EU Risk Management Plan
for
Omlyclo
(CT-P39, omalizumab biosimilar)

RMP version to be assessed as part of this application:	
RMP Version number:	2.0
Data lock point for this RMP:	07 August 2024
Date of final sign-off:	31 Mar 2025
Rationale for submitting an updated RMP:	Addition of new presentations; 75 mg and 150 mg pre-filled pens.
Summary of significant changes in this RMP:	Part I: Product overview • Added new presentations of 75 mg and 150 mg pre-filled pens. Part II: Clinical trial exposure • Added a completed healthy volunteer study CT-P39 1.2. • Updated study status of CT-P39 3.1 to completed.
Other RMP versions under evaluation:	Not applicable
RMP Version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	2.0
Approved with procedure:	EMEA/H/C/005958/II/0004/G
Date of approval (opinion date):	27 Mar 2025
QPPV name:	Oliver Wiedemann
QPPV oversight declaration:	*The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.*

Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

Table of Contents

List of Tables

List of Abbreviations

Abbreviation/Term	Definition
AA	Allergic Asthma
AE	Adverse Event
AI	Auto-injector
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thromboembolic Events
CBV	Cerebrovascular
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
CSS	Churg-Strauss Syndrome
CSU	Chronic Spontaneous Urticaria
CV	Cardiovascular
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
EGPA	Eosinophilic Granulomatosis with Polyangiitis
EMA	European Medicines Agency
EOT	End Of Treatment
EPAR	European Public Assessment Report
EU	European Union
FcεRI	High-affinity IgE Receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GVP	Good Pharmacovigilance Practices
HES	Hypereosinophilic Syndrome
HLT	High Level Term
HLGT	High Level Group Term
IgE	Immunoglobin E
IL	Interleukin
INC	Intranasal Corticosteroids
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Pre-filled Syringe
PK	Pharmacokinetic
PL	Package Leaflet

RDBPC	Randomised, Double-Blind, Placebo-Controlled study
RMP	Risk Management Plan
SC	Subcutaneous
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
TEAEs	Treatment Emergent Adverse Events
TIA	Transient Ischaemic Attack

Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Omalizumab
Pharmacotherapeutic group(s) (ATC Code)	Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases (R03DX05)
Marketing Authorisation Applicant	Celltrion Healthcare Hungary kft.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Omlyclo
Marketing authorisation procedure	Centralised Procedure
Brief description of the product	**Chemical class** Recombinant DNA-derived humanised monoclonal antibody.
	Summary of mode of action Omalizumab binds to immunoglobulin E (IgE) and prevents binding of IgE to high-affinity IgE receptor (FcεRI) on basophils and mast cells, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Treatment of atopic subjects with omalizumab resulted in a marked down-regulation of FcεRI receptors on basophils. Treatment with omalizumab inhibits IgE-mediated inflammation, as evidenced by reduced blood and tissue eosinophils and reduced inflammatory mediators, including IL-4, IL-5, and IL-13 by innate, adaptive and non-immune cells.
	Important information about its composition: The antibody is manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line.
Hyperlink to the Product Information	Product Information (Section 1.3.1)
Indication(s) in the EEA	Current: Allergic asthma Omlyclo is indicated in adults, adolescents and children (6 to <12 years of age). Omlyclo treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma. *Adults and adolescents (12 years of age and older)* Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who

	have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. *Children (6 to <12 years of age)* Omlyclo is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Chronic rhinosinusitis with nasal polyps (CRSwNP) Omlyclo is indicated as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control. Chronic Spontaneous Urticaria (CSU) Omlyclo is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H_1 antihistamine treatment.
	Proposed: Not applicable
Dosage in the EEA	Current: Allergic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP) 75 to 600 mg by subcutaneous injection every 2 or 4 weeks, determined by baseline serum total IgE level and body weight (according to the dose determination charts). Chronic spontaneous urticaria (CSU) 300 mg by subcutaneous injection every 4 weeks.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection in pre-filled syringe (injection); • 75 mg/0.5 mL solution for injection in pre-filled syringe • 150 mg/1 mL solution for injection in pre-filled syringe
	Proposed: Solution for injection; • 75 mg/0.5 mL solution for injection in pre-filled syringe • 75 mg/0.5 mL solution for injection in pre-filled pen • 150 mg/1 mL solution for injection in pre-filled syringe • 150 mg/1 mL solution for injection in pre-filled pen
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Omlyclo, biosimilar omalizumab and CT-P39 may be used in this document to describe the investigational product to which this application refers.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

According to the Guideline on Good Pharmacovigilance Practices (GVP) Module V (EMA/838713/2011 Rev 2) this part of the Risk Management Plan (RMP) is not required for biosimilar medicinal products.

Part II: Module SII - Non-clinical part of the safety specification

Table 2: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies) of CT-P39	Relevance to human usage
Increase of total IgE and decrease of free IgE **Repeat-dose toxicity of CT-P39** Increases in total IgE levels were noted on Days 8 and 29 in animals administered 5 mg/kg/week or 75 mg/kg/week Xolair or CT-P39. No differences in free IgE levels were noted in animals administered CT-P39 or Xolair 5 mg/kg/week. Free IgE levels were Below limit of quantification on Days 8 and 29 of the dosing phase in animals administered CT-P39 or Xolair 75 mg/kg/week, compared to controls.	Despite the presence of omalizumab-IgE complexes in monkey studies, there was no evidence of immune complex-mediated disease. No evidence of a safety concern for the use of omalizumab in the target population.
Thrombocytopenia and blood disorders **Repeat-dose toxicity of CT-P39** The only clinical pathology finding related to omalizumab was a slightly decreased platelet count in monkeys administered Xolair 75 mg/kg/week (5.8-fold higher than the clinical exposure at 600 mg, 2 doses administered 2 weeks apart, Oliver Kornmann et al, 2014). Decreases of platelets were not reported after treatment with CT-P39. The decrease in platelet count was not considered adverse as there were no secondary clinical effects or correlated anatomical or pathological findings. **Repeat-dose toxicity of Xolair (EPAR)** No omalizumab-related effects were observed except thrombocytopenia and changes secondary to thrombocytopenia. Thrombocytopenia appeared at serum concentrations of omalizumab, which were 1.7- to 16.7-fold higher than the concentrations detected in Phase III trial patients. Histopathological evaluation revealed haemorrhage in the subcutaneous tissue at the injection site, in seminal vesicles, in the stomach fundus mucosa, or in the duodenal mucosa of a few animals, in the low and/or high dose groups. In spite of the mechanistic in vivo/vitro studies performed by the Applicant, the mechanism of the omalizumab-platelet interaction and the epitope responsible for the interaction are unknown.	In experimental studies of omalizumab in monkeys, thrombocytopenia was observed. Isolated cases of idiopathic thrombocytopenia have been reported in the post-marketing setting in association with Xolair.

Key Safety findings (from non-clinical studies) of CT-P39	Relevance to human usage
Placental transfer and excretion into milk **Reproductive/Developmental toxicity of CT-P39** Reproductive toxicology studies comparing CT-P39 and Xolair have not been performed because they are not required according to the European Medicines Agency (EMA) guidance on biosimilar products (Committee for Medicinal Products for Human Use [CHMP] Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance - non-clinical and clinical issues [EMEA/CHMP/BMWP/42832/2005 Rev1] and Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues [EMEA/CHMP/BMWP/403543/2010]) **Reproductive/Developmental toxicity of Xolair (EPAR)** Subcutaneous (SC) administration of omalizumab, at doses of 0, 3, 15 and 75 mg/kg once-weekly for 6 weeks (to cover the period of spermatogenesis) did not elicit reproductive toxicity in males. The same doses were administered to females for 13 weeks (three menstrual cycles) before mating, during the mating period (maximum of two menstrual cycles) and during early pregnancy (up to Day 25 of gestation). Omalizumab did not elicit reproductive toxicity in female Cynomolgus monkeys. Administration of omalizumab to pregnant monkeys during organogenesis (gestational Days 20 to 50) at doses of 0, 3, 15 and 75 mg/kg once daily on Days 20-22, and then once weekly through Day 50 did not elicit maternal toxicity, embryotoxicity or teratogenicity. To assess the effect of omalizumab on late gestation, and to evaluate the placental transfer and milk secretion of omalizumab, doses of 75 mg/kg were administered SC to two groups of monkeys (Caesarean section group and natural delivery group). Omalizumab was given once daily on Days 120, 121 and 122 of gestation as a loading dose, and once weekly through Day 150 of gestation for the Cesarean section group, or through Day 28 postpartum for the natural delivery group. There was no evidence of late gestational maternal or offspring toxicity. However, further dosing and evaluation of the offspring were not performed, for example with regard to immunotoxicity. Measurable levels of omalizumab were observed in amniotic fluid (~3.3% of maternal serum levels), milk (~0.154%), and foetal (~33%) and neonatal (~33%) serum.	Omalizumab crosses the placental barrier. However, animal studies do not indicate either direct or indirect harmful effects with respect to reproductive toxicity. Omalizumab is found in non-human primate breast milk at concentrations 0.15% of those found in maternal serum. If clinically needed, the use of omalizumab may be considered during pregnancy and during breast-feeding.

