London, 23 January 2013
EMA/CHMP/137079/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xolair

International non-proprietary name: omalizumab

Procedure no. EMEA/H/C/000606/II/0048

Note

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

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List of abbreviations

AE: adverse event

AESI: AE of special interest

AR: adverse reaction

ATA: anti-therapeutic antibodies; use abbreviation only on line 1695

BMI: body mass index

CHMP: Committee for Medicinal Products for Human Use Line 157

CI: confidence interval

CIU: chronic idiopathic urticaria

Cmin: minimum blood/plasma concentration

CSU: chronic spontaneous urticaria

DLQI: Dermatology Quality of Life Index

EAACI: European Academy of Allergology and Clinical Immunology

EMA: European Medicines Agency

FcεRI: high affinity IgE receptor

IgE: immunoglobulin E

ITP: idiopathic thrombocytopenic purpura

ITT: Intent to treat

LLN: lower limit of normal

LTRA: leukotriene receptor antagonist

MID: minimally important difference

PD: pharmacodynamics

PK: pharmacokinetic

SAE: Serious Adverse Event

SC: subcutaneous

SCE: summary of clinical efficacy

SCS: summary of clinical safety

SD: standard deviation

SOC: system organ class

t½: elimination half-life

UAS: urticaria activity score

UAS7: urticaria activity score over 1 week

ULN: upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 16 July 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Xolair	omalizumab	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of chronic spontaneous urticaria refractory to standard of care in adults and adolescents (12 years of age and above). Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance.

Minor amendments were proposed in sections 4.4 and 4.6 of the SmPC.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/133/2010 on the granting of a product-specific waiver.

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 December 2009. 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 and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Bengt Ljungberg	Co-Rapporteur:	Arantxa Sancho

Submission date:	16 July 2013
Start of procedure:	26 July 2013
Rapporteur's preliminary assessment report circulated on:	16 September 2013
CoRapporteur's preliminary assessment report circulated on:	19 September 2013
Joint Rapporteur's updated assessment report circulated on:	18 October 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	18 October 2013
MAH's responses submitted to the CHMP on:	21 November 2013
Joint Rapporteur's/Co-Rapporteur's assessment report on the responses provided by the MAH circulated on:	20 December 2013
PRAC RMP advice and assessment overview adopted by PRAC:	9 January 2014
Joint Rapporteur's/Co-Rapporteur's updated assessment report on the MAH's responses circulated on:	20 January 2014
CHMP opinion:	23 January 2014

2. Scientific discussion

2.1. Introduction

Xolair (omalizumab) is presently approved for the treatment of severe persistent allergic asthma in adults and adolescents (October 2005 in EU). Inclusion of the paediatric population of 6 to <12 years of age for severe persistent allergic asthma was approved in 2009. In the treatment of allergic asthma, omalizumab is administered every 2 or 4 weeks, with doses (mg) and dosing frequency determined by serum total IgE level (IU/ml) measured pre-treatment, and body weight (kg). Four different approved formulations are available for Xolair, i.e., 75 mg powder and solvent for solution for injection, 150 mg powder and solvent for solution for injection, 75 mg solution for injection in pre-filled syringe and 150 mg solution for injection in pre-filled syringe.

With this variation, the MAH applies for a new therapeutic indication for Xolair (omalizumab) i.e. "*Xolair is indicated for adults and adolescents (12 years of age and above) with chronic spontaneous urticaria refractory to standard of care*".

The proposed recommended posology is:

"Chronic spontaneous urticaria (CSU)

The recommended dose is 300 mg by subcutaneous injection every four weeks. Some patients may achieve control of their symptoms with a dose of 150 mg every four weeks. Patients with angioedema should be treated with 300 mg every four weeks.

Prescribers are advised to periodically reassess the need for continued therapy."

In this variation only the formulation 150 mg powder and solvent for solution for injection and the 150 mg solution for injection in pre-filled syringe are concerned.

Chronic spontaneous urticaria (CSU) is defined as the occurrence of daily, or almost daily, wheals and frequently intractable pruritus (itching) for at least 6 weeks without an obvious cause. Itch is the most concerning symptom for patients, and has the greatest impact on their quality of life. Angioedema or deep tissue swelling occurs in over 40% of patients with CSU; it is unpredictable and can involve swelling anywhere in the body or upper respiratory tract. Swelling of the face, lips or airway is particularly uncomfortable and can be very serious for the patients.

The proposed indication uses the term CSU (as opposed to chronic idiopathic urticaria or CIU) in accordance with recent guidelines published by the European Academy of Allergology and Clinical Immunology (EAACI). The term chronic idiopathic urticaria (CIU) was originally essentially synonymous with CSU but is now reserved for patients with truly idiopathic aetiology. The term CSU is broader and includes patients with a known auto-antibody or prior infection-related chronic urticaria who are not now considered 'idiopathic', as they do have a known trigger. Thus, in this new classification, CSU covers all non-inducible chronic urticaria with CIU (of unknown trigger) being a subset of it. As the population studied in the omalizumab clinical studies included patients with auto-antibodies (all were tested at baseline), the term CSU most accurately reflects the study population and intended use.

Scientific advice was sought from European Medicines Agency (EMEA/H/SA/45/3/2009/III, December 2009) on questions concerning pre-clinical and clinical development of CIU. In the EMA scientific advice it was accepted not to conduct further preclinical studies provided the data already available supported the clinical development in CIU/CSU. The overall clinical development was discussed and it was agreed that the studies should include patients not only unresponsive to H1 antihistamines but also to H1 antihistamines, plus H2 antihistamines or leukotriene receptor antagonist (LTRA) or a combination of all. In addition the placebo control on top of standard of care, the duration of the studies, and the endpoints of itch severity, global severity by urticaria activity scores (UAS) for the previous 7 days (UAS7), and efficacy of severity and frequency of angioedema attacks were highlighted. The primary efficacy endpoint for the Phase III efficacy studies was selected due to comments received from the US Food and Drugs Administration (FDA), which advised that this endpoint be based on the itch severity component of the UAS7. The use of UAS7 and angioedema as secondary endpoints was also agreed with the US FDA in their end of Phase II meeting.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical data have been submitted in this application. As stated by the MAH, the results from a complete non-clinical safety program were submitted in 2004, as part of the initial application (EMEA/H/C/000606), for the use of omalizumab in patients with severe asthma. Since that time no changes in production process or drug substance were made and only minor changes were introduced in the formulation to provide prefilled syringes with liquid solution. None of the changes in excipients are expected to have any influence on clinical or preclinical safety since all compounds used are commonly used excipients in antibody formulations. In addition, the MAH has performed a randomized single-center, single blind, three-way cross over study (CSR Q2569g) to evaluate safety and injection site reactions associated with two subcutaneous excipient formulations. A similar safety profile was identified for the two liquid formulations and no new issues were observed.

The MAH further states that clinical safety data gathered from post-marketing use of omalizumab in patients >6 years of age with moderate to severe allergic asthma inadequately controlled with inhaled corticosteroids (PSUR 16, 15 Feb 2013), and the data from the clinical studies conducted in patients with chronic spontaneous urticaria (CSU) included in this submission (Q4577g, Q3983s, Q3245s and CIGE025ADE05) have not identified any new safety issues that would require additional non-clinical studies.

In conclusion, for the reasons outlined above the MAH is not planning to conduct additional non-clinical safety studies with omalizumab and no non-clinical safety studies are currently ongoing.

2.2.2. Ecotoxicity/environmental risk assessment

The MAH has submitted an updated summary of environmental risk assessment (ERA) aspects. No complete ERA, in accordance with Directive 2001/83/EC and Guideline CHMP/SWP/4447/00, has been conducted. The rationale for this is that it can be expected that any omalizumab adsorbed into the bloodstream after subcutaneous injection is largely catabolized. As other naturally occurring IgGs, proteins or peptides, any omalizumab that reaches water streams via eventual spills during application or after disposal of unused drug is expected to be very rapidly consumed by microbes e.g. as energy/carbon source or incorporated by them. Accordingly, the MAH does not predict any adverse environmental effects from omalizumab.

2.2.3. Discussion on non-clinical aspects

No new non-clinical data were submitted by the MAH. The non-clinical safety package included in the initial application (EMEA/H/C/000606) is considered sufficient for the present variation.

Omalizumab is not expected to pose a risk to the environment, and the new indication sought is not considered to increase the environmental risk.

2.2.4. Conclusion on the non-clinical aspects

No new non-clinical data were submitted by the MAH. The non-clinical safety package included in the initial application (EMEA/H/C/000606) is considered sufficient for the present variation.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of omalizumab. Considering the above data, omalizumab is not expected to pose a risk to the environment.

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 No.	Study objective, population	Study design	Dosing, duration	Randomized patients	Efficacy endpoints
Phase II study					
Q4577g	Dose-ranging, efficacy and safety in patients (12-75 years) with CSU who remain symptomatic despite H1 antihistamine treatment	MC, R, PG, DB,	Single dose plus 12 weeks follow-up	Total: 90 75 mg: 23 300 mg: 25 600 mg: 21 Placebo: 21	Primary: change from baseline to Week 4 in UAS7 Secondary: changes from baseline to Week 4 in weekly scores for pruritus, number of hives, and sleep disturbance Amount of rescue medication
Pivotal Phase III efficacy studies					
Q4881g	Dose-ranging, efficacy and safety in patients (12-75 years) with CSU who remain symptomatic despite H1 antihistamine treatment	MC, R, PG, DB,	4-weekly, 24 weeks treatment (6 doses), plus 16 weeks FU	Total: 319* 75 mg: 78* 150 mg: 80 300 mg: 81 Placebo: 80	Primary: change from baseline to Week 12 in weekly itch severity score (from UAS7) Secondary: change from baseline to Wk 12 in: UAS7; change from baseline to Wk 12 in weekly no. of hives score; time to MID response in weekly itch severity score; proportion of patients at Wk 12 with: UAS7 ≤6; proportion of patients at Wk 12 with weekly itch severity score MID response; change from baseline to Wk 12 in weekly size of largest hive score; change from baseline to Wk 12 in DLQI; proportion of angioedema-free days from Wk 4 to Wk 12; proportion of patients with UAS7 = 0 at Wk 12.
Q4882g	Dose-ranging, efficacy and safety in patients (12-75 years) with CSU who remain symptomatic despite H1 antihistamine treatment	MC, R, PG, DB,	4-weekly, 12 weeks treatment (3 doses), plus 16 weeks FU	Total: 323* 75 mg: 82 150 mg: 83* 300 mg: 79 Placebo: 79	As for Q4881g, but no pre-planned analysis of proportion of patients with UAS7 = 0 at Wk 12
Phase III safety study					
Q4883g	Safety and efficacy in patients (12-75 years) with CSU who remain symptomatic despite H1 or H2 antihistamine and/or LTRA treatment	MC, R, PG, DB,	4-weekly, 24 weeks treatment (6 doses) plus 16 weeks FU	Total: 336* 300 mg: 252 Placebo: 84*	Efficacy was a secondary objective. Endpoints as for Q4881g

MC=multicenter, R=randomized, PG=parallel-group, DB=double-blind; UAS7=urticaria activity score over 1 week, MID=minimally important difference, LTRA=leukotriene receptor antagonist; GAS=global assessment of symptoms; DLQI=dermatology life quality index; Cu-Q2oL=Chronic Urticaria quality of life questionnaire; FU=follow-up

*One patient was randomized but did not receive study medication (in 75 mg group in Q4881g, in 150 mg group in Q4882g, in placebo group in Q4883g)

2.3.2. Pharmacokinetics

Analytical methods

*Total serum concentrations of omalizumab (NBx-RS602700A)*An ELISA method was used for determination of total serum concentrations of omalizumab (*i.e.* the sum of unbound omalizumab and omalizumab bound to IgE) in the concentration range of 28 to 1000 ng/ml.

Free IgE serum concentrations (NBx-RS602700)

Serum concentrations of free IgE were determined by the use of an ELISA assay in the concentration range 2-150 ng/ml.

*Total IgE serum concentrations (NBx-RS630172)*The Phadia ImmunoCAP platform was used for determination of total IgE serum levels. A cross-validation with the earlier used Abbott Imx platform

was performed. The Lower Limit of Quantification was set to 2 kIU/L (4.84 ng/ml) and the Upper Limit of Quantification to 5000 KIU/L (12100 ng/ml).

*Serum levels of anti-omalizumab antibodies (BXSD-R00-011-1560, BXSD-R00-010-1560)*Two screening ELISA assays were used to detect anti-omalizumab antibodies, one to the Fc and one to the Fab component. Sample absorbance was compared to calibrator curve absorbance and samples with titer absorbance ≥2 were reported as positive and samples with absorbance <2 reported as <2.

Exposure

The pharmacokinetics of omalizumab in patients diagnosed with CIU was evaluated in a randomized, double-blind, placebo-controlled, parallel-group phase II study following a single SC dose (Q4577g). A total of 90 patients (randomized approx. 1:1:1:1 ratio) received placebo or 75, 300 or 600 mg omalizumab. Blood samples were collected at regular intervals up 112 days *post* dose and pharmacokinetics of omalizumab calculated by non-compartmental analysis.

The terminal half-life was calculated to about 20 days and the systemic exposure of omalizumab increased proportionally with dose in the study dose range 75-600 mg following a single s.c. injection (table 1).

Table 1 Basic, mean (CV), pharmacokinetics of omalizumab, in CIU patients, following a single SC injection of Xolair

Dose (mg)	C_{max} (µg/ml)	AUC (µg/ml.days)	t_{max} (days)	$t_{1/2}$ (days)
75	11(145)	317(32)	7.4	18
300	33(30)	1260(46)	8.0	17
600	67(40)	2800(41)	6.2	23

2.3.3. Pharmacodynamics

Serum levels of free and total IgE was determined at regular time points following a single SC injection of omalizumab in patients diagnosed with CIU (Q4577g).

2.3.4. PK/PD modelling

2.3.4.1. Analysis of omalizumab PK and IgE response

The pharmacokinetic and pharmacodynamic characteristics of omalizumab in patients with CSU were described by a target-mediated population PK/PD model incorporating omalizumab−IgE binding and turnover. This model had the same structure as the one previously developed for patients with allergic asthma.

Body weight, baseline IgE values, body mass index (BMI), anti-FcεRI autoantibodies (based on the Chronic Urticaria [CU] Index) and concomitant use of H2 antihistamines were identified as statistically significant covariates on PK/PD model parameters. Body weight and body mass index had modest (<26%) effects on omalizumab trough values at Week 12, whereas anti-FcεRI autoantibodies, H2 antihistamines and baseline IgE had negligible overall effect on omalizumab trough values. Age (12−75 years), race/ethnicity, sex, study (study Q4883g vs. others) or the concomitant use of leukotriene receptor antagonists (LTRAs) were not significant covariates for the pharmacokinetics and pharmacodynamics of omalizumab.

Based on the population PK/PD analysis, the apparent clearance and volume of distribution of free omalizumab in a typical CSU patient (with weight of 80 kg, BMI of 30 kg/m2, negative for anti-FCεRI autoantibodies and not receiving concomitant H2 antihistamines) were 0.26 L/day and 8.9 L, respectively, with modest between-subject variability (≤35%). The apparent equilibrium binding constant between omalizumab and free IgE was 2.1 nM in a typical patient (with baseline IgE of 80 IU/mL). These key PK/PD parameter values were similar to the values for patients with allergic asthma.

2.3.4.2. Relation between exposure and efficacy

Exploratory graphical analyses included plots that screened for potential relationships between efficacy measures (itch improvement, UAS7 complete responders at Week 12) and dose, exposure (omalizumab concentrations at Week 12), and patient characteristics of interest (body weight, body mass index [BMI], baseline IgE, angioedema status, and baseline scores).

There was a clear dose-response relationship in the dose range tested (75 to 300 mg q4w). Within each dose level, there seemed to be no effect of body weight, BMI, baseline IgE or angioedema status on itch improvement at Week 12. Increased itch score at baseline appeared to result in greater itch improvement in both the placebo and treated groups.

There was a positive relationship between Week 12 itch score improvement and omalizumab concentration across the dose range tested, i.e. 75 to 300 mg every 4 weeks (q4w).

Longitudinal exposure-response modeling

An exposure-response model including the full itch and hives time course was developed based on the three pivotal Phase III studies in patients with CIU/CSU. First, a model describing the time course of itch and hives in the placebo arms was developed. Second, a drug effect model was developed describing how the omalizumab concentration reduces itch and hives scores with a background time course described by the placebo model. In this step, the previously developed PK/IgE model was incorporated to predict omalizumab concentrations (by use of empirical Bayes estimates) in each patient over the study duration. In this modeling step, the population parameters (fixed effects) for the placebo model and the PK/IgE model were fixed. Using only the itch and hives data of treated patients from Q4881g, Q4882g and Q4883g, but retaining the PK and IgE data, the drug effect population-typical parameters were estimated.

Placebo response was described using an exponential decay function while drug effect was described using an indirect response model. The drug can reduce the itch or hives scores up to an amount Emax depending on a latent response variable EFF. This response variable takes a value of 1 if no drug is present and turns over with a rate which is the reciprocal of the drug mean response time (XRT). The concentration of omalizumab inhibits the production of the response variable via a sigmoidal function with an EC50 and Hill coefficient (γ). A reduction of the response variable leads to an increase in the fraction of the maximal effect Emax which is subtracted from the score due to placebo, natural history or disease progression.

The model fit is exemplified by the overlay of time courses of model predictions and mean itch. The increased quantity of data for the time course analysis increased the precision of the EC50 estimates compared with the Week 12 data analyses (95% confidence interval was 15-16 µg/mL from the time course model compared with 9.8-43 µg/mL for itch). A Hill coefficient of 7.52 was estimated. The estimated EC50 values and Hill coefficient translated into a dynamic range of approximately 12 to 20 µg/ml within which the effect increased from 10% to 90% of the maximal effect for both itch and hives.

Body weight and BMI, which were highly correlated, acted together and in opposition to the effect on the pharmacokinetics, such that in patients with higher body weights the drug appears more potent (lower EC50). Furthermore, although higher body weight gave a higher Emax, this was countered by an opposing effect of BMI. As a result, there was no net effect of body weight nor BMI on clinical responses.

Baseline IgE was also statistically significant, increasing Emax with higher IgE levels. The presence of angioedema at baseline had a statistically significant effect on the drug response time, being 20% shorter in patients presenting with angioedema (i.e. 3.7 days compared with 4.7 days in patients without angioedema). The angioedema status did not, however, affect the drug potency (EC50). Of note, adolescent patients with an age less than 18 had 55% higher EC50 than adult patients.

Simulations of time to effect steady state, tapering and longer dosing intervals

Simulations of different scenarios were performed using 632 individual patients' parameters. For a posology of 300 mg q4w, clinical response steady-state is reached sooner than pharmacokinetic steady-state due to concentrations approaching saturation of the response (Emax). For 150 mg the approach to clinical response steady-state is slower and parallels pharmacokinetic equilibration.

Taking both up and down titration simulations together suggested that an initial dose of 300 mg to control symptoms followed by adaptive down then up titration based upon symptom control, should result in the same symptom control as a fixed 300 mg q4w posology but with a proportion of patients receiving 150 mg q4w. Calculations showed that if dose adaptation based upon complete control (predicted UAS7<1) at 1, 2 and 3 months were carried out, the well-controlled responder rate from a fixed 300 mg q4w posology could be matched, but with 27-38% of patients receiving 150 mg.

With 300 mg and longer dosing intervals than 4 weekly a proportion of the patients will likely show relapses of symptoms before their next treatment. There is, however a fraction of patients for whom longer intervals may suffice.

These simulation exercises show that potentially, individual patient dosage could be changed based upon itch and hive symptom control.

2.3.4.3. Exposure-Safety Analyses

The relationship between safety endpoints and exposure, i.e. omalizumab trough concentration at Week 12, based on pooled data from all three Phase 3 studies (Q4881g, Q4882g, and Q4883g), was analysed by the MAH. In particular, the MAH looked at treatment-emergent adverse events versus omalizumab trough concentrations at Week 12 for any adverse event, any serious adverse event or any severe adverse event during the treatment period

Visual inspection of the 95% confidence intervals of the above data showed no difference in these adverse event rates across omalizumab exposure quartiles, although there were few serious or severe adverse events observed from all studies (hence wide confidence intervals). Overall, no increased adverse event rates were observed in patients with higher exposure to omalizumab in the dose range tested.

2.3.5. Discussion on clinical pharmacology

Population modeling show that the PK of omalizumab and the PD in terms of IgE response is similar for patients with CSU compared to patients with asthma.

There is a clear correlation between dose and response. The relation between omalizumab exposure and the primary endpoint seems to reach a plateau above a trough concentration of 40 ug/mL.

The development of an advanced model to describe the full time course of response and the effect of drug exposure and covariates is acknowledged. To exemplify, the precision in the estimate of EC50 is vastly improved compared to the model including only base line and Week 12 data. As a result from the exercise the model predictions and simulation of different scenarios become more reliable and useful.

For further validation of the simulation approach, visual predictive checks (VPCs) were produced during the assessment which compared the repeated simulations with observed time courses of itch and hives scores as well as well-controlled responder rates (defined as the fraction of patients with UAS7≤6). For the simulations, all patients from the three phase III studies treated with omalizumab were pooled and their estimated individual parameters sampled for the simulations. The number of sampled patients per simulation was chosen to be equal to the number of patients in the dataset to which the simulation was compared to.

In summary, these diagnostic plots indicated that discriminating the placebo and the drug effect in the active treatment groups is challenging leading to an under-prediction of the placebo effect. This may also explain why the simulations for 75 mg under-predict the treatment response since for this dose the contribution of the placebo effect is larger than for the higher doses. Simulations for 150 mg q4w under-predicted the well-controlled responder rates for the first dose by up to 10 percentage points, but provided valid predictions for subsequent doses. Simulations for doses of 300 mg every q4w provided valid predictions for the entire treatment period as well as the follow-up period.

In the view of the CHMP, the model is able to reasonably predict the response following 300 mg q4w but is less reliable for prediction of response to 75 mg q4w. Since the dosing recommendation is revised to only include the 300 mg q4w dose, the issue is of less importance. The MAH is recommended to further develop the model for future applications.

Simulations from the exposure-response model indicate that 300 mg gives a more rapid achievement of effect as compared to 150 mg. Further, dose adaptation based on clinical effect could be an option for patients with well controlled symptoms. Simulations suggest that such adaptive dosing regimen could lead to approximately 1/3 of the patients receiving adequate response with the 150 mg dose. However, such adaptive regimen has not been clinically tested.

The number of patients below 18 years of age in the three Phase III studies was low: 10 on placebo and 11 on 300 mg omalizumab. Therefore the modeling results should be interpreted with caution with respect to this group. The estimated EC50 was 55% higher in adolescents which indicate the possibility that PKPD is different in this population.

As for the adolescents, the number of elderly subjects is small. Since there is an indication that PKPD may be different in adolescents, a similar analysis (within the PKPD model) for the elderly was performed as requested by the CHMP.

EC50 as well as Emax (maximum effect) for itch and hives improvements were respectively 20- 24% and 15% lower in elderly patients as compared to patients < 65 years. However, the majority (at least 75%) of elderly patients treated with 300 mg q4w had omalizumab trough levels above the EC90 in elderly, similar to the results for patients < 65 years. Simulations of well-controlled responder rates suggested that the differences in EC50 and Emax are unlikely to result in relevant differences in the clinical response in elderly patients.

The CHMP noted that at the proposed dose level, 300 mg q4w, elderly patients seem to achieve efficacious trough plasma concentration levels. Therefore, no clinically meaningful difference is expected in the PKPD in this population.

The PK/PD analysis in CSU seems based on a limited number of samples for subjects <70 kg or > 100 kg body-weight, thus subject to a great variability and poor sensitivity to detect changes in response according to body weight. Further to the request by the CHMP, the MAH showed that about 30% of patients included in the PK/PD model had a body weight below 70 kg (n=247) and about 20% (n= 151) had a body weight above 100 kg, which the CHMP deems sufficient for estimating the impact of body weight in all body weight categories. Simulations of well-controlled responder rates (UAS7≤6) for 300 mg q4w show overlapping 95% prediction intervals for the body weight categories <70 kg, between 70 and 100 kg and >100 kg, suggesting similar efficacy in all body weight groups. There was no indication that adolescent patients should have a different dose-response relationship because they weigh less. Therefore, the CHMP concludes that no dose-adjustment by body-weight is deemed necessary.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetics of omalizumab and the IgE pharmacodynamic response to treatment has been adequately characterized in patients with CSU. Simulations from a exposure-response model of the time course of symptoms indicate that 300 mg gives a more rapid achievement of effect as compared to 150 mg.

2.4. Clinical efficacy

The assessment of efficacy in the sought indication is based on the phase II/III studies: a phase II dose finding study Q4577g, and three pivotal phase III studies, Q4881g, Q4882g and Q4883g. Study Q4883g was designed primarily for the evaluation of safety, and so no primary efficacy endpoint was designed. However, the same efficacy analyses were performed as in the other pivotal Phase III studies. Supportive efficacy data are provided by one study performed using a different dose regimen to the Phase II/III program (Study IGE025ADE05).

The submitted studies for the CSU indication are presented in section 2.3.1 of this assessment report.

2.4.1. Dose response study

The dose response was explored in study Q4577g using a single dose, randomized, double-blind, placebo-controlled, parallel-group design, comparing the efficacy of 75 mg, 300 mg and 600 mg single doses of omalizumab and placebo in patients 12-75 years old (18-75 years in centres in Germany) with chronic idiopathic urticaria who remained symptomatic despite H1 antihistamine treatment (N=90 with 21-25 subjects per treatment arm). Patients were followed up for a total of 16 weeks after dosing: the first 4 weeks (corresponding to the dosing interval for omalizumab) were referred to as the treatment period, with the endpoint for efficacy at Week 4.

The primary efficacy endpoint was the change from baseline to Week 4 in UAS7 in the ITT population, analysed using last observation carried forward (LOCF) if a patient's Week 4 diary data were completely missing.

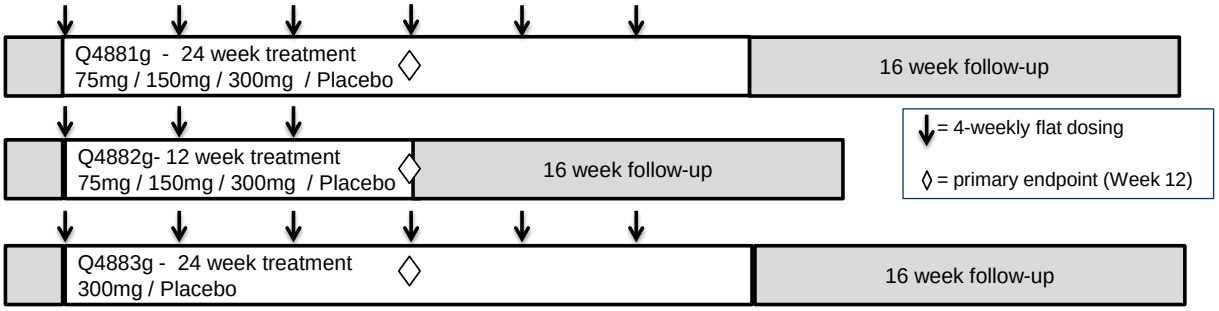
Mean decreases from baseline were 6.91 in the placebo group, and 9.79, 19.93 and 14.56 in the omalizumab 75 mg, 300 mg and 600 mg groups, respectively. The differences to placebo were statistically significant for the 300 mg and 600 mg omalizumab groups (p = 0.0003 and p = 0.0473, respectively; p-values were based on the van Elteren test stratified by baseline weight ≥80 or <80 kg). The secondary efficacy endpoints change from baseline to Week 4 in weekly itch score and weekly hive score showed a similar pattern to UAS7. For change from baseline to Week 4 in weekly sleep disturbance score, while all omalizumab groups showed greater decreases than placebo, the between-group difference was largest for the 600 mg group. There were no major differences between any omalizumab group and placebo in rescue medication use.

The MAH explored doses of 75, 150 and 300 mg by subcutaneous injection every four weeks in the phase III studies.

