EU-RISK MANAGEMENT PLAN FOR DUPIXENT® (DUPILUMAB)

Risk Management Plan (RMP) Version number	Version 14.1
Data Lock Point (DLP)	28-MAR-2025
Date of final sign-off	28-JAN-2026

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

Rationale for submitting an updated RMP	This updated European Union (EU)-RMP v14.1 is prepared to support the application for the new indication of moderate to severe chronic spontaneous urticaria (CSU) in children (2 years and above) with inadequate response to H1 antihistamines and who are naïve to anti-Immunoglobulin E (IgE) therapy for CSU. This new indication is in addition to the currently approved indication for adults and adolescents (12 years and above). The RMP v14.1 incorporates updates based on the European Medicines Agency (EMA) assessment of the previous interim RMP v14.0 (Procedure number EMA/VR/0000282164) and last approved RMP v13.1 (Procedure number EMA/VR/0000257461).
Summary of significant changes in this RMP	Significant changes to each module in version 14.1 as compared to last approved RMP version 13.1: Part I: Addition of new CSU pediatric indication and dosage. Part II: • Module II SI: Update of epidemiology data for CSU indication. • Module II SII: Update in special populations section. • Module II SIII: Addition of CSU Study PKM16982 exposure data and update of clinical trials exposure data. • Module II SIV: Update as of RMP DLP, inclusion of PKM16982 study and alignment with module SIII data. • Module II SV: Update of post-authorization exposure data. • Module II SVII: Update of risk tables as of RMP DLP and inclusion of CSU Study PKM16982 data. Bullous pemphigoid (BP) data, presented in interim RMP v14.0, have been removed from Parts I and II (modules SI, SIII, SIV, and SVII) where they appear independently, as BP is not currently an approved indication. Part III: • Pregnancy outcome database study (R668-AD-1760) - status update. • DUPI PEDISTAD-registry-based Post-Authorization Safety Study (PASS) (CSA0014) - status update. Part VI: Update for consistency with changes in other modules. Annexes: • Annex 2: Update to align with Part III. • Annex 3: Amended protocol for Pregnancy outcome database study (R668-AD-1760) for information.

BP: Bullous Pemphigoid; CSU: Chronic Spontaneous Urticaria; DLP: Data Lock Point; EMA: European Medicines Agency; EU: European Union; IgE: Immunoglobulin E; PASS: Post-Authorization Safety Study; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
12.1	10-Sep-2025	Procedure number EMA/VR/0000248778 New indication for BP

BP: Bullous Pemphigoid; EMA: European Medicines Agency; RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	13.1

Approved with procedure	EMA/VR/0000257461
Date of approval (opinion date)	18-Sep-2025 (Committee for Medicinal Products for Human Use [CHMP] positive opinion) *(European Commission Decision date 06-Nov-2025)*

CHMP: Committee for Medicinal Products for Human Use; EMA: European Medicines Agency; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted] *a*, [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

ABPA:	Allergic Bronchopulmonary Aspergillosis
ACE:	Angiotensin Converting Enzyme
AD:	Atopic Dermatitis
ADA:	Antidrug Antibody
ADR:	Adverse Drug Reaction
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
AGREE:	A Working Group on Proton Pump Inhibitor-Responsive Esophageal Eosinophilia
ALT:	Alanine Aminotransferase
ANA:	Anti-Nuclear Antibody
ASD:	Autism Spectrum Disorder
ATC:	Anatomical Therapeutic Chemical
BID:	Twice a Day
BP:	Bullous Pemphigoid
CAT:	COPD Assessment Test
CD:	Clusters of Differentiation
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
CNS:	Central Nervous System
COPD:	Chronic Obstructive Pulmonary Disease
COVID-19:	Coronavirus Disease
CRS:	Chronic Rhinosinusitis
CRSwNP:	Chronic Rhinosinusitis with Nasal Polyposis
CSU:	Chronic Spontaneous Urticaria
CT:	Computed Tomography
C_{trough}:	Observed Minimum Concentration in Serum After a Dose During a Dosing Interval
CU:	Chronic Urticaria
CXCL8:	C-X-C Motif Chemokine Ligand 8
DALA:	Drug Abuse Liability Assessment
DDD:	Defined Daily Dose
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DPI:	Dry Powder Inhaler
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
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
FEV:	Forced Expiratory Volume
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
HCV-Ab:	Hepatitis C Virus Antibody
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
IGA AD:	Investigator Global Assessment Scale for Atopic Dermatitis
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
LTRA:	Leukotriene Receptor Antagonist
LTT:	Long-Term Treatment
MA:	Marketing Authorization
MAA:	Marketing Authorization Application
mAb:	Monoclonal Antibody
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MART:	Maintenance and Reliever Therapy
MDI:	Metered Dose Inhaler
MedDRA:	Medical Dictionary for Regulatory Activities
mMRC:	modified Medical Research Council
MOA:	Mechanism of Action
mRNA:	Messenger Ribonucleic Acid
N:	Total Number of Patient
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
PL:	Package Leaflet
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:	Person-Year
Q:	Quarter
Q2W:	Every Other Week
Q3W:	Once Every Three 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
SABA:	Short-Acting Beta-Agonist
SAE:	Serious Adverse Event
SAMA:	Short-Acting Muscarinic Antagonists
SAP:	Statistical Analysis Plan
SC:	Subcutaneous
SCORAD:	SCORing Atopic Dermatitis
SCS:	Systemic Corticosteroid
SIR:	Standardized Incidence Ratio
SMI:	Soft Mist Inhaler
SmPC:	Summary of Product Characteristics
SMQ:	Standardized MedDRA Query
SNRI:	Serotonin and Norepinephrine Reuptake Inhibitors
SOC:	System Organ Class
SSRI:	Selective Serotonin Reuptake Inhibitor
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
WOCBP:	Women of Childbearing Potential
YLL:	Year of Life Lost

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Dupilumab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Dermatologicals (D11AH05)
Marketing Authorization Holder (MAH)	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Dupixent
Marketing authorization procedure	Centralized procedure
Brief description of the product	Chemical class: Dupilumab is a fully human Monoclonal Antibody (mAb) that inhibits Interleukin-4 (IL-4) and Interleukin-13 (IL-13) signaling by specifically binding to the Interleukin-4 Receptor Alpha (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/ Interleukin-13 Receptor Alpha [IL-13Rα]).
	Important information about its composition: Fully human mAb produced in Chinese Hamster Ovary cells by recombinant Deoxyribonucleic Acid (DNA) technology.
Hyperlink to the product information	Refer to electronic Common Technical Document (e-CTD) sequence for procedure for the new indication of CSU, Module 1.3.1 English proposed Product Information.
Indication(s) in the EEA	**Current**: ***Atopic dermatitis (AD)*** *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 atopic dermatitis 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. *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 CRSwNP for whom therapy with systemic corticosteroids 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, adolescents and children aged 1 year and older, weighing at least 15 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) characterized 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).* ***Chronic Spontaneous Urticaria (CSU) in adults and adolescents - Procedure Number EMA/VR/0000257461:*** *Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU.*
	Proposed: ***Chronic Spontaneous Urticaria (CSU):*** *Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU.*
Dosage in the EEA	***Current:*** ***Atopic Dermatitis (AD)*** *Adults* *The recommended dose for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W) administered as subcutaneous (SC) injection.* *Adolescents (12 to 17 years of age)* *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

Body weight of patient	***Initial dose***	***Subsequent doses (Q2W)***
less than 60 kg	*400 mg (two 200 mg injections)*	*200 mg*
60 kg or more	*600 mg (two 300 mg injections)*	*300 mg*

Q2W: Every Other Week.

Children 6 to 11 years of age

The recommended dose of dupilumab for children 6 to 11 years of age is specified in Table 5b.

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: Every Other Week; 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 adolescent patients (12 years of age and older) is:

- *For patients with severe asthma and who are on oral corticosteroids (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 and subsequent doses***
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: Every Other Week; 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 every other week administered as SC injection.

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 every other week administered as SC injection.

Chronic Obstructive Pulmonary Disease (COPD):

The recommended dose of dupilumab for adult patients is 300 mg given every other week administered as SC injection.

Eosinophilic Esophagitis (EoE):

Adults, Adolescents and Children 1 Year and Older

The recommended dose of dupilumab for adults, adolescents and children 1 year of age and older, weighing at least 15 kg, is specified in Table 5e.

Table 5e - Dose of dupilumab for Subcutaneous Administration in Adults, Adolescents and Children 1 Year of Age and Older with EoE

Body Weight	***Dose***
15 to less than 30 kg	*200 mg every other week (Q2W)*
30 to less than 40 kg	*300 mg every other week (Q2W)*
40 kg or more	*300 mg every week (QW)*

EoE: Eosinophilic Esophagitis; Q2W: Once Every Other Week; QW: Once Every Week.

Chronic Spontaneous Urticaria (CSU):

Adults

The recommended dose for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

Adolescents (12 to 17 years of age)

The recommended dose for adolescent patients 12 to 17 years of age is specified in Table 5f:

Table 5f: Dose of dupilumab for subcutaneous administration in adolescent patients 12 to 17 years of age with CSU

Body weight	***Initial dose***	***Subsequent doses***
30 to less than 60 kg	*400 mg (two 200 mg injections)*	*200 mg every other week (Q2W)*

		60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

CSU: Chronic Spontaneous Urticaria; Q2W: Every Other Week.

Proposed:

Chronic Spontaneous Urticaria (CSU):

Adults

The recommended dose of dupilumab for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week.

Children and Adolescents (6 to 17 years of age)

The recommended dose of dupilumab for children and adolescent patients 6 to 17 years of age is specified in Table 5g:

Table 5g: Dose of dupilumab for subcutaneous administration in children and adolescent patients 6 to 17 years of age with CSU[a]

Body weight	Initial dose	Subsequent doses
15 to less than 30 kg	300 mg (one 300 mg injection) on Day 1, followed by 300 mg on Day 15	300 mg every four weeks (Q4W), starting 4 weeks after Day 15 dose
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

a For patients weighing 5 to less than 15 kg, the recommended dose is 200 mg every four weeks (Q4W).

CSU: Chronic Spontaneous Urticaria; Q2W: Every Other Week; Q4W: Every Four Weeks.

Children 2 to 5 years of age

The recommended dose of dupilumab for children 2 to 5 years of age is specified in Table 5h:

Table 5h: Dose of dupilumab for subcutaneous administration in children 2 to 5 years of age with CSU

Body weight	Initial and subsequent doses
5 to less than 15 kg	200 mg every four weeks (Q4W)
15 to less than 30 kg	300 mg every four weeks (Q4W)

CSU: Chronic Spontaneous Urticaria; Q4W: Every Four Weeks.

Pharmaceutical form(s) and strength(s)

Current:

Solution for injection

Clear to slightly opalescent, colourless to pale yellow sterile solution, which is free from visible particulates, with a pH of approximately 5.9.

Each single-use pre-filled (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).

Proposed:

Not applicable

Is or will the product (be) subject to additional monitoring in the EU?	No

AD: Atopic Dermatitis; ATC: Anatomical Therapeutic Chemical; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; 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; IgE: Immunoglobulin E; 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; MAH: Marketing Authorization Holder; OCS: Oral Corticosteroid; PF: Pre-Filled; pH: Potential of Hydrogen; PN: Prurigo Nodularis; Q2W: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week; RMP: Risk Management Plan; SC: Subcutaneous; SmPC: Summary of Product Characteristics.

PART II: SAFETY SPECIFICATION

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

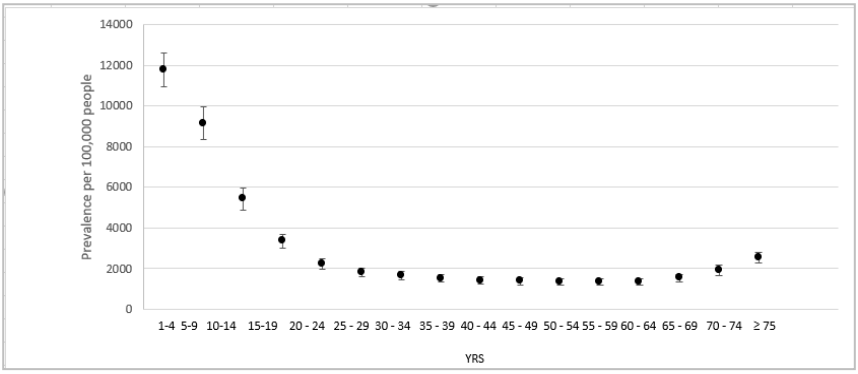
Dupixent is indicated:

- *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 (INCSs) 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 PN who are candidates for systemic therapy.*
- *For the treatment of eosinophilic esophagitis (EoE) in adults, adolescents and children aged 1 year and older, weighing at least 15 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) characterized 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.*
- *For the treatment of moderate to severe chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU.*
- *For the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU. (This indication is subject to approval under this procedural assessment).*

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 Global Burden of Disease (GBD) Study 2019 indicate the incidence of AD in the EU as follows: [1] • All ages: 331/100 000 people/year; • <20 years: 725/100 000 people/year; • ≥20 years: 229/100 000 people/year.
Prevalence	Data from the GBD Study 2019 indicate the prevalence of AD in the EU as follows: [1] • All ages: 2.75/100 people; • <20 years: 6.81/100 people; • ≥20 years: 1.69/100 people.

Indication	Atopic Dermatitis in patients 6 months of age and older
	The prevalence of AD varies globally. The prevalence of AD in young children aged 6 months - 6 years is estimated at 12%, and varies in European countries, from 7% in Germany to 15-19% in Italy, Spain, France and the United Kingdom (UK). [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 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 AD is highest in children and young adolescents versus adults (Figure 1). [1] Prevalence tends to decrease with age, although a slight increase in prevalence can be seen in the oldest age groups eg, ≥65 years. [1] **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 AD in the EU is higher in females than in males in those aged <20 years (8.07/100 versus 5.61/100) and those aged ≥20 years (2.06/100 versus 1.30/100). [1] **Race/ethnicity** In the United States (US) studies, the prevalence of AD 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. [6, 7] Similarly, the prevalence of AD has been reported to be higher in black Caribbean children (16%) compared to white children (9%) in the UK. [8] **Risk factors** Genetic risk factors: Family history [9] and mutations in the Filaggrin (FLG) gene. [10] Environmental risk factors: Climate factors (high temperatures, high humidity, and Ultraviolet (UV) radiation, and high levels of precipitation) [10, 11]; urban areas [10, 12]; the "hygiene hypothesis" for example decreased exposure to viral and bacterial pathogens and smaller family size. [13, 14]
Main existing treatment options	Basic therapy includes hydrating, Topical Corticosteroid (TCS) and Topical Calcineurin Inhibitor (TCI). Topical corticosteroids are the first-line anti-inflammatory treatment option in AD. The two TCIs, tacrolimus ointment and pimecrolimus cream, are licensed for

Indication	Atopic Dermatitis in patients 6 months of age and older
	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. [15, 16, 17] Systemic therapy is necessary if AD cannot be controlled sufficiently with appropriate topical treatments and UV light therapy. Systemic corticosteroids (SCS) are rapidly effective, but their long-term use is associated with an unfavorable benefit-risk ratio. Until recently, rather broad-acting immunosuppressants, such as SCSs, cyclosporine A, azathioprine, 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 Janus Kinase (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 [18, 19], even for long-term treatment [20] and an effectiveness comparable to Cyclosporine A. [21]
Natural history of the indicated condition in the untreated population including mortality and morbidity	Because the incidence and prevalence of AD peaks in childhood, it has traditionally been thought of as a resolving childhood disease. However, it is now understood that AD has several heterogenous trajectories inclusive of early transient disease to relapsing remitting AD to chronic persistent dermatitis to long periods of remission followed by

<table>
<tr><td>Indication</td><td>Atopic Dermatitis in patients 6 months of age and older</td></tr>
<tr><td></td><td>recurrence. [22, 23] Active dermatitis beyond childhood is common, inclusive of newly incident disease and recurrent disease since childhood. [4, 24]
When compared to healthy controls, adult patients with AD have a poorer Quality of Life (QoL). [25] Children with AD often develop food allergy, allergic rhinitis and are also at increased risk of asthma, all as part of the “atopic march”. [26] Patients with AD have a higher rate of serious cutaneous infections (eg, eczema herpeticum), respiratory, multiorgan and systemic infections than patients without AD. [27] Additionally, some evidence suggests that patients with AD have a higher risk of cardiovascular disease and autoimmune diseases than patients without AD. [28, 29]
Mortality due to infectious disease, genito-urinary causes and cardiovascular causes is higher in adult patients with AD versus no AD. [30, 31]</td></tr>
<tr><td>Important co-morbidities</td><td>
<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 [32, 33]</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. [34]</td></tr>
<tr><td>Allergic rhinitis [35]</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. [36, 37, 38, 39]</td><td>Decongestants are not recommended for children <12 years. [40]</td></tr>
<tr><td>Attention deficit/hyperactivity disorder [41]</td><td>Stimulants: methylphenidate and amphetamine Non-stimulants: Atomoxetine, guanfacine [42, 43]</td><td></td></tr>
<tr><td>Urticaria [35]</td><td>Antihistamines and OCS given as symptomatic/rescue treatment in acute events.
Second line agents may include omalizumab, cyclosporin A, leukotriene receptor antagonists, mycophenolate mofetil, tacrolimus [44, 45]</td><td>Second line agents may include leukotriene receptor antagonists (montelukast) and omalizumab [44]</td></tr>
</table>
</td></tr>
</table>

Indication	Atopic Dermatitis in patients 6 months of age and older		
	Food allergies [34]	Epinephrine is given for severe anaphylactic cases. [46]	
	Depression/anxiety and sleep disorders [41]	Selective Serotonin Reuptake Inhibitor (SSRIs), dual Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic anti-depressants, monoamine oxidase inhibitors, α2-antagonists, melatonergic agent agomelatine. Anxiolytics (anti-anxiety agents), benzodiazepines, barbiturates, hypnotics. [49]	Fluoxetine in children and adolescents. [47, 48]
	Cutaneous infections and other infections (bacterial/viral/fungal) [27]	Topical antiseptics/antibiotics/anti-fungals or anti-viral preparations. Systemic antibiotic, antiviral and antifungal-agents.	

ICS: Inhaled Corticosteroid; LABA: Long-Acting Beta-Agonist; OCS: Oral Corticosteroids; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitor.

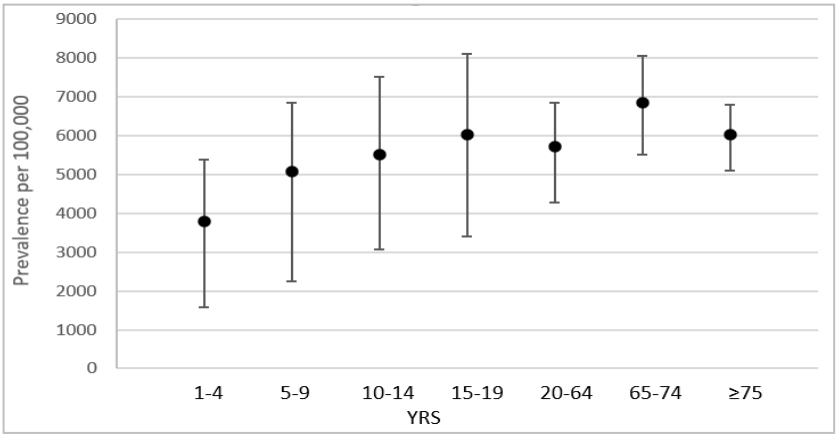
Notes: Common co-medications in the general population are outlined above. Where special treatment scenarios exist for children outside of those medicines highlighted in the general population column, these are flagged in the "specific treatment notes relating to children/adolescents" column.