Key Safety findings (from non-clinical studies) of CT-P39	Relevance to human usage
Genotoxicity/Carcinogenicity of CT-P39 Genotoxicity/carcinogenicity studies comparing CT-P39 and Xolair have not been performed because they are not required according to the EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/ 42832/2005 Rev1; EMEA/CHMP/BMWP/403543/2010) **Genotoxicity/Carcinogenicity of Xolair (EPAR)** A standard Ames test was negative. A full genotoxicity test battery and carcinogenicity evaluation have not been conducted for omalizumab, due to the absence of a relevant species appropriate for such studies. No carcinogenicity study with omalizumab was performed since omalizumab does not bind rodent IgE.	Not applicable
General Safety Pharmacology of CT-P39 No specific safety pharmacology studies were performed. Safety endpoints were incorporated into the monkey repeat-dose toxicity study (Study No. 8401278). No CT-P39- or Xolair-related clinical observations, respiration rate, blood pressure, or body temperature; or changes to ECG parameters were noted. This approach is compatible with CHMP guidance on similar biological medicinal products containing monoclonal antibodies, which states that safety pharmacology studies are not routinely required (CHMP Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues EMEA/CHMP/BMWP/403543/2010). **General Safety Pharmacology of Xolair (EPAR)** Safety parameters were monitored at regular intervals in 4-week and 6-month monkey toxicology studies. These parameters included vital functions such as blood pressure, electrocardiography, heart rate and respiration rate. No drug-related effects were observed for any of these variables. No separate safety pharmacology studies were performed for omalizumab.	Not applicable
Cardiotoxicity of CT-P39 There was no evidence of cardiotoxicity in the repeat-dose study performed. No non-clinical cardiotoxicity studies have been conducted with CT-P39.	Not applicable

Key Safety findings (from non-clinical studies) of CT-P39	Relevance to human usage
Mechanisms for Drug Interactions of CT-P39 No drug interactions have been studied, although omalizumab is intended to be given to patients in combination with various other medicinal products.	Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. There is no pharmacological reason to expect that commonly prescribed medicinal products used in the treatment of asthma, CRSwNP or CSU will interact with omalizumab. There is no clinical evidence for drug-drug interactions with the reference product.
Juvenile Toxicity Studies of CT-P39 Juvenile toxicity studies were not performed in line with the CHMP EMA guidance on similar biological medicinal products and monoclonal antibodies (EMEA/CHMP/BMWP/42832/2005 Rev1) and CHMP guideline on similar biological medicinal products containing monoclonal antibodies (EMEA/CHMP/BMWP/403543/2010).	Not applicable

Conclusion on Non-Clinical Data

Non-clinical investigations comparing CT-P39 with the reference product have not shown them to behave differently from one another in any relevant respects when administered by subcutaneous injection. No unexpected safety findings or signals were identified in the non-clinical programme for CT-P39.

Part II: Module SIII - Clinical trial exposure

The terms Omlyclo and CT-P39 may be used interchangeably in this document.

The clinical development programme for Omlyclo (CT-P39) includes three completed studies; two Phase 1 clinical studies in healthy subjects (Study CT-P39 1.1 and Study CT-P39 1.2) and one Phase 3 study in patients with Chronic Spontaneous Urticaria (CSU) who remain symptomatic despite H_1-antihistamine treatment (Study CT-P39 3.1).

- **Study CT-P39 1.1** (pivotal Pharmacokinetic [PK] study for biosimilarity): a Phase 1, randomised, double-blind, three-arm, parallel group, single-dose study to compare PK and safety of 3 formulations of omalizumab (CT-P39, EU-approved Xolair, and US-licensed Xolair), administered subcutaneously via pre-filled syringe (PFS) in healthy subjects. The study was conducted in 176 healthy male and female subjects. Of those, 62, 64, and 50 subjects received CT-P39, EU-approved Xolair, and US-licensed Xolair, respectively.

- **Study CT-P39 1.2** (PK study between auto-injector [AI] and PFS): a Phase 1, randomised, open-label, two-arm, parallel group, single-dose study to compare the PK and safety of 2 formulations of omalizumab (CT-P39 administered by AI [which is also referred to as pre-filled pen] and EU-approved Xolair administered by PFS) in healthy Japanese subjects. The study was conducted in 129 healthy male and female Japanese subjects. Of those, 65 and 63 subjects received CT-P39 AI and EU-approved Xolair PFS, respectively.

- **Study CT-P39 3.1** (pivotal equivalence study of CT-P39 to EU-approved Xolair): a Phase 3, double-blind, randomised, active-controlled, parallel group, study to compare efficacy and safety of CT-P39 and EU-approved Xolair in patients with CSU who remain symptomatic despite H_1-antihistamine treatment. This study consisted of approximately 600 male and female patients with CSU, aged between 12 and 75 years, randomly assigned in a 2:2:1:1 ratio to receive one of the following: 300 mg of CT-P39, 300 mg of Xolair, 150 mg of CT-P39 or 150 mg of Xolair, administered subcutaneously using a PFS. This study comprised 4 study periods (Screening Period, Treatment Period I, Treatment Period II, and Follow-up Period). The maximum duration of the study per patient was 44 weeks: a Screening Period of 4 weeks, 2 Treatment Periods of 12 weeks each, and a Follow-up Period of 16 weeks. All patients who completed Treatment Period I went through the second randomisation process prior to study drug administration at Week 12 and entered Treatment Period II to receive 3 additional doses of study drug every 4 weeks. During Treatment Period II, patients who were initially randomised to 300 mg of Xolair (Arm 2) in Treatment Period I, were re-randomised in a ratio of 1:1 to switching arm (Arm 2-1) or non-switching arm (Arm 2-2). Patients assigned to switching arm (Arm 2-1) underwent transition to 300 mg of CT-P39 and patients assigned to non-switching arm (Arm 2-2) continued 300 mg of Xolair. All patients who were initially randomly assigned to Arm 1 (300 mg of CT-P39) during Treatment Period I, continued to receive the same drug. All patients who were initially randomly assigned to Arm 3 (150 mg of CT-P39) or Arm 4 (150 mg of Xolair) during Treatment Period I, continued to receive the same drug at an increased dose of 300 mg during Treatment Period II. All patients received 3 doses of either 300 mg of CT-P39 or 300 mg of Xolair every 4 weeks for 12 weeks during Treatment Period II. The last dose of study drug during the Treatment Period II was given at Week 20 study visit and the end-of-treatment (EOT) visit was performed at Week 24. All patients entered the Follow-up Period and were followed up for 16 weeks for assessment. During the Follow-up Period, no study drug was given.

Estimates of the patient exposure from the pivotal study CT-P39 3.1 are presented in the following tables, up to the database lock date for inclusion of data in the first clinical study report including data up to 24-week treatment period for each patient (20 February 2023). In the following tables, patients who received at least one dose were included, excluding those from the Good Clinical Practices (GCP) non-compliance site. Therefore, the 15 participants recruited from the GCP non-compliance site, who all had a record of receiving a dose, were excluded. Additionally, participants in studies CT-P39 1.1 and CT-P39 1.2 have not been included in the tables below because these studies were conducted in healthy subjects (as opposed to patients), who were exposed to one single dose.

Table 3: Duration of exposure

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)								
Duration of exposure	**CT-P39**						**Omalizumab reference product****	
	Total		**CT-P39 only**		**Switched from Omalizumab reference product***			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Duration ≤ 1 month	17	155	14	98	3	57	12	178
1 month < Duration ≤ 3 months	107	6225	14	968	93	5257	101	8398
3 months < Duration ≤ 5 months	278	39261	278	39261	0	0	193	27020
5 months < Duration	4	613	4	613	0	0	2	304
Total	406	46254	310	40940	96	5314	308	35900

Source: Study CT-P39 3.1
Abbreviation: n = number
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**Exposure to reference product during Treatment Period I (12 weeks) in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)
The longest duration of exposure is 22 weeks.
The median and maximum treatment duration for patients treated with CT-P39 was 20.1, 22 weeks respectively.

Table 4: Exposure by Dose

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)								
Dose of exposure	**CT-P39**						**Omalizumab reference product****	
	Total		**CT-P39 only**		**Switched from Omalizumab reference product***			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
Omalizumab 300mg	400	37557	304	32243	96	5314	303	27332
Omalizumab 150mg	107	8697	107	8697	0	0	103	8568
Total	507***	46254	411***	40940	96	5314	406***	35900
The number of patients with dose administered	406	-	310	-	96	-	308	-
Total Cumulative Dose (mg) Mean	1386.21	-	1540.65	-	887.50	-	1288.64	-
Total Cumulative Dose (mg) Median	1350	-	1800	-	900	-	1350	-
Total Cumulative Dose (mg) Min	150	-	150	-	300	-	150	-
Total Cumulative Dose (mg) Max	1800	-	1800	-	900	-	1800	-

Source: Study CT-P39 3.1
Abbreviation: n = number, Min = Minimum, Max = Maximum
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**Exposure to reference product during Treatment Period I (12 weeks) in the switching arm is included in this column.
***Patients who received multiple strengths (150mg and 300mg) due to dose increase in Treatment Period II are included in more than one strength, so the total is greater than the number of individual patients.
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

Table 5: Exposure by Age and Gender

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)																
Age group (years)	**CT-P39**												**Omalizumab reference product****			
	Total				**CT-P39 only**				**Switched from Omalizumab reference product***							
	Patients (n)		**Person time (days)**		**Patients (n)**		**Person time (days)**		**Patients (n)**		**Person time (days)**		**Patients (n)**		**Person time (days)**	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<12[#]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12 – 17	2	5	282	623	2	4	282	567	0	1	0	56	1	5	141	656
18 – 64	133	240	14830	27345	102	181	13106	24101	31	59	1724	3244	101	184	12195	20934
≥ 65	6	20	842	2332	6	15	842	2042	0	5	0	290	3	14	425	1549
Total	141	265	15954	30300	110	200	14230	26710	31	65	1724	3590	105	203	12761	23139

Source: Study CT-P39 3.1
Abbreviation: n = number
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**Exposure to reference product during Treatment Period I (12 weeks) in the switching arm is included in this column.
[#]Following the inclusion criteria, patients between 12 and 75 years of age were enrolled.
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

Table 6: Exposure by Racial Group

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)								
Racial Group	**CT-P39**						**Omalizumab reference product****	
	Total		**CT-P39 only**		**Switched from Omalizumab reference product***			
	Patients (n)	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Asian	80	9154	59	8017	21	1137	60	7324
Black or African American	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0
Not allowed by Investigator country regulations	0	0	0	0	0	0	0	0
White	326	37100	251	32923	75	4177	248	28576
Other	0	0	0	0	0	0	0	0
Total	406	46254	310	40940	96	5314	308	35900

Source: Study CT-P39 3.1
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**Exposure to reference product during Treatment Period I (12 weeks) in the switching arm is included in this column.
Person time (days) = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The important exclusion criteria from the pivotal clinical study, CT-P39 3.1, are presented below.

History of clinically significant allergic reaction and/or hypersensitivity to any component of omalizumab (including history of anaphylactic shock), Chinese hamster ovary cell products, other recombinant human or humanised antibodies, H_1-antihistamines, or dry natural rubber (a derivative of latex).

Reason for exclusion: Local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab. Patients with significant allergic reactions or anaphylactic reactions to any component of the medicinal products were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: Hypersensitivity to omalizumab (or any component of the excipients) is an identified risk and has adequately been described in the product information (Section 4.3 'Contraindication' and Section 4.4 'Special warnings and precautions for use').

Patient with history of and/or concomitant myocardial infarction.