2.4.2. Main studies

The assessment of efficacy in the sought indication is based on the pivotal randomised Phase III studies Q4881g, Q4882g and Q4883g.

Figure 1 - Overview of study design, Q4881g, Q4882g and Q4883g



	Q4881g	Q4882g	Q4883g
Background therapy	H_1-antihistamines **≥8 Weeks**	H_1-antihistamines **≥8 Weeks**	H1 antihistamines up to 4 x approved dose plus H2 antihistamine / LTRA **>6 weeks**
UAS7	**UAS ≥16 for at least 4 out of the 7 days contributing to the UAS7 in the week prior to randomization**		
Weekly itch score	**≥8 for the 7 days prior to randomization**		

Study Q4881g

Title: A Phase III, Multicentre, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study To Evaluate The Efficacy and Safety of Xolair (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1).

Study Q4881g was randomized, double-blind, placebo-controlled, parallel-group, multicentre studies, comparing the efficacy of omalizumab 75 mg, 150 mg and 300 mg, given every 4 weeks (treatment duration: 24 weeks) with placebo in patients 12 to 75 years of age (18 to 75 years in Germany) with CSU who were symptomatic despite treatment with H1 antihistamines.

The study consisted of three distinct periods over 42 weeks:

- Screening period: Day -14 to Day -1
- Treatment Period: Day 1 to Day 169 (Week 0 to Week 24)
- Follow up Period: Day 169 to Day 281 (Week 24 to Week 40)

The primary endpoint was measured at Week 12. After the 24-week treatment period, all patients entered a 16-week follow up period to allow for further characterization of the PK and PD of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients continued to visit the study centre at 4 week intervals. No study treatment was given during the follow-up period.

Study Q4882g

Title: A Phase III, Multicentre, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study To Evaluate The Efficacy, Response Duration And Safety of Xolair® (Omalizumab) in Patients With Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Antihistamine Treatment (H1).

Study Q4882g was a randomized, double-blind, placebo-controlled, parallel-group, multicentre studies, comparing the efficacy of omalizumab 75 mg, 150 mg and 300 mg, given every 4 weeks (treatment duration: 12 weeks) with placebo in patients 12 to 75 years of age (18 to 75 years in Germany) with CSU who were symptomatic despite treatment with H1 antihistamines.

The study consisted of three distinct periods over 30 weeks:

• Screening period: Day − 14 to Day −1

• Treatment Period: Day 1 to Day 85 (Week 0 to Week 12)

• Follow-Up Period: Day 85 to Day 197 (Week 12 to Week 28)

The primary endpoint was measured at Week 12. After the 12-week treatment period, all patients entered a 16-week follow-up period to allow for further characterization of the PK and PD of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients continued to visit the study centre at 4-week intervals. No study treatment was given; patients were required to maintain stable doses of their prerandomization CIU H1 antihistamine treatment.

Study Q4883g

Title: A Phase III, Multicentre, Randomized, Double-Blind, Placebo-Controlled Safety Study of Xolair (Omalizumab) in Patients with Chronic Idiopathic Urticaria (CIU) Who Remain Symptomatic Despite Treatment With H1 Antihistamines, H2 Blockers, and/or Leukotriene Receptor Antagonists

Study Q4883g was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study, designed to assess the safety of omalizumab 300 mg given every 4 weeks (treatment duration 24 weeks) in patients 12 to 75 years of age (18-75 years in Germany) with CSU who were symptomatic despite treatment with H1 antihistamines at increased doses and either or both H2 antihistamines or LTRAs.

The primary endpoint was measured at Week 12. Patients were required to maintain stable doses of their pre-randomization combination therapy with H1 antihistamine treatment, and either H2 blockers or LTRAs, or all three drugs in combination throughout the 24-week treatment period and 16-week follow-up period of the 40-week study. For the duration of the 40-week study, all patients were provided with diphenhydramine 25 mg for itch relief on an as needed basis, up to a maximum of three doses in ≤ 24 hours. Following the 24-week treatment period, patients entered a 16-week follow-up period for further characterization of omalizumab PK-PD, collection of additional safety and efficacy data, and evaluation for the presence of anti-therapeutic antibodies (ATAs).

Methods

Study participants

The study populations were patients with inadequate response to CSU (as indicated by high baseline values of the UAS7 and its components, and the in-clinic UAS), with impaired quality of life (as indicated by high baseline DLQI) despite the use of current standard therapy, and with a history of multiple treatment failures on prior medications. Approximately 40-50% of the patients enrolled had angioedema at baseline (defined as angioedema being present in the week prior to baseline). Patients in Studies Q4577g, Q4881g and Q4882g had inadequate response to H1 antihistamines at currently approved doses, and patients in Study Q4883g had inadequate response to treatment with a combination of H1 antihistamines and H2 blockers, LTRAs or both.

Main inclusion criteria:

Studies Q4881g and Q4882g

1. Aged 12-75 years (age limits may vary dependent upon regional restrictions)

2. Diagnosis of CIU refractory to approved doses of H1 antihistamines at the time of randomization, as defined by all of the following:

The presence of itch and hives for ≥ 8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period

UAS7 score (range 0-42) ≥ 16 and itch component of UAS7 (range 0-21) ≥ 8 during 7 days prior to randomization (Week 0)

In-clinic UAS ≥ 4 on at least one of the screening visit days (Day -14, Day -7, or Day 1)

Patients must have been on an approved dose of an H1 antihistamine for CIU for at least the 3 consecutive days immediately prior to the Day - 14 screening visit and must have documented current use on the day of the initial screening visit

CIU diagnosis for ≥ 6 months

The long-acting H1 antihistamines and doses allowed during the study were as follows:

• Cetirizine 5 or 10 mg once per day (QD)

• Levocetirizine dihydrochloride 2.5 or 5 mg QD

• Fexofenadine 60 mg twice per day or 180 mg QD

• Loratadine 10 mg QD

• Desloratadine 5 mg QD

Study Q4883g

1. Aged 12-75 years (age limits may vary dependent upon regional restrictions)

2. Diagnosis of CIU refractory to approved doses of H1 antihistamines and either H2 blockers or LTRAs, or all three drugs in combination at the time of randomization, as defined by all of the following:

The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine (up to four times the approved dosage), H2 blocker, and/or LTRA treatment during this time period

UAS7 score (range 0-42) ≥ 16 and itch component of UAS7 (range 0-21) ≥ 8 during 7 days prior to randomization (Week 0)

In-clinic UAS ≥ 4 on at least one of the screening visit days (Day -14, Day -7, or Day 1)

Patients must have been on H1 antihistamine (up to four times the approved dosage), and either H2 blocker or LTRAs, or all three drugs in combination for CIU for at least the 3 consecutive days immediately prior to the Day − 14 screening visit and must have documented current use on the day of the initial screening

CIU diagnosis for ≥ 6 months

The long-acting H1 antihistamines, H2 blockers, and LTRAs allowed during the study were (H1 antihistamines could be used at up to four times the approved dose listed below):

a) Antihistamines

• Cetirizine 5 or 10 mg once per day (QD)

• Levocetirizine dihydrochloride 2.5 or 5 mg QD

• Fexofenadine 60 mg twice per day or 180 mg QD

• Loratadine 10 mg QD

• Desloratadine 5 mg QD

b) H2 Blockers

• Cimetidine (Tagamet®) 800 mg twice per day or 400 mg four times per day

• Famotidine (Pepcid®) 40 mg daily or 20 mg once or twice per day

• Nizatidine (Axid®) 150 mg daily

• Ranitidine (Zantac®) 150 mg twice per day

c) LTRAs

• Montelukast (Singulair®) 10 mg QD

• Zafirlukast (Accolate®) 20 mg twice daily

Main exclusion criteria:

Studies Q4881g and Q4882g

In addition to the main exclusion criteria described below for study Q4883g the following exclusion criteria was also employed for studies Q4881g and Q4882g

- Any H2 antihistamine used within 7 days prior to Day -14
- Any leukotriene receptor antagonist (LTRA) (montelukast or zafirlukast) within 7 days prior to Day -14
- Any H1 antihistamines at greater than approved doses within 3 days prior to Day -14

Study Q4883g

1. Treatment with an investigational agent within 30 days of Day −14

2. Weight less than 20 kg (44 lbs)

3. Clearly defined underlying etiology for chronic urticarias other than CIU (main manifestation being physical urticaria). This included the following urticarias:

Acute, solar, cholinergic, heat, cold, aquagenic, delayed pressure or contact

As well as the following diseases, as these diseases may have symptoms of urticaria or angioedema:

Urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer

4. Evidence of parasitic infection defined as having the following three items:

Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal [GI] symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression)

AND

An absolute eosinophil count more than twice the upper limit of normal

AND

Evidence of parasitic colonization or infection on stool evaluation for ova and parasites. Note that stool ova and parasite evaluation were only conducted in patients with both risk factors and an eosinophil count more than twice the upper limit of normal (ULN)

5. Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or other skin disease associated with itch

6. Previous treatment with omalizumab within a year prior to Day −14

7. Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day − 14: systemic or cutaneous(topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide

8. IV immunoglobulin G (IVIG), or plasmapheresis within 30 days prior to Day −14

9. Regular (daily/every other day) doxepin (oral) use within 14 days prior to Day −14

For a more extensive list of inclusion/exclusion criteria, see the respective study reports.

For all three studies, the following medications were omitted from the protocol's list of allowable

H1 antihistamines:

• Ebastine 10 mg and 20 mg QD

• Rupatadine 10 mg QD

• Bilastine 20 mg QD

Treatments

Study Q4881g

Patients were randomly assigned in a 1:1:1:1 ratio to receive omalizumab (75 mg, 150 mg, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the 24 week double blind treatment period.

For the first 12 weeks of the treatment period, patients were required to maintain stable doses of their pre-randomization H1 antihistamine treatment. During the second 12 weeks of the treatment period, patients could add up to one additional H1 antihistamine treatment. Increasing the dose of antihistamine above the approved dose was not permitted. Diphenhydramine (25 mg) was provided and used on an as-needed basis (maximum three times/day) during the screening, treatment and follow-up periods.

Study Q4882g

Patients were randomly assigned in a 1:1:1:1 ratio to receive omalizumab (75 mg, 150 mg, or 300 mg) or placebo by SC injection every 4 weeks (on Day 1, Week 4, and Week 8) during the 12-week double-blind treatment period.

For the duration of the treatment period, patients were required to maintain stable doses of their pre-randomization CIU H1 antihistamine treatment. The last dose of study drug during the treatment period was administered at the Day 57 (Week 8) study visit. In the follow-up period, patients were permitted to add up to one additional H1 antihistamine therapy. Increasing the dose of antihistamine above the approved dose was not permitted. Diphenhydramine (25 mg) was provided and used on an as-needed basis (maximum three times/day) during the screening, treatment and follow-up periods.

Study Q4883g

Patients were randomly assigned in a 3:1 ratio to receive omalizumab 300 mg or placebo by SC injection every 4 weeks (Day 1, and Weeks 4, 8, 12, 16, and 20) during the 24-week double blind treatment period.

Therapy must have included H1 antihistamines and either H2 blockers or LTRAs, or all three drugs in combination. All patients were allowed to take study-defined H1 antihistamine medications at up to four times the approved dose, and either H2 blockers or LTRAs, or all three drugs in combination during the screening, treatment, and follow-up periods. Patients had to remain on a stable treatment regimen of H1 antihistamine, and either H2 blocker or LTRAs, or all three drugs in combination throughout the study period. Diphenhydramine (25 mg) was provided and used on an as-needed basis (maximum three times/day) during the screening, treatment and follow-up periods.

Objectives

Study Q4881g

Primary:

- To evaluate the efficacy of omalizumab compared with placebo in patients with refractory CIU receiving concomitant H1 antihistamine therapy

Secondary:

- To evaluate the safety of omalizumab therapy in patients with refractory CIU
- To evaluate onset of clinical effect of omalizumab therapy in CIU
- To evaluate the dose of omalizumab therapy in patients with refractory CIU
- To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU
- To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU

Study Q4882g

The primary objective for this study was as follows:

· To evaluate the efficacy of omalizumab compared with placebo in patients with refractory CIU receiving concomitant H1 antihistamine therapy

The secondary objectives for this study were as follows:

· To evaluate the safety of omalizumab therapy in patients with refractory CIU

· To evaluate onset of clinical effect of omalizumab therapy in CIU

· To evaluate the dose of omalizumab therapy in patients with refractory CIU

· To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU

· To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU

Study Q4883g

Primary:

· To evaluate the safety of omalizumab compared with placebo in patients with refractory CIU receiving concomitant therapy including H1 antihistamines at increased doses (up to four times the approved dose), and/or H2 blockers and/or leukotriene receptor antagonists (LTRAs)

Secondary:

· To evaluate the efficacy of omalizumab compared with placebo in patients with refractory CIU receiving concomitant therapy including H1 antihistamines at increased doses (up to four times the approved dose), and/or H2 blockers, and/or LTRAs

· To evaluate onset of clinical effect of omalizumab therapy in CIU receiving concomitant therapy including H1 antihistamines at increased doses (up to four times the approved dose), and/or H2 blockers, and/or LTRAs.

· To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU receiving concomitant therapy including H1 antihistamines at increased doses (up to four times the approved dose), and/or H2 blockers, and/or LTRAs.

Outcomes/endpoints

Study Q4881g

Primary Endpoint:

- Change from baseline in the weekly itch severity score at Week 12

Secondary Endpoints:

- Change from baseline in urticaria activity score over seven days (UAS7) at Week 12
- Change from baseline in weekly number of hives score at Week 12
- Time to minimally important difference (MID) response in weekly itch severity score by Week 12
- Proportion of patients with UAS7 $\leq$ 6 at Week 12
- Proportion of weekly itch severity score MID responders at Week 12
- Change from baseline in weekly size of largest hive score at Week 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy
- Proportion of Complete Responders (UAS7 = 0) at Week 12

Study Q4882g

The primary endpoint:

- Change from baseline in the weekly itch severity score at Week 12

Secondary Endpoints

- Change from baseline in urticaria activity score over 7 days (UAS7) at Week 12
- Change from baseline in weekly number of hives score at Week 12
- Time to minimally important difference (MID) response in weekly itch severity score by Week 12
- Proportion of patients with UAS7 ≤ 6 at Week 12
- Proportion of weekly itch severity score MID responders at Week 12
- Change from baseline in weekly size of largest hive score at Week 12
- Change from baseline in health related quality of life as measured by the Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema free days from Week 4 to Week 12 of therapy

Study Q4883g

Primary:

Key Efficacy Endpoint:

- Change from baseline in weekly itch severity score (a component of the urticaria activity score over 7 days [UAS7]) at Week 12

Efficacy Outcomes:

- Change from baseline in UAS7 at Week 12
- Change from baseline in weekly number of hives score at Week 12
- Time to minimally important difference (MID) response in weekly itch severity score by Week 12
- Proportion of patients with UAS7 ≤ 6 at Week 12
- Proportion of weekly itch severity score MID responders at Week 12
- Change from baseline in weekly size of largest hive score at Week 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12
- Proportion of complete responders (UAS7 = 0) at Week 12

The primary efficacy endpoint and many of the secondary and exploratory efficacy endpoints were collected via the Urticaria Patient Daily Diary (UPDD) with an electronic handheld device (eDiary).

The UPDD questions consist of itch severity, number of hives, size of largest hive, sleep interference, daily active interference, rescue medication use, angioedema episodes and management, and health care provider contact for CIU. The eDiary was completed twice per day by the patient for the duration of the study. The eDiary was given to the patient at the Day - 14 visit. The itch severity score was recorded twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (severe). The daily itch severity score was the average of the morning and evening scores. The number of hives was recorded twice daily and scored on a scale of 0 (none), 1 (1 to 6 hives), 2 (7 to 12 hives), or 3 (>12 hives). The UAS, as a composite of the itch and hives scores, could therefore range from 0 to 6. The UAS is commonly analysed as a weekly score (UAS7), which is the sum of the UAS scores for the

previous 7 days, and could range from 0 to 42. Weekly scores for itch and hives were the sums of the respective daily scores over the previous 7 days, and in each case could range from 0 to 21.

Sample size

Studies Q4881g and Q4882g

The sample size for studies Q4881g and Q4882g was primarily based on safety and regulatory considerations. The estimation of power for efficacy assumed a mean change from baseline in the weekly itch severity score at Week 12 to be 9 points and 3.5 points for the omalizumab and placebo groups, respectively, with a common SD of 6 points. A total of 300 patients (1:1:1:1 randomization ratio with 75 patients in each treatment group) were to be included in each study.

Study Q4883g

The sample size for this study was primarily based on safety and regulatory considerations. Approximately 320 patients were planned for randomization to either the omalizumab (300 mg) or placebo treatment groups in a 3:1 ratio. Combining the patients in the omalizumab group in this study with those in its CIU sister studies (Studies Q4881g and Q4882g) was expected to provide a safety database with at least 300 patients treated with omalizumab 300 mg for 24 weeks.

Randomisation

Q4881g and Q4882g

On the Day 1 visit, patients were randomized to one of 3 doses of omalizumab (75 mg, 150 mg, or 300 mg) or placebo at an approximately 1:1:1:1 ratio using an IxRS.

Q4883g

At the Day 1 visit, patients were randomized to receive either omalizumab 300 mg or placebo in a 3:1 ratio, through use of an IxRS.

Q4881g, Q4882g and Q4883g

Within the Phase III studies, patient randomization was stratified by baseline weekly itch severity score (< 13, ≥13), baseline weight (< 80 kg, ≥80 kg), and by study site. A hierarchical dynamic randomization scheme was used to achieve overall balance between treatment groups and within strata. The levels in this hierarchy were overall study treatment balance, treatment balance within the baseline weekly itch severity score strata (<13, ≥ 13), treatment balance within the body weight strata (< 80 kg, ≥ 80 kg), and balance within each study centre.

The goal was to achieve an approximate balance with respect to the overall treatment balance and the stratification factors whilst at the same time preserving enough randomness in the process.

Re-randomization tests for the primary and secondary efficacy endpoints were performed using computer simulations. The simulation study re-randomized the patients (319 patients for study Q4881g, 323 patients for study Q4882g and 336 patients for study Q4883g) 10,000 times with use of the same randomization stratification factors observed in the study, (i.e., baseline weekly itch severity score strata (<13, ≥ 13), body weight strata (< 80 kg, ≥ 80 kg), and study centre). The analyses of the primary and secondary efficacy endpoint were conducted for each of the re-randomized patient cohorts. The test statistics generated by the simulation cohorts were used to generate a “re-randomization distribution” for each of the endpoints. A p-value was then computed as the proportion of simulated test statistics that exceeded the observed test statistic for each endpoint. The p-values obtained by the re-randomization simulations were similar to the model-based p-values for all endpoints, which demonstrate the robustness of the model-based results.

Blinding (masking)

Patients, all study personnel, the designated evaluating physician(s), the Sponsor and its agents (with the exception of the IxRS service provider, the remote unblinded monitoring staff, the unblinding statistician, the unblended pharmacists at the sites, the iDMC members and the independent Data Coordinating Center [iDCC] personnel) were blinded to treatment assignment. Only the IxRS provider, the Sponsor's unblinding statistician, and the iDCC statistician had access to the unblinding code during the study.

Study drug supplies were shipped blinded to each site. Each centre identified an individual responsible (e.g., pharmacist) for the reconstitution procedures. This individual prepared the study drug for each patient prior to administration. An individual not involved with evaluating the patient was identified to administer the study drug. To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels and serum omalizumab concentrations), access to these results were withheld from the site and the Sponsor until study completion.

Statistical methods

Study Q4883g

The analysis of safety consisted primarily of descriptive summaries. No formal statistical testing was performed on the safety endpoints. The evaluation of efficacy was a secondary objective for this study. Efficacy was analysed similarly as for studies Q4881g and Q4882g described below with the exception of the type I error control plan which were not applicable since this study only had two treatment groups.

Studies Q4881g and Q4882g

Modified ITT population was used for efficacy analyses. This population included all patients randomized in the study who received at least one dose of study drug. The treatment group for this population was defined according to the treatment assigned at randomization.

Treatment comparisons were performed between each of the omalizumab groups (75 mg, 150 mg, and 300 mg) and the placebo group. All statistical tests were two-sided using an overall 0.05 level of significance and adjustments for multiple comparisons were performed according to the type I error control plan using a hierarchical order.

Primary analysis:

The primary efficacy endpoint was the change from baseline in the weekly itch severity score at Week 12. The analysis of this endpoint consisted of treatment comparisons between each of the omalizumab groups (75 mg, 150 mg, and 300 mg) and the placebo group using analysis of covariance (ANCOVA), controlling for baseline weekly itch severity score (< 13 vs. ≥ 13), and baseline weight (< 80 kg vs. ≥ 80 kg). A separate ANCOVA model was run for each omalizumab dose group versus placebo. The least squares means (LSM) and the corresponding 95% confidence intervals (CIs) of the differences between each of the omalizumab groups and the placebo group are presented along with the p-values for treatment differences resulting from the ANCOVA model.

Handling of missing data:

For change from baseline weekly score endpoints analysed at particular time points (e.g., Week 12, Week 24, or Week 40 in study Q4881g and Week 12 or Week 28 in study Q4882g), missing post-baseline weekly scores were imputed using the baseline weekly score (BOCF). In addition, for summaries by study week, the weekly scores were imputed using BOCF.

For endpoints that consist of proportions of responders analysed at a particular time point (e.g., Week 12, Week 24, or Week 40 in study Q4881g and Week 12 or Week 28 in study Q4882g), patients with missing weekly scores for the given week were classified as non-responders.

For time to the first event endpoints, the endpoint were considered censored at the week of the last non-missing weekly score in the absence of the event. In addition, it was assumed that an event did not occur during a week with a missing weekly score that occurs between baseline and a study week with a non-missing weekly score.

Sensitivity analyses:

The following sensitivity analyses were performed on the primary endpoint:

- An ANCOVA model was fitted which is similar to the primary analysis but imputes missing Week 12 weekly itch severity scores by the method of last observation carry forward (LOCF).
- A mixed effects model was fitted which included all observed weekly itch severity scores from baseline to Week 12. No imputation was applied to those weeks with a missing weekly itch severity score.
- An ANCOVA model was fitted, which was similar to the primary analysis but imputed the Week 12 weekly itch severity score by carrying forward the baseline weekly itch severity score (BOCF) for patients who received any systemic steroids for any reason during the 2 weeks prior to the Week 12 visit.

Control of type I error:

In order to maintain an overall type I error rate of 0.05 (two-sided) across the three omalizumab dose levels, the testing of the primary endpoint were conducted in hierarchical order starting with the highest dose group.

A hierarchical analysis of the following secondary endpoints was then performed for each dose found to be significant in the primary endpoint. The hierarchical analysis of the secondary endpoints was performed independently for each dose level.

Results

Participant flow

Study Q4881g

Table 2 - Study participation and withdrawals, randomized patients, Study Q4881g

Status, n (%)	Placebo (N=80)	Omalizumab 75 mg (N=78)	Omalizumab 150 mg (N=80)	Omalizumab 300 mg (N=81)	All Patients (N=319)
Completed study drug treatment	61 (76.3%)	67 (85.9%)	64 (80.0%)	73 (90.1%)	265 (83.1%)
Study drug treatment withdrawn					
Total	19 (23.8%)	11 (14.1%)	16 (20.0%)	8 (9.9%)	54 (16.9%)
Adverse Event	7 (8.8%)	2 (2.6%)	4 (5.0%)	2 (2.5%)	15 (4.7%)
Lost to follow-up	1 (1.3%)	0 (-)	0 (-)	0 (-)	1 (0.3%)
Physician decision to discontinue treatment	0 (-)	3 (3.8%)	2 (2.5%)	1 (1.2%)	6 (1.9%)
Subject/legal guardian decision to discontinue treatment	1 (1.3%)	3 (3.8%)	5 (6.3%)	3 (3.7%)	12 (3.8%)
Disease Progression	10 (12.5%)	3 (3.8%)	5 (6.3%)	2 (2.5%)	20 (6.3%)
Completed study	65 (81.3%)	64 (82.1%)	64 (80.0%)	69 (85.2%)	262 (82.1%)
Discontinued early from study					
Total	15 (18.8%)	14 (17.9%)	16 (20.0%)	12 (14.8%)	57 (17.9%)
Adverse Event	2 (2.5%)	1 (1.3%)	1 (1.3%)	1 (1.2%)	5 (1.6%)
Lost to follow-up	1 (1.3%)	1 (1.3%)	0 (-)	0 (-)	2 (0.6%)

Physician decision to withdraw subject from study	0 (-)	1 (1.3%)	1 (1.3%)	1 (1.2%)	3 (0.9%)
Subject/legal guardian decision to withdraw	2 (2.5%)	6 (7.7%)	8 (10.0%)	5 (6.2%)	21 (6.6%)
Disease progression	10 (12.5%)	5 (6.4%)	6 (7.5%)	5 (6.2%)	26 (8.2%)

Study Q4882g

Table 3 - Study participation and withdrawals, randomized patients, Study Q4882g

Status, n (%)	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=83)	Omalizumab 300 mg (N=79)	All Patients (N=323)
Completed study drug treatment	76 (96.2%)	74 (90.2%)	77 (92.8%)	77 (97.5%)	304 (94.1%)
Study drug treatment withdrawn					
Total	3 (3.8%)	8 (9.8%)	6 (7.2%)	2 (2.5%)	19 (5.9%)
Adverse Event	0 (-)	3 (3.7%)	2 (2.4%)	1 (1.3%)	6 (1.9%)
Lost to follow-up	1 (1.3%)	0 (-)	1 (1.2%)	0 (-)	2 (0.6%)
Physician decision to discontinue treatment	0 (-)	1 (1.2%)	1 (1.2%)	0 (-)	2 (0.6%)
Subject/legal guardian decision to discontinue treatment	1 (1.3%)	1 (1.2%)	1 (1.2%)	1 (1.3%)	4 (1.2%)
Disease Progression	1 (1.3%)	3 (3.7%)	1 (1.2%)	0 (-)	5 (1.5%)
Completed study	74 (93.7%)	75 (91.5%)	74 (89.2%)	67 (84.8%)	290 (89.8%)
Discontinued early from study					
Total	5 (6.3%)	7 (8.5%)	9 (10.8%)	12 (15.2%)	33 (10.2%)
Adverse Event	1 (1.3%)	0 (-)	1 (1.2%)	1 (1.3%)	3 (0.9%)
Lost to follow-up	1 (1.3%)	1 (1.2%)	2 (2.4%)	2 (2.5%)	6 (1.9%)
Physician decision to withdraw subject from study	0 (-)	1 (1.2%)	0 (-)	0 (-)	1 (0.3%)
Subject/legal guardian decision to withdraw	3 (3.8%)	4 (4.9%)	3 (3.6%)	3 (3.8%)	13 (4.0%)
Disease progression	0 (-)	1 (1.2%)	3 (3.6%)	6 (7.6%)	10 (3.1%)

Study Q4883g

Table 4 - Study participation and withdrawals, randomized patients, Study Q4883g

Status, n (%)	Placebo (N=84)	Omalizumab 300 mg (N=252)	All Patients (N=336)
Completed study drug treatment	63 (75.0%)	221 (87.7%)	284 (84.5%)
Study drug treatment withdrawn			
Total	21 (25.0%)	31 (12.3%)	52 (15.5%)
Adverse Event	6 (7.1%)	12 (4.8%)	18 (5.4%)
Physician decision to discontinue treatment	1 (1.2%)	3 (1.2%)	4 (1.2%)
Subject/legal guardian decision to discontinue treatment	5 (6.0%)	5 (2.0%)	10 (3.0%)
Disease Progression	9 (10.7%)	11 (4.4%)	20 (6.0%)
Completed study	66 (78.6%)	224 (88.9%)	290 (86.3%)
Discontinued early from study			
Total	18 (21.4%)	28 (11.1%)	46 (13.7%)
Adverse Event	1 (1.2%)	3 (1.2%)	4 (1.2%)
Lost to follow-up	0 (-)	3 (1.2%)	3 (0.9%)
Physician decision to withdraw subject from study	1 (1.2%)	1 (0.4%)	2 (0.6%)
Subject/legal guardian decision to withdraw	8 (9.5%)	10 (4.0%)	18 (5.4%)
Disease progression	8 (9.5%)	11 (4.4%)	19 (5.7%)

Recruitment

Study Q4881g was initiated/completed 16 Feb 2011/17 Oct 2012

Study Q4882g	10 March 2011/27 Jun 2012
Study Q4883g	21 Feb 2011/22 Nov 2012

Conduct of the study

Study Q4881g

There was one amendment to the protocol, dated 11 January 2011.

