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Human Medicines Development and Evaluation

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

Xolair

omalizumab

Procedure no: EMEA/H/C/000606/P46/060

Note

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

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Introduction

On 07-Jul-2017, the MAH submitted a completed paediatric study for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Novartis has completed the study CIGE025AUS33, a 26-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the effect of omalizumab on markers of asthma impairment in patients with persistent allergic asthma. This study was conducted in the United States and randomized a total of 271 patients aged 12 to 82 years. 19 patients were adolescents, aged 12–17 years.

A short critical expert overview written by a Novartis employee has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that CIGE025AUS33 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

Xolair, as approved was used in this study.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- CIGE025AUS33, A 26-week randomized, double-blind, placebo-controlled, multi-center study to evaluate the effect of omalizumab on markers of asthma impairment in patients with persistent allergic asthma. Last patient last visit on 17-Mar-2010.

1.3.2. Clinical study

CIGE025AUS33

Description

This was a multicenter, randomized, double-blind, placebo-controlled study of patients ≥12 years of age who had inadequately controlled persistent allergic asthma and were currently on Step 4 or higher asthma maintenance therapy as defined in the 2007 National Heart, Lung, and Blood Institute (NHLBI) guidelines. Step 4 therapy included at least a medium-dose inhaled corticosteroid (ICS) plus a long-acting betaagonist (LABA) or a medium-dose ICS plus either a leukotriene-receptor antagonist (LTRA), theophylline, or zileuton.

Methods

Objective(s)

Primary objective:

To evaluate the effect of omalizumab on markers of asthma impairment, as measured by the Asthma Control Test (ACT) score at Week 24 of treatment, in patients with inadequately controlled persistent allergic asthma (Step 4 or above therapy, as defined in the 2007 NHLBI guidelines). Inadequately controlled was defined as not well controlled or very poorly controlled according to the Assessing Asthma Control and Adjusting Therapy in Youths ≥ 12 Years of Age and Adults (NHLBI, 2007).

Secondary Objectives:

To evaluate the effect of omalizumab on clinical symptoms as measured by Investigator's Global Evaluation of Treatment Effectiveness (IGETE).

Study design

The trial consisted of 2 periods: a 2-week screening period to establish patient's eligibility for the trial and a 24-week double-blind treatment period during which patients were randomized and received treatment with either omalizumab or placebo as add-on therapy to their current asthma maintenance therapy. The total duration of patient participation in the study was 26 weeks. An eligible patient was randomized to receive omalizumab or placebo s.c. injections every 2 or 4 weeks based on their weight and screening IgE level in a 1:1 ratio, as add-on therapy to their current asthma maintenance therapy.

Results

Recruitment/ Number analysed

A total of 271 patients were randomized, of whom 242 (89%) completed the study. 29 (11%) patients withdrew prematurely from the study, with the frequency being similar between the omalizumab and placebo groups (12% and 10%, respectively).

In the age group 12 to <18 years, 19 patients were randomized (7 patients to omalizumab, 12 patients to placebo). One patient who was allocated to omalizumab (lost follow-up) and two patients who were allocated to placebo (withdrawal of informed, lost follow-up) in the age group 12 to <18 years were discontinued from the study.

Efficacy results

Primary objective:

The primary efficacy variable was the change in ACT total score from baseline, with the primary analysis time point at Week 24/end of study. At baseline, the mean (SD) ACT total scores were similar between the omalizumab and placebo groups: 13.9 (3.3) and 13.7 (3.5), respectively. These values would be considered to represent very poorly controlled asthma. At the end of study (Week 24), the mean (SD) scores increased to 19.3 (3.7) and 18.5 (4.0) in the omalizumab and placebo groups respectively. These vales would be considered asthma that is not well controlled. At Week 24, the omalizumab group had a larger least squares mean increase in total score from baseline than the placebo group: 5.0 vs. 4.4. The least squares mean group difference of 0.64 (95% CI -0.30 to 1.59) was in favor of omalizumab but was not statistically significant (p = 0.1779).

Secondary Objectives:

In the secondary variable of IGETE, the proportion of patients with ratings of excellent or good was larger in the omalizumab group than the placebo group: 55% (70/127) vs. 48% (63/131). The omalizumab group also had a smaller proportion of patients with a rating of poor or worsening: 22%

(28/127) vs. 29% (38/131). The group comparison across all IGETE categories was not statistically significant (p = 0.1177).

