SCIENTIFIC DISCUSSION

1. Introduction

Asthma is a chronic inflammatory condition of the airways that causes repeated attacks of breathlessness, coughing and wheezing. A distinction is made between allergic asthma and non-allergic asthma. Allergic or atopic diseases, also known as Type I hypersensitivity, result from the over-expression of immunglobulin E (IgE) in response to enviromental allergens. Common allergens are house dust mite, pollen, moulds or animal dander. In allergic asthma, exposure to allergen initiates a complex series of events leading to the production of allergen-specific IgE, which binds to high affinity receptors on effector cells such as mast cells and basophils. The cross–linking of these cell-bound IgE molecules by antigen results in the release of pro-inflammatory mediators such as histamine, prostaglandins, leukotrienes, chemokines and cytokines from these cells.

Asthma is primarily treated prophylactically with inhaled corticosteroids and as reliever a short acting β2-agonist. Patients with severe asthma often need both higher doses of inhaled steroids and a long-acting β2-agonist. Other supplemental medications are leucotriene modifiers, sustained-release theophylline and cromones. Some patients might need oral corticosteroids for short or longer periods to control their asthma. Allergen-specific immunotherapy has a documented effect in allergic asthma caused by pollen, cat fur and dust mites. However, multi-allergic patients with severe asthma are very difficult to treat with this method.

The active substance of Xolair is omalizumab. Omalizumab is a recombinant humanized anti-IgE antibody and inhibits the activity of IgE. Omalizumab is inhibiting the binding of IgE to high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reductions in surface bound IgE on FcεRI bearing cells limit the degree of release of mediators of the allergic response.

Xolair indication is:
"Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 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 reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Xolair treatment should only be considered for patients with convincing IgE mediated asthma (see section 4.2)."

The dose applied for is 150 – 375 mg of Xolair subcutaneously every two or four weeks, depending on baseline serum total IgE level measured before the start of the treatment, and body weight.

Xolair is available as 75 mg and 150 mg powder and solvent for solution for injection.

A previous application, for the use of omalizumab in the treatment of Seasonal Allergic Rhinitis (SAR) and Allergic Asthma (AA) in adults and children (from 6 year old), was made to the EMEA in June 2000. The benefit/risk analysis was not assessed positive for this heterogeneous population, e.g. because of a limited effect in a patient population not optimally treated with recommended therapy and safety concern related to thrombocytopenia found in young monkeys. Following discussions with the CPMP, the application for a label for asthma patients below the age of 12 and for patients with SAR was withdrawn, and a sub-population of patients for whom omalizumab could have a better benefit/risk relationship was identified, initially defined as patients at high risk of asthma-related mortality. At that time, a study (2306) was already planned in patients with severe allergic asthma. Following a scientific advice from CPMP in July 2002 the protocol was changed to better reflect the CPMP requirements. The target population was defined as patients with severe allergic asthma inadequately controlled by high doses of inhaled steroids and long acting beta2 agonists, who had experienced either at least two asthma exacerbations or one requiring oral steroids, the year prior study.

2. Part II: Chemical, pharmaceutical and biological aspects

Introduction

Omalizumab, the active substance in Xolair, is a recombinant humanised anti-IgE antibody. Omalizumab binds to the FcεR1 epitope of human IgE, preventing human IgE from binding to its receptor on mast cells and basophils, thus inhibiting the histamine release response normally triggered by exposure to allergens. Omalizumab is produced in suspension cell culture using a Chinese Hamster Ovary (CHO) cell line.
Xolair is a powder and solvent for injection to be administered by subcutaneous injection and is presented in two strengths: 75 and 150 mg of omalizumab. The lyophilised powder is for reconstitution with solvent and is presented in 5 ml glass vials (Type I, Ph. Eur.), with a rubber stopper and an aluminum flip-off cap. The lyophilised powder contains omalizumab, sucrose, histidine, histidine hydrochloride monohydrate, and polysorbate 20. The product does not contain ingredients of animal or human origin. The solvent is sterile water for injection provided in glass ampoules containing 2 ml of water.

Active substance

Manufacture

Omalizumab is manufactured and controlled at the following sites:

- Genentech Vacaville, 1000 New Horizon Way, Vacaville, CA 95688, USA (referred to as "*Vacaville*")
- Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080-4990, USA (referred to as "*SSF*")

The South San Francisco site is the manufacturer of Master and Working Cell Banks only.

The original site of omalizumab manufacture for most of the clinical trial material and the qualification lots was Genentech's South San Francisco facility. The manufacturing facility for the material to be marketed is Genentech's Vacaville facility. A manufacturing site transfer was performed in year 2000. Drug substance manufactured in Vacaville has also been used in clinical study 2306 (pivotal study).

Genetic development
During development a mouse monoclonal antibody was selected from a pool of hybridomas designed to identify an antibody with the desired specificity and affinity for the appropriate site on the target IgE molecule. Humanisation was accomplished by replacing key amino acids in human IgG1 with those from the selected antibody , primarily in the complementary determining regions, and evaluating the properties of the resulting molecules. Subsequently, the humanised antibodies performing best were selected based on their high affinity for free IgE and their inability to bind to IgE when bound to their cell receptor. This ensured that the antibody would not bind to the cell-IgE complex similarly to the formation of an allergen-IgE complex, which would result in histamine release.

The sequence of the entire coding region of the omalizumab DNA has been confirmed. The parent cell line used for hosting the antibody expression sequence was a Chinese Hamster Ovary (CHO) cell line with a well-documented pedigree from the original CHO cell line (CHO-K1). This CHO cell-line is being used by the manufacturer for other marketed recombinant products and was selected for its performance in culture (reduced insulin requirement and growth in serum free medium). Transfection with the plasmid bearing the antibody sequence was accomplished by standard electroporation methods and clones were screened for secretion of intact, active omalizumab molecules. Through screening, a clone was selected based on its high expression levels for production of omalizumab for use in Phase I and II studies. A clone performing better was subsequently selected for producing the antibody at higher scale. The material produced from this second clone was comparable to the material from the first cell line and was used in some Phase I and II studies, in all Phase III studies, and is intended for marketing.

Cell banking system
The manufacturer has prepared both the Master Cell Bank (MCB) and Working Cell Bank (WCB) using serum-free media. The only protein used in the medium for these banks is recombinant human insulin. Both banks were prepared using standard cryopreservation techniques employing DMSO as the cryopreservative and are stored in controlled liquid nitrogen freezers. Additional WCBs can be generated from the MCB as needed and according to an established protocol.
The manufacturer has demonstrated genetic stability of the expression system during production as recommended in the ICH Guideline "Analysis of the expression construct in cells used for production of rDNA-derived proteins" by using restriction digest analysis, copy number analysis, and northern blot and nucleotide sequencing techniques. The nucleotide sequence in the MCB presents no detectable differences with the sequence in the plasmid used for creating the cell line. No rearrangements, deletions or insertions within the protein coding nucleotide sequence were detected in the MCB, or end of production cells (EPC), both of which contain comparable copy numbers of the omalizumab gene. No aberrations were detected in the mRNA of the MCB and EPC and the mRNA transcription pattern (evaluated by northern blot analysis) of the MCB and EPC was also consistent. Peptide mapping confirmed the correct protein sequence of the entire molecule. The maximum cell age has been adequately defined based on omalizumab protein characteristics.

Production
Omalizumab is produced in a batch-fed suspension cell culture. The process, which has been adequately described in the application, involves culturing cells in three stages:

- Seed train stage: the seed train is used to provide a continuous source of cells maintained under selective pressure.
- Inoculum train stage: the inoculum train is used to expand the cell population for introduction into production culture.
- Production stage.

To initiate a seed train, an ampoule from the Working Cell Bank (WCB) is thawed and the culture is expanded under selective pressure in either spinner vessels and/or bioreactors. A process of continuous subcultivation in selective medium is used to maintain the seed train. To provide inocula for omalizumab production cultures, a portion of the seed train cell population is expanded by serial subcultivations using non-selective medium in stainless steel bioreactors of increasing volumes. The production culture is initiated by transferring cells to a bioreactor containing non-selective, serum-free production medium.

Critical parameters are monitored and controlled during the entire cell culture process. All media and gases to be added are passed through a 0.22 µm or less sterile filter. Multiple production batches may be derived from a single seed train. Following production, culture fluid containing omalizumab is separated from the cells by centrifugation and may be held refrigerated prior purification for a limited number of days, which has been adequately justified.

Purification
The purification process has been adequately described and consists of 3 consequential chromatographic steps: immobilised protein A affinity chromatography, followed by cation exchange chromatography (on SP Sepharose), followed by anion exchange chromatography (on Q Sepharose).

The eluate obtained from the last chromatographic step is concentrated by ultrafiltration and diafiltration and formulated as "bulk for storage". For storage the omalizumab formulated drug substance is filtered (0.22 µm) and filled into high capacity stainless steel tanks, which can be used for long-term storage and transportation at -20°C. The formulated drug substance, which undergoes routine release testing, is stored at 2-8ºC or -20°C until further processing to finished product.

Compendial and noncompendial raw materials and reagents are used in cell culture and in the purification steps of omalizumab. Raw materials specifications have been set for each non-compendial reagent. Detailed information on the raw materials of bovine origin is provided and documentation to

demonstrate that there is minimal risk for transmission of TSE is provided. The capability of the manufacturing process to remove or inactivate any potentially introduced adventitious agent is discussed below.

Overall, the production and purification processes are controlled by adequate in-process controls and have been adequately validated on the basis of data obtained from three full-scale batches produced at the "Vacaville" manufacturing site.

- **Specification**

The structure of omalizumab has been extensively characterized using a battery of standard protein and carbohydrate analytical methods on four batches manufactured at SSF. Tests revealed that omalizumab was the major product along with the batch-to-batch consistent occurrence of minor molecular variants of omalizumab, which have been satisfactorily characterized using a combination of physicochemical methods as well as tested for potency. The amounts of soluble aggregates as measured by size exclusion chromatography were consistently less than 1% in all tested batches.

Several biological methods have been used for the determination of the biological activity of omalizumab among which one was chosen as the standard potency assay. This assay measures the ability of omalizumab to inhibit binding of IgE to its receptor which was shown to correlate to the inhibition of release of histamine. For the purpose of biological testing, a primary reference material was established using two lots of omalizumab "*bulk for storage*" manufactured in 1997. A secondary reference material was subsequently prepared for use in all assays requiring omalizumab reference material. This secondary reference material, which is the current reference material, was manufactured in 2001 using the pool of three lots of omalizumab "*bulk for storage*" manufactured in Vacaville and was qualified against the primary reference material. The reference material is stored at -70 ºC.

The process related impurities are host-cell related impurities (DNA and CHO proteins), low molecular weight substances used during production and leached Protein A (from affinity chromatography column). Levels of these impurities have been monitored in numerous batches. The results show consistent reduction of the impurities and their levels were below the quantification limit of the assays used.

Overall, analytical methods have been adequately described and validated and satisfactory specifications have been set based on results obtained with the lots used in the clinical studies, as well as based on the established manufacturing and assay variability. Results were provided for three of the process validation lots manufactured in South San Francisco, three consistency lots manufactured in Vacaville, and two additional commercial scale lots from South San Francisco used in clinical trials and toxicological studies.

- **Stability**

Stability studies for omalizumab have been performed with three qualification lots manufactured in South San Francisco and three commercial scale lots manufactured in Vacaville under long term storage conditions for up to 49 months and under accelerated conditions for up to 1 month. Additionally, a study involving three freeze/thaw cycles has been performed as well as stress tests at higher temperature. With the exception of some tests, all tests in the release specifications were included in the stability studies. This was considered acceptable.
No marked changes in purity, potency, and physical characteristics were observed in the lots tested after storage. After freezing/thawing no changes could be observed in the amount of Fab variants, aggregates, potency, and strength. After storage under stress conditions a significant increase of degradation products (Fab variants) and a decrease in potency could be observed.

Based on the presented stability results, the proposed storage conditions and shelf life with a defined maximum of freeze/thaw cycles, was considered to be acceptable.