The major changes concerned:

- The number of weeks that a patient must have had CIU symptoms despite being on H1 antihistamines was increased from 6 to 8 weeks.
- The secondary objectives were clarified to indicate that a goal of this study was to provide information regarding the recurrence of disease/symptoms after withdrawal of omalizumab in patients with refractory CIU. Secondary and exploratory endpoints were modified as a result.
- Procedures regarding the use of excluded therapy were modified in an effort to continue to follow patients for safety evaluation after they had discontinued study drug treatment.
- The washout period required after regular doxepin use prior to enrolment was reduced from 6 weeks to 14 days.

Study Q4882g

There was one amendment to the protocol, dated 11 January 2011.

The major changes concerned:

- The second treatment period (STP), including the re-randomization portion, was removed. The study duration was 12 weeks shorter as a result. Secondary endpoints were either removed or modified to reflect this change.
- The planned number of patients within each treatment group was changed from 80 in the omalizumab treatment groups and 60 in the placebo group to 75 per group. The total number of approximately 300 patients in the study remained unchanged.
- The number of weeks that a patient must have had CIU symptoms despite being on H1 antihistamines was increased from 6 to 8 weeks.
- The secondary objectives were clarified to indicate that a goal of this study was to provide information regarding the recurrence of disease/symptoms after withdrawal of omalizumab in patients with refractory CIU. Secondary and exploratory endpoints were modified as a result.
- Procedures regarding the use of excluded therapy were modified in an effort to continue to follow patients for safety evaluation after they had discontinued study drug.
- The washout period required after regular doxepin use prior to enrolment was reduced from 6 weeks to 14 days.

Study Q4883g

There was one amendment to the protocol, dated 11 January 2011.

The amendment served to consolidate the two region-specific protocols into one harmonized global document (Version 2.0).

The major changes for the E.U. protocol (Version 1.1) concerned:

- The prescribed washout period after regular doxepin use prior to enrolment was reduced from 6 weeks to 14 days.

Baseline data

Studies Q4881g and Q4882g

In both studies demographic characteristics were broadly well-balanced across treatment groups, although in Q4881g the proportion of white patients was higher in the omalizumab 300 mg group than other treatment groups. The study populations were both predominantly female and white, and there were few patients less than 18 years or more than 64 years of age.

Study Q4881g

Table 5 - Baseline demographic characteristics and baseline urticaria characteristics, mITT population, Study Q4881g

	Placebo (N=80)	Omalizumab 75 mg (N=77)	Omalizumab 150 mg (N=80)	Omalizumab 300 mg (N=81)	All Patients (N=318)
Age (years)					
Mean (SD)	40.4 (15.6)	40.7 (15.2)	41.1 (14.0)	42.4 (13.2)	41.2 (14.5)
Median	37.5	41.0	43.0	42.0	41.0
Range	13 – 74	13 – 72	12 – 68	14 – 72	12 – 74
Age group (years) n (%)					
12-17	4 (5.0%)	5 (6.5%)	7 (8.8%)	2 (2.5%)	18 (5.7%)
18-40	41 (51.3%)	33 (42.9%)	29 (36.3%)	34 (42.0%)	137 (43.1%)
41-64	30 (37.5%)	35 (45.5%)	41 (51.3%)	42 (51.9%)	148 (46.5%)
≥65	5 (6.3%)	4 (5.2%)	3 (3.8%)	3 (3.7%)	15 (4.7%)
Sex n (%)					
Female	52 (65.0%)	55 (71.4%)	64 (80.0%)	60 (74.1%)	231 (72.6%)
Ethnicity n (%)					
Hispanic or Latino	7 (8.8%)	5 (6.5%)	6 (7.5%)	3 (3.7%)	21 (6.6%)
Not Hispanic or Latino	71 (88.8%)	71 (92.2%)	74 (92.5%)	78 (96.3%)	294 (92.5%)
Not Available	2 (2.5%)	1 (1.3%)	0 (-)	0 (-)	3 (0.9%)
Race n (%)					
American Indian or Alaska Native	0 (-)	0 (-)	1 (1.3%)	1 (1.2%)	2 (0.6%)
Asian	3 (3.8%)	4 (5.2%)	6 (7.5%)	1 (1.2%)	14 (4.4%)
Black	10 (12.5%)	9 (11.7%)	9 (11.3%)	5 (6.2%)	33 (10.4%)
White	64 (80.0%)	62 (80.5%)	63 (78.8%)	74 (91.4%)	263 (82.7%)
Not Available	3 (3.8%)	2 (2.6%)	1 (1.3%)	0 (-)	6 (1.9%)
Weight (kg)					
Mean (SD)	83.0 (20.5)	81.1 (19.2)	83.2 (24.4)	81.6 (19.7)	82.2 (21.0)
Median	81.0	80.0	79.8	76.0	80.0
Range	50 – 138	50 – 134	35 – 138	53 – 134	35 – 138
Weight n (%)					
<80 kg	35 (43.8%)	38 (49.4%)	40 (50.0%)	45 (55.6%)	158 (49.7%)
BMI					
Mean (SD)	28.7 (6.2)	29.4 (6.5)	29.8 (7.7)	29.3 (6.9)	29.3 (6.8)
Duration of CIU (years)					
n	78	76	78	81	313
Mean (SD)	7.0 (9.7)	7.0 (9.7)	7.6 (9.2)	6.2 (8.0)	6.9 (9.1)
Median	3.7	3.8	4.3	3.2	3.7
Range	0.5 – 48.2	0.5 – 50.5	0.5 – 44.4	0.5 – 35.4	0.5 – 50.5
In-Clinic UAS^					
n	80	77	80	81	318
Mean (SD)	5.3 (0.8)	5.3 (0.8)	5.3 (0.7)	5.3 (0.8)	5.3 (0.8)
Median	5.0	5.0	5.0	5.0	5.0
Range	4 – 6	4 – 6	4 – 6	4 – 6	4 – 6
UAS7*					
n	80	77	80	81	318
Mean (SD)	31.1 (6.7)	31.7 (6.7)	30.3 (7.3)	31.3 (5.8)	31.1 (6.6)
Median	31.5	31.5	30.8	31.5	31.5
Range	16.0 – 42.0	17.0 – 42.0	16.0 – 42.0	19.5 – 42.0	16.0 – 42.0
Weekly itch severity score*					
n	80	77	80	81	318
Mean (SD)	14.4 (3.5)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.3 (3.5)

Median	14.0	14.0	14.0	14.0	14.0
Range	8.0 – 21.0	8.5 – 21.0	8.0 – 21.0	8.0 – 21.0	8.0 – 21.0
Weekly itch severity score*					
n	80	77	80	81	318
<13	26 (32.5%)	28 (36.4%)	26 (32.5%)	28 (34.6%)	108 (34.0%)
Weekly number of hives score*					
n	80	77	80	81	318
Mean (SD)	16.7 (4.4)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.8 (4.3)
Median	18.3	19.0	17.0	18.5	18.5
Range	5.0 – 21.0	7.5 – 21.0	4.5 – 21.0	8.5 – 21.0	4.5 – 21.0
Presence of angioedema*					
n	80	77	80	81	318
Yes	44 (55.0%)	35 (45.5%)	38 (47.5%)	34 (42.0%)	151 (47.5%)
Previous Number of CIU medications					
n	80	77	80	81	318
Mean (SD)	5.0 (2.8)	4.7 (2.8)	4.5 (3.2)	4.5 (2.3)	4.7 (2.8)
Median	4.5	4.0	4.0	4.0	4.0
Range	1 – 13	1 – 13	1 – 18	1 – 10	1 – 18
Presence of anti-FcεRI auto-antibody (CU index test) n (%)					
n	80	77	79	81	317
Yes	25 (31.3%)	18 (23.4%)	16 (20.3%)	21 (25.9%)	80 (25.2%)
Total IgE level (IU/mL)					
n	77	75	74	80	306
Mean (SD)	161.5 (215.1)	195.3 (334.5)	225.2 (612.6)	152.6 (285.2)	182.8 (387.8)
Median	92.0	91.0	71.0	85.5	83.0
Range	1 – 1010	1 – 2030	1 – 5000	1 – 2330	1 – 5000

mITT: All patients randomized in the study who received at least one dose of study drug
^Baseline in-clinic UAS is defined as the largest value among the Day -14 screening visit, Day -7 screening visit and Day 1 Visit.
*Based on data collected in patient daily eDiary in the week before randomization.

Numbers analysed

Study Q4882g

Table 6 - Baseline demographic characteristics and baseline urticaria characteristics, mITT population, Study Q4882g

	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)	All Patients (N=322)
Age (years)					
Mean (SD)	43.1 (12.5)	39.7 (15.0)	43.0 (13.2)	44.3 (13.7)	42.5 (13.7)
Median	43.0	36.0	43.0	43.0	42.0
Range	17 - 73	14 - 75	14 - 72	15 - 75	14 - 75
Age group (years) n (%)					
12-17	2 (2.5%)	4 (4.9%)	2 (2.4%)	2 (2.5%)	10 (3.1%)
18-40	30 (38.0%)	42 (51.2%)	32 (39.0%)	31 (39.2%)	135 (41.9%)
41-64	44 (55.7%)	31 (37.8%)	45 (54.9%)	39 (49.4%)	159 (49.4%)
≥65	3 (3.8%)	5 (6.1%)	3 (3.7%)	7 (8.9%)	18 (5.6%)
Sex n (%)					
Female	55 (69.6%)	61 (74.4%)	65 (79.3%)	63 (79.7%)	244 (75.8%)

Ethnicity n (%)					
Hispanic or Latino	6 (7.6%)	9 (11.0%)	8 (9.8%)	3 (3.8%)	26 (8.1%)
Not Hispanic or Latino	73 (92.4%)	73 (89.0%)	74 (90.2%)	74 (93.7%)	294 (91.3%)
Not Available	0 (-)	0 (-)	0 (-)	2 (2.5%)	2 (0.6%)
Race n (%)					
American Indian or Alaska Native	0 (-)	0 (-)	1 (1.2%)	0 (-)	1 (0.3%)
Asian	2 (2.5%)	4 (4.9%)	1 (1.2%)	2 (2.5%)	9 (2.8%)
Black	4 (5.1%)	12 (14.6%)	5 (6.1%)	7 (8.9%)	28 (8.7%)
Native Hawaiian or Other Pacific Island	1 (1.3%)	0 (-)	0 (-)	0 (-)	1 (0.3%)
White	70 (88.6%)	64 (78.0%)	70 (85.4%)	68 (86.1%)	272 (84.5%)
Multiracial*	0 (-)	0 (-)	2 (2.4%)	1 (1.3%)	3 (0.9%)
Not Available	2 (2.5%)	2 (2.4%)	3 (3.7%)	1 (1.3%)	8 (2.5%)
Weight (kg)					
Mean (SD)	84.3 (25.7)	82.8 (21.2)	82.4 (20.7)	80.3 (19.9)	82.4 (21.9)
Median	79.0	79.0	79.9	78.0	79.0
Range	46 - 188	50 - 133	49 - 153	43 - 136	43 - 188
Weight n (%)					
<80 kg	41 (51.9%)	43 (52.4%)	41 (50.0%)	41 (51.9%)	166 (51.6%)
BMI					
Mean (SD)	30.0 (7.7)	30.2 (7.7)	30.0 (7.3)	29.0 (6.3)	29.8 (7.3)
Duration of CIU (years)					
n	77	80	81	76	314
Mean (SD)	7.2 (10.7)	5.3 (7.1)	7.2 (8.9)	6.1 (7.3)	6.5 (8.6)
Median	3.3	2.5	3.9	3.5	3.3
Range	0.6 - 66.4	0.5 - 41.9	0.6 - 44.5	0.5 - 36.0	0.5 - 66.4
In-Clinic UAS^					
n	79	82	82	79	322
Mean (SD)	5.3 (0.7)	5.4 (0.8)	5.3 (0.7)	5.3 (0.7)	5.3 (0.7)
Median	5.0	6.0	5.0	5.0	5.0
Range	4 - 6	2 - 6	4 – 6	4 - 6	2 - 6
UAS7*					
n	79	82	82	79	322
Mean (SD)	31.0 (6.6)	30.7 (6.9)	31.4 (7.0)	29.5 (6.9)	30.7 (6.8)
Median	32.0	31.5	31.0	29.0	31.0
Range	17.0 - 42.0	16.5 - 42.0	17.0 - 42.0	16.5 - 42.0	16.5 - 42.0
Weekly itch severity score*					
n	79	82	82	79	322
Mean (SD)	14.0 (3.4)	14.0 (3.7)	14.2 (4.1)	13.7 (3.5)	14.0 (3.7)
Median	14.0	13.5	13.5	13.5	13.5
Range	8.0 - 21.0	8.0 - 21.0	8.0 - 21.0	8.0 - 21.0	8.0 - 21.0
Weekly itch severity score*					
n	79	82	82	79	322
<13	34 (43.0%)	34 (41.5%)	36 (43.9%)	37 (46.8%)	141 (43.8%)
Weekly number of hives score*					
n	79	82	82	79	322
Mean (SD)	17.0 (4.2)	16.8 (4.2)	17.1 (4.1)	15.8 (4.6)	16.7 (4.3)
Median	18.0	17.5	18.5	16.0	17.8
Range	6.0 - 21.0	8.0 - 21.0	7.0 - 21.0	7.0 - 21.0	6.0 - 21.0
Presence of angioedema*					
n	79	82	82	79	322
Yes	30 (38.0%)	31 (37.8%)	38 (46.3%)	32 (40.5%)	131 (40.7%)
Previous Number of CIU medications					
n	79	82	82	79	322
Mean (SD)	4.4 (2.9)	4.1 (2.1)	4.5 (3.2)	4.3 (2.5)	4.3 (2.7)
Median	3.0	4.0	4.0	4.0	4.0
Range	1 - 13	1 - 9	1 – 17	1 - 11	1 - 17
Presence of anti-FcεRI auto-antibody (CU index test) n (%)					
n	79	82	82	78	321
Yes	23 (29.1%)	26 (31.7%)	27 (32.9%)	18 (23.1%)	94 (29.3%)
Total IgE level (IU/mL)					
n	77	79	80	72	308
Mean (SD)	181.2 (249.5)	173.6 (230.5)	133.5 (215.8)	186.9 (231.9)	168.2 (231.9)
Median	76.0	88.0	69.5	93.5	78.0
Range	1 – 966	1 – 1320	1 – 1450	5 – 1040	1 – 1450

*Multiracial includes subjects for whom more than one race was indicated.

mITT: All patients randomized in the study who received at least one dose of study drug

^Baseline in-clinic UAS is defined as the largest value among the Day -14 screening visit, Day -7 screening visit and Day 1 Visit.

*Based on data collected in patient daily eDiary in the week before randomization.

1 patient in the omalizumab 75 mg group had an in-clinic UAS of 2, which violated an inclusion criteria (in-clinic UAS ≥4 on at least one of the screening visit days).

In both studies Q4881g and Q4882g the treatment groups were similar with respect to baseline disease characteristics. Baseline mean UAS7 was approximately 31 (out of a possible 42) in both studies, and mean in-clinic UAS was over 5 (of a possible 6). Baseline itch severity scores were >13 (of a possible 21) in more than half of the patients in both studies. The mean duration of disease was between 6 and 7 years in each study, with a very wide range, from 6 months (the minimum required for entry) to over 66 years. Angioedema was present in over 40% of patients in both studies; this was based on a narrow definition, namely the presence of angioedema during the week prior to randomization. Baseline mean DLQI values ranging from 12.6 to 14.0.

The mean number of prior medications for urticaria was over 4 in both studies, and over 70% of patients had received at least 3 prior medications and indicating that the populations were refractory to current standard therapies. The most common prior medications in both studies were non-sedating antihistamines, and almost 30% of patients in Q4881g and over 20% in Q4882g had been treated with the sedating antihistamine diphenhydramine. Approximately 26% of patients in each study had prior LTRA treatment and 44% of patients had previously received systemic corticosteroids to treat their CSU. CSU medications in use at baseline were most commonly non-sedating antihistamines, most frequently cetirizine, fexofenadine, loratadine, levocetirizine, and desloratadine.

Study Q4883g

In Study Q4883g, the treatment groups were well balanced in terms of baseline demographic characteristics (Table 7). Mean age was 43.1 years, with only 11 patients (3.3%) 12-<18 years old, and 21 (6.3%) over 64 years of age. Most patients were female and white.

Table 7 - Baseline demographic characteristics and baseline urticaria characteristics, mITT population, Study Q4883g

	Placebo (N=83)	Omalizumab 300 mg (N=252)	All Patients (N=335)
Age (years)			
Mean (SD)	44.3 (14.7)	42.7 (13.9)	43.1 (14.1)
Median	46.0	44.0	44.0
Range	14 - 73	14 - 75	14 - 75
Age group (years) n (%)			
12-17	4 (4.8%)	7 (2.8%)	11 (3.3%)
18-40	29 (34.9%)	96 (38.1%)	125 (37.3%)
41-64	41 (49.4%)	137 (54.4%)	178 (53.1%)
≥65	9 (10.8%)	12 (4.8%)	21 (6.3%)
Sex n (%)			
N	83	252	335
Female	55 (66.3%)	186 (73.8%)	241 (71.9%)
Ethnicity n (%)			
Hispanic or Latino	6 (7.2%)	18 (7.1%)	24 (7.2%)
Not Hispanic or Latino	77 (92.8%)	233 (92.5%)	310 (92.5%)
Not Available	0 (-)	1 (0.4%)	1 (0.3%)
Race n (%)			
American Indian or Alaska Native	0 (-)	1 (0.4%)	1 (0.3%)
Asian	1 (1.2%)	8 (3.2%)	9 (2.7%)
Black	6 (7.2%)	15 (6.0%)	21 (6.3%)
White	75 (90.4%)	223 (88.5%)	298 (89.0%)
Multiracial*	1 (1.2%)	1 (0.4%)	2 (0.6%)
Not Available	0 (-)	4 (1.6%)	4 (1.2%)
Weight (kg)			
Mean (SD)	87.2 (25.2)	82.8 (21.5)	83.9 (22.5)
Median	82.3	79.0	79.6
Range	53-164	46-172	46-172
Weight n (%)			
<80 kg	40 (48.2%)	128 (50.8%)	168 (50.1%)
BMI			
Mean (SD)	31.0 (9.6)	29.4 (7.1)	29.8 (7.8)
Duration of CIU (years)			
n	83	246	329
Mean (SD)	8.8 (11.2)	7.0 (8.8)	7.4 (9.5)
Median	4.1	3.4	3.6
Range	0.6-54.1	0.5-50.3	0.5-54.1
Previous Number of CIU medications			
n	83	252	335
Mean (SD)	6.4 (2.9)	5.9 (2.5)	6.0 (2.6)
Median	6.0	6.0	6.0
Range	2-15	2-15	2-15
CIU medications at baseline, n (%) patients			
n	83	252	335
H1 antihistamines + H2 antagonists only	45 (54.2%)	141 (56.0%)	186 (55.5%)
H1 antihistamines + H2 antagonists + LTRAs only	25 (30.1%)	64 (25.4%)	89 (26.6%)
H1 Antihistamines + LTRAs Only	11 (13.3%)	36 (14.3%)	47 (14.0%)
Other CIU Medication Combinations	2 (2.4%)	11 (4.4%)	13 (3.9%)
H1 Antihistamine therapies at baseline n (%)			
n	82	247	329
1 x standard dose	25 (30.5%)	98 (39.7%)	123 (37.4%)
2 x standard dose	36 (43.9%)	80 (32.4%)	116 (35.3%)

3 x standard dose	7 (8.5%)	30 (12.1%)	37 (11.2%)
4 x standard dose	14 (17.1%)	39 (15.8%)	53 (16.1%)
Presence of anti-FcεRI auto-antibody (CU index test) n (%)			
n	83	250	333
Yes	27 (32.5%)	76 (30.4%)	103 (30.9%)
Total IgE level (IU/mL)			
n	82	244	326
Mean (SD)	147.2 (224.4)	162.3 (306.4)	158.5 (287.7)
Median	71.0	79.0	78.0
Range	1-1230	1-3050	1-3050
In-Clinic UAS^			
n	83	252	335
Mean (SD)	5.2 (0.8)	5.2 (0.8)	5.2 (0.8)
Median	5.0	5.0	5.0
Range	4-6	4-6	4-6
UAS7*			
n	83	252	335
Mean (SD)	30.2 (6.7)	31.2 (6.6)	30.9 (6.6)
Median	30.0	32.0	31.5
Range	16.5-42.0	16.0-42.0	16.0-42.0
Weekly itch severity score*			
n	83	252	335
Mean (SD)	13.8 (3.6)	14.0 (3.6)	14.0 (3.6)
Median	14.0	13.5	13.5
Range	7.5-21.0	8.0-21.0	7.5-21.0
Weekly itch severity score*			
n	83	252	335
<13	33 (39.8%)	98 (38.9%)	131 (39.1%)
Weekly number of hives score*			
n	83	252	335
Mean (SD)	16.4 (4.6)	17.1 (4.2)	16.9 (4.3)
Median	18.0	19.0	19.0
Range	6.5-21.0	5.0-21.0	5.0-21.0
Presence of angioedema* n (%)			
n	83	252	335
Yes	41 (49.4%)	137 (54.4%)	178 (53.1%)

*Multiracial includes subjects for whom more than one race was indicated.
mITT: All patients randomized in the study who received at least one dose of study drug
^Baseline in-clinic UAS is defined as the largest value among the Day -14 screening visit, Day -7 screening visit and Day 1 Visit.
*Based on data collected in patient daily eDiary in the week before randomization

In Study Q4883g the mean duration of CIU at baseline was 7.4 years (median 3.6 years), and patients reported using an average of six medications to treat their CIU. Patients had a mean baseline UAS7 of 30.9 (range, 16.0–42.0) and a mean baseline weekly itch severity score, a component of the UAS7, of 14.0 (range, 7.5–21.0). The mean score for the physician assessed in-clinic UAS was 5.2 (range, 4–6). Angioedema was present in 49-54% of patients. Baseline mean DLQI values (13.0 in the placebo group and 13.8 in the omalizumab treated group.

In Study Q4883g the greatest percentage of patients were taking H1 antihistamines and H2 blockers only (55.5%) to manage their CIU, followed by patients who were taking H1 antihistamines, and H2 antihistamines and LTRAs in combination (26.6%), patients taking H1 antihistamines and LTRAs (14.0%), and patients taking other combinations of medications (3.9%). With respect to the use of H1 antihistamines, the majority of patients were taking either the standard approved dose (37.4%) or two times the approved dose (35.3%), followed by patients taking up to three times (11.2%) or four times (16.1%) the approved dose of H1 antihistamines. Regarding the non-sedating H1 antihistamines 30% of patients had used the sedating antihistamine diphenhydramine. The use of H2 blockers was also very common (in 89% of patients), as was LTRA use (58% of patients). A total of 58% of patients had prior use of steroids to treat CSU, and 7% of patients had prior use of cyclosporine. The two treatment groups in Q4883g were generally similar in terms of baseline disease characteristics, although the duration of disease was slightly longer in the placebo group, and a higher proportion of placebo patients were using H1 antihistamines at 2 x standard dose at baseline.

Outcomes and estimation

Primary efficacy endpoint

- **Change from baseline in the weekly itch severity score at Week 12**.

The results are presented below in table 8 below.

Table 8 - Change from baseline to Week 12 in weekly itch severity score, Studies Q4881g, Q4882g, and Q4883g (mITT populations)

	Placebo	Omalizumab 75mg	Omalizumab 150mg	Omalizumab 300mg
Study Q4881g	N=80	N=77	N=80	N=81
Mean (SD)	-3.63 (5.22)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)
Difference in LS means vs. placebo1	-	-2.96	-2.95	-5.80
95% CI for difference	-	−4.71,−1.21	−4.72,−1.18	−7.49,−4.10
p-value vs. placebo2	-	0.0010	0.0012	<0.0001
Study Q4882g	N=79	N=82	N=82	N=79
Mean (SD)	-5.14 (5.58)	-5.87 (6.45)	-8.14 (6.44)	-9.77 (5.95)
Difference in LS means vs. placebo1	-	-0.69	-3.04	-4.81
95% CI for difference	-	−2.54,1.16	−4.85,−1.24	−6.49,−3.13
p-value vs. placebo2	-	0.4637	0.0011*	<.0001
Study Q4883g	N=83			N=252
Mean (SD)	-4.01 (5.87)	-	-	-8.55 (6.01)
Difference in LS means vs. placebo1	-	-	-	-4.52
95% CI for difference	-	-	-	−5.97, −3.08
p-value vs. placebo2	-	-	-	<0.0001

BOCF was used to impute missing data

[1]The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥13) and baseline weight (< 80 kg vs. ≥ 80 kg).

[2]P-value is derived from ANCOVA t-test

Key secondary endpoints

Secondary efficacy endpoints in studies Q4881g and Q4882g, and the corresponding endpoints in study Q4883g were analysed according to a hierarchical testing procedure. Statistical tests were adjusted for multiple comparisons according to the type-I error control plan using the following pre-specified hierarchical order of secondary endpoint tests:

1: Change from baseline to Week 12 in UAS7

2: Change from baseline to Week 12 in the weekly number of hives score

3: Time to weekly itch severity score MID response at Week 12

4: Proportion of patients with UAS7 ≤ 6 at Week 12

5: Proportion of weekly itch severity score MID Responders at Week 12

6: Change from baseline to Week 12 in weekly size of the largest hive score

7: Change from baseline to Week 12 in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI)

8: Proportion of angioedema-free days from Week 4 to Week 12 of therapy

9. Proportion of patients with UAS7 =0 at Week 12 (Q4881g and Q4883g only)

Results

- **Change from baseline in UAS7 at Week 12**

Table 9 -Change from baseline to Week 12 in UAS7, Studies Q4881g, Q4882g, and Q4883g (mITT populations)

		Omalizumab dose		
	Placebo	**75mg**	**150mg**	**300mg**
Study Q4881g	N=80	N=77	N=80	N=81
Mean (SD)	-8.01 (11.47)	-13.82 (13.26)	-14.44 (12.95)	-20.75 (12.17)
Difference in LS means vs. placebo1	-	-5.75	-6.54	-12.80
95% CI for difference	-	-9.59, -1.92	-10.33, -2.75	-16.44, -9.16
p-value vs. placebo2	-	0.0035	0.0008	<0.0001
Study Q4882g	N=79	N=82	N=82	N=79
Mean (SD)	-10.36 (11.61)	-13.08 (12.67)	-17.89 (13.23)	-21.74 (12.78)
Difference in LS means vs. placebo1	-	-2.73	-7.69	-12.40
95% CI for difference		-6.53, 1.07	-11.49, -3.88	-16.13, -8.66
P-value vs. placebo2	-	0.1575	0.0001	<0.0001
Study Q4883g	N=83			N=252
Mean (SD)	-8.50 (11.71)	-	-	-19.01

				(13.15)
Difference in LS means vs. placebo1	-	-	-	-10.02
95% CI for difference	-	-	-	-13.17, -6.86
P-value vs. placebo2	-	-	-	<0.0001

BOCF was used to impute missing data
Baseline UAS7 is calculated using eDiary data from the 7 days prior to the first treatment date.
1The LS mean was estimated using an ANCOVA model. The strata were baseline UAS7 (< median, ≥ median) and baseline weight (< 80 kg vs. ≥ 80 kg).
2P-value is derived from ANCOVA t-test

- **Change from baseline in weekly number of hives score at Week 12**

Change from baseline in weekly number of hives score at Week 12 show that there was an observed difference between placebo and 300 mg omalizumab of -6.93, -7.09 and -5.90 in studies Q4881g, Q4882g, and Q4883g, respectively.

