of MRSA which was treated with IV antibiotics. This patient also reported an allergic reaction to sulfamethoxazole/trimethoprim which manifested as rash and sleep disturbance. In another case, a patient developed an injection site reaction which manifested as severe pain due to which patient fainted. No action was taken with dupilumab, and the outcome was unknown. In another case, a patient had aspiration pneumonia following esophagogastroduodenoscopy (reason for the procedure not provided) and no other details were provided. In the remaining 5 cases, limited information precludes complete medical assessment.

The most frequently reported event is linked to the off-label use in the SOC Injury, poisoning and procedural complications (N = 197 events; with off-label use [N = 88], Product use issue [N = 27]; Product use in unapproved indication [N = 15] and Product prescribing issue [N = 10]. The next most frequently reported SOC included General disorders and administration site conditions [N = 44] with the most commonly reported events of Injection Site Reactions (N = 27) which included the PTs of Injection site pain (N = 8), Injection site erythema (N = 6), Injection site swelling (N = 3) and Injection site pruritus (N = 2) and other injection site PTs reported only once. None of these events were identified as serious and did not led to treatment discontinuation. Injection site reactions have been previously identified as ADRs in the clinical development program and do not represent a new safety concern.

The next most frequently reported SOC included Skin and subcutaneous tissue disorders (N = 26) with most common reported PTs (reported ≥2 events) of pruritus [N = 4], rash [N = 4], eczema [N = 2] and skin irritation [N = 2].

No new safety concerns or pattern of events were identified upon review of these reports.

Chronic Rhinosinusitis with Nasal Polyposis (<18 years of age)

Among 66 postmarketing case reports, 65 were non-serious and 1 was serious. In this serious case PTs reported were Retinal Tear, Eye Disorder and Arthralgia. Upon review of this case, limited information precludes assessment. The most frequently reported events are linked to the off-label use itself (use in an unapproved age group for patients with CRSwNP), in the SOC Injury, poisoning and procedural complications (N = 64, Off label use [N = 39], and Product use issue [N = 8]). No new safety concerns or pattern of events were identified upon review of these reports.

Eosinophilic Esophagitis pediatric patients (<12 years of age)

Among 189 postmarketing case reports, 185 were non-serious and 4 were serious. Among these 4 serious cases, 3 were consumer reports and one HCP report, 1 patient was 5 years, one was 6 years, one was 10 years and one was 11 years of age; outcome was fatal in 1 case and unknown in rest of the cases. In this HCP case with fatal outcome, 5-year-old female patient with medical history of extensive food allergies to multiple food sources including peanuts/sesame/coconut/legumes and milk received dupilumab 300 mg every 4 weeks for EoE. Patient was scheduled for a routine biopsy in June 2022, during which she was noted to have large hematoma in esophagus (related to biopsy procedure) and admitted to hospital. During hospitalization patient was given total parenteral nutrition through nasogastric tube following which she developed pruritus and anaphylactoid / allergic reaction with rapid deterioration leading to cardiac arrest. The patient succumbed in the hospital following an hour of cardiopulmonary resuscitation (it was noted that epinephrine injection was not available in the hospital). No autopsy was done. The cause of death was reported as anaphylactic reaction and cardiac arrest. In another case 6-year-old male with medical history of allergic reaction to XEMBIFY® infusion (immune globulin subcutaneous human–klhw) on dupilumab for Crohn's disease (off-label) and EoE developed allergic reaction, cellulitis and weeping lesions on hand after XEMBIFY infusion. No action taken with dupilumab and outcome is unknown. In another case a 10-year-old boy was admitted to hospital for eczema (unknown latency) with no additional details provided. In one case, an 11-year-old boy with autism who received dupilumab for severe eczema and EoE developed esophageal food impaction and esophageal pain (unknown latency) with reporter describing it as lack of efficacy.

The most frequently reported event is linked to the Off-label use in the SOC Injury, poisoning and procedural complications (N = 239 events; with Off-label use [N = 109], Product use issue [N = 30]; Product administered to patient of inappropriate age [N = 28], Product prescribing issue [N = 19] and Product use in unapproved indication [N = 16]. The next most frequently reported SOC included General disorders and administration site conditions [N = 68] with the most commonly reported AE (reported >2 events) of Injection Site Reactions (N = 37) which included most common PTs of Injection site pain (N = 11), Injection site erythema (N = 5), Injection site swelling (N = 6) and Injection site urticaria (N = 3). None of these events were identified as serious and did not led to treatment discontinuation. Injection site reactions have been previously identified as ADRs in the clinical development program and do not represent a new safety concern.

No new safety concerns or pattern of events were identified upon review of these reports.

Prurigo Nodularis pediatric patients (<18 years of age)

Among 19 postmarketing case reports, 18 were non-serious and 1 case was serious. In this serious case, a 15-year-old male patient experienced blurred vision, keratoconus and reported off label use due to use in unapproved age. Upon review of this case, currently limited information precludes assessment. The most frequently reported event is linked to the off-label use itself (use in an unapproved age group for patients with PN), in the SOC Injury, poisoning and procedural complications (N = 22, off-label use [N = 17], and Product use in unapproved indication [N = 2]). No new safety concerns or pattern of events were identified upon review of these reports.

Conclusion:

Upon review of available clinical trial data including pivotal trials in pediatric patients across AD, asthma, and EOE studies with studies completed in pediatric population up to age of 6 months (refer to Table 42 above) and review of pediatric patient data from postmarketing setting, no new information or trends have been identified with dupilumab use in pediatric patients. The MAH therefore proposes to discontinue ongoing assessment of safety based on postmarketing data in off-label use of dupilumab in pediatric population in the RMP. The MAH would continue to monitor safety in off-label pediatric patients using routine pharmacovigilance surveillance.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Marketing Authorization Holder is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience since December 2019. The MARCO application collects data monthly, as a result, the data may not correspond precisely to the current reporting interval.

Methodology:

- Calculating total sales in mg by multiplying units for parenteral formulation with their strength in mg/mL.
- Total sales in mg was divided by World Health Organization (WHO) Defined Daily Dose (DDD) of 21.4 mg for parenteral formulation and then divided by 365 to estimate PYs.
- Patient years = total sales in mg/(21.4 x 365).

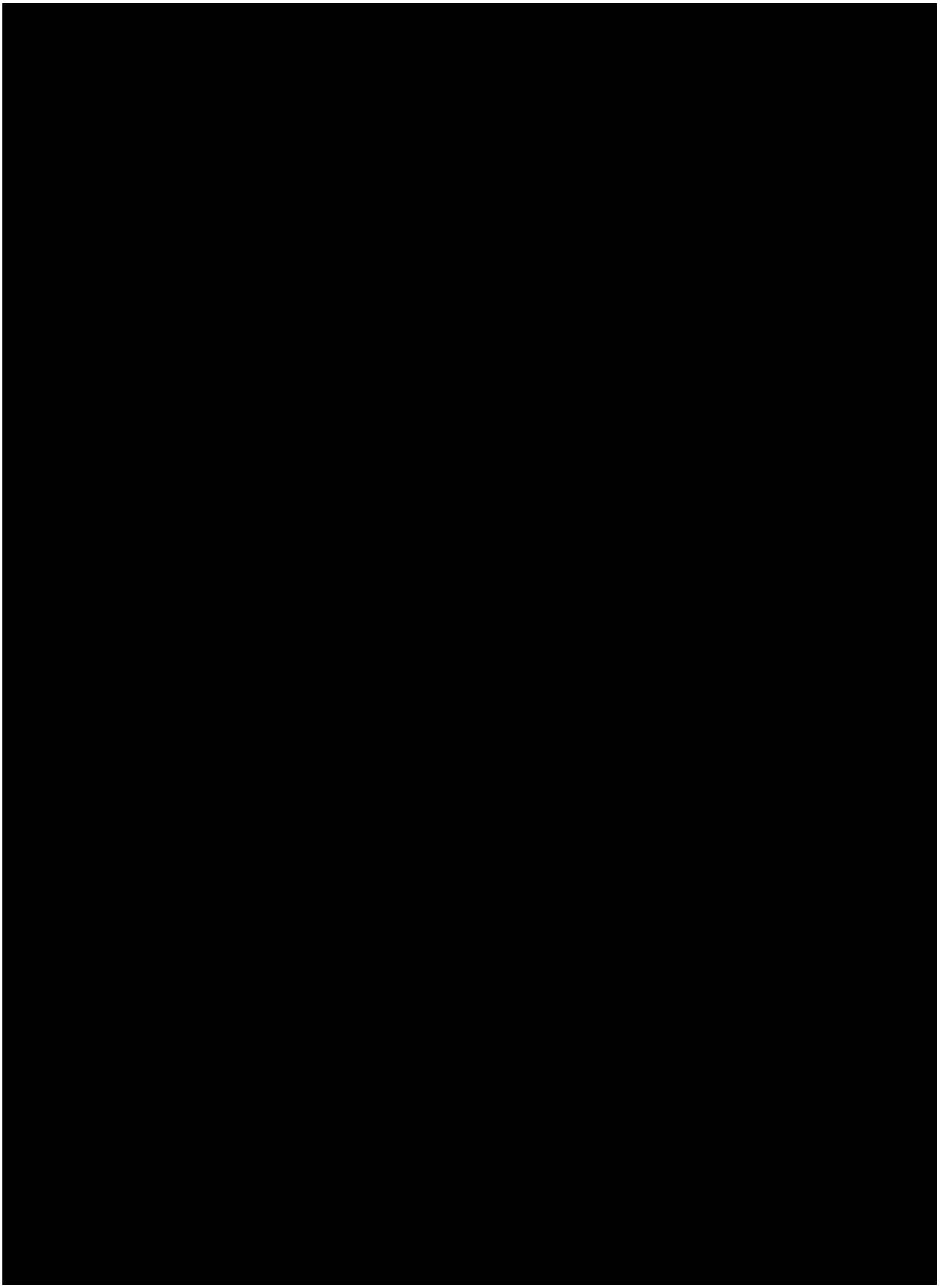
Cumulative Postmarketing exposure:

