European Medicines Agency

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ASSESSMENT REPORT FOR Xolair

International Nonproprietary Name:
omalizumab

Procedure No. EMEA/H/C/606/II/18

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

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I. SCIENTIFIC DISCUSSION

Xolair (omalizumab) is a humanised anti-IgE antibody manufactured by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell line. It is currently indicated for treatment of severe allergic asthma in patients (12 years of age or older) in whom standard treatment has failed. Xolair is usually administered subcutaneously every 2 to 4 weeks. Xolair was first registered in Australia in June 2002. In October 2005 a marketing authorisation was granted in the EU member states.

A CHMP Scientific advice from June 2008 recognised the bioequivalence of the new form (used in study IA05), established in an adult population, was applicable also in the paediatric population.

The scope of the present variation application is to include information on a paediatric indication in children from 6 to <12 years of age as add-on therapy in order to improve asthma control in patients with severe persistent allergic asthma.

I.1 NON-CLINICAL ASPECTS

No new data has been submitted. Adequate non-clinical testing, including repeat dose toxicity studies in juvenile cynomolgus monkeys, has previously been reported by the MAH. The conclusions, in relation to the paediatric indication, are that omalizumab is well tolerated in non-human primates, with the exception of a dose-related and age-dependent decrease in blood platelets, which was seen with a greater sensitivity in juvenile animals. Relevant information has already been included in the SPC.

I.1.1 Environmental Risk Assessment

No additional ERA was provided as the MAH justified that no appreciable risk for the environment emerges from the use of Xolair. The CHMP accepted the justification.

I.2 CLINICAL ASPECTS

I.2.1 Clinical pharmacology

The clinical pharmacokinetic and pharmacodynamic documentation for Xolair (omalizumab) in the paediatric population comprise data from two studies:

- **Study IA05**, which is a 1-year double-blind study in children (6 - <12 years) with moderate-severe, persistent, inadequately controlled allergic asthma. This is the pivotal study and comprises the main evidence for the applied indication.

- **Study 010**, which is a 7-month double-blind trial with a 5-month open-label extension period in children (6-12 years) with allergic asthma requiring daily treatment with inhaled corticosteroids. This study has been submitted in previous applications, and is considered supportive for the present type II variation.

In both studies Xolair was administered by subcutaneous injections every second or fourth week according to patient's pre-treatment body weight and baseline IgE levels although the exact dosing schedule differed somewhat in the two studies. In study 010, the dosing schedule deviates slightly from the one recommended in the proposed SPC for this type II variation. In study IA05, the dosing schedule is the same as the one recommended in the proposed SPC. The pharmaceutical formulation used in these studies was the powder and solvent for solution for injection.

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

I.2.1.2 Pharmaceutical formulation

This variation application concerns both approved pharmaceutical formulations for Xolair: powder and solvent for solution for injection and solution for injection (75 and 150 mg). The extension application for solution for injection (EMEA/H/C/606/X/14**)** recently obtained European Commission Decision on the basis of a study (study 2204), which was a single-dose, parallel-group investigation of omalizumab bioequivalence between the two formulations (150 and 300 mg s.c.) performed in healthy but atopic volunteers with total IgE above normal levels (30– 300 IU/mL) at the screening visit.

Demonstration of bioequivalence in adults is regarded as adequate to detect formulation differences and the results from study 2204 therefore allow extrapolation to other sub-populations. Thus, the clinical studies performed using the original formulation (powder and solvent) are considered to reflect also the efficacy and safety following treatment with the solution for injection.

This issue was discussed in the Scientific Advice.

I.2.1.3 Pharmacokinetic-pharmacodynamic model

A population model describing the binding and turnover of omalizumab and IgE was presented. The starting point for this model was a previously[1] described model. The measurement used for this purpose comprised total omalizumab concentrations, free and total IgE concentrations.

In addition, an investigation of the relationship between model-derived free IgE concentrations and changes in clinical outcomes in paediatric patients was performed. Additional data used for this aim were clinical signs and symptoms of asthma, total symptom score (TSS), peak expiratory flow (PEF), rescue medication use (RESC), forced expiratory flow in one second (FEV1) and exacerbations.

Data used for models
The analysis included data from six studies, whereof two were studies 010 and IA05 as described above.

In addition data from the following studies in non-paediatric subjects were included:

- Studies 8 and 9: 7-month studies with 5-month blinded extension periods in adolescents and adults with moderate-to-severe allergic asthma requiring daily treatment with inhaled corticosteroids
- study 11: 32-week pilot trial to assess corticosteroid reduction in adolescents and adults with severe allergic asthma requiring daily treatment with high-dose inhaled corticosteroids, with or without oral corticosteroid
- Study 2204: single-dose, parallel-group, investigation of omalizumab bioequivalence (150 and 300 mg s.c.) in healthy but atopic volunteers with total IgE above normal levels (30–300 IU/mL) at the screening visit

The model was developed using data from both omalizumab- and placebo-treated patients. The full data set contained 7877 omalizumab concentrations from 1481 subjects, 13645 total IgE concentrations from 2364 subjects, and 7498 free IgE concentrations from 1479 subjects. The demographic data are shown in Table 1. It can be seen here that the baseline IgE levels on average are higher in the paediatric patients compared with adults/adolescents.

Samples were excluded due to one of the following reasons: inappropriate concentration values (*e.g.:* a positive omalizumab concentration in a placebo subject), free IgE measurement greater than the upper limit of quantification, inconsistencies between the PK/PD and clinical databases, missing baseline total IgE (a required covariate for model analysis, in which case the entire subject was removed), or samples not received by the analytical laboratory.

[1] Hayashi *et al. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab.* Br J Clin Pharmacol; 63:548-561, 2006

Following a single omalizumab dose, omalizumab concentrations rises above 10,000 ng/mL while free IgE was suppressed to approximately 10 ng/mL. Following multiple dosing further suppression of free IgE is achieved. At the same time, total IgE increased.

In the next Table 1 below, the observed data at steady state from all the included studies were summarised and grouped on the basis of paediatric/adult and baseline IgE levels. It was noted that it is most paediatric patients having high baseline values, but the distributions were overlapping. As expected, patients with low baseline IgE had the lowest exposure to omalizumab as the dose is adjusted for the baseline IgE level and accordingly, patients with higher baseline IgE had higher exposures. It appeared however, that the used dosing schedule ensures that free IgE was suppressed to the same level irrespective of their baselines and their weight.

Table 1. Observed steady-state trough concentrations of omalizumab, total and free IgE in paediatric and adult patients. Omalizumab PK and IgE concentrations are summarised for trough samples drawn 84 days or more after commencing treatment with active omalizumab in the moderate to severe allergic asthma studies 10, IA05, 8, 9 and 11. Paediatric patients are those less than 12 years of age.

IgE at baseline	Statistic	Omalizumab (µg/mL)		Total IgE (ng/mL)		Free IgE (ng/mL)	
		Pediatric	Adult	Pediatric	Adult	Pediatric	Adult
30-200 IU/mL	№ patients	191	379	191	374	190	380
	5th	15.5	11.3	325	316	3.97	4
	Median	41.6	30.3	1111	963	12.3	12.8
	95th	85.5	76.1	2628	2166	35.0	34.4
	99th	122	96.2	3438	2872	50.3	54.2
200-500 IU/mL	№ patients	205	220	201	217	203	220
	5th	32.3	34.8	1095	1102	6.68	7.08
	Median	77.4	73.0	2521	2498	14.3	14.6
	95th	167	163	4810	4263	37	31.52
	99th	220	203	6587	5834	62.2	46.6
500-700 IU/mL	№ patients	65	40	65	38	65	41
	5th	57.0	47.7	1832	1115	7.40	8.24
	Median	135	117	3883	3446	16	15.4
	95th	218	186	6844	5496	39.8	32.8
	99th	307	205	8820	6000	51.4	57.6
More than 700 IU/mL	№ patients	118	8	119	8	119	8
	5th	96.1	84.7	2380	2886	7.61	10.3
	Median	185	163	4060	5965	14.0	21.5
	95th	318	305	7423	8087	26.8	30.9
	99th	374	305	9383	8087	33.5	30.9

Population model describing the binding and turnover of omalizumab and IgE

The binding and turnover model applied as a starting point is graphically illustrated in Figure 1. The model is defined as a system of differential equations describing the rate of change of omalizumab at the administration site, of total omalizumab and of total IgE. Molar units have been used throughout the modelling.

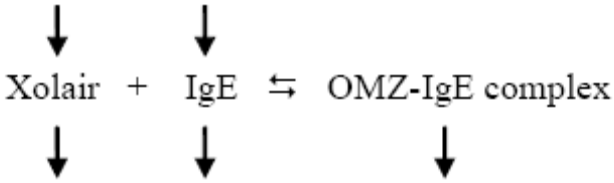

Figure 1. Graphical illustration of the omalizumab-IgE binging and turnover model.