AD: Atopic Dermatitis; EU: European Union; FLG: Filaggrin; GBD: Global Burden of Disease; ICS: Inhaled Corticosteroid; IHME: Institute for Health Metrics and Evaluation; IL-13: Interleukin-13; JAK: Janus Kinase; LABA: Long-Acting Beta-Agonist; mAb: Monoclonal Antibody; OCS: Oral Corticosteroids; QoL: Quality of Life; SCS: Systemic Corticosteroid; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitor; 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 people/year; • 5 to 19 years: 813/100 000 people/year; • ≥20 years: 297/100 000 people/year. Uncontrolled Asthma: • All ages: 100/100 000 people/year; • 5 to 19 years: 190/100 000 people/year; • ≥20 years: 69/100 000 people/year.
Prevalence	Data from the GBD Study 2019 in the EU indicate prevalence as follows: [1] Asthma: • All ages: 5852/100 000 people; • 5 to 19 years: 5746/100 000 people; • ≥20 years: 6043/100 000 people. Uncontrolled Asthma: • All ages: 1364/100 000 people;

Indication	Asthma in patients 6 years of age and older
	• 5 to 19 years: 1339/100 000 people; • ≥20 years: 1409/100 000 people. 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. [50, 51] The exact prevalence of severe asthma is difficult to ascertain due to varying case definitions for severity, measurement, and report for severity. Nonetheless, severe asthma is expected to be present in 2-5% of children and 4-6% of adults with asthma in European countries. [52, 53]
Demographics	**Age** The prevalence of asthma in the EU is lower in children and highest in adults aged 65-74 years (Figure 2). **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. In adults, the prevalence is higher in adult women than in adult men: [1] Prevalence of asthma in the EU (per 100 000 people): • 0 to 14 years: 5228 in males versus 4268 in females; • 15 to 19 years: 5483 in males versus 6910 in females; • ≥20 years: 4584 in males versus 7409 in females. **Race/Ethnicity** In a meta-analysis of seven UK studies, the prevalence of childhood asthma (5-15 years) ranged from 7.6% (95% CI: 3.77 11.4) in South Asian children, 10.6% (95% confidence interval [CI]: 4.6-16.7) in white children, to 15.0% (95% CI: 3.5-26.5) in black children. For both children and adults combined, the risk of admission to hospitals for asthma was larger in South Asian people (Odds ratio [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. [54] In Scotland, relative to a white population, asthma hospitalization rates have been found to be higher in Pakistani and Indian populations (Incidence rate ratio (IRR) ranging from IRR 1.34, 95% CI: 1.16-1.54 to IRR 1.59, 95% CI: 1.30-1.94), but lower in a Chinese population (IRR ranging from 0.49, 95% CI: 0.39-0.61 to 0.62, 95% CI: 0.41-0.94). [55]

Indication	Asthma in patients 6 years of age and older
	Risk factors for childhood asthma Prenatal risk factors: parental asthma [56] and maternal smoking [57] Post-natal risk factors: hospitalization for respiratory syncytial virus in early life, [58] exposure to inhaled and food allergens (eg, house dust mite, pet allergens, cow's milk allergen, cigarette smoke), [59] household mould and dampness [60], traffic related air pollution (particularly nitrous oxide), [61] exposure to tobacco smoke, [62] overweight/obesity. [58] **Risk factors for adult asthma** • Obesity; [63] • Smoking/secondhand smoke; [64, 65] • Occupational risk eg, nursing and cleaning, occupational exposures such as exposure to fire, mixed cleaning products or chemical spills; [66] • Rhinitis. [67]
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 ICSs with or without LABAs and other options include daily leukotriene receptor antagonists or tiotropium. Reliever therapies including short acting beta-2-agonists, or Maintenance and Reliever Therapy (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, likely due to a range of genetic influences. [68] The role of environmental risk factors such as viruses, bacteria and allergens in genetically predisposed individuals, is yet to be fully elucidated, the gene-environment interactions are known to contribute to the development, severity and persistence of asthma. [68] **Children** Most cases of chronic asthma develop in children of preschool age. [69, 70, 71] Wheeze is associated with asthma, but does not necessarily predict progression to asthma. [72] For most children, wheezing before the age of 3 years resolves itself. [72] A proportion of those children who wheeze before 6 years and have persistence of symptoms beyond 6 years will have clinical asthma. [73] This group is characterized by the presence of atopy and severe symptoms at younger ages. [72, 73] Three out of four school-age asthma patients will have outgrown asthma by mid adulthood. [68] **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: smoking, obesity, and history of allergy. [74] **Type 2 asthma** Asthma can be divided into two distinct molecular phenotypes, based on the level of Type 2 helper T cell (Th2) inflammation. "Th2 high" asthma is corticosteroid responsive; however, some patients do not achieve the goals of asthma management

<table>
<tr><th>Indication</th><th>Asthma in patients 6 years of age and older</th></tr>
<tr><td></td><td>despite administration of corticosteroids with or without additional controller agents. [75] T-helper type 2 asthma is mediated by cytokines, including IL-4, Interleukin-5 (IL-5), and IL-13. Biomarkers for the type 2 phenotype, including peripheral blood eosinophils or exhaled nitric oxide, are widely available. [76]
Consequences of untreated asthma:
Approximately 20-60% of severe or persistent asthma is uncontrolled. [77, 78, 79] The adverse health events of uncontrolled or poorly controlled asthma include increased exacerbations, unscheduled urgent care visits, hospitalization for asthma and sleep disturbances. [78, 80] Daily activities such as attendance at school or work and levels of physical activity are also affected, leading to reduced quality of life. [78, 80]
Mortality
Asthma exacerbations can be fatal. [34] 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. [81, 82] Globally, 10.5 million year of life lost (YLL) were attributed to asthma related premature death in 2016, which is 26% lower compared to 2006. As such, asthma ranked 23rd in 2016 among the leading causes of premature mortality (YLL). [83]
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. [84, 85, 86, 87] The risk of mortality is particularly high after a severe exacerbation. [85] The main causes of death in those with asthma are malignancies, cardiovascular disease and infections. [88]</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 [33]</td><td>Refer to Table 6</td><td></td></tr>
<tr><td>Allergic Rhinitis [89, 90, 91]</td><td>Refer to Table 6</td><td>Refer to Table 6</td></tr>
<tr><td>Chronic Rhinitis [91]</td><td>Nasal or OCSs, Nasal or oral antihistamines, anti-cholinergic (Ipratropium bromide), capsaicin [92, 93]</td><td></td></tr>
<tr><td>Nasal Polyposis [89, 94]</td><td>Refer to Table 8</td><td></td></tr>
<tr><td>Food Allergy [95]</td><td>Refer to Table 6</td><td></td></tr>
<tr><td>Eosinophilic Esophagitis [96]</td><td>Refer to Table 10</td><td></td></tr>
<tr><td>Respiratory infections [97]</td><td>Pneumococcal vaccine
Antibiotics - penicillins, macrolides, etc</td><td></td></tr>
<tr><td>Anxiety/Depression [98]</td><td>Refer to Table 6</td><td>Refer to Table 6</td></tr>
<tr><td>Cardiovascular disease in adults [94, 99]</td><td>Antihypertensives inclusive of Angiotensin Converting Enzyme (ACE)-inhibitor /angiotensin receptor blocker, beta-blockers, calcium</td><td></td></tr>
</table>
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Indication	Asthma in patients 6 years of age and older			
			channel blockers and aldosterone antagonists. Nitrates, digoxin, anticoagulants, antiplatelets, thrombolytics, lipid lowering drugs. *100,101, 102*	
		Gastroesophageal reflux disease *94*	Proton pump inhibitors: Omeprazole, lansoprazole, pantoprazole, rabeprazole Histamine-2 blockers: ranitidine, famotidine, nizatidine *103*	
		Obesity *104*	Orlistat, Naltrexone/Bupropion, Liraglutide *105*	Orlistat is not indicated for the treatment of obesity in children. *106* Naltrexone/Bupropion is not indicated in people <18 years. *107* Liraglutide is indicated for obesity in people aged ≥12 years.
		Sleep apnea *108, 109*	Medications are not recommended first line in clinical guidelines, however tirzepatide is licensed by the Food and Drug Administration (FDA) for use in moderate to severe obstructive sleep apnea in adults with obesity. *110*	
	ACE: Angiotensin Converting Enzyme; FDA: Food and Drug Administration; OCS: Oral Corticosteroid.			

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; FDA: Food and Drug Administration; 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; LABA: Long-Acting Beta-Agonist; MART: Maintenance and Reliever Therapy; OCS: Oral Corticosteroid; OR: Odds Ratio; 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 adults

Indication	Chronic rhinosinusitis with nasal polyposis in adults
Incidence	Data for the incidence of CRSwNP are scarce. The incidence of CRSwNP is estimated at 83/100 000 person-years (PYs), from US data. *111, 112* In a European setting, the incidence of symptomatic nasal polyposis has been estimated at 63/100 000 person-years. *113*
Prevalence	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)

Indication	Chronic rhinosinusitis with nasal polyposis in adults
	and 2.7% (95% CI: 1.9-3.5) respectively. [114, 115] 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. [116] In South Korea, the prevalence of CRSwNP has been ranges from 2.5-2.6% of the general population. [112] In the US, 1.1% of the general population is estimated to have prevalent CRSwNP. [117]
Demographics	Age Chronic rhinosinusitis with nasal polyposis is a disease of middle age, with incident cases typically occurring in those aged ≥45 years. [111] Prevalence increases with age; those aged ≥65 years have the highest prevalence of CRSwNP compared to other age groups. [112, 114, 115, 118] Gender Chronic rhinosinusitis with nasal polyposis is more common in men than women with 60-70% of cases occurring in men. [113, 115, 118] However, women report more severe CRSwNP than men and report lower quality of life scores than men. [119, 120] 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 Chronic Rhinosinusitis (CRS) among Asian (7%) and Hispanic (8.6%) populations compared to African American (13.3%) and Caucasian populations (13%). [121] There is some evidence to suggest that the extent of eosinophilia in CRSwNP varies by ethnicity. [122] Risk factors • Family history; [123, 124] • Male gender; [123] • Asthma. [123]
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.[125, 126, 127, 128, 129] 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, Functional Endoscopic Sinus Surgery [FESS]) if medical management is unsuccessful. [127] 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 INCSs for the treatment of adults with severe CRSwNP for whom therapy with SCSs and/or surgery do not provide adequate disease control. [130] 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. [45] Mepolizumab is indicated as an add-on therapy with INCSs for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control. [131] 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. [132] Their effect, as measured by computed tomography (CT) scan, in improving sinus disease is limited. [133]

Indication	Chronic rhinosinusitis with nasal polyposis in adults
	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. [133] 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. [126] Adverse events (AEs) associated with SCS are well documented and most commonly include adrenal suppression and bone loss (ie, osteopenia, osteoporosis). [134] Other more common AEs are gastric upset, glucose intolerance, cataracts, and weight gain. [135] An evidence-based risk analysis of OCS use in CRSwNP found that a breakeven threshold favored surgery over medical therapy when CRSwNP patients required OCSs more than once every 2 years. [136] Thus, in the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR) [126] 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. [137] When INCSs 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 Nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD), Endoscopic Sinus Surgery (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. [138, 139, 140] Multiple surgeries are not infrequent in this population. [139] 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. [132, 135] 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%). [127]
Natural history of disease	Chronic rhinosinusitis with nasal polyposis, characterized by type II inflammation, manifests as severe and recurrent disease. [141] Various aetiologies have been suggested inclusive of hereditary factors, systemic and local allergy, and infection. [142] 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 (Hazard ratio [HR] = 4.1, 95% CI: 1.8-9.4) the risk of developing CRSwNP. [143] 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. [144] Comorbid depressive illness is associated with poorer health-related quality of life (HRQL) than CRS without depressive illness. [145] Chronic rhinosinusitis with nasal polyposis is associated with several comorbidities inclusive of allergic rhinitis, asthma, gastroesophageal reflux disease and sleep apnea. [111,146] The association between CRSwNP and asthma is perhaps the best studied:

<table>
<tr><th>Indication</th><th>Chronic rhinosinusitis with nasal polyposis in adults</th></tr>
<tr><td></td><td>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. [147, 148] 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. [141, 149] Chronic rhinosinusitis with nasal polyposis has been associated with an increased risk of mortality relative to polyp negative CRS patients (HR = 1.4, 95% CI: 1.1-1.8). [150]</td></tr>
<tr><td>Co-morbidities</td><td>
<table>
<tr><th>Co-morbidities</th><th>Co-medications</th></tr>
<tr><td>Asthma [111, 146]</td><td>Refer to Table 7</td></tr>
<tr><td>Atopic Dermatitis [111]</td><td>Refer to Table 6</td></tr>
<tr><td>Allergic Rhinitis [112]</td><td>Refer to Table 6</td></tr>
<tr><td>Aspirin/NSAID-ERD [151]</td><td>See nasal polyposis main existing treatment options and common co-medications for asthma.</td></tr>
<tr><td>Chronic Obstructive Pulmonary Disease</td><td>Refer to Table 11</td></tr>
<tr><td>Esophageal Reflux Disease [111, 152]</td><td>Refer to Table 7</td></tr>
<tr><td>Respiratory infections (upper and lower) [153]</td><td>Refer to Table 7</td></tr>
</table>
NSAID-ERD: Nonsteroidal Anti-Inflammatory Drug-Exacerbated Respiratory Disease.
</td></tr>
</table>

AE: Adverse Event; CI: Confidence Interval; CRS: Chronic Rhinosinusitis; CRSwNP: Chronic Rhinosinusitis with 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; PY: Person-Year; 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. [154] In the UK, the incidence of PN was 9.31/100 000 population in 2019. [155]
Prevalence	Globally, the prevalence of PN ranges from 6/100 000 people (Poland) to 72/100 000 people (US) to 88/100 000 people (UK) to 111/100 000 people (Germany). [154, 155, 156, 157]
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. [154, 156, 157, 158, 159] Gender The prevalence of PN is slightly higher in females than in males, with 50-60% of cases occurring in women. [154, 156, 157, 158, 159]

Indication	Prurigo Nodularis in adults
	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). [160]
Main existing treatment options	There are no Food and Drug Administration (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 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 International Forum for the Study of Itch (IFSI)-guideline on chronic prurigo from 2020 by Stander et al recommends the use of emollients as supportive care. [161] 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 TCIs 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. [162] 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.

<table>
<tr><th>Indication</th><th>Prurigo Nodularis in adults</th></tr>
<tr><td></td><td>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 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. 163
Prurigo Nodularis lesions can start in areas of normal or dry skin, although AD 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. 164
Prurigo Nodularis is associated with several comorbidities inclusive of mental health, dermatological, endocrine, cardiovascular and renal disorders, in addition to Human Immunodeficiency Virus (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. 157, 158 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. 157, 158, 159, 165</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 157</td><td>Topical – TCSs, emollients, calcipotriene/calcitriol, coal tar, tazarotene, tacrolimus/pimeocrolimus, Ultraviolet-B (UV-B) phototherapy.
Systemic – Methotrexate, cyclosporin, adalimumab, etanercept, infliximab, apremilast, brodalumab, certolizumab pegol, guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab and ustekinumab. 166</td></tr>
<tr><td>Asthma 157</td><td>Refer to Table 7</td></tr>
<tr><td>Mental Health</td><td></td></tr>
<tr><td>Depression, Anxiety 157, 158, 167</td><td>Refer to Table 6</td></tr>
<tr><td>Infections</td><td></td></tr>
<tr><td>HIV 158</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</td></tr>
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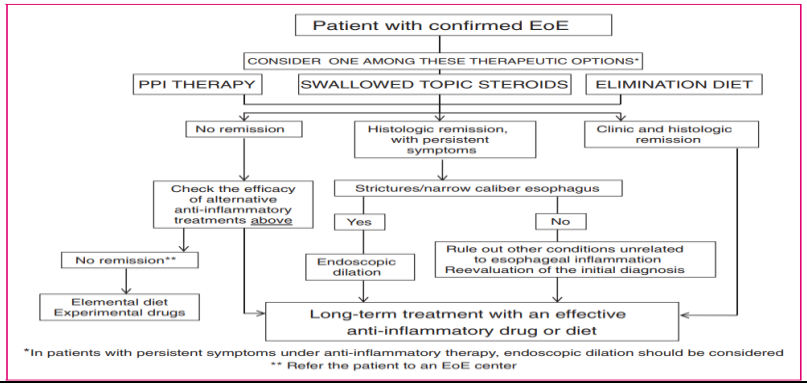
Indication	Prurigo Nodularis in adults		
			inhibitors – atazanavir, darunavir, lopinavir; Protease inhibitor boosting agents: ritonavir, cobicistat; Fusion Inhibitor – enfuvirtide; C-C chemokine receptor type 5 inhibitor – maraviroc; Clusters of Differentiation (CD)4 directed post attachment. HIV1 inhibitor – Ibalizumab. [168]
		Autoimmune	
		Celiac disease [157]	Gluten avoidance.
		Inflammatory Bowel Disease (Crohn's disease, Ulcerative Colitis) [157, 160]	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. [169, 170] Crohn's disease – Ileal release budesonide, oral prednisolone, anti-tumor necrosis factor (TNF) therapy, methotrexate, mesalazine, vedolizumab, ustekinumab, azathioprine or mercaptopurine, adalimumab, proton pump inhibitors. [171, 172]
		Diabetes Mellitus Type I [158]	Insulin
		Endocrine	
		Diabetes Mellitus Type II [158]	Metformin, Sulphonyl Urea (SU)s, α-glucosidase inhibitors, thia-zolidinediones, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon-like peptide-1 receptor agonists and insulin. [173]
		Other systemic illnesses	
		Chronic Kidney disease [158]	Anti-hypertensives - ACE inhibitor or angiotensin II receptor blocker. [174]
		Heart Failure [157, 154, 160]	Angiotensin converting enzyme inhibitor, angiotensin receptor-neprilysin inhibitor, mineralocorticoid receptor antagonists, dapagliflozin, empagliflozin, sacubitril, valsartan. [175]
		Cardiovascular/cerebrovascular disease [157, 160]	Refer to Table 7
		Chronic Obstructive Pulmonary Disease [154, 157,160]	Refer to Table 11
	ACE: Angiotensin Converting Enzyme; CD: Clusters of Differentiation; HIV: Human Immunodeficiency Virus; 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; SU: Sulfonyl Urea; TCI: Topical Calcineurin Inhibitor; TCS: Topical Corticosteroid; TNF: Tumor Necrosis Factor; UK: United Kingdom; US: United States; UV-B: Ultraviolet-B.

The epidemiology of EoE in patients-1 year of age and older is summarized in the following table.

Table 10 - Epidemiology of Eosinophilic Esophagitis in patients 1 year of age and older

Indication	Eosinophilic Esophagitis in patients 1 year of age and older
Incidence	In North America and Europe, the incidence of EoE in adults ranges from 7.2-8.5/100 000 PYs and the incidence in children and adolescents aged ≤19 years is reported to be 6.6 (95% CI: 3-11.7)/100 000 PYs. [176, 177] There is no variation in incidence between the US and Europe, and no studies examined the population-based incidence of EoE in Asian countries. [178]
Prevalence	The prevalence of EoE in adults is 42.2 (95% CI: 31.1-55.0)/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. [176, 177] The prevalence of EoE in children (<16 years) is 34.4 (95% CI: 22.3-49.2)/100 000 people. However, when limited to studies using the newest diagnostic criteria (post 2017 EoE guidelines [179, 180] and A Working Group on Proton Pump Inhibitor–Responsive Esophageal Eosinophilia (AGREE) conference 2018), prevalence is estimated as 53.4 (95% CI: 27.1-88.5)/100 000 people. There is no variation in prevalence of EoE in children between the US and Europe.[176, 177] No studies were found that examined the population-based prevalence of EoE in Asian countries. [178]
Demographics	**Age** Eosinophilic Esophagitis can occur throughout the lifespan, however most cases occur in children, in adolescents and in adults <50 years. [177] **Gender** Males are up to 3.5 times more likely to have EoE than females (range OR 2.00 95% CI: 1.86-2.14 to OR 3.49, 95% CI: 2.52-4.83). [176, 181, 182] **Ethnicity** Eosinophilic Esophagitis is approximately two times more likely to be reported in a Caucasian population relative to other ethnicities eg, African-Americans or Asian. [182, 183]
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 European Academy of Allergy and Clinical Immunology (EAACI), and the European Society of Eosinophilic Oesophagitis; [179] guidance from the American Gastroenterological Association and the Joint Task Force on Allergy-Immunology Practice Parameters. [184] Additional Jorveza® (budesonide orodispersible tablet) clinical data is also included. [185] The example below is the proposed therapeutic algorithm from the United European Gastroenterology. [179] **Figure 3 - Proposed therapeutic algorithm** [179] 

Indication	Eosinophilic Esophagitis in patients 1 year of age and older
	Proton Pump Inhibitors: • As of RMP DLP of 28-Mar-2023, there are no approved proton pump inhibitor (PPI)s for EoE: • 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 [179, 184] • Up to 80% of patients maintained histological remission for 1 year while on PPIs in clinical trials. [179] • Guidelines recommend PPIs doses in adults of omeprazole 20-40 mg twice daily or equivalent; in children, 1-2 mg/kg or equivalent. [179] • PPI use has been associated with increased risk of *Clostridium difficile* infection and bone fractures in children and adults, but this may not be generalizable due to differences in study designs. [186] In the absence of long-term studies, it is recommended that PPIs are progressively decreased to the lowest dose that keeps the disease in remission. [179] **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: As of DLP of 28-Mar-2023, there is no swallowed TCS approved for patients under 18 years old with EoE. [179, 184, 185] • Jorveza 1 mg twice a day (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). [185] • 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. [185] • Over a period of up to 3 years of treatment, over 80% of the patients maintained clinical remission (defined as weekly Eosinophilic Esophagitis Activity Index-Pro $\leq$20). [185] • 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%). [185] • When used off label in children, and if they are receiving high doses of swallowed topical steroids for long periods or use concomitant inhaled/nasal corticosteroids for associated atopic diseases, [179] some guidelines advise monitoring of cortisol to prevent adrenal insufficiency. **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. [179] • 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, [184] and lack of adherence in adult patients. [179] Elimination Diet: • Six food, four food, and two food empiric group elimination diets induce histologic remission (approximately 75%, approximately 50%, approximately 40% respectively). [179] Dilation: [176, 184, 187] • Esophageal dilation is a mechanical widening of the esophagus which typically needs to be repeated to maintain remission of symptoms