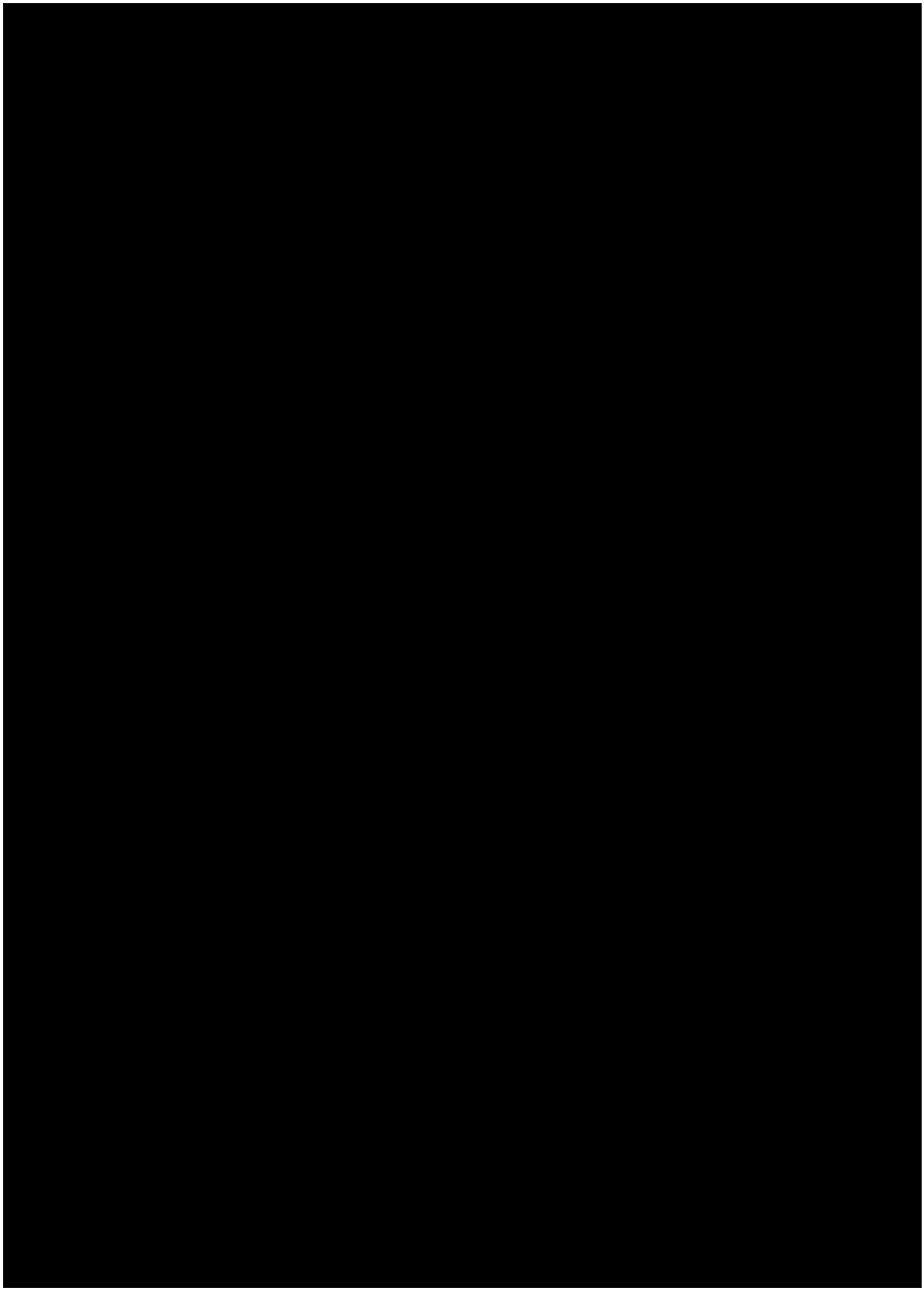
Sales data from the cumulative experience is available from MARCO for the period from 01 March 2017 through 31 March 2023.

The cumulative exposure to dupilumab parenteral formulations is estimated to be 1.2 million PYs.

[redacted]

[redacted]





RISK MANAGEMENT PLAN - PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Based on the data from non-clinical and clinical studies conducted to date, as well as an evaluation of the MOA of dupilumab, there is no evidence of CNS activity or signs associated with drugs of abuse. The molecule structure, known MOA and pharmacokinetic (PK) effects of dupilumab do not predispose it to become subject to drug abuse or dependence. Therefore, the potential risk for misuse for illegal purposes is considered low, and no risk minimization plan is necessary to control distribution.

RISK MANAGEMENT PLAN - PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

Refer to Module 2.7.4 Summary of Clinical Safety of the e-CTD sequence 0000 (initial MAA), sequence 0011 (asthma indication), sequence 0029 (AD 12-17 years indication), sequence 0044 (indication of CRSwNP), sequence 0071 (AD 6 years-11 years indication), sequence 0113 (asthma 6 years-11 years indication), sequence 0156 (AD 6 months - 5 years indication), sequence 0161 (PN indication), sequence 0160 (EoE indication in adults and adolescents), and sequence 0212 for COPD.

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

According to the EMA "Guideline on GVP Module V-Risk Management Systems" (EMA/838713/2011, Rev 2-31 March 2017)" and the "Guidance on the format of the RMP in the EU-in integrated format" (EMA/Pharmacovigilance Risk Assessment Committee [PRAC]/613102/2015, Rev 2-31 March 2017), the Section SVII.1 is expected to be "locked" and not changed after the approval of the initial RMP.

In accordance with these guidelines, the Company has provided in this section the initial list of safety concerns consistently with the information included in the EU-RMP 1.4 approved as part of the initial marketing authorization (MA) for the AD indication (Refer to final assessment report of procedure EMEA/H/C/004390).

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

Safety topics derived from specific situations (eg, potential harm from overdose, potential for transmission of infectious agents, medication errors, risks relative to the administration procedure, potential for off-label use) were extensively discussed in the initial EU-RMP 1.4. In compliance with the revised EU-RMP guideline, and since they do not lead to risks for the product, the data related to these topics in the EU-RMP 1.4 have not been transferred in this EU-RMP update 2.0 and are not further discussed in this RMP update.

The following ADRs listed in the section 4.8 of the SmPC approved as part of the application for the AD indication, were not considered important for inclusion in the list of safety concerns in the approved EU-RMP 1.4 as they have minimal clinical impact on patients (in relation to the severity of the AD indication treated):

- Headache
- Injection site reactions
- Eosinophilia
- Oral herpes

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section describes the initial list of safety concerns as included in the EU-RMP 1.4 approved as part of the initial MA for the AD indication, with corresponding DLP of 27 April 2016.

Table 44 - Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)

Systemic hypersensitivity (including events associated with immunogenicity)	
Scientific evidence that has led to the inclusion	Clinical trial data and literature.
Risk-benefit impact	Frequency A serious related case of serum sickness and serum sickness-like reaction each, had been reported in AD studies. As of DLP of the initial RMP (27-Apr-2016), 2526 patients in AD studies were exposed to dupilumab. The frequency category of serious systemic hypersensitivity reactions was rare (2/2526). Seriousness/outcomes The patient who experienced serum sickness reaction was hospitalized for evaluation of joint pain and fever. The patient who was reported to have serum sickness-like reaction was managed as an outpatient, but the event was considered medically important. Both patients presented with polyarthragia, fever and rash. Both patients recovered. Severity and nature of risk Usually, the inflammatory process itself is self-limited once the offending antigen is removed. Consequently, discontinuation of dupilumab is important once serum sickness is diagnosed. A course of steroids may be needed in severe cases. Background incidence/prevalence The incidence or prevalence of serum sickness/serum sickness like reaction is not well documented and varies by the type of drug. [237] Preventability Immediate hypersensitivity is not predictable or preventable. Preventability of type III hypersensitivity is not known. Hypersensitivity reaction in patients with known hypersensitivity to dupilumab or any of its excipients can be prevented by excluding them from further exposure, as stated in the Contraindication proposed for the dupilumab label. Impact on individual patient These reactions are self-limiting after discontinuation of antigen that causes the reaction. Symptoms associated with serum-sickness like reactions reported in the clinical program resolved upon discontinuation of dupilumab. Potential public health impact of safety concern Minor impact on public health as serious allergic reactions to dupilumab is rare. MedDRA terms Narrow SMQ for hypersensitivity for safety surveillance, followed by medical evaluation of relevant cases.

AD: Atopic Dermatitis; DLP: Data Lock Point; MedDRA: Medical Dictionary for Regulatory Activities; RMP: Risk Management Plan; SMQ: Standardized MedDRA Query.

