25 June 2020
EMA/404869/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xolair

International non-proprietary name: omalizumab

Procedure No. EMEA/H/C/000606/II/0101

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AERD	aspirin exacerbated respiratory disease
ALT	Alanine aminotransaminase
AQLQ	asthma quality of life questionnaire
ARS	anterior rhinorrhoea score
AST	Aspartate aminotransaminase
BID	twice a day
CI	confidence interval
CRS	chronic rhinosinusitis
CRSwNP	chronic rhinosinusitis with nasal polyps
CS	corticosteroids
CSR	clinical study report
CSU	chronic spontaneous urticaria
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5-Dimension 5-Level Questionnaire
FAS	full analysis set
FcεRI	high affinity IgE receptor
FDA	Food and Drug Administration
FESS	functional endoscopic sinus surgery
HRQoL	health-related quality of life
Ig	immunoglobulin
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IL	interleukin
LOE	loss of efficacy
MCID	minimal clinical important difference
MMRM	mixed-effect model repeated measurement
NCS	nasal congestion score
NPS	nasal polyp score

OLE open-label extension

PD progressive disease

PFAS pooled full analysis set

PRS posterior rhinorrhoea score

QoL quality of life

SAE serious adverse event

SAP statistical analysis plan

SCE summary of clinical efficacy

SCS summary of clinical safety

SNOT-22 sino-nasal outcome test-22

SOC system organ class

SSS sense of smell score

Th2 type 2 T helper

TNSS total nasal symptom score

UPSIT University of Pennsylvania Smell Identification Test

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 8 November 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of nasal polyps in adult patients with inadequate response to intranasal corticosteroids for Xolair; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes in section 4.2 of the SmPC and in the PL and to update the phone number of the NL local representative. The RMP version 16.0 has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific advice from the CHMP on 21 April 2017 (EMEA/H/SA/45/4/2017/III). The Scientific advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Kristina Dunder

Timetable	Actual dates
Submission date	8 November 2019
Start of procedure:	30 November 2019
CHMP Rapporteur Assessment Report	24 January 2020
PRAC Rapporteur Assessment Report	24 January 2020
PRAC Outcome	13 February 2020
CHMP members comments	17 February 2020
Updated CHMP Rapporteur Assessment Report	20 February 2020
Request for supplementary information (RSI)	27 February 2020
CHMP Rapporteur Assessment Report	26 May 2020
PRAC Rapporteur Assessment Report	26 May 2020
PRAC Outcome	11 June 2020
CHMP members comments	15 June 2020
Updated CHMP Rapporteur Assessment Report	18 June 2020
CHMP opinion	25 June 2020

2. Scientific discussion

2.1. Introduction

Omalizumab (Xolair) is a recombinant DNA-derived humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to IgE. Omalizumab is designed to treat IgE-mediated disease by reducing the concentration of free IgE in blood and in tissue. Omalizumab selectively binds to human IgE at the same site as the high affinity IgE receptor (FcεRI), thereby reducing surface IgE on basophils and mast cells and reducing basophil and mast cell triggered Type 2 inflammation.

Omalizumab is currently approved for the treatment of allergic asthma in children (≥ 6 years), adolescents and adults, and for the treatment of chronic spontaneous urticaria (CSU) in adolescents (≥ 12 years) and adults.

The current variation application seeks to extend the use of omalizumab for the treatment of nasal polyps in adult patients who have inadequate response to intranasal corticosteroids. The proposed posology is based on a dosing table determined by the baseline IgE level and body weight of each patient as currently approved in the EU for the allergic asthma indication for Xolair.

Nasal polyps occur in a subset of patients with chronic rhinosinusitis (CRS). CRSwith nasal polyposis (CRSwNP) is a predominantly adult disease, with the average age of onset being 42 years and the typical age ranging from 40 and 60 years. Data suggest that while relatively common in adults, CRSwNP is uncommon in children. Overall, the reported relevance of nasal polyps is consistent with limited existing epidemiology studies, globally with a range between 2.1% - 2.7%.

CRSwNP is associated both with reduced quality of life (QoL) as well as significant morbidity, including asthma, which can be severe and refractory, particularly in those patients with aspirin exacerbated respiratory disease (AERD). Patients with CRSwNP and most patients with asthma share a common IgE-mediated Type 2 inflammatory response which is characterized by elevated levels of interleukins 4

(IL-4), IL-5, IL-13, eosinophils, type 2 T helper (Th2) cells and type 2 innate lymphoid cells. In addition, locally produced IgE (often against Staphylococcus aureus enterotoxins) can contribute to the inflammation in CRSwNP, which in particular is associated with comorbid asthma. Because of the common Type 2 inflammatory disease between asthma and CRSwNP, approximately 20% to 40% of patients with asthma have CRSwNP, particularly those with AERD. Conversely, a significant proportion of patients with CRSwNP (20% - 70%) have symptoms of asthma. Therefore, there appears to be a premorbid relationship between asthma and CRSwNP, with the diagnosis of asthma often occurring prior to that of nasal polyposis.

Intranasal and systemic/oral corticosteroids remain the mainstay of treatment of CRSwNP, but many patients fail to achieve complete therapeutic benefit with these medications and resort to Functional Endoscopic Sinus Surgery (FESS) and other complex sinus surgery. Although FESS and intranasal and oral corticosteroids are useful and often effective in reducing the size of nasal polyps and associated symptoms, many patients do not respond sufficiently and/or polyps return rapidly after medication withdrawal or within months or years following surgery. In September 2019, dupilumab was approved as an add-on maintenance treatment in adults with severe chronic rhinosinusitis with nasal polyposis (CRSwNP) who previously failed or are intolerant or contraindicated to systemic corticosteroids and/or surgery; Dupilumab was also approved to reduce the need for surgery and systemic corticosteroid use in adult patients with inadequately controlled severe CRSwNP. Dupilumab is a recombinant human IgG4-monoclonal antibody which inhibits interleukin-4- and interleukin-13 signalling. IL-4 and IL-13 are important in the signalling pathway for type 2-inflammation, which is associated with atopic dermatitis, asthma and CRSwNP.

There has been a number of clinical studies examining the effect of omalizumab on nasal polyps, showing benefits of omalizumab. To support this extension of indication, two pivotal phase III-studies were conducted and presented in this application (studies GA39688 and GA39855).

The terms CRSwNP, nasal polyposis, and nasal polyps have been used interchangeably and are referred to as nasal polyps hereafter in the assessment report.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The MAH provided a justification for not submitting any environmental risk assessment (ERA) studies based on the fact that omalizumab is a protein and therefore unlikely to pose a significant risk to the environment which in accordance with the CHMP guideline on the environmental risk assessment EMEA/CHMP/SWP/4447/00 corr 2.

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted. The safety of omalizumab has previously been studied in cynomolgus monkey, since omalizumab binds to cynomolgus and human IgE with similar affinity. No apparent toxicity was seen.

No ERA has been conducted to support this application. This is acceptable considering that omalizumab is a protein and it is therefore unlikely to be stable or remain biologically active in the environment and pose a risk to the environment even when adding a new therapeutic indication.

The pre-clinical safety data section of the SmPC (section 5.3) remains unchanged.

2.2.3. Conclusion on the non-clinical aspects

The absence of a non-clinical package was considered acceptable by CHMP. The non-clinical aspects of omalizumab remains unchanged.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies

Study Number (Phase) Status	Study Design, Control Type	Population	Number of Patients [a]	Dose [b], Route, and Regimen
GA39688 (Phase III) Pivotal Completed	Randomized, multicenter, double-blind, placebo-controlled, parallel group, efficacy and safety study	Adult patients [c] with nasal polyps whose disease remained inadequately controlled despite daily treatment with intranasal corticosteroids	Overall: 138 Placebo: 66 Omalizumab: 72	150 to 600 mg omalizumab SC every 2 or 4 weeks (or placebo) administered for 24 weeks; dose and frequency determined by serum total IgE level before the start of treatment and body weight; background treatment consisted of stable doses of intranasal corticosteroid (mometasone nasal spray)
GA39855 (Phase III) Pivotal Completed	Randomized, multicenter, double-blind, placebo-controlled, parallel group, efficacy and safety study	Adult patients [c] with nasal polyps whose disease remained inadequately controlled despite daily treatment with intranasal corticosteroids	Overall: 127 Placebo: 64 Omalizumab: 63	150 to 600 mg omalizumab SC every 2 or 4 weeks (or placebo) administered for 24 weeks; dose and frequency determined by serum total IgE level before the start of treatment and body weight; background treatment consisted of stable doses of intranasal corticosteroid (mometasone nasal spray)

Study Number (Phase) Status	Study Design, Control Type	Population	Number of Patients [a]	Dose [b], Route, and Regimen
WA40169 (Phase III OLE) Ongoing	Single-arm, open-label extension study	Adult patients with nasal polyps who completed Studies GA39688 and GA39855	Overall: 249	150 to 600 mg omalizumab SC every 2 or 4 weeks administered for 28 weeks; dose and frequency determined by serum total IgE level and body weight at baseline, 24-week off-treatment follow-up; background intranasal corticosteroid treatment continued throughout the study

[a] All patients enrolled received study drug and were included in the safety analysis set.

[b] Omalizumab was dosed based on a dosing table that provides at least 0.016 mg/kg for every IU/mL of IgE, within a 4 week interval. The patient's weight and IgE value measured on Day −35 (first screening visit) were used to determine study drug dosing. This is the dose range as actually administered during the studies. No patient received doses of less than 150 mg omalizumab.

[c] Adult patients defined as 18 to 75 years of age inclusive, at the time of signing the Informed Consent Form.

Source: [Study GA39688], [Study GA39855], and [Study WA40169 Interim Safety Report]

2.3.2. Pharmacokinetics

The purpose of the pharmacokinetics (PK) analysis was to assess whether the PK of omalizumab and its effect on the pharmacodynamics (PD), in terms of total IgE and free IgE, in nasal polyps were consistent with those in allergic asthma, and to explore the impact of existing and additional covariates on omalizumab PK and IgE kinetics in nasal polyps.

Bodyweight and total IgE at (Day -35) informed omalizumab dosing and dosing frequency (Table 1), similarly with the approach used for the treatment of allergic asthma.

Table 1. Omalizumab dosing table for nasal polyps, as applied in Studies GA39688 and GA39855

Baseline IgE (IU/mL) (Day -35)	Body Weight (kg) (Day -35)							
	>30-40	> 40–50	> 50–60	> 60–70	> 70–80	> 80–90	> 90–125	>125–150
≥ 30–100	75 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	150 mg Q4wk	300 mg Q4wk	300 mg Q4wk
> 100–200	150 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	300 mg Q4wk	450 mg Q4wk	600 mg Q4wk
> 200–300	225 mg Q4wk	300 mg Q4wk	300 mg Q4wk	450 mg Q4wk	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	375 mg Q2wk
> 300–400	300 mg Q4wk	450 mg Q4wk	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	450 mg Q2wk	525 mg Q2wk
> 400–500	450 mg Q4wk	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	375 mg Q2wk	375 mg Q2wk	525 mg Q2wk	600 mg Q2wk
> 500–600	450 mg Q4wk	600 mg Q4wk	600 mg Q4wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	600 mg Q2wk	
> 600–700	450 mg Q4wk	600 mg Q4wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	525 mg Q2wk		
> 700–800	300 mg Q2wk	375 mg Q2wk	450 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk		
> 800–900	300 mg Q2wk	375 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk			
> 900–1000	375 mg Q2wk	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk				
> 1000–1100	375 mg Q2wk	450 mg Q2wk	600 mg Q2wk	DO NOT ADMINISTER				
> 1100–1200	450 mg Q2wk	525 mg Q2wk	600 mg Q2wk					
> 1200–1300	450 mg Q2wk	525 mg Q2wk						
> 1300–1500	525 mg Q2wk	600 mg Q2wk						

Q2wk=once every 2 weeks; Q4wk=once every 4 weeks. Lighter grey shading with black text indicates doses to be administered by subcutaneous injection every 4 weeks. Darker grey shading with white text indicates doses to be administered by subcutaneous injection every 2 weeks.
Source: Xolair EU SmPC, July 2019. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/xolair#product-information-section

Bioanalytical methods

Three validated methods were used in the quantification of omalizumab pharmacokinetic and pharmacodynamic samples collected from the nasal polyps studies GA39688 and GA39855. Details of those methods are provided in the following table (Table 2).

Table 2. Summary of Analytical Methods Used for the Nasal Polyps Studies GA39688 and GA39855

Analyte	Matrix	Method	LLOQ	Reference Validation Report
Total omalizumab	Serum	ELISA	28 ng/mL	NBx-RS602700a
Free IgE	Serum	ELISA	2.0 ng/mL	NBx-RS602700
Total IgE	Serum	ImmunoCAP®	2.0 IU/mL	NBx-RS630172

ELISA = enzyme-linked immunosorbent assay; IgE = human immunoglobulin E; LLOQ = lower limit of qualification.

2.3.3. Pharmacodynamics

Mechanism of action

Omalizumab is a humanized anti-IgE recombinant monoclonal antibody approved to treat allergic asthma in children (≥ 6 years), adolescents and adults and chronic spontaneous urticaria (CSU) in adults and adolescents (≥ 12 years).

In allergic asthma, omalizumab binds to IgE and prevents the binding of IgE to the FcεRI on the surface of mast cells and basophils. Reduction in surface-bound IgE on the FcεRI-bearing cells limits the release of mediators in the allergic response. This, in turn, results in down regulation of FcεRI expression on basophils and mast cells (high-affinity IgE-receptors).

In CSU, the mode of action is less well understood. The observation that many patients with CSU improve with omalizumab implies that there may be an abnormal IgE present, which recognizes an unknown antigen and activates mast cells and basophils. However, the mechanism by which these effects of omalizumab result in an improvement of chronic idiopathic urticaria symptoms is unknown.

As for the effect of omalizumab on IgE in CRSwNP, the MAH applies a similar PK/PD model as in allergic asthma. To some extent, allergic asthma and nasal polyps overlap in affected patients and share a similar inflammatory pathway (type 2 inflammation).

2.3.4. PK/PD modelling

Population pharmacokinetic/pharmacodynamic analysis (omalizumab PK-IgE model)

Data

Omalizumab dose was based on a dosing table that provided at least 0.016 mg/kg for every IU/mL of IgE, within a 4-week interval.

During both studies included in this application, studies GA39688 and GA39855, single blood samples for PK, total IgE and free IgE were drawn prior to drug administration on Days 1, 112 (Week 16), 168 (Week 28), at follow-up (Day 196, Week 28) and in case of unplanned termination of dosing or early termination. An additional assessment of total IgE was performed at screening (Day -35) in order to inform omalizumab dosing and dosing frequency. In the dataset, the baseline IgE values ranged from 20-1470 IU/mL.

Population PK/PD model

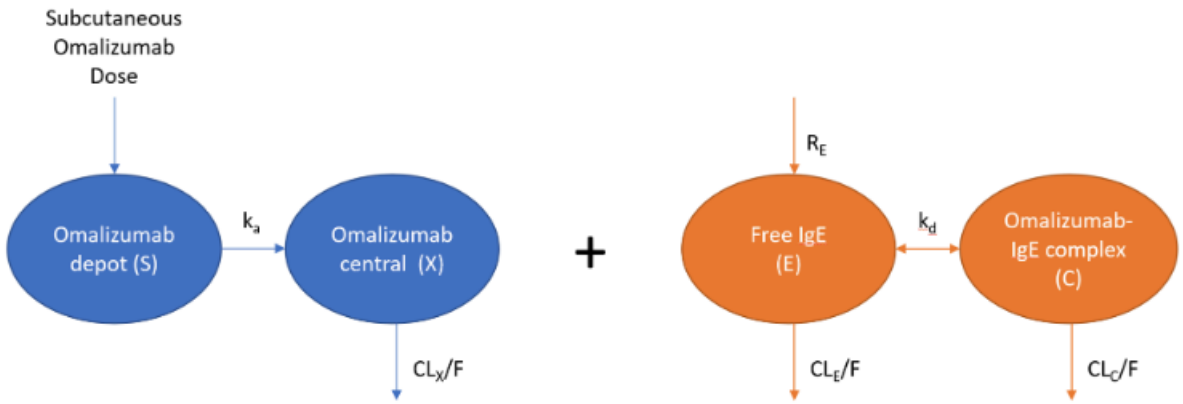
The version of the model published by Honma and colleagues (2016) formed the basis for this analysis (a schematic of the basic model structure is provided in Figure 1). Parameter estimates for the published model appear below in Table 3. A large number of covariate relationships with model parameters were also described by the authors – these appear in Table 4.

Since the omalizumab and IgE concentration data available from the clinical studies in the current analysis consisted solely of pre-dose troughs, refitting the model to the data was not possible. Instead, the model was evaluated for applicability with respect to the nasal polyps indication and population. The Honma model describing omalizumab and free IgE and total IgE concentration over time was modified slightly to accommodate the lack of certain covariates in the nasal polyps dataset (terms describing age under 12 years and Japanese ethnicity, specifically, were removed), and used to

simulate 1000 new datasets using the design of the data obtained from studies GA39688 and GA39855 (doses, individual covariate profiles, and observation times).

The Honma model was subsequently used to generate empirical Bayes estimates of model parameters for all individuals in the nasal polyps dataset (by running the model against the data with MAXEVAL set to 0 in NONMEM, ensuring no actual model fits were performed). These were compared with the expected values from the Honma model in the same way as the individual observations above. Standard continuous-data goodness of fit plots was applied for the assessment of model adequacy. Overprediction of omalizumab concentration at the medians of the bins centred on 112 days and 168 days was 13.9 % and 12.0 %, respectively

Figure 1. Omalizumab PK/IgE model structure.



S is the amount of omalizumab in the absorption compartment, X is the amount of omalizumab in the central volume V_X/F, E is the amount of free IgE in the central volume V_E/F, and C is the amount of omalizumab-IgE complex in the central volume V_C/F. k_a is the absorption rate constant, CL_X/F and V_X/F are the apparent clearance and volume of omalizumab, CL_C/F and V_C/F are the apparent clearance and volume of complex, CL_E and V_E/F are the apparent clearance and volume of free IgE, R_E is the rate of synthesis of free IgE, K_D is the apparent equilibrium binding constant. The model assumes that $V_X=V_E$, consistent with the model for patients with allergic asthma.
Source: Modified from Wada DR, Le K (2013). Population Pharmacokinetics/Pharmacodynamics of Omalizumab in Chronic Idiopathic Urticaria. Population Pharmacokinetics Report 13-0627 [internal]. 2013-05-28_Omalizumab_PPKPD_ Report_Final.docx. Figure A, p. 12

Table 3. Published structural parameter estimates for the Honma model

Parameter	Estimate	Interindividual Variability (variance)
Apparent omalizumab clearance (CL_X/F, $L \cdot d^{-1}$)	0.200	0.117[a]
Apparent free IgE clearance (CL_E/F, $L \cdot d^{-1}$)	1.98	0.0362
Apparent omalizumab-IgE complex clearance (CL_C/F, $L \cdot d^{-1}$)	0.442	0.0348[b]
Apparent omalizumab and free IgE volume of distribution (V_X/F and V_E/F, L)	8.08	0.0711[a]
Apparent omalizumab-IgE complex volume of distribution (V_C/F, L)	1.9	1.62
IgE synthesis rate (R_E, $\mu g \cdot d^{-1}$)	655	0.0627[b]
Absorption rate constant for omalizumab (k_a, d^{-1})	0.635	1.57
Binding constant (k_D, nM^{-1})	1.53	0.0465
Nonlinearity in k_D (α)	0.109	

[a] Covariance = 0.0750

[b] Covariance = -0.0189

Table 4. Published covariate relationships for the Honma model

Parameter	Covariate	Coefficient (theta)
CL_X/F, CL_E/F, CL_C/F, R_E	Body weight (median: 70 kg)	0.945[a]
CL_X/F	BMI (median: 20 kg·m^{-2})	0.164[a]
CL_X/F	Race: Black	1.05[b]
CL_X/F	Race: Oriental	1.08[b]
CL_X/F	Race: Other	1.11[b]
CL_X/F	Japanese ethnicity (vs Caucasian)	1.12[b]
CL_E/F	Baseline IgE (median: 365 ng·mL^{-1})	0.332[c]
CL_C/F	Japanese ethnicity (vs non-Japanese)	1.13[b]
V_X/F, V_E/F, V_C/F	Body weight (median: 70 kg)	0.951[a]
V_X/F	Age: <12 y (non-Japanese)	0.941[b]
V_X/F	Age: ≥12 y (Japanese vs non-Japanese)	0.844[b]
V_X/F	Age: <12 y (Japanese vs non-Japanese)	0.999[b]
R_E	Age: <12 y (Caucasian)	0.890[b]
R_E	Baseline IgE (median: 365 ng·mL^{-1})	0.640[a]
R_E	Race: Black	1.01[b]
R_E	Race: Oriental	1.16[b]
R_E	Race: Other	0.915[b]
R_E	Sex: Female	0.968[b]
k_D	Age: <12 y (Caucasian)	1.23[b]
k_D	Age: ≥12 y (Japanese vs Caucasian)	0.813[b]
k_D	Age: <12 y (Japanese vs Caucasian)	1.14[b]
k_D	Baseline IgE (median: 365 ng·mL^{-1})	0.0727[a]
k_D	Race: Black	0.942[b]
k_D	Race: Oriental	0.822[b]
k_D	Race: Other	0.938[b]

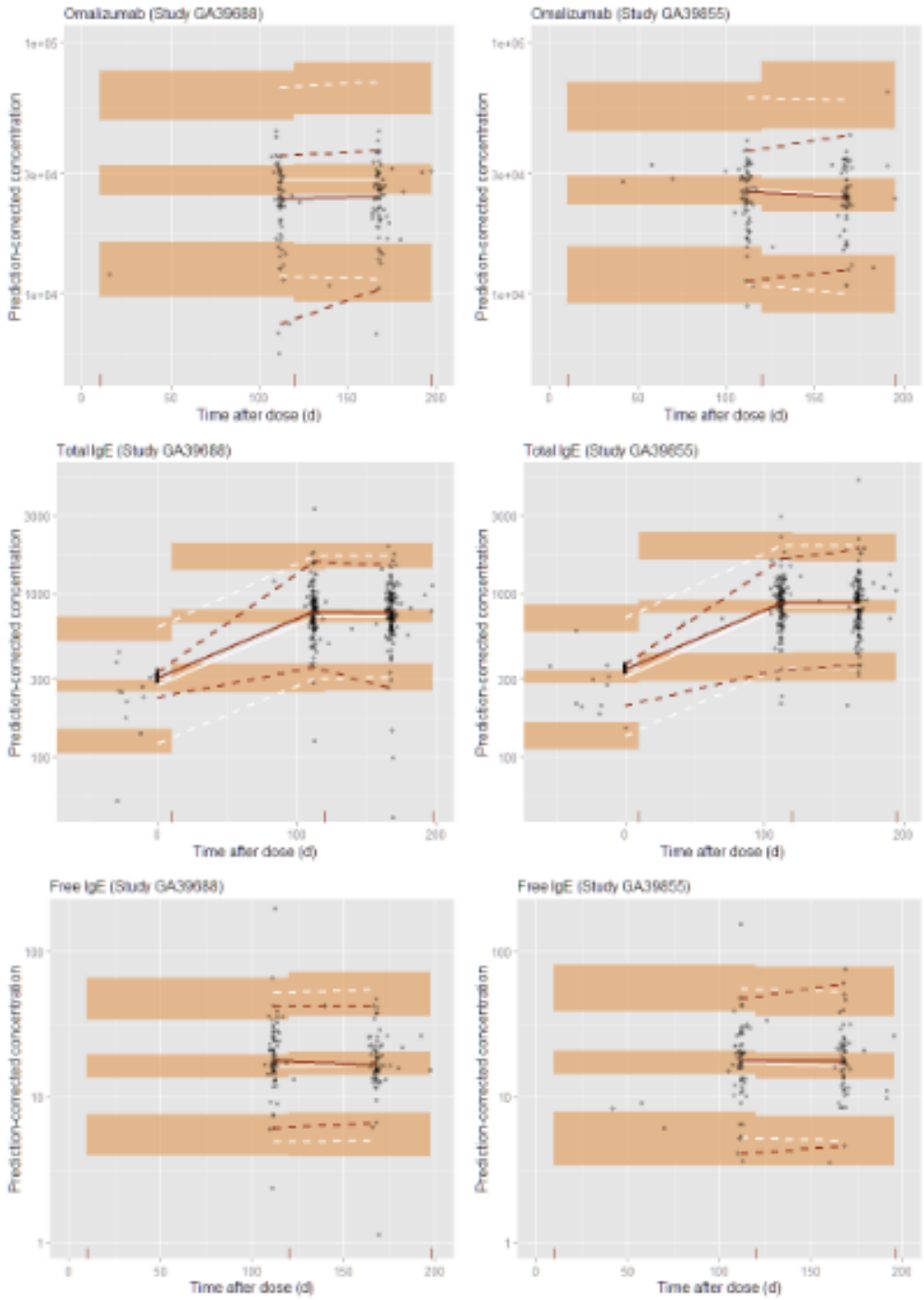
[a] Power model

[b] Ratio

[c] Inverse power model

A graphical exploration of available covariates (additional to those already incorporated into the model) was performed. No noteworthy trends were observed. Shrinkages on CLE/F, VX/F and VE/F, VC/F, and kD were such that covariate-random effect trends were not considered trustworthy.