<table>
<tr><th>Indication</th><th>Eosinophilic Esophagitis in patients 1 year of age and older</th></tr>
<tr><td></td><td>

A systematic review reported symptom improvement in 87% of patients who underwent esophageal dilation. [184, 187]
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%

</td></tr>
<tr><td>Natural history of disease</td><td>
Eosinophilic Esophagitis is a chronic, progressive type 2 inflammatory disease that is thought to start in childhood, and can go undetected until adulthood. [181] Family history studies along with a predominance of EoE amongst males indicate the influence of genetic-environment interactions in the development of EoE. [188, 189] Gene loci associated with EoE fall into 4 main categories: Th2 signaling, epithelial barrier function, fibrosis, and genetic defects associated with multiple atopic comorbidities. [188, 189] Early life exposure to antibiotics is an environmental risk factor. [190, 191] Th2 cytokines IL-4, IL-5, and IL13, thought to be induced primarily by food and airborne allergens, mediate inflammation in EoE, [188, 192, 193]

Eosinophilic Esophagitis does not resolve itself. The disease progresses with age and may develop fibrostenotic features. [177, 181] This explains the differences in clinical presentations between children and adults. [177] For example, young children may experience abdominal pain (mean age 12 years), vomiting (mean age 8.1 years), feeding difficulties/food refusal (mean age 2 years), gastroesophageal reflux, and failure to thrive. Older children and teenagers may have dysphagia (mean age 13.4 years), non-swallowing associated chest pain and in more extreme cases, food impaction (mean age 16.8 years). [194]

Adult symptoms include dysphagia, heartburn, food impaction and upper abdominal pain that will continue without treatment or recur on discontinuation of treatment. [177, 195] The mean age at diagnosis ranges from 5.9 to 12.0 years in children and 29 to 30 years in adults. The average delay from symptom onset until diagnosis ranges from 1.2 to 3.5 years in children, from 3.0 to 8.0 years in adults. [181]

Patients with EoE report reduced health related quality of life scores, especially in severe disease. Specifically, this stems from concerns about eating (eg, food impaction, dysphagia), impact on social relationships, psychological burden including anxiety and depression, and concerns about effective treatments. [196] Patients with EoE do not appear to have an increased risk of mortality in comparison with their siblings and the general population. [197]
</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>Food Allergy [198]</td><td>Epinephrine for anaphylaxis</td><td></td></tr>
<tr><td>Food-pollen allergy [199, 200]</td><td>Epinephrine for anaphylaxis</td><td></td></tr>
<tr><td>Atopic Dermatitis [96]</td><td>Refer to Table 6</td><td></td></tr>
<tr><td>Asthma [96]</td><td>Refer to Table 7</td><td>For children 5 years and younger: SABA, [201] ICS, Leukotriene Receptor Antagonist (LTRA)</td></tr>
<tr><td>Allergic Rhinitis (Hay Fever) [96]</td><td>Refer to Table 6</td><td>Refer to Table 6</td></tr>
<tr><td>Celiac disease [202, 203]</td><td>Gluten avoidance.</td><td>Medications are not recommended as the primary treatment for celiac disease. [204, 205]</td></tr>
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Indication	Eosinophilic Esophagitis in patients 1 year of age and older			
	Inflammatory Bowel Disease [202, 203]	Adults Refer to Table 9	Children Crohn's Disease: [171] enteral nutrition, surgery Ulcerative Colitis: aminosalicylate, corticosteroids
	Adrenal insufficiency [202]	Not applicable	Hydrocortisone, Fludrocortisone [206]
	Cystic Fibrosis [202]	Same as Children	Tobramycin, [207] Dornase alfa, hypertonic saline, Azithromycin with/without P. aeruginosa, Ivacaftor, aztreonam, ibuprofen
	Type 1 diabetes mellitus [202]	Same as Children	insulin [208]
	Autism Spectrum Disorder [202]	Same as Children	Medications used to treat concurrent mental health disorders/symptoms of Autism Spectrum Disorder (ASD) Psychostimulants (≥6 years): methylphenidate, [209] dexmethylphenidate, [210] mixed amphetamine salts, [211] lisdexamfetamine, [212] dextroamphetamine, [213] SNRIs: atomoxetine (≥6 years) [214] α-2 adrenergic agonists: guanfacine (≥6 years) [215] Antipsychotics: aripiprazole (≥6 years), [216] risperidone (≥5 years) [217] SSRIs: fluvoxamine (≥8 years), [218] fluoxetine (≥7 years) [219] Anticonvulsant mood stabilizers (≥10 years): valproic acid, [220] divalproex sodium [221, 222]
	Gastroesophageal Reflux Disease (GERD) [203]	Refer to Table 7	
	Lymphocytic Esophagitis [203]	PPIs, fluticasone, corticosteroids [223]	
	Connective Tissue Disorders [202]	Cardiovascular complications in Marfans Syndrome: Beta-adrenergic receptor blockers, angiotensin II receptor blockers [224]	

Indication	Eosinophilic Esophagitis in patients 1 year of age and older
	Pain management in Erlos Danlos Syndrome [225] Cardiovascular complications in Loeys-Dietz syndrome: beta-blockers, ACE-inhibitors/angiotensin II receptor blockers, anti-coagulants. [226]

ACE: Angiotensin Converting Enzyme; ASD: Autism Spectrum Disorder; GERD: Gastroesophageal Reflux Disease; ICS: Inhaled Corticosteroid; LTRA: Leukotriene Receptor Antagonist; PPI: Proton-Pump Inhibitor; SABA: Short-Acting Beta-Agonist; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor.

ACE: Angiotensin Converting Enzyme; AGREE: A Working Group on Proton Pump Inhibitor–Responsive Esophageal Eosinophilia; AE: Adverse Event; ASD: Autism Spectrum Disorder; BID: Twice a Day; CI: Confidence Interval; DLP: Data Lock Point; EAACI: European Academy of Allergy and Clinical Immunology; EoE: Eosinophilic Esophagitis; EU: European Union; GERD: Gastroesophageal Reflux Disease; ICS: Inhaled Corticosteroid; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-13: Interleukin-13; LTRA: Leukotriene Receptor Antagonist; OR: Odds Ratio; PPI: Proton Pump Inhibitor; RMP: Risk Management Plan; TCS: Topical Corticosteroid; SABA: Short-Acting Beta-Agonist; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake 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

Indication	Chronic Obstructive Pulmonary Disease in adults
Incidence	Data from the GBD Study 2019 indicate the incidence of COPD in the European region to be 305 per 100 000 PYs, 95% uncertainty interval (UI): 290.8 to 318.5. Geographical variation in incidence is provided in Table 11a.
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 11a - Global COPD incidence (per 100 000 person years) from the GBD study, 2019[a]

Location	Incidence	95%UI
Global	209.6	196.8 to 222.6
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.

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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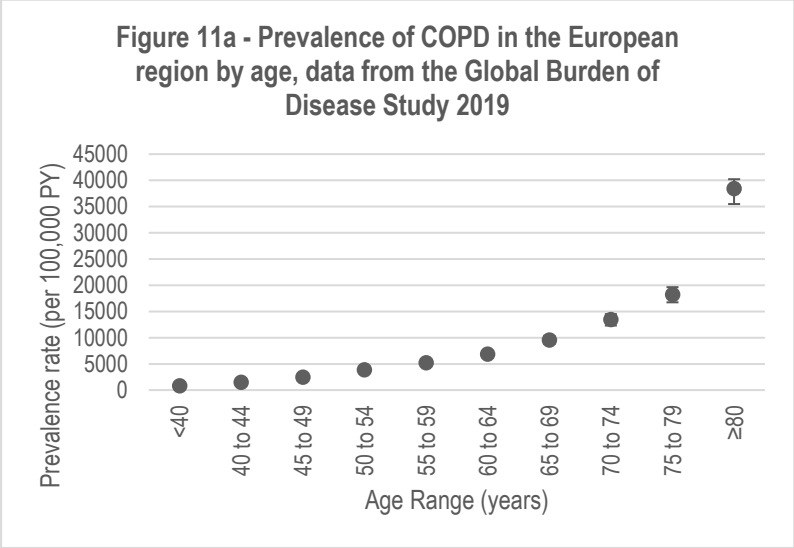
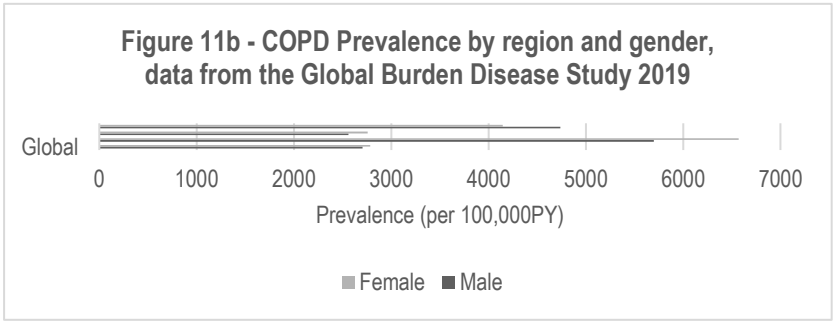
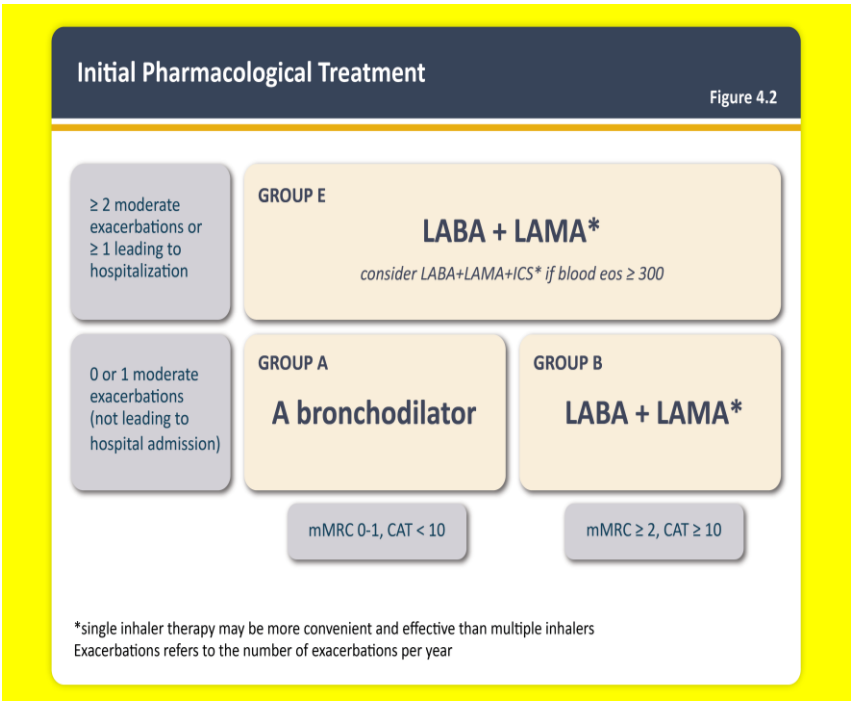
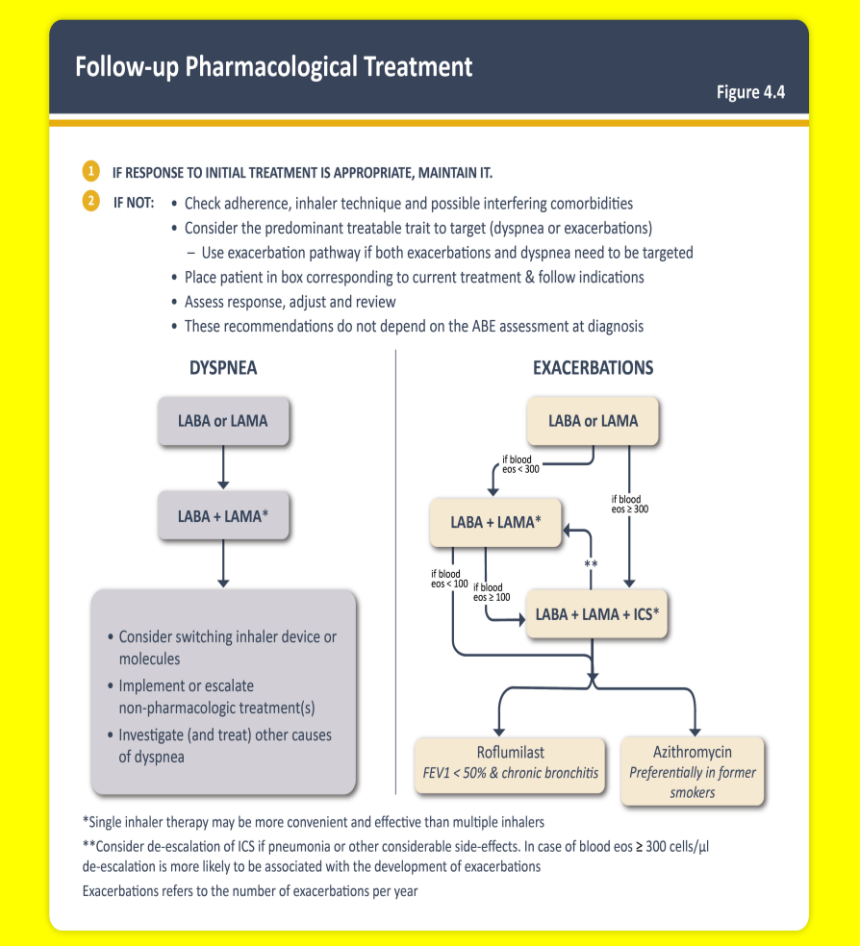
Indication	Chronic Obstructive Pulmonary Disease in adults
	COPD: Chronic Obstructive Pulmonary Disease; GBD: Global Burden of Disease; IHME: Institute for Health Metrics and Evaluation; UI: Uncertainty Interval.
Demographics	**Age** Chronic Obstructive Pulmonary Disease is most commonly diagnosed after age ≥45 years. [227] 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) [Figure 11b]. 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]. **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. [228] 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

Indication	Chronic Obstructive Pulmonary Disease in adults
	of underdiagnosis ranging from OR 1.5 to 3.75 depending on increasing levels of airway obstruction. [229]
Main existing treatment options	The Global Initiative for Chronic Obstructive Lung Disease (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. Inhaled corticosteroids 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 phosphodiesterase-4 (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. [230, 231, 232] 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 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



Indication	Chronic Obstructive Pulmonary Disease in adults

Figure 11e – Commonly Used Maintenance Medications in COPD

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.

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." [233] 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

<table>
<tr><th>Indication</th><th>Chronic Obstructive Pulmonary Disease in adults</th></tr>
<tr><td></td><td>also general environmental pollution, familial history, asthma, and childhood respiratory infections. [234]

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. [234, 235] All smokers have some inflammation in their lungs, however those with COPD have an enhanced response to inhalation of cigarette smoke. [236] 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). [236] The inflammatory response is mediated by macrophages, neutrophils and T-lymphocytes. Exacerbations can be characterized by the presence of increasing numbers of eosinophils. [236]

There is evidence to support the involvement of both type 1 helper T cell (Th1) and Th2 pathways in the development of COPD, and consequently the following cytokines and chemokines may be involved in the pathology of COPD: TNF-α, Interleukin 1 Beta (IL-1β), IL-4, IL-5, Interleukin-6 (IL-6), Interleukin-8 (IL-8) (C X C Motif Chemokine Ligand 8 [CXCL8]), IL-13, IL-17, IL-18, Interleukin-23 (IL-23), Interleukin-33 (IL-33), and thymic stromal lymphopoietin, as well as growth factors such as transforming growth factor-β. [237]

Recent clinical trial evidence supports the involvement of IL-4 and IL-13 in the Th2 pathway. [238] 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. [233, 239, 240]

Survival and Mortality

The overall 5-year survival for COPD patients is between 46% and 89% depending on severity of the disease. [241] In 2020, the World Health Organization (WHO) stated that COPD is the third leading cause of death worldwide. [242] For men in the European region, the mortality rate from COPD is 14/100 000, while it is 6.4/100 000 for women. [243]</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) [244]</td><td>Antihypertensive medications: ACE inhibitors, angiotensin receptor blocker, beta-blockers, calcium channel blockers, or diuretics [245]</td></tr>
<tr><td>Asthma [244]</td><td>Refer to Table 7</td></tr>
<tr><td>Coronary artery disease [244]</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 [246]</td></tr>
<tr><td>Chronic heart failure [244]</td><td>Refer to Table 9</td></tr>
<tr><td>Arrhythmias [244] or atrial fibrillation</td><td>Anti-arrhythmic drugs eg, flecainide or amiodarone, beta-blockers, calcium channel blockers [247]
Vitamin K antagonists: warfarin
Non-vitamin K antagonists: eg, abixaban, dabigatran, edoxaban, rivaroxaban
Anti-platelet agent: aspirin [248]
Treatment of other cardiovascular risk factors eg, hypertension, diabetes as appropriate [248]</td></tr>
<tr><td>Peripheral arterial disease [244]</td><td>Anti-thrombotic therapy, lipid lowering therapy, anti-hypertensive therapy [249]</td></tr>
</table></td></tr>
</table>

Indication	Chronic Obstructive Pulmonary Disease in adults	
	GERD [244]	Refer to Table 7
	Osteoporosis or osteoarthritis [244]	Calcium/Vitamin d supplements, bisphosphonates, denosumab, hormone replacement therapy, raloxifene and strontium ranelate teriparatide, romosozumab [250] Oral/topical non-steroidal anti-inflammatory drug (NSAID), opioids, duloxetine, glucosamine/chondroitin, tramadol, acetaminophen/paracetamol, vitamin D, intra-articular corticosteroid [251]
	Depression/anxiety [244]	Refer to Table 6
	Diabetes [244]	Insulin
	Hyperlipidemia	Statins, ezetimibe, fibrates, nicotinic acid, proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors, n-3 fatty acids [252]
	Chronic Kidney Disease [244]	Refer to Table 9
	Obesity [244]	Refer to Table 7
	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.	

ACE: Angiotensin Converting Enzyme; CAT: COPD Assessment Test; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; CXCL8: C-X-C Motif Chemokine Ligand 8; DPI: Dry Powder Inhaler; FeNO: Fraction of Exhaled Nitric Oxide; FEV: Forced Expiratory Volume; 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; MDI: Metered Dose Inhaler; mMRC: modified Medical Research Council; NSAID: Non-Steroidal Anti-Inflammatory Drug; OR: Odds Ratio; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; PDE4: Phosphodiesterase-4; SABA: Short-Acting Beta Agonists; SAMA: Short-Acting Muscarinic Antagonists; SMI: Soft Mist Inhaler; 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.

The epidemiology of CSU in patients 2 years of age and older is summarized in the following table.