- **Time to minimally important difference (MID) response in weekly itch severity score by Week 12**

In studies Q4881g and Q4882g, median time to MID response was 1 week in the 300 mg groups, and 2 weeks in the 150 mg groups, compared with 4 weeks in the placebo groups.

- **Proportion of patients with UAS7 ≤ 6 at Week 12**

In the studies, the proportion of patients with UAS7 <= 6 at Week 12 were 11-19%, 26-27%, 40-43% and 52-66% in the placebo, 75 mg, 150 mg and 300 mg dose groups, respectively. Statistically significant vales were observed for the 150 mg and 300 mg doses.

- **Proportion of weekly itch severity score MID responders at Week 12**

In the studies, the proportion of weekly itch severity score MID responders (decrease of at least 5 points) at Week 12 were 36-48%, 56%, 56-70% and 70-79% in the placebo, 75 mg, 150 mg and 300 mg dose groups, respectively. Statistically significant vales were observed for the 150 mg and 300 mg doses.

- **Change from baseline in weekly size of largest hive score at Week 12**

Change from baseline in weekly size of largest hives score at Week 12 show that there was an observed difference in LS means between placebo and 300 mg omalizumab of -5.73, -7.15 and -5.61 in studies Q4881g, Q4882g, and Q4883g, respectively.

- **Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) at Week 12**

In all three studies, the change from baseline to Week 12 in overall DLQI was statistically significantly greater for the 300 mg omalizumab group than for placebo. For the 150 mg omalizumab group the difference to placebo only achieved statistical significance in one study.

- **Proportion of angioedema-free days from Week 4 to Week 12 of therapy**

The mean proportion of angioedema-free days from Week 4 to Week 12 was 88-89% in the placebo groups across the studies, and in all three studies, the mean proportion of angioedema-free days was highest in the 300 mg omalizumab group with means in the 300 mg groups of 96% (p<0.0001 vs. placebo) in both Q4881g and Q4882g, and 91% (p=0.0006) in Q4883g. The 75 mg and 150 mg omalizumab groups did not show statistically significant differences to placebo.

Table 10 - Proportion of angioedema-free days from Week 4 to Week 12, mITT population, Studies Q4881g, Q4882g, Q4883g

	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Study Q4881g				
N	66	69	70	74
Mean (SD)	88.2% (19.4%)	86.5% (28.4%)	89.6% (20.6%)	96.1% (11.3%)
Median	98.1%	100.0%	100.0%	100.0%
p-value vs. placebo[1]		0.4867	0.1747	<0.0001
Study Q4882g				
N	70	71	74	74
Mean (SD)	89.2% (19.0%)	93.5% (14.9%)	91.6% (17.4%)	95.5% (14.5%)
Median	100.0%	100.0%	100.0%	100.0%
P-value vs. placebo[1]	-	0.1361	0.0905	<0.0001
Study Q4883g				
N	68	-	-	224
Mean (SD)	88.1% (18.9%)	-	-	91.0% (21.0%)
Median	98.0%	-	-	100.0%
P-value vs. placebo[1]	-	-	-	0.0006

[1]p−value is derived from stratified Wilcoxon test. Stratification variables are presence of angioedema at baseline (Yes vs. No) and baseline weight (< 80 kg vs. >= 80 kg)

The proportion of angioedema−free days from Week 4 to Week 12 is defined as the number of days for which the patient indicated a 'No' response to the angioedema question in the daily diary divided by the total number of days with a non−missing diary entry starting on the Week 4 visit date and ending the day prior to the Week 12 visit date. Patients who withdrew before the Week 4 visit or who have missing responses for > 40% of the daily diary entries between the Week 4 study visit and the Week 12 study visit were not included in this analysis.

- **Proportion of patients with UAS7=0 at Week 12**

In all three studies (Q4881g, Q4882g and Q4883g), the 300 mg dose group consistently achieved a higher complete responder rate, (for total symptom control over 7 days, defined as the proportion of patients with a UAS7 of zero of 33.7 to 44.3%). The difference relative to placebo was statistically significant across the three studies. The corresponding values for placebo, the 75 mg dose and the 150 mg dose groups were 5-9%, 12-16% and 15-22%, respectively. The 75 and 150 mg doses did not achieve statistical significance for this endpoint in the pivotal studies.

Long term efficacy data

Studies Q4881g and Q4883g provided 24-week efficacy data. The results in the changes from baseline to Week 24 are presented below.

Table 11 - Change from baseline to Week 24 in weekly itch severity score, mITT population, Studies Q4881g and Q4883g

	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
Study Q4881g				
N	80	77	80	81
Mean (SD)	−5.41 (5.76)	−6.98 (6.42)	−6.47 (6.50)	−9.84 (5.95)
Difference in LS means vs. placebo[1]	-	−1.73	−1.02	−4.49
95% CI for difference	-	−3.60, 0.13	−2.91, 0.86	−6.31, −2.68
p-value vs. placebo[2]	-	0.0687	0.2860	<0.0001
Study Q4883g				
N	83	-	-	252
Mean (SD)	−4.03 (5.73)	-	-	−8.60 (6.46)
Difference in LS means vs. placebo[1]	-	-	-	−4.53
95% CI for difference	-	-	-	−6.06, −3.01
P-value vs. placebo[2]	-	-	-	<0.0001

BOCF was used to impute missing data
[1]The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥13) and baseline weight (< 80 kg vs. ≥ 80 kg).
[2]P-value is derived from ANCOVA t-test
Source: [Study Q4881g-Table 14.2/2.2]; [Study Q4883g-Table 14.2/1.2]

In both studies, the 300 mg omalizumab group showed changes from baseline at Week 24 that were similar to those at Week 12 for all secondary endpoints assessed, and for the responder analysis for patients with UAS7 ≤6 or UAS=0. From 12 to 24 weeks there was a sustained response observed for the 300 mg omalizumab dose in studies Q4881g and Q4883g. The Week 24 efficacy data showed no tolerance to treatment developing, and indicates that the efficacy of omalizumab is sustainable over the longer-term.

Table 12 - Change from baseline to Week 24 for key secondary endpoints and responder analysis, Studies Q4881g and Q4883g (mITT population)

		Omalizumab dose		
	Placebo	**75mg**	**150mg**	**300mg**
Change from baseline in UAS7 (BOCF), mean				
Study Q4881g	−11.73	−14.92	−14.21	−22.11*
Study Q4883g	−8.85	NA	NA	−19.15*
Proportion of patients with UAS7 ≤ 6, % patients				
Study Q4881g	25.0%	29.9%	36.3%	61.7%*
Study Q4883g	16.9%	NA	NA	55.6%*
Proportion of patients with UAS7 = 0, % patients				
Study Q4881g	12.5%	23.4%	20.0%	48.1%*
Study Q4883g	3.6%	NA	NA	42.5%*

* P-value ≤0.0001 for the treatment difference between omalizumab and placebo (ANCOVA t-test)
NA: Not applicable. BOCF: Baseline Observation Carried Forward

Ancillary analyses

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analysis

Pooled analyses of efficacy data from studies Q4881g and Q4882g were performed. With the exception of treatment period duration, studies Q4881g and Q4882g had identical inclusion and exclusion criteria, treatment frequency, study assessments, and efficacy endpoints. The results are shown below.

Primary endpoint

Table 13 - Change from baseline to Week 12 in weekly itch severity score, mITT population, Studies Q4881g and Q4882g, pooled data

	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
N	159	159	162	160
Mean (SD)	−4.38 (5.44)	−6.15 (6.29)	−7.40 (6.39)	−9.58 (5.83)
Difference in LS means vs. placebo (95% CI)[1]	-	−1.80 (−3.07,−0.53)	−3.02 (−4.28,−1.75)	−5.28 (−6.48,−4.09)
p-value vs. placebo[2]	-	0.0055	<0.0001	<0.0001

BOCF was used to impute missing data
[1]The LS mean was estimated using an ANCOVA model. The strata were baseline weekly itch severity score (< 13 vs. ≥13) and baseline weight (< 80 kg vs. ≥ 80 kg).
[2]P-value is derived from ANCOVA t-test

Key secondary endpoints

Table 14 - Change from baseline to Week 12 in UAS7, mITT population, Studies Q4881g and Q4882g, pooled data

	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
N	159	159	162	160
Mean (SD)	−9.17 (11.56)	−13.44 (12.92)	−16.18 (13.17)	−21.24 (12.45)
Difference in LS means vs. placebo (95% CI)[1]	-	−4.26 (−6.96,−1.57)	−7.14 (−9.81,−4.47)	−12.49 (−15.07,−9.91)
p-value vs. placebo[2]	-	0.0020	<0.0001	<0.0001

BOCF was used to impute missing data
Baseline UAS7 is calculated using eDiary data from the 7 days prior to the first treatment date.
[1]The LS mean was estimated using an ANCOVA model. The strata were were baseline UAS7 (<median vs. ≥ median) and baseline weight (< 80 kg vs. ≥ 80 kg).
[2]P-value is derived from ANCOVA t-test

Table 15 - Proportion of angioedema-free days from Week 4 to Week 12, mITT population, Studies Q4881g and Q4882g, pooled data

	Placebo	Omalizumab 75 mg	Omalizumab 150 mg	Omalizumab 300 mg
N	136	140	144	148
Mean (SD)	88.7% (19.1%)	90.1% (22.7%)	90.6% (19.0%)	95.8% (12.9%)
Median	98.2%	100.0%	100.0%	100.0%
p-value vs. placebo[2]	-	0.0903	0.0301	<0.0001

The proportion of angioedema−free days from Week 4 to Week 12 is defined as the number of days for which the patient indicated a 'No' response to the angioedema question in the daily diary divided by the total number of days with a non−missing diary entry starting on the Week 4 visit date and ending the day prior to the Week 12 visit date. Patients who withdrew before the Week 4 visit or who have missing responses for > 40% of the daily diary entries between the Week 4 study visit and the Week 12 study visit will not be included in this analysis.
^ p−value is derived from stratified Wilcoxon test. Stratification variables are presence of angioedema at baseline (Yes vs. No) and baseline weight (< 80 kg vs. >= 80 kg).

Subgroup analysis

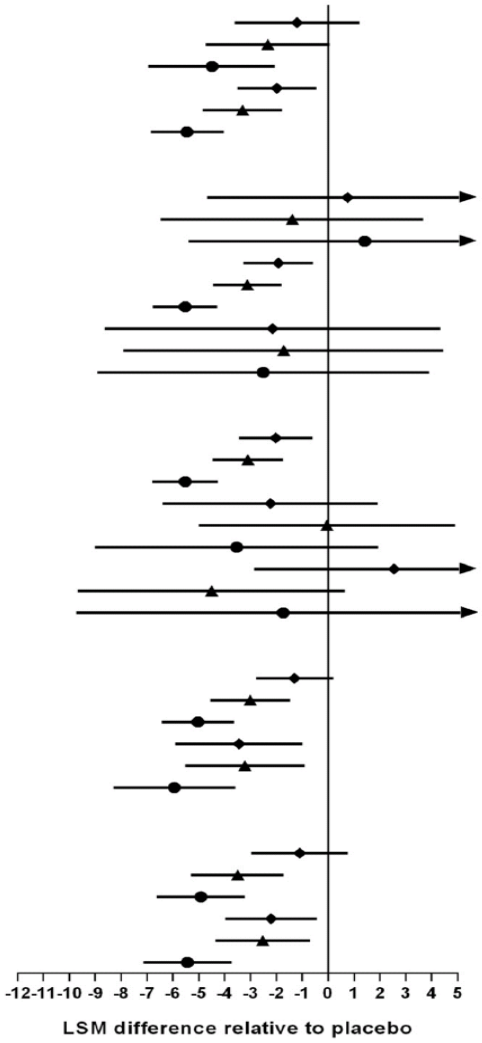
Change from baseline to Week 12 in weekly itch severity score was analysed in the pooled population of studies Q4881g and Q4882g in a range of subgroups defined according to baseline demographic and disease characteristics, or according to prior CSU treatments. Additional subgroup analyses for other endpoints were undertaken in subgroups defined by the presence or absence of angioedema at baseline.

Demographic factors

The results for the subgroup analysis defined by demographic factors are presented below.

Figure 2 - Forest plot of LS mean difference to placebo in change from baseline to Week 12 in weekly itch severity score, by demographic subgroup, mITT population, Q4881g and Q4882g pooled analysis

Subgroups	Treatment group	n	LSM difference (95% CI)
Sex			
Male	75 mg	95	–1.20 (–3.61, 1.21)
	150 mg	85	–2.34 (–4.73, 0.05)
	300 mg	89	–4.49 (–6.93, –2.06)
Female	75 mg	223	–1.99 (–3.51, –0.47)
	150 mg	236	–3.31 (–4.84, –1.78)
	300 mg	230	–5.46 (–6.86, –4.05)
Age			
<18	75 mg	15	0.75 (–4.67, 6.18)
	150 mg	15	–1.39 (–6.46, 3.67)
	300 mg	10	1.41 (–5.40, 8.22)
18-64	75 mg	286	–1.93 (–3.28, –0.59)
	150 mg	292	–3.13 (–4.46, –1.79)
	300 mg	291	–5.53 (–6.77, –4.29)
>= 65	75 mg	17	–2.15 (–8.63, 4.33)
	150 mg	14	–1.72 (–7.90, 4.46)
	300 mg	18	–2.51 (–8.92, 3.90)
Race			
White	75 mg	260	–2.03 (–3.45, –0.61)
	150 mg	267	–3.11 (–4.48, –1.73)
	300 mg	276	–5.53 (–6.79, –4.26)
Black or African American	75 mg	35	–2.24 (–6.40, 1.91)
	150 mg	28	–0.05 (–5.00, 4.91)
	300 mg	26	–3.54 (–9.01, 1.93)
Other	75 mg	23	2.54 (–2.87, 7.95)
	150 mg	26	–4.51 (–9.68, 0.65)
	300 mg	17	–1.74 (–9.74, 6.26)
Region			
US	75 mg	228	–1.30 (–2.79, 0.19)
	150 mg	227	–3.02 (–4.56, –1.47)
	300 mg	226	–5.03 (–6.43, –3.62)
Non-US	75 mg	90	–3.45 (–5.91, –0.99)
	150 mg	94	–3.22 (–5.53, –0.92)
	300 mg	93	–5.95 (–8.30, –3.59)
Body weight			
<80 kg	75 mg	157	–1.10 (–2.97, 0.76)
	150 mg	157	–3.50 (–5.29, –1.71)
	300 mg	162	–4.92 (–6.64, –3.21)
>=80 kg	75 mg	161	–2.21 (–3.97, –0.44)
	150 mg	164	–2.53 (–4.34, –0.71)
	300 mg	157	–5.44 (–7.14, –3.74)



'n' is the total number of patients used to calculate the estimated treatment difference. i.e. number of patients in stated active treatment group + number of patients on placebo.

Adolescents

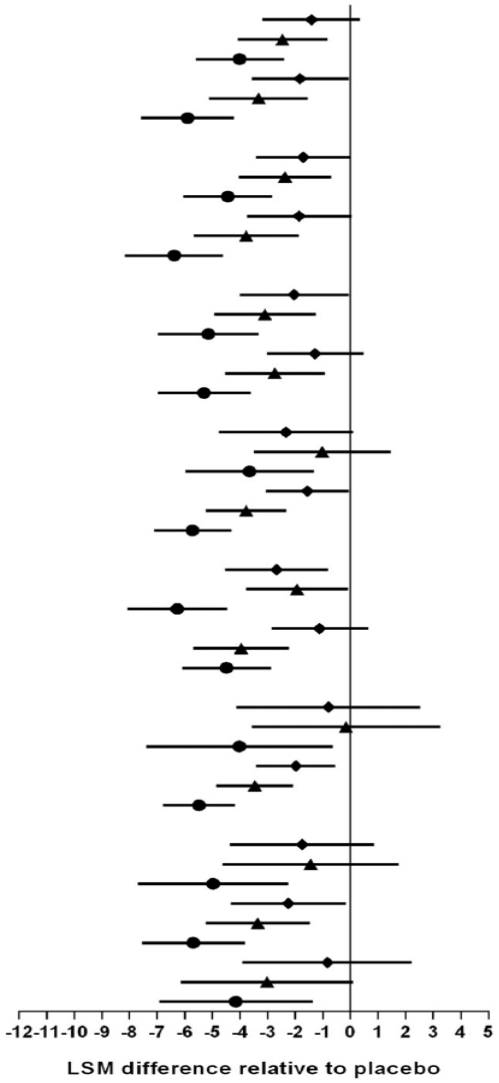
For the <18 years subgroup, a post hoc analysis was performed for the primary endpoint using a mixed effect model for the repeated measurement (MMRM). This analysis was based on the pooled Q4881g and Q4882g studies, and included a total of 25 patients. For week 12, the following treatment differences in LS means (vs placebo) -0.57, -2.22 and -1.65 was observed for the 75 mg, 150 mg and 300 mg dose, respectively. The result was not statistically significant.

Baseline disease factors

The results for the subgroup analysis defined by baseline disease factors are presented below.

Figure 3 - Forest plot of LS mean difference to placebo in change from baseline to Week 12 in weekly itch severity score, by disease factor subgroup, mITT population, Q4881g and Q4882g pooled analysis

Subgroups	Treatment group	n	LSM difference (95% CI)
Baseline weekly itch severity score			
<13	75 mg	122	–1.41 (–3.19, 0.36)
	150 mg	122	–2.46 (–4.09, –0.82)
	300 mg	125	–4.01 (–5.60, –2.41)
>=13	75 mg	196	–1.82 (–3.58, –0.06)
	150 mg	199	–3.33 (–5.13, –1.54)
	300 mg	194	–5.90 (–7.58, –4.22)
Baseline UAS7			
<Median	75 mg	146	–1.70 (–3.41, 0.01)
	150 mg	152	–2.37 (–4.04, –0.70)
	300 mg	157	–4.44 (–6.05, –2.83)
>=Median	75 mg	172	–1.86 (–3.75, 0.04)
	150 mg	169	–3.78 (–5.67, –1.88)
	300 mg	162	–6.38 (–8.16, –4.60)
Baseline total IgE			
<Median	75 mg	147	–2.04 (–4.00, –0.07)
	150 mg	158	–3.10 (–4.94, –1.25)
	300 mg	147	–5.15 (–6.98, –3.33)
>=Median	75 mg	161	–1.28 (–3.03, 0.47)
	150 mg	150	–2.74 (–4.55, –0.92)
	300 mg	159	–5.30 (–6.97, –3.62)
Positive CU index test			
Yes	75 mg	92	–2.33 (–4.76, 0.10)
	150 mg	91	–1.02 (–3.50, 1.46)
	300 mg	87	–3.65 (–5.98, –1.31)
No	75 mg	226	–1.56 (–3.07, –0.05)
	150 mg	229	–3.78 (–5.24, –2.32)
	300 mg	231	–5.72 (–7.12, –4.32)
Presence of angioedema at baseline			
Yes	75 mg	140	–2.67 (–4.55, –0.80)
	150 mg	150	–1.94 (–3.78, –0.09)
	300 mg	140	–6.27 (–8.08, –4.46)
No	75 mg	178	–1.12 (–2.86, 0.63)
	150 mg	171	–3.95 (–5.69, –2.22)
	300 mg	179	–4.49 (–6.09, –2.88)
Level of thyroperoxidase antibody at baseline			
High (>34.99 U/mL)	75 mg	55	–0.80 (–4.13, 2.54)
	150 mg	49	–0.16 (–3.57, 3.26)
	300 mg	42	–4.02 (–7.41, –0.64)
Normal (<=34.99 U/mL)	75 mg	257	–1.98 (–3.41, –0.55)
	150 mg	269	–3.46 (–4.85, –2.08)
	300 mg	270	–5.48 (–6.79, –4.17)
Duration of disease prior to baseline			
<=1 year	75 mg	72	–1.75 (–4.36, 0.86)
	150 mg	58	–1.44 (–4.62, 1.74)
	300 mg	66	–4.97 (–7.70, –2.25)
2-10 years	75 mg	130	–2.25 (–4.34, –0.17)
	150 mg	135	–3.36 (–5.25, –1.47)
	300 mg	128	–5.69 (–7.55, –3.83)
>10 years	75 mg	60	–0.84 (–3.91, 2.22)
	150 mg	72	–3.02 (–6.14, 0.10)
	300 mg	66	–4.15 (–6.94, –1.35)



'n' is the total number of patients used to calculate the estimated treatment difference. i.e. number of patients in stated active treatment group + number of patients on placebo.

Previous CSU therapies

Subgroups defined by prior medications, i.e., previous use of systemic steroids for CIU and previous number of CIU (i.e. CSU) medications, were analysed.

Patients with and without previous use of systemic steroids for CSU showed similar responses in terms of differences to placebo in changes in weekly itch severity score.

For each of the subgroups based on previous number of CSU medications (≤ 2, 3−5, >5) there was a dose response, with differences to placebo being larger with increasing omalizumab dose. Patients with ≤ 2 previous medications showed smaller differences to placebo, at each omalizumab dose level, than in the two subgroups with more previous medications.

For Study Q4883g, additional subgroup analyses were performed based on previous CSU therapies.

Supportive study(ies)

Study IGE025ADE05

Study IGE025ADE05 was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study, comparing the efficacy of omalizumab with placebo in patients aged 18-70 years with chronic urticaria who were symptomatic despite treatment with H1 antihistamines, and who had specific IgE against thyroperoxidase. Treatment duration was 24 weeks. Omalizumab was administered according to the approved dosing table for allergic asthma, with doses ranging from 75 to 375 mg, given 2-, or 4- weekly, according to the patients' body weight and baseline IgE level. A total of 27 patients were randomized to omalizumab and 22 to placebo. Baseline demographic characteristics were broadly similar across the treatment groups, although the placebo group had a higher proportion (86.4%) of female patients than the omalizumab group (70.4%). All patients were white, the mean age of the population as a whole was 40.5 years. The primary efficacy endpoint was the change from screening to Week 24 in UAS7. The LS mean decrease was 7.9 in the placebo group and 17.8 in the omalizumab group: the difference of 9.9 was statistically significant (p = 0.0089). Secondary efficacy parameters also showed greater improvements in the omalizumab group than the placebo group.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program included one phase 2 study (dose response, completed) and three phase 3 studies (all completed). The assessment of efficacy is mainly based on the three pivotal phase III studies, Q4881g, Q4882g and Q4883g. Study Q4883g was designed primarily for the evaluation of safety, and so no primary efficacy endpoint was designed. However, the same efficacy analyses were performed as in the other pivotal Phase III studies.

The three pivotal studies were all randomised, double-blind, placebo controlled and multicentre studies. The efficacy of 75 mg, 150 mg and 300 mg were explored in studies Q4881g and Q4882g and the 300 mg was explored in study 4883g. The study duration was 24 weeks in two studies (Q4881g, Q4883g) and 12 weeks in one study (Q4882g), and all studies had a 16 week follow up time to evaluate symptom recurrence.

The time point for the evaluation of the primary/key efficacy endpoint was at week 12 in all studies. The long term efficacy was assessed at 24 weeks in two of the studies which is considered reasonable.

The primary objective of the pivotal Phase 3 studies was to demonstrate the efficacy of omalizumab in patients with "refractory CIU" receiving concomitant H1 antihistamine therapy at currently approved doses (studies Q4881g and Q4882g) , or receiving concomitant H1 antihistamine therapy (up to four

times the approved dose), and H2 antihistamines and/or leukotriene receptor antagonists, LTRAs (Q4883g). Approximately 40-50% of the patients enrolled had angioedema at baseline.

In accordance with a recent guideline published by the European Academy of Allergology and Clinical Immunology (EAACI) (Zuberbier et al 2009a, Zuberbier et al 2009b), the term chronic idiopathic urticaria (CIU) has recently been reserved for patients with truly idiopathic aetiology. In this new classification, CSU covers all non-inducible chronic urticaria with CIU (of unknown trigger) being a subset of it. As the population studied in the omalizumab clinical studies included patients with auto-antibodies (all were tested at baseline), the term CSU most accurately reflects the study population and intended use. The conclusion of the MAH to use CSU is supported in particular when considering the patient population included in the studies.

In general, the design and the conduct of the studies seem appropriate and are in line with the recommendations given in the centralised scientific advice (EMEA/H/SA/45/3/2009/III).

Efficacy data and additional analyses

In the mITT population, the majority of all patients were Caucasian. More females (approximately 70%) than men, and the majority of the subjects were between 18-64 years. There were few patients in the < 18 years (39 (4.0%) children between 12 to 17 years old were included in the studies) and ≥ 65 years subgroups, there were 10 patients or fewer per treatment group.

Additional analyses were provided by the MAH correlating decrease in free IgE, expressed as the fraction of IgE at baseline (i.e. if relative rather than absolute free IgE levels), with AS7 improvement (reduction from baseline). In addition, relative free IgE levels are inversely correlated with omalizumab concentrations. Therefore, this analysis underpins the primary pharmacological action of omalizumab, i.e. binding to IgE and thus reduction of free IgE levels. The MAH believed that there is no need for another PD study on the mode of action of omalizumab in patients with CSU, which is endorsed by the CHMP. The information on PD proposed for section 5.1 of the omalizumab SmPC in CSU is deemed appropriate.

The results of the primary efficacy endpoint, change from baseline in the weekly itch severity score, show that at Week 12, there was an observed difference between placebo and 300 mg omalizumab of -5.80, -4.81 and – 4.52 in studies Q4881g, Q4882g, and Q4883g, respectively. The difference is statistically significant and is considered clinically relevant. Minimal important differences (MIDs) with respect to changes in individual patients have been defined for the composite score and its components and the MID ranges from 4.5 to 5.0 for weekly average of itch (Mathias et al 2012). In relation to the mentioned MID results for the 150 mg dose of omalizumab with a difference between placebo and 150 mg dose of -2.95 and -3.04 is not considered clinically relevant since the values do not reach the minimal important differences (MIDs) of 4.5-5.0 even though statistically significance is reached. For the 75 mg dose the corresponding difference is -2.96 and -0.69. In general secondary endpoints support these conclusions.

The proposed dose recommendation initially concerned two doses, i.e., 150 mg and 300 mg. The CHMP was of the opinion that convincing meaningful clinical data for the 150 mg dose including long term efficacy were not demonstrated and furthermore the circumstances when to use the 150 mg dose were unclear. The results further showed that for patients at above 80 kg the only relevant dose is 300 mg omalizumab. Since there are no apparent safety issues regarding the 300 mg dose, the use of the 150 dose was questioned especially when considering the very unclear posology recommendation. In addition, the MAH was requested to identify which subgroups/patients were to be started with either the 150 mg dose or the 300 mg dose.

In the absence of a predictive marker for 150 mg responders, and with no safety concerns at

300 mg, the MAH proposed a dose of omalizumab 300 mg every four weeks as this would ensure the maximum efficacy without additional safety risks, thereby providing the optimal benefit risk profile. The MAH was not able to identify any subgroup of patients or individuals that would benefit from the 150 mg dose in comparison to the 300 mg dose and proposed during the assessment to only include the 300 mg dose. The use of the 300 mg dose by subcutaneous injection every 4 weeks is endorsed by the CHMP.

Regarding angioedema, the difference is statistically significant and is considered clinically relevant only for the 300 mg dose. The CHMP agreed that patients with angioedema should be treated with 300 mg omalizumab.

The MAH presented data for all primary, secondary and main exploratory endpoints according to the presence of angioedema at baseline across the three pivotal studies. These data indicated that the presence of angioedema at baseline does not exert a significant impact of patient response to omalizumab. Omalizumab affords comparable therapeutic efficacy for all patients irrespective of their angioedema status at baseline, with a possible added benefit on quality of life for patients with angioedema at baseline. The CHMP concluded that the results show that omalizumab affords comparable therapeutic efficacy for all patients irrespective of the angioedema status at baseline

For adolescents no statistical significant effects were observed which was expected considering the few subjects included. However, the actual values were rather low and the results were not considered to be clinically meaningful. Furthermore, when considering that the estimated EC50 was 55% higher in adolescents as discussed in the clinical pharmacology section, it was not clear that an appropriate dose had been adequately explored for use in adolescents. Since the proposed new indication also involves adolescents 12-18 years, this raised a concern if the indication of CSU can be extended also to adolescents since there are no clinical data from the studies and it is possible that PKPD is different in this population. Therefore, the MAH was requested to provide a thorough analysis of efficacy (main and key secondary endpoints, responder analysis) and safety (adverse events) in this subpopulation. Furthermore, the MAH was requested to discuss to what extent extrapolation for the different entities covered under the CSU umbrella can be done from adults to adolescents, including dose-response similarity, to support an indication in this age subset.