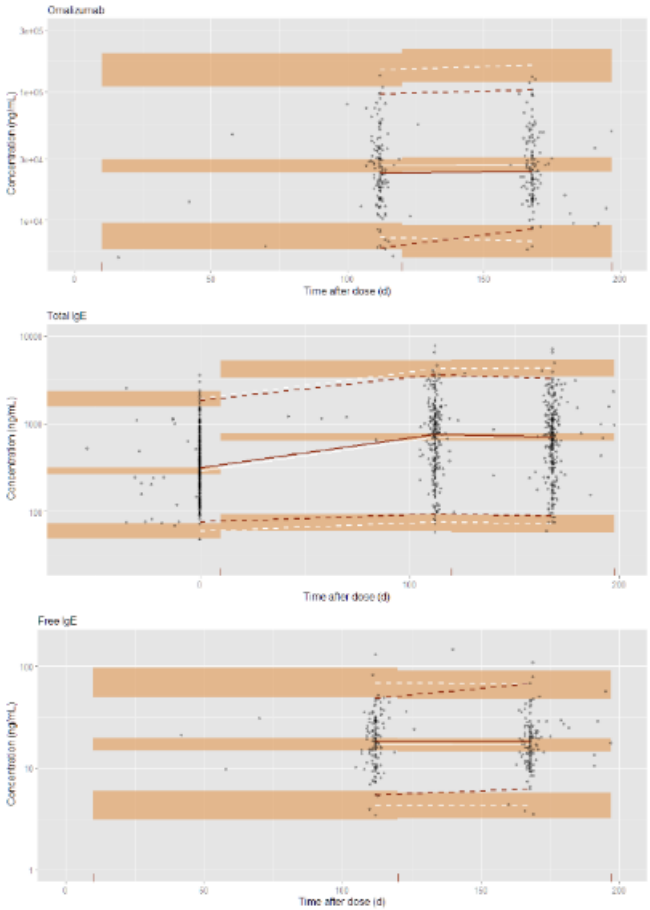
Figure 2. prediction-corrected Visual predictive check of the Honma model given the nasal polyps data, stratified by study.



Points are observations. Red and white lines link the medians and limits of 95% intervals for prediction-corrected observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

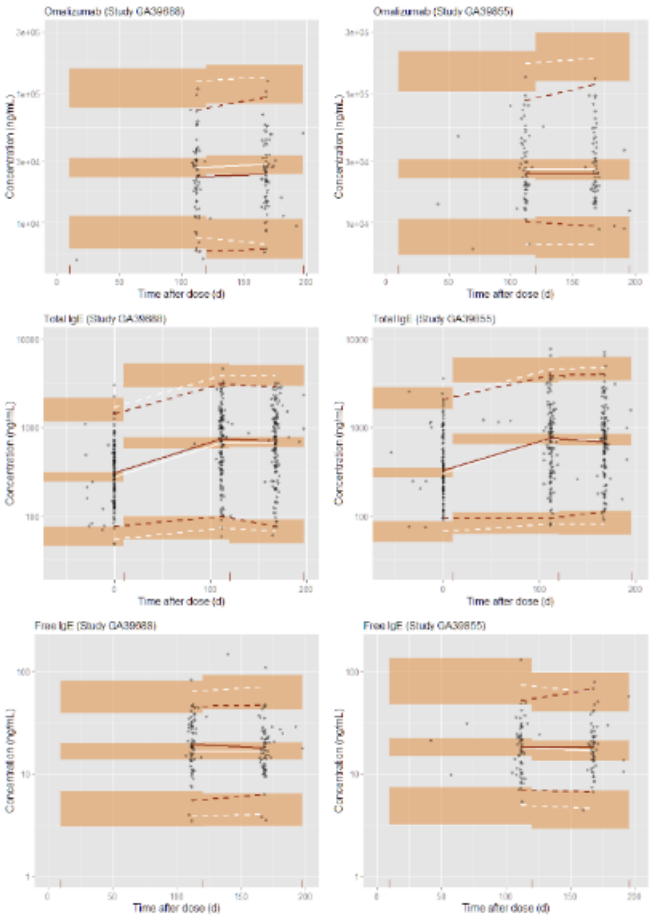
Upon request by CHMP, the MAH presented stratified and unstratified prediction corrected VPCs.

Figure 3-1 **Overall visual predictive check of the Honma model given the nasal polyps data, across dose regimen groups and studies.**



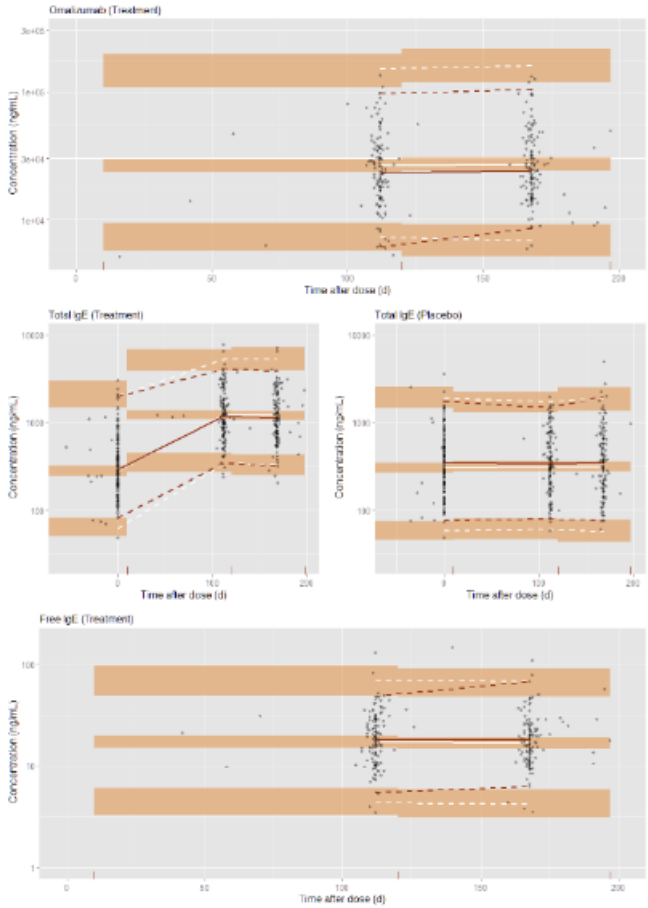
Points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

Figure 3-2 **Visual predictive check of the Honma model given the nasal polyps data, stratified by study.**



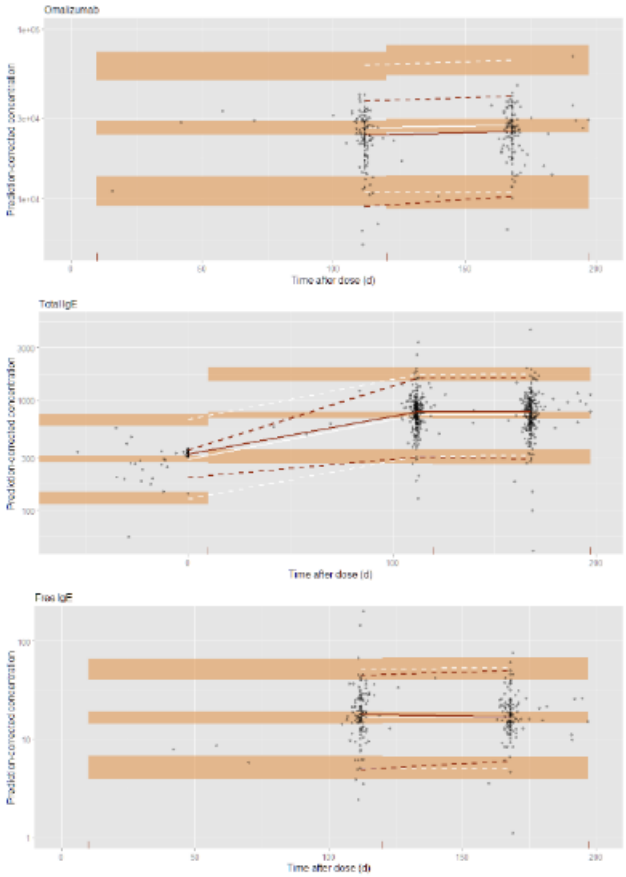
Points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

Figure 3-3 **Visual predictive check of the Honma model given the nasal polyps data, stratified by active treatment/placebo.**



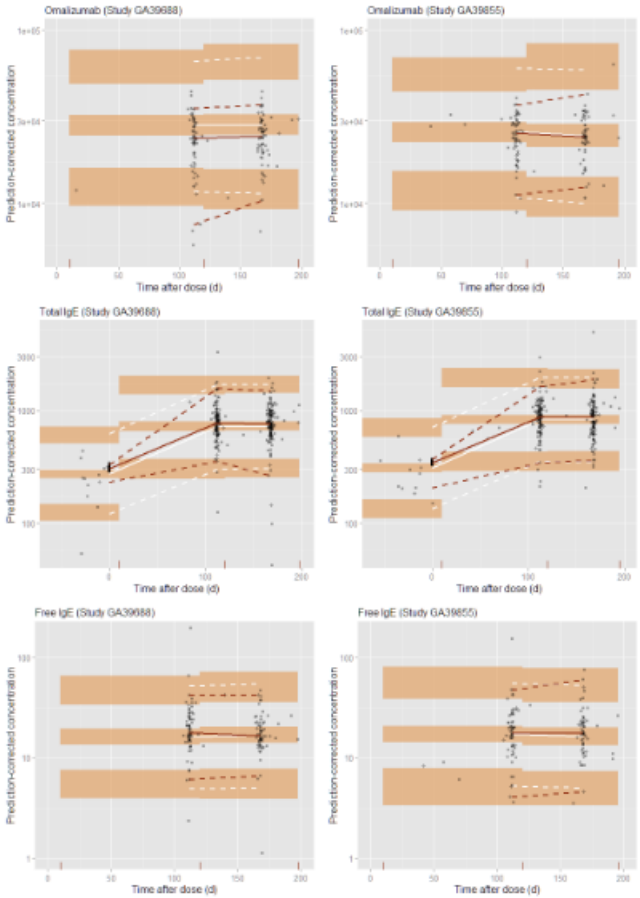
Points are observations. Red and white lines link the medians and limits of 95% intervals for observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

Figure 3-4 **Overall prediction-corrected visual predictive check of the Honma model given the nasal polyps data, across dose regimen groups and studies.**



Points are observations. Red and white lines link the medians and limits of 95% intervals for prediction-corrected observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

Figure 3-5 Prediction-corrected visual predictive check of the Honma model given the nasal polyps data, stratified by study.



Points are observations. Red and white lines link the medians and limits of 95% intervals for prediction-corrected observed and predicted data (respectively) by median time in each bin. Orange shaded areas are 95% prediction intervals for medians and limits of 95% range for predictions. Red ticks indicate bin boundaries. Excluding free IgE concentrations for the placebo treatment and free IgE concentrations pre-treatment.

Exposure-response modelling

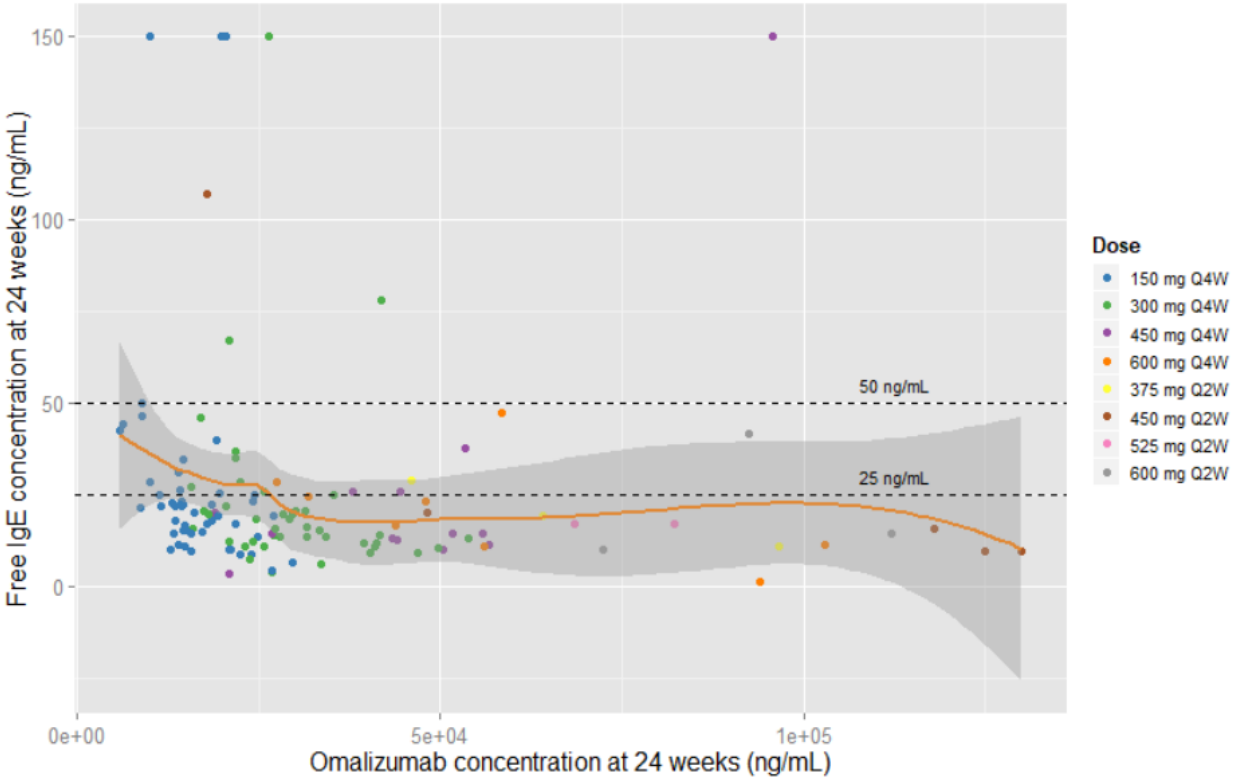
Methods

The objective was to use available PK and free IgE observations at Week 24 from patients with nasal polyps and graphically explore the omalizumab exposure-response and the free IgE-response relationships for the efficacy endpoints of absolute change from baseline at Week 24 in nasal polyps score (NPS), in average daily nasal congestion score (NCS), in average daily total nasal symptom score (TNSS), and in patient-reported health- related quality of life (HRQoL) as assessed by the total Sino-Nasal Outcome Test-22 (SNOT-22). A graphical comparison with corresponding observed omalizumab and free IgE concentrations at Week 24 and Covariates of interest (study, dose regimen/group, baseline age, baseline body weight, baseline body mass index [BMI], sex, race, baseline IgE, comorbidity and baseline score values) was also done.

Results

Using the baseline body weight- and total IgE-based omalizumab dosing table, free IgE suppression at week 24 in nasal polyps studies (GA39688 and GA39855) was achieved with 119 (93.0%) of the subjects on active treatment and with evaluable free IgE concentrations reaching free IgE levels of below 50 ng/mL and 95 subjects (74.2%) reaching free IgE levels of below 25 ng/mL. The relationship between omalizumab concentration and free IgE concentration at week 24 is shown in (Figure 3).

Figure 3. Relationship between total omalizumab concentration and free IgE concentration at week 24, by dose/regimen group



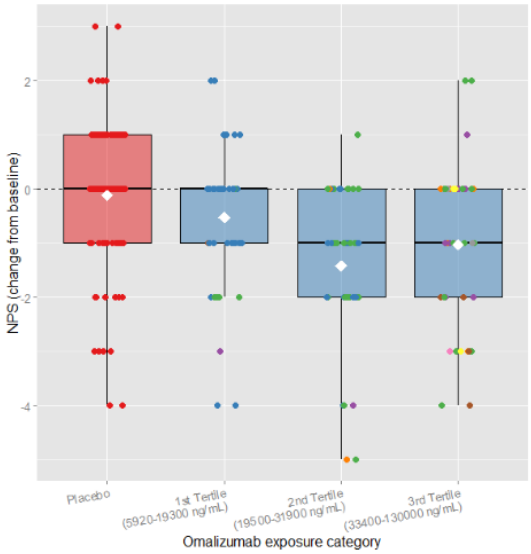
Points are observations. Orange line is a LOESS smooth, and the shaded area is its corresponding 95% confidence interval. 150 ng/mL is the upper limit of quantification (ULQ). Horizontal lines denote 25 ng/mL and 50 ng/mL thresholds for free IgE suppression.

There was no clear or consistent correlation between omalizumab concentration and change from baseline NCS, NPS, TNSS and SNOT-22 responses observed at Week 24 in actively-treated subjects in the tested dose range (150-600 mg every 2 or 4 weeks) (Figure 4). A positive association between omalizumab concentration and NPS response was observed with the lowest concentration tertile group showing a lower NPS response than the other two tertile groups. While the possibility that these patients would have an improved response with a higher dosing regimen cannot be excluded, the trend of lower responses being observed in the first exposure tertile was not observed in the other efficacy endpoints (NCS, TNSS, and SNOT-22) that were evaluated.

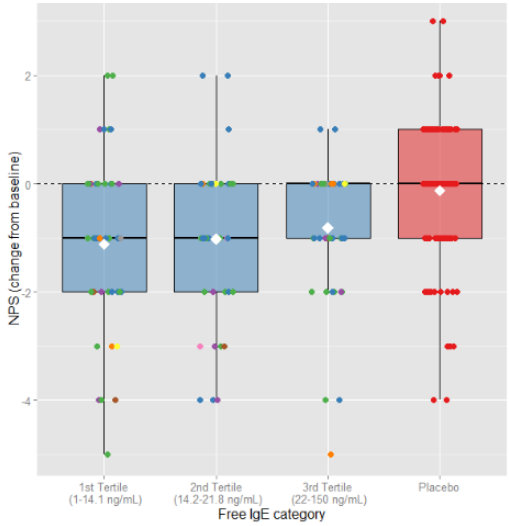
Graphical covariate analyses showed that baseline scores for all four efficacy endpoints had clear or slight correlations with their corresponding efficacy endpoint responses, with higher baseline scores being associated with larger changes from baseline at Week 24. The other covariates studied showed no clear relationships with efficacy responses, baseline IgE or free IgE-response relationships.

Figure 4. ΔNPS (A, B), ΔNCS (C, D), ΔTNSS (E, F) and ΔSNOT-22 (G, H) plotted against omalizumab and free IgE concentration at Week 24, by dose/regimen group.

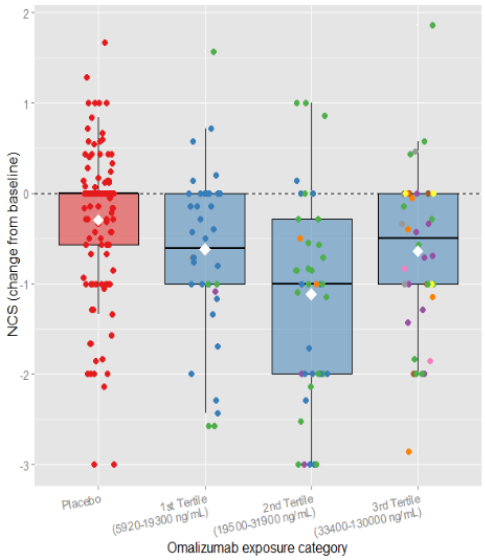
A. Omalizumab vs NPS (CFB, week 24)



B. Free IgE vs NPS (CFB, week 24)



C. Omalizumab vs NCS (CFB, week 24)



D. Free IgE vs NCS (CFB, week 24)

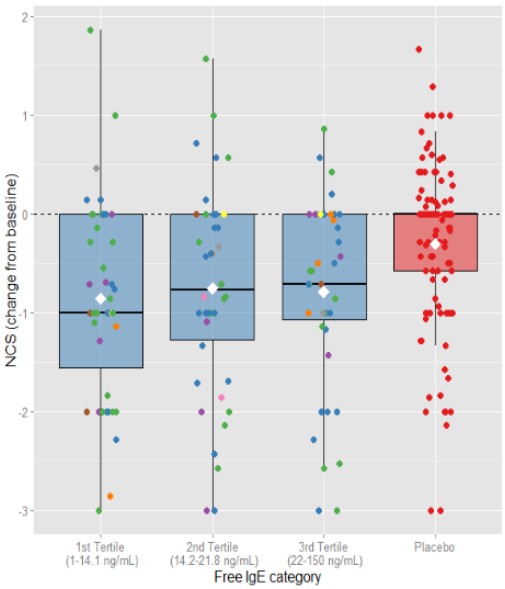
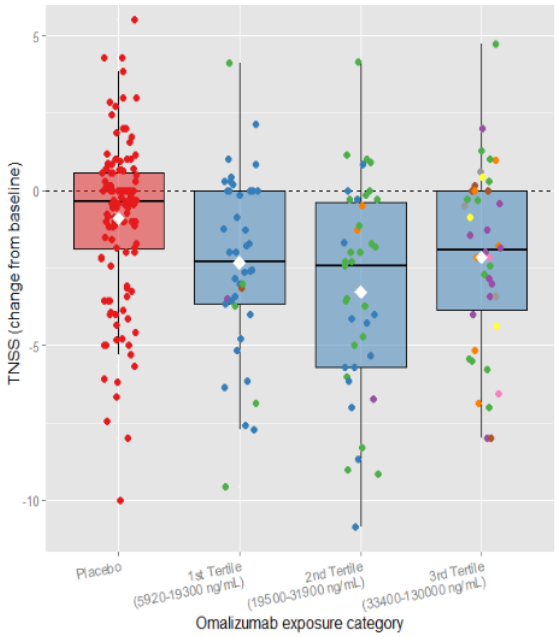
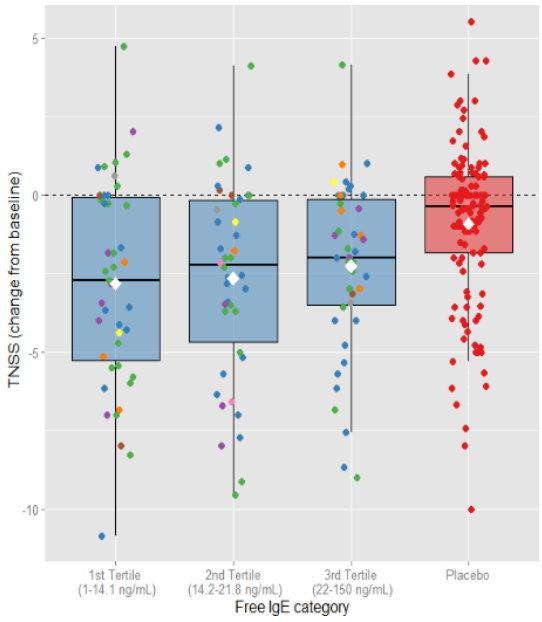


Figure 5. ΔNPS (A, B), ΔNCS (C, D), ΔTNSS (E, F) and ΔSNOT-22 (G, H) plotted against omalizumab and free IgE concentration at Week 24, by dose/regimen group. (continued)

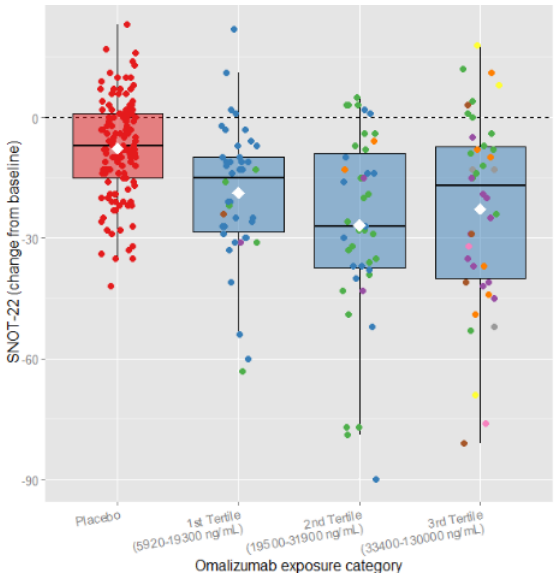
E. Omalizumab vs TNSS (CFB, week 24)



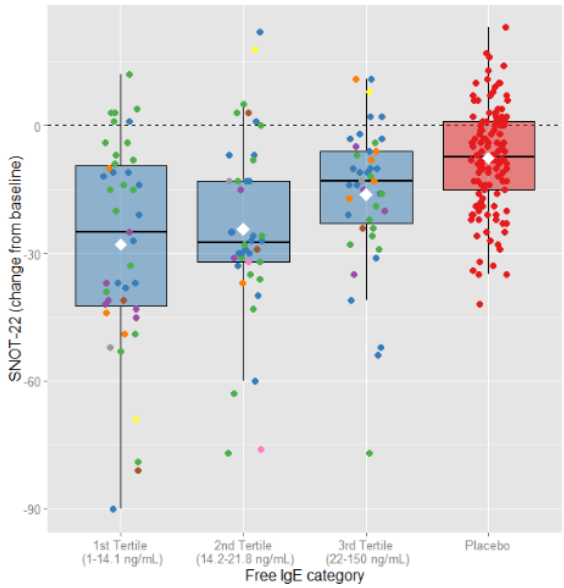
F. Free IgE vs TNSS (CFB, week 24)

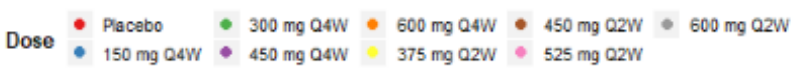


G. Omalizumab vs SNOT-22 (CFB, week 24)



H. Free IgE vs SNOT-22 (CFB, week 24)





For boxplots, jittered points are individuals, boxes represent medians and interquartile ranges, white diamonds are means, and whiskers extend to the most extreme data points which are no more than 1.5 times the length of the box away from the box. 150 ng/mL is the upper limit of quantification (ULQ) for free IgE.