Table 12 - Epidemiology of Chronic Spontaneous Urticaria in patients ≥2 years of age

Indication	Chronic Spontaneous Urticaria in patients 2 years of age and older
Incidence	In the US pediatric population (<18 years), the age-standardized incidence rates of CSU during the identification period (2012-2018) ranged from 0.066 to 0.109 per 100 PY across different data sources. [253] In an Italian population aged ≥15 years, the incidence in 2013 was 1.30 per 1000 PY. [254] In South Korea, the incidence of CSU was reported to be 2.43 per 1000 PY in people aged ≥20 years in 2014. [255]
Prevalence	The one-year diagnosed prevalence of CSU in pediatric patients (0-17 years) across five European countries was 0.75% (95% CI, 0.44-1.08). [256] In an Italian population aged ≥15 years, the prevalence of CSU in 2013 was 0.38%. [254] The prevalence of chronic urticaria, which includes both CSU and chronic inducible urticaria, is 0.5% in the population aged ≥17 years in Europe. [257] In South Korea, the prevalence of CSU in 2014 was 0.45% (≥20 years). [255]
Demographics	**Age** The prevalence of chronic urticaria (CU), a combination of CSU and chronic inducible urticaria, is greater in children than adults: • Children (0-19 years):1.43% (95% CI: 0.89-2.10)

Indication	Chronic Spontaneous Urticaria in patients 2 years of age and older
	• Adults (>19 years): 0.86% (95% CI: 0.12-2.29) [257] **Gender** The prevalence of CSU is 1.25-1.85 times higher in women than in men. [254, 255] **Ethnicity** Among US adults, CU, which is a combination of CSU and chronic inducible urticaria, is less likely to be reported in white patients relative to other ethnicity/race categories. • White: 261.9 (259.5-264.3) per 100 000 adults • Black: 291.6 (285.4-297.9) per 100 000 adults • Other: 330.5 (323.2-337.8) per 100 000 adults [258]
Main existing treatment options	The current international guidelines [259] recommend to commence the treatment of CSU using 2nd generation H1-antihistamines (eg, bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine, loratadine, and rupatadine) on a daily basis to prevent the occurrence of wheals and angioedema, rather than on demand. This is supported by their proven efficacy in randomized controlled trials, and a safety profile with several years of continuous use; modern 2nd generation H1-antihistamines are minimally or non-sedating and free of anticholinergic effects. Since the year 2000, guidelines recommend the off-label use of up to fourfold standard-dose of 2nd generation H1-antihistamines in urticaria patients who show insufficient response to standard-dose. Xolair® (omalizumab) is currently licensed for the treatment of CSU in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment. Omalizumab (anti-IgE) is the only licensed treatment for patients who do not show sufficient benefit from treatment with a 2nd generation H1-antihistamines. The recommended initial dose in CSU is 300 mg every 4 weeks via subcutaneous injection, increasing to 600 mg every 2 weeks in patients with insufficient response to standard-dose omalizumab. Omalizumab updosing is off-label. Patients who do not show sufficient benefit from treatment with omalizumab should be treated with ciclosporin 3.5-5 mg/ kg per day. Ciclosporin is off-label for urticaria and is recommended only for patients with severe disease refractory to any dose of antihistamines and omalizumab in combination. In children: Currently there is no approved / licensed product for the treatment of CSU in children below 12 years of age who remain symptomatic despite H1 antihistamine treatment. International guidelines (Zuberbier et al, 2022) suggest using the same treatment algorithm with caution (eg, weight-adjusted dosage) in children with chronic urticaria. [259] 1st generation H1-antihistamines have an inferior safety profile compared with 2nd generation H1-antihistamines, and are, therefore, not recommended as first- line treatment in children with urticaria. 2nd generation H1-antihistamines with proven efficacy and safety in the pediatric population include bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and rupatadine. The choice of which 2nd generation H1-antihistamines to use in children with urticaria should take into consideration the age and availability as not all are available as syrup or fast dissolving tablet suitable for children. All further steps should be based on individual consideration and be taken carefully (including updosing of antihistamines). Further treatment options are not well studied in children. A short course of corticosteroids as advised in the algorithm should be used as only a very restricted measure in children.
Natural history of disease	Chronic spontaneous urticaria is defined as the presence of wheals with or without angioedema that has been continuous or intermittent for more than 6 weeks. [260, 261, 262] The natural history of CSU is poorly understood. The duration of the disease is generally 1-5 years but is likely to be longer in more severe cases. [263]

Indication	Chronic Spontaneous Urticaria in patients 2 years of age and older
	There are two main hypotheses regarding the development of chronic urticaria. One hypothesis relates to dysregulation in intracellular signaling pathways within mast cells and basophils. These abnormalities can cause issues in the trafficking or functioning of these cells. [264] Another more widely accepted hypothesis, involves the production of autoantibodies targeting FcεRI (high affinity IgE receptor) present on both mast cells and basophils. [264] The release of histamine, IL-4, IL-13, [264, 265]and other mediators from activated mast cells in the skin leads to various effects such as sensory nerve activation, vasodilation, plasma leakage, and recruitment of cells to the urticarial lesions. An external trigger cannot be identified in CSU. [262, 266] Up to 36% of patients with acute spontaneous urticaria could progress to CSU [266] and one-third to 50% of patients with CSU will have remission of their disease within 1 year. [260] In CU, 40-50% of cases are associated with angioedema and its presence typically denotes longer disease duration and higher severity. [268, 269] In pediatric patients with CSU, spontaneous remission occurs in 17%, 39%, and 50% after 1, 3, and 5 years, respectively [270] and it is estimated that 78.4% of pediatric patients have wheals alone, 6.6% have angioedema alone, and 15% have both wheals and angioedema. [271] In adult patients with CSU older age at onset, female sex, long disease duration, hypersensitivity to aspirin and nonsteroidal anti-inflammatory drugs, comorbid inducible urticaria, and concomitant recurrent angioedema are linked to longer CSU duration. [270] Chronic Spontaneous Urticaria is known to affect health related quality of life via physical symptoms/discomfort, interference with daily activities, emotional well-being and sleep. Amongst employed patients, absenteeism and work impairment/performance have been reported. [272]

Co-morbidities

Comorbidities	Comedications	Specific treatment notes relating to children/adolescents ≥2 years
Asthma [273]	Refer to Table 7	
Allergic Rhinitis [273]	Refer to Table 6	
Atopic Dermatitis [273]	Refer to Table 6	
Hashimoto's thyroiditis /Hypothyroidism [275]	Levothyroxine, [274] thyroid extracts, Triiodothyronine, Compounded Thyroid Hormones	Levothyroxine [274]
Graves' disease /Hyperthyroidism [275]	Thionamides [276](Propylthiouracil, Carbimazole, Methimazole), Radioactive Iodine, Propranolol, Atenolol, Bisoprolol	Methimazole, [276] Radioactive Iodine (but generally avoided in children <10 years, unless: poor response to medications, compliance issues or large goiter/relapse) [277]
Depression/Anxiety [278]	Refer to Table 6	Refer to Table 6
Pernicious anemia [279]	Parenteral vitamin B12 [280]	Parenteral vitamin B12, oral vitamin B12 may be considered as well as a first-line treatment [281]
Vitiligo [279]	TCS, topical calcineurin inhibitors, oral betamethasone [282]	Topical corticosteroids, topical calcineurin inhibitors, oral betamethasone is not used as a first-line treatment in children (reserved for rapidly progressive vitiligo) [283]

Indication	Chronic Spontaneous Urticaria in patients 2 years of age and older			
	Celiac disease [279]	Medications are not recommended as the primary treatment for celiac disease. [204, 205]		
	Psoriasis [279]	Refer to Table 9	Topical corticosteroids, topical calcineurin inhibitors, Adalimumab, Cyclosporine (short-term for severe flares), Etanercept, Methotrexate, Ustekinumab, Ixekizumab, Secukinumab [284]	
	Addison's disease [279]	Hydrocortisone, cortisone acetate, prednisolone, dexamethasone, fludrocortisone, dehydroepiandrosterone replacement [206]	Avoid long-acting glucocorticoids in children like dexamethasone due to growth suppression risk [285]	
	Rheumatoid Arthritis [279]	Methotrexate, Glucocorticoids, Hydroxychloroquine, Sulfasalazine, folic/folinic acid, Rituximab [286]	High-dose systemic glucocorticoids (reserved for systemic JAI or severe flares), sulfasalazine, leflunomide, biologic Disease-Modifying Antirheumatic Drugs, Methotrexate, NSAIDs [287]	
	Note: The table displays comorbidities across all age groups, though specific conditions may not appear in every age group. Treatment options vary according to patient age. NSAID: Non-Steroidal Anti-Inflammatory Drug; TCS: Topical Corticosteroid.			

CI: Confidence Interval; CSU: Chronic Spontaneous Urticaria; CU: Chronic Urticaria; IgE: Immunogobulin E; IL-4: Interleukin-4; IL-13: Interleukin-13; NSAID: Non-Steroidal Anti-Inflammatory Drug; PY: Person-Year; TCS: Topical Corticosteroid; US: United States.

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 13.

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. [288]

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 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 13 - 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 no observed effect level (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, T cell dependent antibody response (TDAR), organ weights, macroscopic	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
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 MAH'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 T Helper (TH)1 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 mechanism of action (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. [289]

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; MAH: Marketing Authorization Holder; 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; TARC: Thymus and Activation Related Chemokine; TDAR: T-cell Dependent Antibody Response; TH: T Helper; US: United States.

Safety Findings in Special Populations

Pediatric Study Plans (PSP) and Pediatric Investigation Plans (PIP) 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.

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, COPD, CSU, and BP 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 10 672 patients were exposed to dupilumab in 61 completed/unblinded CSU, EoE, COPD, PN, AD, asthma, CRSwNP, and BP studies (4 studies in CSU, 3 studies in EoE, 2 studies in COPD, 2 studies in PN, 31 studies in AD, 13 in asthma, 5 studies in CRSwNP, and 1 study in BP). Of these, 6988 and 3342 patients were exposed to dupilumab for at least 1 year and 2 years, respectively.

For AD studies R668-AD-1434 and LPS17764, the data cut-off date is 28 March 2025. Asthma study LTS14424 (main) is complete and the data cut-off for the Japanese sub-study of LTS14424 is 28 March 2025. The data cut-off date for BP study R668-BP-1902 is 12 July 2024. The data cut-off for CRSwNP study EFC17026 is 28 March 2025. All other studies are completed as of 28 March 2025.

Table 14 - Duration of exposure – CSU + BP[a] + EoE + COPD + AD + Asthma + CRSwNP + PN

Duration of exposure	Persons	Person-years[b]
Any	10 672	
≥4 weeks	10 533	
≥12 weeks	10 226	16 874.7
≥16 weeks	9706	
≥24 weeks	8890	16 427.2
≥52 weeks	6988	15 180.5
≥76 weeks	4991	
≥104 weeks	3342	
≥130 weeks	2000	
≥156 weeks	1083	
Total person-years		16 922.6

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 with rolled over from Part A and B) and R668-EE-1877 (Part A, Part B, and Part C with rolled over from Part A and B). All studies are completed.

Duration of exposure	Persons	Person-years[b]

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Both studies are completed.

CSU: Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All studies are completed.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 31 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, EFC16823, LPS17250, LPS17244, R668-AD-2217, LPS17764. Data cutoff date for R668-AD-1434 and LPS17764 is 28Mar2025; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. All other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. All other studies are completed.

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

BP: Includes dupilumab exposed patients in phase 3 study R668-BP-1902 with data cutoff date of 12JUL2024.

EoE, Atopic Dermatitis and BP: 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, CSU, 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 The cumulative data in Part II SIII encompasses all currently approved and under-review indications, including BP. Of the total 10 672 patients exposed to dupilumab across all indications, 53 patients were from the BP study.

b 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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BP: Bullous Pemphigoid; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

A total of 213 adult and pediatric patients were exposed to dupilumab in the completed CSU studies.

Table 15 - Duration of exposure - Chronic Spontaneous Urticaria

Duration of exposure	Persons	Person-years[a]
Any	213	
≥4 weeks	211	
≥12 weeks	205	92.3
≥16 weeks	198	
≥24 weeks	170	78.9
Total person-years		93.0

Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All 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: Every Other Week.

A total of 436 adult and pediatric patients were exposed to dupilumab in the completed/unblinded EoE studies. Of these, 243 patients were exposed to dupilumab for at least 1 year.

Table 16 - Duration of exposure – Eosinophilic Esophagitis

Duration of exposure	Persons	Person-years[a]
Any	436	
≥4 weeks	436	
≥12 weeks	423	407.8
≥16 weeks	401	
≥24 weeks	394	400.0
≥52 weeks	243	304.3
≥76 weeks	57	
≥104 weeks	29	
Total person-years		410.1

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 with rolled over from Part A and Part B) and R668-EE-1877 (Part A, and Part B, and Part C with rolled over from Part A and Part B). All 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 + 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/Development/BDM/R668/R668-Inflammation/RMP/2025/202504/Programs/Generated/T_expo_dur_over_Int_ee.sas (SAS Win 9.4)

A total of 938 adults were exposed to dupilumab in the COPD studies. Of these, 744 patients were exposed to dupilumab for at least 1 year.

Table 17 - Duration of exposure – Chronic Obstructive Pulmonary Disease

Duration of exposure	Persons	Person-years[a]
Any	938	
≥4 weeks	929	
≥12 weeks	915	878.2
≥16 weeks	904	
≥24 weeks	890	869.9
≥52 weeks	744	745.0
Total person-years		880.4

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
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IMP: Investigational Medicinal Product; Q2W: Every Other Week.

A total of 4719 adult and pediatric patients were exposed to dupilumab in completed/unblinded AD studies including on-going unblinded studies R668-AD-1434 and LPS17764. Of these, 3327 and 2027 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively. Also, 881 patients were exposed to dupilumab for at least 3 years.

Table 18 - Duration of exposure - Atopic Dermatitis

Duration of exposure	Persons	Person-years[a]
Any	4719	
≥4 weeks	4636	
≥12 weeks	4470	9093.9
≥16 weeks	4206	
≥24 weeks	3647	8821.4
≥52 weeks	3327	8591.5
≥76 weeks	2873	
≥104 weeks	2027	
≥130 weeks	1379	
≥156 weeks	881	
Total person-years		9118.4

Includes dupilumab exposed patients in a total of 31 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, LPS17250, LPS17244, R668-AD-2217, and LPS17764.
Data cutoff date for R668-AD-1434 and LPS17764 is 28March2025; 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: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

A total of 3635 adult and pediatric patients were exposed to dupilumab in completed/unblinded asthma studies including open label extension studies LTS12551, LPS15023 and LTS14424. Of these, 2403 and 1286 patients were exposed to dupilumab for at least 1 and at least 2 years, respectively.

Table 19 - Duration of exposure - Asthma

Duration of exposure	Persons	Person-years[a]
Any	3635	
≥4 weeks	3594	
≥12 weeks	3498	5893.2
≥16 weeks	3312	
≥24 weeks	3155	5778.1
≥52 weeks	2403	5268.6
≥76 weeks	2061	
≥104 weeks	1286	
≥130 weeks	621	
≥156 weeks	202	

Total person-years	5909.6

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. 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: Every Other Week; QW: Once Every Week.

A total of 526 adult patients with CRSwNP were exposed to dupilumab in the completed/unblinded studies. Of these, 245 patients were exposed to dupilumab for at least 1 year.

Table 20 - Duration of exposure - CRSwNP

Duration of exposure	Persons	Person-years[a]
Any	526	
≥4 weeks	522	
≥12 weeks	516	395.6
≥16 weeks	488	
≥24 weeks	452	372.0
≥52 weeks	245	244.8
Total person-years		396.7

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
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CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; QW: Once Every Week; Q2W: Every Other Week.

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

Table 21 - 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 exposure	Persons	Person-years[a]

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: Every Other Week.

Exposure by age group and gender

Overall, a total of 5575 (52.2%) patients exposed to dupilumab are male and 5097 (47.8%) patients are female. Among 10 672 patients, 239 (2.2%) patients are less than 6 years old, 974 (9.1%) patients are between 6 and 11 years old, 604 (5.7%) patients are between 12 and 17 years old and 8855 (83.0%) patients are adults.

Table 22 - Exposure by age group (years) and gender - CSU + BP[a] + EoE + COPD + AD + Asthma + CRSwNP + PN

Age group	Male Persons	Female Persons	Male Person-years[b]	Female Person-years[b]
≥6 months to <2	24	3	54.5	12.3
2 to 5	132	80	378.6	217.9
6 to 11	568	406	1141.5	882.4
12 to 17	359	245	473.1	343.6
18 to 64	3765	3813	6152.0	5753.9
65 to 74	573	462	662.2	583.5
75 to 84	148	84	158.8	98.7
≥85	6	4	5.3	4.5
Total	5575	5097	9026.0	7896.7

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 with rolled over from Part A and B) and R668-EE-1877 (Part A, Part B, and Part C with rolled over from Part A and B). All studies are completed.

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Both studies are completed.

CSU: Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All studies are completed.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 31 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, EFC16823, LPS17250, LPS17244, R668-AD-2217, LPS17764.Data cutoff date for R668-AD-1434 and LPS17764 is 28Mar2025; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. All other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. All other studies are completed.

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

BP: Includes dupilumab exposed patients in phase 3 study R668-BP-1902 with data cutoff date of 12JUL2024.

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

EoE, Atopic Dermatitis and BP: 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, CSU, 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 The cumulative data in Part II SIII encompasses all currently approved and under-review indications, including BP. Of the total 10 672 patients exposed to dupilumab across all indications, 53 patients were from the BP study.

b 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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AD: Atopic Dermatitis; BP: Bullous Pemphigoid; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

A higher proportion of females (63.8%) than males (36.2%) were exposed to dupilumab in CSU studies. The majority (74.6%) of patients were aged between 18 and 64 years.

Table 23 - Exposure by age group and gender – Chronic Spontaneous Urticaria

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
2 to 5	2	2	0.4	0.8
6 to 11	4	10	1.6	3.9
12 to 17	1	5	0.4	2.3
18 to 64	60	99	27.4	43.2
65 to 74	9	14	4.1	5.8
75 to 84	1	6	0.5	2.7
Total	77	136	34.3	58.7

Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_agesex_csu_s_t_i.rtf (13MAY2025 2:33)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

A higher proportion of males (65.8%) than females (34.2%) were exposed to dupilumab in EoE studies. About half (54.4%) of exposed patients; ie, 237, 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 24 - 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	38.8	15.3
6 to 11	51	15	76.5	18.6
12 to 17	72	26	59.3	22.7
18 to 64	139	98	103.9	72.9

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
65 to 74		2		2.2
Total	287	149	278.5	131.6

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 with rolled over from Part A and Part B) and R668-EE-1877 (Part A, and Part B, and Part C with rolled over from Part A and Part B). All 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 + 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. Among 938 patients, 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 25 - 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	232.1	137.0
65 to 74	288	147	264.1	138.4
75 to 84	89	27	83.1	25.6
Total	619	319	579.3	301.0

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_agesex_copd_s_t_i.rtf (13MAY2025 2:33)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

A higher proportion of males (57.2%) than females (42.8%) were exposed to dupilumab in AD studies. The majority (73.6%) of exposed patients were in the 18 to 64 years age range, while 202 (4.3%) were aged 6 months to 5 years old, 485 (10.3%) were aged 6 to 11, 397 (8.4%) were aged 12 to 17, and 164 (3.5%) were aged 65 and older.

Table 26 - Exposure by age group and gender – Atopic Dermatitis

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
<6	129	73	393.9	214.2
6 to 11	249	236	658.8	635.9
12 to 17	220	177	300.5	249.8
18 to 64	1996	1475	3907.6	2539.0
65 to 74	82	53	108.3	69.6
75 to 84	19	6	22.0	13.4
≥85	2	2	3.0	2.5
Total	2697	2022	5394.1	3724.2

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

Includes dupilumab exposed patients in a total of 31 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, LPS17250, LPS17244, R668-AD-2217, and LPS17764.

Data cutoff date for R668-AD-1434 and LPS17764 is28March2025; 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.

/sasdata/Data/Development/BDM/R668/R668-Inflammation/RMP/2025/202504/Programs/Generated/T_expo_ag_over_Int_ad.sas (SAS Win 9.4)

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

The majority of patients (58.7%) exposed to dupilumab in asthma studies were female. Most exposed patients 2757 (75.8%) were in the 18 to 64 years age range, while 409 (11.3%) were aged 6 to 11, 103 (2.8%) were aged 12 to 17, and 366 (10.0%) were aged 65 and older.

Table 27 - Exposure by age group and gender – Asthma

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
6 to 11	264	145	404.7	224.1
12 to 17	66	37	112.9	68.8
18 to 64	1017	1740	1658.9	2795.0
65 to 74	135	183	241.7	322.1
75 to 84	21	27	37.8	43.7
Total	1503	2132	2455.9	3453.7

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153 and EFC13995, R668-AS-1903 and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025.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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_agesex_asthma_s_t_i.rtf (13MAY2025 2:33)

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

The majority of exposed patients (61.2%) in the CRSwNP program were male and 439 (83.4%) were in the range of 18 to 64 years.

Table 28 - Exposure by age group and gender – CRSwNP

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
18 to 64	271	168	200.3	124.9
65 to 74	44	31	35.3	26.4
75 to 84	7	5	6.4	3.4

Age group	Male Persons	Female Persons	Male Person-years[a]	Female Person-years[a]
Total	322	204	242.0	154.7

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_agesex_crswnp_s_t_i.rtf (13MAY2025 2:33)
CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Every Other Week; 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 years age range.

Table 29 - 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_2024/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_agesex_pn_s_t_i.rtf (18NOV2024 19:44)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

Exposure by dose

Among 10 672 patients, the largest group (5926 patients representing 6639.1 patient-years) received the 300 mg Q2W dose, followed by 3196 patients (5748.2 patient-years) who received the 300 mg QW dose.