Table 45 - Important potential risk: Malignancy

Malignancy	
Scientific evidence that has led to the inclusion	None. Although the Company considered that there are no data to support this contention, malignancy was listed as an important potential risk upon EMA request.
Risk-benefit impact	Frequency As of DLP of the initial RMP (27-Apr-2016), the incidence rate of malignancy for the Primary Safety Pool 16 week treatment period was 0.10% (1 of 1047) for dupilumab combined and 0.39% (2 of 517) for placebo group. The incidence rate in R688-AD-1224 52 week treatment period was 1.2% (5 of 425) for dupilumab + TCS combined group and 1.31% (4 of 315) for the placebo group + TCS. Seriousness/outcomes Serious and potentially fatal for many malignancies. Severity and nature of risk Severity depends on the stage and type of cancer. Background incidence/prevalence According to WHO, an estimated 14.1 million new cases of cancer occurred worldwide in the general population in 2012 (incidence rate was 2.0 per 1000). A UK cohort study of AD patients (all ages) estimated the overall cancer crude incidence rate (excluding NMSC) in AD patients was 33.24 (95% CI 30.83-35.80) per 10 000 persons and the IRR for overall cancer compared to patients without AD was 1.49 (95% CI 1.39-1.61). [238] Register-based retrospective cohort study in Sweden by Hagstromer et al [239] of AD patients showed a SIRs of 1.13 (95% CI 1.01-1.25) for cancer in general, significant increase in SIR for esophagus (3.5 [95% CI, 1.3-7.7]), brain (SIR, 1.6; 95% CI, 1.1-2.4), lung (SIR, 2.0; 95% CI, 1.3-2.8) and lymphoma (SIR, 2.0; 95% CI, 1.4-2.9). A large cohort study in Denmark from 1977 to 2006 of AD patients by Jensen et al [240] showed a SIR of 0.59 (95% CI 0.30-1.02) for malignant melanoma but an increased SIR for basal cell carcinoma and squamous cell carcinoma among AD patients (1.41 [95% CI 1.07-1.83] and 2.48 [95% CI 1.00-5.11], respectively). Preventability Avoidance of exposure to known carcinogens, such as part of tobacco smoke and asbestos; cancer screening. Impact on individual patient Potentially disabling; impaired quality of life and reduced life expectancy. Potential public health impact of safety concern Unknown MedDRA terms Malignant tumours narrow SMQ.

AD: Atopic Dermatitis; CI: Confidence Interval; DLP: Data Lock Point; EMA: European Medicines Agency; IRR: Incidence Rate Ratio; MedDRA: Medical Dictionary for Regulatory Activities; NMSC: Non-Melanoma Skin Cancer; RMP: Risk Management Plan; SIR: Standardized Incidence Ratio; SMQ: Standardized MedDRA Query; TCS: Topical Corticosteroid; UK: United Kingdom; WHO: World Health Organization.

Table 46 - Missing information: Use in pediatric AD patients <18 years of age

Use in pediatric AD patients <18 years of age	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	As of DLP of the initial RMP (27-Apr-2016), the safety and efficacy of DUPIXENT in children below the age of 18 years have not been established (see section 5.2 of the EU-SmPC approved as part of the AD indication). No data are available. The PKs of dupilumab in paediatric patients has not been studied.
Risk-benefit impact	The benefit-risk impact for pediatric AD patients cannot be assessed at this time.

AD: Atopic Dermatitis; DLP: Data Lock Point; EU: European Union; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 47 - Missing information: Use in pregnant and lactating women

Use in pregnant and lactating women	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	As of DLP of the initial RMP (27-Apr-2016), the total number of pregnancy cases with known exposure to dupilumab is small. As of DLP, there were 23 (1 placebo, 22 dupilumab) reports of pregnancy in all indications combined in completed or unblinded or open label studies. Of these, there were 15 pregnancies in AD studies for which outcome is available for 13 (2 patients were lost to follow up). A spontaneous abortion was reported for 2 of these 13 pregnancies (15%), which is within the background rate. No still born or congenital anomalies were reported, and 7 pregnancies in asthma studies, 4 of which ended with a spontaneous abortion (57%) with no still births or congenital anomalies reported; of whom. one patient had 2 of the known risk factors for spontaneous abortion. Two women had healthy delivery and 1 had induced abortion. The spontaneous abortion rate in AD studies was similar to the general population. Based on the small number of pregnancies in the asthma program to date (N = 7), an estimate proportion of spontaneous abortions is very imprecise. The background rate of spontaneous abortion in asthmatics (22.4%) estimated from administrative database from Quebec, Canada [241] might underestimate the actual rate due to possible under-reporting.
Risk-benefit impact	Based on very limited data on pregnancy outcomes in women exposed to dupilumab, it is not possible to assess the impact of dupilumab on pregnancy outcomes, and additional data are needed.

AD: Atopic Dermatitis; DLP: Data Lock Point; RMP: Risk Management Plan.

Table 48 - Missing information: Conjunctivitis related events

Conjunctivitis related events	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	A consistent dose response or a consistency in time to onset of these events has not been observed. Conjunctivitis events were prolonged in some dupilumab treated patients and/or were ongoing at the end of study follow up. The etiology of reported bacterial or viral conjunctivitis was not confirmed by microbiological testing. As these events were not serious and as conjunctivitis events were not included as pre-defined AESI, there is limited information regarding these events.
Risk-benefit impact	As of DLP of the initial RMP (27-Apr-2016): in the primary safety pool and the LTT, the majority of patients who reported these events, reported them as mild to moderate in severity.

Conjunctivitis related events	
	Conjunctivitis and related events were easily managed and rarely resulted in permanent sequelae to vision. The benefit-risk balance for AD patients who experience conjunctivitis and related events remains positive. However, additional data is needed to fully understand these observations. The Amendment 6 of study R688-AD-1225 added a sub-study consisting of standardized ophthalmology assessments for participating patients, which include detailed eye history, as well as standardized eye exams conducted routinely (pre-specified time points) and in case of ophthalmic AEs (unscheduled visits). Ophthalmology assessments are not currently planned for asthma or for other indications beyond AD.

AD: Atopic Dermatitis; AE: Adverse Event; AESI: Adverse Event of Special Interest; DLP: Data Lock Point; LTT: Long-Term Treatment; RMP: Risk Management Plan.

Table 49 - Missing information: Long-term safety

Long-term safety	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Safety of prolonged exposure to dupilumab is not known at this time.
Risk-benefit impact	Prolonged exposure is needed to confirm that benefit-risk balance does not change over time. The effect of prolonged exposure to dupilumab on the benefit-risk balance is unknown at this time.

Table 50 - Missing information: Dupilumab effect on live vaccine safety

Dupilumab effect on live vaccine safety	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	Atopic dermatitis is a condition with limited immune deficits that are dependent on the degree of atopy. There is a theoretical concern of live vaccine safety when administered concomitantly with immunosuppressant drugs. Dupilumab has not shown to have any immunosuppressant action based on pre-clinical and clinical data of over 4000 patients exposed to dupilumab (including 52-week placebo-controlled treatment data with concomitant TCS). However, since dupilumab has not been studied with live vaccines as of the DLP of the initial RMP of 27-Apr-2016, live vaccine safety is considered missing information.
Risk-benefit impact	Impact on risk-benefit is unknown.

DLP: Data Lock Point; RMP: Risk Management Plan; TCS: Topical Corticosteroid.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Update to missing information topic of "Long-term safety in adult and pediatric patients"

The missing information topic of "*Long-term safety in adult and pediatric patients"* is renamed "*Long-term safety in pediatric patients"*.

Rationale: The long-term safety study LTS14041 [R668-AD-1225] conducted in adult patients with AD has been completed. No new safety concerns with long-term use of dupilumab in adult patients

were noted in this completed study. Additionally, no further additional pharmacovigilance activities are ongoing or planned in adult patients. The long-term safety of dupilumab in adult patients will continue to be monitored using routine pharmacovigilance.

Update to remove important identified risk "Conjunctivitis and keratitis related events in AD patients" from RMP summary of safety concerns

Rationale: In accordance with the GVP Module V (Rev. 2), the important identified risk "*Conjunctivitis and keratitis related events in AD patients*" is removed from the RMP List of Safety Concerns due to the following considerations:

- The results from the completed long-term safety study LTS14041 (R668-AD-1225) did not yield new conclusions regarding this risk
  - Based on a narrow Customized MedDRA Query search, conjunctivitis was reported in 20% of all participants
    - Most (99%) events of conjunctivitis were assessed by the Investigator as mild to moderate in severity
    - Discontinuation of study drug due to events of conjunctivitis was low (0.5%)
    - Conjunctivitis occurred more frequently among participants with a medical history of conjunctivitis, in participants who had experienced an AE of conjunctivitis in the parent study, and in participants with greater AD disease severity at baseline
    - Nearly all events of conjunctivitis were reported as resolved or resolving while the participant remained on study drug
  - Events of keratitis were reported in 1.0% (PT keratitis) and 0.6% (PT ulcerative keratitis) of participants
    - Most events of keratitis were assessed by the Investigator as mild to moderate in severity, none were reported as serious and all the events of keratitis resolved except one which was ongoing at the time of database lock
- The results from the completed LTS14041 (R668-AD-1225) ophthalmology sub-study were generally consistent with data from the main study and no new ophthalmic safety findings were identified in the ophthalmic substudy participants.
- There are neither additional risk minimization measures nor additional pharmacovigilance activity.
- The benefit-risk balance for dupilumab remains positive when prescribed in accordance with the product label.
- The important identified risk of "Conjunctivitis and keratitis related events in AD patients" remains listed in the summary of safety concerns for the Periodic Benefit-Risk Evaluation Report and as such the MAH will continue to review new information on an ongoing basis.
- Of note, in the completed COPD Study EFC15804, conjunctivitis was reported in both the dupilumab and placebo groups, in 1.1% and 1.9% of participants, respectively. There were no adverse events of keratitis reported. In EFC15805 with interim data cut-off of 29 September 2023, conjunctivitis was reported in both the dupilumab and placebo groups, in 2.1% and 0.9% of participants, respectively; and one event of keratitis (0.2%) was

reported in dupilumab arm. In pooled safety data from both COPD studies, the incidence of conjunctivitis (Customized MedDRA Query [CMQ] broad criteria) was reported in 1.6% in the dupilumab group and 1.4% participants in the placebo group; and treatment-emergent keratitis (as searched by keratitis CMQ) was reported in 1 participant in the dupilumab group (0.1%) and none in placebo group.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for dupilumab (DLP of 29 September 2023):