2.3.5. Discussion on clinical pharmacology

Bioanalysis

The validation of assays for determination of total serum concentrations of omalizumab, free IgE serum levels and total IgE antibodies have been assessed in a previous submission (MAH Reports NBX-

RS602700, NBX-RS602700A and NBX-RS630172; EMEA/H/C/000606/II/48). For this variation, the MAH has not performed parallelism investigation for the omalizumab concentration, which is required according to the guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). Nevertheless, CHMP considered that this issue will not be further pursued based on the totality of the submitted data.

Further, the anti-drug antibody (ADA) method has a too low drug tolerance and therefore, ADA analysis was not conducted during the blinded treatment period. It remains unclear why the MAH has not developed an improved assay, nevertheless, the results will be available when study WA40169 is completed. Given the low immunogenicity in other indications, CHMP considered that it is acceptable to submit these missing data at a later stage. The MAH is therefore expected to submit the ADA-results with the final WA40169 study report.

Mechanism of action

Allergic asthma and nasal polyposis share a common IgE-mediated type 2 inflammatory response. In addition, locally produced IgE, often against Staphylococcus aureus enterotoxins, is associated with local inflammation in CRSwNP and, in particular, with comorbid asthma. CSU on the other hand has a less understood mechanism of disease and thus of omalizumab.

Population pharmacokinetic-pharmacodynamic model

The purpose of the population PK/PD analysis was to assess whether the PK of omalizumab and its effect on the PD (in terms of total IgE and free IgE) in nasal polyps were consistent with those in allergic asthma, and to explore the impact of existing and additional covariates on omalizumab pharmacokinetics and IgE kinetics in nasal polyps.

The Honma model was used, there the covariate model is very complex with all the covariates included. It is unclear why body weight and BMI are included in the model, as these are correlated. Doses are based on body weight and IgE, therefore it is assumed that the rest of the covariates are clinically insignificant. While it would have been of interest to see how a simpler model (without correlated covariates or covariates that have no significant clinical impact) performs, the doses proposed are well established and known to be safe. Justification of the selected model will not be pursued. It has been previously established that the factors affecting apparent clearance (CLx/F) of omalizumab include the processes of IgG clearance processes, clearance via specific binding and complex formation with its target ligand, IgE, as well as body weight. Body weight and baseline IgE levels are also the factors that the dose is adjusted on.

The model parameters were not re-estimated. Empirical Bayes estimates were generated, and standard diagnostic plots were produced to assess whether the pharmacokinetics of omalizumab and its effect on the pharmacodynamics in nasal polyps were consistent with those in asthma. While only few pre-dose samples were available for this analysis, the PK and PD effect of omalizumab does not appear to be different in the new population. Statistical shrinkage was relatively high (>35%) for all parameters except CLX/F, CLC/F and RE. Upon request by CHMP, the MAH provided the requested plots, updated the plot with the error and submitted additional plots for free IgE stratified by treatment (150 mg Q4W, 300 mg Q4W, and the other doses). It appears that it is mainly data from study GA39688 that are overpredicted. The free IgE concentration appears to be adequately predicted.

Exposure-response

No clear or consistent correlation between baseline NCS, NPS, TNSS and SNOT-22 and baseline IgE can be observed. No clear relationship between change from baseline to week 24 NCS, NPS, TNSS and SNOT-22 and baseline IgE can be observed either. Using the proposed posology (based on weight and baseline IgE), free IgE suppression at 24 weeks was achieved in 93.0% of the subjects on active

treatment. The exposure-response analysis consisted of a graphical comparison of the efficacy endpoints as absolute change from baseline at Week 24 in NPS, NCS, TNSS and SNOT-22 versus tertials of concentration and free IgE. A slight positive trend between omalizumab concentration and NPS response is observed with the lowest concentration tertile group, however, a clear trend between the week 24 omalizumab concentration, or free IgE, and the change from baseline in efficacy endpoints is not observed.

Overall, it was considered by CHMP that the PK and PD effect of omalizumab does not appear to be different in the new population. This has been adequately reflected in section 5.2 of the SmPC.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics and pharmacodynamics effect of omalizumab has been adequately characterised and does not appear to be different in subjects with nasal polyps compared to subjects with allergic asthma. The proposed posology based on body weight and IgE level is considered to be adequate to support the use of omalizumab in nasal polyps.

2.4. Clinical efficacy

In this variation application, two Phase-III, randomized, multi-centre, double-blind, placebo-controlled clinical trials of omalizumab in patients with nasal polyps are presented by the MAH. Studies **GA39688** and **GA39855** are completed pivotal, replicate studies which have identical study design. Patients who completed the double-blind treatment period of either study **GA39688** or study **GA39855**, could enrol in study WA40169, an open label extension (OLE) study, which is currently ongoing. No efficacy data from study WA40169 has been submitted initially however, supportive safety data from an interim analysis were submitted and are discussed in the safety section 2.5.

There is a Guideline on the clinical development of medicinal products for the treatment of allergic rhino-conjunctivitis (CHMP/EWP/2455/02), however there is no guideline on medicinal products for nasal polyposis currently available. Nevertheless, there is a European position paper on rhinosinusitis and nasal polyps which can provide some guidance for the current application (EPOS 2012).

CHMP scientific advice (SA) was sought in 2017 (EMEA/H/SA/45/4/2017/III). There were concerns about the posology of choice and the MAH was recommended to conduct an exploratory proof-of-concept and dose-finding study, which has not been done. Comments about adherence to this SA are provided in this report.

2.4.1. Dose response studies

A series of studies for nasal polyps using baseline IgE and body weight-based posology has been presented by the MAH as proof-of-concept. Based on the results from these studies, the EU posology for allergic asthma was adopted for the nasal polyp phase 3 studies. Since the Phase-III studies were to be conducted in adult patients and nasal polyps rarely occurs in patients less than 18 years of age, the posology of omalizumab used in these two nasal polyp studies was adopted from the allergic asthma dosing table by excluding cells of which the body weight is less than 30 kg.

A short summary of studies:

- In 2013, a randomized, double-blind, placebo-controlled study for 16 weeks in 24 patients with nasal polyps and comorbid asthma showed a reduction from baseline in total nasal endoscopic polyp score in the omalizumab arm (-2.67, p=0.001) but not in the placebo arm (-0.12,

p=0.99). In addition, it was claimed that omalizumab treatment reduced symptom scores and improved health related quality of life scores.

- A randomized, double-blind, placebo-controlled study from 2010, with 14 patients, of whom 12 had nasal polyposis, showed, according to the MAH, improvement in the omalizumab group compared to none in the placebo group but the authors concluded that IgE plays at most a small role in the mucosal inflammation of chronic rhinosinusitis.
- A retrospective case control study of totally 8 patients suggested that omalizumab may be effective in the treatment of nasal polyposis.
- A case series from 2011 of 19 patients who were treated with omalizumab for severe asthma associated with nasal polyps, the size of the nasal polyps and the use of intranasal corticosteroids were reduced compared to baseline at follow-up (range 15-28 months).
- A prospective study, published in 2013, 6 patients with severe asthma and chronic rhinosinusitis with eosinophilic enriched nasal polyps were treated with omalizumab for 16 weeks. There was an improvement at 16 weeks compared to baseline in SNOT-20, symptoms of nasal blockage and dysosmia, sinus CT scores using the Lund-Mackay system and Asthma Control Questionnaire scores. Nasal polyp size was reduced in 4 of the 6 patients.
- In 2018, a prospective study compared omalizumab (N = 13) to FESS with polypectomy (N = 24) in the treatment of nasal polyps with comorbid severe allergic asthma, examining the outcome of SNOT-22 improvement 4 and 16 weeks after treatment initiation. The authors concluded that "the improvement seen with omalizumab approached the treatment efficacy as assessed by the SNOT-22 score recorded after surgery".

2.4.2. Main studies

The efficacy of omalizumab in the treatment of patients with nasal polyps who have inadequate response to intranasal corticosteroids (INC) is supported by two pivotal replicate studies i.e. study GA39688 and study GA39855.

Methods

Studies **GA39688** and **GA39855** were replicate Phase-III, randomized, multi-centre, double-blind, placebo-controlled, clinical studies that were conducted in parallel with identical study designs. They were conducted concurrently across different sites in 15 countries across Europe and North America. Each study was designed to enrol approximately 120 adult patients with nasal polyps who had an inadequate response to standard of care treatments (daily treatment with intranasal corticosteroid therapy).

Study participants

To ensure that the patient population recruited across sites in North America, Eastern and Western Europe were similar in their baseline disease characteristics and standard of care therapies, sites were selected after a detailed feasibility assessment and review of their facilities and treatment practices. Furthermore, both pivotal studies required patients to be on a daily standard of care medication, mometasone intranasal corticosteroid, for $\geq$ 4 weeks prior to the first screening visit and during the 5-week run-period prior to potential randomization.

Inclusion and exclusion criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age 18−75 years, inclusive, at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- NPS ≥ 5, with a unilateral score of ≥ 2 for each nostril, at screening (Day -35), and on Day -7 (as assessed by a central panel of independent central readers)
- SNOT-22 score ≥ 20 at screening (Day -35) and at randomization (Day 1)
- Treatment with nasal mometasone at least 200 µg per day, or equivalent daily dosing of another nasal CS, for at least 4 weeks before screening (Day -35)
- Treatment with nasal mometasone 200 µg BID (or QD if intolerant to twice daily) during the run-in period with an adherence rate of at least 70%.
- Presence of nasal blockage/congestion with NCS ≥ 2 (1-week recall) at Day -35 and a weekly average at randomization of NCS > 1 with at least one of the following symptoms prior to screening: nasal discharge (anterior/posterior nasal drip) and/or reduction or loss of smell
- Eligibility per the study drug−dosing table (serum IgE level ≥ 30 to ≤ 1500 IU/mL and body weight ≥ 30 to ≤ 150 kg) and ability to be dosed per the dosing table
- Willingness to maintain all background medications stable for the duration of the treatment and follow-up periods
- Willingness and ability to use electronic device to enter study-related information in electronic devices (electronic diary [eDiary]/electronic tablet [eTablet])
- Demonstration of at least 70% adherence to eDiary daily symptom assessment during run-in period, with fully completed entries on at least 4 days in the week prior to randomization
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for 60 days after the last dose of study drug.

Patients who meet any of the following criteria would be excluded from study entry:

- Known history of anaphylaxis/hypersensitivity to omalizumab
- Treatment with investigational drugs within 12 weeks or 5 half-lives (whichever is longer) prior to screening (Day -35)
- Treatment with monoclonal antibodies (e.g., omalizumab, mepolizumab) for 6 months prior to screening (Day -35)
- Current treatment with leukotriene antagonists/modifiers, unless patient has been on stable dosing of such medication for at least 1 month prior to screening (Day - 35)
- Treatment with non-steroid immunosuppressants
- Treatment with systemic corticosteroids (CS), except when used as treatment for nasal polyposis, within 2 months prior to screening (Day -35)

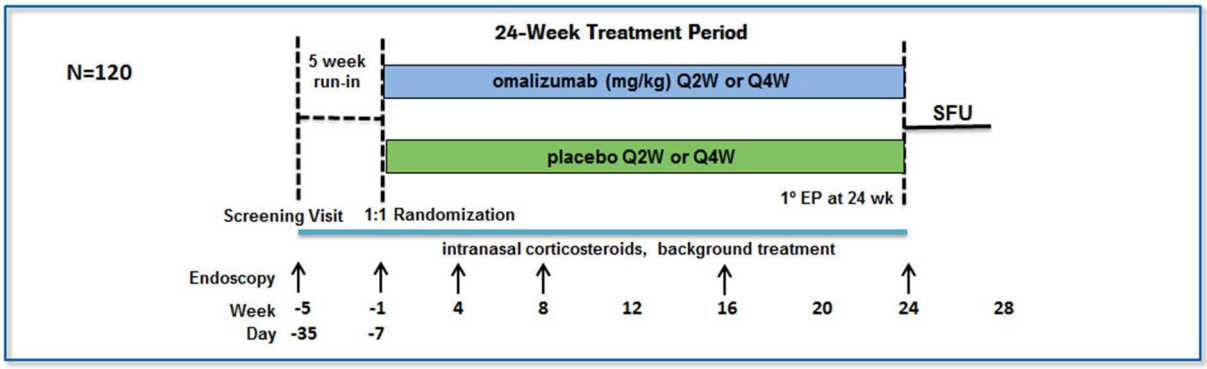
- Usage of systemic CS during the run-in period. Patients requiring systemic CS during run-in may be rescreened after completing systemic CS
- Treatment with intranasal CS drops or CS−administering devices (e.g., OptiNose device or stents) within 1 month prior to screening (Day -35) or during the run-in period
- History of nasal surgery (including polypectomy) within 6 months prior to screening
- History of sinus or nasal surgery modifying the structure of the nose such that assessment of NPS is not possible
- Uncontrolled epistaxis requiring surgical or procedural intervention, including nasal packing, within 2 months prior to screening
- Known or suspected diagnosis of cystic fibrosis, primary ciliary dyskinesia (e.g., Kartagener syndrome) or other dyskinetic ciliary syndromes, hypogammaglobulinemia or other immune deficiency syndrome, chronic granulomatous disease and granulomatous vasculitis, granulomatosis with polyangiitis (e.g., Wegener's Granulomatosis), or eosinophilic granulomatous with polyangiitis (EGPA) (e.g., Churg-Strauss syndrome)
- Presence of antrochoanal polyps
- Concomitant nasal conditions that interfere with evaluation of primary endpoint
- Known HIV infection at screening
- Known acute and chronic infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
- History of myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack or a known history of a hypercoagulable disorder
- Infection that meets certain criteria (not included here, available in the CSR)
- Active tuberculosis requiring treatment within 12 months prior to screening (Day -35) Patients who have completed treatment for tuberculosis at least 12 months prior to screening (Day -35) and have no evidence of recurrent disease are permitted.
- Initiation of or change in allergen immunotherapy within 3 months prior to screening (Day -35) or during the run-in period
- Initiation of or change in aspirin desensitization within 4 months prior to screening (Day -35) or during the run-in period
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 60 days after the last dose of omalizumab
- Current malignancy or history of malignancy within 5 years prior to screening, except for appropriately treated carcinoma in situ of the cervix or non-melanoma skin carcinoma that has been treated or excised and is considered resolved
- Any serious medical condition (including but not limited to significant arrhythmia, uncontrolled hypertension, significant pulmonary disease other than asthma) or abnormality in clinical laboratory tests that precludes the patient's safe participation in and completion of the study
- History of alcohol, drug, or chemical abuse within 6 months of screening

Treatments

Both studies consisted of a 5-week screening/run-in period, a 24-week placebo-controlled treatment period, and a 4-week safety follow-up period (Figure 6).

The 5-week screening/run-in period included two visits, at which patients underwent video endoscopy to quantify the size of the polyps and to assign an NPS prior to baseline.

Figure 6. Study design (studies GA39688 and GA39855)



1°EP = co-primary end point; Q2W = every 2 weeks; Q4W = every 4 weeks; SFU = safety follow-up; wk = week.
Note: All patients were treated during the entire study with intranasal corticosteroids (mometasone nasal spray) as background therapy.

Study drug dosing started on the day of randomization (Day 1, Week 0) and was repeated every 2 or 4 weeks (depending on the patient's IgE value and body weight at Screening) during the 24-week placebo-controlled treatment period. Patients remained on stable doses of intranasal corticosteroids therapy (mometasone nasal spray 200 µg bid) for the entire treatment period. Patients deemed by the investigator to be intolerant to a bid regimen of mometasone remained on a stable dosage of mometasone 200 microgram once a day.

After the treatment period, patients were followed for an additional 4 weeks, unless they enrolled into the open-label extension study WA40169 at Week 24. Patients who discontinued study drug during the treatment period continued the planned study assessments through Week 24 and completed a 4-week safety follow-up period. Patients who were unwilling or unable to continue with the planned assessments in the treatment period, completed a dosing termination visit and entered a 4-week safety follow-up period. Patients who required sinus surgery or required two or more courses of treatment with systemic corticosteroids for $\geqslant$ 3 consecutive days discontinued study drug but continued in the study with assessments.

Objectives

Primary and secondary efficacy objectives:

- To evaluate the efficacy of omalizumab compared with placebo

Outcomes/endpoints

Co-Primary endpoints:

- Change from baseline at Week 24 in NPS
- Change from baseline at Week 24 in average daily NCS

Nasal polyp score is decided with intranasal endoscopy and right and left sides are assessed separately on a scale from 0 to 4 (total maximum 8).

Nasal congestion score (0 to 3) is based on daily patient reports using the mean value of the last 7 days.

Secondary endpoints:

For the EU application, a smaller set of secondary endpoints (Table 5), with a sequential order different from the general sequential testing order (FDA testing scheme) was used. Hypothesis 8, as a secondary endpoint for EU application, was analysed using pooled data.

TNSS grades four symptoms, sneezing, congestion, itching and rhinorrhoea. Each symptom is graded from 0-3 (3 being the worst).

SNOT-22 (0-110 points) is a validated questionnaire of disease specific, quality of life related measures of sinonasal function which has been validated to show a MCID of 8.9 or more. Seven or lower is considered normal.

UPSIT is a test for smell identification to test the function of an individual's olfactory system with the worst being 0 and the best being 40.

These scores were patient reported.

Table 5 Secondary endpoints for EU application

Hypothesis Number	Secondary Efficacy Endpoints in the Order Tested
H3	Change from baseline at Week 24 in average daily TNSS
H4	Change from baseline at Week 24 HRQoL as assessed by the total SNOT-22
H5	Change from baseline at Week 24 in UPSIT
H6	Change from baseline at Week 16 in NPS
H7	Change from baseline at Week 16 in average daily NCS
H8	Requirement of rescue treatment (systemic CS or nasal polypectomy) – through Week 24-tested with pooled data from both Phase III studies
CS= corticosteroid; HRQoL=health-related quality of life; NCS = nasal blockage/congestion score; NPS = nasal polyp score; SNOT-22=Sino-Nasal Outcome Test-22; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.	

Sample size

A planned total of 120 patients were to be enrolled. The sample size of 120 patients (102 patients divided by 0.85 assuming a 15% early withdrawal rate) provided at least 85% power to independently detect both a 0.56-point difference between treatment groups in change from baseline at Week 24 in the average daily NCS (assuming standard deviation [SD]=0.75) and a 1.50-point difference between treatment groups in change from baseline at Week 24 in NPS (assuming SD=2.0). The sample size was calculated using East, Version 6.2, using two-sample Student t-test with equal variances.

The assumed test is two-sided with α = 0.05 and the randomization ratio is 1:1. The standard deviations (SDs) assumed for change from baseline at Week 24 in NCS and NPS were 0.83 and 2.2, respectively.

The sample size of n = 102 patients will provide approximately 92% power to detect a 0.56-point treatment group difference in change from baseline at Week 24 in NCS (SD = 0.83) and approximately 93% power to detect a 1.50-point treatment group difference in change from baseline at Week 24 in NPS (SD = 2.2), for an overall power of approximately 85% (0.93 × 0.92 > 0.85). This sample size of n = 102 patients was inflated to n = 120 to maintain power after an assumed 15% early withdrawal rate.

Randomisation

On Day 1 (Week 0), patients were randomly allocated in a 1:1 ratio to receive double-blind treatment with omalizumab or placebo. Randomization was stratified by comorbid asthma and aspirin sensitivity status at baseline (asthma with aspirin sensitivity, asthma without aspirin sensitivity, and non-asthma regardless of aspirin sensitivity) and geographic region (North America, ex-North America).

Blinding (masking)

The studies were double-blinded. The patients, the designated evaluating physician(s) and study nurses, the central image readers, and the Sponsor and their agents were blinded to treatment assignment throughout the study. To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels), access to these results were restricted to the site and the sponsor until study completion. Treatment assignment may be unblinded to the personnel analysing the data from the treatment period when all data through Week 24 are in the database and the data have been cleaned and verified.

Study drug supplies were shipped blinded to each site. To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drug will not be permitted to conduct any safety or efficacy evaluations. Each centre will identify an individual (e.g., pharmacist) responsible for the reconstitution procedures. This individual will prepare the study drug for each patient prior to administration. An individual not involved with evaluating the patient must be identified to administer the study drug.

Statistical methods

The analysis of data from the 24-week treatment period were performed after all patients had either completed the Week 24 visit or discontinued from the treatment period prematurely, and all data from the treatment period are in the database and had been cleaned and verified. Patients who discontinued early were not replaced.

The analysis of complete data from the study, including data from the safety follow-up period, were performed when all patients have either discontinued the study early or completed the safety follow-up period, all data from the study are in the database, and the database is cleaned and locked.

There are two distinct and equally important estimand of interest in this trial. The first estimand is the treatment group difference in mean change from baseline at Week 24 in NPS in patients with CRSwNP, where the need for rescue medication, nasal polypectomy or study drug discontinuation is accounted for as an unfavourable (worst) outcome. The second estimand is the treatment group difference in mean change from baseline at Week 24 in the average daily NCS in patients with CRSwNP, where the

need for rescue medication, nasal polypectomy or study drug discontinuation is accounted for as an unfavourable (worst) outcome.