In this model the following parameters were estimated:

- k_a the absorption rate constant of omalizumab
- R_E the rate of production of IgE
- CL_n clearance terms for free omalizumab, free IgE and for the omalizumab:IgE complex
- V_n volume terms for omalizumab, free IgE and for the omalizumab:IgE complex
- K_d the *in vivo*, apparent equilibrium binding constant
- α the change in the affinity of binding between omalizumab and IgE as a function of the molar ratio of total omalizumab and total IgE

Body weight was included as a covariate on all clearance and volume terms (apart from volume for free IgE) and on IgE production rate. Further, baseline IgE (IgE_0) was included as a covariate on IgE clearance, IgE production rate and the equilibrium binding constant. The relationships were included as power function:

$$P_i = \theta_1 \left(\frac{WT}{70} \right)^{\theta_2} \left(\frac{IgE_0}{365} \right)^{\theta_3} e^{\eta}$$

Other potential population covariates were explored graphically, using the empirical Bayes estimates of the inter-individual random effects (ETAs). This was performed for age, body mass index (BMI), sex, race and study.

Overall, the model fitted the omalizumab and total IgE well; however, for the free IgE there was a tendency of over-prediction of low and high observations. It can be noted that the exponents describing the effect of body weight were estimated for each parameter, thus, varying estimates were obtained.

The half-lives, as calculated from the clearances and volumes, of the three modelled entities, were 28.5 (free omalizumab), 2.4 (omalizumab:IgE complex) and 2.1 (free IgE) days. However, note that omalizumab in vivo is based on total omalizumab concentrations (free and complex) and therefore the characteristics are recognized as non-linear. Thus, the observed half-life for omalizumab will vary over time and with IgE production.

A predictive check was performed in which the analysis dataset, with dosing regimens, sampling times and covariates (bodyweight and baseline IgE) from each patient, was replicated 10 times, then used with the final model to simulate omalizumab, total IgE and free IgE concentrations at steady state, approximately 6 months after dosing. The patients were then divided into nine subsets, based on the minimum to lower third, lower to middle third, and middle third to maximum baseline IgE values (20, 207.6, 459.4, 1371 IU/mL) and bodyweights (19.3, 40.4, 72.7, 150 kg). For each subset, a histogram of the observed steady-state free IgE levels was overlaid with that predicted from the simulation, to test the ability of the model to predict the free IgE across the dosing table. In general, there is a good agreement between observations and predictions as illustrated with the free IgE observations.

<u>Relationship between model-derived free IgE concentrations and changes in clinical outcomes</u>

This analysis was a graphical analysis. For the phase III studies, based on patients' diary card data, mean changes from baseline were determined for total asthma symptoms score, mean morning peak

expiratory flow and rescue medication use. For each patient, the changes from baseline in these clinical outcomes were summarized into 28-day arithmetic means.

In Study IA05, asthma exacerbation episodes were also reported on a daily basis. The percentage of patients experiencing exacerbations during each 28 day period was calculated.

In addition, for both paediatric studies, forced expiratory volume in one second (FEV1) was measured at scheduled visits. The raw data were then normalised to a percentage of their predicted FEV1 (using the Polgar standard calculation), and both the raw and predicted FEV1 values were adjusted as a change from each patient's baseline value.

Correlations between free IgE and the clinical variables were constructed by producing, for each patient, post-hoc predictions of their free IgE at the midpoint of each 28-day clinical observation period, i.e. at 14 days, 42 days and every 28 days thereafter. The time-matched pairs of values for each observation period were then summarized across patients, using arithmetic means for the change in clinical variables (which were normally distributed) and geometric means for free IgE (log-normally distributed).

The plots revealed that there was a marked placebo response in all the clinical endpoints; from the diary data (*e.g.* peak expiratory flow and rescue medication use) to the investigator measured FEV1. An effect in addition to placebo was indicated from the plots in FEV1 and exacerbations. Further, the suppression of free IgE is rapid, but the effect on clinical outcomes were delayed. In addition, in study IA05, where clinical symptoms were recorded after cessation of treatment, it took some time for the symptoms of asthma to re-emerge, with a distinct time lag being evident especially in the placebo-corrected probability of asthma exacerbation.

I.2.1.4 Discussion on clinical pharmacology

The population binding and turnover model describing omalizumab and IgE levels contain the covariates used in the dosing schedule for omalizumab, i.e. body weight and baseline IgE levels. However, it is not completely clear, that the chosen dosing schedule is the most adequate one. However, it has been used in the pivotal clinical trial in paediatric patients (study IA05) and is indicated to result in sufficient suppression of free IgE levels. During the March 2009 CHMP the MAH was requested to provide additional information on the clinical pharmacology which was submitted in April 2009. With the proposed dosing regimen in children, the free IgE levels are considered sufficiently suppressed irrespective of body weight and baseline IgE levels. There is a general trend that the omalizumab and the total IgE levels are higher in the paediatric patients, and particularly in subjects with high baseline IgE levels. As the free IgE is a good biomarker for the clinical effect, the dosing from a pharmacokinetic-pharmacodynamic perspective appeared reasonable. With the changes proposed in the Product Information the issue has been adequately finalised.

I.2.2 Clinical Efficacy

During the CHMP Scientific Advice the relevance of a proposed application submission for a paediatric indication was discussed.

The main messages in the Scientific Advice were:

- The paediatric population studied in the phase III trial IA05 is not representative of the population that may be treated with omalizumab.
- The onus is on the MAH to demonstrate that the data from the population aged 6 to < 12 years fulfil the criteria as defined in the current label. If the MAH is seeking a broader indication i.e. access to a milder population, this should be done in adults first, than children.
- A clear definition of an asthma cerebration should be used.
- Safety data for targeted population, children with severe persistent allergic asthma, should be presented.

The MAH stated in the Clinical Overview of this variation application that in the paediatric program, the pivotal study design for CIGE025IA05 was set up prior to the EU registration of Xolair in adolescents/adults severe allergic asthmatic patients, at that time the need to examine the most severe paediatric group was anticipated. Therefore, analyses of the primary efficacy variable and secondary variables within a sub-group of patients who were inadequately controlled, on high dose inhaled steroids (ICS) and a long acting beta$_2$-agonist (LABA) was prospectively planned.

The MAH has obtained CHMP Scientific Advice about the proposed extension of the current MA. The response from the CHMP provided guidance for the preparation of this submission.

In the pivotal Study IA05 the predefined analysis plan, identified a specific subset of patients with high dose ICS (≥ 500 mcg/day fluticasone equivalent) plus LABA, henceforth referred to as the *EU(P) population*. This population reflected the approved omalizumab population of patients 12 years or older, as well as following GINA (Global Initiative for Asthma) guidelines. This EUP population subset of patients represents 41% of Xolair patients and 39.5% of placebo patients in study IA05.

To be consistent with the current approved population of 12 years and older, as well as GINA guidelines, omalizumab is proposed for use as add-on therapy to improve asthma control in adult and adolescent patients (6 years of age and above) with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled β_2-agonist.

The two submitted placebo-controlled studies that provide data to support the efficacy claim in the paediatric population are study IA05 and 010. Following the CHMP request, the IA05 study is presented in two parts;

- Including the whole population.
- Including only the EU population as defined above.

Table 2. Summary of placebo-controlled trials

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage*	Efficacy endpoint
IA05	Efficacy and safety in moderate to severe allergic asthma in children 6-<12 years of age	570	52 weeks (of which 24 weeks is fixed steroid period)	omalizumab 75, 150, 225 or 300 mg every 4 weeks or omalizumab 225, 300 or 375 mg every 2 weeks	rate of clinically significant asthma exacerbations
IA05 (EU population)	Efficacy and safety in patients with high ICS (≥500µg/day fluticasone equivalent) and LABA	235	52 weeks (of which 24 weeks is fixed steroid period)	omalizumab 75, 150, 225 or 300 mg1 every 4 weeks or omalizumab 225, 300 or 375 mg	rate of clinically significant asthma exacerbations
010 (core)	Efficacy and safety in moderate to severe allergic asthma in children 6-12 years of age	324	28 weeks (of which 16 weeks is fixed steroid period)	omalizumab 150 or 300 mg every 4 weeks or omalizumab 225, 300 or 375 mg1 every 2 weeks	reduction of asthma exacerbations

* Omalizumab dose according to body weight and baseline IgE level.

I.2.2.1 Main clinical studies

In the following, the IA05 study results from the "EU population" are considered as the main "pivotal" results. The full IA05 study will be assessed in the Supportive Studies section which follows.