Medicinal Product

- **Pharmaceutical Development**

The rationale behind development of the formulation has been adequately documented. Degradation and aggregation can be minimised when omalizumab is formulated at a pH of 5.5 to 6.5, in excipients including histidine, sucrose, and polysorbate 20. These excipients are well known and often used in this type of product to prevent degradation, aggregation and particulate formation during manufacturing, lyophilisation, shipping, and storage. No incompatibilities between these excipients and the drug substance have been observed in stability studies with the drug substance or the drug product. At the final protein concentration of 125 mg/ml, omalizumab shows good solubility, but because of the limited physical and chemical stability at this high concentration, resulting in aggregation, isomerization and charge variants, long-term storage as a lyophilisate was preferable.

Initially, a liquid formulation of omalizumab was used in early clinical trials before efficacy data indicated that a higher dose would be required. A lyophilisate was therefore developed to allow subcutaneous dosing at higher concentrations.

Because of the high viscosity of the drug product after reconstitution, an overfill is necessary to ensure that the required dose can be withdrawn from the vial. For the 150 mg formulation, an overfill of 35% is necessary to ensure that 1.2 ml can be withdrawn. For the 75 mg formulation, the overfill is 73%, and to ensure delivery of 75 mg in 0.6 ml, the lyophilisate has to be reconstituted with 0.9 ml of diluent.

For the 150 mg formulation, a modification to the formulation was introduced late in development (end of 2002). Initially, the drug product vials used in the pivotal clinical trials were stoppered after lyophilisation under "*full vacuum*". This was also used for the process validation. Due to the observation that 1-3% of the vials lacked full vacuum, a process change to stopper the vials under "*partial vacuum*" with nitrogen was introduced. The differences between the manufacturing processes for the product used in the pivotal clinical trials and the product proposed to be marketed were adequately described, and were shown, with a comparability study, to not have any significant impact on quality and stability of the product.

The 75 mg formulation was introduced later during development and is identical to the 150 mg formulation.

- **Manufacture of the Product**

The manufacturing process, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail. The lyophilised powder is manufactured by Genentech (South San Francisco, CA, USA). The reconstitution diluent, i.e. sterilised water for injections (Ph.Eur), provided in a 2 ml ampoule of colourless borosilicate type I glass (Ph.Eur), is manufactured by Nycomed Austria (in Linz). Novartis Pharma SA, Huningue, France, is responsible for batch release in the EEA, and is also the site where batch testing in the EEA takes place.

None of the excipients, which comply with Ph.Eur, are of human or animal origin.

For the production of the lyophilised powder, the omalizumab "*bulk for storage*" solution is filtered at 0.2 µm into a steam-sterilised filling tank. Multiple "*bulk for storage*" containers may be pooled during filtration. Under aseptic conditions, the solution is filled by weight into sterile, depyrogenated 5 ml glass vials and partially stoppered with lyophilisation stoppers. The vials are lyophilised following a cycle of controlled conditions of temperature, pressure, and time. After the lyophilisation cycle is complete, the vial stoppers are fully seated under nitrogen in the sterile chamber. The vials are then removed for capping and are sealed with aluminium/plastic flip-off type caps.

The production batch has been adequately defined. The acceptance limits of the in-process controls used to monitor critical steps of the manufacturing process of the bulk substance are adequate. Filter integrity is confirmed before and after the sterile filtration performed at the stage of filling. Fill

volumes are checked by weight regularly throughout the filling process. Every vial is inspected for defects including product appearance and container/closure defects.

The manufacturing process has been validated on the basis of batch analysis for the 150 mg formulation of 3 full-scale production batches (old "*full vacuum process*) and 3 full-scale production batches using the to-be marketed process ("*partial vacuum*"). Batch analysis was also performed for the 75 mg formulation on 3 full-scale production batches. Given that the manufacturing process for the two formulations is similar, the manufacturing process has not been specifically validated for the 75 mg formulation, except for the freeze-drying process.

- **Product Specification**

The specifications for drug product have been adequately justified and most of the analytical methods used for testing of potency, strength, and purity are similar to the drug substance test methods. Specifications were established on the basis of batch analysis data:

- for the 150 mg formulation: three commercial scale batches manufactured in 2002 and 2003 using the *to-be marketed process* ("*partial va*cuum") at the South San Francisco plant of Genentech as well as data from three batches manufactured in 1999 using the older process ("*full vacuum*")

- for the 75 mg formulation: three commercial scale batches manufactured in 2003 at South San Francisco plant of Genentech

Results confirm the batch-to-batch consistency of the manufacturing process of the product and impurities in the drug product were consistent with those already identified at the level of the drug substance.

- **Stability of the Product**

A shelf life of 48 months at 2-8°C was proposed for both 75 and 150 mg formulations. This was based on 48 months data for the 150 mg formulation but only 12 months data from an ongoing stability study for the 75 mg formulation.

This was acceptable due to the similarity of the products and the stability observed so far in the studies with the 75 mg formulation.

The stability after reconstitution has been studied using two 150 mg "*full vacuum*" (clinical) batches. Results indicated a stability of 24 hours at 5ºC (two batches) and 8 hours at 30ºC (one batch).

All specifications were met at all time points in the studies. No significant changes in the characteristics studied were observed. No difference in stability was seen between the 75 and 150 mg formulations.

A study involving one 150 mg "*full vacuum*" (clinical) batch and one 75 mg pilot scale batch indicated that the product is not sensitive to light.

A shelf life of 5 years for the water for injections was proposed. This was acceptable based on trends observed over 48 months at 25ºC/60% RH (3 batches) and over 6 months at 40ºC/75% RH. The 25ºC-study is planned to go on until end of shelf life (5 years).

The applicant committed to complete the ongoing stability studies on the three commercial scale (to-be-marketed formulation) lots of the 150 mg formulation and the three commercial scale and one pilot scale (to-be-marketed formulation) lots of the 75 mg formulation until end of the proposed shelf life (48 months).

Viral safety

Omalizumab is produced in recombinant CHO (Chinese Hamster Ovarian) cells in serum free culture medium. The composition of the serum free media used for the growth and the storage of MCB and

WCB have been described. Materials of bovine origin are not used in the production process. However, Fetal Bovine Serum (FBS), sourced from New Zealand, Canada or the USA, was used during cell line development. The production of the MCB and WCB was serum-free. Peptone derived from milk casein is used for the manufacture of L-histidine,HCl and L-histidine (excipients). The information given in the application was acceptable and in compliance with current TSE legislation and guidelines.

The MCB and the WCB as well as the preharvest cell culture fluid have been tested for the presence of mycoplasma and results were satisfactory. Testing for adventitious viruses including retroviruses were performed in accordance with the Note for Guidance on "viral safety evaluation of biotechnology products derived from cell lines of human or animal origin" (CPMP/ICH/295/95). Results were satisfactory.

Routine testing on adventitious viruses is performed on samples from the cell culture fluid prior to harvesting. The following tests are used: nucleic acid testing (NAT) for detection of DNA of murine (parvovirus) minute virus (MVM), testing for parvovirus by cultivation on 324K cells; testing for other adventitious viruses using MRC-5, Vero, and CHO-K1 cells). Results and validation reports have been provided. The results from the testing of different batches of preharvest cell culture fluid were satisfactory.

In order to investigate the ability of the manufacturing process to inactivate or remove viruses, validation studies were performed using relevant model viruses (X-MuLV, MVM, and SV40) and involving four production steps identified as critical.

X-MuLV is the model for type A and C retroviruses commonly detected in CHO cells. The non-enveloped viruses MVM and SV40 were used as model viruses in the study of the capacity of the chromatographic process steps to remove viruses.

Complete study reports have been provided. Among the 3 chromatographic steps used in the purification process, two have been investigated. Study results have shown that these steps are capable of adequately removing viruses. The results also show that the reuse of the columns does not affect the capacity to remove the viruses tested. The effectiveness of the sanitation procedure has been shown. Studies also indicated that the process was capable of inactivating type A and C retroviruses.

In conclusion, the effectiveness of the manufacturing process to inactivate or remove viruses has been adequately demonstrated and testing for adventitious viruses in the cell banks and on the preharvest culture media provides an acceptable level of virus safety.

Discussion on chemical, pharmaceutical and biological aspects

Overall, the production and purification processes of the active substance are controlled by adequate in-process controls and have been adequately validated. Tests revealed that omalizumab was the major product along with the batch-to-batch consistent occurrence of minor molecular variants of omalizumab, which have been satisfactorily characterized using a combination of physicochemical methods as well as tested for potency. Analytical methods have been adequately described and validated, and satisfactory specifications have been set based on results obtained with qualification lots and lots used in clinical studies.

The manufacturing process of the finished product, which complies with Good Manufacturing Practice (GMP), has been described in sufficient detail. Given that the manufacturing process of the finished product for the two formulations is similar, the manufacturing process has not been specifically validated for the 75 mg formulation, except for the freeze-drying process. This was considered acceptable. Results confirm the batch-to-batch consistency of the manufacturing process of the product. Impurities in the drug product were consistent with those already identified at the level of the drug substance. The specifications for drug product have been adequately justified.

The effectiveness of the manufacturing process to inactivate or remove viruses has been adequately demonstrated and testing for adventitious viruses in the cell banks and on the pre-harvest culture media provides an acceptable level of virus safety. Omalizumab is produced in recombinant CHO (Chinese Hamster Ovarian) cells in serum free culture medium and materials of bovine origin are not used in the production process. The information given in the application was acceptable and in compliance with current TSE legislation and guidelines.
A shelf life of 48 months at 2-8°C was proposed for both 75 and 150 mg formulations. This was based on 48 months data for the 150 mg formulation but only 12 months data from an ongoing stability study for the 75 mg formulation. This was acceptable due to the similarity of the products and the stability observed so far in the studies with the 75 mg formulation. The applicant committed to complete the ongoing stability studies on the three commercial scale (to-be-marketed formulation) lots of the 150 mg formulation and the three commercial scale and one pilot scale (to-be-marketed formulation) lots of the 75 mg formulation until end of the proposed shelf life (48 months).

3. Part III: Toxico-pharmacological aspects

Introduction

Omalizumab is a recombinant humanised IgG_1 monoclonal anti-IgE antibody which binds to IgE at the same epitope as FcεRI -receptor. The pool of IgE available to interact with mast cells and basophils via FcεRI -receptor is thereby reduced and allergic responses attenuated.

The Cynomolgus monkey was chosen as model to predict human pharmacology and toxicology since omalizumab binds Cynomolgus and human IgE with similar affinity but does not bind non-primate IgE.

All relevant regulatory safety studies were stated to have been undertaken according to internationally accepted Good Laboratory Practice.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

A battery of *in vitro* studies has been conducted to assess the mechanism of action of this anti-IgE monoclonal antibody. *In vitro* binding studies showed that the affinity of omalizumab for Cynomolgus IgE was 0.19 nM. As only primate IgE is bound by omalizumab, other standard species such as the rat, mouse or dog would not be reactive.

In vitro studies on the pharmacodynamic effects of omalizumab indicated that omalizumab competes with the FcεRI-receptor for the binding of IgE. The K_d of omalizumab for human IgE varied between 0.02 and 7.7 nM depending on the assay used. The disparity reflects the complexity of the omalizumab:IgE interaction engendered by the bivalent nature of both molecules. Omalizumab is able to trap IgE from the surface of cell line cells. Histamine release by cross-linking of IgE was not detected, neither in a basophilic cell line nor in whole blood of healthy donors after the addition of omalizumab. The contraction and histamine release of tissue samples, i.e. lung were reduced by the addition of omalizumab to the test system. Omalizumab did not activate the complement cascade based on these data.

Except for skin test reactivity studies in Cynomolgus monkeys sensitised to ragweed, no animal model of disease was used. At the time the studies were performed there were no well-characterised primate asthma models available. Rodent asthma models were not considered because of the species specificity of omalizumab and because there were no appropriate non-anaphylactogenic surrogate antibodies available for evaluation in rodent models. Furthermore, the expression patterns of human and rodent FcεRI are very different, making comparisons difficult. Considering the clinical experience with Xolair, it is not justified to try to develop any new animal models at this stage.

- Safety pharmacology

Safety parameters were monitored at regular intervals in the 4-week and 6-month monkey toxicology studies. These parameters included vital functions such as blood pressure, electrocardiograph measurements, heart rate and respiration rate. No drug-related effects were observed for any of these endpoints. No separate safety pharmacology studies were performed for omalizumab.

- Pharmacodynamic drug interactions

No drug interactions have been studied, although omalizumab is intended to be given to patients in combination with various other medicinal products. Considering the clinical experience with Xolair, this is acceptable.