Reason for exclusion: Patients with history of and/or concomitant myocardial infarction were excluded for safety reasons taking a conservative approach, as there were historical data of numerical increase of cardiovascular disease incidence in patients treated omalizumab.

Is it considered to be included as missing information?: No

Rationale: A numerical imbalance of Arterial thromboembolic events (ATE) was observed during studies conducted with reference product Xolair, which included myocardial infarction. ATE is considered as an important potential risk for omalizumab treatment.

Patient who has a chronic urticaria with clearly defined underlying aetiology (e.g., physical urticaria such as acute, solar, cholinergic, heat, cold, aquagenic, pressure or contact) other than CSU or any disease with symptoms of urticaria or angioedema (e.g., urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukaemia or generalised cancer)

Reason for exclusion: The reference product Xolair was approved to use in the patients with CSU whose aetiology is unknown. Hence, the patients with the above-mentioned diseases other than CSU were excluded as they are not the target of study, and they may complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: Omalizumab is not indicated in these conditions.

Any active skin disease associated with itch including atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, or senile pruritus.

Reason for exclusion: The patients with these diseases were excluded due to the fact that inclusion of these patients may complicate the interpretation of the efficacy endpoints. The primary efficacy endpoint in this study is the effect on itch score at week 12.

Is it considered to be included as missing information?: No

Rationale: Omalizumab is not indicated in these conditions.

Any active malignancy or history of malignancy except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma in situ.

Reason for exclusion: Patients with active malignancy or history of malignancy were excluded for safety reasons as such patients are prone to frequent hospitalisation, hence higher dropout rates.

Is it considered to be included as missing information?: No

Rationale: Malignant neoplasms in adults and adolescents ≥12 years of age and Malignant neoplasms (children 6 to less than 12 years old) are important potential risks of omalizumab treatment based on the safety profile of the reference product, Xolair. For the reference product Xolair, the potential risk was based on an imbalance in numbers of malignancy observed within all the studies. Many of the malignancies occurred in uncontrolled studies. However, based on the further data analysis, neither pooled clinical trial analysis nor the EXCELS study (which provides a long-term assessment of malignancy risk with Xolair) support a relationship between omalizumab treatment and malignancy risk.

Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed, or male patient who is planning to father a child or donate sperm during study period.

Reason for exclusion: To minimise risk to pregnant women and nursing mothers and their children.

Is it considered to be included as missing information?: No

Rationale: Based on the data from the EXPECT study (registry) for Xolair, the risk to pregnant women or nursing mothers and their offspring is adequately characterised; no safety risks were detected to the newborn and mother compared with a disease matched cohort.

History of and/or concomitant immune complex disease (including allergic reaction type III), hyperimmunoglobulin E syndrome, autoimmune disease, or bronchopulmonary aspergillosis.

Reason for exclusion: Patients with the above-mentioned diseases were excluded because the results may complicate interpretation of efficacy study endpoints and safety evaluation. Moreover, these safety concerns may lead to high dropout rates.

Is it considered to be included as missing information?: No

Rationale: Omalizumab has not been studied in patients with autoimmune diseases, immune complex-mediated conditions (including hyperimmunoglobulin E syndrome or allergic bronchopulmonary aspergillosis) or for the prevention of anaphylactic reactions, including those provoked by food allergy, atopic dermatitis, or allergic rhinitis. Omalizumab is not indicated for the treatment of these conditions. However, serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have been observed in patients treated with humanised

monoclonal antibodies including omalizumab. This has adequately been described in the product information (Section 4.4 'Special warnings and precautions for use' and Section 4.8 'Undesirable effects').

A known infection with human immunodeficiency virus , hepatitis B, hepatitis C, or any active infection requiring treatment, except adequately treated and completely recovered past infections.

Reason for exclusion: May confound interpretation of safety evaluation. Moreover, chronic infectious disease may lead to high dropout rates.

Is it considered to be included as missing information?: No

Rationale: Patients with above mentioned conditions were excluded to prevent interference with safety study endpoints.

Patients diagnosed with parasitic diseases or colonisation on stool evaluation for ova and parasites.

Reason for exclusion: These patients were excluded to minimise risk to subjects with helminth infestation, as IgE is involved in the immunological response to helminthic and other intestinal parasitic infestations.

Is it considered to be included as missing information?: No

Rationale: Omalizumab may interfere with the immunological response to intestinal parasitic infestations. The concern has adequately been described in the product information (Section 4.4 'Special warnings and precautions for use' and Section 4.5 'Interaction with other medicinal products and other forms of interaction').

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 rare adverse reactions, or adverse reactions with a long latency or those caused by prolonged or cumulative exposure.

CT-P39 has been studied in patients with CSU. In total, 127 healthy volunteers (62 subjects in study CT-P39 1.1 and 65 subjects in study CT-P39 1.2) and 406 patients with CSU (study CT-P39 3.1) have been treated with CT-P39 in the clinical development programme. The median and maximum treatment duration for patients treated with CT-P39 was 20.1 and 22 weeks respectively (see Table 3).

In addition to CSU, the reference product Xolair is approved for the treatment of Allergic Asthma (AA) in adults and adolescents (12 years of age and older) and children (6 to <12 years of age); and is indicated as add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Paediatric patients	Children less than 12 years of age were not included in the clinical development programme of CT-P39. However, two (2) male and five (5) female patients with the age group of 12-17 years received CT-P39 during the study CT-P39 3.1 (see Table 5).
Elderly patients	Overall, six (6) male and twenty (20) female patients aged ≥ 65 years received CT-P39 in the study CT-P39 3.1 (see Table 5). There are limited data available on the use of omalizumab in patients older than 65 years but there is no evidence that elderly patients have a safety or efficacy profile that differs from younger adult patients.
Pregnant or Breastfeeding women	Pregnant or breastfeeding women were not included in the clinical development programme of CT-P39. There were no confirmed cases of pregnancy in the three studies, CT-P39 3.1, CT-P39 1.1, and CT-P39 1.2. No evaluation of use in pregnancy and lactation was performed for CT-P39. There are no adequate and well-controlled studies of omalizumab in pregnant women. IgG1 molecules are known to cross the placental barrier. Because animal reproduction studies are not always predictive of human response, all patients with childbearing potential were excluded from pivotal trials to avoid foetal harm in pregnant women and to avoid potentially serious developmental adverse effects in newborns. While omalizumab presence in human milk has not been studied, IgG is known to be excreted in human milk and therefore it is expected that omalizumab will be present in human milk. The potential for omalizumab absorption or harm to the infant are unknown. However, given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breast-fed newborns/infants are anticipated. Since Omlyclo is a biosimilar, based on the safety profile of the reference medicinal product Xolair, caution should be exercised when administering omalizumab to a pregnant or a nursing woman.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Patients with hepatic impairment were not studied in the clinical development programme. Omalizumab clearance at clinical doses is predominantly through the reticular endothelial system; it is unlikely to be altered by hepatic impairment. Since Omlyclo is a biosimilar, based on the safety profile of the reference medicinal product Xolair, no dose

Type of special population	Exposure
	adjustment is recommended, however, omalizumab should be administered with caution in these patients.
Patients with renal impairment	Patients with renal impairment were not studied in the clinical development programme. Omalizumab clearance at clinical doses is predominantly through the reticular endothelial system; it is unlikely to be altered by renal impairment. Since Omlyclo is a biosimilar, based on the safety profile of the reference medicinal product Xolair, no dose adjustment is recommended, however, omalizumab should be administered with caution in these patients.
Patients with cardiovascular impairment	Patients with cardiovascular impairment were not studied in the clinical development programme of CT-P39.
Immunocompromised patients	Immunocompromised patients were not studied in the clinical development programme of CT-P39.
Patients with a disease severity different from inclusion criteria in clinical trials	Eight (8) subjects with a severity less than as required by the protocol were included in the study in violation of the protocol.
Population with relevant different ethnic origin	Majority of patients in the clinical trial programme who received CT-P39 were of Caucasian (White) origin (326 patients), followed by Asians (80 patients) (see Table 6). Ethnic origin is not known to be relevant to the response to treatment with omalizumab.
Subpopulations carrying relevant genetic polymorphisms	There are no known relevant genetic polymorphisms.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable as the product has not been sold yet in any jurisdiction.

SV.1.1 Method used to calculate exposure

Not applicable.

SV.1.2 Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the mechanism of action of Omlyclo and its indications, the potential for misuse or abuse for illegal purposes is negligible.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

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

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

1. **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):**

   None.

2. **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:**

   None.

3. **Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):**

   In accordance with the EU requirements, Omlyclo has been shown to have comparable quality, safety and efficacy to the reference product Xolair. The safety profile of Omlyclo is similar to the reference product and has been adequately described in the product information.

   The following risks are labelled in the product information for the reference product and are not important safety concerns for either Xolair or Omlyclo:

   Abdominal pain upper, Allergic bronchospasm, Alopecia, Angioedema, Anti-omalizumab antibody development, Arthralgia, Coughing, Diarrhoea, Dizziness, Dyspeptic signs and symptoms, Fatigue, Flushing, Headache, Idiopathic thrombocytopenia (including severe cases), Influenza-like illness, Injection site reactions (such as swelling, erythema, pain, pruritus), Joint swelling, Laryngoedema, Myalgia, Nausea, Other serious allergic conditions, Paraesthesia, Parasitic infection, Pharyngitis, Photosensitivity, Postural hypotension, Pruritus, Pyrexia, Rash, Serum sickness (may include fever and lymphadenopathy), Sinusitis, Somnolence, Swelling arms, Syncope, Systemic lupus erythematosus (SLE), Upper respiratory tract infection, Urticaria, Weight increase.

4. **Known risks that do not impact the risk-benefit profile:**

   None.

5. **Other reasons for considering the risks not important:**

   None.

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

Important identified risk: Anaphylaxis/anaphylactoid reactions

Risk-benefit impact:

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, even after a long duration of treatment. However, most of these reactions occurred within 2 hours after the first and subsequent injections of omalizumab but some may start beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of the reference product, Xolair. Therefore, the first 3 doses must be administered either by, or under the supervision of, a healthcare professional. A history of anaphylaxis unrelated to omalizumab may be a risk factor for anaphylaxis following omalizumab administration. Therefore, for patients with a known history of anaphylaxis, Omlyclo must be administered by a health care professional, who should always have medicinal products for the treatment of anaphylactic reactions available for immediate use following administration of Omlyclo. If an anaphylactic or other serious allergic reaction occurs, administration of Omlyclo must be discontinued immediately, and appropriate therapy initiated. Patients should be informed that such reactions are possible, and prompt medical attention should be sought if allergic reactions occur. According to the Summary of Product Characteristics (SmPC) of the reference product Xolair and Omlyclo, the frequency of anaphylactic reaction, other serious allergic conditions and anti-omalizumab antibody development are categorised as ‘Rare’. Omlyclo is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients. The benefits of an effective treatment with Omlyclo outweigh the risk of Anaphylaxis/anaphylactoid reactions.