The **Trial Study IGE025A IA05 (EU population)** was a 1 year, randomised, double blind, parallel-group, placebo-controlled, multicenter evaluation of efficacy, safety, pharmacokinetics and pharmacodynamics of omalizumab in children (6-<12 years) with moderate-severe, persistent, inadequately controlled allergic asthma.

Study Participants

Main inclusion criteria:

- Children (outpatient males and females) aged 6 - <12 years on study entry, with body weight between 20 and 150 kg.
- A total serum IgE level ≥30 to ≤1300 IU.
- A diagnosis of allergic moderate or severe persistent asthma (at least National Heart, Lung and Blood Institute (NHLBI) Guidelines step 3) ≥ 1 year duration. This despite therapy at NHLBI step 3 or 4 (at least medium dose ICS – fluticasone DPI ≥200µg/day or equivalent with or without other controller medications).
- A positive prick skin test to at least one perennial allergen.
- Demonstrated ≥ 12% increase in FEV_1 over starting value within 30 minutes of taking up to 4 puffs (4x100 mcg) or up to 5mg nebulized salbutamol.
- A documented history of experiencing asthma exacerbations despite therapy at NHLBI step 3 or 4. (Two exacerbations within last 12 months **or** three within last 24 months whereof on last 12 months **or** acute hospital care within last 12 months due to an exacerbation as defined by Global Initiative for Asthma (GINA) 2002.) All qualifying exacerbations should have occurred while receiving NHLBI Step 3 or 4 therapies according to best clinical practice.
- A demonstrated inadequate symptom control during the last 4 weeks of run-in despite receiving an equivalent dose of fluticasone DPI ≥200µg/day total daily ex-valve dose.

Main exclusion criteria

- Receiving systemic (oral or IV) corticosteroids for reasons other than asthma within 4 weeks of Visit 1 or during the double-blind treatment period.
- Taking methotrexate, gold salts, cyclosporin, troleandomycin or other immunosuppressants not approved for an asthma indication within 3 months of Visit 1 (or anticipated their use during the study).
- Receiving desensitization therapy with less than 3 months of stable maintenance doses prior to Visit 1.
- Being treated for an asthma exacerbation during the 4 weeks immediately prior to randomization.
- Elevated serum IgE levels for reasons other than allergy.

During the Scientific Advice from the CHMP the initial inclusion criteria were not accepted. By narrowing the criteria including only patients with high dose ICS (≥ 500 mcg/day fluticasone equivalent) plus LABA, the study participants profile is acceptable and will mirror the targeted population.

Dosage

The doses selected for this study were based on previous drug exposure limits in adult and paediatric asthmatic patients who were treated with omalizumab. A dosing table was used that aimed to estimate for each patient the amount of active drug needed to reduce the patients total IgE level to ≤ 25 ng/ml to keep within reasonable endotoxin safety margins as determined in toxicology studies.

The omalizumab dose was individualized for each patient, based on their body weight and total serum IgE level at Visit 1. Omalizumab 75 to 375 mg (or placebo) was administered SQ every 2 or 4 weeks depending on the dose. Doses exceeding 150 mg were divided among more than one injection site to limit injections to not more than one 150 mg injection per site.

Patients entering the study were required to be receiving high dose ICS (≥ 500 mcg/day fluticasone equivalent) plus LABA. No changes to the patient's asthma maintenance therapy were permitted throughout the study except for ICS adjustments after the first 24 weeks.

The dose scheme which is based on knowledge from previous studies seems to be adequate.

Outcomes/endpoints

The efficacy assessments were based on:

- Asthma exacerbation data: A clinically significant asthma exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. In addition to these requirements at least one of the following criteria had to be met:
  - PEF or FEV_1 < 60% of personal best - PEF or FEV_1 60-80% of personal best following β_2-agonist administration
  - Fall in PEF of > 20% on at least 2 of any 3 consecutive days compared to personal best.
  - A >50% increase in 24-hour rescue medication use on at least 2 of any 3 consecutive days compared to normal use (≥ 8 puffs of salbutamol)
  - At least 2 night time awakenings due to asthma symptoms requiring rescue medication within the previous 7 days
  - Any other specified clinically important reason
- Rescue medication use: The number of puffs of salbutamol (albuterol) or terbutaline taken during each 24 hour period for intercurrent bronchospasm.
- Clinical symptom scores: Total symptom score is obtained by adding the scores for nocturnal asthma (maximum score = 4), morning asthma symptoms (maximum score = 1), and daytime asthma symptoms (maximum score = 4).
- Global evaluations: PAQLQ(S) (paediatric asthma quality of life questionnaire).
- Pulmonary function: Spirometry and peak expiratory flow rate.

The safety assessments consisted of collecting:

- All adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.
- Regular monitoring of haematology, blood chemistry and urine
- Regular assessments of vital signs, physical examinations including medical history and abbreviated review of systems including height and body weight.

The primary efficacy variable was the rate of clinically significant asthma exacerbations in the 24-week double-blind fixed steroid period. For each treatment group, the rate was defined as the number of exacerbations after adjusting for time at risk.

The evaluation of PK consisted of testing for total omalizumab levels. The evaluation of PD consisted of testing for free IgE and total IgE levels.

Anti-omalizumab (Ab) levels were performed on all patients prior to first dosing at randomization. Patients were also instructed to return to the clinic for an anti-omalizumab Ab blood sample approximately 16 weeks after their final treatment visit.

I.2.2.2 Results

Participant flow

A total of 627 patients were randomised, from a total of 1433 screened patients. Most exclusion at screening was due to unacceptable test procedure results (e.g. IgE levels or weight outside the dosing limit) or not meeting diagnostic/severity criteria. One patient in the placebo group received study medication without being randomised and is included in the safety population but is excluded from the ITT population. In the full study a total of 628 patients were treated and comprised the safety population, 421 randomised to omalizumab and 207 to placebo (includes the one patient that was not randomised but received placebo). All randomised patients were treated with at least one dose of study medication.

The disposition of the EU population is shown in the table below.

Table 3. Patient disposition for each treatment group; EU mITT population

	Omalizumab	Placebo	All
Randomized	159	76	235
Completed treatment phase	134 (84.3)	64 (84.2)	198 (84.3)
Total	25 (15.7)	12 (15.8)	37 (15.7)
Adverse event	2 (1.3)	0 (0.0)	2 (0.9)
Unsatisfactory therapeutic effect	1 (0.6)	0 (0.0)	1 (0.4)
Protocol violation	5 (3.1)	2 (2.6)	7 (3.0)
Subject withdrew consent	12 (7.5)	4 (5.3)	16 (6.8)
Lost to follow-up	4 (2.5)	4 (5.3)	8 (3.4)
Administrative problems	1 (0.6)	2 (2.6)	3 (1.3)

Adverse events include asthma exacerbations.

A total of 34.2% patients randomised to omalizumab and 38.6% patients randomised to placebo.

Patients (all randomised mITT) with major protocol violations were excluded from the Per protocol population as shown in the table below.

Table 4. Patients excluded from the per-protocol population

	Omalizumab	Placebo	All
Total no. of patients	**N=421 n (%)**	**N=207 n (%)**	**N=628 n (%)**
Total	57 (13.5)	27 (13.0)	84 (13.4)
Category for exclusion			
Patients excluded for GCP issues	48 (11.4)	21 (10.1)	69 (11.0)
Inclusion criteria	7 (1.7)	9 (4.3)	16 (2.5)
Exclusion criteria	2 (0.5)	0	2 (0.3)
Study medication	2 (0.5)	1 (0.5)	3 (0.5)

Primary efficacy results

The primary efficacy parameter was a clinically significant asthma exacerbation, as defined above.

The exacerbation rate in the omalizumab group in this period was 34% lower than that in the placebo group, and the proportion of patients who had at least one exacerbation was smaller in the omalizumab group. The proportion of patients experiencing three or more exacerbations was lower in the omalizumab group than the placebo group.

In the primary analysis, the between-group ratio of exacerbation rates was statistically significant (p = 0.047, Poisson regression including terms for treatment, country, dosing schedule and exacerbation history). When this analysis was performed for the EU Per Protocol population the results were similar.

In patients dosed 2-weekly, omalizumab was associated with a statistically significantly lower exacerbation rate than placebo in patients dosed 4-weekly, the exacerbation rate was lower for omalizumab than placebo, but the difference was not statistically significant.

The primary endpoint as specified and calculated according to the study protocol did reach statistical significance (p=0.047), favouring the omalizumab treatment over placebo in this highly selected population. The ratio of the rates of clinically significant asthma exacerbations per treatment period was similar for both the EU mITT and the EU mPP populations (0.42/0.63) but due to statistical technicalities the p-value for the mPP population increased to 0.080.