Three analysis sets were defined:

- The full-analysis set (FAS)included all randomized patients grouped according to the treatment assigned at randomization.
- The pooled full-analysis set (PFAS) included all randomized patients in both studies grouped according to the treatment assigned at randomization.
- The safety analysis set consisted of all patients who received at least one dose of study drug, with patients grouped according to treatment received

Hypothesis testing for all efficacy endpoints were conducted in the full-analysis set (FAS).

The study level type-1 error for the family of primary and select secondary efficacy hypotheses are controlled at $\alpha = 0.05$. The co-primary hypotheses (H1 and H2) are tested simultaneously at first. If both of the co-primary hypotheses are rejected at a two-sided significance level of 0.05, then the secondary hypotheses are tested in a sequential order. Studies GA39688 and GA39855 are identical in design. The requirement of rescue treatment (systemic CS or nasal polypectomy) was tested using the PFAS from Studies GA39688 and GA39855 studies if the analysis findings from the two studies are consistent. The corresponding hypotheses are denoted as H8.

All hypothesis tests are two-sided. Unless otherwise noted, all analyses of efficacy outcome measures are adjusted by geographic region through the use of a categorical variable and by baseline asthma comorbidity and aspirin sensitivity status.

Treatment group comparisons of absolute change from baseline at Week 24 in average daily NCS between treatment groups was assessed using a mixed-effect model repeated measurement (MMRM) model with unstructured covariance. The variance-covariance matrices for each treatment group were assumed equal. The Kenward-Rogers approximation (Kenward and Roger 1997) was used to calculate the denominator degrees of freedom. The dependent variable is absolute change from baseline in average daily NCS. In addition to adjustment for geographic region and asthma/aspirin sensitivity comorbidity status, the model includes terms for treatment group, timepoint (Weeks 4, 8, 12, 16, 20, and 24), baseline value of the dependent variable (baseline average daily NCS in this case), treatment by timepoint interaction, and baseline value of dependent variable by timepoint interaction. Point estimates, 95% confidence intervals, and p-values for the treatment effect (omalizumab vs. placebo) on absolute change from baseline at a timepoint in average daily NCS were calculated on the basis of the model for all post-baseline analysis timepoints.

NPS is the sum of the polyp scores in both nostrils (maximum score of 8) as assessed by independent expert reviewers. The absolute change from baseline at Week 24 in NPS for each patient is defined as the NPS assessment assigned to Week 24 minus the NPS at baseline. The estimand and primary estimator method for NPS followed those used for NCS.

Patients with baseline and no post-baseline data were included in the model for the calculation of the LS means. The LS-means will be calculated using the coefficients of the independent variables weighted according to that observed in the FAS, regardless of treatment assignment. This marginal weighting of coefficients for LS-means may impact the estimates of the means in each treatment arm but would not impact the difference between means in arms because the same covariate values are applied to calculate the means in both arms. The null hypothesis will be tested by the t-test arriving from the treatment group difference in LS-means of the change from baseline at Week 24 in average daily NCS.

Intercurrent events defined are (1) Had rescue treatment not been made available prior to Week 24; (2) regardless of study drug discontinuation due to AE/PD/LOE. All values after the intercurrent event would be coded to worst observed event value carried forward (worst observed value post-randomization and up to and including the day of the intercurrent event for that patient).

Missing data not explicitly covered above will be assumed MAR (i.e., given the observed outcomes and other variables in the statistical model missingness is independent of the unobserved outcomes). This type of missing data will not be explicitly imputed.

Sensitivity analyses on both co-primary endpoints were performed on the following:

- the variability associated with single imputation following an intercurrent event
- the effect of adjusting for baseline mometasone and anti-leukotriene use
- the definition of what qualifies as rescue medication (systemic CS for ≥3 consecutive days)
- the inclusion of patients who did not meet all enrolment eligibility criteria in the protocol
- the IxRS data used for asthma patient classification as pertains to baseline covariate adjustment

As supplementary analyses of both co-primary endpoints cumulative proportion of responder graphs were included.

Results

Participant flow

In study **GA39688**, a total of 355 patients were screened and 217 failed screening. The most common reason of screen failure reported was the failure to meet the NPS inclusion criteria of "NPS ≥5, with a unilateral score of ≥2 for each nostril, at screening (Day -35), and on Day -7 (as assessed by a central panel of independent central readers)" (49.8%). The second most common reason (31.8%) was eligibility per the study drug-dosing table (serum IgE level ≥30 to ≤1500 IU/mL and body weight ≥30 to ≤150 kg) and ability to be dosed per the dosing table. Other reasons of screen failures were each reported in <5% of patients.

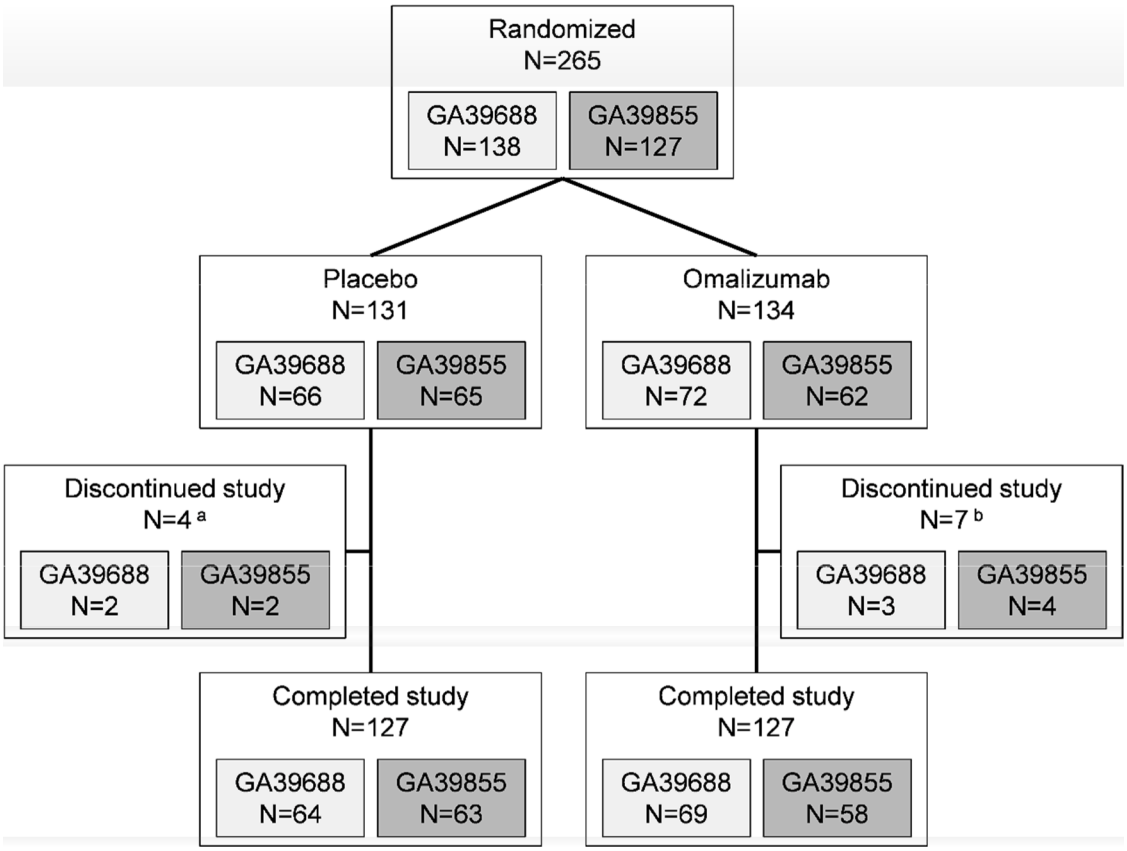
In study **GA39855**, a total of 329 patients were screened and 202 failed screening. The most common reason of screen failure reported was the failure to meet the NPS inclusion criteria of "NPS ≥5, with a unilateral score of ≥2 for each nostril, at screening (Day -35), and on Day -7 (as assessed by a central panel of independent central readers)" (49.0%). The second most common reason (23.3%) was eligibility per the study drug-dosing table (serum IgE level ≥30 to ≤1500 IU/mL and body weight ≥30 to ≤150 kg) and ability to be dosed per the dosing table. Other reasons of screen failures were each reported in <10% of patients.

Patient disposition was similar between studies **GA39688** and **GA39855**. Overall, 265 patients were randomized (138 in study GA39688, 127 in study GA39855), 131 to placebo (66 in study GA39688, 65 in study GA39855) and 134 to omalizumab (72 in study GA39688, 62 in study GA39855). A total of 11 patients (4.2%) discontinued the studies (including the 4 week follow-up), 4 (3.1%) in the placebo arms and 7 (5.2%) in the omalizumab arm, predominantly as per the patient's wish (10 patients; all 4 in the placebo arm and 6 in the omalizumab arm). The 1 remaining patient was withdrawn from the study by the physician.

Reasons for withdrawal from the study in the placebo groups were lack of time, no interest in completing follow-up, disturbing nasal symptoms and one subject resigned without given reason. In the omalizumab groups the reasons were pregnancy, incarceration, lack of time, resignation without given reason and emigration.

Patient Disposition Flowchart of studies **GA39688** and **GA39855** (Full Analysis Sets), and Overall (Pooled Full Analysis Set) is shown in Figure 7.

Figure 7. Patient Disposition Flowchart of Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)



[a] All discontinued as per patient's wish.

[b] All discontinued as per patient's wish, except for 1 patient in Study GA39688 who was withdrawn by the physician.

Recruitment

In the **GA39688** study, the patients were enrolled at 37 investigational sites across 10 countries. A total of 96 patients were enrolled in Europe (69.5%), 33 patients in the US (23.9%), 7 patients in Canada (5.1%), and 2 patients were enrolled in Mexico (1.4%). A listing of investigators and randomization details has been provided.

First patient was enrolled on the 15 November 2017 and the last visit of the last patient was on the 11 March 2019.

In the **GA39855** study, the patients were enrolled at 45 investigational sites across 10 countries. A total of 101 patients were enrolled in Europe (79.5%), 23 patients in the US (18.1%), and 3 patients were enrolled in Mexico (2.4%). A listing of investigators and randomization details has been provided.

The first patient was enrolled on the 21 November 2017 and the last visit of the last patient was on the 7 March 2019.

Conduct of the study

The studies were conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the following sections of the protocol.

Approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) was obtained before study start and was documented in a letter to the investigator specifying the date on which the committee met and granted the approval. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

No modifications were made to the protocol after receipt of the IRB/IEC approval. Protocol amendments were prepared by the Sponsor and were submitted to the IRB/IEC and to Regulatory Authorities in accordance with local regulatory requirements. Approval was obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes. The study protocol for **GA39688** and **GA39855** version2 was signed on 11-Oct-2017.

The first SAP version was signed 24-Jan-2019 and the final SAP was signed 15-Apr-2019. Data of data base lock and unblinding was 2019-Apr-17 for both studies.

In both studies **GA39688** and **GA39855**, all of the reported major protocol deviations were related to inclusion/exclusion criteria or procedural deviations, and not considered to have an impact on the interpretation of efficacy results of those studies, as demonstrated by sensitivity analyses. In the PFAS, 15 patients (11.5%) in the placebo arm and 16 patients (11.9%) in the omalizumab arm had at least one major protocol deviation.

Baseline data

Demographics at baseline were generally similar between Studies **GA39688** and **GA39855**, and between treatment arms within each study (Table 6). Baseline disease characteristics are shown in Table 7.

Table 6. Demographics at Baseline: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

	Study GA39688		Study GA39855		Pooled studies		
Variable	Placebo (N = 66)	Omalizumab (N = 72)	Placebo (N = 65)	Omalizumab (N = 62)	Placebo (N = 131)	Omalizumab (N = 134)	Total (N = 265)
Age at enrollment							
Mean (SD)	52.2 (11.6)	50.0 (14.5)	51.0 (12.0)	49.0 (11.9)	51.6 (11.8)	49.6 (13.3)	50.6 (12.6)
Median (min – max)	54.0 (28 – 74)	51.0 (19 – 73)	51.0 (18 – 75)	49.5 (20 – 71)	52.0 (18 – 75)	50.0 (19 – 73)	51.0 (18 – 75)
Age group, n (%)							
< 65 years	54 (81.8)	59 (81.9)	56 (86.2)	56 (90.3)	110 (84.0)	115 (85.8)	225 (84.9)
≥ 65 years	12 (18.2)	13 (18.1)	9 (13.8)	6 (9.7)	21 (16.0%)	19 (14.2)	40 (15.1)
Sex, n (%)							
Male	41 (62.1)	47 (65.3)	44 (67.7)	39 (62.9)	85 (64.9)	86 (64.2)	171 (64.5)
Female	25 (37.9)	25 (34.7)	21 (32.3)	23 (37.1)	46 (35.1)	48 (35.8)	94 (35.5)
Ethnicity, n (%)							
Hispanic or Latino	5 (7.6)	9 (12.5)	3 (4.6)	5 (8.1)	8 (6.1)	14 (10.4)	22 (8.3)
Not Hispanic or Latino	61 (92.4)	62 (86.1)	61 (93.8)	56 (90.3)	122 (93.1)	118 (88.1)	240 (90.6)
Not Reported	0	0	1 (1.5)	1 (1.6)	1 (0.8)	1 (0.7)	2 (0.8)
Unknown	0	1 (1.4)	0	0	0	1 (0.7)	1 (0.4)
Race, n (%)							
White	66 (100)	65 (90.3)	65 (100)	61 (98.4)	131 (100)	126 (94.0)	257 (97.0)
American Indian or Alaska Native	0	2 (2.8)	0	0	0	2 (1.5)	2 (0.8)
Black or African American	0	2 (2.8)	0	0	0	2 (1.5)	2 (0.8)
Unknown	0	3 (4.2)	0	1 (1.6)	0	4 (3.0)	4 (1.5)
Geographic Region, n (%)							
North America [a]	19 (28.8)	23 (31.9)	14 (21.5)	12 (19.4)	33 (25.2)	35 (26.1)	68 (25.7)
Europe	47 (71.2)	49 (68.1)	51 (78.5)	50 (80.6)	98 (74.8)	99 (73.9)	197 (74.3)
Weight (kg) at enrollment							
Mean (SD)	80.8 (18.0)	78.3 (16.3)	83.4 (16.9)	79.0 (14.7)	82.1 (17.5)	78.6 (15.5)	80.3 (16.6)
Median (min – max)	81.0 (43 – 122)	76.0 (53 – 128)	84.0 (52 – 135)	79.5 (48 – 125)	83.0 (43 – 135)	77.0 (48 – 128)	80.0 (43 – 135)
BMI (kg/m²) at enrollment							
Mean (SD)	27.7 (5.3)	27.4 (4.8)	28.1 (5.0)	26.9 (4.1)	27.9 (5.1)	27.1 (4.4)	27.5 (4.8)
Median (min – max)	27.3 (18.9 – 46.1)	26.5 (19.9 – 42.1)	27.7 (17.5 – 43.1)	26.4 (17.9 – 37.7)	27.5 (17.5 – 46.1)	26.5 (17.9 – 42.1)	27.0 (17.5 – 46.1)
BMI categories, n (%)							
< 18.5 kg/m²	0	0	1 (1.5)	2 (3.2)	1 (0.8)	2 (1.5)	3 (1.1)
18.5 - < 25 kg/m²	21 (31.8)	26 (36.1)	17 (26.2)	15 (24.2)	38 (29.0)	41 (30.6)	79 (29.8)
25 - < 30 kg/m²	25 (37.9)	28 (38.9)	26 (40.0)	32 (51.6)	51 (38.9)	60 (44.8)	111 (41.9)
30 - < 40 kg/m²	19 (28.8)	16 (22.2)	19 (29.2)	13 (21.0)	38 (29.0)	29 (21.6)	67 (25.3)
≥ 40 kg/m²	1 (1.5)	2 (2.8)	2 (3.1)	0	3 (2.3)	2 (1.5)	5 (1.9)

BMI = body mass index; max = maximum; min = minimum; SD = standard deviation.
[a]North America includes Canada, Mexico and United States of America.
Source: [Study GA39688-t_dm_FAS], [Study GA39855-t_dm_FAS], [SCE Appendix 1-t_dm_PFAS]

Table 7. Baseline Disease Characteristics: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

	Study GA39688		Study GA39855		Pooled studies		
Variable	Placebo (N = 66)	Omalizumab (N = 72)	Placebo (N = 65)	Omalizumab (N = 62)	Placebo (N = 131)	Omalizumab (N = 134)	Total (N = 265)
Mometasone Prescribed Dose, n (%) [a]							
200 µg/day	4 (6.1)	4 (5.6)	5 (7.7)	2 (3.2)	9 (6.9)	6 (4.5)	15 (5.7)
400 µg/day	62 (93.9)	68 (94.4)	60 (92.3)	60 (96.8)	122 (93.1)	128 (95.5)	250 (94.3)
NPS [b]							
Mean (SD)	6.3 (0.9)	6.2 (1.0)	6.1 (0.9)	6.4 (0.9)	6.2 (0.9)	6.3 (1.0)	6.3 (1.0)
Median (min – max)	6 (5 – 8)	6 (4 – 8)	6 (5 – 8)	6 (4 – 8)	6 (5 – 8)	6 (4 – 8)	6 (4 – 8)
7-day average of daily NCS [c]							
Mean (SD)	2.5 (0.6)	2.4 (0.7)	2.3 (0.6)	2.3 (0.7)	2.4 (0.6)	2.3 (0.7)	2.4 (0.7)
Median (min – max)	2.7 (0.5 – 3.0)	2.7 (0.3 – 3.0)	2.1 (0.7 – 3.0)	2.2 (0.0 – 3.0)	2.4 (0.5 – 3.0)	2.4 (0.0 – 3.0)	2.4 (0.0 – 3.0)
7-day average of daily SSS [c]							
Mean (SD)	2.8 (0.4)	2.6 (0.8)	2.8 (0.6)	2.6 (0.8)	2.8 (0.5)	2.6 (0.8)	2.7 (0.7)
Median (min – max)	3.0 (1.3 – 3.0)	3.0 (0.0 – 3.0)	3.0 (1.0 – 3.0)	3.0 (0.0 – 3.0)	3.0 (1.0 – 3.0)	3.0 (0.0 – 3.0)	3.0 (0.0 – 3.0)
7-day average of daily PRS [c]							
Mean (SD)	2.0 (0.9)	1.7 (0.9)	1.8 (0.9)	1.6 (0.9)	1.9 (0.9)	1.7 (0.9)	1.8 (0.9)
Median (min – max)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)
7-day average of daily ARS [c]							
Mean (SD)	2.1 (0.8)	1.9 (0.8)	1.9 (0.8)	1.9 (0.9)	2.0 (0.8)	1.9 (0.9)	1.9 (0.8)
Median (min – max)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)	2.0 (0.0 – 3.0)
7-day average of daily TNSS [c]							
Mean (SD)	9.3 (1.9)	8.6 (2.5)	8.7 (2.3)	8.4 (2.6)	9.0 (2.1)	8.5 (2.5)	8.8 (2.4)
Median (min – max)	9.6 (5.8 – 12.0)	8.9 (2.3 – 12.0)	9.0 (3.7 – 12.0)	9.0 (1.3 – 12.0)	9.0 (3.7 – 12.0)	9.0 (1.3 – 12.0)	9.0 (1.3 – 12.0)
UPSIT [b]							
Mean (SD)	13.9 (7.4)	12.8 (7.9)	13.1 (7.3)	12.8 (7.6)	13.5 (7.3)	12.8 (7.7)	13.1 (7.5)
Median (min – max)	11 (3 – 35)	10 (0 – 36)	11 (0 – 33)	10 (0 – 38)	11 (0 – 35)	10 (0 – 38)	10 (0 – 38)
Total SNOT-22 [b]							
Mean (SD)	60.5 (15.3)	59.8 (19.7)	59.8 (18.2)	59.2 (20.5)	60.1 (16.7)	59.5 (20.0)	59.8 (18.4)
Median (min – max)	59 (32 – 104)	57 (20 – 102)	57 (29 – 110)	61 (24 – 102)	58 (29 – 110)	57 (20 – 102)	58 (20 – 110)
Systemic corticosteroids in the 12 months prior screening, n (%) [d]							
Yes	8 (12.1)	18 (25.0)	15 (23.1)	18 (29.0)	23 (17.6)	36 (26.9)	59 (22.3)
No	57 (86.4)	54 (75.0)	50 (76.9)	42 (67.7)	107 (81.7)	96 (71.6)	203 (76.6)
Unknown	1 (1.5)	0	0	2 (3.2)	1 (0.8)	2 (1.5)	3 (1.1)
Prior sinonasal surgery, n (%) [d]							
Yes	40 (60.6)	39 (54.2)	40 (61.5)	39 (62.9)	80 (61.1)	78 (58.2)	158 (59.6)
> 1 surgery	16 (24.2)	16 (22.2)	25 (38.5)	17 (27.4)	41 (31.3)	33 (24.6)	74 (27.9)
No	26 (39.4)	33 (45.8)	25 (38.5)	23 (37.1)	51 (38.9)	56 (41.8)	107 (40.4)
Asthma, n (%) [e]							
Yes	32 (48.5)	42 (58.3)	39 (60.0)	38 (61.3)	71 (54.2)	80 (59.7)	151 (57.0)
Mild	15 (46.9)	13 (31.0)	13 (33.3)	12 (31.6)	28 (39.4)	25 (31.3)	53 (35.1)
Moderate	16 (50.0)	27 (64.3)	25 (64.1)	20 (52.6)	41 (57.7)	47 (58.8)	88 (58.3)
Severe	1 (3.1)	2 (4.8)	1 (2.6)	6 (15.8)	2 (2.8)	8 (10.0)	10 (6.6)
No	34 (51.5)	30 (41.7)	26 (40.0)	24 (38.7)	60 (45.8)	54 (40.3)	114 (43.0)

ARS = anterior rhinorrhea score; NCS = nasal congestion score; NPS = nasal polyps score; PRS = posterior rhinorrhea score; SNOT-22 = sin-nasal outcome test-22; SSS = sense of smell score; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania smell identification test.
[a] At or relative to randomization.
[b] The last assessment on or before the date of randomization.
[c] Baseline was defined as the average of the daily values recorded during the 7-day interval ending on the latest day prior to randomization such that the prior 7-day interval includes a recorded value on at least 4 of the 7 days of that interval.
[d] Relative to first study visit (Day -35). No patients used SCS or had nasal surgery between the first study visit and randomization.
[e] A history of asthma at screening and having used medication for asthma or with a prescription for asthma medication in the last 12 months.
Percentages for asthma severity are based on the number of patients with asthma
Source: [Study GA39688-t_base_FAS], [Study GA39855-t_base_FAS], [SCE Appendix 1-t_base_PFAS]

IgE-levels and dosing

The doses given in the phase-3-studies are shown in Table 8.