Important identified risk: Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)

Risk-benefit impact:

Patients with severe asthma may rarely present systemic HES or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome), both of which are usually treated with systemic corticosteroids.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy. In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy.

Discontinuation of omalizumab should be considered in all severe cases with the above-mentioned immune system disorders.

According to the SmPC of the reference product Xolair and Omlyclo, the frequency of CSS is categorised as ‘Not known’. The benefits of an effective treatment with Omlyclo outweigh the risk of CSS.

Important potential risk: Arterial Thromboembolic Events (ATEs)

Risk-benefit impact:

ATE was identified as an important potential risk for the reference product Xolair, based on a numerical imbalance observed from an interim report of the EXCELS study (primary population = controlled trials data set) for adults. In addition, an externally adjudicated, pooled analysis of all randomised, double-blind, placebo-controlled (RDBPC) trials was conducted to better quantify and qualify the risk. ATEs have also been observed in post-marketing setting with the reference product Xolair.

In the EXCELS study, despite adjustment for measured confounding factors, a numerical imbalance in ATE rates was observed. Although there was no consistent evidence of an association between omalizumab use and risk of ATEs, the confidence intervals (CIs) were wide and could not definitively exclude an elevated risk. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% CI 0.91 to 1.91). In the pooled analysis of RDBPC trials, the rates of ATE were similar between the omalizumab and placebo groups. The 95% confidence intervals for risk of ATE include 1.0, i.e. no difference in risk of ATEs in patients treated with omalizumab when compared to placebo (Iribarren et al 2017).

This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with the reference product Xolair. The benefits of an effective treatment with Omlyclo outweigh the apparent risk of ATE.

Important potential risk: Malignant neoplasms in adults and adolescents ≥12 years of age and children 6 to less than 12 years old

Risk-benefit impact:

There was a signal comprising a numerical imbalance in cases of cancers in the pooled safety data set for the reference product Xolair at the time of marketing authorisation application in 2003. Subsequently, in 2012, the final EXCELS study report became available. In addition, an externally adjudicated, pooled analysis of all RDBPC trials was conducted. The incidence of malignancy in patients with asthma from a meta-analysis of 16 case-control and cohort clinical studies found a pooled incidence ratio for cancer incidence in asthma from 1.03 (95% CI: 0.93, 1.14), with a range from 0.90, 1.27 (Tennis et al 2005). Neither the pooled clinical trial analysis nor the EXCELS study supported a relationship between omalizumab treatment and malignancy risk. The cumulative evidence shows there to be little, if any, excess risk of malignancies attributable to omalizumab. The 95% confidence intervals for risk of malignancy include 1.0, i.e. no difference in risk of malignancies in patients treated with omalizumab when compared to placebo (Long et al 2014).

Therefore, the benefits of an effective treatment with Omlyclo outweigh the apparent risk of malignant neoplasms.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable as this is an initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

Since Omlyclo is a biosimilar, all risks have been included based on the safety profile of the reference medicinal product Xolair, for all three indications, Allergic Asthma (AA), Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) and Chronic spontaneous urticaria (CSU).

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

Important identified risk: Anaphylaxis/anaphylactoid reactions

Medical Dictionary for Regulatory Activities (MedDRA) terms:

Anaphylactic reaction (SMQ narrow), Anaphylactic/anaphylactoid shock conditions (SMQ narrow)

Potential mechanisms:

As an immunoglobulin, omalizumab is a protein, and so hypersensitivity reactions, particularly immediate-type events such as anaphylactic/anaphylactoid reactions, urticaria and other skin rashes may occur due to direct or indirect effects on mast cells or basophils.

Evidence source(s) and strength of evidence:

Anaphylactic and anaphylactoid reactions were rare in the clinical development programmes of Omlyclo and the reference product Xolair. Urticaria and other skin rashes occurred at similar rates in the placebo and omalizumab groups.

Anaphylaxis is a serious allergic reaction that can happen after receiving omalizumab. It can cause symptoms such as swelling of the throat or tongue, difficulty breathing, low blood pressure, fainting, and hives. Studies show that people with asthma who have anaphylaxis from omalizumab are more likely to have severe outcomes compared to those with chronic urticaria. A study using omalizumab data from the US Food and Drug Administration Adverse Event Reporting System database from January 2004 to September 2020 showed an anaphylaxis incidence of less than 0.1% in 3854 subjects. Post-marketing surveillance data from the Food and Drug Administration (FDA) showed that the frequency of anaphylaxis was more than 0.2% in patients receiving omalizumab (Li et al 2021). Based on the literature report and the safety profile of the reference product Xolair, the strength of the evidence is considered good.

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			**Omalizumab reference product** (N=308)**
	Total (N=406)	**CT-P39 only (N=310)**	**Switched from Omalizumab reference product* (N=96)**	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.3%)
N of Patients with TEAEs per 100 PY	0.000	0.000	0.000	1.017

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
95% CI for N of Patients with TEAEs per 100 PY	(0.000, 2.913)	(0.000, 3.291)	(0.000, 25.355)	(0.026, 5.669)

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
Patient Year = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 25.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.3%)
95% CI for proportion of patients with TEAEs	(0.00, 0.90)	(0.00, 1.18)	(0.00, 3.77)	(0.01, 1.80)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1 (0.3%)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	0
Non-serious	0	0	0	1 (0.3%)
Outcome [4]				
Missing	0	0	0	0
Recovered	0	0	0	1 (0.3%)
Recovering	0	0	0	0
Did not recover	0	0	0	0

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Fatal	0	0	0	0

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcome: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

There were no TEAEs related to anaphylaxis/anaphylactoid reactions in the CT-P39 and the switched from reference product groups. The CT-P39 only group, the switched from reference product group, and the reference product group, had 0, 0, and 1 TEAEs, respectively. The number of patients with TEAEs per 100 patient-years was 0.000 in the CT-P39 and the switched from reference product group, and 1.017 in the reference product group with a 95% confidence interval for the incidence rate as (0.026, 5.669).

One TEAE related to anaphylaxis/anaphylactoid reactions in the reference product group was categorised as a non-serious event, with severity grade of 2. The event was reported as "recovered" at the end of the trial period. The 95% confidence interval for the proportion of patients with TEAEs in the reference product group was (0.01, 1.80).

Risk factors and risk groups:

Subjects with history of hypersensitivity and allergic reactions to omalizumab, or to any of the excipients or to any component of the medicinal product may be at increased risk. Additionally, a history of allergic reactions unrelated to omalizumab may be a risk factor for anaphylaxis including genetic tendency to develop allergic diseases such as allergic rhinitis, asthma, eczema and food allergies.

Preventability:

Local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, even after a long duration of treatment. According to the product information of the reference product Xolair, most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. The majority of anaphylactic reactions occurred within the first 3 doses of Xolair. Therefore, the first 3 doses must be administered either by, or under the supervision of, a healthcare professional. For patients with a known history of anaphylaxis, omalizumab must be administered by a healthcare professional, who should be equipped to treat anaphylactic reactions

during administration of omalizumab. If an anaphylactic or other serious allergic reaction occurs, administration of omalizumab must be discontinued immediately, and appropriate therapy initiated.

Impact on the risk-benefit balance of the product:

Anaphylactic and anaphylactoid reactions were rare in the clinical development programs of Omlyclo and the reference product Xolair. Although rare, anaphylaxis can be life threatening and requiring emergency care. This safety concern has a high impact on the benefit-risk balance of omalizumab for the affected individual. The benefit-risk balance is favourable for omalizumab for the treatment of AA, CRSwNP and CSU.

Public health impact:

The impact on public health would be expected to be minimal because serious or severe anaphylactic reactions with omalizumab are rare.

Important identified risk: Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)

MedDRA terms:

Eosinophilic disorders (HLT); Vascular infections and inflammations (HLGT)

Potential mechanisms:

Unknown

Evidence source(s) and strength of evidence:

CSS, also called Eosinophilic Granulomatosis with Polyangiitis (EGPA), is a rare disease. It is a disorder marked by blood vessel inflammation. This inflammation can restrict blood flow to organs and tissues, sometimes permanently damaging them.

It has been reported in literature that there is an increased risk of EGPA onset among asthmatic patients treated with omalizumab, probably related to steroid reduction (Basta et al 2020).

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			**Omalizumab reference product** (N=308)**
	Total (N=406)	**CT-P39 only (N=310)**	**Switched from Omalizumab reference product* (N=96)**	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.3%)
N of Patients with TEAEs per 100 PY	0.000	0.000	0.000	1.017

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
95% CI for N of Patients with TEAEs per 100 PY	(0.000, 2.913)	(0.000, 3.291)	(0.000, 25.355)	(0.026, 5.669)

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
Patient Year = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 25.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Total N of TEAEs	0	0	0	1
N of Patients with TEAEs [1]	0	0	0	1 (0.3%)
95% CI for proportion of patients with TEAEs	(0.00, 0.90)	(0.00, 1.18)	(0.00, 3.77)	(0.01, 1.80)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	0
Grade 3	0	0	0	1 (0.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	1 (0.3%)
Non-serious	0	0	0	0
Outcome [4]				
Missing	0	0	0	0
Recovered	0	0	0	0

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Recovering	0	0	0	1 (0.3%)
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcome: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

There were no TEAEs related to CSS/HES in the CT-P39 and the switched from reference product groups. The CT-P39 only group, the switched from reference product group, and the reference product group, had 0, 0, and 1 TEAEs, respectively. The number of patients with TEAEs per 100 patient-years was 0.000 in the CT-P39 only and the switched from reference product group, and 1.017 in the reference product group with a 95% confidence interval for the incidence rate as (0.026, 5.669).

One TEAE related to CSS/HES in the reference product group was categorised as a serious event, with severity grade of 3. The event was reported as "recovering" at the end of the trial period. The 95% confidence interval for the proportion of patients with TEAEs in the reference product group was (0.01, 1.80).