Because of the dosing scheme, patients with higher IgE concentrations and to some extent with higher weight will be treated every other week. In the SPC addressing adolescents and adult the following is stated:
"*Patients with IgE lower than 76 IU/ml were less likely to experience benefit (see section 5.1). Prescribing physicians should ensure that patients with IgE below 76 IU/ml have unequivocal in vitro reactivity (RAST) to a perennial allergen before starting therapy."* The inclusion criteria for study IA05 was only a total serum IgE level ≥30 to ≤1300 IU.

The CHMP requested that the effectiveness in patients with low IgE baseline values and its relations to the RAST for perennial allergen outcome in the studied paediatric population be discussed in depth by the MAH.

The MAH responded to the CHMP request that there is evidence that patients who have baseline IgE in the lowest quartile benefit from omalizumab treatment. However, they may have a lower probability of showing benefit in terms of exacerbation rate reduction than patients in the upper three quartiles.

Only a few patients were tested only for RAST (n=29, 5.0% of the total population) and thus a relationship of baseline IgE and RAST on efficacy is difficult to establish. However, efficacy was observed across all baseline IgE quartiles with consistent decrease of exacerbations.

In study IA05, patients were required to have a positive prick skin test (diameter of wheal ≥ 3 mm) to at least one perennial allergen (dust mite, cat/dog dander, cockroaches), documented within the past 2 years or taken at Visit 1. Mold allergies are a potential risk factor for severe exacerbations so a mold prick skin test (aspergillus, alternaria, penicillium and cladosporium) could also be performed on each patient but the results were used as an indicator and could not be used to determine positivity for study entry.

In addition, a RAST (radioallergosorbent) test could be performed for patients with a borderline skin prick test result, only after consultation with the MAH's Clinical personnel. A RAST test, using a person's extracted blood, detects the amount of IgE that reacts specifically with suspected or known allergens.

The IgE cutoff point of 76 IU/mL for omalizumab treatment has been accepted for adults as efficacy could be demonstrated. From the MAH's response, benefit is not shown for omalizumab treatment in the asthmatic, paediatric subpopulation with initial IgE values of < 200 IU/mL. As always, a few single patients in any subgroup may benefit, but on a population level (children with IgE values of < 200 IU/mL) this was not shown.
The CHMP concluded that this is also consistent with the observation that children with severe asthmatic disease have higher IgE levels, in general, compared with adult patients. The consequence of the decreased response to omalizumab in this subpopulation needs be included in the SPC 4.2 "Posology and methods of administration" section in a similar way as for the adult population. According to the SPC in the adult population, patients with IgE levels < 76 IU/mL should have a

positive RAST independent of the skin prick test result for initiating an omalizumab treatment. As a result, from the submitted paediatric data the role of RAST for selecting treatment candidates cannot be concluded. However, before any new data indicate otherwise, in children with an IgE level < 200 IU/mL, RAST should be performed and be found positive before beginning treatment with omalizumab.
The MAH has accepted the CHMP comments by amending the SPC accordingly.

Secondary efficacy results

- Change in nocturnal clinical symptom score from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period.

A small decrease in mean nocturnal asthma symptom score was seen in both treatment groups for the EU mITT population from Study IA05, but the between-group difference was not statistically significantly different.

- Rate (time-adjusted number of) clinically significant asthma exacerbations during the 52 week double-blind treatment period

Most patients continued to maintain their ICS dose throughout the study. There was no significant difference in the proportion of patients with defined reductions in ICS dose between the treatment groups.

The results indicate that the exacerbation reduction in the omalizumab treatment arm remains or maybe increased during the 52 week period.

- Change in beta-agonist rescue medication use from baseline to the end (last four weeks) of the 24 week double-blind fixed steroid treatment period.

The omalizumab group showed greater mean and median decreases than the placebo group at the end of the 24-week fixed steroid treatment period for the EU mITT population, although the between-group difference was not statistically significant.

That also the $beta_2$-agonist rescue medication (in addition to the ICS) did not differ more between the treatment groups could depend on the baseline treatment. Overall, the mean normal number of daily puffs of short-acting $beta_2$- agonists at baseline was 2.7. The span for improvement is limited. Taking this into account the difference of -1.3 for omalizumab and -0.71 for placebo could be clinically significant even if not statistically significant.

- Change in quality of life (PAQLQ(S)) in overall score from baseline to the end (last visit) of the 24 week double-blind fixed steroid treatment period.

Changes in quality of life scores from baseline were calculated to the end of Week 12, 24, 28, 40, and 52 in. This outcome is not separately presented by the MAH for the EU mITT population. For the overall mITT population the LS means of change from baseline were broadly similar between treatments. The overall scores were not different between treatments at Weeks 12, 28, 40 or 52 either.

In the adult population (study 2306) highly significant differences in Quality of Life between omalizumab and placebo were recorded. For this paediatric EU population this was not the case. A brief discussion was submitted in the Clinical Overview. The MAH was requested to discuss in depth the clinical impact of these findings. In their response the MAH confirmed that unlike in adult studies, the pediatric clinical program did not show statistical differences in the quality of life of omalizumab patients.

The discrepancy in Quality of Life results between the adult and paediatric program may be due to various reasons. Several studies have described poor agreement in asthma control as perceived by patients, pediatricians, and as indicated by objective guideline criteria. An important cause may be

poor perception of airway obstruction and symptoms in children with asthma. The children in a different study were not able to perceive the difference between excellent and good asthma control. Baker RR, *et al* (2000) demonstrated that 49% of his population of asthma patients had an inadequate perception of asthma symptoms.

The MAH concluded that omalizumab showed some improvements in the Quality of Life scores, for all domains and overall, though not statistically significantly different between the treatment groups. The lack of perception of asthma severity and control might explain the high baseline scores despite being an uncontrolled asthma population. Missed school days, a parameter significantly associated with specific emotional Quality of Life, decreased in omalizumab treated patients. In addition, physician overall assessment showed a greater proportion of omalizumab patients achieved marked improvement.

The CHMP considered that either did not the omalizumab treatment improve the overall Quality of Life to any significant degree or the used instruments could not detect an improvement. This situation is not unique for paediatric asthma studies. Any further analysis of the IA05 data will probably not come closer to a definite explanation.

Exploratory secondary efficacy assessments

- Patient's and investigator's global evaluation of treatment effectiveness

The proportion of investigators rated as having 'Excellent' treatment effectiveness was higher (32.2% vs. 13.2%), and the proportions having 'Moderate' or 'Poor' Treatment effectiveness lower in the omalizumab group compared to the placebo group; the difference between groups was statistically significant ($p < 0.001$) using the Cochran Mantel Haenszel test stratifying for dose schedule. The EU population's results were not presented by the MAH, only for the full mITT population.

I.2.2.3 Supportive studies

Study IGE025A IA05

The results from the IA05 subpopulation with severe asthma defined by the CHMP were presented above. Analysis of all the data showed that both the asthma medication and allergen history at baseline by the treatment groups were similar.

The discontinuation rate between the omalizumab and placebo groups was similar. No apparent attrition bias was introduced. No obvious differences between the two treatment arms can be detected.

The numerical point estimate of the primary endpoint for the full population was very similar to the estimate for the EU population. Due to the increased number of patients, the p-value will be lower. The results support the result of the primary endpoint for the EU population.

The differences in exacerbation rate considering the dosing (2-weekly vs. 4-weekly) was similar as for the EU population.

Study 010C

Study 010C was a 7-month, double-blind, randomised, placebo controlled study with a 5-month open-label extension period with the aim to assess the safety, tolerability, steroid-reduction, pharmacokinetics, and pharmacodynamics of omalizumab in children 6 to 12 years of age with allergic asthma requiring daily treatment with inhaled corticosteroids. Eligible patients were those with moderate to severe allergic asthma, receiving daily inhaled corticosteroids (beclomethasone dipropionate 168-420 mcg/day) and as needed or regular use of bronchodilator therapy. Following a 4-6 week run-in period, patients were randomised to omalizumab or placebo treatment group in a ratio of 2:1 (omalizumab:placebo) for 28 weeks. Inhaled corticosteroid dosing remained stable for the first 16 weeks post-randomisation, followed by steroid dose reduction for the subsequent 12 weeks.

The children included in Study 010C do not fulfil the inclusion criteria requested by the CHMP (high dose ICS (≥ 500 mcg/day fluticasone equivalent) plus LABA) as a basis for a paediatric Xolair indication. The MAH also clearly stated that the 010C study was regarded as supportive.

A paediatric intent-to-treat population (paediatric ITT), a subpopulation of the ITT population, was used for the summaries and analyses of the efficacy data. The paediatric ITT population includes patients who were randomized to double-blind treatment, after excluding patients (a total of 36) who were 12 years or older at the time of randomisation, and who were analysed according to the treatment to which they were randomised. The efficacy data shown in the 010 (core) clinical study report represent the full ITT population which includes all randomized patients.