- Important identified risk:
  - Systemic hypersensitivity (including events associated with immunogenicity)
- Important potential risk:
  - None
- Missing information:
  - Use in pregnant and lactating women
  - Long-term safety in paediatric patients

SVII.3.1 Presentation of important identified risks and important potential risks

Table 51 - Identified risk: Systemic hypersensitivity (including events associated with immunogenicity)

Identified Risk	**Systemic hypersensitivity (including events associated with immunogenicity)**
Potential mechanism	Hypersensitivity reactions to dupilumab (IgG4 mAb) could theoretically be either IgE mediated (local or generalized urticaria) or IgG mediated (or other isotype) mediated with generalized and acute chills, nausea, headache, fever due to Fc-IgG mediated activation of immune cells. In general, clinical manifestations could be either acute or delayed. Serum sickness is a type III immune complex-mediated hypersensitivity disease characterized by rash, arthritis, and fever, with onset several days to weeks after administration of heterologous or foreign protein. Serum sickness-like reactions mimic classic serum sickness but are thought to be caused by a different mechanism. The pathogenesis of serum sickness-like reactions is not dependent upon high titers of antibodies and circulating immune complexes. [242] The potential for hypersensitivity to dupilumab leading to an acute allergic reaction is thought to be partially mitigated because dupilumab blocks IL-4 signaling, a central mediator of isotype class switching to IgE, and of eosinophil recruitment, which are important mediators of type 1 hypersensitivity reactions.
Evidence source(s) and strength of evidence	Clinical trial data, literature and postmarketing pharmacovigilance.
Characterization of the risk	Frequency *AD studies:* *Adults* (as of DLP of 28-Sep-2019):

Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	There were no anaphylactic reactions related to Dupilumab in adult AD patients. A serious case of serum sickness and serum sickness-like reaction each have been reported in adult AD studies. 3195 patients in AD studies were exposed to dupilumab. Based on this exposure estimate (2/3195, 0.063%), the frequency category of serious systemic hypersensitivity reactions is rare in AD. *Adolescents (12-17 years of age)* (as of DLP of 21-Apr-2018): No case of anaphylaxis to dupilumab has been observed. In contrast to the adult program, no case of serum sickness has been observed in the adolescent program, which is possibly related to the smaller number of patients studied in this specific age group. *Children (6-11 years of age)* (as of DLP of 22-Jul-2019): There have been no anaphylactic reactions related to dupilumab in pediatric (age 6-11) patients in clinical trials. No cases of serum sickness have been observed in the pediatric program, which may be partly due to the smaller number of patients studied in this specific age group. *Pediatric patients (6 months to 5 years of age)* (as of study DLP of 31-Jul-2021): There were no reports of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab. This is particularly relevant in a pediatric population given the relative lack of data on immunogenicity with mAbs in this age group as compared to adults. *ASTHMA studies (as of DLP of 28-Sep-2020):* In asthma studies, analysis of hypersensitivity AESIs was based on events identified by hypersensitivity narrow SMQ terms and confirmed as relevant systemic hypersensitivity events by medical review. Selection of relevant systemic hypersensitivity events was made regardless of relatedness to IMP. As such, anaphylaxis to food would be classified as a systemic hypersensitivity AESI during the medical review and be counted as an event of dupilumab in the systemic hypersensitivity frequency table if the patient had received dupilumab during the study. It should also be noted that cutaneous reactions (such as rash and dermatitis) were classified as systemic reactions if they occurred away from injection site or if their locations were not specified. There were no serum sickness or serum sickness-like reactions in the asthma trials. Serious or medically important systemic hypersensitivity reactions identified in the safety pool were limited to anaphylactic reactions. As of DLP of 28-Sep-2020, 3189 patients were exposed to dupilumab in asthma studies. Only 1 anaphylactic reaction related to dupilumab was identified (1/3189, 0.031%), yielding a rare frequency category for anaphylactic reactions in asthma and across all indications. There were 11 additional cases of anaphylaxis (6 in the asthma safety pool, 2 in LTS14424 and 3 in LTS12551). Of these 11 (eleven), 9 had alternate etiologies identified for the anaphylaxis events, and 2 (one patient with cough and flushing and one patient with dyspnea and pruritus occurring within 24 hours) were not considered anaphylactic reactions upon additional medical review and application of Sampson criteria. *Children (6-11 years of age)* (as of DLP 18-Aug-2020): In EFC14153, hypersensitivity reaction and anaphylaxis were noted more in placebo group; (3.7% placebo versus 1.8% dupilumab); anaphylaxis (1.5% placebo versus 0.0% dupilumab). In LTS14424, 2 events of anaphylaxis were reported (moderate to severe) and both ascribed to food allergy and both recovered within hours and were assessed as unrelated. In addition, 7 events (all non-serious and unrelated) of hypersensitivity were reported. *CRSwNP (NP) studies* (as of DLP of 28-Sep-2019): There were no anaphylactic reactions or serum sickness or serum sickness-like reactions related to dupilumab in CRSwNP patients. *EOSINOPHILIC ESOPHAGITIS studies*

Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	Adolescents and adults (as of study DLP 30-Aug-2021) There were no anaphylactic reactions, or serum sickness, or serum sickness-like reactions reported in EoE R668-EE-1774 study. In pooled safety analysis of Part A and Part B of study R668-EE-1774, PT of hypersensitivity has been reported with incidence of 0.9% in placebo group and 0.8% in dupilumab 300 mg QW group. PRURIGO NODULARIS studies (as of DLP 12-Nov-2021) There were no anaphylactic reactions, serum sickness, or serum sickness-like reactions reported in PN studies. In the pooled safety analysis of studies EFC16459 and EFC16460, systemic hypersensitivity has been reported with an incidence of 1.3% in the placebo group and 0.7% in the dupilumab group. *CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) (EFC15804 as of DLP 08-Feb-2023; and EFC15805 as of DLP 29-Sep-2023)* In study EFC15804, the incidence of systemic hypersensitivity reaction was reported as 0.4% in both placebo and dupilumab arms. Anaphylactic reaction incidence was reported as 0.2% in placebo and 0% in the dupilumab arm. In study EFC15805, the incidence of systemic hypersensitivity reaction was reported as 0.4% in placebo arm and 0.2% in dupilumab arm. Anaphylactic reaction incidence was reported as 0.2% in placebo and 0% in the dupilumab arm. Ongoing monitoring of the clinical and postmarketing data up to DLP of 28-Mar-2023 did not reveal any other information impacting the characterization of this important identified risk. Severity and nature of risk The serum sickness and serum sickness-like reaction observed in AD clinical trials were severe in intensity and both these patients had high ADA titer (>10 000). As the inflammatory process is self-limiting, if the offending antigen is removed, discontinuation of dupilumab is an important mitigation step if serum sickness is diagnosed. Postmarketing data up to DLP of 28-Mar-2023 did not reveal any new important safety information with regard to the severity of this particular risk. Due to the potential for life-threatening or fatal outcomes associated with anaphylactic reactions, dupilumab should be discontinued immediately if a dupilumab related anaphylactic reaction is suspected in the patient upon administration of dupilumab. Reversibility In clinical trials, all patients recovered. Seriousness/outcomes Majority of clinical trial cases mentioned above and including these events were serious. The patient who experienced serum sickness was hospitalized for evaluation of joint pain and fever. The patient who was reported to have serum sickness-like reaction was managed as an outpatient but the event was considered medically important. Both patients presented with polyarthralgia, fever and rash. Both patients recovered. The patient with anaphylaxis considered related to dupilumab was hospitalized for 24 hours and recovered completely from the event. Background incidence/prevalence The incidence or prevalence of serum sickness/serum sickness like reaction is not well documented and varies by the type of drug. [237] Based on data from omalizumab, the frequency of anaphylaxis in asthma patients treated with biologic agents ranges from 0.2 to 0.09%. [243] Impact on individual patient These reactions are self-limiting after discontinuation of antigen that causes the reaction. Symptoms associated with serum-sickness like reactions mentioned above and reported in the clinical program resolved upon discontinuation of dupilumab.

Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	Initiation of appropriate treatment of anaphylaxis reaction symptoms resulted in complete recovery.
Risk factors and risk groups	All patients are at risk of developing systemic hypersensitivity reactions. Risk factors for serum sickness include patient age, dose, duration and the heterologous protein involved in medication. Serum sickness-like reactions are more common in children. Intermittent exposure to a heterologous protein is associated with higher rates of serum sickness-like reactions compared with continuous exposure. [244, 245] Risk factors for anaphylaxis include known hypersensitivity to the heterologous protein or excipients in the formulation.
Preventability	Immediate hypersensitivity is not predictable or preventable. Preventability of type III hypersensitivity is not known. Hypersensitivity reaction in patients with known hypersensitivity to dupilumab or any of its excipients can be prevented by excluding them from further exposure, as stated in the Contraindication proposed for the dupilumab label.
Impact on the benefit-risk balance of the product	The significant benefit that dupilumab shows in efficacy endpoints and patient reported outcomes, outweighs a rare case of serum sickness, serum sickness-like reaction or non-fatal anaphylaxis and results in maintenance of a positive benefit-risk balance for dupilumab.
Public health impact	Minor impact on public health as serious systemic hypersensitivity reactions to dupilumab are very rare. The benefit-risk balance remains positive.