Risk factors and risk groups:

Everyone who gets EGPA has a history of asthma and/or allergies (e.g. allergic rhinitis, nasal polyps). Potential risk factors may also include: Drug sensitivities to penicillin, penicillamine, iodides, leukotriene modifiers or mesalazine. Environmental exposure to inhaled allergens such as silica dust (Izquierdo-Domínguez A et al 2016).

Preventability:

There are no known ways to prevent this disease.

Impact on the risk-benefit balance of the product:

This safety concern has a low impact on the benefit-risk balance of omalizumab based on low incidence, and mostly non-severe cases.

Public health impact:

Based on incidences in the Celltrion sponsored clinical trials and the product information of the reference product Xolair, the potential for significant public health impact is very low.

Important potential risk: Arterial Thromboembolic Events (ATEs)

MedDRA terms:

Haemorrhagic central nervous system vascular conditions(SMQ), Ischaemic central nervous system vascular conditions (SMQ), Myocardial infarction (SMQ broad), Other ischaemic heart disease (SMQ broad), Cardiac death (PT), Hemiparesis (PT), Hemiplegia (PT), Sudden cardiac death (PT), Sudden death (PT)

Potential mechanisms:

No potential mechanism was identified.

Evidence source(s) and strength of evidence:

Arterial thrombosis is a blood clot in an artery, which can be very serious because it can stop blood reaching important organs such as heart and brain. A post-marketing observational study EXCELS was conducted with the reference product Xolair to assess the long-term safety (followed up for less than 5 years) of omalizumab and to examine a potential association between omalizumab and the side effects related to heart/brain and blood vessels ((cardiovascular (CV)) / cerebrovascular (CBV) respectively). Analyses included focus on the subset of arterial thromboembolic events (ATEs), comprising death due to blood clot related blockage of blood vessels, heart attack, a stroke, a transient ischaemic attack (TIA) or "mini-stroke", and chest discomfort caused by poor blood flow through the blood vessels of the heart muscle. This observational study demonstrated a higher incidence rate of CV/CBV events in the omalizumab versus the non-omalizumab treated patients, which showed no statistically significant difference (Iribarren et al 2017).

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			**Omalizumab reference product** (N=308)**
	Total (N=406)	**CT-P39 only (N=310)**	**Switched from Omalizumab reference product* (N=96)**	
Total N of TEAEs	4	3	1	1
N of Patients with TEAEs [1]	4 (1.0%)	3 (1.0%)	1 (1.0%)	1 (0.3%)
N of Patients with TEAEs per 100 PY	3.159	2.676	6.873	1.017

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
95% CI for N of Patients with TEAEs per 100 PY	(0.861, 8.087)	(0.552, 7.822)	(0.174, 38.296)	(0.026, 5.669)

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
Patient Year = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences. From the MedDRA dictionary, version 25.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Total N of TEAEs	4	3	1	1
N of Patients with TEAEs [1]	4 (1.0%)	3 (1.0%)	1 (1.0%)	1 (0.3%)
95% CI for proportion of patients with TEAEs	(0.27, 2.50)	(0.20, 2.80)	(0.03, 5.67)	(0.01, 1.80)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	1 (0.3%)
Grade 2	0	0	0	0
Grade 3	3 (0.7%)	2 (0.6%)	1 (1.0%)	0
Grade 4	1 (0.2%)	1 (0.3%)	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	1 (0.2%)	1 (0.3%)	0	0
Non-serious	3 (0.7%)	2 (0.6%)	1 (1.0%)	1 (0.3%)
Outcome [4]				
Missing	0	0	0	0
Recovered	4 (1.0%)	3 (1.0%)	1 (1.0%)	1 (0.3%)

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcome: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

Overall, there were five (5) TEAEs related to ATEs; three (3) in the CT-P39 only group, one (1) in the switched from reference product group, and one (1) in the reference product group. The number of patients with TEAEs per 100 patient-years in CT-P39 group was 2.676 (95% CI: 0.552, 7.822), in the switched from reference product group was 6.873 (95% CI: 0.174, 38.296), and in the reference product group was 1.017 (95% CI: 0.026, 5.669).

Of the five TEAEs related to ATEs, one event in the CT-P39 only group was categorised as a serious event. The remaining four events were non-serious, with two occurring in the CT-P39 only group, and one in the switched from reference product group, and one in the reference product group.
The severity of the TEAEs was graded on a scale of 1 to 5, with Grade 1 being the mildest and Grade 5 being the most severe. There were no Grade 2 events reported, and one Grade 1 event was reported in the reference product group. Of the three events from CT-P39 only group, two events were Grade 3 and one event was Grade 4. The remaining one event was reported in the switched from reference product group and was a Grade 3 event.

All five TEAEs related to ATEs were reported as “recovered” at the end of the trial period. The 95% confidence interval for the proportion of patients with TEAEs in the CT-P39 only group was (0.20, 2.80), in the switched from reference product group was (0.03, 5.67), and in the reference product group was (0.01, 1.80).

Risk factors and risk groups:

Risk factors for arterial thrombosis may include: Smoking; Diabetes; High blood pressure; High cholesterol; Lack of activity and obesity; Poor diet; Family history of arterial thrombosis; Lack of movement, such as after surgery or on a long trip; Older age.

Preventability:

The risk of thrombosis may be reduced by: Being active; Getting back to activity as soon as possible after surgery; Quitting smoking; Losing weight; Managing other health problems such as diabetes, high blood pressure, and high cholesterol.

Impact on the risk-benefit balance of the product:

This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with omalizumab.

Public health impact:

Based on incidences in the Celltrion sponsored clinical trials and the EU RMP of the reference product Xolair, the potential for significant public health impact is very low.

Important potential risk: Malignant neoplasms in adults and adolescents ≥12 years of age

MedDRA terms:

Malignancies (SMQ broad)

Potential mechanisms:

No potential mechanism identified.

Evidence source(s) and strength of evidence:

A prospective observational study of Xolair (omalizumab) was conducted to evaluate clinical effectiveness and long-term safety in patients (≥12 years of age) with moderate-to-severe asthma (EXCELS). The study included patients at high risk of cancers (smokers and family history of cancer) and patients with a history of malignancy. Primary outcome measures focused on assessment of malignancies. Results from the study suggested that omalizumab therapy is not associated with an increased risk of malignancy (Long et al 2014).

Characterisation of the risk:

Frequency with 95 % Confidence Interval (CI) for 100 PY:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			**Omalizumab reference product** (N=308)**
	Total (N=406)	**CT-P39 only (N=310)**	**Switched from Omalizumab reference product* (N=96)**	
Total N of TEAEs	0	0	0	2
N of Patients with TEAEs [1]	0	0	0	2 (0.6%)
N of Patients with TEAEs per 100 PY	0.000	0.000	0.000	2.035

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
95% CI for N of Patients with TEAEs per 100 PY	(0.000, 2.913)	(0.000, 3.291)	(0.000, 25.355)	(0.246, 7.350)

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
Patient Year = ([Date of Last Exposure to Treatment] – [Date of First Exposure to Treatment] + 1) / 365.25 or
([Date of Last Exposure to Treatment] – [Date of First Exposure of Switch] + 1) /365.25 or
([Date of First Exposure of Switch – 1] – [Date of First Exposure to Treatment] + 1) / 365.25
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
From the MedDRA dictionary, version 25.1.

Frequency with Severity, Seriousness and Outcome:

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Total N of TEAEs	0	0	0	2
N of Patients with TEAEs [1]	0	0	0	2 (0.6%)
95% CI for proportion of patients with TEAEs	(0.00, 0.90)	(0.00, 1.18)	(0.00, 3.77)	(0.08, 2.33)
Severity/Nature of risk [2]				
Missing	0	0	0	0
Grade 1	0	0	0	0
Grade 2	0	0	0	1 (0.3%)
Grade 3	0	0	0	1 (0.3%)
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Seriousness [3]				
Serious	0	0	0	2 (0.6%)
Non-serious	0	0	0	0
Outcome [4]				
Missing	0	0	0	0
Recovered	0	0	0	2 (0.6%)

INDICATION: Chronic Spontaneous Urticaria (CT-P39 3.1)				
	CT-P39			Omalizumab reference product** (N=308)
	Total (N=406)	CT-P39 only (N=310)	Switched from Omalizumab reference product* (N=96)	
Recovering	0	0	0	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

Source: Study CT-P39 3.1
Abbreviations: CI = Confidence Interval; MedDRA = Medical Dictionary for Regulatory Activities; N = Number; TEAE = Treatment Emergent Adverse Events.
*Patients assigned to the switching arm switched from reference product to CT-P39 after completion of Treatment Period I (12 weeks).
**TEAEs occurred during Treatment Period I (12 weeks) in the switching arm is included in this column.
[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or occurrences.
[2] Only the most severe event is counted: Severity: Grade 5 > Grade 4 > Grade 3 > Grade 2 > Grade 1 > Missing
[3] Only the most serious event is counted: Seriousness: Serious > Non-serious
[4] Only the most severe outcome is counted: Outcome: Fatal > Did not recover > Recovering > Recovered > Missing
From the MedDRA dictionary, version 25.1.

There were no TEAEs related to malignant neoplasms in adults and adolescents ≥12 years of age in the CT-P39 only and the switched from reference product groups. The CT-P39 only group, the switched from reference product group, and the reference product group, had 0, 0, and 2 (0.6%) TEAEs, respectively. The number of patients with TEAEs per 100 patient-years was 0.000 in the CT-P39 only and the switched from reference product group, and 2.035 in the reference product group with a 95% confidence interval for the incidence rate as (0.246, 7.350).

The severity of two TEAEs reported in the reference product group was Grade 2 and Grade 3. In terms of seriousness, the two TEAEs related to malignant neoplasms in the reference product group were considered serious. The events were reported as "recovered" at the end of the trial period. The 95% confidence interval for the proportion of patients with TEAEs in the reference product group was (0.08, 2.33).

Risk factors and risk groups:

An association between omalizumab and malignancy has not been established. The same risk factors for malignancy apply to patients treated with omalizumab, as apply to the general population.

Preventability:

An association between omalizumab and malignancy has not been established; therefore, there are no known preventive measures. The same behavioral and other general activities that are known to reduce the risk of malignancy apply to patients treated with omalizumab, as apply to the general population.

Impact on the risk-benefit balance of the product:

This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with omalizumab.