The MAH provided data showing that there were a total of 39 adolescents aged 12-17 (4% of all patients) within the three pivotal studies which is consistent with the estimated population prevalence. It is much less prevalent than in adults (0.1–0.3% in children in the United Kingdom, and up to 13% in Thailand). It is estimated that the paediatric population prevalence is around 5% of all CSU (Ghosh, 1993), so the size of the adolescent sub-group in the studies was considered relevant by the CHMP. According to the MAH, and based on the full time course exposure-response analysis, adolescent patients are predicted to have higher EC50 values than adult patients. However, omalizumab trough levels are predicted to be higher in adolescents than in adults, due to the lower average body weight of adolescents. Indeed, in the 300 mg dose group, the median observed trough concentrations were about 50-70% higher for the adolescents, at week 12 and week 24. Thus, the effects on potency and systemic exposure compensate for each other. Simulated well-controlled responder rates indicate a significant treatment effect in adolescents for 300 mg q4w. The MAH stated that the results of all three studies provide evidence of a clear differentiation on weekly itch severity score (ISS) between the 300 mg dose and placebo in adolescents. Further exploration of the reduction in weekly ISS comparing adults and adolescents at 300 mg showed a similar pattern of response. Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6. In summary although the group of adolescents is small and

not powered to see a statistically significant result over placebo, the data comparing the adolescents with adults do show that the responses are similar in both groups.

The MAH concluded that, in the subpopulation of adolescents (aged between 12-17 years) with disease that has been unresponsive to other therapies and which is severe, as evidenced by the high baseline ISS and DLQI, omalizumab is able to control the symptoms of severe itch and wheals in the majority of adolescent patients at the 300 mg dose. This is superior to placebo and there are no specific safety concerns related to this age group. In addition, the MAH was not able to identify any subgroup of patients or individuals that would benefit from the 150 mg dose in comparison to the 300 mg dose. Thus, omalizumab 300 mg q4w appears to be efficacious and safe for adolescent patients. This was agreed by the CHMP.

The MAH's statement that since no differences are known between the pathophysiology of CSU in adolescents and adults it is reasonable to extrapolate from adult data to the adolescent group is accepted by the CHMP. The available data in adolescents who received 300 mg points to roughly similar effects as adults. The median trough concentrations are about 50-70% higher for adolescents when compared to adults further strengthen this.. The CHMP considered this sufficient to also include the adolescent group in the indication. The proposed wording in section 5.1 of the SmPC "*Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.*" is endorsed by the CHMP.

Visual exploration of PK/PD did not reveal a significant effect of age >65 years compared with younger patients. The proportion of complete responders (UAS7=0) was similar between the elderly and the younger subgroups indicating a similar clinical response between the two groups. The CHMP concluded that the extended modeling does not reveal any overt effect of age on the PKPD-profile of omalizumab.

The efficacy of omalizumab for the treatment of patients with chronic spontaneous urticaria (CSU) has been evaluated in three pivotal studies. In two of the studies Q4881g and Q4882g the patients had active disease despite treatment with concomitant H1 antihistamine therapy at currently approved doses (Q4881g, Q4882g). In the third study Q4883g the patients had active disease despite receiving concomitant H1 antihistamine therapy (up to four times the approved dose), and H2 antihistamines and/or leukotriene receptor antagonists (LTRAs). Convincing clinical effects are observed with the 300 mg dose of omalizumab in all three studies.

Current therapeutic recommendations for chronic urticaria are based on a step-up treatment algorithm, where patients are initially treated with approved doses of H1 antihistamines (the only currently approved therapy for chronic urticaria). If patients who do not respond to approved doses of antihistamines, the guidelines suggest to increase the dose up to fourfold if necessary. According to the Guideline on Summary of Product Characteristics, the indication should be stated clearly and concisely and should define the target disease or condition. Current guidelines suggest the addition of a leukotriene receptor antagonist (LTRA), or less commonly a triple regimen of H1 and H2 antihistamines combined with an LTRA (Zuberbier et al 2009b). This is the reason why patients included in study Q4883g should remain symptomatic despite H1 antihistamines at up to a four-fold dose, plus either or both of H2 antihistamines and LTRA. However, patients included in Q4881g and Q4882g studies had to be refractory to approved doses of H1 antihistamines for inclusion. Given that two-thirds of the efficacy outcome have been generated from the last two studies (which only had background therapy of an H1 antihistamines) and higher doses of anti-H1, antiH2 and LTRA are not approved in Europe for the chronic urticaria indication, the restriction of the indication to patients who

remain refractory to H1 antihistamine treatment, as proposed by the MAH, is considered adequate. According to the CHMP, adding the statement "in combination with H1 antihistamines" or "as add-on therapy" is not considered a duplication of the information around the requirement "inadequate response to H1 antihistamine treatment" since an inadequate response to H1 antihistamine treatment does not imply the type of therapy (substitution or add-on therapy) and its omission in the indication could lead to confusion. In conclusion, in order to address the CHMP's requested a revision of the indication which takes into account the fact that Xolair should be given in combination with H1 antihistamines in patients with inadequate response to antihistamine treatment, the MAH proposed the following indication statement:

'Xolair is indicated for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment'.

The CHMP suggested the addition of "*moderate to severe CSU*" in the indication statement to characterise the severity of the disease. However the MAH stated that in current clinical practice there are no guidelines on disease severity for prescribers. Furthermore this terminology has not been adopted by the practicing physicians and there is no consensus on what would constitute moderate or severe disease in CSU. The scores that have been used in the omalizumab development programme such as UAS7 and ISS are not in general use in clinical practice, thus there is no available framework to make this type of decision on disease severity. In order to prevent confusion among prescribers around this classification in the label it is deemed prudent to avoid this wording in patients who will already have a refractory disease. The refractory disease status is appropriately reflected in the indication wording by "*patients with inadequate response to H1 antihistamine treatment".*

As a consequence, the MAH included information regarding the use of omalizumab *as add-on therapy* (as stated for the allergic asthma indication) in the indication as follows: *"Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment".* This proposal is accepted by the CHMP.

Presence of auto-antibodies did not seem to affect significantly trough levels, and both populations (with and without auto-antibodies) did have a good respond to omalizumab. Therefore, the MAH's conclusion that it does not seem warranted to recommend a different dosing for these subpopulations is endorsed.

Regarding treatment duration, and according to clinical trial experience, the MAH stated that treatment duration should be up to 6 months and reassessment for further therapy should occur after this period. The MAH followed the CHMP request to include in section 4.2 of the SmPC that clinical trial experience of long-term treatment beyond 6 months in this indication is limited as follows: "*Prescribers are advised to periodically reassess the need for continued therapy. Clinical trial experience of long-term treatment* ***beyond 6 months*** *in this indication is limited"*.

Regarding the SmPC statement to "*periodically reassess the need for continued therapy*", initially considered insufficient by the CHMP due to irrelevant differences in the itchy severity score (primary endpoint) between week 24 and week 12 in both 4881g and 4883g studies, and the CHMP suggestion for the treatment reassessment to take place after 3 months and to provide a more detailed guidance, the MAH explained that apart from the treatment durations in the phase III studies, no specific clinical data is available from the omalizumab CSU clinical program to support a specific time point or time period for re-assessment whilst the patient is still on omalizumab therapy. Although the mean itch severity score (ISS) values of week 12 and week 24 were almost identical, examination of the proportion of patients achieving a UAS7≤6 or a symptom free state (UAS=0) across both studies, Q4881g and Q4883g demonstrated a consistent trend for more patients (up to 12.3%) to achieve an improved health state at week 24 compared to week 12. The observed increase in the fraction of

patients reaching a symptom free or a robust control of their symptoms with longer treatment does argue for extending treatment to 24 weeks which is also not restricted by safety risks due to the good safety profile of omalizumab. The similar recurrence of itch symptoms towards baseline during the 16 week drug washout period after week 12 (Q4882g) and week 24 (Q4881g and Q4883g) of treatment suggests that the chances of symptoms recurring are apparently independent of the duration of therapy. Therefore, the CHMP agreed that the MAH statement insection 4.2 of the SmPC "periodically reassess the need for continued therapy" provides appropriate and sufficient guidance to the physician.

Given the small number of re-treated patients (only 25), no conclusions can be drawn on re-treatment. Information regarding the limited experience of retreated patients will be included in the SPC (section 5.1) as follows: "There is limited clinical experience in re-treatment of patients with omalizumab".

2.4.4. Conclusions on the clinical efficacy

The results of the primary efficacy endpoint, change from baseline in the weekly itch severity score, show that at Week 12, there was an observed difference between placebo and 300 mg omalizumab of -5.80, -4.81 and – 4.52 in studies Q4881g, Q4882g, and Q4883g, respectively. The difference is statistically significant and is considered clinically relevant.

In the absence of a predictive marker for 150 mg responders, and with no safety concerns at

300 mg, the dose of omalizumab 300 mg every four weeks proposed by the MAH is endorsed as this would ensure the maximum efficacy without additional safety risks, thereby providing the optimal benefit risk profile.

Regarding angioedema, the difference is statistically significant and is considered clinically relevant only for the 300 mg dose. It is agreed that patients with angioedema should be treated with 300 mg omalizumab. Omalizumab affords comparable therapeutic efficacy for all patients irrespective of their angioedema status at baseline, with a possible added benefit on quality of life for patients with angioedema at baseline.

Although the group of adolescents is small and not powered to see a statistically significant result over placebo, the data comparing the adolescents with adults do show that the responses are similar in both groups. Omalizumab 300 mg q4w appears to be efficacious in adolescent patients aged 12 - 17 years of age.

The revised indication which takes into account the fact that Xolair should be given in combination with H1 antihistamines in patients with inadequate response to antihistamine treatment, as shown below, is considered acceptable by the CHMP:

"Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment".

2.5. Clinical safety

2.5.1. Introduction

The historical clinical development program for omalizumab is comprised of studies which evaluated the safety and efficacy of omalizumab in several indications, including the allergic asthma (AA), seasonal and perennial allergic rhinitis (SAR, PAR) and atopic dermatitis indications. The product is approved for the indication of moderate to severe or severe AA only. Omalizumab has been used worldwide since its initial approval in 2003. Its safety profile in patients with allergic asthma has been

well-characterized in clinical trials as well as in the post-marketing setting. As of 31 Dec 2012, the cumulative patient exposure since the first launch of omalizumab is estimated to be approximately 410,890 patient-years.

During these clinical trials in adult and adolescent patients 12 years of age and older, the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema and pruritus, and headaches.

Type I local or systemic allergic reactions, including anaphylaxis and anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair. Anaphylactic reactions were rare in clinical trials. Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have also been reported in patients, frequency unknown.

In rare cases, patients on therapy with anti-asthma medicinal products, including omalizumab, may present or develop systemic eosinophilia and vasculitis and in patients with severe asthma, systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (Churg-Strauss syndrome) has been reported (frequency unknown).

A numerical imbalance of Arterial thromboembolic events (ATE) was observed in controlled clinical trials and an ongoing observational study, ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). The rate of ATE in patients in the controlled clinical trials was 6.29 for Xolair-treated patients (17/2703 patient years) and 3.42 for control patients (6/1755 patient years). In Cox proportional hazards model, Xolair was not associated with ATE risk (hazard ratio 1.86; 95% confidence interval 0.73-4.72). In the observational study, the rate of ATE was 5.59 (79/14140 patients years) for Xolair-treated patients and 3.71 (31/8366 patient years) for control patients. In a multivariate analysis controlling for baseline cardiovascular risk factors, Xolair was not associated with ATE risk (hazard ratio 1.11; 95% confidence interval 0.70-1.76).

In clinical trials a few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in haemoglobin. No pattern of persistent decrease in platelet counts (observed in non-human primates), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia have been reported in post-marketing setting.

In patients at chronic high risk of helminthic infection, a placebo-controlled trial showed a slight numerical increase in infection rate with omalizumab that was not statistically significant. The course, severity, and response to treatment of infections were unaltered.

A comprehensive analysis of the existing safety data up to 31-Dec- 2012 for omalizumab in the treatment of allergic asthma is provided in the latest PSUR [PSUR 16, 1 January 2012 – 31 December 2012]. This update on omalizumab ('Xolair') in allergic asthma concluded the following: "No previously unidentified safety concerns were identified during the review period of current PSUR after thorough analysis of all available preclinical, clinical and post-marketing data of Xolair."

Cumulative exposure data to omalizumab within clinical trials submitted in PSUR 16 is presented in table 15 below.

Table 15 – Cumulative exposure to omalizumab from completed clinical trials by age and sex

	Cumulative subject exposure*			Number of subjects*		
Age Range	Male	Female	Total	Male	Female	Total
<12	719.5	350.3	1,069.7	627	318	945
12-≤17	248.9	157.3	406.2	377	241	618
18-≤64	1,374.4	2,288.5	3,662.8	2,744	4,262	7,006
65 & over	85.6	144	229.6	146	219	365
Total	2,428.4	2,940.1	5,368.3	3,894	5,040	8,934

* Data from completed trials as of 31-Mar-2013, excludes Compassionate Use Program patients.

Based on previous clinical trial data and of reports during post-authorisation exposure, the RMP has included the following important Identified risks : 1/Anaphylaxis/anaphylactoid reactions, 2/ Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD), 3/Antibody formation to omalizumab, 4/Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome, 5/Thrombocytopenia. Important potential risks are 1/Arterial Thromboembolic Events (ATEs)2/Malignant neoplasms (children 6 to less than 12 years old), 3/Malignant neoplasms in adults and adolescents ≥ 12 years of age, and 4/Off label use. Important missing information is 1/Pregnancy outcomes.

Data from pooled clinical studies and from a post-authorisation safety study (EXCELS) presented in the latest PSUR indicate according to the MAH no increased malignancy risk with Xolair.

Submitted safety data of the applied new treatment indication

The submitted clinical program for omalizumab included studies in the chronic spontaneous urticaria (CSU) indications which were conducted to assess the safety, tolerability and efficacy of omalizumab in the treatment of patients with CSU. Based on previous studies, including the 5 year epidemiology study EXCELS, ongoing pharmacovigilance and prescribing information of omalizumab for allergic asthma, the following AESIs were pre-specified for closer scrutiny in the CSU program:

- Anaphylaxis
- Churg-Strauss syndrome
- Hypersensitivity
- Injection-site reaction
- Malignancy
- Serum sickness syndrome
- Skin rash
- Thrombocytopenia and bleeding-related disorders
- Hematopoietic cytopenias
- Arterial thrombotic events
- Asthma/bronchospasm
- Liver-related investigations, signs and symptoms

Patient exposure

The evaluation of safety information for omalizumab for the treatment of patients with CSU who remain symptomatic despite concomitant therapy, is derived from three Phase III studies, including two pivotal efficacy studies (Q4881g, Q4882g) and one safety study (Q4883g). In addition there is supporting safety data from a phase II dose-ranging study (Q4577g (see table 16).

Table 16 – Summary of Key Studies Contributing to Safety Evaluation

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients*	Dose, Route, and Regimen
Q4881g (Phase III)	Global, multicenter, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study	Patients (12-75 years) with refractory CSU who remain symptomatic despite approved-dosed H1 antihistamine treatment	Total: 318 75 mg: 70 150 mg: 87 300 mg: 81 Placebo: 80	Omalizumab 75, 150 or 300 mg, or placebo administered SC every 4 weeks during the double-blind 24 week treatment period (6 doses total) + 16 weeks follow-up
Q4882g (Phase III)	Global, multicenter, randomized, double-blind, placebo-controlled, parallel group, efficacy and safety study	Patients (12-75 years) with refractory CSU who remain symptomatic despite approved-dosed H1 antihistamine treatment	Total: 322 75 mg: 76 150 mg: 88 300 mg: 79 Placebo: 79	Omalizumab 75 mg, 150 mg, 300 mg, or placebo administered SC every 4 weeks during the double-blind 12 week treatment period (3 doses total) + 16 weeks follow-up
Q4883g (Phase III)	Global, multicenter, randomized, double-blind, placebo-controlled, parallel group, safety study	Patients (12-75 years) with refractory CSU who remain symptomatic despite H1 antihistamines at increased doses, H2 antihistamines, and/or LTRA	Total: 335 300 mg: 252 Placebo: 83	Omalizumab 300 mg or placebo administered SC every 4 weeks during the double-blind 24 week treatment period (6 doses total) + 16 weeks follow-up
Q4577g (Phase II)	United States and Germany, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept, dose-ranging efficacy and safety study	Patients with refractory CSU who remain symptomatic despite approved-dosed H1 antihistamine treatment	Total: 90 Placebo:21 75 mg: 23 300 mg: 25 600 mg: 21	Omalizumab 75 mg, 300 mg, 600 mg, or placebo single-dose administered SC, 12-week follow-up period

*Number of safety evaluable patients. Total patients=1065: Placebo=263, Omalizumab 75mg=169, 150mg=175, 300mg=437, 600mg=21
CSU=chronic spontaneous urticaria; LTRA=leukotriene receptor antagonist; SC=subcutaneously

One further study not part of the MAH's original development plan contributed further to supportive safety data in a total of 49 patients and is specified in table 17.

Table 17 – Other completed trials (placebo-controlled)

Study No. (Phase)	Study Design, Control Type	Population	No. of Patients	Dose, Route, and Regimen
DE05 (local study)	Germany, multicenter, randomized, double-blind, placebo-controlled, 24 weeks duration	Patients with chronic urticaria who remain symptomatic despite antihistamine treatment and who have IgE against thyroperoxidase	Total: 49 Omalizumab: 27 Placebo: 22	75-375 mg, administered SC, 2- or 4-weekly, according to dosing table

A total of 975 patients enrolled in the three Phase III studies received at least one dose of study drug and were included in the safety-evaluable population. Of these, a total of 733 patients received omalizumab, the numbers of patients and the different doses are specified in Table 1-5 below. With study Q4577g included, these four placebo-controlled studies comprised a total of 1065 patients, 802 having received one or more doses of omalizumab. Safety data from study DE05 (table 17) was not included in the planned analysis for the SCS. However, data from that study is presented in a stand-alone manner within the SCS. A total of 39 (4.0%) patients were 12 to 17 years old. The majority of the patients were white (85.4%) and female (73.4%).

Table 18 – Extent of Exposure to Study Drug for Studies Q4881g, Q4882g, and Q4883g Pooled (Core safety analysis set)

		Omalizumab			
	Placebo N=242	75mg N=146	150mg N=175	300mg N=412	All Patients N=975
Exposure duration (weeks)					
Mean (SD)	17.6 (6.9)	16.3 (6.7)	16.7 (6.4)	20.3 (6.0)	18.4 (6.6)
Median	23.0	12.0	12.0	24.0	24.0
Range	4 - 25	4 - 25	4 - 26	4 - 25	4 - 26
Exposure duration (weeks)	n (%)	n (%)	n (%)	n (%)	n (%)
1-4	13 (5.4)	8 (5.5)	4 (2.3)	12 (2.9)	37 (3.8)
5-8	13 (5.4)	6 (4.1)	8 (4.6)	11 (2.7)	38 (3.9)
9-12	80 (33.1)	68 (46.6)	80 (45.7)	84 (20.4)	312 (32.0)
13-16	10 (4.1)	4 (2.7)	9 (5.1)	5 (1.2)	28 (2.9)
17-20	1 (0.4)	(0.0)	3 (1.7)	4 (1.0)	8 (0.8)
21-24	119 (49.2)	58 (39.7)	64 (36.6)	282 (68.4)	523 (53.6)
>24	6 (2.5)	2 (1.4)	7 (4.0)	14 (3.4)	29 (3.0)
Number of Doses					
Mean (SD)	4.4 (1.7)	4.1 (1.7)	4.2 (1.6)	5.1 (1.5)	4.6 (1.6)
Median	6.0	3.0	3.0	6.0	6.0
Range	1 - 6	1 - 6	1 - 6	1 - 6	1 - 6
Cumulative Dose (mg)					
Mean (SD)	NE (NE)	306.1 (124.0)	606.4 (232.5)	1526.3(450.6)	1063.7(644.1)
Median	NE	225.0	450.0	1800.0	900.0
Range	NE - NE	75 - 450	150 - 913	300 - 1800	75 - 1800
Missed Doses	n (%)	n (%)	n (%)	n (%)	n (%)
0	199 (82.2)	126 (86.3)	152 (86.9)	371 (90.0)	848 (87.0)
1	4 (1.7)	3 (2.1)	7 (4.0)	7 (1.7)	21 (2.2)
2	8 (3.3)	10 (6.8)	6 (3.4)	5 (1.2)	29 (3.0)
3	7 (2.9)	1 (0.7)	3 (1.7)	7 (1.7)	18 (1.8)
4	13 (5.4)	4 (2.7)	6 (3.4)	11 (2.7)	34 (3.5)
5	11 (4.5)	2 (1.4)	1 (0.6)	11 (2.7)	25 (2.6)

Duration of study drug exposure in weeks will be defined as the date of the last treatment visit minus the date of the first study drug administration + 1 + 4 weeks (28 days).
NE: not estimable

The pooled Phase III safety population was organized into 4 analysis sets, according to the length of treatment period (12 or 24 weeks) and by the permitted background therapy.

The 'Core safety analysis set' comprised the pooled safety population from all three Phase III placebo-controlled studies. This analysis set is used to summarize pooled data from Day 1 to Week 12, and the 16-week follow-up data, as both these study periods are common to all three Phase 3 studies. Because all patients are included in this population, it is also used for all background demographic, disease and other baseline safety presentations.

The 'Core safety analysis set by co-medications' included all patients from the Core safety analysis set but presented the outputs by the permitted background CSU therapy, which was different for Study Q4883g compared to Studies Q4881g and Q4882g. Data were therefore presented side-by-side for Q4881g/Q4882g pooled versus Q4883g for the first 12 weeks of the treatment period and for the 16-week follow-up period.

The 'Extended safety analysis set' comprised the pooled safety population from the two placebo-controlled studies of 24 weeks duration (Q4881g and Q4883g), and is used to summarise pooled data from Day 1 to Week 24, and the respective 16-week follow-up data.

The 'Extended safety analysis set by co-medications' included all patients from the Extended safety analysis set, but presented the outputs by background CSU therapies, side-by side for the two studies for the 24 weeks treatment and 16-week follow-up periods.

Phase II Study Q4577g is a stand-alone presentation of the safety data from this study.

In general, the four treatment groups showed no major differences with respect to baseline Demographics (see table 19).

Table 19 – Demographic and Baseline Characteristics for Studies Q4881g, Q4882g, and Q4883g Pooled (Core safety analysis set)

		Omalizumab			
	Placebo N=242	75mg N=146	150mg N=175	300mg N=412	All Patients N=975
Age (years)					
Mean (SD)	42.6 (14.4)	39.5 (14.9)	42.5 (13.8)	42.9 (13.7)	42.3 (14.1)
Range	13 - 74	13 - 75	12 - 72	14 - 75	12 - 75
Age group (years)					
12-17	10 (4.1%)	8 (5.5%)	10 (5.7%)	11 (2.7%)	39 (4.0%)
18-40	100 (41.3%)	72 (49.3%)	64 (36.6%)	161 (39.1%)	397 (40.7%)
41-64	115 (47.5%)	58 (39.7%)	94 (53.7%)	218 (52.9%)	485 (49.7%)
≥65	17 (7.0%)	8 (5.5%)	7 (4.0%)	22 (5.3%)	54 (5.5%)
Sex					
Male	80 (33.1%)	41 (28.1%)	35 (20.0%)	103 (25.0%)	259 (26.6%)
Female	162 (66.9%)	105 (71.9%)	140 (80.0%)	309 (75.0%)	716 (73.4%)
Ethnicity					
Hispanic or Latino	19 (7.9%)	12 (8.2%)	16 (9.1%)	24 (5.8%)	71 (7.3%)
Not Hispanic or Latino	221 (91.3%)	133 (91.1%)	159 (90.9%)	385 (93.4%)	898 (92.1%)
Not Available	2 (0.8%)	1 (0.7%)	(0.0%)	3 (0.7%)	6 (0.6%)
Race					
American Indian or Alaska Native	0	0	2 (1.1%)	2 (0.5%)	4 (0.4%)
Asian	6 (2.5%)	8 (5.5%)	7 (4.0%)	11 (2.7%)	32 (3.3%)
Black	20 (8.3%)	16 (11.0%)	19 (10.9%)	27 (6.6%)	82 (8.4%)
Native Hawaiian Other Pacific Island	1 (0.4%)	0	0	0	1 (0.1%)
White	209 (86.4%)	119 (81.5%)	140 (80.0%)	365 (88.6%)	833 (85.4%)
Multiracial*	1 (0.4%)	0	2 (1.1%)	2 (0.5%)	5 (0.5%)
Not Available	5 (2.1%)	3 (2.1%)	5 (2.9%)	5 (1.2%)	18 (1.8%)
Weight (kg)					
Mean (SD)	84.9 (23.9)	81.2 (20.2)	83.4 (22.4)	82.1 (20.9)	82.9 (21.8)
Range	46 - 188	50 - 134	35 - 153	43 - 172	35 - 188
Weight category					
<80 kg	116 (47.9%)	77 (52.7%)	85 (48.6%)	214 (51.9%)	492 (50.5%)
≥80 kg	126 (52.1%)	69 (47.3%)	90 (51.4%)	198 (48.1%)	483 (49.5%)
BMI					
Mean (SD)	29.9 (8.0)	29.5 (7.1)	30.1 (7.5)	29.3 (6.9)	29.6 (7.3)
Range	18 - 69	18 - 50	16 - 54	18 - 67	16 – 69
Tobacco Use History					
Never	146 (60.3%)	92 (63.0%)	115 (65.7%)	247 (60.0%)	600 (61.5%)
Current	38 (15.7%)	21 (14.4%)	34 (19.4%)	70 (17.0%)	163 (16.7%)
Previous	58 (24.0%)	33 (22.6%)	26 (14.9%)	95 (23.1%)	212 (21.7%)

* Multiracial includes patients for whom more than one race was indicated.

The patient populations of the Phase III studies are representative of the CSU target population. For baseline disease characteristics see table 1-7. At baseline, all but 5 patients were being treated with concomitant medications for CSU, and all but 8 patients were being treated with H1 antihistamines for CSU. Concomitant medication use at baseline was generally similar across all four treatment groups.