AD: Atopic Dermatitis; ADA: Anti-drug Antibody; AESI: Adverse Event of Special Interest; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; Fc: Fragment Crystallizable; IgE: Immunoglobulin E; IgG: Immunoglobulin G; IgG4: Immunoglobulin G4; IL-4: Interleukin-4; IMP: Investigational Medicinal Product; mAb: Monoclonal Antibody; PN: Prurigo Nodularis; QW: Once Every Week; RMP: Risk Management Plan; SMQ: Standardized MedDRA Query; SOC: System Organ Class; TEAE: Treatment Emergent Adverse Event.

SVII.3.2. Presentation of the missing information

Table 52 - Missing information: Use in pregnant and lactating women

Missing Information	Use in pregnant and lactating women
Evidence source(s) and strength of evidence	Pregnant and lactating women were excluded from the clinical development program of dupilumab and no specific studies in pregnant/lactating women have been conducted with dupilumab. The use of dupilumab in pregnant and lactating women is considered as missing information. *AD studies (*as of 28-Mar-2023)*:* In all dupilumab trials investigating AD, 48 patients reporting 49 pregnancies (as 1 of these patients had a twin pregnancy) were noted. Among these, 41 patients (*with 42 pregnancies as 1 of these patients had a twin pregnancy*) received dupilumab and 7 patients received placebo. The outcomes of the 7 AD placebo patients include 2 elective abortions, 2 normal live births, 1 spontaneous abortion, 1 unknown outcome, and 1 not reported. The outcomes of the 41 AD dupilumab exposed patients correspond to 42 outcomes including 24 normal live births, 6 spontaneous abortions, 3 elective abortions, 1 premature birth (with no fetal defect), 1 with unknown outcome, 1 not reported and 6 lost to follow-up. Of note, 1 dupilumab exposed patient had a twin pregnancy (live, normal birth of one twin and spontaneous abortion of the other). *ASTHMA studies* (as of 28-Mar-2023):

Missing Information	Use in pregnant and lactating women
	A total of 31 pregnancies were reported in the unblinded (DRI12544 and EFC13579) and open-label (LTS12551, LPS15023, EFC13691, and ACT11457) asthma studies. Of the 31 pregnancies, 5 pregnancies occurred in placebo patients in study EFC13579 with three pregnancies resulted in live births of normal infants, 1 elective abortion and 1 ectopic pregnancy. Among the 26 pregnancies in dupilumab-treated patients, outcomes include 7 spontaneous abortions, 2 elective abortions, 14 full term live births, and 3 premature births. One woman in study EFC13579 delivered a baby with congenital anomaly of Turner's syndrome associated with bicuspid aortic valve. One woman in study LTS12551, who had been diagnosed with tuberculosis meningitis, delivered a live, very low birth weight infant at 23 weeks gestation via caesarian delivery; on the same day, the patient died and no information about the child's health status was reported. At the time of this report, there are no ongoing pregnancies in asthma patients who were exposed to dupilumab. *CRSwNP (NP) studies* (as of DLP of 28-Mar-2023): Within the CRSwNP studies (ACT12340, EFC14146, and EFC14280), 1 pregnancy with a normal live birth was reported in a placebo patient. No pregnancies or partner pregnancies were reported in dupilumab-exposed patients in the CRSwNP safety pool, composed of EFC14146 and EFC14280 studies. There is no data on the use of dupilumab in lactating women. *EOSINOPHILIC ESOPHAGITIS studies* (as of DLP 28-Mar-2023): Within the two EoE studies (R668-EE-1324 and R668-EE-1774), a total of 4 pregnancies were reported. Of the 4 pregnancies, 1 occurred in a dupilumab-treated patient and 3 in patients on placebo. The pregnancy in the dupilumab-treated patient resulted in spontaneous abortion (assessed as not related in view of patient medical history of cervical surgery due to cervical cancer) and among the pregnancy in the placebo patients 1 patient reported spontaneous abortion and for other 2 patients outcome was unknown. *PRURIGO NODULARIS studies* (as of DLP 28-Mar-2023): No pregnancy case has been reported. *CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) (EFC15804 as of DLP 28-Mar-2023; and EFC15805 as of DLP 29-Sep-2023)* No pregnancy case has been reported.
Population in need for further characterization	The very limited data on pregnancy outcomes do not provide adequate information to characterize the safety profile of dupilumab use in pregnant patients, or potential effects on the developing fetus or fetal outcomes. In the absence of data on use of dupilumab in lactating women and limited data on pregnancy outcomes, it is not possible to assess the benefit-risk balance of dupilumab use in these subsets of AD, EoE, PN, COPD, asthma and NP patients.

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disorder; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; NP: Nasal Polyposis; PN: Prurigo Nodularis; PT: Preferred Term; RMP: Risk Management Plan.

Table 53 - Missing information: Long-term safety in paediatric patients

Missing Information	Long-term safety in paediatric patients
Evidence source(s) and strength of evidence	As of 28-Mar-2023, 197 pediatric patients[a] with EoE have received dupilumab with 178.8 person-years of exposure, 993 pediatric patients with AD have received dupilumab with 1929.5 person-years exposure, 503 pediatric patients with asthma have received dupilumab with 799.4 person-years exposure have been reported. No pediatric patients were enrolled in COPD, CRSwNP and PN studies.

Missing Information	Long-term safety in paediatric patients
	A review of postmarketing data up to the DLP 28-Mar-2023 identified no change in the characterization of this topic. No safety concerns emerged from postmarketing cases reporting long-term exposure of paediatric patients to dupilumab.
Population in need for further characterization	Additional data are needed to detect safety concerns associated with prolonged exposure in the paediatric population.

a Exposure data for EoE in patients 1 to 12 years of age have been included (subject to an ongoing submission).

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disorder; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis.

RISK MANAGEMENT PLAN - PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women
	Long-term safety in paediatric patients

RISK MANAGEMENT PLAN - PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The following routine pharmacovigilance activities beyond adverse reactions reporting and signal detection will be in place:

- Analysis of systemic hypersensitivity events in ongoing clinical studies: To detect any modifications in the risk characterization.
- Hypersensitivity questionnaire for systemic hypersensitivity (including events associated with immunogenicity) to collect data from healthcare professionals for hypersensitivity events received in postmarketing setting and detect any modifications in the risk characterization.
- Pregnancy questionnaire for postmarketing events: To monitor pregnancy and infant outcomes in women exposed to commercially supplied dupilumab.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Use in pregnant and lactating women:

The effect of exposure to dupilumab on pregnancy outcomes is not well understood due to the small number of pregnancies in patients exposed to dupilumab in clinical studies and the mandatory requirement to discontinue investigational drug upon discovery of pregnancy. No clinical trial of dupilumab in pregnant patients has been conducted.

In addition to routine pharmacovigilance activities, the company has included in the EU-RMP the following Post-Authorization Safety Study (PASS) to study the safety of dupilumab use during pregnancy:

- A prospective postmarketing pregnancy registry (R668-AD-1639): the objective of this study is to evaluate the potential effect of exposure to dupilumab in pregnancy compared to the primary comparison group of disease-matched pregnant women who are not exposed to dupilumab, and the secondary comparison group of healthy pregnant women. The registry includes the following 5 main study cohorts with planned samples sizes of 100 patients in each:
  - With AD and exposed to dupilumab,
  - With AD and not exposed,
  - With asthma and exposed to dupilumab,
  - With asthma and not exposed, and
  - Healthy (without any dupilumab indications) and not exposed.

  This registry also includes an “exposure series” cohort wherein women with any dupilumab exposure during pregnancy (regardless of meeting eligibility criteria or indication) can enroll. The related data are collected similarly to the main cohorts.

- An additional retrospective cohort study: this is a pregnancy outcome study (R668-AD-1760) using administrative healthcare databases conducted in multiple large US administrative healthcare databases to evaluate whether dupilumab treatment in AD patients is associated with adverse pregnancy and infant outcomes.

Long-term safety in paediatric patients:

The ongoing, open label extension study (LTS1434 [R668-AD-1434] in pediatric patients ≥6 months to <18 years of age) will provide long-term safety data in AD patients to support the benefit-risk assessment with long-term use of dupilumab in AD.

A global registry-based category 3 PASS study will also evaluate the long-term safety of dupilumab in paediatric patients aged ≥6 months to <6 years with moderate-to-severe AD.