Table 8. Study drug exposures, pooled analysis set

Duration of exposure	Placebo N=130	Omalizumab N=135
Planned Dosing regimen		
Total Number of Patients With Planned Dosing every 4 weeks	113 (86.9%)	122 (90.4%)
75 mg every 4 weeks	0	0
150 mg every 4 weeks	37 (28.5%)	51 (37.8%)
225 mg every 4 weeks	0	0
300 mg every 4 weeks	51 (39.2%)	46 (34.1%)
450 mg every 4 weeks	15 (11.5%)	14 (10.4%)
600 mg every 4 weeks	10 (7.7%)	11 (8.1%)
Total Number of Patients With Planned Dosing every 2 weeks	17 (13.1%)	13 (9.6%)
300 mg every 2 weeks	0	0
375 mg every 2 weeks	4 (3.1%)	3 (2.2%)
450 mg every 2 weeks	3 (2.3%)	5 (3.7%)
525 mg every 2 weeks	4 (3.1%)	2 (1.5%)
600 mg every 2 weeks	6 (4.6%)	3 (2.2%)
Total Number of Doses Received per Patient		
n	130	135
Mean (SD)	6.7 (2.1)	6.5 (1.9)
Median	6.0	6.0
Min-Max	1 - 12	1 - 12
Treatment duration(a)(weeks)		
n	130	135
Mean (SD)	20.02 (2.53)	19.92 (2.44)
Median	20.14	20.14
Min-Max	0.1 - 22.6	0.1 - 22.4
0 - 4	1 (0.8%)	1 (0.7%)
>4 - 8	1 (0.8%)	0
>8 - 12	1 (0.8%)	1 (0.7%)
>12 - 16	1 (0.8%)	3 (2.2%)
>16 - 20	26 (20.0%)	31 (23.0%)
>20 - 24	100 (76.9%)	99 (73.3%)
>24	0	0
Total Exposure (Patient-years)	49.9	51.5

Planned Dosing Regimen is based on baseline IgE and body weight combination. Baseline IgE is defined as the first assessment before but not on the day of randomization. Cases where this assessment of IgE and body weight does not meet protocol inclusion criteria are excluded from calculation of baseline value. (a) Treatment duration is the difference [in days] between the date of the first dose and date of the last dose of study drug plus 1 divided by 7 days.

Source: [SCS Appendix 1-t_ex_PSAS]

Mean IgE at baseline was 168 IU/mL, median 121 IU/mL, and the lower tertial had an IgE-concentration of 70 IU/mL or lower, i.e. below the threshold of 76 IU/mL where patients with allergic asthma were less likely to experience benefit from the treatment. As opposed to allergic asthma, in CSU the mechanism of action is unclear, and dosing cannot be based on IgE-levels. The CHMP concluded that 300 mg every 4 weeks was needed to significantly improve symptoms.

Numbers analysed

Study GA39688

138 patients were randomized to the study: 66 and 72 patients each were randomized to receive placebo and omalizumab respectively, comprising the full analysis set.

Study GA39855

127 patients were randomized to the study: 65 and 62 patients each were randomized to receive placebo and omalizumab respectively, comprising the full analysis set.

Overall, 265 patients were randomized (138 in Study GA39688, 127 in Study GA39855), 131 to placebo (66 in Study GA39688, 65 in Study GA39855) and 134 to omalizumab (72 in Study GA39688, 62 in Study GA39855).

Outcomes and estimation

Co-primary endpoints

In both pivotal Phase-III studies **GA39688** and **GA39855**, the co-primary endpoints of the changes from baseline at Week 24 in NPS and the average daily NCS were met. For each of the co-primary endpoints, the between-treatment difference in the adjusted mean changes at Week 24 was statistically significant in favour of omalizumab.

Nasal polyp score (NPS)

Nasal polyp score ranges from 0 (best) to 8 (worst). The results for the separate studies as well as the pooled analysis are shown in Table 9.

Table 9. Absolute Change from Baseline at Week 24 in the Nasal Polyp Score (Co-Primary Endpoint) for Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

	Study GA39688		Study GA39855		Pooled studies	
Timepoint						
Statistic	**Placebo (N = 66)**	**Omalizu-mab (N = 72)**	**Placebo (N = 65)**	**Omalizu-mab (N = 62)**	**Placebo (N = 131)**	**Omalizu-mab (N = 134)**
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	6.32 (0.12)	6.19 (0.12)	6.09(0.12)	6.44(0.12)	6.21(0.08)	6.31(0.09)
Change at Week 24 (primary endpoint)						
n	65	69	64	59	129	128
Adj. mean (SE)	0.06 (0.16)	-1.08 (0.16)	-0.31 (0.16)	-0.90 (0.17)	-0.13 (0.12)	-0.99 (0.11)
Difference						
Adj. mean (SE)	-1.14 (0.23)		-0.59 (0.23)		-0.86 (0.16)	
95% CI	(-1.59, -0.69)		(-1.05, -0.12)		(-1.18, -0.54)	
p-value	<0.0001		0.0140		<0.0001	

Adj. = adjusted; CI = confidence interval; SE = standard error.
Source: [Study GA39688-t_nps_mmrm_FAS], [Study GA39855-t_nps_mmrm_FAS], and [SCE Appendix 1-t_nps_mmrm_PFAS]

When evaluated over time, in both study **GA39688** and study **GA39855**, the difference between the two treatment arms was observed at the first assessment at Week 4, with adjusted mean differences of -0.92 (95% CI: -1.37, -0.48) in study **GA39688** and -0.52 (95% CI: -0.94, -0.11) in study

GA39855. However, statistical tests at this timepoint were not included in the type 1 error control plan.

An exploratory analysis compared the number of patients with an improvement (i.e. a reduction) from baseline to Week 24 in NPS of ≥1.0 and ≥2.0 between treatment arms based on the PFAS. An improvement of ≥1.0 was achieved by 37/129 patients (28.7%) in the placebo arm and 72/128 patients (56.3%) in the omalizumab arm (OR: 3.38; 95% CI: 1.99, 5.76; p<0.0001). Corresponding frequencies for an improvement of ≥2.0 were 15/129 patients (11.6%) and 40/128 patients (31.3%), respectively (OR: 3.43; 95% CI: 1.77, 6.68; p=0.0003).

The results in individual studies were similar. In study **GA39688**, the corresponding between-treatment ORs were 4.07 (95% CI: 1.91, 8.66; p=0.0003) for an improvement of ≥1.0 and 5.44 (95% CI: 1.91, 15.03; p=0.0011) for an improvement of ≥2.0. In study **GA39855**, these ORs were 2.84 (95% CI: 1.32, 6.14; p=0.0077) and 2.39 (95% CI: 0.95, 6.05; p=0.0649), respectively.

Average daily nasal congestion score (NCS)

NCS ranges from 0 (best) to 3 (worst). The results for the separate studies as well as the pooled analysis are shown in Table 10.

Table 10. Absolute Change from Baseline at Week 24 in Average Daily Nasal Congestion Score (Co-Primary Endpoint): Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizu-mab (N = 72)	Placebo (N = 65)	Omalizu-mab (N = 62)	Placebo (N = 131)	Omalizu-mab (N = 134)
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	2.46 (0.07)	2.40 (0.08)	2.29 (0.08)	2.26 (0.09)	2.38 (0.05)	2.34 (0.06)
Change at Week 24 (primary endpoint)						
n	65	70	64	59	129	129
Adj. mean (SE)	-0.35 (0.11)	-0.89 (0.10)	-0.20 (0.11)	-0.70 (0.11)	-0.28 (0.08)	-0.80 (0.08)
Difference						
Adj. mean (SE)	-0.55 (0.15)		-0.50 (0.15)		-0.52 (0.11)	
95% CI	(-0.84, -0.25)		(-0.80, -0.19)		(-0.73, -0.31)	
p-value	0.0004		0.0017		<0.0001	

Adj. = adjusted; CI = confidence interval; SE = standard error.
Source: [Study GA39688-t_ncs_mmrm_FAS], [Study GA39855-t_ncs_mmrm_FAS], and [SCE Appendix 1-t_ncs_mmrm_PFAS]

When evaluated over time, in both study **GA39688** and study **GA39855**, the difference between the two treatment arms was observed at the first assessment at Week 4, with adjusted mean differences of -0.25 (95% CI: -0.46, -0.04) in study **GA39688** and -0.26 (95% CI: -0.45, -0.07) in study **GA39855**. However, statistical tests at this timepoint were not included in the type 1 error control plan.

An exploratory analysis compared the number of patients with an improvement (i.e. a reduction) from baseline to Week 24 in average daily NCS of ≥0.5 and ≥1.0 between treatment arms in patients of the PFAS eligible for respective improvement. An improvement of ≥0.5 was achieved by 38/129 patients (29.5%) in the placebo arm and 75/126 patients (59.5%) in the omalizumab arm (OR: 3.77; 95% CI: 2.20, 6.46; p<0.0001). Corresponding frequencies for an improvement of ≥1.0 were 27/126 patients (21.4%) and 56/126 patients (44.4%), respectively (OR: 3.17; 95% CI: 1.79, 5.61; p<0.0001).

In study **GA39688**, the corresponding between-treatment ORs were 3.00 (95% CI: 1.44, 6.23; p=0.0033) for an improvement of ≥0.5 and 2.55 (95% CI: 1.19, 5.44; p=0.0158) for an improvement of ≥1.0. In study **GA39855**, these ORs were 5.66 (95% CI: 2.44, 13.16; p<0.0001) and 4.46 (95% CI: 1.83, 10.84; p=0.0010), respectively.

Secondary endpoints

There were two separate and distinct sets of secondary endpoints with different type 1 error control testing hierarchy. This was done to accommodate different prioritizations of secondary endpoints for the EU and the US applications. Overview of secondary efficacy endpoints for the EU application are shown in Table 11. For totality of data, a summary of the US endpoints (Study **GA39688** and **GA39855** separately) are shown in Table 12 and Table 13.

Table 11. Overview of Secondary Efficacy Endpoints Based on the Type 1 Error Control of Secondary Endpoints for the EU Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Secondary endpoint [a]	Study GA39688		Study GA39855		Pooled studies	
	Difference or odds ratio (95% CI)	P value [b]	Difference or odds ratio (95% CI)	P value [b]	Difference or odds ratio (95% CI)	P value
H3: Change from baseline at Week 24 in average daily TNSS (scale: 0/best–12/worst)	-1.91 (-2.85, -0.96) [c]	0.0001	-2.09 (-3.00, -1.18) [c]	<0.0001	-1.98 (-2.63, -1.33)	<0.0001
H4: Change from baseline at Week 24 in HRQoL (Total SNOT-22 [scale 0/best-110/worst])	-16.12 (-21.86, -10.38) [c]	<0.0001	-15.04 (-21.26, -8.82) [c]	<0.0001	-15.36 (-19.57, -11.16)	<0.0001
H5: Change from baseline at Week 24 in UPSIT (scale: 0/worst-40/best)	3.81 (1.38, 6.24) [c]	0.0024	3.86 (1.57, 6.15) [c]	0.0011	3.84 (2.17, 5.51)	<0.0001
H6: Change from baseline at Week 16 in NPS	-1.01 (-1.43, -0.60) [c]	<0.0001	-0.91 (-1.39, -0.44) [c]	0.0002	-0.93 (-1.24, -0.63)	<0.0001
H7: Change from baseline at Week 16 in average daily NCS	-0.57 (-0.83, -0.31) [c]	<0.0001	-0.59 (-0.87, -0.30) [c]	<0.0001	-0.57 (-0.76, -0.38)	<0.0001
H8: Requirement of rescue treatment (systemic CS or nasal polypectomy) through Week 24	0.61 (0.05, 5.51) [d]	0.6716	0.20 (0.02, 1.89) [d]	0.1594	0.38 (0.10, 1.49) [d]	0.1639

CS = corticosteroid; H = hypothesis; HRQoL = health-related quality of life; NCS = nasal blockage/congestion score; NPS = nasal polyp score; SNOT-22 = Sinonasal Outcome Test-22; TNSS = total nasal symptom score; UPSIT = University of Pennsylvania Smell Identification Test.

Note: Gray shaded row indicates that the null hypothesis for this endpoint could not be rejected.

[a] H3-H7 were tested using individual study data. H8 was tested using pooled data from both Studies GA39688 and GA39855.

[b] p-values are from two-sided equivalence tests and are unadjusted for multiplicity.

c Difference computed as omalizumab adjusted mean minus placebo adjusted mean, and associated 95% CI.

d Odds ratio adjusted with placebo as the reference, and associated 95% CI. An odds ratio >1.0 is in favor of omalizumab when the event is a favorable outcome (e.g. reduction in the need for surgery) and odds ratio is <1.0 is in favor of omalizumab when the event is an unfavorable outcome (e.g. requirement of rescue treatment).

Source: [Study GA39688-Table 14], [Study GA39855-Table 14], [Study GA39688-t_resurg_log_FAS], [Study GA39855-t_resurg_log_FAS]

Table 12. Secondary Efficacy Endpoints: Study GA39688 (Full Analysis Set)

Hypothesis Number	Efficacy Endpoint	Treatment Comparison Difference or Odds Ratio (95% CI)	p-value [b]
H3	Change from baseline at Week 24 in average daily SSS (scale: 0/best–3/worst)	-0.33 (-0.60, -0.06) [a]	0.0161
H4	Change from baseline at Week 24 in average daily PRS (scale: 0/best–3/worst)	-0.56 (-0.84, -0.28) [a]	0.0001
H5	Change from baseline at Week 16 in NPS	-1.01 (-1.43, -0.60) [a]	<0.0001
H6	Change from baseline at Week 16 in average daily NCS	-0.57 (-0.83, -0.31) [a]	<0.0001
H7	Change from baseline at Week 24 in patient-reported HRQoL (Total SNOT-22 [scale 0/best-110/worst])	-16.12 (-21.86, -10.38) [a]	<0.0001
H8	Change from baseline at Week 24 in average daily ARS (scale: 0/best–3/worst)	-0.43 (-0.70, -0.16) [a]	0.0023
H9 [c]	Requirement of rescue treatment (systemic CS for ≥3 consecutive days) through Week 24	0.38 (0.10, 1.49) [d]	0.1639
H10 [c]	Nasal polypectomy through Week 24	0.00 (0.00, 3.47) [d, e]	0.4981
H11 [c]	Change from baseline at Week 24 in AQLQ of ≥0.5 (in patients with comorbid asthma only)	3.86 (1.53, 9.74) [d]	0.0043
H12 [c]	Requirement of rescue medication (systemic CS or nasal polypectomy) through Week 24	0.38 (0.10, 1.49) [d]	0.1639
H13	Reduction in the need for surgery by Week 24 (unilateral NPS ≤2 on each side and improvement in SNOT-22 score of ≥ 8.9)	6.25 (1.32, 29.60) [d]	0.0209
H14	Change from baseline at Week 24 in average daily TNSS (scale: 0/best–12/worst)	-1.91 (-2.85, -0.96) [a]	0.0001
H15	Change from baseline at Week 24 in the UPSIT (scale: 0/worst-40/best)	3.81 (1.38, 6.24) [a]	0.0024

Note: Grey shaded rows indicate those endpoints for which the null hypothesis could not be rejected, and p-values should be considered as descriptive only.

Table 13. Secondary Efficacy Endpoints: Study GA39855 (Full Analysis Set)

Hypothesis Number	Efficacy Endpoint	Treatment Comparison Difference or Odds Ratio (95% CI)	p-value [b]
H3	Change from baseline at Week 24 in average daily SSS (scale: 0/best–3/worst)	-0.45 (-0.73, -0.16) [a]	0.0024
H4	Change from baseline at Week 24 in average daily PRS (scale: 0/best–3/worst)	-0.54 (-0.81, -0.27) [a]	0.0001
H5	Change from baseline at Week 16 in NPS	-0.91 (-1.39, -0.44) [a]	0.0002
H6	Change from baseline at Week 16 in average daily NCS	-0.59 (-0.87, -0.30) [a]	<0.0001
H7	Change from baseline at Week 24 in patient-reported HRQoL (Total SNOT-22 [scale 0/best-110/worst])	-15.04 (-21.26, -8.82) [a]	<0.0001
H8	Change from baseline at Week 24 in average daily ARS (scale: 0/best–3/worst)	-0.63 (-0.90, -0.35) [a]	<0.0001
H9 [c]	Requirement of rescue treatment (systemic CS for ≥3 consecutive days) through Week 24	0.38 (0.10, 1.49) [d]	0.1639
H10 [c]	Nasal polypectomy through Week 24	0.00 (0.00, 3.47) [d, e]	0.4981
H11 [c]	Change from baseline at Week 24 in AQLQ of ≥0.5 (in patients with comorbid asthma only)	3.86 (1.53, 9.74) [d]	0.0043
H12 [c]	Requirement of rescue medication (systemic CS or nasal polypectomy) through Week 24	0.38 (0.10, 1.49) [d]	0.1639
H13	Reduction in the need for surgery by Week 24 (unilateral NPS ≤2 on each side and improvement in SNOT-22 score of ≥ 8.9)	6.22 (1.23,60.23) [d]	0.0139
H14	Change from baseline at Week 24 in average daily TNSS (scale: 0/best–12/worst)	-2.09 (-3.00, -1.18) [a]	<0.0001
H15	Change from baseline at Week 24 in the UPSIT (scale: 0/worst-40/best)	3.86 (1.57, 6.15) [a]	0.0011

Note: Grey shaded rows indicate those endpoints for which the null hypothesis could not be rejected, and p-values should be considered as descriptive only.

Change from Baseline at Week 24 in Average Daily Total Nasal Symptom Score (TNSS)

In both studies **GA39688** and **GA39855**, the difference between omalizumab and placebo in the change from baseline at Week 24 in the average daily TNSS (scale: 0 [best] to 12 [worst]) showed a benefit for the omalizumab arm (Table 14).

Table 14. Absolute Change from Baseline at Week 24 in Average Daily Total Nasal Symptom Score: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizu-mab (N = 72)	Placebo (N = 65)	Omalizu-mab (N = 62)	Placebo (N = 131)	Omalizu-mab (N = 134)
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	9.33 (0.24)	8.56 (0.30)	8.73 (0.28)	8.37 (0.33)	9.03 (0.19)	8.47 (0.22)
Change at Week 24						
n	65	70	64	59	129	129
Adj. mean (SE)	-1.06 (0.34)	-2.97 (0.33)	-0.44 (0.32)	-2.53 (0.33)	-0.77 (0.23)	-2.75 (0.23)
Difference						
Adj. mean (SE)	-1.91 (0.48)		-2.09 (0.46)		-1.98 (0.33)	
95% CI	(-2.85, -0.96)		(-3.00, -1.18)		(-2.63, -1.33)	
p-value	0.0001		<0.0001		<0.0001	

Adj. = adjusted; CI = confidence interval; N = total number of patients; n = number of evaluable patients; SE = standard error.
Source: [Study GA39688-t_tnss_mmrm_FAS], [Study GA39855-t_tnss_mmrm_FAS] and [SCE Appendix 1-t_tnss_mmrm_PFAS]

Change from Baseline at Week 24 in Total Sinonasal Outcome Test-22 (SNOT-22)

In both studies **GA39688** and **GA39855**, omalizumab was shown to be superior over placebo in the change from baseline at Week 24 in the total SNOT-22 (scale: 0 [best] to 110 [worst]), see Table 15

Table 15. Absolute Change from Baseline at Week 24 in Total Sinonasal Outcome Test-22: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizu-mab (N = 72)	Placebo (N = 65)	Omalizu-mab (N = 62)	Placebo (N = 131)	Omalizu-mab (N = 134)
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	60.26 (1.90)	59.82 (2.32)	59.80 (2.26)	59.21 (2.60)	60.03 (1.47)	59.54 (1.73)
Change at Week 24						
n	65	69	63	59	128	128
Adj. mean (SE)	-8.58 (2.08)	-24.70 (2.01)	-6.55 (2.19)	-21.59 (2.25)	-7.73 (1.51)	-23.10 (1.50)
Difference						
Adj. mean (SE)	-16.12 (2.90)		-15.04 (3.14)		-15.36 (2.13)	
95% CI	(-21.86, -10.38)		(-21.26, -8.82)		(-19.57, -11.16)	
p-value	<0.0001		<0.0001		<0.0001	

Adj. = adjusted; CI = confidence interval; N = total number of patients; n = number of evaluable patients; SE = standard error.
Source: [Study GA39688-t_snot_mmrm_FAS], [Study GA39855-t_snot_mmrm_FAS], and [SCE Appendix 1-t_snot_mmrm_PFAS]

In both studies **GA39688** and **GA39855**, all patients having experienced an intercurrent event were imputed as not having realized an improvement at Week 24 in SNOT-22 of at least the MID.

The proportion of patients who experienced an improvement from baseline at Week 24 of at least the MID (8.9 points) in SNOT-22 score was 30/65 (46.2%) in the placebo arm and 53/69 (76.8%) in the omalizumab arm in study **GA39688** and 23/63 (36.5%) in the placebo arm and 39/59 (66.1%) in the omalizumab arm in study **GA39855**, resulting in an OR of 4.55 (95% CI 2.07, 9.97; p=0.0002) in study **GA39688** and 3.71 (95% CI: 1.72, 8.04; p=0.0009) in study **GA39855** in favour of omalizumab.

Change from Baseline at Week 24 in the University of Pennsylvania Smell Identification Test (UPSIT)

In both studies **GA39688** and **GA39855**, the difference between omalizumab and placebo in the change from baseline at Week 24 in the UPSIT (scale: 0 [worst] to 40 [best]) showed a benefit for the omalizumab arm (Table 16).

Table 16. Absolute Change from Baseline at Week 24 in the University of Pennsylvania Smell Identification Test Score: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizu-mab (N = 72)	Placebo (N = 65)	Omalizu-mab (N = 62)	Placebo (N = 131)	Omalizu-mab (N = 134)
Baseline						
n	61	69	63	60	124	129
Adj. mean (SE)	13.56 (0.89)	12.78 (0.95)	13.27 (0.93)	12.87 (0.99)	13.41 (0.64)	12.82 (0.68)
Change at Week 24						
n	61	67	62	58	123	125
Adj. mean (SE)	0.63 (0.89)	4.44 (0.84)	0.44 (0.81)	4.31 (0.83)	0.54 (0.60)	4.38 (0.59)
Difference						
Adj. mean (SE)	3.81 (1.23)		3.86 (1.16)		3.84 (0.85)	
95% CI	(1.38, 6.24)		(1.57, 6.15)		(2.17, 5.51)	
p-value	0.0024		0.0011		<0.0001	

Adj. = adjusted; CI = confidence interval; N = total number of patients; n = number of evaluable patients; SE = standard error.
Source: [Study GA39688-t_upsit_mmrm_FAS], [Study GA39855-t_upsit_mmrm_FAS] and [SCE Appendix 1-t_upsit_mmrm_PFAS]

Change from baseline at Week 16 in Nasal Polyp Score (NPS)

The between-treatment difference in the change from baseline in NPS at Week 16 is shown in Table 17.

Table 17. Absolute Change from Baseline at Week 16 in the Nasal Polyp Score for Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizumab (N = 72)	Placebo (N = 65)	Omalizumab (N = 62)	Placebo (N = 131)	Omalizumab (N = 134)
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	6.32 (0.12)	6.19 (0.12)	6.09(0.12)	6.44(0.12)	6.21(0.08)	6.31(0.09)
Change at Week 16 (secondary endpoint)						
n	64	69	63	58	127	127
Adj. mean (SE)	0.03 (0.15)	-0.98 (0.14)	-0.29 (0.16)	-1.20 (0.17)	-0.14 (0.11)	-1.07 (0.11)
Difference						
Adj. mean (SE)	-1.01 (0.21)		-0.91 (0.24)		-0.93 (0.16)	
95% CI	(-1.43, -0.60)		(-1.39, -0.44)		(-1.24, -0.63)	
p-value	<0.0001		0.0002		<0.0001	

Adj. = adjusted; CI = confidence interval; SE = standard error.
Source: [Study GA39688-t_nps_mmrm_FAS], [Study GA39855-t_nps_mmrm_FAS] and [SCE Appendix 1-t_nps_mmrm_PFAS]

Change from baseline at Week 16 in average daily Nasal Congestion Score (NCS)

The between-treatment difference in the change from baseline in average daily NCS at Week 16, a secondary efficacy endpoint of the study, was statistically significant in favour of omalizumab (Table 18).