The proposed dose, based on body weight, for CSU adult and adolescent patients 12 years and older is 200 mg Q2W or 300 mg Q2W, and the dose proposed for children 2 years and older is 200 mg Q4W, 300 mg Q4W, 200 mg Q2W, or 300 mg Q2W. The authorized doses in adults for AD, COPD, CRSwNP and PN is 300 mg Q2W which is also the proposed dose for BP indication. 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 200 mg Q2W and 300 mg Q4W. The authorized dose for EoE adult and pediatric patients 12 years and older is 300 mg QW, 200 mg Q2W and 300 mg Q2W.

Refer to Part I for more details on proposed and authorized dosage for each indication.

Table 30 - Exposure by dose - CSU + BP[a] + EoE + COPD + Atopic Dermatitis + Asthma + CRSwNP + PN

Dose of exposure	Persons	Person-years[b]
Dupilumab 75 mg QW	8	0.6
Dupilumab 100 mg Q4W	65	17.1
Dupilumab 100 mg Q2W	165	138.3
Dupilumab 100 mg Q2W to 200 mg Q2W	22	26.7
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 100 mg Q2W to 200 mg Q3W to 200 mg Q2W	1	2.1
Dupilumab 150 mg QW	22	1.6
Dupilumab 200 mg Q4W	183	81.9
Dupilumab 200 mg Q4W to 200 mg Q2W	2	4.2
Dupilumab 200 mg Q4W to 200 mg Q3W	1	1.2
Dupilumab 200 mg Q4W to 300 mg Q4W to 200 mg Q2W	2	3.7
Dupilumab 200 mg Q2W	1789	1438.9
Dupilumab 200 mg Q2W to 100 mg Q2W to 200 mg Q2W	1	2.1
Dupilumab 200 mg Q2W to 300 mg Q2W	13	20.1
Dupilumab 200 mg Q2W to 300 mg Q2W to 300 mg QW	5	8.7
Dupilumab 200 mg Q2W to 300 mg QW	2	4.3
Dupilumab 200 mg QW	336	120.3
Dupilumab 200/300 mg Q2W	548	1055.7
Dupilumab 200/300 mg Q4W	854	899.1
Dupilumab 300 mg Q8W	84	56.0
Dupilumab 300 mg Q4W	633	283.0
Dupilumab 300 mg Q4W to 200 mg Q2W	12	20.1
Dupilumab 300 mg Q4W to 200 mg Q2W to 300 mg Q2W	5	9.6
Dupilumab 300 mg Q4W to 300 mg Q2W	3	5.5
Dupilumab 300 mg Q4W to 300 mg Q2W to 300 mg QW	1	1.9
Dupilumab 300 mg Q2W to 300 mg Q4W	148	144.5
Dupilumab 300 mg Q2W to 300 mg QW	4	7.8
Dupilumab 300 mg Q2W	5926	6639.1
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	27.9

Dose of exposure	Persons	Person-years[b]
Dupilumab 4 mg/kg QW	35	54.2
Dupilumab 6 mg/kg QW	18	19.6
Total	10 672	16 920.8

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 with rolled over from Part A and B) and R668-EE-1877 (Part A, Part B, and Part C with rolled over from Part A and B). All studies are completed.

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Both studies are completed.

CSU: Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All studies are completed.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 31 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, EFC16823, LPS17250, LPS17244, R668-AD-2217, LPS17764. Data cutoff date for R668-AD-1434 and LPS17764 is 28Mar2025; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. All other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. All other studies are completed.

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

BP: Includes dupilumab exposed patients in phase 3 study R668-BP-1902 with data cutoff date of 12JUL2024.

EoE, Atopic Dermatitis and BP: 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, CSU, 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 The cumulative data in Part II SIII encompasses all currently approved and under-review indications, including BP. Of the total 10 672 patients exposed to dupilumab across all indications, 53 patients were from the BP study.

b 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_all_v1_s_t_i.rtf (13MAY2025 2:33)

BP: Bullous Pemphigoid; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Every Other Week; Q3W: Once Every Three Weeks; Q4W: Once Every Four Weeks; Q8W: Once Every Eight Weeks; QW: Once Every Week; SC: Subcutaneous.

The most commonly studied dose in the CSU clinical trials was 300 mg Q2W (193 persons and 85.5 person-years).

Table 31 - Exposure by dose – Chronic Spontaneous Urticaria

Dose of exposure	Persons	Person-years[a]
Dupilumab 200 mg Q4W	1	0.4
Dupilumab 200 mg Q2W	13	5.2
Dupilumab 300 mg Q4W	6	1.9
Dupilumab 300 mg Q2W	193	85.5
Total	213	93.0

Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All studies are completed.

Dose of exposure	Persons	Person-years[a]
Dupilumab 200 mg Q4W	1	0.4

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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_csu_s_t_i.rtf (13MAY2025 2:33)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

The most commonly studied dupilumab dose in EoE clinical trials was 300 mg QW (219 persons and 160.9 person-years) and 300 mg Q2W (134 persons and 115.1 person-years).

Table 32 - Exposure by dose – Eosinophilic Esophagitis

Dose of exposure	Persons	Person-years[a]
Dupilumab 100 mg Q2W	1	0.7
Dupilumab 100 mg Q2W to Dupilumab 200 mg Q2W	6	11.0
Dupilumab 100 mg Q2W to Dupilumab 200 mg Q3W to Dupilumab 200 mg Q2W	1	2.1
Dupilumab 200 mg Q2W	19	27.2
Dupilumab 200 mg Q2W to Dupilumab 100 mg Q2W to Dupilumab 200 mg Q2W	1	2.1
Dupilumab 200 mg Q2W to Dupilumab 300 mg Q2W	13	20.1
Dupilumab 200 mg Q2W to Dupilumab 300 mg Q2W to Dupilumab 300 mg QW	5	8.7
Dupilumab 200 mg Q2W to Dupilumab 300 mg QW	2	4.3
Dupilumab 300 mg Q2W	134	115.1
Dupilumab 300 mg Q2W to Dupilumab 300 mg QW	4	7.8
Dupilumab 300 mg Q4W	5	3.8
Dupilumab 300 mg Q4W to Dupilumab 200 mg Q2W	11	19.1
Dupilumab 300 mg Q4W to Dupilumab 200 mg Q2W to Dupilumab 300 mg Q2W	5	9.6
Dupilumab 300 mg Q4W to Dupilumab 300 mg Q2W	3	5.5
Dupilumab 300 mg Q4W to Dupilumab 300 mg Q2W to Dupilumab 300 mg QW	1	1.9
Dupilumab 300 mg QW	219	160.9
Dupilumab 200 mg Q4W	1	1.0
Dupilumab 200 mg Q4W to Dupilumab 200 mg Q2W	2	4.2
Dupilumab 200 mg Q4W to Dupilumab 200 mg Q3W	1	1.2
Dupilumab 200 mg Q4W to Dupilumab 300 mg Q4W to Dupilumab 200 mg Q2W	2	3.7
Total	436	410.1

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 with rolled over from Part A and Part B) and R668-EE-1877 (Part A, and Part B, and Part C with rolled over from Part A and Part B). All 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 + 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: Every Other Week; Q3W: Once Every Three Weeks; Q4W: Once Every Four Weeks; QW: Once Every Week.

The dose of dupilumab studied in the COPD clinical trial was 300 mg Q2W (938 persons, 880.4 person-years).

Table 33 - Exposure by dose – Chronic Obstructive Pulmonary Disease

Dose of exposure	Persons	Person-years[a]
Dupilumab 300 mg Q2W	938	880.4

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_copd_s_t_i.rtf (13MAY2025 2:33)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

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

Table 34 - Exposure by dose – Atopic Dermatitis

Dose of exposure	Persons	Person-years[a]
Dupilumab 2 mg/kg QW	34	53.9
Dupilumab 2 mg/kg SC	38	3.6
Dupilumab 3 mg/kg	20	0.4
Dupilumab 3 mg/kg QW	17	27.9
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	323	150.6
Dupilumab 200 mg QW	336	120.3
Dupilumab 200/300 mg Q2W[b]	548	1055.7
Dupilumab 300 mg Q2W	1519	849.1
Dupilumab 300 mg Q4W	460	203.9
Dupilumab 300 mg Q8W	84	56.0
Dupilumab 300 mg QW	2895	5566.9
Dupilumab 200 mg Q4W	31	14.7
Dupilumab 200/300 mg Q4W	854	899.1
Total	4719	9118.4

Dose of exposure	Persons	Person-years[a]

Includes dupilumab exposed patients in a total of 31 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, EFC16823, LPS17250, LPS17244, R668-AD-2217, and LPS17764.

Data cutoff date for R668-AD-1434 and LPS17764 is 28March2025; 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: Every Other Week; 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 (2589 persons and 4351.1 person-years).

Table 35 - Exposure by dose – Asthma

Dose of exposure	Persons	Person-years[a]
Dupilumab 100 mg Q2W	101	118.2
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	1434	1255.9
Dupilumab 300 mg Q4W	162	73.4
Dupilumab 300 mg Q4W to 200 mg Q2W	1	1.0
Dupilumab 300 mg Q2W	2589	4351.1
Dupilumab 300 mg QW	52	11.4
Total	3635	5907.8

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025.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: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

The most commonly studied dose in CRSwNP clinical trials is 300 mg Q2W (348 persons, 243.3 person-years).

Table 36 - 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	348	243.3
Dupilumab 300 mg QW	30	8.9
Total	526	396.7

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_crswnp_s_t_i.rtf (13MAY2025 2:33)
CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Every Other Week; Q4W: 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 37 - 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_2024/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_dose_pn_s_t_i.rtf (18NOV2024 19:44)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

Exposure by ethnic origin and race

The majority of subjects exposed to dupilumab in the clinical trial program were non-Hispanic or Latino (8938 persons) and were Caucasian (7887 persons).

Table 38 - Exposure by ethnic origin and race - CSU + BP[a] + EoE + COPD + Atopic Dermatitis + Asthma + CRSwNP + PN

	Persons	Person-years[b]
Ethnicity		
Hispanic or Latino	1639	2449.8
Non-Hispanic or Latino	8938	14 364.2
Not Reported	86	101.8
Unknown	9	6.9
Race		
Caucasian	7887	13118.3
Black	661	852.4

	Persons	Person-years[b]
Asian	1821	2516.6
Other	260	359.5
Not Reported	43	75.8
Total	10 672	16 922.6

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 with rolled over from Part A and B) and R668-EE-1877 (Part A, Part B, and Part C with rolled over from Part A and B). All studies are completed.

COPD: Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. Both studies are completed.

CSU: Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All studies are completed.

Atopic Dermatitis: Includes dupilumab exposed patients in a total of 31 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, EFC16823, LPS17250, LPS17244, R668-AD-2217, LPS17764. Data cutoff date for R668-AD-1434 and LPS17764 is 28Mar2025; all other studies are completed.

Asthma: Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 5 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. All other studies are completed.

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. All other studies are completed.

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

BP: Includes dupilumab exposed patients in phase 3 study R668-BP-1902 with data cutoff date of 12JUL2024.

EoE, Atopic Dermatitis and BP: 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, CSU, 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 The cumulative data in Part II SIII encompasses all currently approved and under-review indications, including BP. Of the total 10 672 patients exposed to dupilumab across all indications, 53 patients were from the BP study.

b 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_all_v1_s_t_i.rtf (13MAY2025 2:33)

BP: Bullous Pemphigoid; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; IMP: Investigational Medicinal Product; PN: Prurigo Nodularis; Q2W: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

In CSU studies, among patients with reported ethnicity and race exposed to dupilumab, 85.3% of patients were non-Hispanic or Latino, and most were Caucasian (61.5%).

Table 39 - Exposure by ethnic origin and race – Chronic Spontaneous Urticaria

	Persons	Person-years[a]
Ethnicity		
Hispanic Or Latino	31	13.1
Non-Hispanic Or Latino	180	79.0
Unknown	2	0.9
Race		
Caucasian	131	55.7

	Persons	Person-years[a]
Black	5	2.3
Asian	62	28.3
Other	15	6.7
Total	213	93.0

Includes dupilumab exposed patients in phase 3 studies: EFC16461 (Part A, Part B, and Part C), and PKM16982. All 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_2025/REPORT/PGM/cdc_exp_s_t.sas
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IMP: Investigational Medicinal Product; Q2W: Every Other 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 40 - Exposure by ethnic origin and race – Eosinophilic Esophagitis

	Persons	Person-years[a]
Ethnicity		
Hispanic Or Latino	25	25.0
Not Hispanic Or Latino	407	379.7
Not Reported	4	5.4
Race		
Caucasian	394	363.9
Black Or African American	20	22.7
Asian	7	7.8
Other	12	13.9
Not Reported	3	1.9
Total	436	410.1

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 with rolled over from Part A and Part B) and R668-EE-1877 (Part A, and Part B, and Part C with rolled over from Part A and Part B). All 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 + 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/Development/BDM/R668/R668-Inflammation/RMP/2025/202504/Programs/Generated/T_expo_re_over_Int_ee.sas (SAS Win 9.4)

In the COPD studies, among 934 patients with reported ethnicity exposed to dupilumab, 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 41 - Exposure by ethnic origin and race – Chronic Obstructive Pulmonary Disease

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	282	265.9
Non-Hispanic or Latino	652	610.5
Unknown	4	4.0
Race		
Caucasian	815	766.6
Black	7	5.7
Asian	74	68.8
Other	40	37.7
Not Reported	2	1.5
Total	938	880.4

Includes dupilumab exposed patients in phase 3 studies: EFC15804 and EFC15805. 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: Every Other Week.

Among 4647 patients with reported ethnicity exposed to dupilumab in the AD studies, 93.2% were non-Hispanic or Latino. Among 4690 patients with reported race exposed to dupilumab in the AD studies, 67.6% were Caucasian, 10.0% were Black and 20.0% were Asian.

Table 42 - Exposure by ethnic origin and race – Atopic Dermatitis

	Persons	Person-years[a]
Ethnicity		
Hispanic Or Latino	315	456.6
Not Hispanic Or Latino	4332	8574.1
Not Reported	72	87.7
Race		
Caucasian	3172	6645.2
Black Or African American	468	624.9
Asian	936	1602.8
American Indian Or Alaska Native	13	12.4
Other	101	168.1
Not Reported	29	64.9
Total	4719	9118.4

Includes dupilumab exposed patients in a total of 31 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, LPS17250, LPS17244, R668-AD-2217, and LPS17764.

	Persons	Person-years[a]

Data cutoff date for R668-AD-1434 and LPS17764 is 28March2025; 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
/sasdata/Data/Development/BDM/R668/R668-Inflammation/RMP/2025/202504/Programs/Generated/T_expo_re_over_Int_ad.sas (SAS Win 9.4)
Q2W: Every Other Week; Q4W: Once Every Four Weeks; QW: Once Every Week.

In asthma studies, among 3633 patients with reported ethnicity exposed to dupilumab, approximately 76.4% of patients were non-Hispanic or Latino, and among 3635 patients with reported race exposed to dupilumab most were Caucasian (78.3%).

Table 43 - Exposure by ethnic origin and race – Asthma

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	858	1582.2
Non-Hispanic or Latino	2775	4326.4
Unknown	2	1.0
Race		
Caucasian	2845	4913.7
Black	142	185.4
Asian	586	703.5
Other	62	107.0
Total	3635	5909.6

Includes dupilumab exposed patients in 3 phase 2 studies, ACT11457, DRI12544, and PDY14192, 4 phase 3 studies, EFC13579, EFC13691, EFC14153, EFC13995, and R668-AS-1903, and 3 open-label extension studies LTS12551, LPS15023 (patients from unblinded DRI12544, EFC13579, EFC13691 and PDY14192 studies) and LTS14424 (patients from unblinded EFC14153 study), and two phase 4 studies LPS15834 and LPS16677. The main study for LTS14424 is completed, data cut-off date for the Japanese substudy is 28Mar2025. 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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OUT=REPORT/OUTPUT/cdc_exp_ethnic_asthma_s_t_i.rtf (13MAY2025 2:33)
IMP: Investigational Medicinal Product; Q2W: Every Other Week; QW: Once Every Week.

In the CRSwNP studies, among 525 patients with reported ethnicity exposed to dupilumab, approximately 81.0% of patients exposed to dupilumab were non-Hispanic or Latino; among 525 patients with reported race exposed to dupilumab, most patients were Caucasian (78.7%).

Table 44 - Exposure by ethnic origin and race – CRSwNP

	Persons	Person-years[a]
Ethnicity		
Hispanic or Latino	100	94.1

	Persons	Person-years[a]
Non-Hispanic or Latino	425	301.7
Unknown	1	1.0
Race		
Caucasian	413	306.6
Black	7	5.2
Asian	93	73.0
Other	12	11.4
Not Reported	1	0.5
Total	526	396.7

CRSwNP: Includes dupilumab exposed patients in a total of 5 studies: ACT12340, EFC14146, EFC14280, LPS16872, and EFC17026. Data cut-off date for EFC17026 is 28Mar2025. 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_2025/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_crswnp_s_t_i.rtf (13MAY2025 2:33)
CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; IMP: Investigational Medicinal Product; Q2W: Every Other Week; 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 45 - 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_2024/REPORT/PGM/cdc_exp_s_t.sas
OUT=REPORT/OUTPUT/cdc_exp_ethnic_pn_s_t_i.rtf (18NOV2024 19:44)
IMP: Investigational Medicinal Product; Q2W: Every Other Week.

Exposure in blinded studies in approved indications

The number of patients enrolled in ongoing, blinded, clinical studies at the cut-off date of 28 March 2025 is presented below:

Asthma: approximately 721 patients exposed to dupilumab

- Approximately 49 pediatric patients (2 to <6 years old) were enrolled in blinded phase 3 study EFC14771 with approximately two thirds (33) on one of 2 dose regimens: participants ≥5 to <15kg received 200 mg dupilumab Q4W and participants ≥15 to <30 kg received 300 mg dupilumab Q4W.
- Approximately 12 adult and adolescent patients were enrolled in blinded phase 3 study R668-AS-2373 with approximately half (6) on dupilumab 300 mg Q2W.
- Approximately 1023 adult patients were enrolled in blinded phase 4 study LPS16676 with approximately two thirds (682) on dupilumab 300 mg Q2W.

CRSwNP: approximately 176 patients exposed to dupilumab

- Approximately 352 adult patients were enrolled in blinded phase 4 study LPS16747 with approximately half (176) on dupilumab 300 mg Q2W.

EoE: approximately 37 patients exposed to dupilumab

- Approximately 52 adult patients were enrolled in blinded phase 4 study LPS17558 with approximately 37 patients on dupilumab 300 mg QW.