Pharmacokinetics

Assays developed to quantitate omalizumab, free and total IgE, and anti-omalizumab antibodies were primarily enzyme linked immunosorbent assays (ELISAs), with the exception of the free IgE assay, which was a fluorescence activated cytometry (FACS) assay.

The cynomolgus monkey and the mouse have been used as experimental models. The mouse was used to characterize the antigen-independent pharmacokinetics of omalizumab in the absence of complex formation with IgE.

The bioavailability of omalizumab after SC administration was □ 90 % in mice and ranged from 64 % to 104 % in monkeys. The mean bioavailability of omalizumab in humans is estimated to be 53%~71 %.

Pharmacokinetic studies revealed an elimination half-life of approximately 7 days with a maximal concentration after sc application after approximately 5 days. Clearance of omalizumab: IgE-complexes was significantly reduced in comparison to clearance of free IgE. As a result, levels of total IgE rose up to 20-fold higher than the baseline levels.

Distribution studies show that >90% of the test material was in the circulation of Cynomolgus monkeys. Uptake of omalizumab: ^{125}I-IgE-complexes was greatest in the liver and spleen. Sinusoidal endothelial cells and cells of the reticuloendothelial system were involved in the clearance of the complexes.

Standard *in vitro* tissue binding studies were undertaken with human and Cynomolgus tissues. Staining of cryo-sections of tissues of human or Cynomolgus monkey origin did not result in binding with the exception of lymphoid cells synthesising IgE.

Pharmacokinetics after repeated administration and toxicokinetics were comparable to the kinetics after single dose administration.

Toxicology

- Single dose toxicity

No evidence of toxicity was observed following single iv administration of up to 100 mg/kg in mice and following single iv and sc administration of up to 50 mg/kg in monkeys. The high doses represented the maximum that could be delivered as a single iv bolus of a 5 mg/ml formulation.

- Repeat dose toxicity

Two pivotal repeated-dose toxicity studies were performed in Cynomolgus monkeys: a 4-week iv/sc study with a 4-week recovery period, dosing three times weekly in the range 0.1-5.0 mg/kg, and a 6-month iv/sc study with an 8-week recovery period, dosing three times weekly in the range 0.1-5.0 mg/kg. In mice, weekly iv bolus injections of up to 50 mg/kg of omalizumab were administered for

4 weeks with a 4-week recovery period. Omalizumab had no effect on standard toxicological parameters after repeated administration to Cynomolgus monkeys or mice. Despite the presence of omalizumab:IgE complexes in the monkey studies, there were no indications of immune complex-mediated disease.

Juvenile (8- to 10-month old) Cynomolgus monkeys received sc doses of 50 or 250 mg/kg omalizumab weekly for 26 weeks. Reversibility of any toxic effects was assessed during a 26-week recovery period. No omalizumab-related effects were observed with the exception of thrombocytopenia and changes secondary to thrombocytopenia. Thrombocytopenia appeared at serum concentrations of omalizumab, which were 1.7- to 16.7- fold higher than the concentrations detected in Phase III trial patients. Histopathological evaluation revealed haemorrhage in the subcutaneous tissue at the injection site, in seminal vesicles, in the stomach fundus mucosa, or in the duodenal mucosa of a few animals, in the low and/or high dose groups. In spite of the mechanistic *in vivo*/*vitro* studies performed by the Applicant, the mechanism of the omalizumab-platelet interaction and the epitope responsible for the interaction remain unknown. In clinical trials, a few patients have had platelet counts below the lower limit of normal variation. So, even if the pattern of severe and dose-related decreases in platelets seen in non-human primates has not been detected in humans, the observation of thrombocytopenia is mentioned under 4.8 Undesirable effects and 5.3 Preclinical safety data sections of the summary of product characteritics (SPC)..

The induction of antibodies to omalizumab could not be studied in most serum samples from treated Cynomolgus monkeys since the assay systems detecting anti-omalizumab-antibodies were highly susceptible to disturbances by either the presence of omalizumab in the serum itself and/or omalizumab:IgE-complexes. Some of the sera of monkeys, which could be evaluated, tested positive. It is likely that the actual antibody response to omalizumab in monkeys was underestimated. The applicant was requested to develop an assay, which could be used in the presence of high IgE titers, to study the induction of anti-omalizumab-antibodies. Such an assay was subsequently developed. In this assay, pre-treatment of serum samples with acidic potassium thiocyanate, which selectively aggregates IgE, eliminates IgE interference. Anti-omalizumab-antibodies did not affect the pharmacokinetics of omalizumab (with the exception of one juvenile monkey) nor did they have neutralising activity, nor did they elicit any toxicity, based on data from monkey toxicology studies.

In a 60-day repeated inhalation study using aerosolised liquid omalizumab, daily 12-minute exposure to approximately 400 µg omalizumab was well tolerated. However, omalizumab was highly immunogenic, 30 of 31 monkeys could be tested for anti-omalizumab antibodies, and all were positive. These findings point to the development of anti-omalizumab antibodies also after inhalation exposure.

- Genotoxicity *in vitro* and *in vivo*

A standard Ames test was negative. A full genotoxicity test battery and carcinogenicity evaluation have not been conducted for omalizumab, due to the absence of a relevant species appropriate for such studies.

- Carcinogenicity

No carcinogenicity study with omalizumab was performed since omalizumab does not bind rodent IgE.

- Reproductive and developmental studies

Male and female fertility, embryotoxicity/teratology, and late gestational/placental transfer were studied in Cynomolgus monkeys, since omalizumab would not bind to rodent/rabbit IgE, and a non-anaphylactogenic anti-murine IgE Mab surrogate antibody was not available.

Sc administration of omalizumab, at doses of 0, 3, 15 and 75 mg/kg once weekly for 6 weeks (to cover the period of spermatogenesis) did not elicit reproductive toxicity in males. The same doses were

administered to females for 13 weeks (three menstrual cycles) before mating, during the mating period (maximum of two menstrual cycles) and during early pregnancy (up to Day 25 of gestation). Omalizumab did not elicit reproductive toxicity in female Cynomolgus monkeys.

Administration of omalizumab to pregnant monkeys during organogenesis (gestational Days 20 to 50) at doses of 0, 3, 15 and 75 mg/kg once daily on Days 20-22, and then once weekly through Day 50 did not elicit maternal toxicity, embryotoxicity or teratogenicity.

To assess the effect of omalizumab on late gestation, and to evaluate the placental transfer and milk secretion of omalizumab, doses of 75 mg/kg were administered sc to two groups of monkeys (Caesarean section group and natural delivery group). Omalizumab was given once daily on Days 120, 121 and 122 of gestation as a loading dose, and once weekly through Day 150 of gestation for the Cesarean section group, or through Day 28 postpartum for the natural delivery group.
There was no evidence of late gestational maternal or offspring toxicity. However, further dosing and evaluation of the offspring were not performed, for example with regard to immunotoxicity.

Measurable levels of omalizumab were observed in amniotic fluid (~3.3% of maternal serum levels), milk (~0.154%), and fetal (~33%) and neonatal (~33%) serum. Since there was an increased risk of thrombocytopenia in juvenile non-human primates, a restrictive wording in 4.6 Pregnancy and lactation section of the SmPC is appropriate.

- Local tolerance

Studies of local tolerance in rabbits did not indicate local toxicity.

Ecotoxicity/environmental risk assessment

No adverse environmental effects are predicted from omalizumab based on the data submitted. Omalizumab has high water solubility and is susceptible to enzymatic degradation. After disposal it will most likely be confined to the aquatic compartment. This active substance will undergo rapid enzymatic proteolysis by micro-organisms which are resident in waste water systems resulting in a mixture of unmodified natural amino acids. The massive dilutions involved would only allow very low aqueous concentrations in any event. Other components of the clinical formulation are in use as excipients in many medicinal drugs and have been so for many years.

Discussion on the non-clinical aspects

Omalizumab is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Omalizumab binds to IgE and prevents binding of IgE to the high-affinity FCεRI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade.

The safety of omalizumab has been studied in the cynomolgus monkey. Chronic administration of omalizumab was well tolerated in non-human primates, with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4 to 20-fold higher than anticipated maximum clinical serum concentrations. In addition, acute haemorrhage and inflammation were observed at injection sites in cynomolgus monkeys.

Formal carcinogenicity studies have not been conducted with omalizumab. Assessment on carcinogenic potential should be made on the basis of available clinical safety data.

Omalizumab crosses the placental barrier and has been associated with decreases in blood platelets in juvenile non-human primates. Xolair should therefore not be used during pregnancy unless clearly necessary. Omalizumab is excreted into non-human primate breast milk. Nursing mothers should not breast-feed during Xolair therapy.

No studies of the risk of parasitic infections during omalizumab administration have been performed. However, this has been addressed adequately in the clinical documentation, therefore clinical experience obviates the need for new preclinical data.

4. Part IV: Clinical aspects

Introduction

The clinical development program for omalizumab included studies which evaluated its use in allergic asthma (AA), and seasonal and perennial allergic rhinitis (SAR, PAR). The current submission claims only for maintenance therapy in severe allergic asthma. Data from studies in other indications were used to provide additional evidence of the safety and tolerability of omalizumab.

Efficacy data was provided mainly by seven allergic asthma (AA) studies including one study for efficacy in the specific target indication of patients with severe allergic asthma inadequately controlled (Study 2306) and six studies in predominantly severe allergic asthmatics. These are 4 double-blind, placebo controlled studies in severe persistent allergic asthma (studies 2304, 008 core/extension, 009 core/extension, and 011), and 2 standard therapy-controlled open-label studies predominantly in severe persistent allergic asthma (studies IA04 and Q2143 (ALTO)).

The safety profile of omalizumab is based on data from over 7000 patients (over 5000 on omalizumab) who participated in studies in AA, SAR, PAR and other indications and more than 23000 patients treated with marketed product in the USA.

One comparability study compared the formulation used in the pivotal phase III trials with the formulation intended for marketing. There were no signals of altered pharmacokinetic or pharmacodynamic characteristics after administration of the marketing formulation.

Pharmacokinetics

The pharmacokinetic characteristics of omalizumab were determined on the basis of data provided by 17 studies: 7 Phase I trials, 5 Phase II trials and 5 Phase III trials (007, 008, 009, 010, 011). Apart from one study, no studies were conducted in healthy volunteers as the pharmacokinetics of omalizumab is governed by the pharmacodynamic response i.e. IgE levels. Omalizumab was originally developed as a formulation for i.v. administration, and much of the early PK data was obtained in studies using both i.v. and s.c. dosing.

A majority of the PK studies were performed using lower doses than applied for and therefore the pharmacokinetic assessment is mainly based on population pharmacokinetic analyses data from sparse sampling in the pivotal clinical studies with the addition of some patients where full PK profiles have been collected. Different population analyses were performed because of the different populations studied.

- Absorption

Omalizumab is slowly absorbed with a Tmax at around 5 days. Mean bioavailability after SC dosing was 62%.

Whether the bioavailability of omalizumab differs depending on the injection site has not been determined. Data from study come mainly (99%) from administrations in the upper arm. Omalizumab should therefore be administered subcutaneously in the deltoid region of the arm. Only in case that this is not feasible, the thigh may be recommended as an alternative site of injection.

- Distribution

Distribution volumes (Vd/F = 78 ± 32 ml/kg) were close to or slightly larger than the serum volume and were typical of those seen with large macromolecules.

- Elimination

The metabolism of omalizumab is determined by its IgG1 framework, and specific binding to IgE. Liver is one site of elimination for IgG, including degradation in the liver reticulo-endothelial system and endothelial cells. The omalizumab:IgE complexes are believed to clear via interactions with Fc-gamma-Rs at rates that are generally faster than IgG clearance. Relative clearance of free omalizumab, free IgE, and complexes is summarized as: free IgE clearance > > omalizumab:IgE clearance > omalizumab clearance.

Omalizumab appears to be eliminated through one fast pathway as IgE complex and by slower hepatic elimination as free omalizumab. In therapeutic dosing, omalizumab concentrations in blood are markedly higher than the concentrations of IgE. Thus, the slow pathway greatly dominated during therapeutic dosing but the faster pathway has a greater role at subtherapeutic doses.

The elimination of omalizumab is dose-dependent. Clearance of omalizumab is low (around 0.181 l/day) and the half-life is long; around 35-40 days or even longer. The partial accumulation ratio from day 112 to day 336 was 1.1-1.4.