The analysis methodology applied to Study 010 (core) paediatric ITT population was identical to the planned analysis used for Study IA05. From the rate of asthma exacerbations the population in this study had less severe asthma than the CHMP requested in its Scientific Advice.

I.2.2.4 Conclusions on efficacy

The efficacy of omalizumab in this paediatric group with severe asthma is primarily based on study IA05. The efficacy calculations concern a subset of the patients forming the full IA05 population. CHMP requested that any claims of efficacy should be based on children taking at least 500 mcg/day fluticasone equivalent plus LABA treatment.

The allocation and attrition bias in study IA05 is considered being low.

The primary endpoint was the rate of clinically significant asthma exacerbations during the 24-week fixed steroid treatment period using an imputation method. The endpoint was pre-specified to be measured as the between-group ratio of exacerbation rates using Poisson regression including terms for treatment, country, dosing schedule and exacerbation history.

The rate of clinically significant asthma exacerbations per treatment period using imputation was 0.42 for omalizumab and 0.63 for placebo. The ratio omalizumab/placebo was 0.662 with a 95% confidence interval of 0.441;0.995. The p-value was 0.047.

Clinically relevant and statistically robust effects in favour of omalizumab was demonstrated in the analysis of time to the first clinically significant asthma exacerbation (hazard ratio = 0.627, p = 0.018).

The corresponding results for the adjustable ICS 28 week period and the whole 52 week period demonstrate a continuing and slightly increasing positive effect for omalizumab vs placebo. The ICS adjustments in the EU population during the last 28 weeks of the study were very small indicating that the asthma condition had still room for improvement. However, the decrease in $beta_2$-agonist rescue medication was higher for the omalizumab population than for the placebo population, even if the result was not statistically significant.

Patients with low IgE baseline values seem to benefit less from the treatment than patients with high baseline values, which seems logical considering the underlying biological effect of omalizumab. The cut-off value at which omalizumab may be beneficial is not clear.

The subjective improvements as calculated by e.g. PAQLQ(S) were small in contrast to investigator's global evaluation of effectiveness which was statistically in favour of the omalizumab treatment.

The studies IA05 including the full number of patients, and 010 support the findings from IA05 EUP population.

I.2.3 Clinical safety

The MAH has presented the safety data for five different populations according to the type of clinical trial. The safety population comprised all patients 6 to < 12 years of age from clinical studies who received at least one dose of study drug, or for a standard therapy-controlled patient, had been randomised and provided any post-randomisation data.

Table 5. Population groupings for safety assessment

Database	Studies	Patients aged 6-11 (safety population)	Safety topics Subgroup analyses
AAP population (all double-blind, placebo-controlled studies in allergic asthma)	IA05, 010 (core) (<12 years at baseline)	926	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs. Subgroups: by age group, gender, race, disease severity
AAO population (open-label, controlled and uncontrolled studies in allergic asthma)	Q2143g, Q2195g, Q2461g, 010ext, 010ext1 (<12 years at baseline)	407	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results
APC population (all double-blind, placebo-controlled studies in any indication)	IA05, 010 (core), D01 (<12 years at baseline)	1026	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results. Subgroups: by age group, gender, race, disease severity
EUP population (sub-group of double-blind, placebo-controlled studies in allergic asthma)	Pre-planned sub-group of IA05, for use in the EU pediatric indication.*	246	Topics: deaths, SAEs, other significant AEs, all AEs, clinical laboratory results, vital signs. Subgroups: by disease severity.
TOT population (all studies with patients < 12 years at baseline)	IA05, 010 (core), 010ext, 010ext1, Q2143g, Q2195g, Q2461g, 0113, D01, Q0626g, Q0723g, Q0694g (<12 years at baseline)	1217	Topics: malignancies

* Pre-planned because this subgroup reflected the severity criteria in the adult/adolescent severe asthma population for which omalizumab is already authorised in the EU.

- The **Allergic Asthma Placebo-controlled** (AAP) population comprises the pooled safety populations from both double-blind, placebo-controlled studies in allergic asthma (IA05 and 010 (core)).
- The **Allergic Asthma Open-label** (AAO) population comprises the pooled safety populations from controlled and uncontrolled open-label studies in allergic asthma (Q2143g, Q2195g, Q2461g, 010E, 010E1).
- The **All Placebo-Controlled** (APC) population comprises the pooled safety populations from all controlled, double-blind studies in any indication (IA05, 010 (core), D01).
- The **EU Pre-planned** (EUP) population is a sub-group of the IA05 study population.
- The **'Total' from all studies** (TOT) population comprises the pooled safety populations from all trials.

The focus on this safety assessment will primarily be on the Allergic Asthma Placebo-controlled and EU Pre-planned populations

Patient exposure

A summary of the overall number of patients exposed and the duration of exposure for the AAP, AAO and EUP populations is presented in the 3 following tables:

Table 6. Duration of exposure to study drug; AAP population

Exposure	**Omalizumab (N=624) n(%)**	**Placebo (N=302) n(%)**
≥ 0 Weeks	624 (100)	302 (100)
> 1 Weeks	624 (100)	302 (100)
> 4 Weeks	620 (99.4)	301 (99.7)
> 12 Weeks	613 (98.2)	291 (96.4)
> 24 Weeks	583 (93.4)	282 (93.4)
> 28 Weeks	487 (78.0)	228 (75.5)
> 52 Weeks	292 (46.8)	145 (48.0)
Exposure (Weeks)		
Mean (SD)	42.0 (13.51)	42.3 (13.85)
Median	52.0	52.0
Min	2.1	2.1
Max	68.4	64.3
Total patient-years	502.9	244.6
Mean patient exposure (years)	0.81	0.81

Table 7. Overall exposure of study medication by treatment group; AAO population

Exposure (Weeks)	**Controlled**		**Uncontrolled**		**Total**
	Omalizumab (N=85) n(%)	**Control (N=43) n(%)**	**Omalizumab Re-treatment (N=240) n(%)**	**Omalizumab New treatment (N=110) n(%)**	**Omalizumab (N=386) n(%)**
Mean	25.3	25.4	121.6	91.2	103.5
SD	8.03	8.64	80.08	79.64	81.69
Median	24.4	25.0	69.7	28.2	54.0
Min	2.1	0.1	29.3	6.1	2.1
Max	41.2	20.9	559.3	192.2	765.6
Mean patient exposure (years)	0.49	0.49	2.33	1.75	1.98

Table 8. Duration of exposure to study drug; EUP population

Exposure	Omalizumab (N=624) n(%)	Placebo (N=302) n(%)
≥ 0 Weeks	166 (100)	80 (100)
> 1 Weeks	166 (100)	80 (100)
> 4 Weeks	166 (100)	80 (100)
> 12 Weeks	164 (98.8)	76 (95.0)
> 24 Weeks	155 (93.4)	75 (93.8)
> 28 Weeks	154 (92.8)	74 (92.5)
> 52 Weeks	111 (66.9)	53 (66.3)
Exposure (Weeks)		
Mean (SD)	49.8 (9.57)	49.1 (11.11)
Median	52.1	52.3
Min	8.3	7.0
Max	68.4	58.6
Total patient-years	158.3	75.2
Mean patient exposure (years)	0.95	0.94

In the AAP population, a higher percentage of placebo treated patients aged 6-9 years had exposure for greater than 28 weeks (and subsequent categories) than those aged 10-11 years by approximately 10% (> 28 weeks exposure 69.1% in 10-11 years, 79.2% in 6-9 years). Mean and median durations of exposure were similar between age categories, as was the mean exposure in patient years.
In the AAP population, exposure was similar between males and females, with a mean exposure duration to omalizumab of 41.7 and 42.9 weeks, respectively.

In the uncontrolled studies included in the Allergic Asthma Open-label (AAO) population, a higher percentage of re-treatment patients had over 28 weeks treatment than new treatment patients (100% re-treatment versus 50.0% new treatment). This is due to the original treatment period being included in the exposure calculation.

Mean patient exposure in years was similar between treatment groups in the controlled study, but lower for new treatment patients in the uncontrolled studies. Overall mean exposure to omalizumab in all AAO studies was approximately 2 years.

The demographics in the treatment arms were fairly similar except for the fact that there were almost double males than females in the overall population (AAP, AAO and EUP).

The main population for analysis is the AAP population consisting of patients from the pivotal IA05 study, and Study 010 (core). Both of these studies were restricted to children with allergic asthma who demonstrated reversibility in FEV1 following the administration of a short acting $beta_2$-agonist and were confirmed to have allergies. The severity of disease did vary between groups since patients in Study IA05 were to have demonstrated inadequate symptom control as well as exacerbations in the past year, and to therefore be uncontrolled on their current medication, whilst in Study 010 (core), it was intended that patients should be controlled on their current dose of ICS.