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

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

Table 46 - 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, COPD, and CSU 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, Tuberculosis [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 INCSs was not associated with increased risks of infections (bacterial, viral, opportunistic, or parasitic). There was no imbalance in the proportions of patients that reported treatment emergent adverse event (TEAE)s 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 opportunistic infections 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 and CSU studies).			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). In CSU studies, TEAEs reported within the system organ class (SOC) of infections and infestations were similar between dupilumab and placebo groups, with one serious infection reported both in the dupilumab and placebo groups. 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, COPD and CSU 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 high sensitivity C reactive protein (hs-CRP) and autoantibodies (anti-double stranded deoxyribonucleic acid [dsDNA] and anti-thyroid peroxidase (TPO) and anti-nuclear antibody [ANA]) from baseline between dupilumab treatment group and placebo to suggest an effect of dupilumab on autoimmunity. In the AD-1307 study, messenger ribonucleic acid

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			(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 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 high level group term (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

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
			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 studies (EFC15804 and EFC15805), treatment emergent TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders, were similar and numerically low in both dupilumab and placebo groups. Of the 198 patients exposed to dupilumab in the CSU studies (EFC16461 Study A, Study B and Study C), none experienced TEAEs in the HLGT autoimmune disorders, under the primary SOC of Immune system disorders.
Infections and infestations (AD, asthma, EoE, PN, CRSwNP, COPD, and CSU 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); (within 2 weeks before the screening visit and during the screening period for CSU); • Positive for Hepatitis B Surface Antigen (HBsAg), Hepatitis B Core Antibody (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	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, CSU studies (including pivotal), and pivotal Phase 3 CRSwNP studies to suggest that use of dupilumab in patients with infections would constitute a safety concern.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
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)			
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 baseline visit, other than treated vaginal trichomoniasis. Chronic Obstructive Pulmonary Disease, and CSU: • 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.	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. *290, 291, 292, 293, 294, 295, 296, 297, 298* 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.	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 adverse drug reaction (ADR) in children 6-11 years old with asthma in section 4.8 Paediatric population of the SmPC.
Atopic dermatitis adults, asthma, EoE, PN, CRSwNP, COPD, and CSU 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.	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 16 922 PYs of exposure up to DLP of 28-Mar-2025 in clinical studies does not support an increase in the risk of malignancy with dupilumab. The clinical data corroborate preclinical data, indicating IL4 and IL13 actions via the IL4Rα activation pathway to be predominantly protumorigenic. As agreed with several regulatory Health Authorities (including EMA and FDA), no additional specific

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Atopic dermatitis/asthma pediatric studies: History of malignancy before the baseline visit.			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. In CSU study EFC16461, 1 patient (0.5%) in the dupilumab group reported a malignancy versus none in the placebo group. In EoE pediatric (R668-EE-1877) clinical trials, there were no reports of malignancy in either treatment group. In EoE clinical study R668-EE-1774 (adult and adolescent), the incidence of malignancy was low (1.8% in dupilumab versus 0 in placebo).
Atopic dermatitis and asthma studies: Use of live attenuated vaccines within 12 weeks before baseline. CRSwNP, EoE, PN, asthma, atopic dermatitis pediatric studies, COPD, and CSU: 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, COPD, and CSU 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 is established in non-pregnant patients.	Yes	Adequately addressed in section 4.6 of the SmPC.
Atopic dermatitis pediatric, AD, asthma, EoE, CRSwNP, PN, CSU, 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).	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

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
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-human chorionic gonadotropin (hCG) test at Visit 1 or negative urine pregnancy test at Visit 2. EoE pediatric study: Female patients who experience menarche and who are unwilling to follow the precautions for women of childbearing potential (WOCBP).			
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. CSU studies: History of systemic hypersensitivity or anaphylaxis to omalizumab, dupilumab or any biologic therapy, including any excipients	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, CRSwNP, and CSU studies: Liver injury related criteria: • Clinically significant/active hepatobiliary disease (asthma, EoE, PN, and CRSwNP only) or • Alanine aminotransferase >3 upper limit of normal (ULN) (asthma, EoE, PN, and CRSwNP only) • 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.
Atopic dermatitis and asthma studies:	Signs and symptoms associated with liver injury may confound the	No	Dupilumab, as a mAb, is not expected to undergo significant hepatic elimination. No specific

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
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. CSU studies: Current history of substance and/or alcohol abuse.	safety profile of dupilumab treated study participants		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 (EGPA) (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 *H. 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 Good Pharmacovigilance Practices (GVP) module V.
Chronic Obstructive Pulmonary Disease study: • Significant pulmonary disease other than COPD (eg, lung fibrosis, sarcoidosis, interstitial	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
lung disease, pulmonary 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, Investigator Global Assessment Scale for Atopic Dermatitis (IGA AD) of 3 or 4, eczema area and severity index (EASI) ≥16, SCORing atopic dermatitis [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.
CSU studies: • Clearly defined underlying etiology for CUs other than CSU	Skin conditions other than CSU may confound the ability to assess the	No	This exclusion criterion does not meet the criteria to be retained in

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
(main manifestation being physical urticaria). Presence of skin morbidities other than CSU that may interfere with the assessment of the study outcomes. • Patients with active AD.	data for potential effects of the investigational product and may interfere with assessment of the outcomes.		missing information as per GVP module V.
<u>Prurigo Nodularis, COPD, and CSU studies</u>: • Severe renal conditions (eg, patients with uremia and/or on dialysis) - for PN only. • Participants with uncontrolled thyroid disease - for PN only. • Patients with cardiovascular conditions (eg, Class III or IV heart failure according to the New York Heart Association classification) • Clinically significant abnormal electrocardiogram (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.	These are severe concomitant illness(es) under poor control that, in the investigator's judgment, would adversely affect the patient's participation in the study.	No	This exclusion criterion does not meet the criteria to be retained in missing information as per GVP module V.
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, COPD, and CSU 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,	Patients with clinically significant laboratory abnormalities were excluded as they might have an unknown clinical	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
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/mm3 or • Eosinophils >1500 cells/mm^3 Atopic dermatitis pediatric studies 6 to <12 years: Presence of any 1 or more of the following abnormalities in laboratory test results at Screening: • Platelets ≤100 x 103/µL • Neutrophils <1.5 x 103/µL • Creatine phosphokinase >5 x ULN • Serum creatinine >1.5 x ULN Atopic dermatitis (6 months to 5 years): 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 Asthma pediatric studies <12 years, PN, EoE, CSU and COPD (at the time of screening): • At any time: Patients with positive (or indeterminate) test for HBs-Ag; positive IgM HBc-Ab; positive total HBc-Ab confirmed by positive hepatitis B virus deoxyribonucleic acid (HBV-DNA); positive hepatitis C virus antibody (HCV-Ab) confirmed by positive hepatitis C	disease. Inclusion of such patients might also confound the safety evaluation of dupilumab safety profile.		

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
virus ribonucleic acid (HCV-RNA). Eosinophilic Esophagitis studies: • 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 Chronic Obstructive Pulmonary Disease: Clinically significant laboratory tests at screening: • Alanine aminotransferase (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. • 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; CSU: Chronic Spontaneous Urticaria; CU: Chronic Urticaria; DLP: Data Lock Point; 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-Ab: Hepatitis C Virus Antibody; 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; IGA AD: Investigator Global Assessment Scale for Atopic Dermatitis; INCS: Intranasal 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-Year; Q2W: Every Other Week; QW: Once Every Week; RMP: Risk Management Plan; SC: Subcutaneous; SmPC: Summary of Product Characteristics; SOC: System Organ Class; SCORAD: SCORing Atopic Dermatitis; 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; WOCBP: Women of Childbearing Potential.

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 10 672 patients were exposed to dupilumab in completed/unblinded CSU, BP, EoE, 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 0.03% of the population, meaning that AEs with a frequency greater than 3 in 10 000 patients (ie, 0.03%) could be detected in the dupilumab treatment group.

Of the 10 672 patients in completed/unblinded studies, 6988 and 3342 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 10 000 patients have been exposed to dupilumab in the clinical program across several indications. Among completed/unblinded dupilumab studies, 213 adult and pediatric patients were in the CSU program, 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, 4719 adult and pediatric patients were in the AD program, 3635 adult and pediatric patients were in the asthma program, and 526 adult patients were in the CRSwNP program.	Based on the number of patients exposed to dupilumab, adverse reactions with crude incidence rate of ≥0.03% in 10 000 patients could be detected in the dupilumab group with at least 95% probability.
Due to prolonged exposure	As of the DLP, the total number of patient (N)s across the unblinded/completed trials exposed to dupilumab for ≥52 weeks was 6988, with over 3342 exposed for 2 years or more. Since this long-term exposure includes 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 dupilumab is intended for chronic/long-term use. Safety information on patients treated with dupilumab for over 2 years has been adequately characterized following completion of long-term safety study LTS14041 [R668AD1225] conducted in adult patients with 5-years of exposure. Thus, missing information topic “Long-term safety in adult and pediatric patients” was renamed “Long-term safety in pediatric patients” in RMP version 10.3.

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; N: Total Number of Patient; PN: Prurigo Nodularis; RMP: Risk Management Plan.

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

Table 47 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	As of the DLP of 28-Mar-2025, there were 94 pregnancies in completed and ongoing phase 2/3 placebo controlled or open label asthma, EoE, AD, CSU, Allergic Bronchopulmonary Aspergillosis (ABPA) and CRSwNP studies [4 in EoE

Type of special population	Exposure
	(1 in dupilumab arm, 3 in placebo arm), 34 in asthma (27 in dupilumab arm and 7 in placebo arm), 51 in AD (42 in dupilumab arm (1 patient had twin pregnancy); 9 in placebo arm), 1 in ABPA (placebo arm), 2 in CRSwNP (1 in dupilumab arm, 1 in placebo arm), and 2 in CSU studies (1 in dupilumab arm, 1 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.
Populations with relevant different ethnic origin/race (Completed/unblinded studies)	
Ethnicity	
Hispanic or Latino	AD: 315 (456.6 PY); asthma: 858 (1582.2 PY); CRSwNP: 100 (94.1 PY); EoE: 25 (25.0 PY); PN: 28 (13.0 PY); COPD: 282 (265.9 PY); CSU: 31 (13.1 PY)
Non-Hispanic or Latino	AD: 4332 (8574.1 PY); asthma: 2775 (4326.4 PY); CRSwNP: 425 (301.7 PY); EoE: 407 (379.7 PY); PN: 124 (56.4 PY); COPD: 652 (610.5 PY); CSU: 180 (79.0 PY)
Not reported/missing	AD: 72 (87.7 PY); asthma: 2 (1.0 PY); CRSwNP: 1 (1.0 PY); EoE: 4 (5.4 PY); COPD 4 (4.0 PY); CSU: 2 (0.9 PY)
Race	
White / Caucasian	AD: 3172 (6645.2 PY); asthma: 2845 (4913.7 PY); CRSwNP: 413 (306.6 PY); EoE: 394 (363.9 PY); PN: 82 (37.4 PY); COPD: 815 (766.6 PY); CSU: 131 (55.7 PY)
Black or African American	AD: 468 (624.9 PY) asthma: 142 (185.4 PY); CRSwNP: 7 (5.2 PY); EoE: 20 (22.7 PY); PN: 11 (5.2 PY); COPD: 7 (5.7 PY); CSU: 5 (2.3 PY)
Asian	AD: 936 (1602.8 PY); asthma: 586 (703.5 PY); CRSwNP: 93 (73.0 PY); EoE: 7 (7.8 PY); PN: 54 (24.5 PY); COPD: 74 (68.8 PY); CSU: 62 (28.3 PY)
American Indian or Alaska Native	AD: 13 (12.4 PY)
Other	AD: 101 (168.1 PY); asthma: 62 (107.0 PY); CRSwNP: 12 (11.4 PY); EoE: 12 (13.9 PY); PN: 5 (2.3 PY); COPD: 40 (37.7 PY); CSU: 15 (6.7 PY)
Not reported	AD: 29 (64.9 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	Both genders ≥6 months and ≤11 years: AD (687; 1902.8 PY), asthma (409; 628.8 PY), EoE (99; 149.2 PY), 0 (PN), 0 (COPD), 0 (CRSwNP), CSU (18, 6.7 PY) • Males: ≥6 months and ≤11 years: AD (378; 1052.7 PY), asthma (264; 404.7 PY); 0 (CRSwNP); EoE (76; 115.3 PY), 0 (PN), 0 (COPD), CSU (6, 2.0 PY).

Type of special population	Exposure
	• Females: ≥6 months and ≤11 years: AD (309; 850.1 PY), asthma (145; 224.1 PY); EoE (23; 33.9 PY); 0 (CRSwNP); 0 (PN), 0 (COPD), CSU (12, 4.7 PY). Both genders ≥12 and ≤17: AD (397; 550.3 PY); asthma (103; 181.7 PY); EoE (98; 82.0 PY); 0 (CRSwNP); 0 (PN), 0 (COPD), CSU (6, 2.7 PY). • Males ≥12 and ≤17: AD (220; 300.5 PY); asthma (66; 112.9 PY); EoE (72; 59.3 PY); 0 (CRSwNP); 0 (PN); 0 (COPD); CSU (1; 0.4 PY) • Females ≥12 and ≤17: AD (177; 249.8 PY); asthma (37; 68.8 PY); EoE (26; 22.7 PY); 0 (CRSwNP); 0 (PN); 0 (COPD); CSU (5, 2.3 PY)
Other Elderly (>65)	Both genders: AD (164; 218.8 PY); asthma (366; 645.3 PY); CRSwNP (87; 71.5 PY); EoE (2; 2.2 PY); PN (37; 16.3); COPD (551; 511.2 PY); CSU (30, 13.1 PY)
Males (>65)	Males: AD (103; 133.3 PY); asthma (156; 279.5 PY); CRSwNP (51; 41.7 PY); EoE (0); PN (15; 6.9 PY); COPD (377; 347.2 PY); CSU (10, 4.6 PY)
Females (>65)	Females: AD (61; 85.5 PY); asthma (210; 365.8 PY), CRSwNP (36; 29.8 PY); EoE (2; 2.2 PY); PN (22; 9.4 PY); COPD (174; 164.0 PY); CSU (20, 8.5 PY)

ABPA: Allergic Bronchopulmonary Aspergillosis; AD: Atopic Dermatitis; BP: Bullous Pemphigoid; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis; PY: Patient-Year.

Pregnant and breastfeeding women:

As of the DLP of 28 March 2025, there were 94 pregnancies in completed and ongoing phase 2/3 placebo controlled or open label asthma, EoE, AD, CSU, ABPA and CRSwNP studies [4 in EoE (1 in dupilumab arm, 3 in placebo arm), 34 in asthma (27 in dupilumab arm and 7 in placebo arm), 51 in AD (42 in dupilumab arm (1 patient had twin pregnancy); 9 in placebo arm), 1 in ABPA (placebo arm), 2 in CRSwNP (1 in dupilumab arm, 1 in placebo arm), and 2 in CSU studies (1 in dupilumab arm, 1 in placebo arm)].

No pregnancy cases were reported in PN and COPD studies.

Among the 94 pregnancies in all dupilumab trials for AD, EoE, asthma, CSU, ABPA and CRSwNP, 51 pregnancies (in 50 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 9 patients received placebo. The outcomes of the 9 AD placebo patients include 3 elective abortions, 2 normal live births, 2 unknown outcome, 1 spontaneous abortion, 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 94 pregnancies as of the DLP of 28 March 2025, 34 pregnancies were reported in the unblinded (DRI12544,EFC13579, and R668-AS-1903) and open label (LTS12551, LPS15023, EFC13691 and ACT11457) asthma studies. Of the 34 pregnancies reported in asthma studies, 7 pregnancies occurred in placebo patients in study EFC13579, of which four pregnancies resulted in live births of normal infants, 2 ectopic pregnancies, and 1 elective abortion. Among the 27 pregnancies in dupilumab-treated patients in asthma studies, outcomes include 7 spontaneous

abortions, 2 elective abortions, 14 full term live births, and 3 premature births. Outcome was unknown in one patient. 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's 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, the outcome was unknown.

Two pregnancies were reported in the CRSwNP safety pool (ACT12340, EFC14146, EFC14280, and LLPS16747 studies). One pregnancy occurred in a placebo-exposed patient and the outcome was reported as normal live birth. The second pregnancy occurred in a patient who received the investigational product and the outcome was reported as elective termination of pregnancy.

Two pregnancies were reported in CSU studies, including 1 patient each from completed EFC16461 Study A and Study B. One pregnancy occurred in a dupilumab-treated patient with a reportedly uncomplicated delivery and 1 was reported in a placebo recipient patient.

One pregnancy was reported in ABPA (R668-ABPA-1923) which ended in miscarriage (reportedly week of pregnancy could not be determined as fetus did not grow) and fetus was reported to have Trisomy-16. This patient was on placebo arm.

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 were not adequate for a meaningful interpretation/conclusion. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (See Table 13). 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 [299], 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]).

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 respective strength in mg/mL.
- The total sales in mg were divided by WHO Defined Daily Dose (DDD) of 21.4 mg for parenteral formulation and then divided by 365 to estimate patient years (PYs).
- Patient years = total sales in mg/(21.4 x 365).

Cumulative Postmarketing exposure:

Exposure from the cumulative experience is available from MARCO for the period from 01 March 2017 through 31 March 2025.

The cumulative exposure to dupilumab parenteral formulations is estimated to be 2.74 million PYs.

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.

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 marketing authorization application [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), sequence 0212 for COPD, sequence 0218 for pediatrics EoE, sequence 0262 for CSU in adults and adolescents and e-CTD sequence for CSU in adult, adolescent and pediatric population.

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 48 - Important identified risk considered for inclusion in the list of safety concerns: 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. [300] 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. Medical Dictionary for Regulatory Activities (MedDRA) terms Narrow Standardized MedDRA Query (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 49 - Important potential risk considered for inclusion in the list of safety concerns: 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 non-melanoma skin cancer [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). [301] Register-based retrospective cohort study in Sweden by Hagstromer et al [302] of AD patients showed a standardized incidence ratio (SIR)s 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 [303] 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 50 - Missing information considered for inclusion in the list of safety concerns: 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	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

Use in pediatric AD patients <18 years of age	
particular subpopulation/use that has led to the inclusion	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 51 - Missing information considered for inclusion in the list of safety concerns: 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 [304] 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 52 - Missing information considered for inclusion in the list of safety concerns: 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 adverse event of special interest (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 long-term treatment (LTT), the majority of patients who reported these events, reported them as mild to moderate in severity. 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

Conjunctivitis related events	
	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 53 - Missing information considered for inclusion in the list of safety concerns: 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 54 - Missing information considered for inclusion in the list of safety concerns: 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

Not applicable since no changes are proposed in EU-RMP 14.1 as compared to last approved EU-RMP 13.1.

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

The following risks have been identified for dupilumab (DLP of 28 March 2025):

- 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 55 - Important Identified risk: Systemic hypersensitivity (including events associated with immunogenicity)

Important 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 Immunoglobulin G (IgG) mediated (or other isotype) mediated with generalized and acute chills, nausea, headache, fever due to fragment crystallizable (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. [305] 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	• **Atopic dermatitis studies:** <u>Adults</u> The safety of dupilumab monotherapy was evaluated through week-16 based on data from three randomized, double-blind, placebo-controlled multicenter studies (SOLO 1 [R668-AD-1334], SOLO 2 [R668-AD-1416], and a Phase 2 dose-ranging study) that included 1564 adult patients with moderate-to-severe AD. The safety of dupilumab with concomitant TCS was evaluated based on data from one randomized, double-blind, placebo-controlled multicenter study (CHRONOS [R668-AD-1224]). A total of 740 patients were treated up to 52-weeks. The long-term safety of repeat doses of dupilumab was assessed in the completed study R668-AD-1225, in 2677 adults with moderate-to-severe AD. <u>Adolescents (12 to 17 years of age)</u> The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe AD (R688-AD-1526). The long-term safety of dupilumab was assessed in an ongoing open-label extension study in 275 patients 12 to 17 years of age with moderate-to-severe AD (R688-AD-1434 first-step analysis). <u>Pediatric patients (six to 11 years of age)</u> The safety of dupilumab was assessed in a trial of 367 patients six to 11 years of age with severe AD (R688-AD-1652).

Important Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	The long-term safety of dupilumab + TCS was assessed in an ongoing open-label extension study of 368 patients six to 11 years of age with AD (R688-AD-1434 second-step analysis). Pediatric patients (six months to five years of age) The safety of dupilumab + TCS was assessed in a study of 161 patients six months to five years of age with moderate-to-severe AD (R688-AD-1539). The long-term safety of dupilumab was assessed in an ongoing open-label extension study of 180 patients six months to five years of age with AD (R688-AD-1434 third-step analysis). Hand and foot dermatitis (adults and adolescents) The safety of dupilumab was assessed in 133 adult and adolescent patients 12 to 17 years of age with moderate-to-severe atopic HFE (R688-AD-1924). • **Asthma studies:** Adult and adolescents A total of 2888 adult and adolescent patients with moderate-to-severe asthma were evaluated in three randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (DRI12544; EFC13579, QUEST; and EFC13691, VENTURE). The long-term safety of dupilumab was assessed in an open-label extension study in 2282 patients 12 years and older with moderate-to-severe asthma (LTS12551, TRAVERSE). In this study, patients were followed for up to 96-weeks, resulting in 3169 PYs cumulative exposure to dupilumab. Pediatric patients (six to 11 years of age) The safety of dupilumab was assessed in 405 patients six to 11 years of age with moderate-to-severe asthma (EFC14153, VOYAGE). The long-term safety of dupilumab was assessed in an open-label extension study (LTS14424, EXCURSION) in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in VOYAGE. Among 365 patients who entered EXCURSION, 350 completed 52 of weeks treatment and 228 patients completed a cumulative treatment duration of 104-weeks (VOYAGE and EXCURSION). • **Chronic rhinosinusitis with nasal polyposis studies:** A total of 722 adult patients with uncontrolled, severe CRSwNP on a background therapy with intranasal corticosteroids were evaluated in two pivotal randomized, double-blind, placebo-controlled, parallel-group studies of 24-week (EFC14146, SINUS-24) and 52-week duration (EFC14280, SINUS-52) in adult patients. In EFC14280, a total of 440 adult patients (≥18 years) were randomized to receive dupilumab or placebo, and in EFC14146, 282 adult patients (>18 years) were randomized to receive dupilumab or placebo. • **Eosinophilic esophagitis studies:** Adults and adolescents A total of 321 adult and pediatric patients 12 to 17 years of age with EoE were evaluated in a randomized, double-blind, parallel-group, multicenter, placebo-controlled protocol consisting of two 24-week treatment studies (R668-EE-1774, TREET part A and TREET part B). Adolescents (12 to 17 years of age) The safety of dupilumab was assessed in 99 adolescents aged 12 to 17 years with EoE that were enrolled in the TREET (parts A and B) studies. Pediatric patients (one to 11 years of age) The safety of dupilumab was assessed in a trial of 101 patients one to 11 years of age with EoE (R668-EE-1877, EoE KIDS part A). • **Chronic obstructive pulmonary disease studies (adults only):** A total of 1872 adult patients with COPD were evaluated in two randomized, double-blind, multicenter, parallel group, placebo-controlled trials with a 52-week treatment period (BOREAS, EFC15804 and NOTUS, EFC15805).