Public health impact:

Based on incidences in the Celltrion sponsored clinical trials and the product information of the reference product Xolair, the potential for significant public health impact is very low.

Important potential risk: Malignant neoplasms (children 6 to less than 12 years old)

MedDRA terms:

Malignancies (SMQ broad)

Potential mechanisms:

No potential mechanism identified.

Evidence source(s) and strength of evidence:

There are no data in literature to support any link between anti-IgE therapy such as omalizumab and malignancy risk (Johnston et al 2019). No cases of malignancy have been reported in clinical trials involving omalizumab for children of ages 6 to 12 years old (Yu et al 2021).

Characterisation of the risk:

There are no data for the important potential risk of malignant neoplasms (children 6 to less than 12 years old) because children less than 12 years old were not included in the study CT-P39 3.1.

Risk factors and risk groups:

An association between omalizumab and malignancy has not been established. The same risk factors for malignancy apply to patients treated with omalizumab, as apply to the general population.

Preventability:

An association between omalizumab and malignancy has not been established; therefore, there are no known preventive measures. The same behavioral and other general activities that are known to reduce the risk of malignancy apply to patients treated with omalizumab, as apply to the general population.

Impact on the risk-benefit balance of the product:

This safety concern has a low impact on the benefit-risk balance of omalizumab considering no causal association has been established with omalizumab.

Public health impact:

Based on incidences in the Celltrion sponsored clinical trials and the product information of the reference product Xolair, the potential for significant public health impact is very low.

SVII.3.2 Presentation of the missing information

There is no missing information available for inclusion in the list of safety concerns in the RMP.

Part II: Module SVIII - Summary of the safety concerns

Table 8: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Anaphylaxis/anaphylactoid reactions • Churg Strauss Syndrome (CSS)/Hypereosinophilic Syndrome (HES)
Important potential risks	• Arterial Thromboembolic Events (ATEs) • Malignant neoplasms in adults and adolescents ≥12 years of age • Malignant neoplasms (children 6 to less than 12 years old)
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Specific AE follow-up checklists will be used to collect further data to help further characterise and/or closely monitor each of the respective safety concerns specified below. Targeted follow-ups with specific checklist are applicable only for serious adverse events for the following risks:

- Anaphylaxis/anaphylactoid reactions
- Arterial Thromboembolic Events (ATEs)
- Malignant neoplasms in adults and adolescents ≥12 years of age and Malignant neoplasms (children 6 to less than 12 years old)

Other forms of routine pharmacovigilance activities:

None.

III.2 Additional pharmacovigilance activities

Not applicable as there are no additional pharmacovigilance activities planned for Omlyclo.

III.3 Summary Table of additional Pharmacovigilance activities

Table 9: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
None				

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable, since there are no post authorisation efficacy studies planned for Omlyclo.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Anaphylaxis/anaphylactoid reactions (Important identified risk)	Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8. PL sections - 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendations for monitoring and managing anaphylaxis, training, and selecting appropriate patient for home use to lower the risk for anaphylaxis are included in SmPC sections 4.2 and 4.4. • Guidance is given in PL section 2 for patients to recognise early symptoms of severe allergic reactions including anaphylaxis and how to manage this risk. Other routine risk minimisation measures beyond the Product Information: *Legal status:* Restricted medical prescription (Prescription only medicine).
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES) (Important identified risk)	Routine risk communication: SmPC sections 4.4 and 4.8. PL sections - 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance for physicians to monitor sign and symptoms related to CSS and HES, and how to manage this risk, is given in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Arterial Thromboembolic Events (ATEs) (Important potential risk)	Routine risk communication: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Malignant neoplasms in adults and adolescents ≥	Routine risk communication: None

Safety concern	Routine risk minimisation activities
12 years of age (Important potential risk)	Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).
Malignant neoplasms (children 6 to less than 12 years old) (Important potential risk)	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: *Legal status*: Restricted medical prescription (Prescription only medicine).

V.2 Additional Risk Minimisation Measures

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

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anaphylaxis/anaphylactoid reactions (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.3 and 4.8* • *SmPC sections 4.2 and 4.4 where recommendations for monitoring and managing anaphylaxis, training, and selecting appropriate patient for home use to lower the risk for anaphylaxis are included.* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES) (Important identified risk)	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where guidance for physicians is given to monitor sign and symptoms related to CSS and HES, and how to manage this risk.* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Arterial Thromboembolic Events (ATEs) (Important potential risk)	Routine risk minimisation measures: • *SmPC section 4.8* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None
Malignant neoplasms in adults and adolescents ≥ 12 years of age (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None
Malignant neoplasms (children 6 to less than 12 years old) (Important potential risk)	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire. Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Omlyclo (omalizumab biosimilar)

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

Omlyclo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Omlyclo should be used.

This summary of the RMP for Omlyclo 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 Omlyclo's RMP.

I. The medicine and what it is used for

Omlyclo is authorised for IgE (immunoglobulin E) mediated Allergic asthma (AA) in adults and adolescents (12 years of age and older) and children (6 to <12 years of age). It is also authorised as an add-on therapy with intranasal corticosteroids (INC) for the treatment of adults (18 years and above) with severe Chronic rhinosinusitis with nasal polyps (CRSwNP) for whom therapy with INC does not provide adequate disease control; and as an add-on therapy for the treatment of Chronic spontaneous urticaria (CSU) in adult and adolescent (12 years and above) with inadequate response to H_1 antihistamine treatment (see SmPC of Omlyclo for the full indication).

It contains omalizumab as the active substance and it is given as subcutaneous injection every 2 or every 4 weeks for AA and CRSwNP (75 mg to 600 mg according to body weight and baseline IgE levels), and every 4 weeks for CSU (300 mg).

Further information about the evaluation of Omlyclo's benefits can be found in Omlyclo's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage *https://www.ema.europa.eu/en/medicines/human/EPAR/omlyclo*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Omlyclo, together with measures to minimise such risks and the proposed studies for learning more about Omlyclo's risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised 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 (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Omlyclo are risks that need special risk management activities to further investigate or minimise 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 Omlyclo. 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 (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Anaphylaxis/anaphylactoid reactions Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)
Important potential risks	Arterial Thromboembolic Events (ATEs) Malignant neoplasms in adults and adolescents ≥ 12 years of age Malignant neoplasms (children 6 to less than 12 years old)
Missing information	None

II.B Summary of important risks

Important identified risk: Anaphylaxis/anaphylactoid reactions	
Evidence for linking the risk to medicine	Anaphylactic and anaphylactoid reactions were rare in the clinical development programmes of Omlyclo and the reference product Xolair. Urticaria and other skin rashes occurred at similar rates in the placebo and omalizumab groups. Anaphylaxis is a serious allergic reaction that can happen after receiving omalizumab. It can cause symptoms such as swelling of the throat or tongue, difficulty breathing, low blood pressure, fainting, and hives. Studies show that people with asthma who have anaphylaxis from omalizumab are more likely to have severe outcomes compared to those with chronic urticaria. A study using omalizumab data from the US Food and Drug Administration Adverse Event Reporting System database from January 2004 to September 2020 showed an anaphylaxis incidence of less than 0.1% in 3854 subjects. Post-marketing surveillance data from the Food and Drug Administration (FDA) showed that the frequency of anaphylaxis was more than 0.2% in patients receiving omalizumab (Li et al 2021[a]). Based on the literature report and the safety profile of the reference product Xolair, the strength of the evidence is considered good.

Risk factors and risk groups	Subjects with history of hypersensitivity and allergic reactions to omalizumab, or to any of the excipients or to any component of the medicinal product may be at increased risk. Additionally, a history of allergic reactions unrelated to omalizumab may be a risk factor for anaphylaxis including genetic tendency to develop allergic diseases such as allergic rhinitis, asthma, eczema and food allergies.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.3 and 4.8* • *SmPC sections 4.2 and 4.4 where recommendations for monitoring and managing anaphylaxis, training, and selecting appropriate patient for home use to lower the risk for anaphylaxis are included.* • *PL sections 2 and 4.* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important identified risk: Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)	
Evidence for linking the risk to medicine	CSS, also called Eosinophilic Granulomatosis with Polyangiitis (EGPA), is a rare disease. It is a disorder marked by blood vessel inflammation. This inflammation can restrict blood flow to organs and tissues, sometimes permanently damaging them. It has been reported in literature that there is an increased risk of EGPA onset among asthmatic patients treated with omalizumab, probably related to steroid reduction (Basta et al 2020[b]).
Risk factors and risk groups	Everyone who gets EGPA has a history of asthma and/or allergies (e.g. allergic rhinitis, nasal polyps). Potential risk factors may also include: Drug sensitivities to penicillin, penicillamine, iodides, leukotriene modifiers or mesalazine. Environmental exposure to inhaled allergens such as silica dust (Izquierdo-Domínguez A et al 2016[c]).
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.8* • *SmPC section 4.4 where guidance for physicians is given to monitor sign and symptoms related to CSS and HES, and how to manage this risk.* • *PL sections 2 and 4* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Arterial Thromboembolic Events (ATEs)	
Evidence for linking the risk to medicine	Arterial thrombosis is a blood clot in an artery, which can be very serious because it can stop blood reaching important organs such as heart and brain. A post-marketing observational study EXCELS was conducted with the reference product Xolair to assess the long-term safety (followed up for less than 5 years) of omalizumab and to examine a potential association between omalizumab and

	the side effects related to heart/brain and blood vessels ((cardiovascular (CV)) / cerebrovascular (CBV) respectively). Analyses included focus on the subset of arterial thromboembolic events (ATEs), comprising death due to blood clot related blockage of blood vessels, heart attack, a stroke, a transient ischaemic attack (TIA) or "mini-stroke", and chest discomfort caused by poor blood flow through the blood vessels of the heart muscle. This observational study demonstrated a higher incidence rate of CV/CBV events in the omalizumab versus the non-omalizumab treated patients, which showed no statistically significant difference(Iribarren et al 2017[d]).
Risk factors and risk groups	Risk factors for arterial thrombosis may include: Smoking; Diabetes; High blood pressure; High cholesterol; Lack of activity and obesity; Poor diet; Family history of arterial thrombosis; Lack of movement, such as after surgery or on a long trip; Older age.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.8.* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Malignant neoplasms in adults and adolescents ≥ 12 years of age	
Evidence for linking the risk to medicine	A prospective observational study of Xolair (omalizumab) was conducted to evaluate clinical effectiveness and long-term safety in patients (≥12 years of age) with moderate-to-severe asthma (EXCELS). The study included patients at high risk of cancers (smokers and family history of cancer) and patients with a history of malignancy. Primary outcome measures focused on assessment of malignancies. Results from the study suggested that omalizumab therapy is not associated with an increased risk of malignancy (Long et al 2014[e]).
Risk factors and risk groups	An association between omalizumab and malignancy has not been established. The same risk factors for malignancy apply to patients treated with omalizumab, as apply to the general population.
Risk minimisation measures	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None
Important potential risk: Malignant neoplasms (children 6 to less than 12 years old)	
Evidence for linking the risk to medicine	There are no data in literature to support any link between anti-IgE therapy such as omalizumab and malignancy risk (Johnston et al 2019[f]). No cases of malignancy have been reported in clinical trials involving omalizumab for children of ages 6 to 12 years old (Yu et al 2021[g]).
Risk factors and risk groups	An association between omalizumab and malignancy has not been established. The same risk factors for malignancy apply to patients treated with omalizumab, as apply to the general population.