In the AAP population, 86.7% of randomised patients completed the trials, with the main reasons for discontinuation being withdrawal of consent and administrative problems. Adverse event discontinuations were seen for 4 patients, with no abnormal laboratory values leading to discontinuation.

Adverse events

Approximately 90% of patients in both treatment arms experienced an AE. The most frequently affected organ classes were infections and infestations, respiratory thoracic and mediastinal disorders and gastrointestinal disorders (all greater than 25%).

Table 9. Most frequently affected primary system organ classes (at least 3% of patients in any group); AAP population

Primary system organ class	Omalizumab (N=624) n (%)	Placebo (N=302) n (%)
Patients with ≥1 AE	**560 (89.7)**	**277 (91.7)**
Infections and infestations	480 (76.9)	253 (83.8)
Respiratory, thoracic and mediastinal disorders	199 (31.9)	104 (34.4)
Gastrointestinal disorders	166 (26.6)	79 (26.2)
Nervous system disorders	148 (23.7)	69 (22.8)
General disorders and administration site conditions	122 (19.6)	59 (19.5)
Skin and subcutaneous tissue disorders	104 (16.7)	46 (15.2)
Injury, poisoning and procedural complications	92 (14.7)	41 (13.6)
Musculoskeletal and connective tissue disorders	55 (8.8)	29 (9.6)
Eye disorders	33 (5.3)	27 (8.9)
Immune system disorders	24 (3.8)	16 (5.3)
Psychiatric disorders	16 (2.6)	12 (4.0)
Blood and lymphatic system disorders	8 (1.3)	9 (3.0)

The most frequently reported AEs were nasopharyngitis, upper respiratory tract infection and headache. The majority of AEs were reported by a higher percentage of patients in the placebo group.

All differences of adverse events which had a 3% or greater difference in their frequency within treatment groups between dosing frequency subgroups were less than or equal to 8%. The majority of the differences were seen in the placebo treatment group, with all but viral upper respiratory tract infection, otitis media, and pharyngitis streptococcal being more frequently reported by patients on the 2-weekly dosing schedule. In the omalizumab treatment group, four AEs were more frequent by at least 3% in the 4-weekly schedule, and two on the 2-weekly schedule. Vomiting and upper respiratory tract infections were seen more frequently with 4-weekly dosing in the omalizumab group but were more frequent with twice weekly dosing in the placebo group.

The incidence of AEs was generally higher in the uncontrolled studies than for the controlled. In the study, the percentage of patients reporting AEs by system organ class was similar in the omalizumab and control treatment groups, with the exception of nervous system disorders, skin and subcutaneous tissue disorders and general disorders and administration site conditions which were reported by a higher percentage of patients in the omalizumab treatment group.

In the controlled studies the incidence of AEs was similar between the omalizumab and control treatment groups. Sinusitis was more frequently reported in the control group, as was influenza, gastroenteritis, wheezing and status asthmaticus.

In the uncontrolled studies, upper respiratory tract infection, sinusitis and headache were the most frequently reported preferred terms.

Approximately 94% of all patients experienced at least one AE in the EUP population. The profile of system organ classes affected by AEs in the EUP population was similar to that in the AAP

population, although rates of AEs in some system organ classes were slightly higher in the EUP population than the AAP. These system organ classes were infections and infestations; respiratory, thoracic and mediastinal disorders; nervous system disorders; general disorders and administration site conditions; injury, poisoning and procedural complications; eye disorders; immune system disorders; and psychiatric disorders.

The most frequently reported AEs in the EU population treatment groups were nasopharyngitis, upper respiratory tract infection and sinusitis. The majority of AEs were reported by a higher percentage of patients in the placebo group. For those preferred terms reported more frequently in the omalizumab group, the following AEs showed a greater than 1.5% difference between treatment groups: abdominal pain upper; pyrexia; nasopharyngitis; ear infection; gastroenteritis viral; viral infection; urinary tract infection; postnasal drip; and eczema. Of these AEs, the greatest difference between omalizumab and placebo was seen for pyrexia, where the difference was 10%.

There was no apparent pattern in terms of which dosing schedule subgroup was more likely to be affected by AEs that showed at least 3% differences between subgroups.

For the APP population the incidence of AEs was less frequent in the omalizumab treatment group than in the placebo group, in particular in the >28-52 week period. The greatest percentage of patients experiencing AEs was during the >12-28 week period. This period corresponds to the steroid reduction phase in Study 010 (core) and the beginning of the steroid adjustable phase in study IA05.

There was no apparent pattern in terms of which dosing schedule subgroup was more likely to be affected by AEs that showed at least 3% differences between subgroups. There are no obvious safety signals in the presented data. Pyrexia had similar frequencies between treatment arms in the AAP population, but was considerably higher for the omalizumab arm in the EUP population

Adverse events by exposure in the EUP population

Up to 12 weeks, the total rate of AEs was very similar in each treatment group, but in later periods, the placebo group showed a higher total rate of AEs, as also was seen in the whole IA05 safety population. The total rate of AEs in the omalizumab group remained constant up to week 52, but increased somewhat after week 12 in the placebo group. Infections and infestations was the system organ class most commonly affected by AEs in all time periods.

Up to 12 weeks, a few AEs, notably gastrointestinal disorders (vomiting and diarrhea) pyrexia and nasopharyngitis were more frequent in the omalizumab group, although upper respiratory tract infection was more common with placebo.

From week 12 to 28, there were again few differences in AEs rates between treatments: headache and cough were more frequent in the omalizumab group and pharyngitis, viral upper respiratory tract infection and pharyngolaryngeal pain were more frequent in the placebo group

From week 28 to 52, nasopharyngitis and gastroenteritis were more frequent in the omalizumab group, whereas vomiting, sinusitis, upper respiratory tract infection, bronchitis, pharyngitis, headache, and cough were more frequent in patients receiving placebo.

Beyond week 52, AEs were reported by 15.3% of patients in the omalizumab group and 20.8% in the placebo group. The only notable difference between treatment groups was for nasopharyngitis, which was more frequent in the placebo group.

Adverse events related temporally to injection days or representing injection site reactions

In the AAP population 6.1% of patients in the omalizumab, and 7.0% of patients in the placebo treatment groups experienced an adverse event on the first day of injection.

In the EUP population, a higher proportion of the placebo group (16.3%) experienced an AE on the first day of injection than was the case in the omalizumab group (6.0%). Most of these AEs were mild: only one severe AE was reported, a case of abdominal pain in a patient in the omalizumab group.

In the AAP population, adverse events were reported on any injection day for 33.2% of the omalizumab treated patients, and 36.1% of the placebo treated patients.

In the EUP population, adverse events occurring on any injection day were reported by 41.6% of the patients in the omalizumab group and 51.3% of the placebo. Infections and infestations was the system organ class most commonly affected by AEs. There were no major differences between treatment groups in rates of specific AEs.

Injection site reactions (in the combined safety population from studies 010 (core), D01, IA05 and Q2143g) were for erythema 0.8% and 0.1% (omalizumab vs. placebo). The corresponding numbers for pruritus were 1.0% and 0.5%.

In the omalizumab EUP population group 4/166 (2.4%) patients reported a local injection site reaction compared to 4/80 (5%) in the placebo group. Injection site pain and injection site swelling were the most common AEs of this type in the placebo group; injection site pruritus was the most common reaction in the omalizumab group (1.2% vs. 1.3% for placebo). Injection site reactions in both treatment groups were more often of mild than of moderate intensity.

However, there is no consistent pattern in the injection site reactions

Events suspected to be related to treatment.

In the AAP population, there were no adverse events suspected by the investigator of being study drug related with a frequency of 3% or higher. Those AEs suspected of being related to the study drug with a frequency of 1% or greater were: headache, dizziness, cough, abdominal upper pain, erythema and urticaria.

In the EUP population, only one adverse event (headache) was suspected by the investigator of being study drug related in more than 1% of omalizumab-treated patients.

The MAH has already included the relevant information above in the proposed SPC.

Deaths - SAEs

There were no deaths during any of the studies.

In the AAP population there was a higher percentage of patients with SAEs in the placebo treatment group than in the omalizumab group. Most SAEs were reported by only one or two patients, with the exception of appendicitis (higher in omalizumab group) and pneumonia (higher in placebo group). The incidence of respiratory or infectious SAEs was similar in the omalizumab and placebo groups.

In the EUP population a greater proportion of patients in the placebo treatment group had SAEs than was the case in the omalizumab group. With one exception (pneumonia in the placebo group, which was reported in two patients) SAEs were reported by at most only one patient per treatment group. Most SAEs were infections; the rate of these was higher in the placebo group than the omalizumab group. There were no SAEs in either treatment group affecting the system organ class Respiratory, thoracic or mediastinal disorders. One pregnancy was reported in the placebo group. One SAE was suspected of being study drug related, a case of tic in the omalizumab group.