- Dose proportionality and time dependencies

Exposure increased in proportion to dose at doses greater than ~0.5 mg/kg. Non-linear PK observed at low doses (less than ~0.5 mg/kg) was due to a larger contribution of complex formation with IgE to observed overall systemic clearance and distribution of omalizumab.

- Special populations

No effect of age was seen in population PK analyses.

Children apparently had a mean omalizumab clearance that was 26% higher than that in adults and half-lives of omalizumab were longer in children and adolescents but the clinical relevance is questionable.

There are no studies investigating the effect of impaired renal function on the pharmacokinetics of omalizumab which is acceptable because elimination is not expected to take place in the kidney.

Omalizumab clearance at clinical doses is dominated by the reticular endothelial system (RES) and therefore unlikely to be altered by hepatic insufficiency. Therefore, the applicant has conducted no studies in hepatic impairment.

Weight, IgE levels and dose recommendation

A population PK analysis identified weight as the most important covariate. CL was directly proportional to weight. Other covariates with statistically significant but much smaller effects were baseline IgE levels, ethnic origin and indication (SAR vs. AA). Another population pharmacokinetic analysis from studies 006, 006 extension, 007, 008, 009, 010, 011, and 2306 consisting of 1460 patients 12-79 years old (i.e. excluding patients younger than 12 years) showed similar results to those of the previous analysis. Doubling the weight increased the apparent clearance by 101% and increased the apparent volume of distribution by 86%. Quadrupling the baseline IgE increased apparent clearance by 13%. For a patient with the bodyweight 70 kg, apparent clearance will be 2.8 ml/day/kg and apparent volume of distribution 98ml/kg. After accounting for covariates the remaining intersubject variability for CL/F decreased from 44 % to 38%.

The Company presented simulations of plasma concentrations courses obtained in patients of some different bodyweights and baseline IgE levels. The exposure of omalizumab was higher in patients with a bodyweight ≤ 25 kg than in other patients within the same IgE range. Aiming for similar exposure within IgE-groups, the company presented simulation of plasmaconcentration – time courses

obtained with the different dosing tables. Proposed dosing-regimen were considerd acceptable with the exception of patients in the weight range 20-25 kg with an baseline level IgE level between 500 and 700 IU/ml; these patients should be dosed with 150 mg every 2 weeks instead of 300 mg every 4 weeks. The Applicant committed to explore alternative dosing regimens for patients with IgE baseline levels above 700 IU/ml.

- Pharmacokinetic interaction studies

No pharacokinetic interaction studies have been performed. This is acceptable since as stated in the SPC: Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of omalizumab; thus, there is little potential for drug-drug interactions. No vaccine interaction studies have been performed with Xolair.

A warning about the lack of knowledge regarding possible interactions with specific immunotherapy (hypo-sensitisation) has been included in the SPC.

Pharmacodynamics

- Mechanism of action

Omalizumab is designed to reduce the pool of free IgE available to interact with effector cells and thereby attenuate the subsequent allergic responses in atopic patients. Omalizumab forms complexes of limited size (dominant species ~490 kD) with IgE, thus decreasing free IgE levels. Omalizumab would interrupt the allergic cascade by: 1) forming complexes with IgE and preventing the arming of effector cells, 2) aiding off-loading of mast cells and basophils by trapping IgE as it dissociates from the receptor and, 3) down-modulating FcεRI as a direct consequence of the reduction in free IgE levels.

- Primary and Secondary pharmacology

Based on *in vitro* studies, a reduction in serum free IgE to < 10 ng/mL was expected to prevent IgE receptor cross-linking and degranulation of effector cells. Based on clinical response (phase I and II), 25 ng/mL was the average serum free IgE level associated with potential clinical benefit.
The dose of Xolair required to maintain the average serum free IgE level below 25 ng/mL was 0.016 (mg/kg)/(IU/mL) q4wk. The Xolair dosing table, based on individual serum IgE level and body weight, ensures that each patient receives a dose of at least 0.016 (mg/kg)/(IU/mL) q4wk. Although there seems to be some relationship between the target IgE level and effect, there are some uncertainties about the validity of such assumption. Observing the results from study 008 the OR for the reduction of asthma exacerbations in patients attaining an IgE level below 25 ng/ml was 1.5 during the stabilisation phase, which means a favourable trend when compared with those patients attaining an IgE level between 25 and 50 ng/mL (OR 0.95). However, the trend is not confirmed when considering those patients with IgE levels between 50 and 150 ng/mL (OR 1.26). This apparent lack of relationship between achieved IgE level and effect was also observed in patients with allergic rhinitis.
In the patient population with asthma, it has not been demonstrated that IgE baseline levels have a direct relationship with clinical severity. However, omalizumab exerts its effect by blocking the immunological cascade triggered by IgE. Thus, it is reasonable to think that high IgE levels must be a pre-requisite for omalizumab having an effect and the results of the exploratory multivariate and subgroup analyses performed by the company consistently supported this view. Therefore, and despite the lack of relationship between baseline IgE and asthma severity, there should be a relationship between baseline IgE levels and omalizumab therapeutic effect. Since it might have relevant implications for what patients would benefit most from omalizumab therapy, it should be further investigated by the company.

There were no significant differences in the percentage of eosinophils and eosinophil cationic protein in sputum (and other inflammation markers as the percentage of neutrophils) between omalizumab and placebo. omalizumab significantly reduced the basophil histamine release and the eosinophils count in

peripheral blood in patients with moderate to severe asthma. Reactivity to skin prick tests was also significantly reduced.

Clinical efficacy

- Dose response studies

Five Phase II dose selection studies were performed, including two in patients with seasonal allergic rhinitis. Three dose-finding studies were carried out in patients with asthma. Studies 0630 (n=20) and 0634 (n=19) included populations with mainly mild asthma and low levels of IgE. Omalizumab was dosed by weight without considering the IgE level. In study 0630 the overall administered dose was similar to that currently proposed in the SPC, but given intravenously and at a different dosing schedule. In study 0634 the dosing schedule was 0.5 mg/kg weekly without initial loading dose. The value of the results of these studies is considered to be limited.

The proposed dosing schedule for omalizumab is mainly based on the results of study Q0694g. As recommended in the "NfG on the clinical investigation of medicinal products in the treatment of asthma", this is a, randomised, double-blind, parallel, dose finding study, in which different dosing schedules of omalizumab were evaluated. The dose was adjusted by body weight and baseline IgE levels. Patients were to have moderate to severe asthma requiring chronic corticosteroid therapy (oral or inhaled). The study lasted 35 weeks, including a 4-week run-in phase, a 12-week placebo-controlled phase, an 8-week corticoid tapering phase and a 10-week follow-up-up phase. There were 4 treatment arms randomised according to 1:1:2:2 ratio: high-dose placebo, low-dose placebo (n placebo=105), high-dose omalizumab (0.014 (mg/kg)/(IU/ml) IV of omalizumab per IgE at baseline, q2wk) (n=106), or low-dose omalizumab (0.006 (mg/kg)/(IU/ml) IV of omalizumab per IgE at baseline, q2wk) (n=106). Mean baseline IgE levels were 331 UI/ml, ranging from 17 to 1957 UI/ml. This is beyond the upper limit proposed in the SPC (700 UI/ml). A significant effect on IgE levels and symptoms was attained with both doses, with a trend toward a positive dose-response relationship. The company chose the lower dose, and on this basis, the actual dosing proposal has been built. It should be noted that it limits the total amount/dose of omalizumab to 375mg, thus preventing the administration of omalizumab to patients with baseline IgE levels above 700 UI/mL. This limitation might deny treatment to some patients that could benefit from omalizumab therapy.

- Main studies

They consist in four early placebo-controlled studies (summarised in the table below) and the later study 2306 targeting the population of the claimed indications. Two supportive open-label studies are described in the subsequent section.

Study No.	Study Objective, Population	Randomized Patients	Treatment Duration	Medication dose/day	Efficacy Endpoint
2304	efficacy, safety study in co-morbid severe AA and PAR	405	28 weeks	at least 0.016mg/kg/IgE [IU/ml] every 4 weeks or placebo	incidence of asthma exacerbation episodes, QoL
008 + extension	efficacy, safety, and PK/PD study in severe AA	525 (core), 460 (extension)	52 weeks (28 weeks + 24 weeks extension)	at least 0.016mg/kg/IgE [IU/ml] every 4 weeks or placebo	rate of asthma exacerbation episodes
009 + extension	efficacy, safety, and PK/PD study in severe AA	546 (core), 483 (extension)	52 weeks (28 weeks + 24 weeks extension)	at least 0.016mg/kg/IgE [IU/ml] every 4 weeks or placebo	rate of asthma exacerbation episodes
011	efficacy, safety, steroid reduction and PK/PD study in severe AA	341 (246 requiring high dose inhaled CS, 95 requiring oral and high dose CS	32 weeks	at least 0.016mg/kg/IgE [IU/ml] every 4 weeks or placebo	reduction in inhaled corticosteroid use in the population not requiring oral corticosteroids

Note: AA=Allergic asthma, PAR= Perennial allergic rhinitis, BDP= beclomethasone dipropionate, QoL= Quality of life; CS = corticosteroids

Study 2304

This study was a double-blind study comparing omalizumab with placebo as add-on therapy to inhaled corticosteroid therapy (with or without long-acting β-2 agonist use and with short-acting β-2 agonist use as needed) for 28 weeks in adult and adolescent patients (aged 12 to 75 years) with co-morbid severe allergic asthma (GINA 2002) and perennial allergic rhinitis.

Eligible patients had allergic asthma for at least one year with a positive skin prick test to at least one perennial allergen, a total IgE level ≥ 30 to ≤ 700 IU/mL, and a ≥ 12% increase in FEV1 over baseline within 30 minutes of receiving inhaled salbutamol documented within the past year, at screening or during the run-in phase. Patients were also required to have had at least 2 unscheduled medical visits or asthma exacerbations in the past year (or at least 3 visits/exacerbations in the past 2 years), a total AQLQ score of >64 from 192, moderate to high dose inhaled corticosteroid use for at least 3 months (equivalent to ≥400µg/day budesonide turbohaler) and moderate to severe PAR symptoms of sneezing, itchy, runny or stuffy nose, itchy, watery or red eyes or post-nasal drip for at least 2 years, and a total RQOL score >56 from 168 at randomization. Patients were randomized (1:1 ratio) to either omalizumab or placebo.

Of the 462 planned patients, a total of 405 patients were randomized and treated during the study of whom 95% completed 28 weeks of active treatment. The co-primary efficacy endpoints were the incidence of patients with asthma exacerbations during the treatment period, defined as a worsening of asthma requiring treatment with rescue oral or IV corticosteroids or a doubling of baseline budesonide dose, and asthma and rhinitis Quality of life assessments where a responder was defined as having an improvement ≥1.0 on both AQLQ and RQOL questionnaires. Secondary measures of efficacy included asthma exacerbation rate and QOL evaluation.

Study 008

This study was a double-blind study comparing omalizumab with placebo as add-on therapy to inhaled corticosteroids and β-2 agonists (on-demand short-acting β-2 agonists throughout the study, with long-acting β-2 agonists and xanthines allowed during the extension study) for 52 weeks (28 weeks double-blind core with 24 week double-blind extension) in adult and adolescent patients (aged 12 to 75 years) with severe allergic asthma (GINA 2002) requiring daily treatment with inhaled corticosteroids.

Eligible patients had allergic asthma for at least one year with a positive skin prick test to at least one perennial allergen, a total IgE level ≥ 30 to ≤ 700 IU/mL, ≥ 12% increase in FEV1 over baseline within 30 minutes of receiving inhaled salbutamol. Patients were also required to have had a baseline FEV1 (following washout-from bronchodilators) of ≥ 40 to ≤ 80% of the predicted normal value as well as a mean daily total symptom score ≥ 3 (out of a maximum score of 9) during the 14 days prior to randomization, despite treatment with inhaled corticosteroids at doses equivalent to 500 to

1000µg/day of beclomethasone dipropionate. Patients were randomized (1:1 ratio) to either omalizumab or placebo. The general study design is provided below.