Table 18. Absolute Change from Baseline at Week 16 in Average Daily Nasal Congestion Score: Studies GA39688 and GA39855 (Full Analysis Sets), and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizumab (N = 72)	Placebo (N = 65)	Omalizumab (N = 62)	Placebo (N = 131)	Omalizumab (N = 134)
Baseline						
n	65	72	65	62	130	134
Adj. mean (SE)	2.46 (0.07)	2.40 (0.08)	2.29 (0.08)	2.26 (0.09)	2.38 (0.05)	2.34 (0.06)
Change at Week 16 (secondary endpoint)						
n	65	70	64	61	129	131
Adj. mean (SE)	-0.32 (0.10)	-0.89 (0.09)	-0.21 (0.10)	-0.80 (0.10)	-0.27 (0.07)	-0.84 (0.07)
Difference						
Adj. mean (SE)	-0.57 (0.13)		-0.59 (0.14)		-0.57 (0.10)	
95% CI	(-0.83, -0.31)		(-0.87, -0.30)		(-0.76, -0.38)	
p-value	<0.0001		<0.0001		<0.0001	

Adj. = adjusted; CI = confidence interval; SE = standard error.
Source: [Study GA39688-t_ncs_mmrm_FAS], [Study GA39855-t_ncs_mmrm_FAS] and [SCE Appendix 1-t_ncs_mmrm_PFAS]

Requirement of Rescue Treatment through Week 24

In both studies **GA39688** and **GA39855**, the number of patients requiring rescue treatment anytime from randomization through Week 24 was small (Table 19). Treatment differences were not statistically significant in either study or in the pooled analysis. Among the patients considered as requiring rescue treatment were 2 patients in the placebo arm, 1 in each study, and none in the omalizumab arms, who had an intercurrent event of early discontinuation of study drug due to an adverse event or lack of efficacy. As per the SAP, these 2 patients were imputed as having required rescue treatment for each of the endpoints shown in table, although they did not actually receive respective rescue treatment.

In study **GA39688**, the proportion of patients with rescue treatment (systemic corticosteroids for ≥ 3 consecutive days or nasal polypectomy) was 4.6% (3/65 patients) in the placebo arm and 2.9% (2/70 patients) in the omalizumab arm (treatment comparison: unadjusted odds ratio [OR]: 0.61; 95% CI: 0.05, 5.51; nominal p=0.6716. Corresponding frequencies in study **GA39855** were 7.8% (5/64 patients) and 1.7% (1/59 patients), respectively (OR: 0.20; 95% CI: 0.02, 1.89; p=0.1594).

In the pooled analysis, which comprised the pre-specified secondary endpoint analysis in each of the studies, the proportion of patients who required rescue treatment was 6.2% (8/129 patients) in the placebo arm and 2.3% (3/129 patients) in the omalizumab arm (table). As in the individual studies, the resulting treatment arm difference was not statistically significant (OR: 0.38; 95% CI: 0.10, 1.49; nominal p=0.1639).

All patients who required rescue treatment through Week 24, required medication with systemic corticosteroids for ≥ 3 consecutive days. Hence, the results for the endpoint of the number of patients who required systemic corticosteroids for ≥ 3 consecutive days were identical to those described above for the combined rescue treatment endpoint.

No patients had nasal polypectomy during the study. However, the 2 aforementioned patients of the pooled placebo arm were imputed as having had nasal polypectomy as per the SAP. Treatment arm differences were not statistically significant, neither in the individual studies nor in the pooled analysis which comprised the pre-specified secondary endpoint analysis in each of the studies.

Table 19. Requirement of Rescue Treatment through Week 24: Studies GA39688 and GA39855, and Overall (Pooled Full Analysis Set)

Timepoint	Study GA39688		Study GA39855		Pooled studies	
Statistic	Placebo (N = 66)	Omalizu-mab (N = 72)	Placebo (N = 65)	Omalizu-mab (N = 62)	Placebo (N = 131)	Omalizu-mab (N = 134)
Requirement of rescue treatment [a] through Week 24						
Number of patients requiring rescue treatment, n/M (%)	3/65 (4.6)	2/70 (2.9)	5/64 (7.8)	1/59 (1.7)	8/129 (6.2)	3/129 (2.3)
Trt. Comparison						
Odds ratio (95% CI)	0.61 (0.05, 5.51)[b]		0.20 (0.02, 1.89)		0.38 (0.10, 1.49)	
p-value	0.6716[c]		0.1594		0.1639	
Requirement of systemic CS for ≥3 consecutive days						
Number of patients systemic CS for ≥3 days, n/M (%)	3/65 (4.6)	2/70 (2.9)	5/64 (7.8)	1/59 (1.7)	8/129 (6.2)	3/129 (2.3)
Trt. Comparison						
Odds ratio (95% CI)	0.61 (0.05, 5.51)[b]		0.20 (0.02, 1.89)		0.38 (0.10, 1.49)	
p-value	0.6716[c]		0.1594		0.1639	
Nasal polypectomy through Week 24						
Number of patients with polypectomy, n/M (%)	1/65 (1.5)	0/70 (0.0)	1/64 (1.6)	0/59 (0.0)	2/129 (1.6)	0/129 (0.0)
Trt. Comparison						
Odds ratio (95% CI)	0.00 (0.00, 17.64)[b]		0.00 (0.00, 20.61)[b]		0.00 (0.00, 3.47)[b]	
p-value	0.4815[c]		1.0000[c]		0.4981[c]	

CI = confidence interval; CS = corticosteroids; M=number of evaluable patients; N = total number of patients; n = number of evaluable patients; Trt. = treatment.
Note: Wald 95% CIs and Chi-square tests were used unless otherwise noted.
[a] Systemic CS for ≥ 3 consecutive days or having had nasal polypectomy.
[b] Exact CIs, unadjusted for baseline covariates.
[c] Fisher's exact test.
Source: [Study GA39688-t_resurg_log_FAS], [Study GA39855-t_resurg_log_FAS] and [SCE Appendix 1-t_resurg_log_PFAS]

Ancillary analyses

Sub-group analyses

Subgroup analyses were performed for the co-primary efficacy endpoints

- Change from baseline at Week 24 in NPS
- Change from baseline at Week 24 in average daily NCS

This was based on pooled data from studies **GA39688** and **GA39855**. Separate analysis models were fitted for each subgroup. The statistical methods for each model were the same as specified for the individual studies, with the exception that an adjustment factor for study was added to the models as an additional covariate. There were no issues with model convergence due to small sample size. Estimates of 95% CIs of between-treatment arm differences in adjusted means within subgroups were not adjusted for multiplicity.

Subgroups defined by demographic factors were:

- Age: < 65 years, ≥ 65 years
- Sex: male, female
- IxRS geographic location: North America, ex-North America

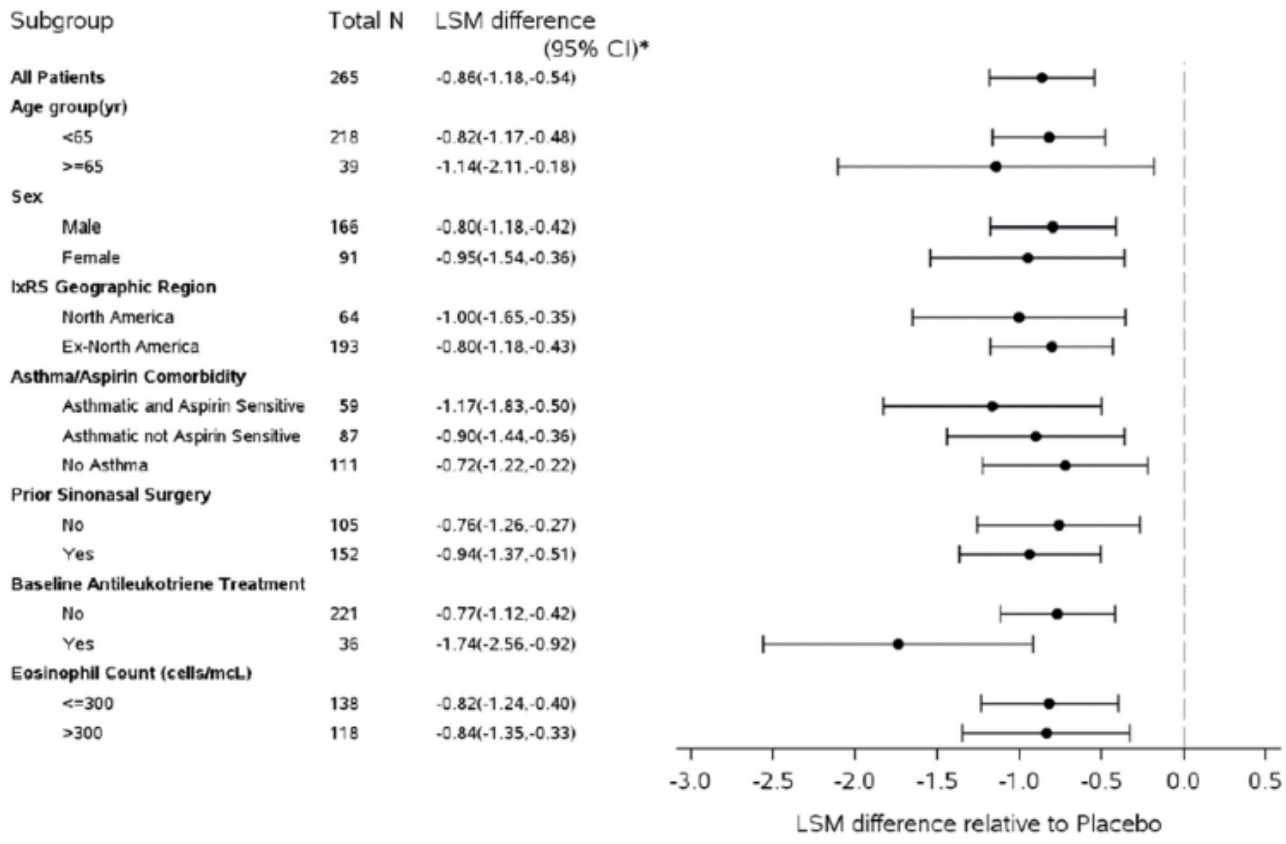
Subgroups defined by baseline disease factors were:

- Asthma aspirin comorbidity: asthmatic and aspirin sensitive, asthmatic not aspirin sensitive, no asthma
- Prior sinonasal surgery: No, Yes
- Baseline antileukotriene treatment: No, Yes
- Eosinophil count: ≤ 300, > 300

NPS and NCS

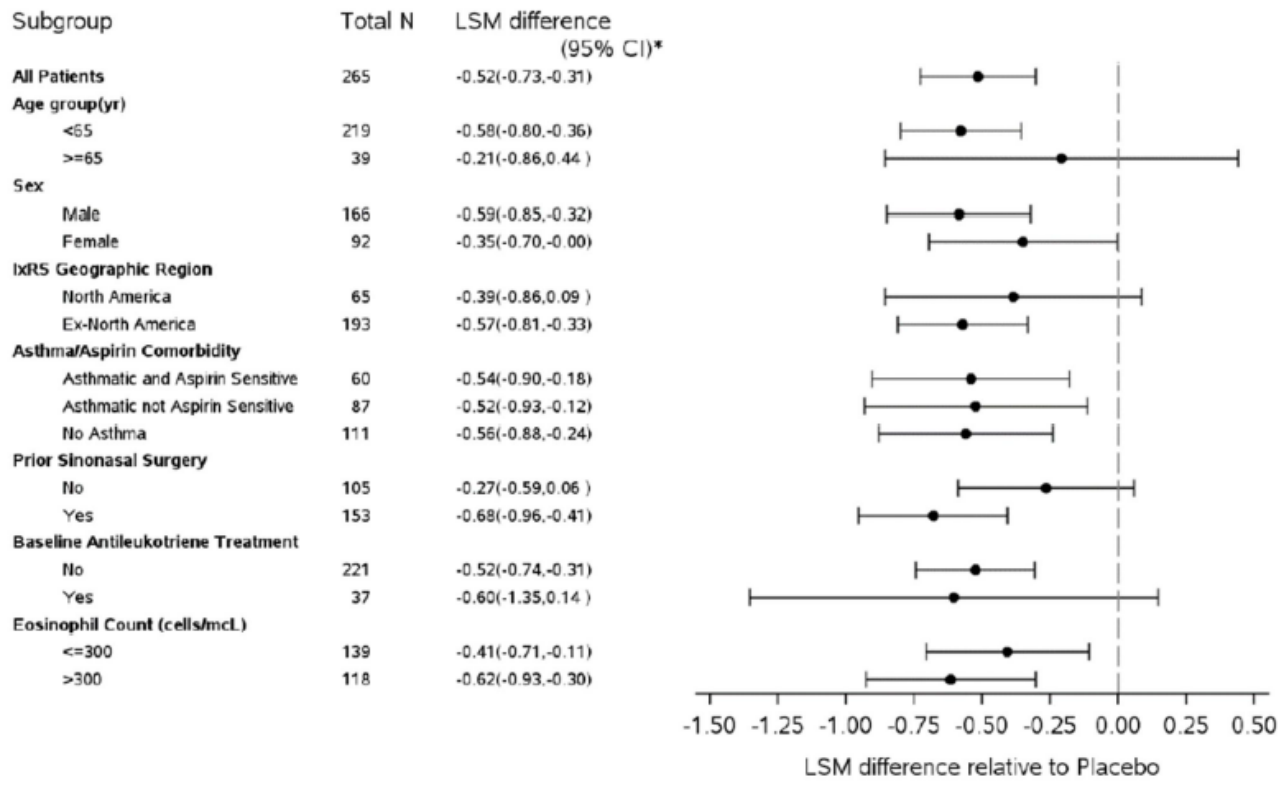
There were no significant differences in the treatment effect between any prespecified subgroup and its complementary group, as indicated by overlapping 95% CIs for respective estimated between-treatment difference within subgroups (Figure 8 and Figure 9).

Figure 8 Forest Plot of Adjusted Mean (95% Confidence Interval) Absolute Change in Nasal Polyp Score from Baseline to Week 24, by Baseline Characteristic Subgroup (Pooled Full Analysis Set)



*: LSM Difference = Treatment Difference in LS Means (Relative to Placebo) in Change from Baseline in Nasal Polyps Score

Figure 9 Forest Plot of Adjusted Mean (95% Confidence Interval) Absolute Change in Average Daily Nasal Congestion. Score from Baseline to Week 24, by Baseline Characteristic Subgroup (Pooled Full Analysis Set)



Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 20. Summary of GA39688.

Title: Polyp 1			
Study identifier	GA39688		
Design	Phase-III, randomized, multicentre, double-blind, placebo-controlled clinical trial in in adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments (daily treatment with intranasal corticosteroid therapy)		
	Duration of main phase: Duration of Run-in phase: Duration of Follow-up phase:	24 Wks 5 Wks 4 Wks	
Hypothesis	Superiority		
Database lock	17 April 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set Week 24		
Descriptive statistics and estimate variability	Treatment group	Placebo (subcutaneous injections at each treatment visit)	Omalizumab (subcutaneous Injections 150-600 mg every 2 or 4 weeks)
	Number of subjects	66	72
	NPS (0-8) change from baseline at week 24 Adjusted mean (SE)	0.06 (0.16)	-1.08 (0.16)
	NCS (0-3) change from baseline at week 24 Adjusted mean (SE)	-0.35 (0.11)	-0.89 (0.10)
	TNSS (0-12) change from baseline at week 24 Adjusted mean (SE)	-1.06 (0.34)	-2.97 (0.33)
	SNOT-22(0-110) change from baseline at week 24 Adjusted mean (SE)	-8.58 (2.08)	-24.70 (2.01)
	UPSIT (0-40) change from baseline at week 24 Adjusted mean (SE)	0.63 (0.89)	4.44 (0.84)

	NPS (0-8) change from baseline at week 16 Adjusted mean (SE)	-0.03 (0.15)	-0.98 (0.14)
	NCS (0-3) change from baseline at week 16 Adjusted mean (SE)	-0.32 (0.10)	-0.89 (0.09)
Effect estimate per comparison	Co-Primary endpoint NPS (0-8) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.14 (0.23)
		95% CI	-1.59, -0.69
		P-value	p<0.0001
	Co-Primary endpoint NCS (0-3) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.55 (0.15)
		95% CI	-0.84, -0.25
		P-value	p=0.0004
	Secondary endpoint TNSS (0-12) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-1.91 (0.48)
		95% CI	-2.85, 0.96
		P-value	p=0.0001
	Secondary endpoint SNOT-22(0-110) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-16.12 (2.90)
		95% CI	-21.86, -10.38
		P-value	p<0.0004
	Secondary endpoint UPSIT (0-40) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	3.81 (1.23)
		95% CI	1.38, 6.24
		P-value	p=0.0024
	Secondary endpoint NPS (0-8) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-1.01 (0.21)
		95% CI	-1.43, -0.60
		P-value	p<0.0001
	Secondary endpoint NCS (0-3) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.57 (0.13)
		95% CI	-0.83, -0.31
		P-value	p<0.0001
Notes	All presented p-values are adjusted for multiplicity.		

Table 21. Summary of study GA39855.

Title: Polyp 2	
Study identifier	GA39855
Design	Phase-III, randomized, multicentre, double-blind, placebo-controlled clinical trial in in adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments (daily treatment with intranasal corticosteroid therapy)

	Duration of main phase: Duration of Run-in phase: Duration of Follow-up phase:	24 Wks 5 Wks 4 Wks	
Hypothesis	Superiority		
Database lock	17 April 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set Week 24		
Descriptive statistics and estimate variability	Treatment group	Placebo (subcutaneous injections at each treatment visit)	Omalizumab (subcutaneous Injections 150-600 mg every 2 or 4 weeks)
	Number of subjects	65	62
	NPS (0-8) change from baseline at week 24 Adjusted mean (SE)	-0.31 (0.16)	-0.90 (0.17)
	NCS (0-3) change from baseline at week 24 Adjusted mean (SE)	-0.20 (0.11)	-0.70 (0.11)
	TNSS (0-12) change from baseline at week 24 Adjusted mean (SE)	-0.44 (0.32)	-2.53 (0.33)
	SNOT-22(0-110) change from baseline at week 24 Adjusted mean (SE)	-6.55 (2.19)	-21.59 (2.25
	UPSIT (0-40) change from baseline at week 24 Adjusted mean (SE)	0.44 (0.81)	4.31 (0.83)
	NPS (0-8) change from baseline at week 16 Adjusted mean (SE)	-0.29 (0.16)	-1.20 (0.17)
	NCS (0-3) change from baseline at week 16 Adjusted mean (SE)	-0.21 (0.10)	-0.80 (0.10)
Effect estimate per comparison	Co-Primary endpoint NPS (0-8) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.59 (0.23)
		95% CI	-1.05 , -0.12

		P-value	p=0.0140
	Co-Primary endpoint NCS (0-3) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.50 (0.15)
		95% CI	-0.80, -0.19
		P-value	p = 0.0017
	Secondary endpoint TNSS (0-12) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-2.09 (0.46)
		95% CI	-3.00, 1.18
		P-value	p<0.0001
	Secondary endpoint SNOT-22(0-110) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-15.04 (3.14)
		95% CI	-21.26,8.82
		P-value	p<0.0001
	Secondary endpoint UPSIT (0-40) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	3.86 (1.16)
		95% CI	1.57, 6.15
		P-value	p=0.0011
	Secondary endpoint NPS (0-8) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.91 (0.24)
		95% CI	1.39,-0.44
		P-value	p=0.0002
	Secondary endpoint NCS (0-3) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.59 (0.14)
		95% CI	-0.87, -0.30
		P-value	p<0.0001
Notes	All presented p-values are adjusted for multiplicity.		

Table 22. Summary of pooled data from GA39688 and GA39855.

Title: Pooled data from Polyp 1 and Polyp 2		
Study identifier	GA39688 and GA39855	
Design	Phase-III, randomized, multicentre, double-blind, placebo-controlled clinical trial in in adult patients with CRSwNP who have had an inadequate response to standard-of-care treatments (daily treatment with intranasal corticosteroid therapy)	
	Duration of main phase:	24 Wks
	Duration of Run-in phase:	5 Wks
	Duration of Follow-up phase:	4 Wks
Hypothesis	Superiority	
Database lock	17 April 2019	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	Full analysis set	

Descriptive statistics and estimate variability	Treatment group	Placebo (subcutaneous injections at each treatment visit)	Omalizumab (subcutaneous Injections 150-600 mg every 2 or 4 weeks)
	Number of subjects	131	134
	NPS (0-8) change from baseline at week 24 Adjusted mean (SE)	-0.13 (0.12)	-0.99 (0.11)
	NCS (0-3) change from baseline at week 24 Adjusted mean (SE)	-0.28 (0.08)	-0.80 (0.08)
	TNSS (0-12) change from baseline at week 24 Adjusted mean (SE)	-0.77 (0.23)	-2.75 (0.23)
	SNOT-22(0-110) change from baseline at week 24 Adjusted mean (SE)	-7.73 (1.51)	-23.10 (1.50)
	UPSIT (0-40) change from baseline at week 24 Adjusted mean (SE)	0.54 (0.60)	4.38 (0.59)
	NPS (0-8) change from baseline at week 16 Adjusted mean (SE)	-0.14 (0.11)	-1.07 (0.11)
	NCS (0-3) change from baseline at week 16 Adjusted mean (SE)	-0.27 (0.07)	-0.84 (0.07)
Effect estimate per comparison	Co-Primary endpoint NPS (0-8) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.86 (0.16)
		95% CI	1.18, -0.5
		P-value	p<0.0001
	Co-Primary endpoint NCS (0-3) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.52 (0.11)
		95% CI	-0.73,-0.31
		P-value	p<0.0001
	Secondary endpoint	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-1.98 (0.33)

	TNSS (0-12) change from baseline at week 24	95% CI	-2.63, -1.33
		P-value	p<0.0001
	Secondary endpoint SNOT-22(0-110) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-15.36 (2.13)
		95% CI	-19.57, -11.16
		P-value	p<0.0001
	Secondary endpoint UPSIT (0-40) change from baseline at week 24	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	3.84 (0.85)
		95% CI	2.17, 5.51
		P-value	p<0.0001
	Secondary endpoint NPS (0-8) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.93 (0.16)
		95% CI	-1.24, -0.63
		P-value	p<0.0001
	Secondary endpoint NCS (0-3) change from baseline at week 16	Comparison groups	Placebo vs. Omalizumab
		Adjusted mean (SE) difference	-0.57 (0.10)
		95% CI	-0.76, -0.38
		P-value	p<0.0001
	Requirement of rescue treatment (systemic CS or nasal polypectomy)	Comparison groups	Placebo vs. Omalizumab
		OR	0.38
		95% CI	0.10, 1.49
		P-value	p=0.1639
Notes	The p-value for requirement of rescue treatment (systemic CS or nasal polypectomy) is controlled for multiplicity.		

2.4.3. Discussion on clinical efficacy

The MAH submitted a variation application for the following indication:

Xolair is indicated for the treatment of nasal polyps in adult patients (18 years and above) with inadequate response to intranasal corticosteroids.

The MAH received Scientific Advice (SA) from the CHMP on 21 April 2017 (EMEA/H/SA/45/4/2017/III); the advice given then has mostly been adhered to but there are deviations with regard to the dose as discussed below.

Design and conduct of clinical studies

In support of this new indication application, the MAH conducted two identical pivotal phase-III, randomized, multi-centre, double-blind, placebo-controlled clinical studies to assess the efficacy and safety of omalizumab in patients with nasal polyps (studies **GA39688** and **GA39855)**. The design of the studies was mostly in line with the SA given in 2017. The studies length was 24 weeks, with a 5-week run-in period and a 4-week safety follow-up period, and not 52 weeks as recommended in the SA for the durability of the response and the potentially delayed maximum efficacy to be explored over a longer timeframe. Nevertheless, the MAH has conducted the Polyp studies for 24 weeks and has initiated an open-label extension study, WA40169 (the OLE study) with safety as primary objective.

The patient population was recruited across sites in North America (25%) and Europe (70%). There were no differences in baseline NPS or NCS, nor end-of-study, between the regions. The MAH has included sites able to carry out the study with maintained patient safety. There was no apparent impact on the final results.

In total, 265 patients were randomised, and 254 patients completed the studies, 127 in each of the treatment arms (pooled data). Upon request by CHMP, the reasons for discontinuation (4 in the placebo arms and 7 in the omalizumab arms) were provided by the MAH. Those were acknowledged by CHMP. Study GA39688 over-enrolled by more than 10%, however this is not considered to have any impact on the conclusions reached. The number of patients is considered to be adequate for the hypothesis.