Table 20 - Baseline Disease Characteristics for Studies Q4881g, Q4882g, and Q4883g Pooled (Core safety analysis set)

		Omalizumab			
	Placebo (N=242)	75mg (N=146)	150mg (N=175)	300mg (N=412)	All Patients (N=975)
Duration of CIU (years)	n=238	n=144	n=171	n=403	n=956
Mean (SD)	7.7 (10.5)	5.9 (8.0)	7.5 (9.4)	6.7 (8.3)	6.9 (9.1)
Median	3.8	2.9	4.2	3.3	3.6
Range	0.5 - 66.4	0.5 - 49.9	0.5 - 50.5	0.5 - 50.3	0.5 - 66.4
Duration of CIU	n=238	n=144	n=171	n=403	n=956
≤1 year	43 (18.1%)	34 (23.6%)	26 (15.2%)	82 (20.3%)	185 (19.4%)
>1 - <2 years	38 (16.0%)	21 (14.6%)	25 (14.6%)	59 (14.6%)	143 (15.0%)
2-10 years	100 (42.0%)	67 (46.5%)	80 (46.8%)	174 (43.2%)	421 (44.0%)
>10 years	57 (23.9%)	22 (15.3%)	40 (23.4%)	88 (21.8%)	207 (21.7%)
Previous Number of CIU medications					
Mean (SD)	5.3 (3.0)	4.4 (2.5)	4.5 (3.1)	5.3 (2.6)	5.0 (2.8)
Median	5.0	4.0	4.0	5.0	4.0
Range	1 - 15	1 - 13	1 - 18	1 - 15	1 - 18
Previous Number of CIU medications					
≤2	45 (18.6%)	34 (23.3%)	48 (27.4%)	59 (14.3%)	186 (19.1%)
3-5	97 (40.1%)	72 (49.3%)	76 (43.4%)	166 (40.3%)	411 (42.2%)
>5	100 (41.3%)	40 (27.4%)	51 (29.1%)	187 (45.4%)	378 (38.8%)
Use of CIU therapies at baseline (Study Day 1)					
H1 antihistamines only	147 (60.7%)	135 (92.5%)	163 (93.1%)	155 (37.6%)	600 (61.5%)
H1 antihistamines + H2 antagonists only	52 (21.5%)	9 (6.2%)	2 (1.1%)	151 (36.7%)	214 (21.9%)
H1 antihistamines + H2 antagonists + LTRAs only	25 (10.3%)	(0.0%)	1 (0.6%)	64 (15.5%)	90 (9.2%)
H1 antihistamines + LTRAs only	16 (6.6%)	1 (0.7%)	7 (4.0%)	37 (9.0%)	61 (6.3%)
Other medication combinations	2 (0.8%)	1 (0.7%)	2 (1.1%)	5 (1.2%)	10 (1.0%)
Previous use of systemic steroids					
Yes	112 (46.3%)	74 (50.7%)	73 (41.7%)	187 (45.4%)	446 (45.7%)
No	130 (53.7%)	72 (49.3%)	102 (58.3%)	225 (54.6%)	529 (54.3%)
In-Clinic UAS^					
Mean (SD)	5.3 (0.7)	5.3 (0.8)	5.3 (0.7)	5.2 (0.8)	5.3 (0.8)
Median	5.0	6.0	5.0	5.0	5.0
Range	4 - 6	2 - 6	4 - 6	4 - 6	2 – 6
UAS7*					
Mean (SD)	30.8 (6.6)	31.4 (6.7)	30.7 (7.1)	30.9 (6.5)	30.9 (6.7)
Median	31.3	32.0	31.0	31.5	31.5
Range	16.0 - 42.0	16.5 - 42.0	16.0 - 42.0	16.0 - 42.0	16.0 - 42.0
Weekly itch severity score*					
Mean (SD)	14.1 (3.5)	14.3 (3.7)	14.1 (3.9)	14.0 (3.5)	14.1 (3.6)
Median	14.0	14.0	13.5	13.5	14.0
Range	7.5 - 21.0	8.0 - 21.0	8.0 - 21.0	8.0 - 21.0	7.5 - 21.0
<13	93 (38.4%)	55 (37.7%)	69 (39.4%)	163 (39.6%)	380 (39.0%)

	Placebo (N=242)	Omalizumab 75mg (N=146)	Omalizumab 150mg (N=175)	Omalizumab 300mg (N=412)	All Patients (N=975)
≥13	149 (61.6%)	91 (62.3%)	106 (60.6%)	249 (60.4%)	595 (61.0%)
Weekly number of hives score*					
Mean (SD)	16.7 (4.4)	17.1 (4.2)	16.6 (4.4)	16.9 (4.2)	16.8 (4.3)
Median	18.0	18.8	17.5	18.5	18.5
Range	5.0 - 21.0	7.5 - 21.0	4.5 - 21.0	5.0 - 21.0	4.5 - 21.0
Presence of angioedema*					
Yes	115 (47.5%)	59 (40.4%)	83 (47.4%)	203 (49.3%)	460 (47.2%)
No	127 (52.5%)	87 (59.6%)	92 (52.6%)	209 (50.7%)	515 (52.8%)
Positive CU index test	n=242	n=146	n=174	n=409	n=971
Yes	75 (31.0%)	38 (26.0%)	49 (28.2%)	115 (28.1%)	277 (28.5%)
No	167 (69.0%)	108 (74.0%)	125 (71.8%)	294 (71.9%)	694 (71.5%)
Level of thyroperoxidase antibody	n=237	n=143	n=175	n=405	n=960
High (>34.99 U/mL)	37 (15.6%)	30 (21.0%)	30 (17.1%)	58 (14.3%)	155 (16.1%)
Normal (≤34.99 U/mL)	200 (84.4%)	113 (79.0%)	145 (82.9%)	347 (85.7%)	805 (83.9%)
Total IgE level (IU/mL)	n=236	n=143	n=165	n=396	n=940
Mean (SD)	162.9 (229.5)	187.3 (293.0)	175.2 (439.3)	164.8 (289.5)	169.6 (308.5)
Median	80.0	88.0	72.0	79.0	79.0
Range	1 - 1230	1 - 2030	1 - 5000	1 - 3050	1 - 5000
Tablets/Week Diphenhydramine (25mg)*					
Mean (SD)	7.5 (7.8)	7.3 (8.3)	7.9 (8.9)	7.6 (8.7)	7.6 (8.4)
Median	6.0	5.0	6.0	5.0	6.0
Range	0.0 - 42.0	0.0 - 54.0	0.0 - 57.0	0.0 - 60.0	0.0 - 60.0

^Baseline in-clinic UAS is a physician's estimate of disease activity and is defined as the largest value among the Day -14 screening visit, Day -7 screening visit and Day 1 Visit.
* Baseline weekly scores are calculated using eDiary data from the 7 days prior to the first treatment date.

An overview of the participation and withdrawals in the Core safety analysis set, which contains all patients from the three Phase III studies, is shown for each of the treatment groups in Table 21.

Table 21 – Patient disposition (Core safety analysis set)

Disposition/Reason	Placebo N=242 n (%)	Omalizumab dose 75 mg N=146 n (%)	150 mg N=175 n (%)	300 mg N=412 n (%)
Received at least one dose of study drug*	242 (100%)	146 (100%)	175 (100%)	412 (100%)
Completed study drug treatment	200 (82.6)	128 (87.7)	154 (88.0)	371 (90.0)
Study drug treatment withdrawn	42 (17.4)	18 (12.3)	21 (12.0)	41 (10.0)
Adverse event	13 (5.4)	5 (3.4)	6 (3.4)	15 (3.6)
Lost to follow-up	2 (0.8)	0	1 (0.6)	0
Physician decision to discontinue treatment	0	3 (2.1)	3 (1.7)	4 (1.0)
Subject/legal guardian decision to discontinue treatment	7 (2.9)	4 (2.7)	5 (2.9)	9 (2.2)
Disease Progression	20 (8.3)	6 (4.1)	6 (3.4)	13 (3.2)
Completed study	205 (84.7)	127 (87.0)	150 (85.7)	360 (87.4)
Discontinued from study	37 (15.3)	19 (13.0)	25 (14.3)	52 (12.6)
Adverse event	4 (1.7)	0	3 (1.7)	5 (1.2)
Lost to follow-up	2 (0.8)	2 (1.4)	2 (1.1)	5 (1.2)
Physician decision to withdraw subject from study	(0.0)	1 (0.7)	1 (0.6)	2 (0.5)
Subject/legal guardian decision to withdraw	13 (5.4)	10 (6.8)	10 (5.7)	18 (4.4)
Disease progression	18 (7.4)	6 (4.1)	9 (5.1)	22 (5.3)

A total of 11 (1.1%) patients had AEs leading to withdrawal from the study including 4 (1.7%) in the placebo group, none in the omalizumab 75 mg group, 3 (1.7%) in the omalizumab 150 mg group, and 4 (1.0%) in the omalizumab 300 mg group.

Adverse events

The Core safety analysis set is the primary safety population used for safety presentations in the clinical overview, the studies having similar inclusion and exclusion criteria, treatment frequency, study assessments, and safety endpoints,. They differed only in terms of treatment duration (previous table 18 and 22 below) and in allowed doses of co-medication with antihistamines for CSU.

Table 22 – Duration of exposure (weeks) to omalizumab after randomization in Studies Q4881g, Q4882g, and Q4883g Pooled (Core safety analysis set)

Exposure statistic		Omalizumab dose		
	Placebo	75 mg	150 mg	300 mg
Total patients exposed*	242	146	175	412
Duration (weeks)				
Mean (SD)	17.6 (6.9)	16.3 (6.7)	16.7 (6.4)	20.3 (6.0)
Median	23.0	12.0	12.0	24.0
Exposure categories (mutually exclusive)				
1 to 12 weeks	106 (43.8%)	82 (56.2%)	92 (52.6%)	107 (26.0%)
13 to >24 weeks	136 (56.2%)	64 (43.8%)	83 (47.4%)	305 (74.0%)

*Includes all treatment groups from studies Q4881g, Q4882g, and Q4883g. In this presentation exposure is over the whole active treatment period in each study (12 or 24 weeks to completion).

Table 23 – Treatment emergent adverse event incidence during the treatment period (Day 1 to Week 12) overall and by system organ class (Core safety analysis set)

		Omalizumab dose		
	Placebo	75 mg	150 mg	300 mg
No. (%) of patients studied*	242	146	175	412
No. (%) of patients with AE(s)	103 (42.6%)	62 (42.5%)	96 (54.9%)	210 (51.0%)
System organ class	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	0	0	2 (1.1)	3 (0.7)
Cardiac disorders	2 (0.8)	1 (0.7)	1 (0.6)	2 (0.5)
Congenital, familial and genetic disorders	0	0	1 (0.6)	0
Ear and labyrinth disorders	2 (0.8)	0	2 (1.1)	3 (0.7)
Endocrine disorders	1 (0.4)	0	0	1 (0.2)
Eye disorders	3 (1.2)	1 (0.7)	4 (2.3)	7 (1.7)
Gastrointestinal disorders	22 (9.1)	9 (6.2)	12 (6.9)	42 (10.2)
Gen. disorders & administration site conditions	8 (3.3)	9 (6.2)	9 (5.1)	32 (7.8)
Hepatobiliary disorders	0	0	0	2 (0.5)
Immune system disorders	2 (0.8)	1 (0.7)	1 (0.6)	2 (0.5)
Infections and infestations	44 (18.2)	28 (19.2)	41 (23.4)	96 (23.3)
Injury, poisoning and procedural complications	8 (3.3)	2 (1.4)	2 (1.1)	17 (4.1)
Investigations	1 (0.4)	2 (1.4)	1 (0.6)	5 (1.2)
Metabolism and nutrition disorders	3 (1.2)	1 (0.7)	2 (1.1)	3 (0.7)
Musculoskeletal & connective tissue disorders	10 (4.1)	9 (6.2)	17 (9.7)	26 (6.3)
Neoplasms benign, malignant and unspecified	1 (0.4)	2 (1.4)	2 (1.1)	2 (0.5)
Nervous system disorders	14 (5.8)	10 (6.8)	27 (15.4)	43 (10.4)
Psychiatric disorders	4 (1.7)	0	3 (1.7)	10 (2.4)
Renal and urinary disorders	1 (0.4)	0	1 (0.6)	2 (0.5)
Reproductive system and breast disorders	8 (3.3)	1 (0.7)	1 (0.6)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	11 (4.5)	7 (4.8)	9 (5.1)	29 (7.0)
Skin and subcutaneous tissue disorders	23 (9.5)	14 (9.6)	12 (6.9)	45 (10.9)
Surgical and medical procedures	1 (0.4)	0	1 (0.6)	3 (0.7)
Vascular disorders	2 (0.8)	0	3 (1.7)	5 (1.2)

*Includes all treatment groups from studies Q4881g, Q4882g, and Q4883g

The proportions of patients with at least one AE were similar in the omalizumab 150 mg and 300 mg groups (54.9% and 52 % respectively) but higher than those in the placebo and omalizumab 75 mg groups (42.6 % and 42.5 % respectively). The majority of AEs reported in all safety analysis sets were categorized by the investigators as mild or moderate in severity.

The summary table of system organ class classified events for the extended safety analysis set (Day 1 to Week 24) is presented in Table 3.1 below.

Table 3-1 **Treatment emergent adverse event incidence during the treatment period (Day 1 to Week 24) overall and by system organ class (Extended safety analysis set)**

		Omalizumab dose		
	Placebo	75 mg	150 mg	300 mg
No. (%) of patients studied*	163	70	87	333
No. (%) of patients with AE(s)	94 (57.7)	41 (58.6)	60 (69.0)	210 (63.1)
System organ class				
Blood and lymphatic system disorders	2 (1.2%)	0	1 (1.1%)	4 (1.2%)
Cardiac disorders	2 (1.2%)	0	2 (2.3%)	3 (0.9%)
Congenital, familial and genetic disorders	0	1 (1.4%)	1 (1.1%)	0
Ear and labyrinth disorders	5 (3.1%)	0	1 (1.1%)	5 (1.5%)
Endocrine disorders	0	0	1 (1.1%)	1 (0.3%)
Eye disorders	1 (0.6%)	0	2 (2.3%)	10 (3.0%)
Gastrointestinal disorders	18 (11.0%)	7 (10.0%)	5 (5.7%)	45 (13.5%)
Gen. disorders & administration site conditions	10 (6.1%)	3 (4.3%)	7 (8.0%)	37 (11.1%)
Hepatobiliary disorders	1 (0.6%)	0	0	3 (0.9%)
Immune system disorders	2 (1.2%)	2 (2.9%)	1 (1.1%)	2 (0.6%)
Infections and infestations	47 (28.8%)	20 (28.6%)	32 (36.8%)	109 (32.7%)
Injury, poisoning and procedural complications	9 (5.5%)	2 (2.9%)	0	25 (7.5%)
Investigations	4 (2.5%)	1 (1.4%)	1 (1.1%)	7 (2.1%)
Metabolism and nutrition disorders	3 (1.8%)	0	2 (2.3%)	2 (0.6%)
Musculoskeletal & connective tissue disorders	8 (4.9%)	7 (10.0%)	12 (13.8%)	33 (9.9%)
Neoplasms benign, malignant and unspecified	2 (1.2%)	3 (4.3%)	0	4 (1.2%)
Nervous system disorders	14 (8.6%)	7 (10.0%)	14 (16.1%)	47 (14.1%)
Psychiatric disorders	4 (2.5%)	1 (1.4%)	5 (5.7%)	13 (3.9%)
Renal and urinary disorders	2 (1.2%)	0	1 (1.1%)	2 (0.6%)
Reproductive system and breast disorders	6 (3.7%)	1 (1.4%)	2 (2.3%)	4 (1.2%)
Respiratory, thoracic and mediastinal disorders	19 (11.7%)	5 (7.1%)	12 (13.8%)	39 (11.7%)
Skin and subcutaneous tissue disorders	25 (15.3%)	13 (18.6%)	10 (11.5%)	51 (15.3%)
Surgical and medical procedures	1 (0.6%)	2 (2.9%)	1 (1.1%)	2 (0.6%)
Vascular disorders	4 (2.5%)	0	1 (1.1%)	6 (1.8%)

*Includes all treatment groups from studies Q4881g, and Q4883g
Includes AEs reported during the 24-week treatment period
Source: [SCS-Appendix 1-Table 8.3]

The summary table of SAEs in the extended safety analysis set (Day 1 to Week 24) is presented in Table 3-2 below.

Table 3-2 Patients With Treatment-Emergent SAEs Occurring During the Treatment Period Day 1 to Week 24 – (Extended safety analysis set)

MedDRA System Organ Class Preferred Term	Placebo (n=163)	Omalizumab 75 mg (n=70)	Omalizumab 150 mg (n=87)	Omalizumab 300 mg (n=333)
Any serious adverse event	7 (4.3)	2 (2.9)	3 (3.4)	7 (2.1)
Cardiac disorders	1 (1.6)	0	1 (1.1)	0
Angina unstable	1 (1.6)	0	1 (1.1)	0
Gastrointestinal disorders	0	1 (1.4)	0	0
Gastrooesophageal reflux disease	0	1 (1.4)	0	0
Hepatobiliary disorders	0	0	0	1 (0.2)
Cholelithiasis	0	0	0	1 (0.2)
Immune system disorders	1 (0.6)	0	0	0
Hypersensitivity	1 (0.6)	0	0	0
Infections and infestations	0	0	1 (1.1)	5 (1.5)
Appendicitis	0	0	1 (1.1)	0
Gastroenteritis	0	0	0	1 (0.3)
Retroperitoneal infection	0	0	0	1 (0.3)
Pelvic abscess	0	0	0	1 (0.3)
Lower respiratory tract infection	0	0	0	1 (0.3)
Gastroenteritis viral	0	0	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.6)	0	0	0
Radius fracture	1 (0.6)	0	0	0
Metabolism and nutrition disorders	2 (1.2)	0	0	0
Type 2 diabetes mellitus	1 (0.6)	0	0	0
Hyperglycemia	1 (0.6)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (1.1)	0
Pain in extremity	0	0	1 (1.1)	0
Reproductive system and breast disorders	1 (0.6)	0	0	0
Cervical dysplasia[a]	1 (0.6)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.6)	0	0	0
Chronic obstructive pulmonary disease	1 (0.6)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (1.4)	0	1 (0.3)
Angioedema	0	0	0	1 (0.3)
Urticaria	0	1 (1.4)	0	0
Vascular disorders	0	0	1 (1.1)	1 (0.3)
Intermittent claudication	0	0	0	1 (0.3)
Hypertension	0	0	1 (1.1)	0

[a]Cervical dysplasia event experienced by [Study Q4882g-Patient 13004] (placebo group) was found to be a cervical adenocarcinoma in situ post database lock.
Multiple occurrences of a specific adverse event for a patient were counted once in the frequency for the adverse event. Similarly, multiple occurrences of adverse events within a specific system organ class for a patient were counted once in the frequency for the system organ class.
Includes treatment-emergent adverse events that started on or after the first treatment date.
Source: [SCS-Appendix 1-Table 10.3]

The table 24 below provides the most common adverse events (≥1%) by preferred term.

Table 24 – Treatment emergent event occurring during the treatment period (Day 1 to Week 12) with incidence >=1% in any treatment group (Core safety analysis set)

MedDRA System Organ Class Preferred Term	Placebo N=242 n (%)	Omalizumab dose 75 mg N=146 n (%)	 150 mg N=175 n (%)	 300 mg N=412 n (%)
Ear and labyrinth disorders				
Vertigo	2 (0.8)	0	2 (1.1)	1 (0.2)
Gastrointestinal disorders				
Diarrhoea	7 (2.9)	3 (2.1)	2 (1.1)	12 (2.9)
Nausea	6 (2.5)	2 (1.4)	2 (1.1)	12 (2.9)
Abdominal pain upper	2 (0.8)	1 (0.7)	2 (1.1)	2 (0.5)
Constipation	3 (1.2)	1 (0.7)	0	2 (0.5)
Flatulence	0	0	2 (1.1)	2 (0.5)
Toothache	1 (0.4)	2 (1.4)	2 (1.1)	2 (0.5)
Abdominal pain	4 (1.7)	1 (0.7)	3 (1.7)	1 (0.2)
Gen. disorders and admin. site conditions				
Fatigue	3 (1.2)	2 (1.4)	0	8 (1.9)
Oedema peripheral	1 (0.4)	3 (2.1)	3 (1.7)	4 (1.0)
Influenza like illness	0	2 (1.4)	2 (1.1)	1 (0.2)
Injection site swelling	0	0	0	4 (1.0)
Infections and infestations				
Nasopharyngitis	17 (7.0)	10 (6.8)	16 (9.1)	27 (6.6)
Sinusitis	5 (2.1)	4 (2.7)	2 (1.1)	20 (4.9)
Upper respiratory tract infection	5 (2.1)	3 (2.1)	3 (1.7)	14 (3.4)
Bronchitis	5 (2.1)	4 (2.7)	1 (0.6)	7 (1.7)
Urinary tract infection	1 (0.4)	3 (2.1)	3 (1.7)	7 (1.7)
Fungal infection	1 (0.4)	0	3 (1.7)	3 (0.7)
Influenza	3 (1.2)	1 (0.7)	1 (0.6)	2 (0.5)
Viral upper respiratory tract infection	0	1 (0.7)	4 (2.3)	2 (0.5)
Pharyngitis	0	2 (1.4)	2 (1.1)	1 (0.2)
Rhinitis	1 (0.4)	2 (1.4)	1 (0.6)	1 (0.2)
Injury, poisoning and procedural complications				
Ligament sprain	3 (1.2)	0	0	3 (0.7)
Fall	1 (0.4)	0	0	4 (1.0)
Musculoskeletal and conn. tissue disorders				
Arthralgia	1 (0.4)	1 (0.7)	5 (2.9)	12 (2.9)
Pain in extremity	1 (0.4)	1 (0.7)	3 (1.7)	4 (1.0)
Myalgia	1 (0.4)	3 (2.1)	1 (0.6)	3 (0.7)
Muscle spasms	1 (0.4)	2 (1.4)	0	3 (0.7)
Back pain	3 (1.2)	0	2 (1.1)	2 (0.5)
Joint swelling	1 (0.4)	2 (1.4)	0	2 (0.5)
Bursitis	0	0	2 (1.1)	0
Musculoskeletal pain	1 (0.4)	1 (0.7)	3 (1.7)	0
Nervous system disorders				
Headache	7 (2.9)	4 (2.7)	22 (12.6)	26 (6.3)
Dizziness	3 (1.2)	2 (1.4)	0	4 (1.0)

MedDRA System Organ Class Preferred Term	Placebo N=242 n (%)	75 mg N=146 n (%)	150 mg N=175 n (%)	300 mg N=412 n (%)
Migraine	3 (1.2)	1 (0.7)	1 (0.6)	4 (1.0)
Presyncope	0	0	2 (1.1)	3 (0.7)
Psychiatric disorders				
Anxiety	0	0	1 (0.6)	1 (0.4)
Reproductive system and breast disorders				
Dysmenorrhoea	4 (1.7)	0	0	0
Resp., thoracic and mediastinal disorders				
Cough	3 (1.2)	5 (3.4)	2 (1.1)	10 (2.4)
Asthma	1 (0.4)	0	1 (0.6)	5 (1.2)
Nasal congestion	2 (0.8)	1 (0.7)	2 (1.1)	3 (0.7)
Oropharyngeal pain	4 (1.7)	0	3 (1.7)	2 (0.5)
Skin and subcutaneous tissue disorders				
Idiopathic urticaria	6 (2.5)	6 (4.1)	1 (0.6)	9 (2.2)
Urticaria	6 (2.5)	2 (1.4)	3 (1.7)	7 (1.7)
Angioedema	5 (2.1)	2 (1.4)	0	6 (1.5)
Eczema	2 (0.8)	0	2 (1.1)	4 (1.0)
Pruritus	1 (0.4)	2 (1.4)	1 (0.6)	2 (0.5)
Alopecia	2 (0.8)	1 (0.7)	1 (0.6)	6 (1.5)
Dry skin	0	0	2 (1.1)	0
Vascular disorders				
Hypertension	1 (0.4)	0	2 (1.1)	2 (0.5)

Multiple occurrences of a specific AE for a patient were counted once in the frequency for the adverse event. Events are ordered by alphabetical SOC, then by descending percentage occurrence in the 300 mg group

Overall, the three most frequent AEs were nasopharyngitis, headache, and sinusitis. Other frequently reported AEs in were upper respiratory tract infection, cough, and idiopathic urticaria.

The MAH also provided the treatment-emergent AEs occurring during the treatment period (Day 1 to Week24) in the Week 24 pooled data (Studies Q4881g and Q4883g pooled) in the Extended safety analysis set (all patients=653).

The percentage of patients reporting events in the Day 1 to Week 24 was higher, as would be expected from a doubling of exposure duration; however, no marked difference was apparent in the pattern of reporting (distribution across treatment groups) or type of event reported. The profile of most common AEs was broadly similar to that in the 12-week pooled data, with nasopharyngitis being the most common AE in each treatment group other than the 75 mg omalizumab group (where the most common AEs, all occurring in 7.1% of patients, were sinusitis, urticaria and idiopathic urticaria). The SOCs in which AEs were most frequently reported were Infections and infestations (31.9% of patients across all treatment groups), Skin and subcutaneous tissue disorders (15.2%), Nervous system disorders (12.6%), Gastrointestinal disorders (11.5%) and Respiratory, thoracic, and mediastinal disorders (11.5%). Nasopharyngitis was the only AE to occur in more than 10% of patients in any treatment group: 10.4% in the placebo group, 4.3% in the 75 mg omalizumab group, 12.6% in the omalizumab 150 mg group and 9.3% in the 300 mg group. Other frequent AEs included sinusitis, headache, and upper respiratory tract infection.

None of the most common AEs showed a clear dose relationship, although headache was more common in the two highest dose groups (150 mg: 9.2%, 300 mg: 8.1%, 75 mg 5.7% and placebo 3.1%) as was arthralgia (150 mg: 5.7%, 300 mg: 3.0%, 75 mg 1.4% and placebo 1.2%).

Several AEs were more frequent in the 150 mg omalizumab group than the other groups, as reflected in the higher total incidence of AEs in this group. These were, in addition to arthralgia and headache as noted above, oropharyngeal pain (5.7%, with rates of 1.8% to 4.3% in other groups), urinary tract infection (4.6%, other groups 1.4% to 2.4%), pain in extremity (3.4%, other groups zero to 1.4%),

fungal infection (3.4%, other groups zero to 0.6%), pyrexia (3.4%, other groups 0.9% to 1.4%), and migraine (3.4%, other groups zero to 1.8%)

Overall, the three most frequent AEs in the Core safety and Extended safety analysis sets were nasopharyngitis, headache, and sinusitis. Other frequently reported AEs in both analysis sets were upper respiratory tract infection, cough, and idiopathic urticaria. Most of these events were reported at similar rates across treatment groups, with the exception of headache, which was reported more frequently relative to placebo in the omalizumab 150 mg and 300 mg dose groups. Nasopharyngitis, sinusitis, upper respiratory tract infection, arthralgia, and pain in extremity were seen slightly more frequently in one or more omalizumab groups relative to placebo, while idiopathic urticaria was reported at slightly higher rate in the lower dose (75 mg dose omalizumab group), and urticaria was seen least frequently in the 300 mg group over the longer 24-week treatment period.

AEs reported during follow-up

The Phase III studies incorporated a 16-week follow-up period into their design. This period was assessed separately (Core safety analysis set and Core safety analysis set by co-medications) for the incidence of all AEs, for AEs by severity, and for SAEs.

The overall incidence of AEs during follow-up was similar between placebo (43.0%) and omalizumab 75 mg (42.5%), and higher in the 150 mg and 300 mg omalizumab groups (49.7% and 50.0% respectively. In the omalizumab groups, the AE profile was broadly similar to that seen in placebo. Most SOCs showed a similar percentage of patients reporting events; however, one or more of the omalizumab groups did show an imbalance compared to placebo for two SOCs. Imbalances were seen in Infections and infestations: placebo (19.4%) vs. omalizumab 150 mg (26.3%) and 300 mg (22.1%); Skin and subcutaneous tissue disorders: placebo (9.1%) vs. omalizumab 75 mg (15.8%), 150 mg (12.6%) and 300 mg (17.7%). The difference in skin and subcutaneous events seem likely to be due to the re-emergence of symptoms that were controlled under active treatment.

To further assess the possibility of rebound in the pooled Phase III studies, adverse events which occurred during the follow-up period of the studies were evaluated to identify CSU related SAEs or severe AEs that occurred after discontinuation of study medication. In addition, changes from baseline in itch severity score, UAS7 and weekly number of hives score were also evaluated during the follow-up period to identify patients who reported weekly scores which were ≥125% or ≥150% of their baseline score at any time after their last dose of study medication. These analyses were all performed on the Core safety analysis set.

Overall, and in combination with summary statistics of efficacy parameters over time during the follow-up period, the results of these analyses did not suggest significant rebound effects after the discontinuation of treatment. In general, the treatment differences between omalizumab and placebo for potential rebound events were relatively small and did not increase with increasing dose.

The events noted above as being higher or slightly higher with omalizumab than with placebo were among a number of events identified in a pooled analysis to identify candidates as potential adverse reactions (ARs) in the CSU program. Events suspected to be drug-related for which there is some medical basis to suspect a causal relationship between the drug and the event occurring during the treatment were identified primarily on the basis of the safety experience in the 975 patients with CSU in the three Phase III studies. The pooled Phase III safety population was organized into two analysis sets, according to the length of treatment period (Day 1 to Week 12 and Day 1 to Week 24). AE data pertaining to these two doses of 150 mg and 300 mg respectively were taken into consideration for the purpose of identifying ARs.