Screening	Run-in	Double-blind core treatment	Double-blind extension treatment
Week –7 (7 days) Visit 1	Weeks -6/-4 to 0 (4/6 weeks) Visits 2	Weeks 0 – 28 (28 weeks) Visits 3 to 13	Weeks 29 – 52 (24 weeks) Visits 14 to 20

The 28-week double-blind treatment period of the core study comprised of a 16 week stable-steroid phase where patients were required to remain on their baseline inhaled corticosteroid dose, followed by a 12 week steroid dose reduction phase where attempts were made to progressively reduce the dose of inhaled corticosteroids in strict adherence to pre-defined stopping rules. During the 24 week double-blind extension study the dose of inhaled corticosteroids could be increased or decreased as deemed appropriate by the investigator.

Study 008 core: Of the 550 planned patients, a total of 525 patients were randomized and treated during the study of whom 90% completed 28 weeks of core study treatment. Treatment groups were balanced for baseline demographic and disease characteristics.
Efficacy was assessed by the rate and incidence of asthma exacerbations, defined as a worsening of asthma requiring treatment with oral or IV corticosteroids or a doubling of the patient's inhaled corticosteroid (BDP) dose.
The exploratory variables measured during the double-blind stabilization period were: asthma free days, morning PEFR, evening PEFR, the difference between the two PEFR measurements, FEV-1, FVC, FEF 25-75%, total and individual (nocturnal, morning, and daytime) asthma symptom scores.

Study 008 extension: In study 008 extension a total of 460 patients (245 omalizumab and 215 placebo) entered the extension from the core study and maintained their double-blind treatment.

Combined clinical efficacy of the core and extension studies are thereafter presented to evaluate treatment effect over 52 weeks of double-blind treatment.

Study 009
This study was a 52 week, double-blind, placebo-controlled study with an identical study design, objectives and population to Study 008. Eligible patients had the same entry requirements as for Study 008 with the exception in Study 009 that patients required treatment with inhaled corticosteroids at doses equivalent to 500 to 1200µg/day of beclomethasone dipropionate.

Study 009 core: Of the 550 planned patients, a total of 546 patients were randomized and treated during the study of whom 89% completed 28 weeks of core study treatment. Efficacy was assessed by the rate and incidence of asthma exacerbations during the double-blind phase, defined as a worsening of asthma requiring treatment with oral or IV corticosteroids or a doubling of the patient's inhaled corticosteroid (BDP) dose. Exploratory efficacy variables included PEFR, spirometry and asthma symptom scores.

Study 009 extension: In study 009 extension a total of 483 patients (254 omalizumab and 229 placebo) entered the extension from the core study and maintained their double-blind treatment.

Combined clinical efficacy of the core and extension studies are thereafter presented to evaluate treatment effect over 52 weeks of double-blind treatment.

Study 011
This study was a double-blind study comparing the steroid-reduction potential of omalizumab with placebo as add-on therapy to high dose inhaled corticosteroids, with or without oral corticosteroids or long-acting β-2 agonists, for 32 weeks in adult and adolescent patients (aged 12 to 75 years) with severe allergic asthma requiring daily treatment with high dose corticosteroids. Eligible patients had chronic severe allergic asthma for at least one year with a positive skin prick test to at least one

perennial allergen, a total IgE level ≥ 30 to ≤ 700 IU/mL, ≥ 12% increase in FEV1 over baseline within 30 minutes of receiving inhaled salbutamol with a baseline FEV1 ≥ 40 of the predicted normal value. During a run-in period, patients demonstrated a need for high dose inhaled corticosteroid (fluticasone 1000-2000µg/day) with or without oral corticosteroid use to optimally control asthma symptoms. Patients were also required to have had mean daily total symptom scores <4 during the 7 days prior to randomization and for asthma medication to remain unchanged in the 4 weeks prior to randomization. Patients were randomized (1:1 ratio) to either omalizumab or placebo. Patients were stratified into two subpopulations: those taking inhaled corticosteroids only (inhaled subpopulation) and those taking inhaled and oral corticosteroids (oral subpopulation). The general study design is provided below. The double-blind core treatment period comprised of a 16 week stable treatment period followed by a 16 week steroid dose reduction period.

Screening	Run-in	Double-blind treatment	Post-treatment follow-up
Week -11/-7 to -10/-6 (7 days) Visit 1	Weeks -10/-6 to 0 (6 to 10 weeks) Visits 2.1 to 2.5	Weeks 0 – 32 (32 weeks) Visits 3 to 15	Weeks 32 – 44 (12 weeks) Visits 16 to 19

Of the 350 planned patients, a total of 341 patients were randomized and treated during the study including 176 omalizumab (126 inhaled steroid subpopulation and 50 oral steroid subpopulation) and 165 placebo patients (120 inhaled steroid subpopulation and 45 oral steroid subpopulation). Of these 91% completed 32 weeks of study treatment. Efficacy was assessed by reduction in inhaled corticosteroid use in those patients receiving high dose inhaled corticosteroid therapy without oral corticosteroids. Secondary efficacy parameters included a reduction in oral and overall corticosteroid use, a reduction in asthma exacerbations, a decrease in rescue medication use, improved lung function, improvements in asthma-related QoL and pharmacoeconomic effects.

Main results of the four early studies

Study participation

Study	**Group**	**No of patients**			**Reason for Withdrawal**			**Time**
		Planned	Enrolled	Discont	AE	IE	Other	(mo)
2304	Pl omalizumab	231 231	196 209	15 5	2 0	2 0	11 5	193 199
008C/E	Pl omalizumab	275 275	257 268	42 31	2 2	15 2	25 27	326 345
009C/E	PI omalizumab	275 275	272 274	66 29	8 2	11 3	47 24	322 350
011	PI omalizumab	175 175	165 176	14 16	2 1	2 0	10 15	224 222

Demographics and baseline characteristics

	2304 (N=405)	**008 C/E** (N=525)	**009 C/E** (N=546)	**011** (N=341)
Age (yrs)				
Mean	37.8	39.2	39.5	42.6
SD	14.70	13.19	14.33	14.94
Sex n (%)				
Male	182 (44.9)	215 (41.0)	268 (49.1)	129 (37.8)
Female	223 (55.1)	310 (59.0)	278 (50.9)	212 (62.2)
Race n (%)				
Caucasian	386 (95.3)	467 (89.0)	498 (91.2)	282 (82.7)
Black	1 (0.2)	37 (7.0)	22 (4.0)	3 (0.9)
Oriental	1 (0.2)	4 (0.8)	8 (1.5)	3 (0.9)
Other	17 (4.2)	17 (3.2)	18 (3.3)	53 (15.5)
Serum total IgE (IU/mL)				
Mean	231.9	179.3	214.4	253.1
SD	176.61	141.65	165.11	198.13
Baseline ICS in BDP equivalent (µg/day)				
Mean	1088.3	677.0	770.5	2784.5
SD	565.96	176.54	250.71	766.79
Range	500–3000	400–1200	200–2000	1000–5000
Baseline LABA use n (%)				
Yes	157 (38.8)	0	0	149 (43.7)
Clinical symptom score[§]				
Mean	16.4	4.3	4.0	1.6
SD	7.89	1.17	1.33	1.55
Range	0–38	1.5–8.6	0–8.1	0–8.4
FEV_1 (% of predicted)				
Mean	78.1	67.9	69.8	71.7
SD	16.61	14.54	14.70	19.33
Range	28–127	30–112	22–112	12–127
%Reversibility				
Mean	17.5	26.4	26.1	20.1
SD	11.99	14.26	14.19	21.75
Range	-5 – 76	10.8 – 109	10.4 – 103	-98.7 – 115

§ Clinical symptom score is obtained by adding scores for nocturnal asthma, morning asthma symptoms and daytime asthma symptoms at baseline for studies 008C/E, 009C/E and 011 (0-9); the Wasserfallen symptom score (0-40) at baseline is used for studies 2304.

Efficacy results

The annualized asthma exacerbation rate with and without imputation in all controlled studies using Poisson regression by study (ITT) is shown in the table below. The definition of a clinically significant asthma exacerbation differed slightly between the studies. For study 011, the rate of asthma exacerbation was a secondary endpoint.

Study		Exacerbation rate per year			Ratio (95% CI)	P-value
		Omalizumab	Control	Treatment difference		
2304	Imputation*	0.491	0.785	0.294	0.625 (0.412, 0.949)	0.027
(N=405)	No imputation	0.454	0.670	0.216	0.678 (0.432, 1.062)	0.090
008C/E	Imputation	0.592	0.992	0.400	0.597 (0.453, 0.786)	<0.001
(N=525)	No imputation	0.468	0.842	0.373	0.556 (0.409, 0.756)	<0.001
009C/E	Imputation	0.514	1.212	0.698	0.424 (0.329, 0.548)	<0.001
(N=546)	No imputation	0.376	0.898	0.522	0.419 (0.309, 0.568)	<0.001
011	Imputation	1.176	1.600	0.424	0.735 (0.476, 1.135)	0.165
(N=339)	No imputation	0.878	1.266	0.388	0.694 (0.432, 1.114)	0.130

* Imputations for missing values: For patients discontinuing prematurely an extra exacerbation was added unless the patient had an exacerbation in the seven days prior to the premature exacerbation.

The number of severe asthma exacerbations and the annualized incidence in the placebo-controlled studies and in the pooled population is shown in the table below. Severe exacerbations were defined as PEF or FEV1 < 50% of predicted/ personal best.

Study	Severe exacerbations No. patients (No. events)		Exacerbation rate/year		Ratio (95% CI)	P-value*
	Omalizumab	Control	Omalizumab	Control		
2304 (n=405)	5 (6)	3 (3)	0.052	0.028	1.849 (0.432, 7.910)	0.407
008C/E (n=525)	6 (6)	20 (25)	0.024	0.114	0.213 (0.085, 0.533)	0.001
009C/E (n=546)	4 (4)	14 (19)	0.021	0.108	0.192 (0.061, 0.604)	0.005
011 (n=339)	4 (5)	10 (12)	0.043	0.114	0.378 (0.112, 1.277)	0.117
Pooled (n=2234)	54 (70)	102 (159)	0.073	0.170	0.431 (0.303, 0.613)	<0.001

*Poisson regression analysis, exacerbations analyzed without imputation

The controlled studies used Juniper Adult Asthma Quality of Life Questionnaire, which assesses responses to 32 individual questions in four domain scores: symptoms, activities, emotions and environmental exposure. The scores for the four domains are then combined as an overall score. An improvement in overall score ≥ 0.5 from baseline was considered a clinically detectable improvement in Quality of Life with an increase ≥ 1.5 reflecting a large improvement.

Changes from baseline to treatment endpoint in Quality of life (ITT population)

Study	Omalizumab		Placebo		LSM	
	N	LSM	N	LSM	difference	p-value
2304	208	1.33	192	1.07	0.25	0.014
008C/E	245	1.19	215	0.91	0.28	<0.01
009C/E	225	1.16	189	0.85	0.32	<0.001
011	151	0.35	143	0.06	0.28	0.008

LSM = Least squares mean

Number of patients with clinically detectable improvements of total Quality of Life score

	Omalizumab n (%)	Placebo/Control† n (%)	p-value
2304 AQLQ	164 (78.8)	134 (69.8)	0.002
008C/E AQLQ	183 (74.6)	141 (65.5)	<0.01
009C/E AQLQ	154 (68.4)	131(69.3)	0.849
011	79 (52.3)	51 (35.7)	0.004

In study 011, Percent reduction in fluticasone dose was greater in omalizumab groups compared to placebo, for the all randomized population (median 60% vs. 50%, p-value 0.003) and in the inhaled steroid subpopulation (median 61.3% vs. 46.4%, p-value 0.004). In the oral steroid subpopulation,

percent and absolute reduction in prednisolone dose at the end of treatment did not differ between omalizumab and placebo patients.

See also section "Analyses performed across trials"

Study 2306
Study 2306 was a multicenter, randomized, double-blind, placebo-controlled study comparing the efficacy, safety and tolerability of subcutaneous omalizumab with placebo for 28 weeks in adult and adolescent patients with severe persistent allergic asthma who have reduced lung function and inadequate asthma symptom control despite treatment with high dose inhaled corticosteroids and long-acting β2 agonists.