Table 54 - Additional pharmacovigilance activities (category 1 to 3) summary

Pregnancy registry (R668-AD-1639) (Cat. 3)
Study short name and title
Pregnancy registry (R668-AD-1639)
Rationale and study objectives
To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes. The study initially included exposed and unexposed cohorts of women with moderate-to-severe AD. The study was amended to include separate exposed and unexposed cohorts of women with asthma. Although there is no specific concern surrounding differential risks of dupilumab exposure for pregnant women with asthma from the clinical trials, the effect of dupilumab on pregnancy outcomes for women with asthma is still considered missing information. Further, the risk of adverse pregnancy outcomes is known to be greater for women with asthma from the general population than for other populations of women. Therefore, it is considered to be of importance to study these outcomes separately to better identify risks that may be associated with dupilumab exposure and asthma. Data from women exposed to dupilumab with other indications (including CRSwNP, EoE, and PN) will be collected in the "exposure series".
Study design
Prospective, observational, registry study
Study populations
Five hundred (500) pregnant women will be enrolled in the registry in five primary cohorts. Cohort 1: One hundred (100) women who were exposed to dupilumab during pregnancy for the treatment of moderate-to-severe atopic dermatitis (AD exposed cohort); Cohort 2: One hundred (100) pregnant women who are frequency matched by AD diagnosis to the exposed cohort (AD comparison cohort); Cohort 3: One hundred (100) pregnant women who do not have a diagnosis of an approved indication for dupilumab (healthy comparison cohort). The study amendment added 2 additional cohorts of 100 women each. These cohorts are Cohort 4: One hundred (100) pregnant women who were exposed to dupilumab during pregnancy for the treatment of asthma (asthma exposed cohort); and Cohort 5: One hundred (100) pregnant women with asthma who are not exposed to dupilumab during pregnancy (asthma comparison cohort). In addition to the main study cohorts, an "exposure series" cohort will be followed for pregnancy and infant outcomes. This cohort will be comprised of women who were exposed to dupilumab during pregnancy but who do not qualify for the main study. Any pregnant woman who lives in the study area and was exposed to dupilumab during pregnancy can enroll in the registry exposure series cohort. This study will take place in North America (US and Canada).

Milestones

Synopsis: Submitted with RMP v1.0

Original protocol submitted in Jan-2018 and amended protocol (amendment #1) submitted in Sep-2018

Recruitment started in Oct-2018

Amended protocol that includes asthma cohorts submitted for information in the EU-RMP v5.0

Final report: Jan-2027

Pregnancy Outcomes Database Study (R668-AD-1760) (Cat. 3)

Study short name and title

Pregnancy Outcome Database Study (PODS) R668-AD-1760

Rationale and study objectives

To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy and compare these to each of the two comparator cohorts of pregnant women with AD; one exposed to other systemic medications or phototherapy used for the treatment of AD (never exposed to dupilumab) and the other comprised of women who were not exposed to these treatments during pregnancy.

Study design

Retrospective, observational, cohort study using large administrative healthcare databases

Study populations

Pregnant women with AD in the administrative databases will be identified and split into three (3) cohorts:

1) Women with AD exposed to dupilumab during pregnancy,

2) Women with AD who are exposed to systemic medication(s) used to treat AD and/or phototherapy during pregnancy, and

3) Women with AD who are not exposed to any systemic medications used to treat AD or to phototherapy during pregnancy.

Milestones

Amendment 1 of protocol submitted for information in the EU-RMP v5.0

Final report: Apr-2027

An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) (Cat. 3)

Study short name and title

LTS1434 (R668-AD-1434)

Rationale and study objectives

To assess the long-term safety of dupilumab in pediatric patients with AD.

Study design

Phase 3, open-label extension study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in pediatric patients (6 months to 18 years) with AD who have previously completed a clinical study with dupilumab in patients with AD.

Study populations

Pediatric patients with AD, including a cohort of adolescents (12-17 years), a cohort of children (5-11 years) and a cohort of pediatric patients (6 months to 5 years). Planned total number of patients is approximately 800.

Milestones

Final report: Q4 2024

A registry-based non-interventional post-authorization safety study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis using the PEDISTAD registry: a cohort design (Cat. 3)

Study short name and title

DUPI PEDISTAD-registry-based PASS (CSA0014)

Rationale and study objectives

Primary objective:

- To describe long-term safety of dupilumab in terms of the incidence rate of safety outcomes (AEs and SAEs) among patients in the "DUPI-All" cohort and separately, if sufficient sample size, in the DUPI-Steroid and Pure-DUPI sub-cohorts.

Secondary objectives:

- To describe patient characteristics, severity of AD by clinician assessment and by patient/caregiver assessment (PRO), medical history and selected comorbidities at index date for patients in the DUPI-All cohort, as well as in DUPI-Steroid and Pure-DUPI sub-cohorts.
- To describe the patient characteristics, severity of AD by clinician assessment and by PROs, medical history and selected comorbidities at index date for patients in the Other AD therapies cohort.
- To describe the AD drug utilization up to and after the index date (ie, date of initiation of cohort-defining treatment) for patients in the DUPI-All cohort and the Other AD therapies cohort.
- To describe the incidence rate of safety outcomes (AEs and SAEs) among patients in the Other AD therapies cohort.

Study design

An international, observational, registry-based cohort study.

Study populations

DUPI-All cohort:

- Initiated treatment with dupilumab, with index date at or after PEDISTAD enrollment date
- No restriction based on usage of prior or overlapping "other AD therapies"
- Aged ≥6 months to <6 years at index date

DUPI-Steroid sub-cohort:

- As for the DUPI-All cohort, but with prior or overlapping use of SCS or high potency TCS at the index date. Prior or overlapping use of other systemic agents at the index date is not permitted.

Pure-DUPI sub-cohort:

- As for the DUPI-All cohort, but with no prior or overlapping use of any "other AD therapy" at the index date

Other AD therapies cohort criteria:

- Initiated treatment with SCS, UV therapy, immunosuppressants (cyclosporine, methotrexate, mycophenolate and azathioprine), JAK inhibitors (abrocitinib, upadacitinib, tofacitinib, baricitinib), other systemic biologic treatments for moderate-to-severe AD (eg, tralokinumab) or high potency TCS with index date at or after PEDISTAD enrollment date. For both JAK inhibitors and other systemic biologic treatments, other agents that come to market during the study period will also be added as appropriate.
- Aged ≥6 months to <6 years at index date

Milestones

- Protocol submitted to PRAC on 18-Sep-2023
- Registration in the EU PAS register (once protocol approved)
- Study start Q3 2024[a]
- Study end Q3 2031[a]
- Progress report Q4 2024-2030
- Final report Q3 2032

a As per GVP VIII: for studies that use secondary data, study start is the date of first data extraction. Study end is the date on which the analytical dataset for purposes of registry-based study is completely available.

AD: Atopic Dermatitis; AE: Adverse Event; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EASI: Eczema Area and Severity Index; EoE: Eosinophilic Esophagitis; EU: European Union; GVP: Good Pharmacovigilance Practices; JAK: Janus Kinase; PASS: Post-Authorization Safety Study; PK: Pharmacokinetic; PN: Prurigo Nodularis; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan; SAE: Serious Adverse Event; SC: Subcutaneous; SCS: Systemic Corticosteroid; TCS: Topical Corticosteroid; US: United States; UV: Ultraviolet.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 55 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3- Required additional pharmacovigilance activities				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018)
			Amended protocol (asthma cohorts)	Submitted for information with EU-RMP v5.0
			Final report	Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Final report	Apr-2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2024
A registry-based non-interventional post-authorization safety study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis using the PEDISTAD registry: a cohort design CSA0014 Planned	To assess the long-term safety of dupilumab in pediatric patients with moderate-to-severe AD.	Long-term safety of dupilumab in paediatric patients (≥6 months to <6 years) with AD	Synopsis v1.0 provided in Annex 3.1 of EU-RMP submitted within procedure EMEA/H/C/004390/II/0060	
			Protocol submitted to PRAC on	18-Sep-2023
			Annual progress report	Q4 2024-2030
			Final Report	Q3 2032

AD: Atopic Dermatitis; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the MA or which are specific obligations in the context of conditional MA or MA under exceptional circumstances are planned or ongoing for dupilumab (DUPIXENT).

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 56 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk communication** • SmPC section 4.8 • PIL section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC section 4.3: contraindication in case of hypersensitivity to the active substance or to any of the excipients. SmPC section 4.4: recommendation to discontinue immediately DUPIXENT and to initiate appropriate therapy if a systemic reaction occurs. PIL section 2: how to detect signs and symptoms of allergic reactions, and recommendation to stop using DUPIXENT, tell the doctor or get medical help immediately if the patient notices any signs of an allergic reaction. **Other routine risk minimization measures beyond the Product Information** Prescription only medicine
Use in pregnant and lactating women	**Routine risk communication** • SmPC sections 4.6 and 5.3 • PIL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC section 4.6: recommendation that a decision must be made whether to discontinue breastfeeding or to discontinue DUPIXENT therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. PIL section 2: recommendation for the patient to ask doctor for advice before using DUPIXENT: if the patient is pregnant, thinks may be pregnant, or is planning to have a baby; and if breastfeeding or planning to breast-feed. **Other routine risk minimization measures beyond the Product Information** Prescription only medicine
Long-term safety in paediatric patients	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Prescription only medicine

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Section V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 57 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4 and 4.8 • PIL sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Use in pregnant and lactating women	**Routine risk minimization measures:** • SmPC sections 4.6 and 5.3 • PIL section 2 • Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639), Pregnancy Outcomes Database Study (R668-AD-1760)
Long-term safety in paediatric patients	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** LTS1434 (R668-AD-1434) and DUPI PEDISTAD registry-based study (CSA0014)

PIL: Patient Information Leaflet; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

RISK MANAGEMENT PLAN - PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for DUPIXENT (Dupilumab)

This is a summary of the risk management plan (RMP) for DUPIXENT. The RMP details important risks of DUPIXENT, how these risks can be minimized, and how more information will be obtained about DUPIXENT's risks and uncertainties (missing information).

DUPIXENT's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how DUPIXENT should be used.