Risk minimisation measures	Routine risk minimisation measures: *None* Legal status: Restricted medical prescription (Prescription only medicine). Additional risk minimisation measures: None

[a]Li L, Wang Z, Cui L, Xu Y, Guan K, et al. Anaphylactic risk related to omalizumab, benralizumab, reslizumab, mepolizumab, and dupilumab. Clin Transl Allergy 2021;3:11(4).

[b]Basta F, Mazzuca C, Nucera E, Schiavino D, Afeltra A, et al. Omalizumab in eosinophilic granulomatosis with polyangiitis: friend or foe? A systematic literature review. Clin Exp Rheumatol 2020;38 (Suppl. 124): S214-S220.

[c]Izquierdo-Domínguez A, Castillo AC, Alobid I, and Mullol J. Churg-Strauss Syndrome or Eosinophilic Granulomatosis with Polyangiitis. Sinusitis 2016; 1:24-43; doi:10.3390/sinusitis1010024.

[d]Iribarren C, Rahmaoui A, Long AA, Szefler SJ, Bradley MS, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study in moderate to severe asthma. J Allergy Clin Immunol 2017; 139(5):1489-1495.

[e]Long AA, Rahmaoui A, Rothman KJ, Guinan E, Eisner M, et al. Incidence of malignancy in patients with moderate-to severe asthma treated with or without omalizumab. J Allergy Clin Immunol 2014;134:560-7.

[f]Johnston A, Smith C, Zheng C, et al. Influence of prolonged treatment with omalizumab on the development of solid epithelial cancer in patients with atopic asthma and chronic idiopathic urticaria: a systematic review and meta-analysis. Clin Exp Allergy. 2019; 49(10):1291–1305.

[g]Yu L, Zhang H, Pan J, and Ye L. Pediatric usage of Omalizumab: A promising one. World Allergy Organ J. 2021;14(12):100614.

PL: Package Leaflet; SmPC: Summary of Product Characteristics

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Omlyclo.

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

There are no studies required for Omlyclo.

Part VII: Annexes

Table of contents

Annex 4 – Specific adverse drug reaction follow-up forms

The targeted follow-up forms will be used for the follow up of cases for the following risks:

- Anaphylaxis/anaphylactoid reactions
- Arterial Thromboembolic Events (ATEs)
- Malignant neoplasms (children 6 to less than 12 years old) and Malignant neoplasms in adults and adolescents ≥ 12 years of age

Targeted Follow-up Checklist for Omlyclo (Omalizumab) - Hypersensitivity including Anaphylaxis (Version 1.0)

In addition to collecting routine information for this adverse event reported to Celltrion as 'Anaphylaxis' following the use of Omlyclo, please ensure the following additional information is provided and/or confirmed.

Administration of Omlyclo:

1. Where was Omlyclo administered immediately prior to the adverse event?:
   ☐ In the Home setting [Home setting includes: Self-injection (patient gave himself the medication) at home or elsewhere or by a lay caregiver (spouse, parent or others) at home or elsewhere]
   ☐ In the Office setting [Office setting includes a doctor's office, hospital/clinic, or by a Health Care Professional (includes doctor, nurse, physician's assistant etc.) at the patient's home or a Health Care Professional's office]
   ☐ Unknown
2. How many times has the patient received Omlyclo prior to the adverse event? ☐_____ (*indicate number*) ☐ Unknown
3. In case Omlyclo has been administered at Home, did the patient receive Omlyclo at least three times in an Office setting? ☐ **Yes** ☐ **No**
4. If **No,** were the first 3 doses of medication given by a doctor, nurse or other health care professional in another location (not in a doctor's office)? ☐ **Yes** ☐ **No**
5. If Omlyclo is now administered at Home, was the patient/caregiver trained/explained on how to recognise the signs and symptoms of severe allergic reactions including Anaphylaxis?
   ☐ **Yes** ☐ **No**

Event Description:

Was a type I hypersensitivity and/or anaphylaxis/anaphylactoid reaction noted in the patient?

☐ **Yes**
☐ **No**
☐ **Unknown**

Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Asthma/Wheezing
☐ Hyperventilation
☐ Erythema/Flushing oedema/Spasm/Swelling
☐ Chest discomfort
☐ Urticaria/Rash
☐ Mouth/Circumoral (excluding lips)
☐ Upper airway obstruction/Choking
☐ Papules
☐ Tongue
☐ Sensation of foreign body/Upper
☐ Fixed eruption

- ☐ Oropharyngeal airway obstruction/Choking
- ☐ Itching
- ☐ Laryngeal
- ☐ Stridor
- ☐ Oedema/Swelling
- ☐ Tracheal
- ☐ Cough or sneezing
- ☐ Allergic
- ☐ Bronchial
- ☐ Eye/Eyelid
- ☐ Respiratory arrest
- ☐ Cardiac arrest
- ☐ Skin
- ☐ Respiratory distress/failure
- ☐ Heart failure
- ☐ Other (*please specify*)
- ☐ Dyspnoea
- ☐ Hypotension (systolic and/or diastolic)
- ☐ None of the above

Diagnostic Tests: Check all that apply and specify dates, results and if possible, include copies of test results

- ☐ Laboratory tests including full blood count/Coombs
- ☐ Skin biopsy Test/LFTs/Complement as appropriate
- ☐ Skin allergy tests
- ☐ IgE levels
- ☐ Drug sensitivity lymphocyte test
- ☐ Bone marrow aspiration
- ☐ Antibodies to drug detected
- ☐ None of the above

Patient History:
Does the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply

- ☐ Allergic asthma
- ☐ Previous drug hypersensitivity reaction (*please specify*)
- ☐ Allergic rhinitis
- ☐ Alcohol abuse
- ☐ Atopic dermatitis
- ☐ Drug abuse
- ☐ Food allergies, including colorants (dyes) and preservatives
- ☐ Recent pregnancy

☐ Urticaria
☐ Allergens (*please specify*)
☐ Rash
☐ Family history of allergies (*please specify*)
☐ Viral infection
☐ Malignancies
☐ Bacterial infection
☐ Autoimmune disease
☐ Foreign travel
☐ Other relevant history (*please specify*)
☐ Photosensitivity
☐ Other infections (e.g. fungal, protozoal) (*please specify*)
☐ None of the above

Has the patient taken/received any of the following (in reasonably close proximity to the event)?
Check all that apply

☐ Recent blood/Serum/Blood-product transfusion
☐ Vaccination
☐ Injectable or oral antibiotics
☐ NSAIDs
☐ Narcotic analgesics
☐ Local anaesthetics
☐ Hormones (ACTH/insulin/calcitonin)
☐ Herbals/alternative medicine/vitamin supplements (*please specify*)
☐ Neuromuscular blockers
☐ Chemotherapy
☐ None of the above

Targeted Follow-up Checklist for Omlyclo (Omalizumab) - Arterial Thromboembolic Events (ATEs) (Version 1.0)

Cardiac Conduction Abnormalities

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:
Did the patient present with any of the following signs or symptoms? **Check all that apply**

- ☐ Palpitations
- ☐ Light-headedness/ dizziness/near-syncope
- ☐ Shortness of breath
- ☐ Fatigue
- ☐ Fainting/syncope
- ☐ Chest pressure or pain
- ☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

- ☐ Additional ECGs
- ☐ Holter monitor/ECG telemetry
- ☐ Exercise stress test
- ☐ Electrophysiology study
- ☐ Potassium level
- ☐ None of the above

Patient History:
Did the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply

- ☐ Heart attack/Myocardial infarction
- ☐ Cardiomyopathy
- ☐ Myocarditis
- ☐ Cardiac surgery
- ☐ Congenital heart condition (*please specify*)
- ☐ Hypothyroidism
- ☐ Other relevant history (*please specify*)
- ☐ Stroke / Brain tumour / CNS disease (*please specify*)
- ☐ Recent strenuous athletic training
- ☐ Vasovagal episode
- ☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

- ☐ Antiarrhythmics (e.g. flecainide, propafenone)
- ☐ Cholinomimetics (e.g. donepezil, verapamil)

☐ Antidepressants/Antipsychotics (e.g. tricyclic antidepressants)
☐ Beta-blockers
☐ Digitalis
☐ None of the above

Ischemic Heart Disease/Myocardial Infarction

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided and/or confirmed.

Event Description:
Did the patient present with any of the following signs or symptoms? **Check all that apply**

☐ Palpitations
☐ Light-headedness/dizziness/near-syncope
☐ Shortness of breath
☐ Fatigue
☐ Fainting/syncope
☐ Chest pressure or pain
☐ None of the above

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

☐ Additional ECGs
☐ Holter monitor/ECG telemetry
☐ Exercise stress test
☐ Electrophysiology study
☐ Potassium level
☐ None of the above

Patient History:
Did the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply

☐ Heart attack/Myocardial infarction
☐ Cardiomyopathy
☐ Myocarditis
☐ Cardiac surgery
☐ Congenital heart condition (*please specify*)
☐ Hypothyroidism
☐ Other relevant history (*please specify*)
☐ Stroke / Brain tumour / CNS disease (*please specify*)
☐ Recent strenuous athletic training
☐ Vasovagal episode
☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

- ☐ Antiarrhythmics (e.g. flecainide, propafenone)
- ☐ Cholinomimetics (e.g. donepezil verapamil)
- ☐ Antidepressants/Antipsychotics (e.g. tricyclic antidepressants)
- ☐ Beta-blockers
- ☐ Digitalis
- ☐ None of the above

Stroke

In addition to collecting routine information for this adverse event, please ensure the following additional information is provided.