METHODS

Study Participants
Adult and adolescent patients were (aged 12 to 75 years) with severe persistent allergic asthma of at least one year duration, who remained inadequately controlled despite GINA (2002) Step 4 therapy. Eligible patients had reduced lung function (FEV1 between 40 and 80%), inadequate asthma symptom control and in the past 12 months had either at least two independent asthma exacerbations requiring systemic corticosteroid treatment or a severe asthma exacerbation resulting in hospitalization or emergency room treatment, despite regular treatment with high dose inhaled corticosteroids (>1000 μg beclomethasone dipropionate or equivalent) and long-acting β2 agonists. They had a positive skin test to at least one perennial allergen (e.g. dust mite, animal dander, cockroaches), an increase in FEV1 over baseline within 30 minutes of taking salbutamol.

Treatments
Omalizumab was compared with placebo as add-on therapy to a high dose inhaled corticosteroid and long-acting β-2 agonist for 28 weeks. The omalizumab dose administered was based on the patient's body weight and total serum IgE level at Visit 1 and the number of injections and injection volume was determined from the dosing tables below.

ADMINISTRATION EVERY 4 WEEKS. (mg per dose)

	Body weight (kg)								
Baseline IgE (IU/ml)	>20–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125-150
≥30–100	150	150	150	150	150	150	150	300	300
>100–200	150	150	300	300	300	300	300		
>200–300	150	300	300	300					
>300–400	300	300							
>400–500	300								
>500–600	300								

ADMINISTRATION EVERY 2 WEEKS: SEE table below

ADMINISTRATION EVERY 2 WEEKS (mg per dose)

	Body weight (kg)								
Baseline IgE (IU/ml)	>20–30	>30–40	>40–50	>50–60	>60–70	>70–80	>80–90	>90–125	>125-150
≥30-100	**ADMINISTRATION EVERY 4 WEEKS: SEE** table above								
>100–200								225	300
>200–300					225	225	225	300	375
>300–400			225	225	225	300	300	**DO NOT DOSE**	
>400–500		225	225	300	300	375	375		
>500–600		225	300	300	375				
>600–700	225	225	300	375					

Objectives

The primary objective of the study was to determine the effect of subcutaneous administration of omalizumab, compared to placebo, on clinically significant asthma exacerbation rates. The secondary objectives was to assess other efficacy factors and to evaluate the safety and tolerability of omalizumab in this population.

Outcomes/endpoints

The primary efficacy variable was the clinically significant asthma exacerbation rate during the 28 week double-blind treatment phase of the study, defined as a worsening of asthma requiring treatment with rescue oral or IV corticosteroids.

The secondary efficacy variables were use of asthma rescue medication (number of puffs/day), AQLQ evaluation, evaluation of total daily clinical symptom score and morning PEF. Exploratory efficacy variables included frequency of hospital admissions, emergency visits and unscheduled doctor´s visits, time to first clinically asthma exacerbation, evaluation of AQLQ domains, individual clinical symptom scores, pulmonary function (FEV1, FVC, FEF25-75%), evening PEF and patient and investigator global evaluation of treatment effectiveness.

Sample size

The sample size estimate was based on a meta-analysis of exacerbation rate data on subjects whose disease severity characteristics are similar to those for patients in this study. With a significance level of 5% and a power of 90% this leads to a sample size of about 197 patients per treatment arm.

Randomisation

Patients were randomized (1:1 ratio) to either omalizumab or placebo.

In order to minimize between treatment group imbalance patients were randomized into one of three strata:

- Patients not receiving theophyllines, oral long acting □-2 agonists, anti-leukotrienes or maintenance oral steroids at baseline.
- Patients receiving one or more from theophillines, oral long acting □2 agonists, anti-leukotrienes, but not receiving maintenance oral steroids at baseline.
- Patients receiving maintenance oral steroids at baseline.

Blinding (masking)

The investigators and personnel involved in monitoring remained blinded throughout all periods of the study, except in the case of an emergency.

Statistical methods
For the primary analysis of the number of asthma exacerbations Poisson regression was used. In all test a significance level of 5% were used. Four patient populations were defined for the purpose of summaries and analysis: Post-amendment 2 intent-to-treat patients, all intent-to-treat patients, per-protocol patients and all safety patients. Post-amendment 2 intent-to-treat patients are all patients who were randomized into the study after the introduction of protocol amendment 2 (see below "Conduct of the study"). This is the primary analysis population (PITT).
Imputations for missing values: For patients discontinuing prematurely an extra exacerbation was added unless the patient had an exacerbation in the seven days prior to the premature exacerbation. For other data the Last Observation Carried Forward (LOCF) was used where apropriate.

RESULTS

Participant flow
Four hundred and eighty two patients were randomized, from a total of 1006 screened patients. Most exclusions were due to IgE levels or weight outside the dosing limit, withdrawal of patient consent, and patients not meeting diagnostic/severity criteria.
The 482 patients who entered the study comprised the safety population, 245 were randomized to omalizumab and 237 to placebo. All randomized patients were treated with at least one dose of study medication. A total of 63 patients were randomized prior to protocol amendment 2. The primary ITT population (PITT) excluded these patients and consisted of 419 patients, 209 in the omalizumab group and 210 in the placebo group. Almost 90% of all patients completed treatment.
Discontinuations were mainly due to either withdrawal of patient consent (3.9%) or adverse events (3.1%). Both of these reasons were more frequent in the omalizumab treatment group.
Conduct of the study

The protocol of study 2306 was amended four times.
The most relevant of these was "Amendment 2" (dated 22 Mar 2002). The GINA guidelines that were used as a basis to determine the patient population for this study were revised after the protocol was issued in September 2001. The baseline inhaled corticosteroid dose, defined as a high dose in the GINA guidelines (2002 edition), was revised to reflect the revision to the GINA guidelines. Patient's mould allergies were assessed by skin prick tests at screening, since it has been documented that mould allergy may be a risk factor for respiratory arrest. This amendment was implemented after 63 patients had been enrolled, and changed the entry criteria for the study. The key difference was that prior to amendment 2, patients were recruited immediately after an asthma exacerbation requiring emergency treatment. Post-amendment 2, this requirement was dropped, and patients had to have had a severe asthma exacerbation resulting in hospitalization or ER admission in the past 12 months or had any asthma related intubation prior to randomization.
The "Amendment 3" (dated 31 Jul 2002) was produced to make study design changes following scientific advice and protocol review by the Committee for Propriety Medicinal Products (CPMP):
Reduced emphasis on the high risk population by: allowing patients with multiple asthma exacerbations in the 12 months prior to screening to be included as an alternative to a severe exacerbation resulting in emergency care or hospitalization and deleting the inclusion criteria for patients being intubated at any time.
Stratification of the enrollment based on concomitant medication use.
Exclusion of patients receiving >20 mg/day of prednisolone as asthma maintenance therapy (or equivalent oral corticosteroid dose).
Revision of the primary analysis population to only include those patients recruited after protocol amendment 2. Patients recruited prior to amendment 2 differ to those recruited after amendment 2, due to major changes in the inclusion criteria.

Baseline data

The table below shows the demographic and background characteristics by treatment group. The treatment groups were similar. The majority of patients were females and most patients were Caucasian.

Demographic and background characteristics by treatment group (PITT and safety populations)

	PITT population		**Safety population**	
	Omalizumab N=209	**Placebo N=210**	**Omalizumab N=245**	**Placebo N=237**
Age (yr)				
Mean (SD)	43.4 (13.29)	43.3 (13.49)	42.3 (13.77)	43.0 (13.57)
Median	44.0	44.0	43.0	44.0
Range	(12-79)	(13-71)	(12-79)	(13-74)
Sex - n(%)				
Male	68 (32.5)	72 (34.3)	74 (30.2)	76 (32.1)
Female	141 (67.5)	138 (65.7)	171 (69.8)	161 (67.9)
Race - n(%)				
Caucasian	163 (78.0)	164 (78.1)	187 (76.3)	174 (73.4)
Black	14 (6.7)	14 (6.7)	14 (5.7)	15 (6.3)
Oriental	2 (1.0)	3 (1.4)	3 (1.2)	3 (1.3)
Other	30 (14.4)	29 (13.8)	41 (16.7)	45 (19.0)
Weight (kg)				
Mean (SD)	81.2 (19.75)	79.2 (17.48)	79.2 (19.68)	77.9 (17.66)
Median	77.0	77.0	76.0	76.0
Range	(45-148)	(45-146)	(45-148)	(39-146)
FEV1 (% of predicted)				
Mean (SD)	61.0 (14.42)	61.6 (13.83)	63.2 (15.83)	63.0 (14.43)
Median	62.2	61.9	64.1	64.0
Range	(18-101)	(30-96)	(18-116)	(30-115)
Reversibility* (%)				
Mean (SD)	28.9 (23.27)	24.5 (23.27)	n/a*	N/a*
Median	21.5	19.5		
Range	(-20-158)	(-87-169)		
Serum total IgE (IU/ml)				
Mean (SD)	197.6 (145.2)	189.6 (153.1)	201.7 (153.4)	190.7 (156.3)
Median	150	138.0	148.0	143.0
Range	(21-607)	(22-632)	(21-699)	(22-898)

*FEV1 reversibility demonstrated prior to or at baseline, safety population not relevant as pre-amendment 2 patients could demonstrate PEF reversibility instead

The table below describes patients' exacerbations during the previous year and during the run-in Study 2306, Primary ITT population. It consists of corrected data submitted by the company during the assessment after the company discovered an error in counting these historical exacerbations. (Historical exacerbations could be recorded by investigators in several places in the eCRF and investigators were instructed to record a single exacerbation only in one place. Despite this instruction, double recording of exacerbations ocurred at some centres.) Prior to correction the difference in asthma exacerbations was statistically greater in the omalizumab group. Therefore the company analysed the primary endpoint without and with adjustment for baseline excarbation.

Number of asthma exacerbations in previous year + run-in period (14 months prior to starting study drug)	n (%) patients		
	Omalizumab N=209	Placebo N=210	P–value*
			0.303
0	2 (1.0%)	0 (-)	
1	31 (14.8%)	32 (15.2%)	
2	90 (43. 1%)	100 (47.6%)	
3	47 (22.5%)	55 (26.2%)	
4	19 (9.1%)	13 (6.2%)	
5	11 (5.3%)	5 (2.4%)	
6	4 (1.9%)	3 (1.4%)	
7	3 (1.4%)	2 (1.0%)	
9	1 (0.5%)	0 (-)	
14	1 (0.5%)	0 (-)	
No. of exacerbations	551	506	

*Cochran Mantel Haenszel test

Outcomes and estimation

Primary endpoint's results are presented below; Analysis of clinically significant exacerbation rate with imputation - Study 2306 (Primary ITT population).

	Omalizumab (N=209)	Placebo (N=210)
Frequency of clinically significant asthma exacerbations – n (%)		
0	119 (56.9)	108 (51.4)
1	59 (28.2)	57 (27.1)
2	18 (8.6)	20 (9.5)
3	6 (2.9)	15 (7.1)
≥4	7 (3.3)	10 (4.8)
Primary analysis (unadjusted)		
Rate of clinically significant asthma exacerbations per treatment period	0.74	0.92
Omalizumab / Placebo (95% CI)	0.806 (0.600 , 1.083)	
‡p-value	0.153	

‡ Poisson regression including terms for treatment, schedule, country grouping, and asthma medication strata

The primary efficacy analysis was also analyzed after adjustment for baseline exacerbations. With adjustment, the rate of clinically significant asthma exacerbations was statistically significant (0.68 versus 0.91, p=0.042)

Sensitivity analyses have been performed. The analysis is summarized in the table below for clinically significant exacerbations, severe exacerbations and all emergency visits for the primary ITT and IgE ≥ 76 IU/mL populations.

	PITT		PITT excluding IgE <76 IU/mL	
	Omaliz N = 209	Control N = 210	Omaliz N = 163	Control N = 143
Clinically significant exacerbations (with imputation)				
Exacerbation rate/28wk	0.74	0.92	0.69	1.16
Ratio of exacerbation rates (95% CI)	0.806 (0.600, 1.083)		0.596 (0.430, 0.827	
p-value for ratio	0.153		0.002	
Severe exacerbations				
Rate/28wk	0.24	0.48	0.23	0.47
Ratio of exacerbation rates (95% CI)	0.499 (0.321, 0.777)		0.493 (0.293, 0.830)	
p-value for ratio	0.002		0.008	
Total emergency visits				
Rate/28wk	0.24	0.43	0.19	0.48
Ratio of exacerbation rates (95% CI)	0.561 (0.325, 0.968)		0.397 (0.205, 0.766)	
p-value for ratio	0.038		0.006	

Secondary efficacy variables

QoL-questionnaire: Significant effects were seen in all domains. Given that a change of 0.5 in the total score or is clinically detectable, a clinically relevant effect on Quality of Life in favor of omalizumab was shown.