This summary of the RMP for DUPIXENT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of DUPIXENT's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

DUPIXENT is authorized for:

Atopic dermatitis:

Adults and adolescents

DUPIXENT is indicated for the treatment of moderate-to-severe atopic dermatitis (AD) in adults and adolescents 12 years and older who are candidates for systemic therapy.

Children 6 months to 11 years of age

DUPIXENT is indicated for the treatment of severe AD in children 6 months to 11 years old who are candidates for systemic therapy.

Asthma:

Adults and adolescents

DUPIXENT is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1 of SmPC, who are inadequately controlled with high dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment.

Children 6 to 11 years of age

DUPIXENT is indicated in children 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), see section 5.1 of SmPC, who are inadequately controlled with medium to high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

Chronic rhinosinusitis with nasal polyposis (CRSwNP):

DUPIXENT is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) for whom therapy with systemic corticosteroids (SCSs) and/or surgery do not provide adequate disease control.

Prurigo Nodularis (PN):

DUPIXENT is indicated for the treatment of adults with moderate to severe prurigo nodularis (PN) who are candidates for systemic therapy.

Eosinophilic Esophagitis (EoE):

DUPIXENT is indicated for the treatment of eosinophilic esophagitis in adults and adolescents 12 years and older, weighing at least 40 kg, who are inadequately controlled by, are intolerant to, or who are not candidates for conventional medicinal therapy (see section 5.1 of SmPC).

Chronic Obstructive Pulmonary Disease (COPD):

DUPIXENT is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate (see Section 5.1 of SmPC).

See SmPC for the full indication.

It contains dupilumab as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of DUPIXENT's benefits can be found in DUPIXENT's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/dupixent

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of DUPIXENT, together with measures to minimize such risks and the proposed studies for learning more about DUPIXENT's risks, are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including periodic safety update report (PSUR) so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of DUPIXENT is not yet available, it is listed under "missing information" outlined in the next section.

II.A. List of important risks and missing information

Important risks of DUPIXENT are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of DUPIXENT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

Table 58 - List of important risks and missing information

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women
	Long-term safety in paediatric patients

II.B. Summary of important risks

Table 59 - Important identified risk with corresponding risk minimization activities: Systemic hypersensitivity (including events associated with immunogenicity)

Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)	
Evidence for linking the risk to the medicine	Clinical trial data, literature and postmarketing pharmacovigilance.
Risk factors and risk groups	All patients are at risk of developing systemic hypersensitivity reactions. Risk factors for serum sickness include patient age, dose, duration and the heterologous protein involved in medication. Serum sickness-like reactions are more common in children. Intermittent exposure to a heterologous protein is associated with higher rates of

Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)	
	serum sickness-like reactions compared with continuous exposure. [244, 245] Risk factors for anaphylaxis include known hypersensitivity to dupilumab or the excipients in the formulation.
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 60 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use in pregnant and lactating women

Missing information: Use in pregnant and lactating women	
Risk minimization measures	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639), Pregnancy Outcomes Database Study (R668-AD-1760)

PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

Table 61 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety in paediatric patients

Missing information: Long-term safety in paediatric patients	
Risk minimization measures	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** LTS1434 (R668-AD-1434), and DUPI PEDISTAD registry-based study (CSA0014)

II.C. Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the MA or specific obligation of DUPIXENT.

II.C.2 Other studies in post-authorization development plan

Table 62 - Other studies in post-authorization development plan

Pregnancy registry (R668-AD-1639) (Cat. 3)
Purpose of the study: To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes. The study initially included exposed and unexposed cohorts of women with moderate-to-severe AD. The study was amended to include separate exposed and unexposed cohorts of women with asthma. Although there is no specific concern surrounding differential risks of dupilumab exposure for pregnant women with asthma from the clinical trials, the effect of dupilumab on pregnancy outcomes for women with asthma is still considered missing information. Further, the risk of adverse pregnancy outcomes is known to be greater for women with asthma from the general population than for other populations of women. Therefore, it is considered to be of importance to study these outcomes separately to better identify risks that may be associated with dupilumab exposure and asthma. Data from other indications (including CRSwNP, EoE, and PN) will be collected in the "exposure series.
Pregnancy Outcomes Database Study (R668-AD-1760) (Cat. 3)
Purpose of the study: To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy and compare these to each of the two comparator cohorts of pregnant women with AD; one exposed to other systemic medications or phototherapy used for the treatment of AD (never exposed to dupilumab) and the other comprised of women who were not exposed to these treatments during pregnancy.
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) (Cat. 3)
Purpose of the study: To assess the long-term safety of dupilumab in pediatric patients with AD.
A registry-based non-interventional post-authorization safety study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis (AD) using the PEDISTAD registry: a cohort design (CSA0014) (Cat. 3)
Purpose of the study: To assess the long-term safety of dupilumab in pediatric patients with AD.

AD: Atopic Dermatitis; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis.

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RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

TABLE OF CONTENTS

TARGETED FOLLOW-UP QUESTIONNAIRE FOR DRUG HYPERSENSITIVITY

Dupilumab (Dupixent)

Drug Hypersensitivity

Targeted Follow-up Form (coversheet)

- **In the 'Adverse Event Information (Describe Event)' section of Individual Safety Information (ISI) Documentation Form and in the 'Description of the Case' of Unsolicited Individual Safety Information (ISI) Report Form, ensure to:**

  - Specify if the patient had any of the following hypersensitivity associated cutaneous symptoms: Also, provide start and stop date of the symptoms
    - Local/generalized flushing/erythema of skin
    - Maculopapular exanthema
    - Pruritus (itch)
    - Urticaria (itchy rash)
    - Angioedema
    - Angioedema lips/eyelids
    - Angioedema of oral mucosa
    - Conjunctivitis
    - Contact dermatitis
    - Any other skin lesions (e.g. macules, papules, purpuric lesions, vesicles/bullae (blisters), pustules etc. please specify)

  - Specify if the patient had any of the following hypersensitivity associated gastrointestinal symptoms:
    - Nausea/emesis
    - Abdominal pain/gastrointestinal cramps
    - Any other gastrointestinal symptoms (please specify)

  - Specify if the patient had any of the following hypersensitivity associated symptoms:
    - Fever (provide the body temperature)
    - Lower back pain
    - Malaise
    - Pain/burning (provide the location)
    - Headache

- Arthralgia/myalgia (provide the location)
- Lymphadenopathy
- Any other associated symptoms

- Specify if the patient had any of the following hypersensitivity related respiratory symptoms:
  - Cough
  - Dysphonia
  - Dyspnea
  - Wheezing/bronchospasm (provide PEFR or FEV1 value)
  - Rhinitis
  - Rhinorrhea
  - Sneezing
  - Nasal obstruction
  - Any other associated symptoms (please specify)

- Specify if the patient had any of the following hypersensitivity related cardiac symptoms:
  - Tachycardia (provide pulse rate)
  - Hypotension (provide blood pressure value)
  - Collapse/syncope
  - Arrhythmia
  - Any other cardiac symptoms (please specify)

- For the management of acute drug reactions, specify if the patient had received any of the following drugs (provide dose, route of administration, start date and stop date):
  - Antihistamines
  - Corticosteroids
  - Bronchodilators
  - Epinephrine/adrenaline
  - Any other shock treatment

- Provide the differential diagnosis of the hypersensitivity associated signs and symptoms

In the 'Adverse Event Information (Describe Event)' section of ISI Documentation Form and in the 'Complementary Investigations' of Unsolicited ISI Report Form, ensure to:

- Specify if the diagnosis was based on clinical manifestation/temporality
- Specify if photographs of skin the lesions were taken

- Specify if the patient underwent following blood tests (provide test results with values and normal ranges):
    - Complete blood count (CBC) with Differential
    - Mast cell tryptase
    - Other relevant blood tests

- Specify if the patient underwent following skin tests (provide the results accordingly):
    - Skin biopsy (pathology result)
    - Skin Prick Test
    - Intradermal Allergy Test
    - Scratch-Patch or Patch Test
    - Lymphocyte transformation test (TTL)

- Specify if the patient underwent following liver function tests (LFTs) (provide test result values with normal range):
    - ALT (Alanine aminotransferase)
    - ALP (Alkaline phosphatase)
    - AST (Aspartate aminotransferase)
    - Bilirubin
    - Albumin
    - Total protein
    - GGT (gamma-glutamyl transferase)
    - Blood LDH
    - Prothrombin time

- Specify if any other hypersensitivity related laboratory tests were formed. Provide results with values and normal ranges.

In the 'Medical History/Risk Factors' section of ISI Documentation Form and in the 'Ongoing Illness/Medical History/Risk Factors' of Unsolicited ISI Report Form, ensure to:

- Specify the contributing factors for hypersensitivity reaction such as concurrent infections (e.g. viral, bacteria etc.), medical history or any other contributing factors
- Specify if similar symptoms of hypersensitivity reactions were observed in the absence of the suspect drug
- Specify if the patient had medical history of:
    - Cardiovascular disease
    - Respiratory disease
    - Kidney disease
    - Hematological disease
    - Malignancy

    - Autoimmune disorder
    - Any psychological conditions (please specify)

- Specify if the patient had any:
    - Atopic allergic disease
    - Atopic dermatitis
    - Allergic asthma
    - Food hypersensitivity/allergies
    - Hymenoptera hypersensitivity
    - Drug hypersensitivity
    - Recurrent/chronic urticarial angioedema
    - Recurrent/eczematous exanthema

- Specify any family history of allergies/drug allergies.