In the patient group aged 12 to <18 years, no separate efficacy analysis was performed due to the small number of patients (19 patients).

Safety results

In the entire study population, a total of 183 (68%) patients reported at least 1 AE during the study, with the proportions being similar between the omalizumab and placebo groups (66% and 69%, respectively). The most common preferred terms were asthma (17%), upper respiratory tract infection (12%), sinusitis (8%), bronchitis (6%), and headache (6%). All events of asthma were reported as exacerbations or worsening of asthma symptoms. The proportion of patients with asthma (worsening or exacerbation) was smaller in the omalizumab group than the placebo group (15% vs. 20%). The proportion of patients with severe AEs was smaller in the omalizumab group than the placebo group (4% vs. 7%).

15 patients had at least 1 AE suspected to be related to study drug, 11 of whom were in the omalizumab group. The most frequently reported related AEs were injection site pain (6 patients) and injection site hematoma (2 patients).

SAEs were reported in 3 patients in the omalizumab group and 5 patients in the placebo group. None were considered related to study drug. No deaths occurred during the study.

Due to the small number of patients (19 patients) aged 12 to <18 years included, no separate safety analysis in these patients group was performed.

Table 3-1 lists AEs reported in the patients aged 12 to <18 years in this study. All AEs were mild or moderate in severity, and not suspected to be study treatment judged by the investigator. No SAEs and AEs leading to treatment discontinuation were reported in these patients.

Table 3-1 Adverse events in patients aged 12 to less than 18 years (Study CIGE025AUS33)

Patient ID	Age/gender	Treatment	Adverse event (Preferred term)	SAE	Severity	Causality
0515/00012	13/M	Omalizumab	Ear pain	No	Moderate	Not suspected
			Asthma	No	Moderate	Not suspected
			Asthma	No	Moderate	Not suspected
0516/00008	17/F	Omalizumab	Pharyngitis streptococcal	No	Mild	Not suspected
0516/00016	13/F	Omalizumab	Herpangina	No	Mild	Not suspected
			Upper respiratory tract infection	No	Mild	Not suspected
			Influenza	No	Moderate	Not suspected
			Gastroenteritis viral	No	Mild	Not suspected
0529/00009	13/M	Omalizumab	Mouse injury	No	Moderate	Not suspected

Patient ID	Age/gender	Treatment	Adverse event (Preferred term)	SAE	Severity	Causality
0536/00013	15/F	Omalizumab	Sinusitis	No	Mild	Not suspected
			Pyrexia	No	Mild	Not suspected
			Oropharyngeal pain	No	Mild	Not suspected
			Cough	No	Mild	Not suspected
0516/00009	12/F	Placebo	Headache	No	Mild	Not suspected
			Upper respiratory tract infection	No	Mild	Not suspected
0516/00012	16/F	Placebo	Bronchitis	No	Mild	Not suspected
			Hepatitis infectious mononucleos	No	Moderate	Not suspected
0516/00015	12/M	Placebo	Upper respiratory tract infection	No	Mild	Not suspected
0521/00001	12/M	Placebo	Pharyngitis	No	Mild	Not suspected
0521/00003	14/F	Placebo	Asthma	No	Moderate	Not suspected
			Costochondritis	No	Moderate	Not suspected
			Rhinitis allergic	No	Mild	Not suspected
0542/00002	14/M	Placebo	Arthralgia	No	Mild	Not suspected
0545/00010	14/M	Placebo	Asthma	No	Mild	Not suspected
0550/00016	15/M	Placebo	Asthma	No	Mild	Not suspected

1.3.3. Discussion on clinical aspects

The study did not meet the primary efficacy objective between omalizumab and placebo in terms of change in ACT total score from baseline at Week 24 in entire study population. One potential reason for this result is that a broader patient population was enrolled in this study compared with prior clinical trials.

Omalizumab therapy was well tolerated and exhibited a safety profile that was generally similar to placebo.

In conclusion, the results of this trial raised no new safety concerns and do not change the overall risk/benefit profile of Xolair® (omalizumab).

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The study report for Study CIGE025AUS33 has been provided as requested according to Article 46 of Regulation (EC) No1901/2006, as amended. There were no unexpected findings.

Recommendation

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

Additional clarifications requested

Not applicable.