25 September 2014
EMA/521869/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xolair

International non-proprietary name: Omalizumab

Procedure no.: EMA/H/C/606/P46 039.2

Marketing authorisation holder (MAH): Novartis Europharm Ltd

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Invented name of the medicinal product:	Xolair
INN (or common name) of the active substance(s):	Omalizumab
MAH:	Novartis Europharm Ltd
Currently approved Indication(s)	Xolair is indicated in adults, adolescents and children (6 to <12 years of age). Xolair treatment should only be considered for patients with convincing IgE (immunoglobulin E) mediated asthma
Pharmaco-therapeutic group (ATC Code):	R03DX05
Pharmaceutical form(s) and strength(s):	Powder and solvent for solution for injection, 75 mg, 150 mg Solution for injection, 75 mg, 150 mg
Rapporteur:	Kristina Dunder
Start of the procedure:	27 July 2014
Date of this report:	26 August 2014
Deadline for Rapporteur's AR:	26 August 2014
Deadline for CHMP member's comments:	10 September 2014
Date of the Rapporteur's final report:	15 September 2014

1. Introduction

On June 17 2014, the MAH submitted data from an extension (E1) to the paediatric study CIGE025B1301 for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Data from study CIGE025B1301 has previously been presented as P46 039. This was a 24 week, open label, multi-center evaluation of pharmacokinetics and pharmacodynamics, efficacy and safety of omalizumab in Japanese children (6-15 years) with inadequately controlled allergic asthma despite current recommended treatment. The extension study presented here was designed to offer continuation of omalizumab treatment to pediatric patients who had previously completed the core study and required continuous treatment with omalizumab, and to further assess the long-term safety and tolerability of omalizumab. The study (study drug administration) lasted until omalizumab was approved/launched for pediatric indication in Japan (20-Aug-2013).

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report for CIGE025B1301E1.

2.2.2. Clinical study

Clinical study number and title

CIGE025B1301E1: An extension study to CIGE025B1301 to evaluate the long-term safety, tolerability and efficacy of omalizumab in Japanese children (6 - 15 years) with inadequately controlled allergic asthma despite current recommended treatment.

Description

This study was the extension study of the core study (CIGE025B1301). This was a multi-centre, single-arm, open-label study which consisted of a treatment period and an optional follow-up investigation for anti-omalizumab antibody. This study (study drug administration) lasted until omalizumab was approved/launched for paediatric indication in Japan (20- Aug-2013).

Methods

Objective(s)

Primary objective: to assess the long-term safety and tolerability of omalizumab as add-on therapy in Japanese paediatric patients with inadequately controlled allergic asthma despite current recommended treatment.

Exploratory objectives:

• To explore the effect of omalizumab in Japanese paediatric patients on:

• Asthma control based on Japanese Paediatric Asthma Control Program (JPAC)

• Quality of life questionnaire(s) score

• Use of asthma long-term control medications

• Pulmonary function (FEV1, FVC, V_{50} [FEF_{50}], V_{25} [FEF_{75}], $FEF_{25-75\%}$)

· To collect the data on the number of hospitalizations, emergency room (ER) visits due to asthma

· To collect the data of pharmacokinetics and pharmacodynamics (serum free IgE level) in Japanese paediatric patients.

Assessor's comment:

Although PK/PD was listed as objectives of the study no PK data was presented.

Study population /Sample size

Patients who had completed the core study and who in the investigator's clinical judgment could benefit from continued treatment with omalizumab were considered for the study.A total of 38 patients entered the extension study and were treated with omalizumab. Of 38 patients, 35 patients completed the study and 3 discontinued.

The mean age of the patient population was 11.5 years (range: 7 - 16 years), with approximately 30% of the patients being 9 years or younger. The ratio of male and female was 3:2. The mean weight was 40.13 kg (range: 24.2 - 69.8 kg). The mean FEV1 (% of predicted value) was 89.82% and was shown near normal value as baseline value (90.29%) in the core study. The mean duration of asthma was 9.3 years. 29 patients (76.3%) had inadequately controlled asthma evaluated by Japanese paediatric asthma control program (JPAC) score.

Assessor's comment:

All 38 patients that completed the core study entered the extension phase.

Treatments

Xolair 75 to 375 mg was given subcutaneously every 2 to 4 weeks. The starting doses (mg) and dosing frequency of this study were the same as those of the core study (allowing for adjustment in case of considerable change in body weight).

Outcomes/endpoints

Efficacy: Asthma control, spirometry measurements (FEV_1, FVC, V_{50} [FEF_{50}], V_{25} [FEF_{75}], $FEF_{25-75\%}$), use of asthma long-term control medications, hospitalization and ER visits, and QOL.

Safety: Collection of all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. They included the regular monitoring of haematology, blood chemistry and urine performed at the central laboratory and regular assessments of vital signs, physical examination, height and body weight.

Bioanalytics: PK/PD parameters evaluated were serum total omalizumab, free IgE and total IgE. Antiomalizumab antibody was also evaluated.

Results

Efficacy results

At the last assessment, 29 patients (76.3%) achieved complete asthma control or were well controlled compared to 9 patients (23.7%) at the start of the extension study. Mean JPAC score (SD) was 9.9 (2.80) at start of the extension study, and mean change from baseline (95% CI) was 2.6 (1.5, 3.6) at 48 weeks, 2.9 (1.9, 3.8) at 96 weeks, and 3.0 (2.0, 4.0) at the last assessment, respectively. At the last assessment, the median of two QOL domain scores (physical and emotional) and overall QOL score are 29.0, 19.0 and 48.0, respectively and reached almost full scores (full scores are 30, 20, and 50, respectively). A statistically significant improvement in each of QOL scores at the last assessment was observed compared to baseline of the core a study ($p < 0.001$, Wilcoxon signed-rank test).