Important Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	• **Prurigo nodularis studies (adults only):** A total of 309 adult patients with PN were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials (EFC16459, LIBERTY-PN PRIME and EFC16460, PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both studies. • **Chronic spontaneous urticaria studies:** A total of 392 adult and adolescent patients 12 to 17 years of age with CSU were evaluated in three randomized, double-blind, parallel-group, multicenter, placebo-controlled 24-week treatment studies, Study A, Study B, and Study C, conducted under a master protocol (EFC16461, LIBERTY-CSU-CUPID). An additional five pediatric patients, six to 11 years of age, were also included in Studies A and C. The safety pool consisted of 397 patients in studies A, B, and C. The safety pool included data from the 24-week treatment and 12-week follow-up periods from all three studies. An additional 15 pediatric patients aged ≥2 years to <12 years were included in PKM16982. **Postmarketing data:** For a comprehensive review of postmarketing data, a cumulative search of the Sanofi global pharmacovigilance database was performed for individual case safety reports from all postmarketing sources using the MedDRA SMQ *Hypersensitivity (narrow)* through 28-Mar-2025.
Characterization of the risk	**Frequency:** • **Atopic dermatitis studies:** <u>Adults</u> SOLO 1 (R668-AD-1334), SOLO 2 (R668-AD-1416), a Phase 2 dose-ranging study, and CHRONOS (R668-AD-1224): There were no anaphylactic reactions related to dupilumab in adult AD patients. One patient experienced a serious serum-sickness-like reaction of moderate severity on study Day 15 after receiving three doses of study drug. The event was considered by the investigator to be related to study drug and led to the patient's permanent discontinuation from study drug. R688-AD-1225 (Adult AD OLE): All anaphylaxis cases that occurred during the study were unrelated to the study drug. One patient experienced an adverse event with a Preferred Term (PT) of *Circulatory collapse* (included within the MedDRA SMQ *Narrow Anaphylactic Reaction*), which was considered related to the study drug, mild, non-serious and did not lead to study drug discontinuation. The event resolved on the same day (study Day 220). One participant with a positive neutralizing antibody had a serious TEAE of Serum sickness, which was considered related to study drug by the investigator; this participant discontinued treatment. <u>Adolescents (12 to 17 years of age)</u> R688-AD-1526 (AD Adol): There were no reports of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab. R688-AD-1434 (pediatric AD OLE), first-step analysis: There were no reports of anaphylactic reaction in this age group. <u>Pediatric patients (six to 11 years of age)</u> R688-AD-1652 (AD Peds): There were no events of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab. R688-AD-1434 (pediatric AD OLE), second-step analysis: No events of systemic hypersensitivity related to dupilumab were seen in the study in this age group. <u>Pediatric patients (six months to five years of age)</u> R688-AD-1539 (AD preschool): There were no reports of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab.

Important Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	R688-AD-1434 (Pediatric AD OLE), third-step analysis: There were no reports of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab in this age group. Hand and Foot Dermatitis (adults and adolescents) R688-AD-1924 (AD-HAFT): There were no reports of systemic hypersensitivity, including anaphylactic reactions, related to dupilumab. • **Asthma studies**: Adult and adolescents DRI12544 and EFC13579, QUEST: In the safety pool, five cases of anaphylaxis were reported, four of which were not related and had clear identified inciting agents. In the fifth case, a causal relationship to dupilumab could not be ruled out. Due to this one case, the Sponsor considered anaphylaxis to be an ADR of dupilumab. 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. EFC13691 (QUEST): There were no reports of systemic hypersensitivity, including anaphylactic reactions reported in either group. LTS12551 (TRAVERSE, adult, and adolescent OLE): None of the cases of anaphylactic reaction were assessed as related to dupilumab. Of the four cases of anaphylactic reaction, three were related to known triggers. In the remaining case, a cluster of events (dyspnea and pruritus) occurred. This case was identified by the *Anaphylactic reaction* SMQ algorithm due to temporal relationship between dyspnea and pruritus events, however it does not represent a true anaphylactic reaction due to long latency of dyspnea and the fact that pruritus occurred 90 days after the last IMP administration. Pediatric patients (six to 11 years of age): EFC14153 (VOYAGE): Anaphylactic reactions were reported by two patients in the placebo group and none in the dupilumab group. LTS14424 (Ped OLE): Two patients, both previously receiving dupilumab in the parent study, reported non-serious anaphylactic reactions, suspected to be due to food allergy, and assessed as not related to the IMP. • **Chronic rhinosinusitis with nasal polyposis studies**: There were no anaphylactic reactions or serum sickness, or serum sickness-like reactions related to dupilumab in CRSwNP patients. • **Eosinophilic esophagitis studies**: Adults and adolescent (12 to 17 years of age) There were no dupilumab related anaphylactic reactions, or serum sickness, or serum sickness-like reactions reported in the EoE study. In pooled safety analysis of part A and part B of study R668-EE-1774, PT of *Hypersensitivity* was reported with incidence of 0.9% in placebo group and 0.8% in dupilumab 300 mg QW group. Pediatric patients (one to <12 years of age) In part A, anaphylactic reactions were reported in one participant in the lower exposure dupilumab group (classified as serious and of moderate intensity) and one participant in the higher exposure dupilumab group (non-serious [did not require hospitalization or steroid treatment] and of severe intensity). Both AESIs of anaphylactic reactions were related to preexisting food allergy (milk and dairy products, respectively) and not to IMP. No patients reported anaphylactic reactions in the placebo group. No event of systemic hypersensitivity, serum sickness, or serum sickness-like reactions were reported. • **Chronic obstructive pulmonary disease studies:** In study EFC15804 (BOREAS), the incidence of systemic hypersensitivity reaction was reported as 0.4% in both placebo and dupilumab arms. Anaphylactic reaction incidence was

Important Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	reported as 0.2% in placebo and 0% in the dupilumab arm. Anaphylactic reaction was assessed as not related to IMP by the investigator. In study EFC15805 (NOTUS), 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. Anaphylactic reaction was assessed as not related to IMP by the investigator. • **Prurigo nodularis studies**: There were no anaphylactic reactions, serum sickness, or serum sickness-like reactions reported in PN studies EFC16459 (LIBERTY-PN PRIME) and EFC16460 (PRIME2). In the pooled safety analysis of studies EFC16459 and EFC16460, systemic hypersensitivity was reported with an incidence of 1.3% in the placebo group (two patients, both with PT *Urticaria*) and 0.7% in the dupilumab group (one patient with PT *Dermatitis allergic*). • **Chronic spontaneous urticaria studies:** There were no dupilumab related anaphylactic reactions, serum sickness, or serum sickness-like reactions reported in EFC16461, LIBERTY-CSU-CUPID study (Studies A, B, and C). In the dupilumab group, one participant presented with a systemic hypersensitivity event (PT *Urticaria*, reported as "hives and itching all over the body in reaction to the Coronavirus Disease (COVID-19) vaccine" one day after receiving the first dose of a COVID-19 vaccine), which was treated with one dose of OCS. The participant reported recovery without recurrence on the second COVID-19 vaccine dose (while still on IMP). The event was assessed as not related to the IMP by the Investigator. There were no dupilumab related anaphylactic reactions, serum sickness, or serum sickness-like reactions reported in PKM16982. **Postmarketing experience:** The data presented below are based on recently updated methodology (see Evidence source(s) and strength of evidence row above) and therefore are not directly comparable to data presented in previous RMPs, which were based on ADRs from postmarketing sources. As of 28-Mar-2025, cumulatively there were 153 854 cases reporting 199 570 events (serious n = 4751/non-serious n = 194 819). These cases refer to 195 unique MedDRA PTs within the SMQ Hypersensitivity (narrow). The five most frequently reported MedDRA PTs were Rash (n = 48 677 events, 24.4%), Dermatitis Atopic (n = 44 692 events, 22.4%), Eczema (n = 27 929 events, 14.0%), Urticaria (n = 7965 events, 4.0%), and Rash macular (n = 7063 events, 3.5%). Other relevant PTs included Anaphylactic reaction (n = 696 events, 0.3%), Anaphylactic shock (n = 135 events, 0.07%), Angioedema (n = 256 events, 0.1%), Serum sickness (n = 178 events, 0.09%), and Serum sickness-like reaction (n = 58 events, 0.02%). Distribution of hypersensitivity cases by age-group was as follows: Neonate: n = 10 (0.006%), Infant: n = 789 (0.5%), Child: n = 10 209 (6.6%), Adolescent: n = 11 161 (7.3%), Adult: n = 97 303 (63.2%), Elderly: n = 29 639 (19.3%), Unknown: n = 4743 (3.1%). Distribution of hypersensitivity cases by gender was as follows: Male: n = 57 429 (37.3%), Female: n = 93 486 (60.8%), Unknown: n = 2939 (1.9%). The review of postmarketing data up to DLP of 28-Mar-2025 did not reveal any new information to further characterize this important identified risk. **Severity and nature of risk**: The serum sickness, serum sickness-like reaction and anaphylaxis cases observed in clinical trials were severe or moderate. Antidrug antibody positive patient's data in completed AD and asthma clinical studies as of 02-Feb-2023 were reviewed. With the exception of one patient who experienced serum sickness, and one patient reported to have serum sickness like reaction, there was no correlation between TEAEs and the presence of ADA. Both of these patients had high ADA titer (>10 000). As the inflammatory process

Important Identified Risk	Systemic hypersensitivity (including events associated with immunogenicity)
	itself is self-limited if the offending antigen is removed, discontinuation of dupilumab is important once serum sickness is diagnosed. Due to the potential for life-threatening or fatal outcomes associated with anaphylactic reactions, dupilumab should be discontinued immediately. **Seriousness/outcomes**: Most of the above-mentioned clinical trial cases were assessed as 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 from pooled safety data in asthma studies was hospitalized for 24 hours and recovered completely from the event. **Reversibility:** In clinical trials, all patients either recovered or recovering. **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. [300] Based on data from omalizumab, the frequency of anaphylaxis in asthma patients treated with biologic agents ranges from 0.2 to 0.09%. [306] **Impact on individual patient**: Symptoms associated with serum-sickness like reactions reported in the clinical program resolved upon discontinuation of dupilumab. Initiation of appropriate treatment of anaphylaxis reaction symptoms resulted in complete recovery or recovering at the time of final report.
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. [307, 308] 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 in the dupilumab label.
Impact on the risk-benefit balance of the product	The significant benefit that dupilumab shows in efficacy endpoints and patient reported outcomes, outweighs rare cases 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; ADR: Adverse Drug Reaction; AESI: Adverse Event of Special Interest; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: Coronavirus Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; 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; MedDRA: Medical Dictionary for Regulatory Activities; OCS: Oral Corticosteroid; PN: Prurigo Nodularis; PT: Preferred Term; PY: Patient-Year; QW: Once Every Week; RMP: Risk Management Plan; SMQ: Standardized MedDRA Query; TCS: Topical Corticosteroid; TEAE: Treatment Emergent Adverse Event.

SVII.3.2. Presentation of the missing information

Table 56 - Missing information: Use in pregnant and lactating women

Missing Information	Use in pregnant and lactating women
Evidence source(s)	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. **Atopic dermatitis studies (as of DLP 28-Mar-2025):** In all dupilumab trials investigating AD, 50 patients reporting 51 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 9 patients received placebo. The outcomes of the 9 AD placebo patients include 3 elective abortions, 2 normal live births, 2 unknown outcome, 1 spontaneous abortion, 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 DLP 28-Mar-2025):** A total of 34 pregnancies were reported in the unblinded (DRI12544, EFC13579, and R668-AS-1903) and open label (LTS12551, LPS15023, EFC13691 and ACT11457) asthma studies. Of the 34 pregnancies reported in asthma studies, 7 pregnancies occurred in placebo patients in study EFC13579, of which four pregnancies resulted in live births of normal infants, 2 ectopic pregnancies, and 1 elective abortion. Among the 27 pregnancies in dupilumab-treated patients in asthma studies, outcomes include 7 spontaneous abortions, 2 elective abortions, 14 full term live births, and 3 premature births. Outcome was unknown in one patient. 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. **Chronic rhinosinusitis with nasal polyposis studies (as of DLP 28-Mar-2025):** Two pregnancies were reported in the CRSwNP safety pool (ACT12340, EFC14146, EFC14280, and LLPS16747 studies). One pregnancy occurred in a placebo-exposed patient and the outcome was reported as normal live birth. The second pregnancy occurred in a patient who received the investigational product and the outcome was reported as elective termination of pregnancy. **Eosinophilic esophagitis studies (as of DLP 28-Mar-2025):** 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-2025):** No pregnancy case has been reported.

Missing Information	Use in pregnant and lactating women
	Chronic obstructive pulmonary disease studies (EFC15804 and EFC15805 as of DLP 28-Mar-2025): No pregnancy case has been reported. **Chronic spontaneous urticaria studies (as of DLP 28-Mar-2025):** Two pregnancies were reported in the completed/unblinded CSU studies, including 1 patient each from completed EFC16461 Study A and Study B. One pregnancy occurred in a dupilumab-treated patient with a reportedly uncomplicated delivery and 1 occurred in a placebo-treated patient. **Allergic bronchopulmonary aspergillosis study (as of DLP 28-Mar-2025):** One pregnancy was reported in ABPA (R668-ABPA-1923) which ended in miscarriage (reportedly week of pregnancy could not be determined as fetus did not grow) and fetus was reported to have Trisomy-16. This patient was on placebo arm.
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, CSU, asthma, BP and NP patients.

ABPA: Allergic Bronchopulmonary Aspergillosis; AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disorder; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; DLP: Data Lock Point; EoE: Eosinophilic Esophagitis; NP: Nasal Polyposis; PN: Prurigo Nodularis.

Table 57 - Missing information: Long-term safety in paediatric patients

Missing Information	Long-term safety in paediatric patients
Evidence source(s)	As of 28-Mar-2025, in clinical studies, 197 pediatric patients with EoE have received dupilumab with 231.2 PYs of exposure, 1084 pediatric patients with AD have received dupilumab with 2453.1 PYs exposure, 512 pediatric patients with asthma have received dupilumab with 810.5 PYs exposure, and 24 pediatric patients with CSU have received dupilumab with 9.4 PYs of exposure. No pediatric patients were enrolled in COPD, CRSwNP, and PN studies. Overall exposure in pediatric patients across approved pediatric indications is 3504.2 PYs.
Population in need for further characterization	Additional data are needed to detect safety concerns associated with prolonged exposure in the paediatric population.

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disorder; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; PN: Prurigo Nodularis; PY: Person-Year.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 58 - 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

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 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) conducted in multiple large US administrative healthcare databases to evaluate whether dupilumab treatment in AD patients is associated with adverse pregnancy and infant outcomes.

  The protocol and Statistical Analysis Plan (SAP) for R668-AD-1760 titled "Dupilumab and Pregnancy Outcomes: A retrospective cohort study using Administrative Healthcare Databases (Dupi PODS)" were amended in May 2025 (post RMP DLP). The protocol amendment reflected changes made to the SAP that were requested by the US FDA.

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 59 - 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.

Amendment 3 of protocol submitted for information in the EU-RMP v14.0.

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 (6-11 years) and a cohort of pediatric patients (6 months to 5 years). Planned total number of patients is approximately 800.

Milestones

Final report: Quarter (Q)4 2027

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 serious adverse event [SAE]s) 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
- Protocol approved by PRAC on 14-Dec-2023
- Registration in the EU PAS register on 08-May-2024
- Study start Q3 2024[a] on 25-Apr-2024
- Study end Q3 2031[a]
- Progress report Q4 2024-2030 – Q4 2024 report submitted on 18-Dec-2024
- 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 60 - 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
			Amendment 3	Submitted for information with EU-RMP v14.0
			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 2027
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 Ongoing	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
			Protocol approved by PRAC on	14-Dec-2023
			Annual progress report	Q4 2024-2030 Q4 2024 report submitted on 18-Dec-2024
			Final Report	Q3 2032

AD: Atopic Dermatitis; EMEA: European Medicines Agency; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: 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).

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

V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 61 - 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 • Patient Information Leaflet (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 immediately discontinue Dupixent administration 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 Dupixent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus and a decision must be made whether to discontinue breastfeeding or to discontinue Dupixent therapy taking into account the benefit of breastfeeding 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 62 - 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; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Dupixent (Dupilumab)

This is a summary of the 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 SmPC and its package leaflet (PL) give essential information to 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 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 atopic dermatitis 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 CRSwNP for whom therapy with systemic corticosteroids 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, adolescents and children aged 1 year and older, weighing at least 15 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) characterized 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).

Chronic Spontaneous Urticaria (CSU):

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU.

The indication below is subject to approval under this procedural assessment:

Chronic Spontaneous Urticaria (CSU):

Dupixent is indicated for the treatment of moderate to severe chronic spontaneous urticaria in adults, adolescents, and children (2 years and above) with inadequate response to H1 antihistamines and who are naïve to anti-IgE therapy for CSU.

See SmPC for the full indication.

It contains dupilumab as the active substance and it is given by 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 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 below.

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" below.

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 63 - 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 64 - 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	• **Atopic dermatitis studies:** Adults The safety of dupilumab monotherapy was evaluated through week-16 based on data from three randomized, double-blind, placebo-controlled multicenter studies (SOLO 1 [R668-AD-1334], SOLO 2 [R668-AD-1416], and a Phase 2 dose-ranging study) that included 1564 adult patients with moderate-to-severe AD. The safety of dupilumab with concomitant TCS was evaluated based on data from one randomized, double-blind, placebo-controlled multicenter study (CHRONOS [R668-AD-1224]). A total of 740 patients were treated up to 52-weeks. The long-term safety of repeat doses of dupilumab was assessed in the completed study R668-AD-1225, in 2677 adults with moderate-to-severe AD. Adolescents (12 to 17 years of age) The safety of dupilumab was assessed in a study of 250 patients 12 to 17 years of age with moderate-to-severe AD (R688-AD-1526). The long-term safety of dupilumab was assessed in an ongoing open-label extension study in 275 patients 12 to 17 years of age with moderate-to-severe AD (R688-AD-1434 first-step analysis). Pediatric patients (six to 11 years of age) The safety of dupilumab was assessed in a trial of 367 patients six to 11 years of age with severe AD (R688-AD-1652). The long-term safety of dupilumab + TCS was assessed in an ongoing open-label extension study of 368 patients six to 11 years of age with AD (R688-AD-1434 second-step analysis). Pediatric patients (six months to five years of age) The safety of dupilumab + TCS was assessed in a study of 161 patients six months to five years of age with moderate-to-severe AD (R688-AD-1539). The long-term safety of dupilumab was assessed in an ongoing open-label extension study of 180 patients six months to five years of age with AD (R688-AD-1434 third-step analysis). Hand and foot dermatitis (adults and adolescents) The safety of dupilumab was assessed in 133 adult and adolescent patients 12 to 17 years of age with moderate-to-severe atopic HFE (R688-AD-1924). • **Asthma studies:** Adult and adolescents A total of 2888 adult and adolescent patients with moderate-to-severe asthma were evaluated in three randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (DRI12544; EFC13579, QUEST; and EFC13691, VENTURE). The long-term safety of dupilumab was assessed in an open-label extension study in 2282 patients 12 years and older with moderate-to-severe asthma (LTS12551, TRAVERSE). In this study, patients were followed for up to 96-weeks, resulting in 3169 PYs cumulative exposure to dupilumab. Pediatric patients (six to 11 years of age) The safety of dupilumab was assessed in 405 patients six to 11 years of age with moderate-to-severe asthma (EFC14153, VOYAGE).

Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)	
	The long-term safety of dupilumab was assessed in an open-label extension study (LTS14424, EXCURSION) in children 6 to 11 years of age with moderate-to-severe asthma who previously participated in VOYAGE. Among 365 patients who entered EXCURSION, 350 completed 52 of weeks treatment and 228 patients completed a cumulative treatment duration of 104-weeks (VOYAGE and EXCURSION). • **Chronic rhinosinusitis with nasal polyposis studies:** A total of 722 adult patients with uncontrolled, severe CRSwNP on a background therapy with intranasal corticosteroids were evaluated in two pivotal randomized, double-blind, placebo-controlled, parallel-group studies of 24-week (EFC14146, SINUS-24) and 52-week duration (EFC14280, SINUS-52) in adult patients. In EFC14280, a total of 440 adult patients (≥18 years) were randomized to receive dupilumab or placebo, and in EFC14146, 282 adult patients (>18 years) were randomized to receive dupilumab or placebo. • **Eosinophilic esophagitis studies:** <u>Adults and adolescents</u> A total of 321 adult and pediatric patients 12 to 17 years of age with EoE were evaluated in a randomized, double-blind, parallel-group, multicenter, placebo-controlled protocol consisting of two 24-week treatment studies (R668-EE-1774, TREET part A and TREET part B). <u>Adolescents (12 to 17 years of age)</u> The safety of dupilumab was assessed in 99 adolescents aged 12 to 17 years with EoE that were enrolled in the TREET (parts A and B) studies. <u>Pediatric patients (one to 11 years of age)</u> The safety of dupilumab was assessed in a trial of 101 patients one to 11 years of age with EoE (R668-EE-1877, EoE KIDS part A). • **Chronic obstructive pulmonary disease studies (adults only):** A total of 1872 adult patients with COPD were evaluated in two randomized, double-blind, multicenter, parallel group, placebo-controlled trials with a 52-week treatment period (BOREAS, EFC15804 and NOTUS, EFC15805). • **Prurigo nodularis studies (adults only):** A total of 309 adult patients with PN were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials (EFC16459, LIBERTY-PN PRIME and EFC16460, PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both studies. • **Chronic spontaneous urticaria studies:** A total of 392 adult and adolescent patients 12 to 17 years of age with CSU were evaluated in three randomized, double-blind, parallel-group, multicenter, placebo-controlled 24-week treatment studies, Study A, Study B, and Study C, conducted under a master protocol (EFC16461, LIBERTY-CSU-CUPID). An additional five pediatric patients, six to 11 years of age, were also included in Studies A and C. The safety pool consisted of 397 patients in studies A, B and C. The safety pool included data from the 24-week treatment and 12-week follow-up periods from all three studies. An additional 15 pediatric patients aged ≥2 years to <12 years were included in PKM16982. **Postmarketing data:** For a comprehensive review of postmarketing data, a cumulative search of the Sanofi global pharmacovigilance database was performed for individual case safety reports from all postmarketing sources using the MedDRA SMQ *Hypersensitivity (narrow)* through 28-Mar-2025.

Important identified risk: Systemic hypersensitivity (including events associated with immunogenicity)	
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. *307, 308* 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

AD: Atopic Dermatitis; COPD: Chronic Obstructive Pulmonary Disease; CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis; CSU: Chronic Spontaneous Urticaria; EoE: Eosinophilic Esophagitis; MedDRA: Medical Dictionary for Regulatory Activities; PN: Prurigo Nodularis; PY: Patient-Year; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics; SMQ: Standardized MedDRA Query; TCS: Topical Corticosteroid.

Table 65 - 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 66 - 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 67 - 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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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)

Please provide the below requested information in the dedicated sections of the support used to provide the data (i.e., safety collection form or Sanofi Portal).

- **Medical History/Risk Factors:**

  - 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.

- **Description of the Reported Event(s)/Clinical Course:**

  - 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

- **<u>Complementary Investigations (including lab tests):</u>**

- 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.

Discharge summary should be attached if needed/applicable.

Solicited Individual Safety Information (ISI) Collection & Documentation Form

All ISI (Adverse Events and Special Situations) must be reported to Sanofi within agreed timelines. Please complete all fields where information is available. **Fields to be completed in compliance with local data privacy regulation.

General Information

Initial Report	Choose an item.	**Country of occurrence**	
Sanofi Case ID (if applicable)		**Service Provider** First and Last Name / Phone or Email	
Program/Study Name		**ISI receipt date**	
Program/Study ID		**Local PV Receipt Date (if applicable)**	
Are you responding to Sanofi PV Follow-up Request?	Choose an item.	**Are you responding to Sanofi PV Follow-up Questionnaire?**	Choose an item.

Reporter Information** (the person who reported the ISI to you)

Name or Initials		**Postal Address**	
Healthcare Professional?	Choose an item.		
Telephone/Fax			
Email Address		**Country**	
Reporter Type	Choose an item.	**If 'Other' please specify**	

Consent for Follow-Up Information for ISI reported by Consumers**

Has the patient provided informed consent for Sanofi to contact his/her treating health care professional (HCP) about the reported ISI in order to obtain additional medical information? Choose an item.

HCP First and Last Name		**HCP Postal Address**	
HCP Email Address			
HCP Telephone/Fax		**HCP Country**	

Patient Information**(provide Age/Age Group at time of adverse event)

Name (First and Last Name)		**Initials**		**Gender**	Choose an ite
Patient ID (include Center ID if applicable)		**Age**	Choose an item.		
Date of Birth		**Age Group**	Choose an item.		
Pregnant	Choose an iter	**Breastfeeding:**	Choose an item	**Was there parental drug exposure?**	Choose an item.

Relevant Medical History/Risk factors (please add any additional information on Page 5)

No	History/Risk factors	Start Date	Stop Date	Ongoing?	Notes
1				☐ Yes	
2				☐ Yes	
3				☐ Yes	

Relevant Lab Test (please add any additional information on Page 5)

No	Test Name	Test Date	Test Result	Test Unit	Notes
1					
2					
3					

Relevant Investigations (please add any additional information on Page 5)

No	Investigations	Date	Result	Notes
1				
2				

Suspect Product 1			
Trade Name 1		Active Ingredient 1	
Formulation 1	Choose an item.	Indication 1	
Location of Administration 1	Choose an item.	Route of administration 1	Choose an item.
Dosage Details 1 (dose, unit)		Action taken 1	Choose an item.
Dosage Frequency 1	Choose an item	Did reaction reappear after reintroduction? 1	Choose an item.
Start Date 1		Stop Date 1	Ongoing ☐
Batch/Lot number 1		Expiry Date 1	
To be completed only if used outside the terms of the approved product labelling	Is it intentional? Choose an item. at the initiative of Choose an item. for a therapeutic purpose? Choose an item.		

Suspect Product 2			
Trade Name 2		Active Ingredient 2	
Formulation 2	Choose an item.	Indication 2	
Location of Administration 2	Choose at item.	Route of administration 2	Choose an item.
Dosage Details 2 (dose, unit)		Action taken 2	Choose at item.
Dosage Frequency 2	Choose an item	Did reaction reappear after reintroduction? 2	Choose an item.
Start Date 2		Stop Date 2	Ongoing ☐
Batch/Lot number 2		Expiry Date 2	

Suspect Product 3			
Trade Name 3		Active Ingredient 3	
Formulation 3	Choose an item.	Indication 3	
Location of Administration 3	Choose an item.	Route of administration 3	Choose an item.
Dosage Details 3 (dose, unit)		Action taken 3	Choose an item.
Dosage Frequency 3	Choose an item	Did reaction reappear after reintroduction? 3	Choose an item.
Start Date 3		Stop Date 3	Ongoing ☐
Batch/Lot number 3		Expiry Date 3	

Suspect Product 4			
Trade Name 4		Active Ingredient 4	
Formulation 4	Choose an item.	Indication 4	
Location of Administration 4	Choose an item.	Route of administration 4	Choose an item.
Dosage Details 4 (dose, unit)		Action taken 4	Choose an item.
Dosage Frequency 4	Choose an item	Did reaction reappear after reintroduction? 4	Choose an item.
Start Date 4		Stop Date 4	Ongoing ☐
Batch/Lot number 4		Expiry Date 4	

Adverse Event 1					
Event Verbatim 1				Event Outcome 1	Choose an item.
Event resulted in Death? 1	☐	Congenital Anomaly?1	☐	Onset Date 1	
Life threatening? 1	☐	Resulted in Hospitalization 1	☐	End Date 1	Ongoing ☐
Disability? 1	☐	Required Medical Intervention? 1	☐	Transmission of an Infectious agent via product 1	☐
Causality 1 to Suspect Product 1	Choose an item.			Causality 1 to Suspect Product 2	Choose an item.
Causality 1 to Suspect Product 3	Choose an item.			Causality 1 to Suspect Product 4	Choose an item.
For Post-Trial Access Programs: Is this information related to an adverse event already reported in the context of the Parent Study Choose an item. If Yes, provide the Parent Study ID ☐ and AE Number ☐					

Adverse Event 2					
Event Verbatim 2				Event Outcome 2	Choose an item.
Event resulted in Death? 2	☐	Congenital Anomaly? 2	☐	Onset Date 2	
Life threatening? 2	☐	Resulted in Hospitalization 2	☐	End Date 2	Ongoing ☐
Disability? 2	☐	Required Medical Intervention? 2	☐	Transmission of an Infectious agent via product 2	☐
Causality 2 to Suspect Product 1	Choose an item.			Causality 2 to Suspect Product 2	Choose an item.
Causality 2 to Suspect Product 3	Choose an item.			Causality 2 to Suspect Product 4	Choose an item.
For Post-Trial Access Programs: Is this information related to an adverse event already reported in the context of the Parent Study Choose an item. If Yes, provide the Parent Study ID ☐ and AE Number ☐					

Adverse Event 3					
Event Verbatim 3				Event Outcome 3	Choose an item.
Event resulted in Death? 3	☐	Congenital Anomaly? 3	☐	Onset Date 3	
Life threatening? 3	☐	Resulted in Hospitalization 3	☐	End Date 3	Ongoing ☐
Disability? 3	☐	Required Medical Intervention? 3	☐	Transmission of an Infectious agent via product 3	☐
Causality 3 to Suspect Product 1	Choose an item.			Causality 3 to Suspect Product 2	Choose an item.
Causality 3 to Suspect Product 3	Choose an item.			Causality 3 to Suspect Product 4	Choose an item.
For Post-Trial Access Programs: Is this information related to an adverse event already reported in the context of the Parent Study Choose an item. If Yes, provide the Parent Study ID ☐ and AE Number ☐					

Adverse Event 4					
Event Verbatim 4				Event Outcome 4	Choose an item.
Event resulted in Death? 4	☐	Congenital Anomaly? 4	☐	Onset Date 4	
Life threatening? 4	☐	Resulted in Hospitalization 4	☐	End Date 4	Ongoing ☐
Disability? 4	☐	Required Medical Intervention? 4	☐	Transmission of an Infectious agent via product 4	☐
Causality 4 to Suspect Product 1	Choose an item.			Causality 4 to Suspect Product 2	Choose an item.
Causality 4 to Suspect Product 3	Choose an item.			Causality 4 to Suspect Product 4	Choose an item.
For Post-Trial Access Programs: Is this information related to an adverse event already reported in the context of the Parent Study Choose an item. If Yes, provide the Parent Study ID ☐ and AE Number ☐					

If the Outcome is Fatal, please provide Death Details:			
Date of Death		Cause(s) of Death	
Autopsy performed?	Choose an item.		
Autopsy Report available? if yes please attach	Choose an item.		

Concomitant Product 1			
Trade name C1			
Active Ingredient C1		Indication C1	
Formulation C1	Choose an item.	Route of administration C1	Choose an item.
Dosage Details C1 (dose, unit)		Dosage Frequency C1	Choose an item
Start Date C1		Stop date C1	Ongoing ☐

Concomitant Product 2			
Trade name C2			
Active Ingredient C2		Indication C2	
Formulation C2	Choose an item.	Route of administration C2	Choose an item.
Dosage Details C2 (dose, unit)		Dosage Frequency C2	Choose an item
Start Date C2		Stop date C2	Ongoing ☐

Concomitant Product 3			
Trade name C3			
Active Ingredient C3		Indication C3	
Formulation C3	Choose an item.	Route of administration C3	Choose an item.
Dosage Details C3 (dose, unit)		Dosage Frequency C3	Choose an item
Start Date C3		Stop date C3	Ongoing ☐

Concomitant Product 4			
Trade name C4			
Active Ingredient C4		Indication C4	
Formulation C4	Choose an item.	Route of administration C4	Choose an item.
Dosage Details C4 (dose, unit)		Dosage Frequency C4	Choose an item
Start Date C4		Stop date C4	Ongoing ☐

Concomitant Product 5			
Trade name C5			
Active Ingredient C5		Indication C5	
Formulation C5	Choose an item.	Route of administration C5	Choose an item.
Dosage Details C5 (dose, unit)		Dosage Frequency C5	Choose an item
Start Date C5		Stop date C5	Ongoing ☐

Additional Information:

Please provide additional details such as signs & symptoms, progression, possible causes that may explain the occurrence of the Adverse Event, vaccination details, family history, past drug history, corrective treatments, severity

Unsolicited (Spontaneous) Individual Safety Information (ISI) Collection & Documentation Form

sanofi

All ISI (Adverse Events and Special Situations) must be reported to Sanofi within agreed timelines. Please complete all fields where information is available. **Fields to be completed in compliance with local data privacy regulation.

General Information

Initial Report	Choose an item.	**Country of occurrence**	
Sanofi Case ID (if applicable)		**Service Provider or Collecting Org /First and Last Name / Phone or Email**	
Registry/Digital Media ID		**ISI identification / receipt date**	
		Local PV Receipt Date (if applicable)	
Are you responding to Sanofi PV Follow-up Request?	Choose an item.	**Are you responding to Sanofi PV Follow-up Questionnaire?**	Choose an item.

Reporter Information** (the person who reported the ISI to you)

Name or Initials		**Postal Address**	
Healthcare Professional?	Choose an item.		
Telephone/Fax			
Email Address		**Country**	
Reporter Type	Choose an item.	**If 'Other' please specify**	

Consent for Follow-Up Information for ISI reported by Consumers**

Has the patient provided informed consent for Sanofi to contact his/her treating health care professional (HCP) about the reported ISI in order to obtain additional medical information? Choose an item.

HCP First and Last Name		**HCP Postal Address**	
HCP Email Address			
HCP Telephone/Fax		**HCP Country**	

Patient Information**(provide Age/Age Group at time of adverse event)

Name (First and Last Name)		**Initials**		**Gender**	Choose an ite
Patient ID (include Center ID if applicable)		**Age**	Choose an item.		
Date of Birth		**Age Group**	Choose an item.		
Pregnant	Choose an iter	**Breastfeeding:**	Choose an item	**Was there parental drug exposure?**	Choose an item.

Relevant Medical History/Risk factors (please add any additional information on Page 5)

No	History/Risk factors	Start Date	Stop Date	Ongoing?	Notes
1				☐ Yes	
2				☐ Yes	
3				☐ Yes	

Relevant Lab Test (please add any additional information on Page 5)

No	Test Name	Test Date	Test Result	Test Unit	Notes
1					
2					
3					

Relevant Investigations (please add any additional information on Page 5)

No	Investigations	Date	Result	Notes
1				
2				

Suspect Product 1			
Trade Name 1		Active Ingredient 1	
Formulation 1	Choose an item.	Indication 1	
Location of Administration 1	Choose an item.	Route of administration 1	Choose an item.
Dosage Details 1 (dose, unit)		Action taken 1	Choose an item.
Dosage Frequency 1	Choose an item	Did reaction reappear after reintroduction? 1	Choose an item.
Start Date 1		Stop Date 1	Ongoing ☐
Batch/Lot number 1		Expiry Date 1	
To be completed only if used outside the terms of the approved product labelling	Is it intentional? Choose an item. at the initiative of Choose an item. for a therapeutic purpose? Choose an item.		

Suspect Product 2			
Trade Name 2		Active Ingredient 2	
Formulation 2	Choose an item.	Indication 2	
Location of Administration 2	Choose at item.	Route of administration 2	Choose an item.
Dosage Details 2 (dose, unit)		Action taken 2	Choose at item.
Dosage Frequency 2	Choose an item	Did reaction reappear after reintroduction? 2	Choose an item.
Start Date 2		Stop Date 2	Ongoing ☐
Batch/Lot number 2		Expiry Date 2	

Suspect Product 3			
Trade Name 3		Active Ingredient 3	
Formulation 3	Choose an item.	Indication 3	
Location of Administration 3	Choose an item.	Route of administration 3	Choose an item.
Dosage Details 3 (dose, unit)		Action taken 3	Choose an item.
Dosage Frequency 3	Choose an item	Did reaction reappear after reintroduction? 3	Choose an item.
Start Date 3		Stop Date 3	Ongoing ☐
Batch/Lot number 3		Expiry Date 3	

Suspect Product 4			
Trade Name 4		Active Ingredient 4	
Formulation 4	Choose an item.	Indication 4	
Location of Administration 4	Choose an item.	Route of administration 4	Choose an item.
Dosage Details 4 (dose, unit)		Action taken 4	Choose an item.
Dosage Frequency 4	Choose an item	Did reaction reappear after reintroduction? 4	Choose an item.
Start Date 4		Stop Date 4	Ongoing ☐
Batch/Lot number 4		Expiry Date 4	

Adverse Event 1					
Event Verbatim 1				Event Outcome 1	Choose an item.
Event resulted in Death? 1	☐	Congenital Anomaly?1	☐	Onset Date 1	
Life threatening? 1	☐	Resulted in Hospitalization 1	☐	End Date 1	Ongoing ☐
Disability? 1	☐	Required Medical Intervention? 1	☐	Transmission of an Infectious agent via product 1	☐
Causality 1 to Suspect Product 1	Choose an item.			Causality 1 to Suspect Product 2	Choose an item.
Causality 1 to Suspect Product 3	Choose an item.			Causality 1 to Suspect Product 4	Choose an item.

Adverse Event 2					
Event Verbatim 2				Event Outcome 2	Choose an item.
Event resulted in Death? 2	☐	Congenital Anomaly? 2	☐	Onset Date 2	
Life threatening? 2	☐	Resulted in Hospitalization 2	☐	End Date 2	Ongoing ☐
Disability? 2	☐	Required Medical Intervention? 2	☐	Transmission of an Infectious agent via product 2	☐
Causality 2 to Suspect Product 1	Choose an item.			Causality 2 to Suspect Product 2	Choose an item.
Causality 2 to Suspect Product 3	Choose an item.			Causality 2 to Suspect Product 4	Choose an item.

Adverse Event 3					
Event Verbatim 3				Event Outcome 3	Choose an item.
Event resulted in Death? 3	☐	Congenital Anomaly? 3	☐	Onset Date 3	
Life threatening? 3	☐	Resulted in Hospitalization 3	☐	End Date 3	Ongoing ☐
Disability? 3	☐	Required Medical Intervention? 3	☐	Transmission of an Infectious agent via product 3	☐
Causality 3 to Suspect Product 1	Choose an item.			Causality 3 to Suspect Product 2	Choose an item.
Causality 3 to Suspect Product 3	Choose an item.			Causality 3 to Suspect Product 4	Choose an item.

Adverse Event 4					
Event Verbatim 4				Event Outcome 4	Choose an item.
Event resulted in Death? 4	☐	Congenital Anomaly? 4	☐	Onset Date 4	
Life threatening? 4	☐	Resulted in Hospitalization 4	☐	End Date 4	Ongoing ☐
Disability? 4	☐	Required Medical Intervention? 4	☐	Transmission of an Infectious agent via product 4	☐
Causality 4 to Suspect Product 1	Choose an item.			Causality 4 to Suspect Product 2	Choose an item.
Causality 4 to Suspect Product 3	Choose an item.			Causality 4 to Suspect Product 4	Choose an item.

If the Outcome is Fatal, please provide Death Details:			
Date of Death		Cause(s) of Death	
Autopsy performed?	Choose an item.		
Autopsy Report available? if yes please attach	Choose an item.		

Concomitant Product 1			
Trade name C1			
Active Ingredient C1		Indication C1	
Formulation C1	Choose an item.	Route of administration C1	Choose an item.
Dosage Details C1 (dose, unit)		Dosage Frequency C1	Choose an item
Start Date C1		Stop date C1	Ongoing ☐

Concomitant Product 2			
Trade name C2			
Active Ingredient C2		Indication C2	
Formulation C2	Choose an item.	Route of administration C2	Choose an item.
Dosage Details C2 (dose, unit)		Dosage Frequency C2	Choose an item
Start Date C2		Stop date C2	Ongoing ☐

Concomitant Product 3			
Trade name C3			
Active Ingredient C3		Indication C3	
Formulation C3	Choose an item.	Route of administration C3	Choose an item.
Dosage Details C3 (dose, unit)		Dosage Frequency C3	Choose an item
Start Date C3		Stop date C3	Ongoing ☐

Concomitant Product 4			
Trade name C4			
Active Ingredient C4		Indication C4	
Formulation C4	Choose an item.	Route of administration C4	Choose an item.
Dosage Details C4 (dose, unit)		Dosage Frequency C4	Choose an item
Start Date C4		Stop date C4	Ongoing ☐

Concomitant Product 5			
Trade name C5			
Active Ingredient C5		Indication C5	
Formulation C5	Choose an item.	Route of administration C5	Choose an item.
Dosage Details C5 (dose, unit)		Dosage Frequency C5	Choose an item
Start Date C5		Stop date C5	Ongoing ☐

Additional Information:

Please provide additional details such as signs & symptoms, progression, possible causes that may explain the occurrence of the Adverse Event, vaccination details, family history, past drug history, corrective treatments, severity

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

NOT APPLICABLE