Adverse events of special interest

The most common adverse events with special interest were under the terms skin rash, urticaria, hypersensitivity and bleeding disorders for the both AAP and EUP populations.

Patients with the cluster of adverse events considered possible components of serum sickness are shown in the table below for the AAP population. The percentage of patients with clusters of terms potentially related to serum sickness syndrome was small, and similar between treatment groups.

The MAH has already included the relevant information in the proposed SPC.

Anaphylaxis

In the AAP population, one patient in each treatment group experienced an adverse event described as anaphylaxis by the investigator, both were moderate. One omalizumab patient reacted to pethidine hydrochloride, and one placebo to ingestion of nuts.

The proposed SPC mentions anaphylactic reactions, however the above findings were not deemed related to the data presented for the paediatric population.

Malignancy

The total populations from all studies were used to assess the incidence of malignancy. There was one patient who reported a malignancy (medulloblastoma) and this patient received placebo treatment in Study IA05. No other cases were reported.

Laboratory findings - Haematology

There was a shift from baseline to post-baseline measurements for the AAP population for the main hematology parameters. There were five patients who shifted to low platelet count by notable criteria.

In Study IA05, there were three omalizumab patients with platelet counts ≤ 75x109/L or with a ≥ 50% decrease from baseline had values within normal range at baseline.

None of these patients experienced AEs associated with bleeding disorders or viral illnesses.

In study 010 (core), there was one omalizumab patient and one placebo patient with a low platelet count reported post-treatment.

The shift from baseline to post-baseline measurements for the EUP population for the main hematology parameters was similar to the AAP population.

One patient in the omalizumab group shifted to low platelet count by notable criteria. This patient had no AEs associated with bleeding disorders or viral illnesses.

The shift of White Blood Cell count (WBC) to low values was more pronounced in the EU population compared with the AAP population. In the AAP population 10.4% of the omalizumab patients had a low WCB count vs. 9.6% for placebo. The corresponding numbers for the EUP population was 21.7% for omalizumab vs. 16.3% for placebo.

Thrombocytopenia has earlier been identified as a potential problem following treatment with omalizumab. The paediatric data can support that view due to different pattern in WBC shifts in the AAP and EU population. Information about this issue is present in the proposed SPC text. The CHMP requested that the different pattern in WBC shift in the AAP and EU populations should be commented by the MAH.

The MAH responded that there has been increasing evidence in the scientific literature that the number of neutrophils in the airways is increased in patients with chronic severe or acute fatal asthma. Neutrophils have been shown to be associated with severe asthma, instability of asthma, sudden-onset fatal asthma and status asthmaticus. The magnitude of neutrophilic inflammation has been correlated with eosinophilic inflammation in severe persistent asthma. Patients with high neutrophilic inflammation have showed a significantly higher percentage of sputum eosinophils as compared with 'non neutrophilic' asthmatic patients. The effects of the different treatment options available have shown that long-acting β_2 agonists may have an antineutrophilic effect.

In pivotal Study IA05 the predefined analysis plan identified a specific subset of patients with high dose ICS (≥ 500 µg/day fluticasone equivalent) plus LABA, henceforth referred to as the EUP population. This population reflected the approved omalizumab population of patients 12 years or older, as well as following GINA guidelines. This EUP population subset of patients represents 41% of Xolair patients and 39.5% of placebo patients in study IA05.

The Allergic Asthma Placebo-controlled (AAP) population comprised the pooled safety populations from both double-blind, placebo-controlled studies in allergic asthma (IA05 and 010 (core)). The AAP population as a whole is not identical to the IA05 population. In the overall pediatric clinical program a different pattern in white blood cell count (WBC) shift was seen between the AAP and EUP populations. The frequency of low WBC in AAP (Omalizumab: 10.4% vs placebo: 9.6%) was different from the frequencies observed in the EUP pop (Omalizumab: 21.7% vs placebo: 16.3%). However, the changes of WBC from baseline to final visit in both in the AAP and in the EUP populations were similar in omalizumab and placebo groups.

The appropriate population comparison was done between what was denominated as the EUP population (those with high ICS dose plus LABA at baseline) and the rest of patients, which are referred to as the non-EUP. A comparison of the AAP population and EUP population was not appropriate as the AAP population includes the EUP population.

There was no statistically significant difference in the frequency of low WBC among treatment groups in each population studied. However, there is a higher % of patients, both in omalizumab and placebo treated groups, with low WBC in the EUP population. The EUP population, as previously described, is a specific subset of patients with high dose ICS (≥ 500 µg/day fluticasone equivalent) plus LABA, within study IA05. The EUP population received an average ICS dose (fluticasone equivalent) of 744 µg/day, whereas the non-EUP received at baseline an average ICS dose (fluticasone equivalent) of 282.1 µg/day. With respect to additional co-medications, all patients in the EUP population were exposed to LABA, whereas only 26% of patients in the non-EUP were.

In summary, there were no significant differences in the frequency of low WBC between omalizumab and placebo patients, but there were differences among populations. The EUP exposed to higher doses of ICS, and to LABAs have a higher frequency of low WBC. The CHMP concluded that the MAH's explanation of the WBC counts in the different populations is supported by data. Any direct influence of omalizumab on the WBC is likely to be minimal.

Conclusions on clinical safety

The safety data presented in this paediatric variation application has not identified any unknown safety concerns regarding omalizumab.

The omalizumab exposure in the paediatric population (> 6 years of age) is considered to be large enough, both in time and in numbers of patients, to have a relatively adequate opinion of the expected safety concerns concerning omalizumab treatments with duration of at least 1 year in 156 patients and 3 years in 81 patients. Longer follow up should additionally be considered.

The initial apprehensions about potential severe adverse events related to omalizumab have been modified (reduced) as continuously new safety data are analysed.

The most commonly reported adverse event were respiratory infections which occurred for slightly more placebo patients. Most adverse events frequencies were similar between the omalizumab and placebo treatment arms.

Two anaphylactic reactions in the paediatric studies were most probably not related to any of the study drugs.

"Serum sickness" is present also in the paediatric population, even if the symptoms in the vast majority were mild.

Local reactions were not a cause for concern.

A limited number of cases of thrombocytopenia are reported. Two cases of severe thrombocytopenia were reported in study 010, one in the omalizumab and one in the placebo arm (31 and 21 $x10^9$ respectively). All thrombocytopenia patients returned to acceptable levels.

I.2.4 Pharmacovigilance – Risk Management Plan

The MAH submitted an updated version (Version 3) of the omalizumab RMP with the paediatric variation. This updated Risk Management Plan (RMP) addresses the safety profile of omalizumab in patients 6 years of age and older. The experience in the paediatric population of approximately 1200 patients 6 - < 12 years of age has been included in this version of the RMP.

Hypersensitivity Reactions – "skin prick" test results

During the latest RMP (Version 3) assessment there was noted that there were no milestones for the development of the two types of "skin prick" tests. The MAH was advised that in the updated RMP it should be present the estimated dates when the tests may be finalised and how the results will be communicated to health authorities. Also, the MAH was asked to present a more detailed description of the two "skin prick" tests, e.g. how they were intended to be used as well as a detailed description of the study designs.
In their answers the MAH committed to develop a "Skin Prick" test in patients with clinically reported hypersensitivity reactions associated with omalizumab administration to detect reactive IgE antibodies to Omalizumab or excipients in the formulation. Thirty normal subjects and allergic asthmatic patients will be studied to examine the validity and safety of the procedure.
In a second phase the MAH committed to establish an observational repository of cases of severe hypersensitivity reaction associated with omalizumab administration and appropriate controls. This repository will be a prerequisite to the conduct of a subsequent study that will assess the risk of severe hypersensitivity reaction associated with omalizumab use among repository cases and controls. Data collected for each case will consist of clinical history, serum for reactive antibody tests and allergy skin test results.
In the RMP version 3, the MAH also stated that a Risk Minimisation Action Plan (RiskMAP, which in the meantime has been replaced by the REMS.) is planned to be submitted to the Regulatory Authorities concerning anaphylaxis / anaphylactoid reactions.

Since hypersensitivity reactions are of major concern, information on the riskMAP study plans as well as future results are also requested for submission to EMEA and the CHMP. In Europe these measures would be components of a Pharmacovigilance plan. In addition close surveillance and characterisation of such reactions should continue for more than the first two years.

Off-label Use

Off-label use has now been included as a potential risk, and information on the magnitude of the problem from drug utilisation study (DUS) has been provided.

However not all forms of potential off-label use were mentioned in RMP Version 3.0. Use in children with weight under 20 kg and in persons with weight over 150 kg should also be mentioned and reported, as well as other underlying disease states than asthma. Continuous reporting on all kinds of off-label use in PSURs is recommended .