The selection of potential AR candidates from all reported AEs in the above mentioned studies was based on the following approach:

• All AEs occurring during the treatment period with an incidence of ≥1% in any treatment group in studies Q4881g, Q4882g and Q4883g were reviewed.

• Among the AEs identified above, those occurring at a ≥ 2% higher rate in either of the 150 mg or 300 mg omalizumab groups than in the placebo group were generally considered ARs, unless the medical analysis provided sufficient evidence for confounding, thereby not justifying a classification as ARs.

Events identified as AR candidates are shown for the Day 1 to Week 12 treatment period in Tables 25 and 26.

Table 25 – Adverse Reaction (AR) candidates occurring during Day 1 to Week 12 with incidence >=1% in any treatment group and >=2% higher than placebo in any Omalizumab Group (Core safety analysis set)

		Omalizumab dose	
MedDRA System Organ Class Preferred Term	Placebo N=242 n (%)	150 mg N=175 n (%)	300 mg N=412 n (%)
Infections and infestations			
Nasopharyngitis	17 (7.0)	16 (9.1)	27 (6.6)
Sinusitis	5 (2.1)	2 (1.1)	20 (4.9)
Viral upper respiratory tract infection	0	4 (2.3)	2 (0.5)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.4)	5 (2.9)	12 (2.9)
Nervous system disorders			
Headache	7 (2.9)	22 (12.6)	26 (6.3)

Multiple occurrences of a specific adverse event for a patient were counted once in the frequency for the adverse event. Includes treatment–emergent adverse events that started on or after the first treatment date.

Table 26 – Adverse Reaction (AR) candidates occurring during Day 1 to Week 24 with incidence >=1% in any treatment group and >=2% higher than placebo in any Omalizumab Group (Extended safety analysis set)

		Omalizumab dose	
MedDRA System Organ Class Preferred Term	Placebo N=163 n (%)	150 mg N=87 n (%)	300 mg N=333 n (%)
Gastrointestinal disorders			
Toothache	0	2 (2.3)	3 (0.9)
General disorders & administration site conditions			
Pyrexia	2 (1.2)	3 (3.4)	3 (0.9)
Infections and infestations			
Nasopharyngitis	17 (10.4)	11 (12.6)	31 (9.3)
Upper respiratory tract infection	5 (3.1)	3 (3.4)	19 (5.7)
Urinary tract infection	3 (1.8)	4 (4.6)	8 (2.4)
Fungal infection	1 (0.6)	3 (3.4)	2 (0.6)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (1.2)	5 (5.7)	10 (3.0)
Pain in extremity	0	3 (3.4)	3 (0.9)
Musculoskeletal pain	0	2 (2.3)	3 (0.9)
Myalgia	0	2 (2.3)	3 (0.9)
Nervous system disorders			
Headache	5 (3.1)	8 (9.2)	27 (8.1)
Sinus headache	0	2 (2.3)	1 (0.3)
Psychiatric disorders			
Anxiety	0	2 (2.3)	3 (0.9)

Multiple occurrences of a specific adverse event for a patient were counted once in the frequency for the adverse event. Includes treatment–emergent adverse events that started on or after the first treatment date.

Table 27 – Adverse reactions in pooled CSU safety database

Following a medical evaluation by the MAH toothache, fungal infection, and anxiety were excluded from being identified as ARs. The remaining reaction candidates were considered ARs.

Based on the above discussion, Table 2-5 was prepared, which represents the confirmed ADRs to be included in the CDS. Adverse reactions are ranked according to their frequency, the most frequent first, using the following convention: Very common (≥10%); common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000), including isolated reports.

	Omalizumab Studies Q4881g, Q4882g and Q4883g Pooled			
Adverse reactions (by MedDRA preferred term)	Placebo N=242	150 mg N=175	300 mg N=412	Frequency category
Infections and infestations				
Nasopharyngitis	17 (7.0%)	16 (9.1%)	27 (6.6%)	Common
Sinusitis	5 (2.1%)	2 (1.1%)	20 (4.9%)	Common
Viral upper respiratory tract infection	0	4 (2.3%)	2 (0.5%)	Common
Nervous system disorders				
Headache	7 (2.9%)	22 (12.6%)	26 (6.3%)	Very common
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.4%)	5 (2.9%)	12 (2.9%)	Common

Additional events reported anytime during the 1-24 week treatment period (studies Q4881g and Q4883g) that met the definition of adverse reactions (events occurring in ≥1% of patients in any treatment group and ≥ 2% more frequently in any omalizumab treatment group than in the placebo group) are listed below:

• Infections and infestations: upper respiratory tract infections (placebo 3.1%, 150 mg 3.4%, 300 mg 5.7%), urinary tract infection (placebo 1.8%, 150 mg 4.6%, 300 mg 2.4%)

• Musculoskeletal and connective tissue disorders: myalgia (placebo 0%, 150 mg 2.3%, 300 mg 0.9%), pain in extremity (placebo 0%, 150 mg 3.4%, 300 mg 0.9%), musculoskeletal pain (placebo 0%, 150 mg 2.3%, 300 mg 0.9%)

• General disorders and administration site conditions: pyrexia (placebo 1.2%, 150 mg 3.4%, 300 mg 0.9%)

• Nervous system disorders: sinus headache (placebo 0%, 150 mg 2.3%, 300 mg 0.3%)

Injection site reactions identified from search results were reported in the omalizumab 300 mg group, where 11 (2.7%) patients reported an event; this compares to 1 (0.6%) patient in the 150mg group and 2 (0.8%) patients with placebo. The event did not meet the criterion of being ≥ 2% higher than placebo, but all cases were suspected to be related to study drug by the investigators. Therefore it was felt to be a notable reaction in the label.

Core safety analysis set by co-medications

To assess any impact of concomitant medications on the AE profile of omalizumab in CSU patients, AEs were summarized separately for Studies Q4881g and Q4882g pooled and Study Q4883g (Day 1 to Week 12), as the latter study included patients with a wider range of other medications used to treat CSU. When comparing these two outcomes, the proportion of patients experiencing at least one AE was higher for the omalizumab 300 mg group in Study Q4883g (56.7%) than for the corresponding group in the pooled Q4881g and Q4882g data (41.9%); the corresponding placebo groups showed similar proportions of patients with AEs (43.4% and 42.1%, respectively). The SOCs in which AEs were most commonly reported were similar. However, in most of these SOCs, the placebo group and the 300 mg group in Q4883g tended to have higher rates of AEs than the corresponding groups in the pooled Q4881g and Q4882g data. There were some differences between the two outcomes groups

considering the most frequent AE preferred terms that may be related to differences in concomitant medications at baseline. Such were i.e. diarrhea and nausea. Headache also showed a greater difference between 300 mg omalizumab and placebo in the Q4883g data. Among less frequent AEs, asthma showed a greater difference from placebo in Q4883g as did eczema.

Similar findings were detected of treatment-emergent AEs occurring during the extended treatment period (Day 1 to Week24) for Studies Q4881g and Q4883g separately. In Study Q4881g the rate of GI AEs was much lower (in the 300 mg groups 15.9% and 6.2% for studies Q4883g and Q4881g respectively). The rates of GI disorders in the placebo groups in both studies were similar to those for the 300 mg groups, and the difference between studies may reflect the difference between studies in background medications that may affect the GI system at a low level.

Serious adverse event / deaths / other significant events

No deaths were reported in the studies contributing to the safety evaluation of the applied new treatment indication.

Table 28 – Patients with deaths, other serious and other clinically significant AEs over whole study treatment period (Core safety analysis set)

		Omalizumab dose		
Type of adverse event within overall AE profile on treatment	Placebo N=242 n (%)	75 mg N=146 n (%)	150 mg N=175 n (%)	300 mg N=412 n (%)
Any AE on treatment	166 (68.6%)	100 (68.5%)	131 (74.9%)	320 (77.7%)
Death	0	0	0	0
Serious adverse event	12 (5.0%)	3 (2.1%)	6 (3.4%)	25 (6.1%)
Discontinued study due to an AE	4 (1.7%)	0	3 (1.7%)	4 (1.0%)
Withdrawn from treatment*				
Due to an AE	13 (5.4%)	5 (3.4%)	6 (3.4%)	14 (3.4%)
Due to a SAE	4 (1.7%)	0	1 (0.6%)	1 (0.2%)
AE Suspected due to study drug	18 (7.4%)	13 (8.9%)	17 (9.7%)	49 (11.9%)
SAEs Suspected due to study drug	0	0	0	0
Severe AE	28 (11.6%)	11 (7.5%)	13 (7.4%)	61 (14.8%)

*Patient not necessarily discontinued from study, may still continue off-treatment

Patients experiencing treatment-emergent SAEs within the Core safety data set (Day1-Week 12) are summarized in Table 29 below.

There were few SAEs during the treatment period: a total of 15 patients (1.5%) had at least one SAE. SAEs in total were more common in the placebo group than in any of the omalizumab treatment groups.

Table 29 – Patients with Treatment-Emergent SAEs Occurring During the treatment period Day 1 to Week 12 (Core safety analysis set)

MedDRA System Organ Class Preferred Term	Placebo (n=242)	Omalizumab 75 mg (n=146)	Omalizumab 150 mg (n=175)	Omalizumab 300 mg (n=412)
Any serious adverse event	8 (3.3)	1 (0.7)	1 (0.6)	5 (1.2)
Gastrointestinal disorders	1 (0.4)	0	0	1 (0.2)
Hemorrhoids	1 (0.4)	0	0	0
Melena[a]	0	0	0	1 (0.2)
Immune system disorders	1 (0.4)	0	0	0
Hypersensitivity	1 (0.4)	0	0	0
Infections and infestations	1 (0.4)	0	0	2 (0.5)
Retroperitoneal infection	0	0	0	1 (0.2)
Pelvic abscess	0	0	0	1 (0.2)
Pneumonia	1 (0.4)	0	0	0
Injury, poisoning and procedural complications	1 (0.4)	0	0	0
Radius fracture	1 (0.4)	0	0	0
Metabolism and nutrition disorders	2 (0.8)	0	0	0
Type 2 diabetes mellitus	1 (0.4)	0	0	0
Hyperglycemia	1 (0.4)	0	0	0
Reproductive system and breast disorders	1 (0.4)	0	0	0
Cervical dysplasia[b]	1 (0.4)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0	0	0
Chronic obstructive pulmonary disease	1 (0.4)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (0.7)	0	1 (0.2)
Angioedema	0	1 (0.7)	0	1 (0.2)
Surgical and medical procedures	0	0	0	1 (0.2)
Tonsillectomy	0	0	0	1 (0.2)
Vascular disorders	0	0	1 (0.6)	0
Hypertension	0	0	1 (0.6)	0

[a] Melena experienced by [Study Q4882g-Patient 25802] (omalizumab 300 mg group) was downgraded to a non-serious AE after database lock
[b] Cervical dysplasia event experienced by [Study Q4882g-Patient 13004] (placebo group) was found to be a cervical adenocarcinoma in situ post database lock.
Multiple occurrences of a specific adverse event for a patient were counted once in the frequency for the adverse event. Similarly, multiple occurrences of adverse events within a specific system organ class for a patient were counted once in the frequency for the system organ class.
Includes treatment-emergent adverse events that started on or after the first treatment date.

No SAE preferred term, other than angioedema, was reported in more than one patient. The SAEs were distributed across various SOCs and did not occur predominantly in one SOC. There was no particular pattern of occurrence of SAEs within or across the treatment groups. None of the SAEs was considered by the investigators to be related to study medication.

The SOC for which SAEs were reported most commonly was Infections and infestations, in which SAEs were reported for 3 patients:

• 1 patient in the placebo group [Study Q4882g] had an SAE of severe pneumonia, which required hospitalization but resolved in 4 days following treatment. The SAE was not suspected to be related to study medication, and the patient continued in the study

• 1 patient in the omalizumab 300 mg group [Study Q4883g-] had an SAE of severe retroperitoneal infection, reported as retroperitoneal granulomatous disease due to Mycobacterium tuberculosis. The patient had a remote history of tuberculosis. This SAE was treated with a combination of antibiotics, but led to discontinuation of the patient from the study, having received only 1 dose of study drug. The patient did not complete follow-up and the event was ongoing at the last visit. The SAE was not suspected to be related to study medication.

• 1 patient in the omalizumab 300 mg group [Study Q4883g-] had an SAE of pelvic abscess, which occurred 3 days after the last dose of study drug, following an elective hysterectomy. Following treatment, the event resolved within 10 days. The SAE was not suspected to be related to study medication.

Two patients had SAEs of angioedema in the omalizumab 75mg group and omalizumab 300 mg group respectively. The first patient (75 mg) had a medical history of severe angioedema prior to enrolment. The second patient (300 mg) developed severe angioedema of 2 days duration 30 days after last study drug administration. Both cases were considered to be life-threatening, resolved following treatment and both patients continued the study drug

It should be noted that there were 2 further patients ([Study Q4883g] in the placebo group and [Study Q4881g] in the omalizumab 150 mg group) who had SAEs of angioedema during the treatment period, but both of these patients took excluded medications between Day 1 and Week 12 and so AEs occurring on or after the start date of the excluded medication were summarised for the follow-up period.

The SAEs in this analysis set may therefore represent a range of intercurrent illnesses and elective surgery, and do not appear to be related to study treatment or (with the exception of the two angioedema SAEs) the indication studied.

Extended safety analysis set of SAEs (Day 1 to Week 24)

In the extended analysis (Day1-24Weeks) the proportion of patients experiencing at least one SAE was low, 19 patients (2.9%) and the proportion of patients experiencing an SAE was greater in the placebo group (7 patients, 4.3%) compared with the omalizumab 75 mg (2 patients, 2.9%), 150 mg, (3 patients, 3.4%) and 300 mg groups (7 patients, 2.1%). The SAEs reported were:

Placebo group: angina unstable, hypersensitivity*, radius fracture*, type 2 diabetes mellitus*, hyperglycaemia*, cervical dysplasia (subsequently discovered to be cervical adenocarcinoma)*, and chronic obstructive pulmonary disease*

Omalizumab 75 mg group: gastroesophageal reflux disease and urticaria

Omalizumab 150 mg group: angina unstable, appendicitis, pain in extremity, and hypertension*

Omalizumab 300 mg: cholelithiasis, gastroenteritis, retroperitoneal infection*, pelvic abscess*, lower respiratory tract infection, gastroenteritis viral, angioedema*, and intermittent claudication.

(Those events marked with an asterisk (*) were also present in the core safety analysis set (pooled Day 1 to Week 12 data))

None of these SAEs was suspected to be related to study medication by the investigators.

Safety analyses of SAEs by co-medications

Considering the placebo and 300 mg omalizumab treatment groups (Study Q4883g did not have 75 mg or 150 mg omalizumab treatment groups), SAEs occurred at very similar rates in the Core safety analysis set (Day 1 to Week 12) by co-medications when comparing the 300 mg groups in Study Q4883g (1.2%) and the Q4881g/Q4882g pooled data (1.3%).

In the Extended analyses (Day 1-Week 24) of reported SAEs of both studies (Q4881g vs. Q4883g) the placebo groups had higher rates of SAEs than the omalizumab 300 mg groups (Q4881g, placebo: 5.0%, omalizumab 300 mg: zero; Q4883g, placebo 3.6%, omalizumab 300 mg 2.8%).

Apart from SAES in the Infections and Infestations SOC being more common in the 300 mg group in Q4883g there were no other obvious patterns of difference between the two studies in SAE profile.

Concentration-safety relationship

Relationships between safety and omalizumab concentrations were examined graphically based on pooled data from the three Phase III studies Q4881g, Q4882g, and Q4883g. The safety endpoints evaluated included any treatment-emergent adverse event, serious adverse event or severe adverse event during the treatment period. The concentration measure used in this analysis was the observed omalizumab trough at Week 12 as the common PK measurement during the treatment phase across all Phase III studies.

There was no evidence for an increased rate of treatment-emergent adverse events, serious or severe adverse events during the treatment period in patients with higher concentrations of omalizumab over the dose range tested (75 to 300 mg every 4 weeks). However, it is stated in the updated RMP, version 9 with track changes, page 63, that a summary of AEs suspected by the investigators to be related to study drug for the core safety analysis set was assessed across all treatment groups. In this 8.0% of patients had at least one AE suspected to be treatment-related and that there was a possible dose relationship for the total incidence of suspected treatment-related AEs, with 5.8%, 7.5%, 8.6%, and 9.2% of patients in the placebo, omalizumab 75 mg, 150 mg, and 300 mg groups, respectively, having at least one such AE.

In addition no effect of body weight or baseline IgE concentration was observed on any treatment emergent, serious, or severe adverse event rates during the treatment period adverse event, although few serious or severe adverse events were observed.

Adverse events of special interest (AESIs)

A number of adverse events groupings were pre-specified for the safety analysis as being of special interest for omalizumab treatment based on previous clinical experience. Of these AESI, only hypersensitivity and injection site reactions demonstrated an imbalance (higher incidence in omalizumab) that could be clinically significant. Most of these events were of mild to moderate severity, not serious, and did not generally lead to discontinuation from the study.

As one of the most clinically important AESI, potential anaphylaxis events were screened and evaluated. In Phase III CSU program, no cases of anaphylaxis attributed to omalizumab were reported during the treatment period. Some of the adverse events, such as urticaria and angioedema, could be symptoms of the background CSU. However as some of these disease features can also be components of potential anaphylaxis therefore any potential anaphylaxis events identified in Studies Q4881g, Q4882g and Q4883g were reviewed by a blinded, independent Anaphylaxis Review Committee (ARC), which conducted an expert review of the suspected anaphylaxis events. In summary, the Anaphylaxis Review Committee determined no evidence to indicate anaphylaxis in CSU patients being treated with omalizumab

Laboratory findings

Biochemistry parameters were analysed in all the individual studies. No consistent or clinically relevant changes from baseline in any biochemistry parameter were seen compared to placebo, nor were any noteworthy differences seen in the rate of biochemistry abnormalities reported in individual patients within the Phase II and Phase III studies.

Both thrombocytopenia and hematopoietic cytopenias were pre-specified as AEs of special interest but were rarely reported and showed no imbalance as laboratory abnormalities in the omalizumab treatment groups. In total seven patients reported such an event with no imbalance between treatment groups: placebo 2/242 (0.8%) patients, omalizumab 75 mg 1/146 (0.7%) patients, omalizumab 150 mg 1/175 (0.6%) patients, omalizumab 300 mg 3/412 (0.7%) patients. Most low counts were transient, but for [Study Q4883g-patient-34601] in the 300 mg omalizumab group, the count was low (although >LLN) at baseline, lowered from baseline to Week 4, and then worsened during Follow-up. An AE of ‘worsening thrombocytopenia’ was reported for this patient approximately 3

months after the week 4 visit that was considered of severe intensity and related to study drug. This AE required medical intervention, but was not considered an SAE, and was ongoing at the end of the study.

All patients were tested for anti-therapeutic antibodies at Day 1 (pre-dose) and at Week 40 (end of follow-up period) or early termination. Only one patient in the omalizumab 300 mg group had a positive result; this was recorded pre-dose, but the patient had a negative result for ATA after treatment with omalizumab so this finding was not considered relevant.

Safety in special populations

There were no trials performed in special populations. The pooled data from clinical studies in CSU indicate no new additional safety concerns, and no change in pattern and frequency of the known safety signals. The safety profile in patients with refractory CSU was similar to the previously observed profile in allergic asthma. The studied population matched the intended target population, and included representation from patients in all subgroups likely to be included within that target population, including adolescents and the elderly. Subgroup analysis was performed on the incidence of SAEs during the treatment period for all four safety analysis sets. In addition, subgroup analysis was performed on the incidence of AESIs during the treatment period for the Core safety analysis set and Core safety analysis set by co-medications.

A total of 39 (4.0%) children between 12 to 17 years old were included in the studies. Of these 29 were exposed to omalizumab. AEs were evaluated in demographic subgroups (age, sex, race), by baseline weekly itch severity score, by presence or not of angioedema at baseline, by body weight category, by geographical region of recruitment (US or non-US); also by background and previous CSU medications taken. None of these subgroup analyses appeared to reveal a sub-population who were particularly at risk of adverse outcomes, or revealed a relevant difference in SAE profile compared to that seen in the overall CSU population. The background medication received by the patients also made no detectable difference to the safety profile. However, it should be noted that there was a very small numbers of patients in some subgroups, and a small number of SAEs reported overall, meaning that the subgroup data presented needs to be interpreted with caution.

- Pregnancy, birth and lactation

A total of eight pregnancies are known to have occurred during the CSU clinical trials. At the time of document preparation, four pregnancies were ongoing, three had proceeded to successful delivery, and one therapeutic medical abortion had been performed. A pregnancy registry (EXPECT, in the US) is in operation for the allergic asthma indication. There have been no adequate and well-controlled studies of omalizumab in pregnant women, and omalizumab should only be used during pregnancy if the benefits clearly outweigh the risks. Women of childbearing age constitute a significant proportion of the typical CSU patient population, and in the completed CSU clinical studies, 8 pregnancies occurred. Based on experience in the allergic asthma indication, omalizumab treatment does not appear to have untoward effects on pregnancy outcome. However, it is expected that omalizumab will be excreted in milk, and caution should therefore be exercised when administering omalizumab to a nursing woman.

Safety related to drug-drug interactions and other interactions

There is no new information available related to drug interaction specific to omalizumab.

Based on the mechanism of action of omalizumab, there are no anticipated interactions with the background medication used as the current standard of care in CSU.

Within the CSU development program, in the two efficacy studies (Q4881g and Q4882g) where H1 antihistamines were used, there was no evidence that the safety of omalizumab was altered relative to the known safety profile of omalizumab in allergic asthma. In the safety study Q4883g with

concomitant use of one or more of H1 antihistamines, and either one or both of H2 blockers or LTRAs, the safety profile for omalizumab also appeared to be unaltered.

In addition, a population pharmacokinetic / pharmacodynamic analysis of the data from studies Q4577g, Q4881g, Q4882g and Q4883g showed no relevant effect of H2 antihistamines and LTRAs on omalizumab pharmacokinetics.

Discontinuation due to adverse events

No studies were prematurely discontinued.

Post-marketing experience

Omalizumab has been used worldwide since its initial approval for the indication of allergic asthma in 2003. Its safety profile in patients with allergic asthma has been well-characterized in clinical trials as well as in the post-marketing setting. As of 31 Dec 2012, the cumulative patient exposure since the first launch of omalizumab is estimated to be approximately 410,890 patient-years. For further information and discussion see the Introduction section.

2.5.2. Discussion on clinical safety

The safety profile of omalizumab has been characterised in clinical trials of patients with AA and over a 10-year post-authorisation period. As of 31 Dec 2012, the cumulative patient exposure since the first launch of omalizumab is estimated to be approximately 410,890 patient-years. During these clinical trials, the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema and pruritus, and headaches in adult and adolescent patients 12 years of age and older.

In the pivotal studies of patients with chronic spontaneous urticaria (CSU), 975 patients between the ages of 12 -75 were treated 12-24 weeks. The number of included children between 12-17 years of age was 39 (4 % of the study population) whereof 29 received omalizumab. There were no children below the age of 12 included. Of the 412 patients who were exposed to the recommended dose of 300 mg omalizumab every 4th week, 282 were exposed for 21-24 weeks. In the pooled core safety analysis of the three pivotal studies in total 404 patients were exposed to any dose of omalizumab for 21-24 weeks and only 23 patients extended their exposure to omalizumab >24 weeks.

The information presented in the submitted summary table of system organ class classified events for the Extended analyses support the finding of a similar safety profile compared with the data characterized in the Core safety analyses data set (12 weeks of treatment). In general the absolute percentage of patients with reported AEs increased by a bit more than 10 % within all treatment groups including placebo (i.e. approx. 15 % within the placebo group, 14 % within the group treated with 150 mg omalizumab and 12 % within the group treated with 300 mg omalizumab). However, as noted, the increase is balanced between treatment groups including placebo. There are no outstanding AEs during the extended period of Day 1 to Week 24 that differ from the period of Day 1 to Week 12.

Long-term clinical trial data of CSU patients beyond 24 weeks study treatment plus 16 weeks follow-up is sparse. Of the 412 patients who were exposed to the recommended dose of 300 mg omalizumab every 4th week, 282 were exposed for 21-24 weeks. In the pooled core safety analysis of the three pivotal studies in total 404 patients were exposed to any dose of omalizumab for 21-24 weeks and only 23 patients extended their exposure to omalizumab >24 weeks. However, this deficiency in long-term follow-up is balanced by the fact that the product has been in use since 10 years and its safety profile well-characterized in patients with allergic asthma both in clinical trials and post-marketing setting. As the reported adverse events during CSU trials show consistency with the known safety profile of omalizumab in the treatment of allergic asthma (AA) and no new safety signals have been

detected, the data from the AA trials are supportive to the CSU data of an acceptable long-term safety profile.

The safety profile presented in this variation application was consistent with the known safety profile of omalizumab in the treatment of allergic asthma (AA). There were no evident signals of increased incidence of adverse events in patients with chronic spontaneous urticaria (CSU), nor was there any evidence of an increased rate of treatment-emergent adverse events, serious or severe adverse events during the treatment period in patients with higher concentrations of omalizumab over the dose range tested (75 to 300 mg every 4 weeks).

In order to rule out the possibility of a dose relationship of selected AEs suspected to be related to the study drug, a more detailed analysis of individual AEs was provided by the MAH. This analysis did not show a clear dose relationship or clusters of AEs for any SOC with the exception of Nervous system disorders SOC and General disorders and administration site conditions SOC, both of which were mainly driven by events which are listed in the proposed product information (i.e. headache and injection site reactions).

Overall, the three most frequent AEs were nasopharyngitis, headache, and sinusitis. Other frequently reported AEs in both analysis sets were upper respiratory tract infection, cough, and idiopathic urticaria and arthralgia. The majority of AEs reported in all safety analysis sets were categorised by the investigators as mild or moderate in severity. Among the more frequently reported AEs, headache was more common relative to placebo in the omalizumab 150 mg and 300 mg dose groups.

Nasopharyngitis, sinusitis, upper respiratory tract infection, arthralgia, and pain in extremity were seen at slightly higher rates in one or more omalizumab groups relative to placebo, and idiopathic urticaria was reported at a slightly higher rate in the 75 mg dose. Urticaria was seen least frequently in the 300 mg group over the longer 24-week treatment period, consistent with superior efficacy at the higher dose.

The MAH provided a thorough discussion which included CSU symptom profile classification of subjects who experienced CSU-related AEs during the follow up period. The presented results based on the post-treatment CSU profiles measured as itch severity score and weekly number of hives score show the proportion of patients with CSU related AEs are 18/242 (7.4%), 18/146 (12.3%), 21/175 (12.0%), and 66/412 (16.0%) in the placebo group, 75 mg group, 150 mg group and 300 mg group, respectively. The CHMP agreed that patients treated with omalizumab in particular the 300 mg dose, in contrast to placebo, have the highest rates of CSU related AEs during the follow-up period. In summary there was neither a clear imbalance nor a dose dependent increase in the incidence of patients reporting a worsening of ≥ 150% over baseline of the weekly CSU signs and symptom scores (itch, hives, UAS7). Furthermore, the analysis of AEs with regards to the CSU symptom profiles strongly suggests that the imbalance in CSU-related AEs is most probably due to the observed robust therapeutic benefit experienced by patients in response to omalizumab treatment followed by loss of that protection after cessation of treatment. This is particularly evident in the 300 mg group where withdrawal of the therapeutic afforded by omalizumab, leads to the greatest CSU-related AEs reported by patients. In view of this, the addition of a statement in the label pertaining to the development of flares or to worsening of symptoms to an extent greater than those present before the commencement of omalizumab therapy is not deemed justified.