Most spirometry measurements increased from baseline of the core study at all visits during the treatment period, but the changes in these measurements from baseline of the core study were small. The mean change from baseline of the core study in FEV1 (% of predicted value) was −1.05% (95% CI: −6.17, 4.08) at the last assessment. The mean change from baseline of the core study in FEF25-75% (per cent of predicted value) was −1.23% (95% CI: −9.45, 6.99) at the last assessment.

Safety results

Of a total of 38 patients in the Safety set, all patients experienced at least one AE during the treatment period. The most common AE (≥ 50%) by primary SOC was infections and infestations (92.1%), followed by gastrointestinal disorders (71.1%), respiratory, thoracic and mediastinal disorders (57.9%), and skin and subcutaneous tissue disorders (55.3%). The most common AE by PT (≥ 30%) was nasopharyngitis (52.6%), followed by influenza (39.5%), upper respiratory tract infection (36.8%), and asthma (34.2%). Eleven patients (28.9%) experienced at least one AE suspected to be related to the study drug during the treatment period of the extension study. The AEs suspected to be related to the study drug (reported in ≥ 2 patients) were injection site swelling (4 patients), headache (2 patients). Other suspected AEs were reported each in one patient. Most of AEs were moderate (97.4%) and only one patient was mild (2.6%) in severity. Severe AEs were not reported. The incidence of AEs did not increase with prolonged use of the study drug. No major difference was observed in the incidences of AEs by subgroup compared to overall incidences of AEs. No patients died nor discontinued the study or interrupted the study drug temporarily due to an AE. A total of 10 patients (26.3%) experienced SAEs (hospitalization) during the treatment period. Asthma exacerbation (PT: asthma) was reported in 7 patients and SAEs other than asthma exacerbation was reported in 7

events (tonsillitis, viral pharyngitis, peritonsillar abscess, lymphadenitis, appendicitis, pneumonia, and foot fracture) for 4 patients.

Table 12-4 Number (%) of patients with adverse events by preferred term in at least 3% of the patients during the treatment period of the extension study (Safety set)

PT	Omalizumab N=38 n (%)
Total no. of patients with AEs	38 (100.0)
Nasopharyngitis	20 (52.6)
Influenza	15 (39.5)
Upper respiratory tract infection	14 (36.8)
Asthma	13 (34.2)
Headache	11 (28.9)
Eczema	10 (26.3)
Pyrexia	9 (23.7)
Contusion	8 (21.1)
Enterocolitis	7 (18.4)
Pharyngitis	7 (18.4)
Stomatitis	7 (18.4)
Gastroenteritis	6 (15.8)
Ligament sprain	6 (15.8)
Vomiting	6 (15.8)

PT	Omalizumab N=38 n (%)
Conjunctivitis allergic	5 (13.2)
Upper respiratory tract inflammation	5 (13.2)
Urticaria	5 (13.2)
Acne	4 (10.5)
Injection site swelling	4 (10.5)
Otitis externa	4 (10.5)
Rhinitis allergic	4 (10.5)
Abdominal pain	3 (7.9)
Bronchitis	3 (7.9)
Constipation	3 (7.9)
Dermatitis allergic	3 (7.9)
Diarrhoea	3 (7.9)
Growing pains	3 (7.9)
Hand fracture	3 (7.9)
Migraine	3 (7.9)
Myalgia	3 (7.9)
Pneumonia	3 (7.9)
Abdominal discomfort	2 (5.3)
Arthralgia	2 (5.3)
Arthropod sting	2 (5.3)
Back pain	2 (5.3)
Epicondylitis	2 (5.3)
Epistaxis	2 (5.3)
Foot fracture	2 (5.3)
Gastritis	2 (5.3)
Gastrooesophageal reflux disease	2 (5.3)
Heat illness	2 (5.3)
Impetigo	2 (5.3)
Laryngitis	2 (5.3)
Mumps	2 (5.3)
Myopia	2 (5.3)
Oral herpes	2 (5.3)
Orthostatic intolerance	2 (5.3)
Pain in extremity	2 (5.3)
Rash	2 (5.3)
Visual acuity reduced	2 (5.3)

Follow-up investigation for anti-omalizumab antibody (Visit 999) was performed in 10 patients; no antiomalizumab antibodies were detected.

Bioanalytical results

The mean serum free IgE level was suppressed below 25 ng/mL (target level) during the treatment period. Mean total omalizumab and total IgE levels at the steady state were also comparable with those observed in the core study.

2.2.3. Discussion on clinical aspects

The data presented in this extension study is difficult to interpret as the study is open, single armed and all comparisons are made relatively baseline values, i.e. values at the end of the core phase of the

study. There is no positive or negative control that that would allow direct comparisons. Nevertheless, no unexpected findings were recorded neither with regard to efficacy of safety. Efficacy appears to be maintained and the adverse events recorded were expected considering the known safety profile of Xolair. Due to the relatively low number of subjects (35 completing) less common adverse events are not captured with precision.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The study report for study CIGE025B1301E1 is taken note of. Both efficacy and safety data as collected were consistent with previous paediatric data recorded for Xolair. Benefit/risk remains unchanged.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

Additional clarifications requested

Not applicable.