Event Description:

Did the patient present with any of the following signs or symptoms? **Check all that apply**

- ☐ Sensory deficit
- ☐ Difficulty swallowing
- ☐ Motor deficit (e.g. paralysis, paresis)
- ☐ Headache (severe or of abrupt onset)
- ☐ Difficulty speaking/Expressive aphasia
- ☐ Unexplained change in the pattern of headaches
- ☐ Difficulty understanding when spoken to/Receptive aphasia
- ☐ Confusion
- ☐ Unexplained dizziness
- ☐ Disorientation to place, time, person
- ☐ Blurred or poor vision in one or both eyes
- ☐ Unconsciousness
- ☐ Loss of balance or coordination
- ☐ Dysarthria
- ☐ Difficulty walking or an unexplained fall
- ☐ Cerebral topographical localisation (*please specify*)
- ☐ Other (*please specify*)
- ☐ None of the above

What type of stroke(s) was/were reported? (*please specify*, e.g., ischaemic, haemorrhagic, TIA):

_____

_____

_____

Were any of the following diagnostic tests performed? **Check all that apply and please specify which test(s), dates and results**

☐ Electroencephalogram (EEG)
☐ Electrocardiogram (ECG)
☐ Imaging studies (i.e. CT scan, MRI scan, magnetic resonance angiography)
☐ Blood or urine tests
☐ None of the above

Relevant medical history (concurrent and pre-existing conditions)
(Please specify medical condition and date of onset)

Did the patient have a history of any of the following prior to the start of the suspect drug?
Check all that apply

☐ Cerebral Vascular Attacks or Transient Ischaemic Attacks
☐ Hypertension (*please explain*)
☐ Diabetes
☐ Cardiovascular disease including cardiac arrhythmias, hyperlipidaemia rheumatic heart disease, or recent myocardial infarction (MI)
☐ Hypercoagulable disease/disorder (e.g. polycythaemia (*please explain*), sickle cell anaemia, dysproteinaemia)
☐ Peripheral vascular disease
☐ Head injury
☐ Smoking
☐ Drug abuse (i.e. cocaine, amphetamines, heroin)
☐ Migraine
☐ Malignancy or neoplasm
☐ None of the above

Was the patient taking any of the following drugs? **Check all that apply**

☐ Ergotamines
☐ Antihypertensive agents
☐ Lipid lowering agents
☐ Anticoagulants
☐ Oral contraceptives/Hormone therapy
☐ None of the above

<u>Sudden Death or Unexplained Death</u>
In addition to collecting routine information for this SAE, please ensure the following additional information is provided and/or confirmed.
Event Description:
Autopsy performed: ☐ **Yes** (Please provide cause of death if available) ☐ **No**

_____

_____

If patient was hospitalised, please provide relevant information

_____

_____

_____

If the death was witnessed, were any symptoms or signs noted (convulsions, mouth foaming, incontinence, confusion, etc.)

_____

_____

_____

If the death was not witnessed, when was the patient last seen alive; please include any information about the health of the patient on that date.

_____

_____

_____

If resuscitation was attempted, please describe the initial response to treatment if applicable.

_____

_____

_____

If death certificate was issued, please summarise primary and secondary cause(s) of death.

Primary:

Secondary:

What was the initial cardiac rhythm noted? (e.g. ventricular fibrillation, Torsade de Pointes, etc.)

_____

_____

Were any of the following diagnostic tests performed? **Check all that apply and specify the test, date and result**

- ☐ Relevant cardiac investigations during life (e.g. stress ECG, angiogram, ECG, Holter monitor, etc.)
- ☐ Relevant CNS investigations (e.g. investigations for epilepsy)
- ☐ Recent blood tests (electrolytes, enzymes)
- ☐ Additional relevant post-mortem findings
- ☐ None of the above

Patient History:

Does the patient have a history of any of the following? **Check all that apply**

- ☐ Congenital heart disease
- ☐ Hypertrophic obstructive cardiomyopathy
- ☐ Alcohol abuse
- ☐ Cardiac disease (e.g. angina, valvular heart disease, drugs of abuse CAD, myocardial infarction) (*please specify*)
- ☐ Family history of sudden death
- ☐ Unexplained syncope
- ☐ Major surgery (e.g. heart, abdomen) (*please specify*)
- ☐ Arrhythmias, palpitations
- ☐ Epilepsy/Seizures
- ☐ Thromboembolic or haemorrhagic
- ☐ Thyrotoxicosis
- ☐ Myocarditis events including CVA, TIA
- ☐ Diabetes
- ☐ Wolff-Parkinson-White syndrome
- ☐ Malignancies
- ☐ Asthma
- ☐ Attempted suicide
- ☐ Psychiatric disease
- ☐ Severe vomiting, diarrhoea
- ☐ Hypertension
- ☐ Morbid obesity
- ☐ Oral contraceptives

Has the patient recently taken any of the following? **Check all that apply**

- ☐ Antiarrhythmics (e.g. quinidine, amiodarone)
- ☐ Beta blockers
- ☐ QT prolonging medication (antihistamine, antibiotics etc.)
- ☐ Digoxin
- ☐ Chemotherapy
- ☐ None of the above

Targeted Follow-up Checklist for Omlyclo (Omalizumab) – Malignancy (Version 1.0)

AER:	
Site No:	
Patient ID/Initials	
Patient Gender:	☐ M ☐ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy)	

Malignancy has been observed in some patients treated with omalizumab.

By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information			
Name of reporter completing this form (if other than addressee, provide contact information below):			
Health Care Provider? ☐ Yes ☐ No-Specify:			
Phone number:		Fax number:	
Email address:			

Details of treatment with Omlyclo				
Indication	Route	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or Ongoing
				☐ Ongoing
				☐ Ongoing
				☐ Ongoing

Details of Patient weight and IgE levels prior to treatment with Omlyclo		
Date	Patient weight	Patient serum IgE level

Diagnosis of Malignancy			
Clinical Diagnosis:	Stage of Malignancy Event:		ICD-10 code:
Histology of Malignancy Event	Histological confirmation?	☐ Yes ☐ No ☐ Unknown	
	Histology grading:	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV	
	Histology findings:		
Cytology of Malignancy Event	Cytological confirmation?	☐ Yes ☐ No ☐ Unknown	
	Cytological grading:	☐ Grade 0 ☐ Grade I ☐ Grade II ☐ Grade III ☐ Grade IV	
	Cytological findings		
Nature of Malignancy	Is this a primary malignancy?		☐ Yes ☐ No ☐ Unknown
	Is this a secondary malignancy (cancer following a previously treated malignant neoplasm, but not considered a metastasis of the initial neoplasm)?		☐ Yes ☐ No ☐ Unknown **If yes**, specify:

Diagnosis of Malignancy		
	Is tumour a recurrence of a tumour existing before treatment with Omlyclo (omalizumab) (disease progression)?	☐ Yes ☐ No ☐ Unknown **If yes**, specify:
	If tumour is recurrence, is recurrence confirmed by a pathologist?	☐ Yes ☐ No ☐ Unknown
Relevant Cancer Biomarkers?	☐ Yes ☐ No ☐ Unknown	
	If yes, specify:	

List any immunosuppressants and/or chemotherapy medications and/or radiation therapy the patient has received IN THE PAST						
Drug Name (generic or trade name)	Indication	Route	Total # of cycles received by time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or Ongoing
						☐ Ongoing
						☐ Ongoing
						☐ Ongoing
						☐ Ongoing

List any immunosuppressants and/or chemotherapy medications and/or radiation therapy the patient was receiving AT THE TIME OF EVENT ONSET						
Drug Name (generic or trade name)	Indication	Route	Total # of cycles received by time of event onset	Dosing Regimen & Frequency of Dosing	Start Date	Stop Date or Ongoing
						☐ Ongoing
						☐ Ongoing
						☐ Ongoing
						☐ Ongoing

Relevant Medical History				
History of immunodeficiency?	☐ Yes	☐ No	☐ Unknown	Specify:
History of autoimmune disease?	☐ Yes	☐ No	☐ Unknown	Specify:
History of recurrent infections?	☐ Yes	☐ No	☐ Unknown	Specify:

Relevant Medical History				
History of opportunistic infections?	☐ Yes	☐ No	☐ Unknown	Specify:
History of previous malignancy?	☐ Yes	☐ No	☐ Unknown	Specify:
Family history of malignancy?	☐ Yes	☐ No	☐ Unknown	Specify:
History of smoking?	☐ Yes	☐ No	☐ Unknown	Specify:
History of alcohol use?	☐ Yes	☐ No	☐ Unknown	Specify:
History of exposure to other known carcinogens? (e.g. Excessive ultraviolet radiation [sunlight or PUVA/UVB] if malignancy is skin cancer), etc.	☐ Yes	☐ No	☐ Unknown	Specify:
Other relevant history – specify:				

Treatment for Malignancy		
Did patient refuse treatment for malignancy?		
☐ Yes	☐ No – please provide treatment details in the tables(s) below	☐ Unknown

Surgical Treatment for the Malignancy (planned or completed)		
Type of Surgery	Date of Surgery	
	☐ Date completed:	☐ Planned
	☐ Date completed:	☐ Planned
	☐ Date completed:	☐ Planned

Chemotherapy/Radiation treatment or other treatment for the malignancy (planned, ongoing or completed):				
Drug Name	Dosing Regimen and Frequency	Status of Treatment		
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing
		☐ Date completed:	☐ Planned	☐ Ongoing

Outcome of Malignancy					
Was patient sent to hospice care? ☐ Yes ☐ No					
Current status of malignancy?					
☐ Complete remission	☐ Partial remission	☐ Stable	☐ Regression	☐ Progressive disease	☐ Fatal outcome- date of death:

Autopsy Data		
If applicable, please provide the following information: ☐ Not applicable		
If the patient has expired, was an autopsy performed?		
☐ Yes -please provide autopsy results including cause of death	☐ No	☐ Unknown

Completed by:

Name: ..... Position .....

Signature: ..... Date: .....

Email: .....

Annex 6 – Details of proposed additional risk minimisation activities (if applicable) Not applicable as there are no proposed additional risk minimisation activities.