Nasal steroids were to be taken throughout the studies. For moderately or severely symptomatic nasal polyps, clinical experience suggests that intranasal delivery of glucocorticoids may be improved by the use of topical drops (instead of spray). Upon request by CHMP, the MAH clarified that as mometasone intranasal spray was deemed broadly available, it was chosen as standard of treatment to which omalizumab or placebo was added. Further, protocol exclusion criteria included the use of intranasal corticosteroid spray (INCS) drops. There was one screen failure and one protocol eligibility deviation involving the use of corticosteroid topical drops. The CHMP considered that further analysis is thus not feasible.

The choice of the dosing regimen was not fully discussed in the initial application and no dose-finding study as recommended in the SA given in 2017 was submitted by the MAH. Although exposure-response analyses were conducted in the phase III studies, the uncertainties with regards to the appropriate posology for the newly proposed indication remained. Therefore, the MAH was requested by CHMP to provide further support that the mechanism of action of omalizumab is similar to the one of allergic asthma and to provide further data supporting the choice of the dosing regimen as proposed in section 4.2 of the SmPC. Based on the scientific publications provided by the MAH, the CHMP considered that the clinical association between allergic asthma and chronic rhinitis with or without nasal polyps is well-established and that many of the patients share a common inflammatory response. With regard to the dose issue, the MAH has performed subgroup analyses with comparison of the effect of the doses 150 q4wk, 300 mg q4wk and higher doses, for NPS, NCS, TNSS and SNOT-22. Patients with baseline IgE <76 IU/ml and ≥76 IU/ml were also analysed in subgroups. There were no general differences between the dose subgroups with omalizumab showing better results than placebo in all groups. Omalizumab showed numerically better results in all subgroup analyses, with remaining statistical significance in most analyses. Based on the current knowledge about the pathophysiology of nasal CRSwNP and its similarity to allergic asthma, as opposed to CSU (where the pathophysiology has not been established), CHMP agreed that the same dosing regimen can be chosen for both allergic asthma and CRSwNP. The description of mechanism of action in the new indication in section 5.1 as well as the dosing regimen proposed in section 4.2 of the SmPC were endorsed by CHMP.

To ensure inclusion of patients with prominent polyposis, NPS ≥5 and NCS ≥2 were two of the inclusion criteria. The NCS score were discussed in the SA given in 2017 and the MAH has followed the recommendation to include patients with NCS ≥2, which would ensure inclusion of a more severely affected population. Furthermore, patients must have a SNOT-22 score ≥ 20 at screening (Day -35) and at randomization (Day 1); inclusion of persons with a score as low as 20 might provide a risk to include patients with only moderate disease. However, in conjunction with the other inclusion criteria, this level is considered acceptable. Since omalizumab would be a top-on treatment in patients not adequately controlled on nasal steroids, the patients continued their nasal steroid treatment during the study which was considered acceptable by CHMP. The exclusion criteria were considered to be generally relevant.

There were 2 co-primary endpoints i.e. change in nasal polyp score (NPS) and change in 7-day average of daily nasal congestion score (NCS) at week 24. This approach is in line with the SA received in 2017 and is considered to be acceptable by CHMP as change in nasal polyp size on its own is not considered sufficient but adding an endpoint evaluating the impact of symptoms is of importance in measuring outcomes in nasal polyposis. Furthermore, severity of disease is primarily based on symptoms rather than polyp size. There are no established limits for clinically relevant effect for these endpoints, but the applicant used a 0.56 point difference for NCS and 1.50 for NPS as basis for their samples size calculations.

Secondary endpoints comprised change in TNSS, SNOT-22 and UPSIT at week 24, and change from baseline at week 16 in NPS and NCS. SNOT-22 is a quality of life-related score that has been validated to have minimal clinical important difference (MCID) of 8.9 points. The other scores, including NPS and NCS, do not have any established MCIDs but upon request by CHMP, the MAH has discussed what changes in the observed scores would be clinically relevant. The last secondary endpoint was requirement of rescue treatment [systemic corticosteroids for ≥3 consecutive days or nasal polypectomy].

Randomisation was stratified by comorbid asthma, aspirin sensitivity and geographic region (North America and others).

In the SA from 2017, the MAH was recommended to stratify for prior sinonasal surgery (in addition to comorbid asthma, aspirin sensitivity and geographic region) but this was not done which could be acceptable considering difficulties with too many strata. It is noted that both studies are balanced and when pooling the data from the two studies, approximately 60% of the included patients in the different treatment arms had sinonasal surgery.

Further, as only two patients could be classified as having asthma according to GINA step 5, a subgroup efficacy analysis of this group is not warranted, which is also applicable to the group of patients with uncontrolled asthma. It can be concluded that the results obtained in the studies were not, more than possibly marginally, biased by the effect of Xolair in severely asthmatic patients.

There are two distinct and equally important estimands of interest defined in this trial. The first estimand is the treatment group difference in mean change from baseline at Week 24 in NPS in patients with CRSwNP, where the need for rescue medication, nasal polypectomy or study drug discontinuation is accounted for as an unfavourable (worst) outcome. The second estimand is the treatment group difference in mean change from baseline at Week 24 in the average daily NCS in patients with CRSwNP, where the need for rescue medication, nasal polypectomy or study drug discontinuation is accounted for as an unfavourable (worst) outcome. The analysis population is the FAS.

The chosen statistical method is a MMRM together with failure imputation for patients with intercurrent events. It is not apparent that the handling of intercurrent events and missing data provides a conservative estimate of the treatment effect. The number of intercurrent events by type and treatment group together with the observed and imputed data were presented by the MAH. The numbers are low and the impact on the estimate of treatment effect was considered to be minor.

The type 1 error is controlled at 5% for the co-primary endpoints and the 6 secondary endpoints. All other p-values presented are unadjusted and should be interpreted as descriptive.

The statistical method is considered to be acceptable for the two pivotal studies.

Efficacy data and additional analyses

In both pivotal Phase-III studies **GA39688** and **GA39855**, the co-primary endpoints of the changes from baseline at Week 24 in NPS and the average daily NCS were met. For each of the co-primary endpoints, the between-treatment difference in the adjusted mean changes at Week 24 was statistically significant in favour of omalizumab (p-value of <0.05 in both studies for both co-primary endpoints).

At baseline, the participants had a mean NPS (the range of the score is 0/best-8/worst) of 6.21 in the placebo group and 6.31 in the omalizumab treatment arm (pooled data). Both groups improved with 0.13 (placebo) resp. 0.99 (omalizumab), nominal p<0.0001 for pooled data. For NCS, the inclusion criterion was ≥2 and the treatment groups had 2.38 (placebo) resp. 2.34 (omalizumab) at baseline (the range of the score is 0/best-3/worst). Both groups improved with 0.28 (placebo) resp. 0.80 (omalizumab), nominal p<0.0001 for the pooled data. Thus, the primary objectives to show superiority of omalizumab to placebo were formally met.

The sample size calculations were based on a 0.56 point difference for NCS and 1.50 for NPS. These differences were not achieved. However, omalizumab was statistically significantly better than placebo in both pivotal studies and both co-primary endpoints. As there are no formal MCIDs established for the co-primary endpoints (NPS and NCS), the MAH was requested to discuss the clinical relevance of these outcomes. The MAH presented literature data from relevant published studies, describing the use of INCS (placebo as comparator in the majority of studies) or biologics (placebo as comparator) where these endpoints were applied. Although results should be interpreted with caution as there are differences in study designs and included populations, the effect as recorded by NPS and NCS appears to be of similar magnitude as in publications describing patients responding to intranasal corticosteroids (INCS) which is deemed clinically relevant. Comparison to other biologics is more difficult due to the smaller number of studies and heterogeneity of publications. Furthermore, biologics acts through different pathways in the inflammatory cascade. Omalizumab affects primarily only IgE-binding on mast cells and basophils whereas mepolizumab and reslizumab affects IL-5 with a following decrease in eosinophils. Dupilumab affects IL-4 and IL-13, which leads to an impact on both eosinophils and IgE. The effect level as compared with other biologicals remain uncertain as there are no directly comparing studies. The point estimates of effect appeared higher in dupilumab studies, but these studies had different enrolment criteria with respect to requirement for prior surgeries and systemic steroids, differences in populations enrolled, and other differences in study conduct.

For the secondary endpoints TNSS, SNOT-22 and UPSIT, omalizumab showed improvement compared to placebo (all three endpoints had a p-value of <0.05 in both studies and the nominal p-value for the pooled data was p<0.0001). Approximately 40% of the patients in the placebo arms and 70% of the patients in the omalizumab arms had a change of at least 8.9 points in SNOT-22. The adjusted mean (SE) for the change in SNOT-22 at week 24 compared to baseline was -7.73(1.51) in the pooled placebo arm, i.e. below the threshold for clinical relevance, but -23.10(1.50) in the pooled omalizumab group. NPS and NCS change at 16 weeks were included to show consistent efficacy, which was demonstrated (both endpoints had a p-value of <0.05 in both studies and the nominal p for the pooled data was p<0.0001).

Requirement of rescue treatment was compared between the treatment arms, with 8/129 (6.2%) in the placebo group and 3/129 (2.3%) in the omalizumab group. All required systemic corticosteroids of ≥3 consecutive days while two patients in the placebo arm (one in each study) required surgery. The number of events was greater in the placebo group, but the overall numbers were too small to power any relevant comparison and thus, no firm conclusion could be drawn. In the SA, the CHMP asked for this endpoint, but a study length of 24 weeks is too short to yield any assessable data.

Subgroup analyses showed no relevant differences in the co-primary endpoints.

When entering the OLE-study WA40169 after 24 weeks in the parent studies, the patients received omalizumab for 28 weeks, followed by 24 weeks without omalizumab. Upon request by CHMP, a preliminary data cut was performed on 24 February 2020 when 213 patients had completed the follow-up period to evaluate long-term efficacy and durability of the response. Analysis of the co-primary endpoints as well as secondary endpoints (TNSS, SNOT-22 and UPSIT) showed greater improvement in those receiving omalizumab in both the parent study and the OLE-study, compared to those receiving omalizumab in the OLE-study following placebo treatment in the parent studies, although the results for the latter group approached those of the former group when omalizumab was introduced. Improvement was sustained during omalizumab treatment. After 28 weeks of open-label treatment, omalizumab was withdrawn. After the follow-up period of 24 weeks, all endpoints had started to deteriorate, however, were still improved compared to baseline in the parent studies for both treatment arms.

As allergic rhinitis can be of a more seasonal character, and thus a 24-week study might miss symptoms that only occur in a certain season, the MAH was requested to report occurrence of allergic rhinitis and how it was handled during the study. The CHMP considered that since there were a small number of reported rhinitis, and that all patients received nasal corticosteroids, it is unlikely that there would be a significant larger number of reports of symptoms of allergic rhinitis if the studies were performed during a whole year. Thus, it is considered that allergic rhinitis co-morbidity did not impact the efficacy analyses.

The initially proposed indication *(Xolair is indicated for the treatment of nasal polyps in adult patients (18 years and above) with inadequate response to intranasal corticosteroids)* was considered to be too broad and not sufficiently covered by the data provided. The studied population was considered to represent patients with severe disease based on baseline severity scores. The indication granted by CHMP istherefore 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.

2.4.4. Conclusions on the clinical efficacy

The efficacy results from the two pivotal studies GA39688 and GA39855 demonstrated that the omalizumab dose regimen based on IgE-level and weight, provided statistically significant and clinically relevant improvements in NPS and NCS at week 24 compared to placebo, in adult patients with severe CRSwNP with inadequate response to intranasal corticosteroid treatment.

2.5. Clinical safety

Introduction

Xolair is currently approved for the treatment of allergic asthma in children (≥ 6 years), adolescents and adults, and for the treatment of CSU in adolescents (≥ 12 years) and adults, in the EU and USA, and in numerous other countries worldwide. The overall safety profile of omalizumab has been well-characterized. The estimated cumulative omalizumab exposure is >16,000 patients in clinical trials and >1 million patient years in the post-marketing setting, as of 31 December 2018.

The safety database for the new indication treatment of nasal polyps in patients who have inadequate response to intranasal corticosteroids consists of data from the two pivotal clinical studies GA39688

and GA39855. Supportive data from an interim analysis of the ongoing, OLE study (WA40169) are also included. This latter study is ongoing, and the data presented are retrieved from an interim analysis (clinical data cut-off date of 11 March 2019).

Patient exposure

During the two pivotal studies, a total of 265 patients were exposed to omalizumab or placebo. Of these, 249 continued into the OLE study.

- 135 patients received omalizumab during the two Phase III studies GA39688 and GA39855, corresponding to a total of 51.5 patient-years. Of these, 124 patients continued into the OLE study WA40169.
- 130 patients received placebo only during the two Phase III Studies GA39688 and GA39855. Of these, 125 patients continued into the OLE study WA40169.
- Across all three studies, 260 patients received at least one dose of omalizumab during either the parent studies or the OLE study.

At the time of the interim analysis, the median duration of OLE treatment with omalizumab was 8.1 weeks (range 0.1 to 26.7 weeks). Including exposure to omalizumab in the parent studies, patients who received omalizumab in the parent study were exposed to omalizumab for median 28.6 weeks (12.6 to 45.4 weeks), while patients who received placebo in the parent study were exposed to omalizumab for 8.1 weeks (range 0.1 to 26.7 weeks) during the OLE extension study. This corresponds to a total exposure to omalizumab of 43.0 patient years from patients treated during the OLE study, plus a total exposure of 51.5 patient years from patients who received omalizumab in the parent study.

For details on the demographics and baseline disease characteristics of the included patients, please see Table 6 and Table 7 in the efficacy part.

In all 3 studies, omalizumab was administered using the proposed dose regimen, i.e., SC injections every 2 or 4 weeks. This dose level is similar to that already approved for allergic asthma. The safety analysis population was defined as all randomized patients who received at least one dose of study drug.

In both treatment arms, the majority of patients received the planned dosing regimen of study drug once every 4 weeks (omalizumab 90.4%, placebo 86.9%) (Table 23). The median treatment duration was 20 weeks in both arms, and the median overall duration of post-randomization follow-up was 26 weeks in both studies. The total exposure in patient years was 51.5 and 49.9 for the omalizumab and placebo arms, respectively. The majority of patients reported they were adherent to the intranasal mometasone regimen throughout the 24-week blinded treatment period (placebo 89.2%, omalizumab 89.6% of patients).

Table 23 Study drug exposure, studies GA39688 and GA39855 (pooled safety analysis set)

Duration of exposure	Placebo N=130	Omalizumab N=135
Planned Dosing regimen		
Total Number of Patients With Planned Dosing every 4 weeks	113 (86.9%)	122 (90.4%)
75 mg every 4 weeks	0	0
150 mg every 4 weeks	37 (28.5%)	51 (37.8%)
225 mg every 4 weeks	0	0
300 mg every 4 weeks	51 (39.2%)	46 (34.1%)
450 mg every 4 weeks	15 (11.5%)	14 (10.4%)
600 mg every 4 weeks	10 (7.7%)	11 (8.1%)
Total Number of Patients With Planned Dosing every 2 weeks	17 (13.1%)	13 (9.6%)
300 mg every 2 weeks	0	0
375 mg every 2 weeks	4 (3.1%)	3 (2.2%)
450 mg every 2 weeks	3 (2.3%)	5 (3.7%)
525 mg every 2 weeks	4 (3.1%)	2 (1.5%)
600 mg every 2 weeks	6 (4.6%)	3 (2.2%)
Total Number of Doses Received per Patient		
n	130	135
Mean (SD)	6.7 (2.1)	6.5 (1.9)
Median	6.0	6.0
Min-Max	1 - 12	1 - 12
Treatment duration(a)(weeks)		
n	130	135
Mean (SD)	20.02 (2.53)	19.92 (2.44)
Median	20.14	20.14
Min-Max	0.1 - 22.6	0.1 - 22.4
0 - 4	1 (0.8%)	1 (0.7%)
>4 - 8	1 (0.8%)	0
>8 - 12	1 (0.8%)	1 (0.7%)
>12 - 16	1 (0.8%)	3 (2.2%)
>16 - 20	26 (20.0%)	31 (23.0%)
>20 - 24	100 (76.9%)	99 (73.3%)
>24	0	0
Total Exposure (Patient-years)	49.9	51.5

Adverse events

Adverse events (AEs) were reported during the studies until the end of the safety follow-up (4-week follow-up in pivotal studies GA39688 and GA39855; up to data cut-off in the ongoing OLE study WA40169).

For pivotal studies GA39688 and GA39855, treatment emergent AEs were defined as any AE or any worsening of a pre-existing condition with an onset after the first dose of study drug.

For the ongoing OLE Study WA40169, treatment emergent AEs are defined as any new AE with an onset during the OLE study (i.e., after the first dose of open-label treatment with omalizumab), or any worsening of a pre-existing condition during the OLE study (i.e., ongoing AE from parent study which increased in severity during open-label treatment with omalizumab) and prior to 29 days after the last dose of omalizumab. Non-treatment emergent AEs for OLE Study WA40169 are defined as those AEs occurring during the parent study and continuing into the OLE study without worsening.

An overall summary of the adverse events recorded is presented in table 25.

Common adverse events - pivotal trials

The majority of adverse events (AEs) were of mild or moderate intensity (patients with severe AEs: placebo 6 of 76 (7.9%); omalizumab 5 out of 68 (7.4%). The most frequently reported AEs overall (incidence ≥ 3% of patients in either treatment arm) included headache, nasopharyngitis, asthma,

injection site reaction, upper abdominal pain, arthralgia, back pain, dizziness, epistaxis, rhinitis, sinusitis, nasal polyps, and nasal congestion. Treatment-emergent AEs (TEAEs) reported in ≥3% of patients and reported at a numerically higher incidence with omalizumab than with placebo (PT level) included headache, injection site reaction, arthralgia, dizziness, sinusitis and upper abdominal pain (Table 26 and Table 27). All of these AEs have been known to be associated with omalizumab and (except for sinusitis) are listed as adverse reactions in the Xolair product information. AEs of sinusitis were medically judged as likely to be associated with the disease under study rather than with study drug.

Table 25. Overview of treatment emergent adverse events, studies GA39688 and GA39855, Pooled Safety Analysis Set

	Placebo (N=130)	**Omalizumab (N=135)**
Total number of AEs	210	178
Total number of serious AEs	2	3
Total number of deaths	0	0
Total number (%) of patients with at least one AE	76 (58.5)	68 (50.4)
Severe AE (at greatest severity)	6 (4.6)	5 (3.7)
AE assessed as related to study drug by investigator	5 (3.8)	9 (6.7)
Serious AE	2 (1.5) [a]	3 (2.2) [b]
AE leading to discontinuation of study drug	1 (0.8) [c]	0
AEs of special interest [d]	0	0
AEs identified as risks associated with omalizumab [e]		
Arterial thrombotic events	1 (0.8)	0
Malignant neoplasms	1 (0.8)	0
Antibody formation to omalizumab	0	0
Eosinophilic Granulomatosis with Polyangiitis / Churg Strauss syndrome and/or hypereosinophilic syndrome	0	0
Parasitic infections	0	0
Serum sickness syndrome / Serum Sickness Like Disease	0	0
Thrombocytopenia	0	0

[a] SAEs included PTs of myocardial infarction and pneumonia; not considered as related to study drug.

[b] SAEs included PTs of asthma, snake bite, and hand fracture; not considered as related to study drug.

[c] One patient in the placebo arm discontinued study drug due to an AE of anaphylactic reaction (moderate intensity). However, this AE was not adjudicated as an AE of special interest or identified as risk associated with omalizumab.

[d] AEs of special interest include: adjudicated anaphylaxis per Sampson's criteria, drug-induced liver injury, and suspected transmission of an infectious agent by the study drug.

[e] AEs previously considered as potential or identified risks associated with omalizumab (Section 1.1.2.3.2).

Source: [SCS Appendix 1-t_ae_safety_PSAS], [SCS Appendix 1-t_ae_ser_PSAS], [SCS Appendix 1-t_ae_rel_PSAS], [Study GA39688-l_ae_SAS], [Study GA39688-Section 8.7]

Table 26. Frequent adverse event categories (SOC; at least 3% of patients in any treatment arm), studies GA39688 and GA39855

	Placebo (N=130)	Omalizumab (N=135)
Total number (%) of patients with at least one AE	**76 (58.5)**	**68 (50.4)**
Infections and infestations	33 (25.4)	35 (25.9)
Respiratory, thoracic and mediastinal disorders	30 (23.1)	21 (15.6)
Musculoskeletal and connective tissue disorders	12 (9.2)	12 (8.9)
Nervous system disorders	11 (8.5)	12 (8.9)
Gastrointestinal disorders	9 (6.9)	11 (8.1)
General disorders and administration site conditions	6 (4.6)	10 (7.4)
Injury, poisoning, and procedural complications	4 (3.1)	10 (7.4)
Skin and subcutaneous tissue disorders	4 (3.1)	9 (6.7)
Ear and labyrinth disorders	4 (3.1)	1 (0.7)

AE = (treatment emergent) adverse event.
Source: [SCS Appendix 1-t_ae_PSAS]

Table 27. Adverse events (PTs) reported in >/= 3% of patients in any treatment arm), studies GA39688 and GA39855, Pooled Safety Analysis Set

	Placebo (N=130)	Omalizumab (N=135)
Total number (%) of patients with at least one AE	**76 (58.5)**	**68 (50.4)**
Headache	7 (5.4)	11 (8.1)
Nasopharyngitis	11 (8.5)	8 (5.9)
Clustered injection site terms	2 (1.5) [a]	7 (5.2)
Injection site reaction	2 (1.5)	6 (4.4)
Injection related reaction	0	1(0.7)
Injection site pain	1 (0.8)	0
Asthma	15 (11.5)	5 (3.7)
Abdominal pain upper	1 (0.8)	4 (3.0)
Arthralgia	2 (1.5)	4 (3.0)
Back pain	5 (3.8)	4 (3.0)
Dizziness	1 (0.8)	4 (3.0)
Epistaxis	4 (3.1)	4 (3.0)
Rhinitis	4 (3.1)	4 (3.0)
Sinusitis	3 (2.3)	4 (3.0)
Nasal polyps [b]	4 (3.1)	3 (2.2)
Nasal congestion	4 (3.1)	0

[a] One patient in the placebo arm of Study GA39855 experienced injection site reaction (1 event) and injection site pain (1 event).

[b] Worsening of pre-existing disease.

Common adverse events – OLE study (interim report)

Overall, 63 patients (25.3%) experienced at least one TEAE with onset during open-label omalizumab treatment. As of the clinical cut-off date, the overall proportions of patients reporting TEAE switch onset during open-label omalizumab treatment was similar between patients who had received either placebo (31 patients [24.8%]) or omalizumab (32 patients [25.8%]) in the parent study. The most commonly reported system organ class SOCs) with onset during open-label omalizumab treatment (>5% incidence of overall events) were infections and infestations (25 patients [10.0%]; of these were 7 cases nasopharyngitis and 6 cases upper respiratory tract infection) and respiratory, thoracic and mediastinal disorders (14 patients [5.6%]).

Two additional events with onset during open-label omalizumab treatment were considered of interest even though they were reported in less than 2% of patients: pruritus and hypertension. The 4 patients with pruritus all experienced events of moderate severity and all received treatment; at the time of the clinical cut-off 2 events were resolved, 1 event was resolving, and 1 event was unresolved. The unresolved event led to discontinuation of omalizumab treatment.

Seven patients (2.8%) experienced at least one TEAE with onset during open-label omalizumab treatment suspected to be related to omalizumab or mometasone by the investigator. The 13 TEAEs considered related to omalizumab by the investigator included the following preferred terms: injection site pain (1 patient), injection site bruising (2 patients), injection site inflammation (1 patient), injection site reaction (1 patient), nervousness (1 patient), and pruritus (1 patient). All 13 TEAEs with onset during open-label omalizumab treatment were of mild or moderate severity and, with exception of pruritus and nervousness, had occurred within 2 days of omalizumab injection.

Serious adverse event/deaths/other significant events

Omalizumab was not associated with an increased risk (versus placebo) of any serious adverse events (SAEs). There were no deaths in either treatment arm during the course of the studies (pooled analysis (studies GA39688 and GA39855) and ongoing OLE study WA40169 (data cut-off date of 11 Mar 2019).