Awareness, Tracking, Usage (ATU) study

The Awareness, Tracking, Usage (ATU) study (market research) for the specific monitoring is described in the RMP and information is summarised in the table below:

Table 3-2 Specific monitoring plan

Approach	Description	Methodology
ATU (annual)	Physician Market research study conducted annually across Top5 EU Markets (Germany, France, UK, Italy and Spain) designed to assess utilization of omalizumab and awareness of key aspects of the omalizumab EU label plus awareness of the risks associated with prescribing omalizumab . The survey is designed to be representative of the broader universe of omalizumab prescribers. Specific questions will address the following areas: Awareness of omalizumab indication for severe, persistent, allergic asthma and prescribing within this indication Awareness of indicated age range Awareness of indicated weight & IgE ranges Awareness of EU dosing table Awareness of 16 week responder Identification using GETE and associated clinical response Awareness of the risk of post injection Omalizumab anaphylaxis & the need to monitor for an appropriate period of time	Survey targets 50-75 physicians Participants are randomly selected Survey conducted via phone and, or internet Standard market research methodologies employed to ensure surveyed Physicians are representative of overall target list Baseline performance will be established in first research Results will measured by comparison of future survey waves with both the baseline results The first survey is planned to take place during the 2nd half of 2009 with results available by the end of 2009

The comments by the CHMP were that although this market research study has been outlined with a plan for the first survey during 2009, it was not stated how the results will be reported to the authorities.

The MAH responded on this by stating that indeed, an ATU study to assess the effectiveness of related RMP activities on anaphylaxis was conducted in Europe in 2007. Participating countries were United Kingdom, France, Italy, Spain and Germany. The sample population was composed of a total of 296 physicians practicing in these countries. Results became available in 2008, and were presented in PSUR-11 submitted to EMEA and CHMP members on 24 February 2009.

In 2008, another ATU study assessing the same criteria as in 2007 was conducted. The 2008 results will be reported in the upcoming PSUR 12 (cut-off date 31 December 2009).

From 2009 onwards, the ATU study will be changed into an omnibus market research survey. This survey will cover wider respiratory questionnaire than the ATU study was. The criteria assessed in the

2007 and 2008 ATU will continue to be part of the questionnaire and are planned to be reported in future PSURs.

Safety Specification in RMP Version 3.0

Table 1-58 Ongoing safety concerns

Risk group	Risks
Important identified risks	• Anaphylaxis/anaphylactoid reactions • Malignant neoplasms (in adult and adolescent patients ≥ 12 years old)
Important potential risks	• Malignant neoplasms (in pediatric patients 6 to < 12 years old) • Serum Sickness Syndrome (SSS) / Serum Sickness Like Disease (SSLD) • Antibody formation to omalizumab • Churg Strauss Syndrome / Hypereosinophilic Syndrome • Thrombocytopenia • Parasitic (helminth) infections • Off label use
Important missing information	• Pregnancy outcomes

The list of identified and potential risks for adults and children (from 6 years) can be considered to cover the important suggested safety concerns. It should however be highlighted that knowledge on safety is sparse and long-term data >3 years are missing in the 6 - <12 years old, such that close monitoring of all possible safety concerns including in addition to malignancies also infectious, respiratory, cardiac, neurological and other reactions is mandatory in this population. The MAH has identified methods to collect more information for spontaneous malignancies reports which is appropriate. The MAH following the request by the CHMP will submit a detailed description of how information on the malignancies reports will be collected and discuss the suitability and value of using other data sources.

The only difference in mentioned safety concerns for children 6 - <12 years compared to adolescents and adults concerned malignancy which has been regarded as a potential and not an identified risk, due to absence of any signal in the paediatric clinical program and interim data from the EXCELS study (see also below) of adolescent and adult patients.

Ongoing studies

The studies EXCELS and EXPECT are still on-going. The third interim report of the EXCELS study was provided within this variation application but also in EMEA/H/C/606/FU2/13.3 procedure. Comments and issues identified such as the need for further risk evaluation for specific malignancies and for cardiovascular events, and a discussion on the possible lack of statistical power to detect some increased risks were taken into account during this variation application. The full statistical analysis plan (SAP) for the EXCELS study has been provided by the MAH to the EMEA and it is under assessment by the CHMP.

I.2.4.1 RMP assessment conclusions

Safety specification

The safety profile of omalizumab is mainly established from adult and adolescent patients. However, in data from this variation application, no new safety concerns have been found in children 6-<12 years from a maximal follow up duration of at least 1 year in 156 patients and 3 years in 81 patients (among all reported patients in this age category treated with omalizumab).

In March 2009 the MAH was asked by the CHMP to re-consider the exclusion of patients with a known history of allergies. The MAH agreed to reword the RMP as proposed, in order to provide more clarity on the clinical programme conclusion and actual defined exclusion criteria.

In addition the CHMP had proposed that Serum sickness syndrome (SSS) and Serum sickness like disease (SSLD) should be included as identified instead of potential risks. The MAH agreed to change the risk status of SSS/SSLD from potential to identified and has amended the RMP accordingly.

The list of identified and potential risks for adults and children (from 6 years) is considered to cover the important ongoing safety concerns. In the RMP (Version 3), the only difference in the safety specification for children 6 - <12 years compared to adolescents and adults concerns malignancy which has been regarded as a potential and not an identified risk in children due to absence of a signal in the pediatric clinical program and interim data from the EXCELS 5 year follow-up study in adolescent and adult patients. This is considered acceptable, under the general condition of close monitoring of reports of malignancies and other adverse events in paediatric patients.

Pharmacovigilance plan

Since hypersensitivity reactions are of major concern, the future results of the RiskMAP study plans are requested to be submitted also to the EMEA and the CHMP.

Not all forms of potential off-label use were mentioned in the detailed action plan for off-label use. Use in children with weight under 20 kg and in persons with weight over 150 kg should also be mentioned and reported, as well as other underlying disease states than asthma in all age groups. Continuous reporting on all kinds of off-label use in future PSURs is recommended.

The MAH has committed to gather additional information on the long term safety of omalizumab. In addition to routine pharmacovigilance with reporting in PSURs, also riskMAP studies (including skin tests) concerning hypersensitivity reactions, blood anti-therapeutic antibody identification for suspected cases, the post-marketing studies EXCELS and EXPECT, and targeted follow-up with questionnaires concerning anaphylaxis and malignant neoplasms are included in the Pharmacovigilance plan. Paediatric patients are encompassed in these follow-up measures (except for the EXCEL and EXPECT studies), and overall the Pharmacovigilance plan is considered to adequately cover the important risks at present. However, long-term experience in the new paediatric population (6-<12 years) is insufficient.

The MAH has identifying methods to collect more information for spontaneous malignancies reports which is appropriate. The MAH will submit a detailed description of how information on the malignancies reports will be collected and discuss the suitability and value of using other data sources.

Risk minimisation plan

The ATU market research study has been outlined with a plan for the first survey during 2009. In March 2009 the CHMP requested clarifications on how the results will be reported to the authorities. The status of the ATU-studies performed, have been clarified in the RMP Version 4 and the study will be reported in the next PSUR. The results will available in the future will all be reported in the appropriate PSUR.

The CHMP is of the view that with the paediatric RMP now further updated (Version 4) an adequate risk management level is being fulfilled.

I.3. Overall Discussion

The proposed dosing schedule used in the pivotal clinical trial in paediatric patients (study IA05) has shown to result in suppression of free IgE levels. Under the assumption that free IgE is a good biomarker for the clinical effect, the dosing from a pharmacokinetic pharmacodynamic perspective appears reasonable.

The effect of omalizumab in this subset of severe asthmatic paediatric population (IA05 EU population; 159 in the omalizumab arm, 76 in the placebo arm) was approximately of the same magnitude as for the adult population with similar asthma severity. The pre-specified primary endpoint in the "pivotal" study IA05 was statistically in favour of omalizumab vs. placebo.

The full study IA05 and study 010 support the findings for the EU population.

Secondary endpoints, including time to first clinically significant asthma exacerbation were all in favour for omalizumab vs. placebo or similar between the treatment arms, even if statistically significance was reached only for a few of these endpoints.

Up till now there are no obvious new safety signals detected in the combined paediatric omalizumab studies compared with those found in the adolescent and adult populations.

The RMP (Version 4) has been updated during the assessment of this variation in order to include the comments received by the CHMP.

I.4 Conclusions and Benefit / Risk Assessment

Following the assessment of the new clinical data on safety and efficacy the CHMP concluded that the benefit-risk ratio of Xolair in the proposed new indication for children between 6 and less than 12 years old is positive.

The additional indication for children between 6 and less than 12 years of age is:

> *Children (6 to <12 years of age)*
> *Xolair is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.*