Although the mechanism of omalizumab is not entirely understood, it is known that omalizumab binds to IgE and lowers free IgE levels. Subsequently, IgE receptors (FcεRI) on cells down-regulate. In clinical studies in CSU patients, maximum suppression of free IgE was observed 3 days after the first subcutaneous dose. After repeated dosing once every 4 weeks, pre-dose serum free IgE levels

remained stable between 12 and 24 weeks of treatment. After discontinuation of Xolair, free IgE levels increased towards pre-treatment levels over a 16-week treatment-free follow-up period. Taking into account that the mechanism is mediated through a binding to IgE and thus lowering of free IgE levels, and that there is extensive experience for patients with allergic asthma where no observed rebound in IgE levels is observed after washout, the CHMP considered that this will also be applicable for the patients with CSU. The data presented by the MAH do not point to that patients' experience 'flare' after study drug termination.

It is known from studies related to asthma treatment that discontinuation of Xolair treatment generally results in a return to elevated free IgE levels and associated symptoms. The information on allergic asthma in section 5.1 of the SmC describes the following: '*In clinical studies in allergic asthma patients, serum free IgE levels were reduced in a dose-dependent manner within one hour following the first dose and maintained between doses. One year after discontinuation of Xolair dosing, the IgE levels had returned to pre-treatment levels with no observed rebound in IgE levels after washout of the medicinal product.*'

No deaths were reported and there were fairly few SAEs within the CSU trials. No new signals have appeared within the trials of CSU.

There appeared to be no difference in the proportions of patients reporting at least one AE between the omalizumab 150 mg and 300 mg groups (54.9% and 52 % respectively).

AEs of special interest have so far included anaphylactic reactions, thrombocytopaenia, CSS and serum sickness syndrome. In the most recent PSUR assessment report it was stated that there was no evidence of a change in pattern, frequency or severity of these events when used in the approved AA indication.

Baseline angioedema rates seem to be balanced and the analyse of Day 1 to Week 12 data of incidences of the AE "angioedema" showed higher figures in placebo treated patients. Among the patients who continued on study treatment following the experience of angioedema, there were no positive rechallenges according to the presented data. The proposal by the MAH not to add angioedema as an AE in CSU in the product information is accepted by the CHMP.

Most cases of hypersensitivity were unrelated to study treatment. The hypersensitivity reactions are addressed in the RMP and will be closely monitored.

Co-medication with standard therapy of urticaria does not seem to have a major impact on the safety profile of omalizumab. Although the proportion of patients with experience of AEs was higher in the group with a wider range of co-medications used to treat the CSU, the general safety profile appeared similar.

The review of adverse events of urticaria reported during the treatment period did not show a visible trend for lack of efficacy. This is supported by the following points:

• A markedly higher incidence of urticaria was observed in the placebo and 75 mg treatment arms in both, the 12 Week and the 24 Week periods

• A positive dose-response was observed, showing lower incidences of urticaria with higher doses in both, the 12 Week and the 24 Week periods

• A majority of the mild cases were observed in the highest dose groups combined compared to placebo and 75 mg.

Clinically relevant effects are achieved with the 300 mg dose. For the 300 mg dose there is no tendency of higher incidences of urticaria. The higher incidences of urticaria are only observed in the placebo and 75 mg treatment arms. Thus, there is no lack of efficacy for the 300 mg dose.

It seems unlikely that the imbalances in the incidence of infections ((upper respiratory tract infection, urinary tract infection and lower respiratory tract infection) seen in the omalizumab groups compared to placebo were linked to the omalizumab treatment. Neither of the infection reports was considered related to study medication by the investigator. Furthermore, the time-to-onset (post-last dose) analysis performed showed that most of the cases were clustering in the interval between 49-120 days after the last dose. The MAH stated that omalizumab concentrations are predicted to decrease to levels corresponding to EC10 within 38 and 62 days after the last dose in the 150 mg and 300 mg dose groups, respectively. This is endorsed by the CHMP.

The CHMP is of the view that there is no evidence of a different adverse event profile in adolescents; specifically there were no deaths, no SAE related to omalizumab and no omalizumab related AE of special interest reported in these patients. The safety of omalizumab in a population aged 6 to <18 years has also been fully explored within large clinical trials in a paediatric population with severe allergic asthma.

The number of included children between 12-17 years of age is low making the evaluation of the safety profile of CSU patients within this cohort difficult to evaluate. However, a considerable amount of individuals within this age range has been included in the AA trials (with a maximum recommended dose is 600 mg omalizumab every 2 weeks) and data from these trials support an acceptable safety profile in this age group. The CHMP concluded that from a safety point of view there are no concerns in the adolescent group.

A reduced number of elderly patients have been included in the efficacy and safety studies: only 51 patients aged 65-74 and 3 patients aged 75-84 were included. No patients >85 years were included. There appears to be some imbalances between these age groups in the AES suspected by the investigator. There is a higher incidence of nervous system disorders in the 65-74 age subgroup (3.9%) compared to the age <65 subgroup (2.7%) and there is a higher incidence in the sum of postural, hypotension, falls, black outs, syncope, dizziness, ataxia and fractures (2.0% in 65-74 age subgroup compared to 0.5% in the age <65 subgroup). However, given the small number of patients included, conclusions cannot be drawn. The CHMP concluded that the safety profile associated with the elderly subgroup is comparable between older and younger patients, and no different to the known safety profile of omalizumab.

2.5.3. Conclusions on clinical safety

No new safety signals have been detected within the CSU trials. In view of the previously characterised safety profile of omalizumab in the treatment of AA, the reported adverse events during CSU trials show consistency with this known safety profile.

There are no outstanding AEs during the extended period of Day 1 to Week 24 that differ from the period of Day 1 to Week 12. Long-term clinical trial data of CSU patients beyond 24 weeks study treatment plus 16 weeks follow-up is sparse. However, this is balanced by the fact that the product has been in use since 10 years and its safety profile well-characterized in patients with allergic asthma both in clinical trials and post-marketing setting. As the reported adverse events during CSU trials show consistency with the known safety profile of omalizumab in the treatment of AA and no new safety signals have been detected, the data from the AA trials are supportive to the CSU data of an acceptable long-term safety profile.

Overall, the three most frequent AEs were nasopharyngitis, headache, and sinusitis. Other frequently reported AEs in both analysis sets were upper respiratory tract infection, cough, and idiopathic urticaria and arthralgia.

From a safety point of view there are no concerns in the adolescent group. There is no evidence of a different adverse event profile in adolescents; specifically there were no deaths, no SAE related to omalizumab and no omalizumab related AE of special interest were reported in these patients. The safety of omalizumab in a population aged 6 to <18 years has also been fully explored within large clinical trials in a paediatric population with severe allergic asthma.

The CHMP also concluded that the safety profile associated with the elderly subgroup is comparable between older and younger patients, and no different to the known safety profile of omalizumab.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The next data lock point will be 30 June 2014.

The Annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns

Important identified risks	Anaphylaxis/anaphylactoid reactions Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD) Antibody formation to omalizumab Churg Strauss Syndrome (CSS) / Hypereosinophilic Syndrome Thrombocytopenia
Important potential risks	Arterial Thromboembolic Events (ATEs) Malignant neoplasms (children 6 to less than 12 years old) Malignant neoplasms in adults and adolescents ≥ 12 years of age Off label use
Missing information	Pregnancy outcomes

Pharmacovigilance plans

Safety concerns and overview of planned pharmacovigilance actions

Anaphylaxis/ anaphylactoid reactions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance activities (including cumulative review) in the PSUR. Pharmaco-surveillance data repository of patients with and without history of anaphylactic reactions subsequent to Xolair dosing (X-PAND). Characterization of pattern of anaphylaxis in children 6 to <12 years old (to be included in PSURs). Targeted follow up with the use of a questionnaire / checklist for all serious-spontaneous adverse events and clinical trial SAE reports. 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. Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402). A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1).	To study the reporting rate, severity and outcomes of anaphylaxis on an ongoing basis. X-PAND: Evaluate the association between the presence of ATA and risk of anaphylactic reactions among patients with prior Xolair exposure. Assess anaphylaxis in children age 6 to < 12 years of age

Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including interval analysis in the next PSUR. Characterization of pattern of serum sickness and serum sickness-like in children 6 to <12 years old (to be included in PSURs). Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402). A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	To monitor the risk SSS/SSLD via pharmacovigilance. Assess serum sickness and serum sickness-like in children 6 to <12 years old (to be included in PSURs).

Antibody formation to omalizumab

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including cumulative analysis in PSUR. ATA testing when requested by HCP. Pharmacosurveillance data repository of patients with and without history of anaphylactic reactions subsequent to Xolair dosing (X-PAND) Characterization of pattern of serum sickness and	To determine ATA formation following omalizumab administration. X-PAND: Evaluate the association between the presence of ATA and risk of anaphylactic reactions

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	serum sickness-like in children 6 to <12 years old (to be included in PSURs). Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402). A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	among patients with prior Xolair exposure. Assess serum sickness and serum sickness-like in children 6 to <12 years old (to be included in PSURs).

Churg Strauss Syndrome / Hypereosinophilic Syndrome

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including interval analysis in PSUR. Characterization of pattern of CSS/hyper-eosinophilic syndrome in children 6 to <12 years old (to be included in PSURs). Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	Routine pharmacovigilance aims to closely monitor, evaluate and further characterize symptoms of this risk. For all reports, to identify and/or characterize the following: - Clinical characteristics of the events - Types of patients at risk (demographic factors) - Risk factors - Characteristics of exposure (dose, duration, co-medications) Assess CSS/ hyper-eosinophilic syndrome in children 6 to <12 years old (to be included in PSURs).

Thrombocytopenia

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including cumulative analysis in PSUR. Characterization of pattern of thrombocytopenia in children 6 to <12 years old (to be included in PSURs). Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402). A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	Routine pharmacovigilance aims to closely monitor, evaluate and further characterize symptoms of this risk. To identify and/or characterize the following: Clinical characteristics of the events Types of patients at risk (demographic factors) Risk factors Characteristics of exposure (dose, duration, co-medications) Assess thrombocytopenia in children 6 to <12 years old (to be included in PSURs)

Arterial Thromboembolic Events (ATEs)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including cumulative analysis in the PSUR. According to the Xolair PSUR 15 Final Assessment Report dated 14 May 2012, a cumulative review of arterial thromboembolic events is not required in the next PSUR Targeted follow up with the use of a questionnaire / checklist for all serious-spontaneous adverse events and clinical trial SAE reports Characterization of pattern of arterial thromboembolic events in children 6 to <12 years old (to be included in PSURs). Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	Assess I arterial thromboembolic events in children 6 to <12 years old (to be included in PSURs).

Malignant neoplasms (Adult and adolescent patients ≥ 12 years old)

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including interval analysis in the next PSUR. Targeted follow up with the use of an event-specific questionnaire / checklist. Targeted follow up with the use of a questionnaire / checklist for all serious-spontaneous adverse events and clinical trial SAE reports Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan (CIGE025A1402) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	To monitor the risk for malignant neoplasms via pharmacovigilance Assess malignancy in adolescents age 12 to 15 years of age (Japanese study)

Malignant neoplasms in children 6 to less than 12 years old

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including interval analysis in PSUR. Characterization of pattern of malignant neoplasms in children 6 to <12 years old (to be included in PSURs). Targeted follow up with the use of an event-specific questionnaire / checklist Special Drug Use Observational Study of Xolair Subcutaneous Injection for Bronchial Asthma in Japan	Assess malignant neoplasms in pediatric patients 6 to < 12 years old, (to be included in PSURs).

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
	(CIGE025A1402) A study to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 – 15 years) with inadequately controlled AA despite current recommended treatment (CIGE025B1301E1)	

Off-label use

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including cumulative analysis in PSUR.	To study trends of reporting rates in off label use as described in Part II Module SVI.5 Potential for Off-label use

Pregnancy outcomes

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
None	Routine pharmacovigilance including cumulative analysis in PSUR. Protocol Q2952g (EXPECT) Pregnancy Registry	To demonstrate that omalizumab is safe when administered during pregnancy

Risk minimisation measures

Summary table of Risk Minimization Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Identified risks		
Anaphylaxis/ Anaphylactoid reactions	Safety risk addressed in the current EU SmPC sections 4.4 and 4.8; Section 4.4: Type I local or systemic allergic reactions, including anaphylaxis & anaphylactic shock, may occur when taking omalizumab, also with onset after a long duration of treatment. Most of these reactions occurred within 2 hours after the first and subsequent injections of Xolair but some started beyond 2 hours and even beyond 24 hours after the injection. Therefore medicinal products for the treatment of anaphylactic reactions should always be available for immediate use following administration of Xolair. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur. Anaphylactic reactions were rare in clinical trials. No confirmed case of omalizumab related anaphylaxis in Phase III CSU program. Section 4.8:	None in the EU

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Table 4 lists anaphylactic reaction as a rare adverse reaction.	
Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD)	Safety risk addressed in SmPC sections 4.4 and 4.8. as mentioned below: Section 4.4: Serum sickness and serum sickness-like reactions, which are delayed allergic type III reactions, have rarely been seen in patients treated with humanized monoclonal antibodies including omalizumab. The suggested pathophysiologic mechanism includes immune-complex formation and deposition due to development of antibodies against omalizumab. The onset has typically been 1-5 days after administration of the first or subsequent injections, also after long duration of treatment. Symptoms suggestive of serum sickness include arthritis / arthralgias, rash (urticaria or other forms), fever and lymphadenopathy. Antihistamines and corticosteroids may be useful for preventing or treating this disorder, and patients should be advised to report any suspected symptoms. No cases of SSS/SSLD in Phase III CSU program Section 4.8: Table 4 lists serum sickness as a post-marketing adverse reaction with a “not known” frequency.	None
Antibody formation to omalizumab	Safety risk is addressed in SmPC sections 4.4 and 4.8. Section 4.4: Antibodies to omalizumab have been detected in a low number of patients in clinical trials (see section 4.8). The clinical relevance of anti-Xolair antibodies is not well understood No antibodies to omalizumab have been detected in CSU clinical trials. Section 4.8: Table 4 lists anti-omalizumab antibody development as a post-marketing adverse reaction with a “rare” frequency.	None
Churg Strauss Syndrome/ Hypereosinophilic Syndrome	Safety risk addressed in SmPC sections 4.4 and 4.8. Section 4.4. Patients with severe asthma may rarely present systemic hypereosinophilic syndrome or allergic eosinophilic granulomatous vasculitis (CSS), both of which are usually treated with systemic corticosteroids. In rare cases, patients on therapy with anti-asthma agents, including omalizumab, may present or develop systemic eosinophilia and vasculitis. These events are commonly associated with the reduction of oral corticosteroid therapy. In these patients, physicians should be alert to the development of marked eosinophilia, vasculitic rash, worsening pulmonary symptoms, paranasal sinus abnormalities, cardiac complications, and/or neuropathy. Discontinuation of omalizumab should be considered in all severe cases with the above mentioned immune system disorders. No cases of Churg-Strauss Syndrome in Phase III CSU program Section 4.8: Table 4 lists Churg Strauss syndrome / Hypereosinophilic Syndrome as a post-marketing adverse reaction with a “not known.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Thrombocytopenia	Safety risk addressed in SmPC section 4.8. Section 4.8: Table 4 lists idiopathic thrombocytopenia including severe cases as a post-marketing adverse reaction with a “not known” frequency. Platelets In clinical trials few patients had platelet counts below the lower limit of the normal laboratory range. None of these changes were associated with bleeding episodes or a decrease in hemoglobin. No pattern of persistent decrease in platelet counts, as observed in non-human primates (see Section 5.3), has been reported in humans (patients above 6 years of age), even though isolated cases of idiopathic thrombocytopenia including severe cases have been reported in the post-marketing setting.	None
Potential risks		
Arterial thromboembolic events (ATEs)	Safety risk is addressed in SmPC section 4.8 Section 4.8: Table 4 lists Arterial thromboembolic events (ATEs) as a post-marketing adverse reaction with a “not known” frequency. Arterial thromboembolic events (ATE) In controlled clinical trials and during interim analyses of an observational study, a numerical imbalance of ATE was observed. ATE included stroke, transient ischaemic attack, myocardial infarction, unstable angina, and cardiovascular death (including death from unknown cause). In the final analysis of the observational study, the rate of ATE per 1,000 patient years was 7.52 (115/15,286 patient years) for Xolair-treated patients and 5.12 (51/9,963 patient years) for control patients. In a multivariate analysis controlling for available baseline cardiovascular risk factors, the hazard ratio was 1.32 (95% confidence interval 0.91-1.91). In a new analysis of pooled clinical trials, which included all randomised double-blind, placebo-controlled clinical trials lasting 8 or more weeks, the rate of ATE per 1,000 patient years was 2.69 (5/1,856 patient years) for Xolair-treated patients and 2.38 (4/1,680 patient years) for placebo patients (rate ratio 1.13, 95% confidence interval 0.24-5.71). In Phase III CSU program: One case in placebo and one in study Q4881g, both had pre-existing history.	None
Malignant neoplasms- adults and adolescents ≥ 12 years old	According the outcome from Type II var 046 (CHMP opinion 24–Oct-2013) the entire wording for malignancy was removed from SmPC sections 4.4 and 4.8, as there is no indication from randomized controlled clinical trials, from the post-marketing safety study (EXCELS) or from the post-marketing data, that Xolair is associated with an increased risk of malignancies. As part of this procedure the RMP was revised to reflect the changes of removal of the wording in the SmPC and downgrading of Malignant neoplasms in adults and adolescents ≥ 12 years old to important potential risk. CHMP opinion is pending, awaiting revised RMP to reflect the changes of removal of the wording in the SmPC and downgrading of Malignant neoplasms in adults and adolescents ≥ 12 years old to important potential risk.	None
Malignant neoplasms- in	According the outcome from Type II var 046 (CHMP opinion 24–Oct-2013)	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
children 6 to less than 12 years old)	The entire wording for malignancy was removed from SmPC sections 4.4 and 4.8, as there is no indication from randomized controlled clinical trials, from the post-marketing safety study (EXCELS) or from the post-marketing data, that Xolair is associated with an increased risk of malignancies. As part of this procedure the RMP was revised to reflect the changes of removal of the wording in the SmPC and downgrading of Malignant neoplasms in adults and adolescents ≥ 12 years old to important potential risk	
Off label use	Safety risk is addressed in SmPC sections 4.1 and 4.2. Section 4.1 Xolair is indicated in adults, adolescents and children (6 to <12 years of age). Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma (see section 4.2). Adults and adolescents (12 years of age and older): Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent AA who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a long-acting inhaled beta2-agonist. Children (6 to <12 years of age): Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent AA who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a long-acting inhaled beta2-agonist. Section 4.2 Patients whose baseline IgE levels or body weight in kilograms are outside the limits of the dose table should not be given Xolair. The maximum recommended dose is 600 mg omalizumab every two weeks. For subcutaneous administration only. Do not administer by the intravenous or intramuscular route. The safety and efficacy of Xolair in children below age 6 have not been established. No data are available In response to increasing off label use in individuals with CIU, a development effort is underway to assess efficacy and safety. As part of this effort, assessing and characterizing risk for this new population is planned.	None
Missing Information		
Pregnancy outcomes	Safety risk is addressed in section 4.6 and 5.3. of SmPC Section 4.6: There are limited data from the use of omalizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Omalizumab crosses the placental barrier and the potential for harm to the fetus is unknown. Xolair should not be used during pregnancy unless clearly necessary. It is un known whether omalizumab is excreted in human milk.	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	Available pharmacodynamics/toxicological data in non-human primates have shown excretion of omalizumab into milk. A risk to the new born/infants cannot be excluded. Omalizumab should not be given during breast-feeding. Section 5.3: In reproduction studies in cynomolgus monkeys, subcutaneous doses up to 75 mg/kg (about 12-fold exposure ratio based on 28-day AUC values at 75 mg/kg versus the clinical maximum dose) did not elicit maternal toxicity, embryotoxicity or teratogenicity when administered throughout organogenesis and did not elicit adverse effects on foetal or neonatal growth when administered throughout late gestation, delivery and nursing. Omalizumab is excreted in milk in cynomolgus monkeys. Milk levels of omalizumab were 1.5% of the maternal blood concentration. Phase III CSU Studies: Seven cases of pregnancies have been reported for omalizumab in adults and adolescents ≥ 12 years of age. There was one pregnant patient in the placebo group in the clinical program. One patient underwent therapeutic medical abortion and the pregnancy was terminated; the outcome of the remaining pregnancies is unknown.	

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated for Xolair 150 mg powder and solvent for solution for injection and for Xolair 150 mg solution for injection in pre-filled syringe. The Package Leaflet has been updated accordingly.

Section 4.8 of the SmPC was updated to include the QRD statement promoting the reporting of suspected adverse reactions via the national reporting systems.

Additionally, minor amendments were made to sections 4.4 of the SmPC, Annex II and Package Leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The effects of omalizumab are mainly based on the three pivotal phase III studies, Q4881g, Q4882g and Q4883g. Study Q4883g was designed primarily for the evaluation of safety, and so no primary efficacy endpoint was designed, although the same efficacy analyses were performed as in the other pivotal Phase III studies. The results of the primary efficacy endpoint, change from baseline in the weekly itch severity score, showed that at Week 12, there was an observed difference between placebo

and 300 mg omalizumab of -5.80, -4.81 and – 4.52 in studies Q4881g, Q4882g, and Q4883g, respectively. The difference is statistically significant and is considered clinically relevant. Minimal important differences (MIDs) with respect to changes in individual patients have been defined for the composite score and its components and the MID ranges from 4.5 to 5.0 for weekly average of itch (Mathias et al 2012). Patients included in studies Q4881g and Q4882g studies had to be refractory to approved doses of H1 antihistamines for inclusion. Given that two-thirds of the efficacy outcome have been generated from these two studies (which only had background therapy of an H1 antihistamines) and higher doses of anti-H1, antiH2 and LTRA are not approved in Europe for the chronic urticaria indication, the indication is restricted *as add-on therapy* to patients who remain refractory to H1 antihistamine treatment.

Clinical trial data on adolescents (12 to 17 years) included a total of 39 patients, of whom 11 received the 300 mg dose. Results for the 300 mg are available for 9 patients at week 12 and 6 patients at week 24, and show a similar magnitude of response to omalizumab treatment compared to the adult population. Mean change from baseline in weekly itch severity score showed a reduction of 8.25 at week 12 and of 8.95 at week 24. The responder rates were: 33% at week 12 and 67% at week 24 for UAS7=0, and 56% at week 12 and 67% at week 24 for UAS7≤6.

Uncertainty in the knowledge about the beneficial effects

Clinical trial experience of long-term treatment beyond 6 months in this indication is limited. Therefore, a statement has been included in section 4.2 of the SmPC to explain that treatment duration should be up to 6 months and reassessment for further therapy should occur after this period.

Only 39 adolescents were included in the studies and only 11 subjects were treated with 300 mg omalizumab. Although the group of adolescents is small and not powered to see a statistically significant result over placebo, the data comparing the adolescents with adults do show that the responses are similar in both groups. Since no differences are known between the pathophysiology of CSU in adolescents and adults it is reasonable to extrapolate from adult data to the adolescent group.

As for the adolescents, the number of elderly subjects is small. Since there is an indication that PKPD may be different in adolescents, a similar analysis (within the PKPD model) for the elderly was performed. The majority (at least 75%) of elderly patients treated with 300 mg q4w had omalizumab trough levels above the EC90 in elderly, similar to the results for patients < 65 years. Differences between elderly subjects and patients < 65 years were found for EC50 and Emax. However, simulations of well-controlled responder rates suggested that these differences are unlikely to result in relevant differences in the clinical response in elderly patients. The CHMP therefore concluded that there is no evidence that elderly patients require a different dose from younger adult patients.

Risks

Unfavourable effects

In the pivotal studies of patients with chronic spontaneous urticaria (CSU), 975 patients between the ages of 12 -75 were treated 12-24 weeks. The number of included children between 12-17 years of age was 39 (4 % of the study population) whereof 29 received omalizumab. There were no children below the age of 12 included. Of the 412 patients who were exposed to the recommended dose of 300 mg omalizumab every 4th week, 282 were exposed for 21-24 weeks. In the pooled core safety analysis of the three pivotal studies in total 404 patients were exposed to any dose of omalizumab for 21-24 weeks and only 23 patients extended their exposure to omalizumab >24 weeks.

Overall, the three most frequent AEs were nasopharyngitis, headache, and sinusitis. Other frequently reported AEs in both analysis sets were upper respiratory tract infection, cough, and idiopathic urticaria. Most of these events were reported at similar rates across treatment groups, with the exception of headache, which was reported more frequently relative to placebo in the omalizumab 150 mg and 300 mg dose groups. Nasopharyngitis, sinusitis, upper respiratory tract infection, arthralgia, and pain in extremity were seen slightly more frequently in one or more omalizumab groups relative to placebo, while idiopathic urticaria was reported at slightly higher rate in the lower dose (75 mg dose omalizumab group), and urticaria was seen least frequently in the 300 mg group over the longer 24-week treatment period, consistent with superior efficacy at the higher dose.

The number of reported SAEs was limited and no specific pattern of SAEs has been identified within the presented data set. Only the event of angioedema is described in more than one subject and two of the cases are referred to the follow-up period as the subjects were taking inappropriate co-medications. However, angioedema has been reported also in AA studies as well and is labelled in the present section 4.8 (frequency rare) of the SPC addressing AA patients.

In view of the previously characterised safety profile of omalizumab in the treatment of AA, the reported adverse events during CSU trials show consistency with this known safety profile.

Uncertainty in the knowledge about the unfavourable effects

Long-term clinical trial data of CSU patients beyond 24 weeks study treatment plus 16 weeks follow-up is sparse. However, this deficiency in long-term follow-up is balanced by the fact that the product has been in use since 10 years and its safety profile well-characterized in patients with allergic asthma both in clinical trials and post-marketing setting. As the reported adverse events during CSU trials show consistency with the known safety profile of omalizumab in the treatment of allergic asthma (AA) and no new safety signals have been detected, the data from the AA trials are supportive to the CSU data of an acceptable long-term safety profile.

A reduced number of elderly patients have been included in studies and there appears to be some imbalances between these age groups in the AES suspected by the investigator. However the CHMP concludes that the safety profile associated with the elderly subgroup is comparable between older and younger patients, and no different to the known safety profile of omalizumab.

The number of included children between 12-17 years of age is low making the evaluation of the safety profile of CSU patients within this cohort difficult to evaluate. In addition long-term clinical trial data of SCU patients beyond 24 weeks study treatment plus 16 weeks follow-up is sparse. These deficiencies are balanced by the fact that the product has been in use since 10 years (both in adult and patients above from 12 year of age) and its safety profile is well-characterized in patients with AA both in clinical trials and post-marketing setting. In view of the findings that the reported adverse events during CSU trials show consistency with the previously known safety profile of omalizumab in the treatment of AA and that no new safety signals have been detected, the data from the AA trials are supportive to the CSU data concerning the above addressed safety aspects.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

A statistical significant and a clinical relevant effect has been convincingly demonstrated for the 300 mg dose.

It is of importance to clearly state that Xolair should be used in combination with antihistamines and the wording "*Xolair is indicated as add-on therapy for the treatment of chronic spontaneous urticaria in*

adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment" clearly describes and reflects the clinical situation.

The proposed new indication also involves adolescents, 12-17 years. Overall the results for the adolescents seem comparable to the results observed in adults. Since no differences are known between the pathophysiology of CSU in adolescents and adults it is reasonable to extrapolate from adult data to the adolescent group.

No new safety signals have been detected within the CSU trials. In view of the previously characterized safety profile of omalizumab in the treatment of AA, the reported adverse events during CSU trials show consistency with this known safety profile.

Benefit-risk balance

The MAH showed that omalizumab has demonstrated a clinical response and a clinical relevant effect for the 300 mg dose. No new safety signals have been detected within the CSU trials.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of omalizumab as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment is considered positive.

Discussion on the Benefit-Risk Balance

The benefit-risk balance of omalizumab in chronic spontaneous urticaria is positive.

4. Recommendations

The application for this variation is approvable since the major objection and other concerns have all been resolved.

Outcome

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

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include Xolair as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with inadequate response to H1 antihistamine treatment. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet is updated in accordance.

Section 4.8 of the SmPC was updated to include the QRD statement promoting the reporting of suspected adverse reactions via the national reporting systems.

Additionally, editorial changes were made to sections 4.4 of the SmPC, Annex II and Package Leaflet.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.