Improvement from baseline	Omalizumab (N=209)	Placebo (N=210)	p-value
Number of patients included	204 (100)	205 (100)	
≥ 0.5	124 (60.8)	98 (47.8)	0.008
≥ 1.0	92 (45.1)	51 (24.9)	<0.001
≥ 1.5	56 (27.5)	35 (17.1)	0.011

Asthma symptom score: Omalizumab patients had statistically significantly greater improvements from baseline for total asthma score. However, the clinical relevance of the average treatment difference of about 0.35 points is not immediately transparent.

Pulmonary function: There was a statistically significantly greater improvement in mean morning PEF for omalizumab patients (p=0.042). Statistical significance was achieved from week 12 and onwards. At the end of treatment there was a significant difference in favor of omalizumab (p=0.043). The average positive effects in PEF and FEV1 were modest. However, the twice as high probability to achieve a clinical benefit (FEV1 increase of ≥200 ml) on omalizumab treatment (28% vs 13.8%) supports clinical relevance.

Global assessment The outcome of the investigator and patient global assessment is statistically and clinically significant. Approximately 20 % more investigators and patients rated the effect of omalizumab as excellent or good.

Rescue medication: Reduction of rescue medication use was approximately 0.5 puffs/day with omalizumab compared to placebo (non-significant).

- Clinical studies in special populations

Efficacy data for the controlled studies was pooled for analysis by demographic subgroups. No analysis of efficacy by race was performed, due to the very small proportion of patients of other than Caucasian race. No effect of sex on efficacy was observed. Omalizumab was statistically significantly more effective than control in patients aged 12 - < 18 years, and 18 - < 65 years. In patients aged ≥ 65 years the rate ratio for asthma exacerbations was close to that in the 18 - < 65 years subgroup but the between-treatment difference was not statistically significant. This may be due to the relatively small number of patients in the ≥ 65 years subgroup.

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

Exploratory analysis
A subgroup analysis of high-risk adult and adolescent patients from studies 008C/E, 009C/E and 011C was performed to evaluate the effect of omalizumab treatment in a cohort of patients at high risk of asthma-related death. In accordance with GINA guidelines, patients were termed "high risk" if one or more of the following criteria was fulfilled at screening: (1) an overnight hospitalization in the prior year, (2) an intensive care unit (ICU) stay in the prior year, (3) an emergency room visit in the prior year or (4) an intubation at anytime before screening. In addition, lung function impairment severity was graded mild if baseline % predicted FEV1 was >80%, moderate if 60-80% and severe if <60%. A total of 254 patients (135 omalizumab and 119 placebo) from the study intent-to-treat (ITT) populations were pooled and included in the high-risk population. Results are summarised below.

	Asthma exacerbation rate per patient year, with/without imputation					
	Imputed			Non-imputed		
Study period	Omal (N=135)	Placebo (N=119)	p-value	Omal (N=135)	Placebo (N=119)	p-value
Stabilization phase						
Significant exacerbations	0.69	1.56	0.007	0.64	1.47	0.008
All exacerbations	0.95	1.93	0.010	0.90	1.84	0.011
Whole study period						
Significant exacerbations	0.92	2.04	<0.001	0.79	1.83	0.001
All exacerbations	1.20	2.56	<0.001	1.08	2.35	<0.001

Asthma exacerbation rates by FEV1 severity with imputation in the stabilization phase

FEV_1 subgroup	Exacerbation rate per year			Ratio (95% CI)
	Omalizumab	Control	Treatment difference	
≤60%	0.804	2.364	1.56	0.340 (0.126, 0.917)
>60% - ≤80%	0.668	1.335	0.67	0.501 (0.223, 1.123)
>80%	0.618	0.856	0.24	0.722 (0.193, 2.703)

Efficacy data for the seven controlled studies were also pooled to investigate demographic subgroups for age, gender, predicted FEV_1, total serum IgE and by 2 or 4 weekly dosing. A consistent pattern of an effect in all subgroups emerged. There were indication that adolescents and patients with a baseline % predicted FEV1 below 60 benefits more.

Pooled analyses of efficacy data

- Exacerbation rate per year in all patients in early studies (008, 009, 010 [a pediatric study] and 011) were 0.48 versus 0.85 in omalizumab and placebo groups respectivelly.

- Exacerbation rate per year in all patients in all adult controlled studies (2306, IA04, 2304, 008, 009, 011, 2143)

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		Exacerbation rate per year			Ratio (95% CI)	P-value
		Omalizumab	Control	Treatment difference		
Pooled (N=4273)	Imputation	0.910	1.474	0.564	0.617 (0.535, 0.712)	<0.001
	No imputation	0.766	1.266	0.500	0.605 (0.514, 0.711)	<0.001

- Severe exacerbation rate per year in all patients in all placebo-controlled studies (2306, 2304, 008, 009, 011)

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Study	Severe exacerbations No. patients (No. events)		Exacerbation rate/year		Ratio (95% CI)	P-value*
	Omalizumab	Control	Omalizumab	Control		
Pooled (n=2234)	54 (70)	102 (159)	0.073	0.170	0.431 (0.303, 0.613)	<0.001

- *Supportive studies*

Study IA04:
Study IA04 included a population similar to the currently identified target population. In an open-label design omalizumab on top of current asthma treatment according to best medical practice was compared to standard treatment alone. The results were statistically impressive and clinically relevant for most variables, but the open-label design together with the subjective primary endpoint (a composite of decisions of the treating physician) reduced the confirmatory value of the study. However, for the more objective variable FEV_1, which should be less prone to bias due to the open-label design, a mean difference of 200 ml, which would be clinically meaningful for an individual patient, was shown. Furthermore, more pronounced effects on exacerbations and FEV_1 in the more severely ill patients (patients with clinical features of Step 3 or worse despite Step 4 treatment according to the GINA (2002) Severity criteria) were observed.

Study Q2143g
This study was an open-label study to evaluate the safety of subcutaneous omalizumab for 24 weeks in adult and adolescent patients (aged 6 to 75 years) with predominantly severe persistent asthma (GINA 2002) already treated with other therapies (ALTO). Patients were randomized (2:1 ratio) to either active treatment or the control group. Treatment was given in combination with ongoing asthma treatment. A total of 1899 patients were randomized and treated during the study including 1262 omalizumab and 637 control patients. The study was primary designed to evaluate safety and the primary outcome measure was the incidence of all serious adverse events. Secondary measures included the incidence of the incidence of protocol-defined asthma exacerbation episodes (AEEs) during the treatment phase of the study.

- Discussion on clinical efficacy

Early studies showed that there was an overall statistical significant effect, but the clinical relevance for the entire study population was questionable (0.48 vs 0.85 exacerbations per year in the omalizumab and placebo groups, respectively). Subgroup analyses identified a target population of patients with more severe allergic asthma in which a more pronounced effect of potential clinical relevance was apparent (0.69 vs 1.56 exacerbations per year).

Study 2306 assessed omalizumab in the later target population. In this study, the primary endpoint - clinically significant asthma exacerbation rate - did not reach statistical significance. Several plausible explanations have been provided, such as baseline imbalances with respect to incidence of previous exacerbations, a low rate of exacerbations during treatment (more than 50% with no exacerbation and more than 75% with at most one exacerbation in the placebo group) making the primary endpoint an insensitive variable, and a conservative imputation rule in case of missing values. In *post hoc* analyses

adjusted for baseline imbalances, with and without imputations, statistically significant results were obtained.

Analyses of the rate severe exacerbations (defined as PEF/FEV1<60% of personal best) as well as the rate of total emergency visits were approximately halved in the omalizumab group (0.24 vs 0.48, p=0.008 and 0.24 vs 0.43, p=0.034, respectively).

In a GCP inspection of study 2306 it was found that the patients, in case of an exacerbation, usually attended a clinic or hospital other than the investigational site, and that the recording of exacerbation data and emergency visits was often based on the patient's recollection rather than on verifiable source data. This questioned the validity of all analyses based on exacerbation data and emergency visits. After the inspection 90% of the exacerbations and emergency visits have been verified by retrieved hospital records. There is no imbalance with respect to numbers in the remaining 10% of records and no other indication of a bias between treatments. Thus, the analyses of exacerbation and emergency visits data can be considered reliable.

In addition, results of secondary endpoints show evidence of statistically significant and clinically relevant benefits with respect to Quality of Life, FEV_1, and investigator's and patient's global evaluation of treatment effectiveness.

Subgroups analyses suggested that baseline FEV_1, IgE levels, and concomitant oral corticosteroid treatment might be useful as predictors of treatment response. In a subsequent exploratory multivariate analysis, baseline IgE was retained as a consistent predictor of response. By excluding patients with a baseline total IgE<76 IU/ml a more pronounced and statistically significant effect is obtained. This finding is consistent with the mode of action of omalizumab. However, it is of limited value for identifying a target population because total IgE is an insensitive and variable indicator of the importance of the allergic factor for asthma symptoms and thus, maybe, of limited predicted value in an individual patient.

In summary, the extent of the database, statistically significant differences in several (but not all) studies in term of reduction of asthma exacerbation, benefit in other secondary endpoints such as quality of life, and, statistical difference in term of severe exacerbation (life-threatening condition) in study 2306 show that some patients respond in a clinically relevant manner to omalizumab. Together with the safety concerns, omalizumb should be restricted to severe patients and that the indications should define the population that is likely to benefit from the product on the basis of inclusion criteria of clinical studies (in particular 2306), the mechanism of action of the product (i.e. patients with convincing IgE mediated asthma), the severity of the disease and clinical need in daily practice. The treatment should not be limited to patients treated by oral corticosteroids (In study 2306, 21.7 % of the ITT study population in the study had daily use of oral corticosteroids).

Based on mechanistic rationale and clinical data, it was agreed that treatment with omalizumab should be discontinued after 16 weeks if no improvement is seen.

There are no controlled data on the use of Omalizumab in patients with allergic asthma beyond 28 weeks. Although non-controlled data suggest that there is no significant rebound in either the disease clinical course or the IgE level, the information provided does not allow to assess what would be the optimal treatment duration, when stopping omalizumab treatment could be attempted and what could be the optimal way of tapering omalizumab.

Clinical safety

- Patient exposure

The safety study population comprised over 5300 patients exposed to omalizumab for a relevant duration. Approximately fifty percent of those were patients with allergic asthma. Thereby they also represent a population at risk for allergic reactions to treatment. Of the exposure to omalizumab in controlled studies, exposure in allergic asthma patients represented the major part, >1560 patient years

of the total 1934 patient years. The majority of them seem to have been patients with severe persistent allergic asthma.

- Adverse events

Adverse events were reported by 82% of the asthma patients in both treatments groups in placebo-controlled studies. In the same studies, less than 2% of patients in both groups discontinued treatment due to adverse events or abnormal laboratory values. In the placebo-controlled studies, the overall incidence of suspected drug-related AEs was similar in both treatment groups. The majority of adverse events were of mild to moderate severity. The incidence of adverse events did not increase with the duration of exposure to Xolair.

The table below provides the most common adverse events (≥ 3% in any group) in controlled Allergic Asthma studies (in AAP population - studies [2306, 2304, 008C/E, 009C/E, 011C, 0112] and AAS population – studies IA04 and Q2143g).