Unsolicited Individual Safety Information (ISI) Report Form

Grey fields are for Sanofi use only

1 ADMINISTRATIVE SECTION FOR AFFILIATE/PARTNER ONLY

Company contact date: Click or tap to enter a date. Local PV receipt date: Click or tap to enter a date.

Country of Occurrence: Click here to enter text.

Social Media case: Yes ☐ No ☐ If Yes: Name of the social media: Click here to enter text.

☐**INITIAL** ☐ **FOLLOW-UP** Global Safety Database ID: Click here to enter text.

Local Reference ID: Click here to enter text. Local PTC ID: Click here to enter text. Global PTC ID: Click here to enter text.

2 PATIENT

Title, Name (first, middle, last)/Initials: Click here to enter text. Gender: F ☐ M ☐ Unk ☐

Address, city, postal code, state: Click here to enter text.

Country: Click here to enter text. Phone: Click here to enter text.

Email address: Click here to enter text.

Date of Birth (DD/MM/YYYY): Click or tap to enter a date. Age or Age Group (at time of the reaction)**:** Click here to enter text.

Height: Click here to enter text. cm/feet & inches Weight: Click here to enter text. kg/lb Registry ID #: Click here to enter text.

3 REPORTER

First Name: Click here to enter text. Last Name: Click here to enter text.

Occupation: Click here to enter text.

Address: Click here to enter text.

Zip / Postal Code: Click here to enter text.

3 REPORTER

Country: Click here to enter text.

Phone: Click here to enter text.

Fax: Click here to enter text.

E-mail address: Click here to enter text.

If the primary reporter is a consumer, is contact information provided for a HealthCare Professional? *Yes ☐ No ☐ NA ☐

If your country requires patient consent to contact the HCP, has the patient given their consent? *Yes ☐ **No ☐ NA ☐

*If YES, attempts should be made to contact the HCP **If NO, do not contact the HCP and document the exchange

Was FU request sent to reporter? Yes ☐ No ☐ NA ☐

The reporter will not have any further information ☐

The reporter does not wish to be contacted by the Pharmacovigilance Department ☐

4 SUSPECT MEDICATION / MEDICAL DEVICE (MD) / VACCINE (V)

Brand Name /INN	Indication	Dosage/ Unit/ Frequency / Amount	Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO)	Start Date (DD/MM/YYYY)	Stop Date or duration (DD/MM/YYYY)	Route of Administration	Company product (Yes/No)	Primary/ Booster (V)	Site of Injection (V)	Side (V)
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										

Is medical device available for evaluation (MD)? ☐Yes ☐No

Did the problem occur with initial use or during re-use of the medical device (MD)? ☐Yes ☐No

For company suspect product inappropriately used as per local Marketing Authorization:
Is it intentional? ☐Yes ☐No ☐Unk *at the initiative of* ☐HCP ☐Consumer ☐Unk *for a therapeutic purpose?* ☐Yes ☐No ☐Unk

Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions): Click here to enter text.

5 CONCOMITANT MEDICATION / MEDICAL DEVICE / VACCINE

Brand Name /INN	Indication	Dosage/ Unit/ Frequency / Amount	Batch Number	Start Date (DD/MM/ YYYY)	Stop Date or duration (DD/MM/ YYYY)	Route of Administration	Company product (Yes/No)	Primary/ Booster (V)	Site of Injection (V)	Side (V)
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										
Click here to enter text.										

Comments (Complementary information: presentation, syringe, single dose, multidose, storage conditions): Click here to enter text.

6 REACTION DESCRIPTION

Reaction	Date of Onset (DD/MM/YYYY)	Stop Date or Duration (DD/MM/YYYY)	Outcome	Corrective Treatment	Action Taken	Did reaction abate after product was stopped?	Did reaction recur after product was started again?	Kind of Reaction (V)	Lack of efficacy / failure (V)
Click here to enter text.									
Click here to enter text.									
Click here to enter text.									

6 REACTION DESCRIPTION

Click here to enter text.									
Click here to enter text.									

7 DESCRIPTION OF THE CASE *(signs & symptoms, possible causes, progression, treatments, relevant medical history, investigations, severity ….)*

Click here to enter text.

8 ONGOING ILLNESS / MEDICAL HISTORY / RISK FACTORS

Personal *(if relevant for the reaction described in this form)*: Click here to enter text.

Family *(if relevant for the reaction described in this form)*: Click here to enter text.

9 HISTORY OF ADVERSE REACTION TO PREVIOUS ADMINISTRATION OF VACCINE (V)

Product Name / Therapeutic Class	Date of Occurrence (DD/MM/YYYY)	Reaction	Duration
Click here to enter text.			
Click here to enter text.			
Click here to enter text.			

Comments: Click here to enter text.

10 COMPLEMENTARY INVESTIGATIONS Type / Results ***(indicate unit / attach photocopies if relevant. If patient died please specify if autopsy was performed and what was result)***

Click here to enter text.

11 SERIOUSNESS

☐**Non-Serious** ☐ **Serious (select at least one criteria below)**

☐Death *Date of Death:*Click or tap to enter a date. *Autopsy performed*: Yes ☐ No ☐ Unk ☐

☐Life threatening

☐Medically Significant (as per HCP)

☐Hospitalization or prolongation of hospitalization *Duration of hospitalization:* Click here to enter text.

☐Persistent or significant disability or incapacity

☐Suspected transmission of infectious agent

☐Congenital anomaly, birth defect

Was this reaction reported to Regulatory Authority? Yes☐ No ☐

NAME & SIGNATURE :

SANOFI

Individual Safety Information Documentation Form

Person completing this form:

Name, Title:_____ Telephone Number: _____

Services Provider Name: _____

☐ Initial ☐ Follow-up

Name of Program: _____ Name of Collecting Organization: _____

Study ID: _____ Center ID: _____ Patient ID: _____

Local Reference ID: _____ Global PV Database ID: _____

Local PTC ID (if applicable): _____ Global PTC ID (if applicable): _____

Date AE was First Reported to Services Provider: _____

Local PV receipt date: _____

Patient Information *(Complete any known information and as per local data privacy regulations):*

Patient First, Middle and Last Names / Initials (not to be collected for case report from clinical studies): _____

Sex: _____

Date of Birth (For clinical study, Year of birth to be collected only): _____

Age or Age Group: _____

Suspect Product(s) Information (*Complete any known information):*

Product Name (INN, Brand)	Company product (Yes/No)	Was AE Related to Product?	Indication / Taken For	Dose/ Unit	Frequency	Route	Start Date	Stop Date / Ongoing?	Action Taken	Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO)
	Click here to enter text.									
	Click here to enter text.									

Adverse Event Information *Complete any known information. (If more than one AE reported, complete additional AE pages)**:***

Date AE started: _____ Date AE stopped/Duration: _____

Describe event (*Provide clinical details below, including other reasons that may explain the occurrence of the AE, relevant test results and necessary treatment. If more than one event is reported, complete additional AE pages*):

Outcome of Event: _____ **If fatal outcome:** Date of Death: _____
Cause of death: _____
Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

Concomitant Medicines (e.g. drugs, devices, vaccines) taken when AE occurred, but which are not suspected (*Complete any known information):*

Product Name (INN/Brand)	Indication / Taken For	Dose/ Unit	Frequency	Route	Start Date	Stop Date/Ongoing?

Medical History/Risk Factors *(Describe additional relevant information, e.g. medical or surgical history, past drug history, ongoing illness, risk factors such as allergies, alcohol use, drug abuse, etc.)*:

Reporter Information (*Who told you about this adverse event?):*

Name: _____ Address (postal code, city, state): _____

Country: _____

Department/Institution: _____

Phone: _____ Email: _____

Is the reporter a Health Care professional?: _____

Treating Physician Information (if not the reporter):

Name: _____ Address: _____

Phone: _____ Email: _____

The reporter will not have any further information ☐

The reporter does not wish to be contacted by the Pharmacovigilance-Department ☐

Name and Signature:

Signature:

ADVERSE EVENT 2

Suspect Product Information (*Complete any known information):*

Product Name (INN, Brand)	Company product (Yes/No)	Was AE Related to Product?	Indication / Taken For	Dose/ Unit	Frequency	Route	Start Date	Stop Date / Ongoing?	Action Taken	Batch Number (Mandatory. If not available, enter NA/ if not obtainable at all enter NO
	Click here to enter text.									

Date AE started: _____ Date AE stopped/Duration: _____

Describe event and any necessary treatment (*Provide clinical details for each of the adverse events listed below*)**:**

Outcome of Event: _____ **If fatal outcome:** Date of Death: _____

Cause of death: _____

Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

ADVERSE EVENT 3

Suspect Product Information (*Complete any known information*)**:**

Product Name (INN, Brand)	Company product (Yes/No)	Was AE Related to Product?	Indication / Taken For	Dose/ Unit	Frequency	Route	Start Date	Stop Date / Ongoing?	Action Taken	Batch Number (Mandatory. If not available, enter NA/ if not obtainable at al enter NO

Date adverse event started: _____ Date adverse event stopped/Duration: _____

Describe event and any necessary treatment (*Provide clinical details for each of the adverse events listed below*):

Outcome of Event: _____ **If fatal outcome:** Date of Death: _____

Cause of death: _____

Autopsy results: _____

Did AE lead to hospitalization or to prolonged hospitalization? _____

Did AE result in immediate risk of death? _____

Did AE result in persistent or significant disability or incapacity? _____

Is the AE a congenital anomaly/birth defect? _____

Is there suspected transmission of an infectious agent via the product? _____

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

NOT APPLICABLE