SAEs included the following PTs: pneumonia (placebo), myocardial infarction (placebo), asthma (omalizumab), snake bite (omalizumab), and hand fracture (omalizumab).

Adverse events of special interest

Potential cases of anaphylaxis (anaphylactic, anaphylactoid, and hypersensitivity reactions) were to be identified and sent for adjudication by an independent anaphylaxis adjudication Committee (AAC). There were no such cases recorded in the studies.

Events that have been previously identified as risks associated with omalizumab from the overall safety database and prescribing information (anaphylaxis, serum sickness syndrome, antibody formation to omalizumab, confirmed Churg Strauss syndrome and hypereosinophilic syndrome, thrombocytopenia, ATEs, malignancies, and parasitic infections) were to be summarized separately. There were no such cases recorded in the studies.

Laboratory findings

Haematology values were assessed by visit (baseline, Weeks 16, 24 and Week 28/SFU), and change from baseline. At Week 24, there was an increase in mean percent eosinophils assessed from baseline in the placebo arm (1.445 % and 1.127 % resp. mean change from baseline for placebo versus -0.264% and 0.497 % for omalizumab), however these changes did not result in any manifestations and/or sequelae. There were no shifts >grade 2 post-baseline for haematology parameter assessed and no patient developed abnormal platelet values post-baseline.

Serum chemistry were measured at screening (Day−35), baseline, Week 24 and Week 28/SFU. Values were assessed by visit and change from baseline. Overall there were no clinically relevant mean changes from baseline observed in either treatment arm for the chemistry values assessed. There were no cases of drug-induced liver injury which included an elevated Alanine aminotransaminase (ALT) or Aspartate aminotransaminase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law. One patient in the omalizumab treatment arm in study GA39688 developed grade 3 ALT and grade 2 AST values at Week 24 (Study Day 169), although this was not in combination with elevated total bilirubin (i.e. >2 × ULN) and the patient had no signs of clinical

jaundice. The patient was reported with autoimmune hepatitis; the investigator considered this event unrelated to omalizumab treatment and possibly a pre-existing (autoimmune hepatitis; hemochromatosis mutation) condition which was detected during the scheduled chemistry testing. The patient was first diagnosed with elevated liver enzymes following laboratory work-up on Study Day 169, but this diagnosis was subsequently updated to non-serious autoimmune hepatitis (moderate intensity) following a liver biopsy, performed 26 days later. The liver biopsy indicated moderate fibrosis. The investigator thought that the event developed slowly prior to study participation and the routine lab follow-up per study protocol picked up the AST and ALT elevations as the disease progressed. Reportedly, AST and ALT were both normal during the initial screening chemistry panel (see table below), but by week 24 they began to be elevated.

A summary of vital signs (pulse rate and blood pressure) values at each visit, change from baseline at each visit, as well as the minimum and maximum post-baseline and change from baseline values is provided. No clinically relevant mean changes from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), or pulse rate were noted in either treatment arm.

Anti-drug antibodies

ADA testing was not planned per protocol unless the investigator suspected ADA formation and prescribed ADA testing. No events suggesting antibody formation to omalizumab were identified in the two pivotal studies.

Safety in special populations

To evaluate the impact of patient age on the safety of omalizumab in patients with nasal polyps, AE data were analysed in patient subgroups aged <65 years and ≥ 65 years (elderly patients). Overall, 7 of 20 elderly patients in the omalizumab arm (35.0%), compared with 12 of 20 elderly patients in the placebo arm (60.0%) reported one or more AEs. The higher incidence of AEs in the placebo arm was mainly driven by an increased incidence of AEs in the SOC of respiratory, thoracic, and mediastinal disorders (placebo 6 patients, 30.0%; omalizumab 1 patient, 5.0%).

To evaluate the impact of concomitant asthma disease and of aspirin sensitivity on the safety of omalizumab, AE data were analysed in patient subgroups with asthma, with asthma and additional aspirin sensitivity, and in patients with no asthma at screening. Treatment emergent AEs of asthma were generally more common in patients with concurrent asthma at screening (with or without additional aspirin sensitivity) than in patients without asthma. There was also a slight trend for more injection site reactions reported in patients with asthma (with or without additional aspirin sensitivity) versus patients without asthma.

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with omalizumab. In the nasal polyp studies, omalizumab was used in conjunction with intranasal mometasone spray per protocol. Other commonly used concomitant medications included other intranasal corticosteroids, bronchodilators, antihistamines, leukotriene receptor antagonists, adrenergics/sympathomimetics, and local nasal anaesthetics. There was no indication that the safety of omalizumab was altered with these other commonly used medications, which are the current standard of care for patients with nasal polyps.

Discontinuation due to adverse events

No AE leading to discontinuation occurred in omalizumab treated patients in the pivotal trials. During the OLE study, 1 patient discontinued open-label omalizumab treatment due to a nonserious TEAE of pruritus, which occurred 7 days after the first dose of open-label omalizumab. In addition, the patient with autoimmune hepatitis recorded in study GA39688 discontinued after inclusion to the OLE-study.

Post marketing experience

Based on the extensive post-marketing experience from approved indications (>1 million patient years of exposure), the general safety profile of omalizumab has been well established. The important risks are well characterised and routine risk management applies (see Risk Management Plan section 2.6.).

2.5.1. Discussion on clinical safety

The overall safety profile of omalizumab has been well-characterized in the current authorised indications i.e. treatment of allergic asthma in children (≥ 6 years), adolescents and adults, and treatment of CSU in adolescents (≥ 12 years) and adults. The estimated cumulative omalizumab exposure is >16,000 patients in clinical trials and >1 million patient years in the post-marketing setting, as of 31 December 2018.

The safety database for the new indication consists of data from the two pivotal clinical trials GA39688 and GA39855. Both studies had identical inclusion and exclusion criteria, study assessments, and safety endpoints; therefore, pooling of safety data is considered acceptable. Supportive data from an interim analysis of the ongoing, OLE study (WA40169) are also included; with a clinical data cut-off date of 11 March 2019, which is the date of last patient enrolled in the OLE study.

In the two pivotal studies, a total of 135 patients received omalizumab, and 130 patients received placebo. A total of 249 patients from the completed pivotal studies enrolled into the OLE study WA40169 and started open-label omalizumab treatment (parent study drug treatment received: omalizumab 124, placebo 125).

The safety database presented with this application is considered to be relatively small. Considering the relative similarity between the patient population with nasal polyps and the patient population with allergic asthma, it is considered acceptable to extrapolate the safety from the existing safety database (pre and post-approval).

In the pooled analysis of the two pivotal studies, the adverse events recorded were generally mild and recorded in similar numbers in the omalizumab and placebo groups (50.4% versus 58.5%). The only obvious imbalances are injection site reactions and asthma which is expected. Injection site reactions are listed with the frequency "common" in the approved SmPC and the unbalance for asthma can be attributed to the fact that approximately half of the population had asthma as co-morbidity at inclusion. There were no unexpected findings presented in the OLE interim report. The pattern of adverse events presented in the interim analysis are similar to the findings in the pivotal trials and consistent with the known safety pattern for Xolair.

Section 4.8 of the SmPC has been updated to reflect that arthralgia was more common in the nasal polyps trial.

No deaths occurred in the pooled analysis (studies GA39688 and GA39855) and in the ongoing OLE study WA40169.

There were no cases of anaphylaxis (anaphylactic, anaphylactoid, and hypersensitivity reactions) recorded in the pivotal studies or in the OLE study (safety interim report). It can be anticipated that the frequency of anaphylaxis is similar to that in the already approved populations. Other rare events such as serum sickness syndrome, Churg Strauss syndrome/hypereosinophilic syndrome and idiopathic thrombocytopenia were not recorded in the studies, nor were any parasitic infections. Due to the limited size of the clinical safety database, occurrence/frequency of such events could nevertheless not be estimated but are probably independent of population. Anaphylaxis and Churg Strauss Syndrome/hypereosinophilic syndrome are well described in the Xolair EU SmPC and well managed through routine pharmacovigilance measures as described in the RMP. Furthermore, no change in frequency and severity of these risks has been observed during the periodic evaluation in the PSURs. Therefore, no further actions were deemed warranted in the present application.

There was one case of autoimmune hepatitis (AIH) reported during the clinical studies. As AIH is currently not listed in section 4.8 of the SmPC, the MAH was requested to present the case in more detail and discuss possible relation with omalizumab treatment. Based on the data provided by the MAH, the CHMP considered that a causal association between omalizumab and AIH is considered unlikely and that the single case recorded in the study does not warrant further regulatory action. Thus, there is no need to update section 4.8 of the SmPC. The MAH should nevertheless closely monitor 'autoimmune hepatitis' in future PSURs.

ADA testing was not planned per protocol unless the investigator suspected ADA formation and prescribed ADA testing. Furthermore, no events suggesting antibody formation to omalizumab were identified in the two pivotal studies. Antibody formation to omalizumab is already listed as an adverse drug reaction in section 4.8 of the SmPC (frequency rare). Differences in antibody formation between the approved indications and patients with nasal polyposis are not expected.

2.5.2. Conclusions on clinical safety

The overall safety profile as recorded in the two pivotal clinical studies supports the known safety profile of the product with injection site reactions being the only obvious unbalance vs placebo. The amount of data is nevertheless too limited to allow for any estimation of occurrence/frequency of more rare adverse reactions. Thus, the conclusion on safety relies mainly on the previously known safety data on omalizumab in the currently approved indications. Nevertheless, longer-term safety data will be available from the ongoing OLE study.

Furthermore, the MAH was requested to closely monitor 'autoimmune hepatitis' (AIH) in future PSURs.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 16.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 16.0 with the following content:

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

Pharmacovigilance plan

Routine pharmacovigilance activities beyond ADRs reporting and signal detection are planned. They consist of specific adverse reaction follow-up questionnaires.

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

There are no additional pharmacovigilance activities planned.

Risk minimisation measures

Safety concern	**Risk minimization measures**	**Pharmacovigilance activities**
Important Identified risks		
Anaphylaxis/anaphylactoid reactions	Routine risk minimization measures: SmPC sections – 4.2, 4.4 and 4.8. PL sections - 2 and 4 Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. -Expedited reporting to the EMA (and to other countries as per local regulations) of all cases of serious anaphylaxis, anaphylactoid reactions, or a combination of individual symptoms meeting accepted diagnostic criteria and assessed as related to omalizumab. Additional pharmacovigilance activities: None.
Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome (HES)	Routine risk minimization measures: SmPC sections - 4.4 and 4.8. PL sections - 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	None.
Important potential risks		
Arterial Thromboembolic Events (ATEs)	Routine risk minimization measures: SmPC section - 4.8 (This is not an ADR. The available data from the pooled CT database and observational study has been summarized) PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.
Malignant neoplasms in adults and adolescents ≥ 12 years of age	Routine risk minimization measures: SmPC sections – None. PL sections – None. Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.
Malignant neoplasms (children 6 to less than 12 years old)	Routine risk minimization measures: SmPC sections - None PL sections - None Legal status: Prescription only medicine. Medicinal product subject to restricted medical prescription. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: -Follow-up using a targeted checklist. Additional pharmacovigilance activities: None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which were accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of NL.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable, because the proposed changes are minor and not considered to significantly affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a heterogeneous disease characterized by inflammation of the nose and paranasal sinuses, tissue oedema, nasal obstruction, and increased mucus production causing symptoms including nasal congestion/obstruction, loss of sense of smell, and rhinorrhoea that persist for at least 12 week.

It is a predominantly adult disease with a prevalence estimated to be 2.1% to 2.7%. It is associated both with reduced quality of life (QoL) and significant morbidity, including asthma, which can be severe and refractory, particularly in those patients with aspirin exacerbated respiratory disease. The diagnosis is made in patients who exhibit a combination of symptoms with the presence of nasal polyps.

Patients with CRSwNP and many patients with allergic asthma share a common IgE-mediated type 2 inflammatory response, characterized by elevated levels of IL-4, IL-5, IL-13, eosinophils, Th2 cells, and type 2 innate lymphoid cells. Histological examination usually shows mixed infiltrates of mononuclear cells and eosinophils. In addition, locally produced IgE against staphylococcal enterotoxins, is associated with local inflammation in CRSwNP and, in particular, with comorbid asthma. Approximately 20%−40% of patients with asthma have CRSwNP, particularly those patients with severe asthma. A substantial proportion of patients with CRSwNP have symptoms of asthma, with higher percentages associated with patients who have greater nasal polyp disease severity. There appears to be a premorbid relationship between asthma and CRSwNP, with the diagnosis of asthma often occurring prior to that of nasal polyposis.

Nasal polyposis is not a potential fatal condition, but severe polyposis can contribute to symptoms and conditions associated with a substantial impact on quality of life and health.

3.1.2. Available therapies and unmet medical need

Intranasal and systemic/oral corticosteroids is the main treatment of nasal polyps. When these treatments are insufficient, i.e. in patients with severe disease, surgery, like Functional Endoscopic Sinus Surgery (FESS) and other sinus surgeries, can be performed. Although FESS and intranasal and systemic/oral corticosteroids are useful and often effective in reducing the size of nasal polyps, polyps return after medication withdrawal and within months to years following surgery.

There is a monoclonal antibody approved for treatment of nasal polyposis dupilumab which acts against IL4-receptor alpha that inhibits IL-4/IL-13 signalling. Interleukins 4 and 13 affects both eosinophils and IgE-levels. It is indicated as add-on therapy in adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery has not provided adequate disease control.

3.1.3. Main clinical studies

The efficacy and safety of omalizumab in nasal polyps is supported by two identical phase-III, randomized, multi-centre, double-blind, placebo-controlled clinical trials of 24 weeks performed in patients with chronic rhinosinusitis with nasal polyps (GA39688 and GA39855). Both pivotal studies included adult patients with nasal polyps whose disease remained inadequately controlled despite daily treatment with intranasal corticosteroids.

Changes from baseline to Week 24 in NPS and the average daily NCS were co-primary endpoints. Nasal polyp score is decided with intranasal endoscopy and right and left sides are assessed separately on a scale from 0 to 4 (total maximum 8). Nasal congestion score (0 to 3) is based on daily patient reports using the mean value of the last 7 days.

Secondary endpoints were change from baseline at week 24 in the average daily TNSS, a composite score, change from baseline at week 24 in patient–reported HRQoL as assessed by total SNOT-22, change from baseline at week 24 in UPSIT, change from baseline at week 16 in NPS and in the average daily NCS and requirement of rescue treatment (systemic CS for $\geq$ 3 consecutive days) through week 24. TNSS grades four symptoms, sneezing, congestion, itching and rhinorrhoea. Each symptom is graded from 0-3 (3 being the worst). SNOT-22 (0-110 points) is a validated questionnaire of disease specific, quality of life related measures of sinonasal function which has been validated to show a minimal clinical important difference (MCID) of 8.9 or more. Seven or lower is considered normal. UPSIT is a test for smell identification to test the function of an individual's olfactory system with the worst being 0 and the best being 40. These scores were patient reported.

3.2. Favourable effects

In both pivotal Phase-III studies (GA39688 and GA39855), the co-primary endpoints of the changes from baseline at Week 24 in NPS and the average daily NCS were met. For each of the co-primary endpoints, the between-treatment difference in the adjusted mean changes at Week 24 was statistically significant in favour of omalizumab (p-value of <0.05 in both studies for both co-primary endpoints).

At baseline, the participants had a mean NPS (range 0-8) of 6.21 in the placebo group compared to 6.31 in the omalizumab treatment arm (pooled data). Both groups improved with 0.13 resp. 0.99, nominal p<0.0001 for pooled data. For NCS (range 0-3), the inclusion criterion was $\geq$2 at baseline and the treatment groups had 2.38 (placebo) resp. 2.34 (omalizumab) at baseline. Both groups improved with 0.28 resp. 0.80, nominal p<0.0001 for pooled data. Thus, the primary objectives to show superiority of omalizumab to placebo were formally met.

For the secondary efficacy endpoints TNSS, SNOT-22 and UPSIT, omalizumab showed improvement compared to placebo (all three endpoints had a p-value of <0.05 in both studies and the nominal p-value for the pooled data was p<0.0001). Approximately 40% of the patients in the placebo arms and 70% of the patients in the omalizumab arms had a change of at least 8.9 points in SNOT-22. The adjusted mean (SE) for the change in SNOT-22 at week 24 compared to baseline was -7.73(1.51) in the pooled placebo arm, i.e. below the threshold for clinical relevance, but -23.10(1.50) in the pooled omalizumab group.

The MAH presented an adequate literature review contextualizing the results of both co-primary endpoints (NPS and NCS). The effect level appears similar to intranasal corticosteroids in the responding population which is deemed clinically relevant.

3.3. Uncertainties and limitations about favourable effects

The choice of dosing regimen was initially not fully discussed in comparison with allergic asthma and chronic spontaneous urticaria. However, similar pathophysiological mechanisms in allergic asthma and nasal polyposis; and similar mechanism of action of omalizumab supported the choice of dosing regimen and the proposed information included in the product information.

The chosen statistical method is a MMRM together with failure imputation for patients with intercurrent events. It is not apparent that the handling of intercurrent events and missing data provides a conservative estimate of the treatment effect. The number of intercurrent events by type and treatment group together with the observed and imputed data were presented by the MAH. The numbers are low and the impact on the estimate of treatment effect was considered to be minor.

The sample size calculations were based on a 0.56 point difference for NCS and 1.50 for NPS. These differences were not achieved. However, omalizumab was statistically significantly better than placebo in both pivotal studies and both co-primary endpoints, and the effect size was considered clinically relevant when put into context by a literature review presented by the MAH. The effect level as compared with other biologicals remain uncertain as there are no directly comparing studies. The point estimates of effect appeared higher in dupilumab studies, but these studies had different enrolment criteria with respect to requirement for prior surgeries and systemic steroids, differences in populations enrolled, and other differences in study conduct.

There were no differences recorded for the secondary endpoint Requirement of rescue treatment (systemic corticosteroids ≥3 consecutive days or nasal polypectomy) between omalizumab and placebo, these results should nevertheless be interpreted with caution as there were few events and the study was short (24 weeks).

The long-term efficacy is an uncertainty as CRSwNP is a chronic lifelong disease and the current efficacy data remain limited over long term.

3.4. Unfavourable effects

Of the 135 patients (corresponding to a total of 51.5 patient-years) who received omalizumab during the two Phase III Studies GA39688 and GA39855, 7 (5.2%) experienced injection site reactions to be compared with 2 patients (1.5 %) treated with placebo. All other adverse events were recorded in similar numbers in the omalizumab and placebo group respectively. There were no severe events recorded that could be attributed to omalizumab treatment.

One of the known serious adverse events of omalizumab is anaphylactic reactions. There were no such cases recorded in the pivotal studies or in the OLE study presented with this application. It can be

anticipated that the frequency of anaphylaxis is similar to that in the already approved populations. Anaphylactic reaction is currently listed as an adverse reaction with a frequency 'rare' in section 4.8 of the SmPC and adequate warnings have already been included in section 4.4 of the SmPC. Therefore, no further actions are deemed warranted. Other rare events such as serum sickness syndrome, Churg Strauss syndrome/hypereosinophilic syndrome and idiopathic thrombocytopenia were not recorded in these studies, nor were any parasitic infections. Due to the limited size of the clinical safety database, occurrence/frequency of such events could nevertheless not be estimated but are probably independent of population.

Section 4.8 of the SmPC has been updated to reflect that arthralgia was more common in the nasal polyps studies.

There was one case of autoimmune hepatitis (AIH) reported during the clinical studies. As AIH is currently not listed in section 4.8 of the SmPC, the MAH was requested to present the case in more detail and discuss possible relation with omalizumab treatment. Based on the data provided by the MAH, the CHMP considered that a causal association between omalizumab and AIH is considered unlikely and that the single case recorded in the study does not warrant further regulatory action. Thus, there is no need to update section 4.8 of the SmPC. Nevertheless, the MAH was requested to closely monitor 'autoimmune hepatitis' in the post-marketing setting i.e. future PSURs.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety experience is limited in CRSwNP patients as the majority of the safety data (from the pooled analysis) comes from 24 weeks of data. Long-term safety data will be provided with the submission of the final study report of the currently ongoing OLE study (WA40169).

Due to the size of the database, the occurrence/frequency of rare events could not be estimated based on observed data in patients treated with omalizumab for nasal polyps. Thus, the safety profile was extrapolated partly from the already approved indications.

3.6. Effects Table

Table 1. Effects Table for Xolair (omalizumab) in nasal polyposis

Effect	Short description	Unit	Treatment Xolair	Control Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
NPS at wk 24	Change in NPS from baseline to week 24		-0.99	-0.13	p<0.0001	Pooled results from pivotal phase 3 studies
NCS at wk 24	Change in NCS from baseline to week 24		-0.80	-0.28	p<0.0001	
TNSS at wk 24	Change in TNSS from baseline to week 24		-2.75	-0.77	p<0.0001	
SNOT-22 at wk 24	Change in SNOT-22 from baseline to week 24		-23.10	-7.73	p<0.0001	
UPSIT at wk 24	Change in UPSIT from baseline to week 24		4.38	0.54	p<0.0001	
Unfavourable Effects						

Effect	Short description	Unit	Treatment Xolair	Control Placebo	Uncertainties / Strength of evidence	References
Adverse event	Injection site reactions	%	5.2	1.5		Pooled results from pivotal phase 3 studies

Abbreviations: NPS = nasal polyp score; NCS= nasal congestion score; TNSS = total nasal symptom score; SNOT = sino-nasal outcome test-22; UPSIT = University of Pennsylvania Smell Identification Test

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Omalizumab was studied as an add-on therapy to intranasal corticosteroids (INC) in adult patients with severe CRSwNP for whom therapy with INC had not provide adequate disease control.

Nasal polyposis is not a potential fatal condition, but severe polyposis can contribute to symptoms and conditions associated with a substantial impact on quality of life and health.

In the pivotal studies presented, GA39688 and GA39855, statistical significance was reached for the 2 co-primary efficacy endpoints (change from baseline in NPS and NCS at Week 24). Thus, the primary objectives to show superiority of omalizumab to placebo were met. These results were overall supported by secondary endpoints (TNSS, SNOT-22 and UPSIT) investigated. The clinical relevance of omalizumab in the treatment of adult patients with severe CRSwNP who have inadequate response to intranasal corticosteroids has been further discussed and contextualised by the MAH and is considered sufficiently justified with respect to clinical relevance. The effect seems to be of the same magnitude as for intranasal corticosteroids. The effect may be less pronounced compared to dupilumab based on cross study comparison. However, there are no directs comparisons.

Overall, omalizumab was well tolerated in the target population of patients with severe nasal polyps who have inadequate response to intranasal corticosteroids, and generally consistent with the established safety profile in patients with currently approved indications in allergic asthma and CSU. No new or unexpected safety signals were observed in the nasal polyps population.

3.7.2. Balance of benefits and risks

There is a documented effect of omalizumab over placebo in patients with severe chronic rhinosinusitis with nasal polyps with improvements within the range of other available treatment options. This benefit is to be weighed against a well-known and rather benign safety profile of the drug which as previously been found acceptable for asthma and CSU.

Based on the data provided on efficacy and safety, the CHMP considers that the favourable effects outweigh the unfavourable effects.

3.7.3. Additional considerations on the benefit/risk balance

The initially proposed indication *(Xolair is indicated for the treatment of nasal polyps in adult patients (18 years and above) with inadequate response to intranasal corticosteroids)* was considered to be too

broad and not sufficiently covered by the data provided. The studied population was considered to represent patients with severe disease based on baseline severity scores.

The indication granted by CHMP was therefore 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.

3.8. Conclusions

The overall benefit/risk balance of Xolair for the treatment of adults (18 years and above) with severe CRSwNP for whom therapy with INC does not provide adequate disease control is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include Xolair 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 for whom therapy with INC does not provide adequate disease control; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet (PL) is updated in accordance. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of the Netherlands. Furthermore, the product information is brought in line with the latest QRD template version 10.1. The risk management plan version 16.0 has also been agreed.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Xolair-H-C-Product Number-II-101'