	AAP†		**AAS‡**	
MedDRA Organ Class Preferred term	**Omalizumab (N=1192)**	**Placebo (N=1150)**	**Omalizumab (N=1338)**	**STC* (N=666)**
Infections & infestations	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nasopharyngitis	277 (23.2)	274 (23.8)	151 (11.3)	58 (8.7)
Upper respiratory tract infection	210 (17.6)	214 (18.6)	209 (15.6)	83 (12.5)
Sinusitis	150 (12.6)	168 (14.6)	160 (12.0)	74 (11.1)
Influenza	110 (9.2)	114 (9.9)	43 (3.2)	19 (2.8)
Bronchitis	77 (6.5)	86 (7.5)	96 (7.2)	45 (6.8)
Gastroenteritis	49 (4.1)	36 (3.1)	28 (2.1)	8 (1.2)
Pharyngitis	54 (4.5)	53 (4.6)	33 (2.5)	10 (1.5)
Viral infection	45 (3.8)	46 (4.0)	33 (2.5)	12 (1.8)
Lower respiratory tract infection	58 (4.9)	55 (4.8)	34 (2.5)	24 (3.6)
Respiratory, thoracic and mediastinal disorders				
Pharyngolaryngeal pain	98 (8.2)	98 (8.5)	61 (4.6)	13 (1.9)
Cough	81 (6.8)	103 (9.0)	56 (4.2)	13 (1.9)
Rhinitis	57 (4.8)	53 (4.6)	16 (1.2)	17 (2.5)
Nasal congestion	43 (3.6)	35 (3.0)	25 (1.9)	12 (1.8)
Rhinitis allergic	25 (2.1)	37 (3.2)	20 (1.5)	9 (1.3)
Nervous system disorders				
Headache	230 (19.3)	229 (19.9)	121 (9.0)	25 (3.7)
Gastrointestinal disorders				
Diarrhea	59 (4.9)	53 (4.6)	41 (3.1)	5 (0.7)
Nausea	59 (4.9)	47 (4.1)	46 (3.4)	8 (1.2)
Dyspepsia	44 (3.7)	65 (5.6)	16 (1.2)	2 (0.30)
Musculoskeletal and connective tissue disorders				
Back pain	96 (8.0)	92 (8.0)	44 (3.3)	10 (1.5)
Arthralgia	72 (6.0)	56 (4.9)	41 (3.1)	4 (0.6)
Myalgia	52 (4.4)	48 (4.2)	22 (1.6)	3 (0.4)
Pain in extremity	40 (3.4)	27 (2.3)	18 (1.3)	3 (0.4)
Gen. disorders and admin. site conditions				
Pyrexia	43 (3.6)	39 (3.4)	13 (1.0)	4 (0.6)
Psychiatric disorders				
Insomnia	29 (2.4)	37 (3.2)	11 (0.8)	4 (0.6)
Injury, poisoning, and procedural complications				
Joint sprain	40 (3.4)	25 (2.2)	17 (1.3)	8 (1.2)

† AAP studies: 008C/E, 009C/E, 011C, 0112, 2304, 2306
‡ AAS studies: IA04 and Q2143g
*STC = standard therapy control

Injection site reactions, exanthema/urticaria, gastrointestinal disorders (gastroenteritis symptoms as nausea and diarrhoea) and other infections (sinusitis) were observed more frequently in omalizumab treated patients. Respiratory reactions were also observed frequently, however more frequently in the control group. In placebo-controlled studies, the incidence rate of exanthema/urticaria was dose

related, probably because the correlation with the degree of baseline IgE on which the individual dose is based. The overall frequency of injection site reactions was similar in both treatment groups, 45.1% omalizumab and 43.4 % placebo. The overall incidence of severe injections site reactions was slightly higher in the omalizumab group, 11.9% and 8.5%, respectively. Fewer than 1% of patients discontinued as a result of injection site reactions. In general, there was a tendency to have more local AEs with increasing numbers of injections in both treatment groups and the duration of the reaction was similar in the two groups. In a significant proportion, the duration of the reaction was > 1 week. Skin rash including urticaria and other allergic reactions were observed in a large proportion of patients in both groups, and there was no clinically significant difference between them concerning severity and concomitant symptoms except a small number of anaphylactic reactions in close relation to the injection, 4 cases (0.11%) with omalizumab and 1 case (0.04%) with placebo.

- Serious adverse event/deaths/other significant events

In total, five deaths occurred in clinical studies (3 Xolair, 2 Placebo), and they were all judged as unrelated to treatment.

Serious adverse events were reported by around 4 % of the patients in both groups. Severe reactions were more common in the placebo group, mainly due to a higher incidence of infections.

- Laboratory findings

No clinically meaningful effects were observed on serum biochemistry parameters, including renal and liver function tests; no major differences between omalizumab and placebo were observed.

Decreases in hemoglobin levels occurred slightly more frequently in the omalizumab group (9.1% of patients) than the placebo group (7.0%) in the key safety population. In the majority of patients, the decrease from baseline in hemoglobin was < 10%. A decrease in hemoglobin of 20-25% was reported in < 0.5% of patients in both treatment groups; in most cases these were isolated occurrences.

In experimental studies in monkeys thrombocytopenia was observed at high doses. No indications of severe platelet or other blood disorders could be found in the clinical safety database. A few cases of rapidly reversible leukopenia and agranulocytosis, several of which probably were related to other factors, give no clear indication of this being a safety issue. Yet, blood disorders cannot be excluded to be a risk associated with omalizumab and further focused surveillance is warranted.

- Safety in special populations

12 – 17 years of age: In all controlled studies, 325 omalizumab patients and 214 control patients were 12-17 years of age. The overall frequency of AEs was 76% in the omalizumab group and 79% in the control group. There was just one AE with a ≥ 2% difference between the omalizumab and control groups, respectively, i.e. nasopharyngitis.
The experience of treatment of patients >65 years of age is limited. The overall incidence of adverse events in the elderly (>65 years of age) was higher with omalizumab than with placebo, yet the number of events was small. The pattern of adverse events was the same as in patients ≤ 65 years.

- Safety related to drug-drug interactions and other interactions

Omalizumab was administered in combination with other antiasthmatic drugs in all AA studies. All patients received inhaled corticosteroids, other medications administered included oral corticosteroids, long- and short-acting β_2-agonists, theophyllines, cromolyns, and leukotrienes. No interactions between omalizumab and any of these medications were observed.

- Discontinuation due to adverse events

In placebo-controlled studies, less than 2% of patients in both groups discontinued treatment due to adverse events or abnormal laboratory values.

- Post marketing experience

Xolair was first registered in Australia in June 2002 and in the USA in June 2003. The MAH has submitted the 4Th PSUR covering the period 1 July to 31 December 2004. In this PSUR period, the estimated exposed number of patients was 2355 in clinical studies and about 11 000 treatment years based on sales. The estimated cumulative figure based on sales is 18 000 treatment years.
In total, 324 case reports were received, of which 57 serious unlisted, 18 serious listed and 84 non-serious unlisted. The majority of them were spontaneous reports. No new safety issues appeared, except a large number of "listed" anaphylactic reactions, urticaria, allergic reactions and some more cases of "unlisted" angioedemas and laryngoedema, the latter which the CHMP suggests should be included as rare ADRs in the current proposed SPC.

- Discussion on clinical safety

The safety population is extensive and comprises over 5300 patients exposed to omalizumab for a significant duration. Approximately fifty percent patients have allergic asthma.

The majority of adverse events were mild to moderate in their severity. Overall, omalizumab was well-tolerated but the following potential risks were discussed: thrombocytopenia or other blood disorders, parasitic infections, malignancy and allergic reactions.

Theoretically, patients treated with omalizumab could by its mechanism, the anti-IgE effect, increase the risk of parasitic infections. A targeted study of this (2303), enrolled 137 patients with allergic asthma and/or perennial rhinitis (PAR) who were infected with intestinal geohelminths. Overall, the study 2303 showed an increased number of intestinal geohelminth infections occurring with omalizumab compared with placebo. The difference was small and not significant, although a real difference in the risk cannot be excluded. However, due to difficulties to carry out this study and the lack of a representative geohelminth species effect model in this study, the observations and comparisons are complicated to interpret. This issue may be of clinical significance for individuals in endemic areas and travellers. Further controlled studies are difficult to conduct and are not feasible due to the scientific, practical and ethical problems to be taken into consideration. Furthermore, the possible increased risk of parasitic infections rarely would result in severe morbidity, which was also indicated in the parasitic infection study 2303. Caution is therefore recommended in patients at high risk of helminth infection in section 4.4 of the SPC.

The effect of omalizumab on the immune system has been discussed. No signs of immune-complex disorders or autoimmune disorders were found. However, there was an increased incidence of neoplasms in the safety population exposed to omalizumab compared to controls (placebo or standard asthma therapy). Across all 35 completed studies, malignant neoplasms were reported in 25 out of 5015 (0.50%) omalizumab patients compared to 5 out of 2854 (0.18%) control patients. The tumours occurred within 1 year in 20 of 25 (80%) omalizumab and 5 of 5 (100%) control patients; no cancers were reported in 590 patients treated with omalizumab for >2 years with the exception of a basal cell carcinoma in 1 patient. This would suggest that many of these malignant neoplasms reported were likely pre-existing since drug-induced cancers, especially solid tumours, usually occur after long exposure. An immunosuppressive effect of omalizumab is the only likely situation in which the malignancies would progress rapidly in relation to treatment with omalizumab, i.e. within the first years of treatment. There is no experimental evidence of a plausible mechanism for IgE inhibition to be associated with carcinogenesis. Moreover, the analysis was based on a small number of malignancies. As part of the requested Pharmacovigilance Plan, the issue will be further studied in an already ongoing 5-year comparative observational prospective cohort study (EXCELS) in which all serious adverse events are planned to be captured by continuous monitoring and regular follow-up visits. The study will enroll 5000 patients treated with Xolair and 2500 controls. Thereby, both a formal study of the incidence of malignancies (primary outcome) and signal detection/signal evaluation should be possible.

Regarding re-treatment experience, no indications of a significant safety issue was found in patients with allergic asthma and/or seasonal allergic rhinitis exposed > 3 months and up to 9 months after a previous period of exposure to omalizumab.

The pharmacivigilance plan has been presented, an will mainly include the EXCELS post-marketing safety study above-mentioned, a pregnancy registry and monitoring of the following categories of events: malignancy, anaphylaxis/anaphylactoid reactions, serum sickness, significant blood dyscrasias (Neutropenia, Lymphopenia and Thrombocytopenia), severe hypersensitivity reactions including, angioedema, severe cutaneous reactions and parasitic infections.

5. Overall conclusions and benefit/risk assessment

Quality

Except for a limited number of points, which can be addressed as part of post-authorisation commitments, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Viral safety or freedom from other adventitious agents (including TSE) has been adequately demonstrated. Batch to batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

Non-clinical pharmacology and toxicology

The safety of omalizumab has been studied in the cynomolgus monkey since omalizumab binds to cynomolgus and human IgE with similar affinity. Chronic administration of omalizumab was well tolerated in non-human primates, with the exception of a dose-related and age-dependent decrease in blood platelets, with a greater sensitivity in juvenile animals. The serum concentration required to attain a 50% drop in platelets from baseline in adult cynomolgus monkeys was roughly 4 to 20-fold higher than anticipated maximum clinical serum concentrations.

Efficacy

In early studies in a broader asthma population, there was a significant overall effect on exacerbations which clinical relevance was questioned. This effect was more pronounced in patients with more severe allergic asthma. Although the pre-specified primary analysis of study 2306 did not reach statistical significance, the large total clinical documentation for omalizumab supports the treatment of severe allergic asthma considering the overall effect on exacerbation in the complete database, the statistically significant effects in rate of severe exacerbations and total emergency visits which were halved in the omalizumab group and the significant findings in other clinically relevant secondary variables in study 2306 (Quality of Life-responders, FEV_1-responders and investigator's as well as patient's global evaluation). Results that were consistent with other study results or analysis such as a statistically significant and clinically relevant effect on FEV_1 in study IA04, again more pronounced in more severely ill patients.

Xolair treatment should only be considered for patients with convincing IgE mediated asthma. Patients with IgE lower than 76 IU/ml were less likely to experience benefit. 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.

Safety

During clinical trials the most commonly reported adverse reactions were injection site reactions and headaches. Most of the reactions were mild or moderate in severity. Potential safety risks will be followed up through a pharmacovigilance plan.

As with any protein, local or systemic allergic reactions, including anaphylaxis, may occur. Anaphylactic reactions were rare in clinical trials. Medications for the treatment of anaphylactic reactions should be available for immediate use following administration of Xolair.

Benefit/risk assessment

Overall, there is a pattern of significant results that show that omalizumab efficacy is of clinical relevance for patients with severe allergic asthma. Based on the large database, there is no safety alarming signal even some concerns for long-term use will have to be followed through the risk management programme. As a consequence, the benefit-risk is considered positive in the following indications:

> *"Xolair is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 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 reduced lung function (FEV_1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Xolair treatment should only be considered for patients with convincing IgE mediated asthma."*

Xolair treatment should be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered majority decision that the benefit/risk ratio of Xolair in the treatment of the above-mentioned approved indication was favourable and therefore recommended the granting of the marketing authorisation.