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Human Medicines Evaluation Division

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/P46/056

Note

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

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1. Introduction

On Dec 07 2016, the MAH submitted the study, CIGE025A2437 for Xolair, including paediatric subjects, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Xolair is approved as add-on therapy to children 6-12 years of age to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. A similar indication is approved for adolescents and adults. It is also indicated for adults and adolescents (12 years of age and above) with chronic spontaneous urticaria (CSU) refractory to standard of care.

Study CIGE025A2437 was an exploratory, randomized, double-blind, placebo controlled study conducted in Belgium, Germany, Ireland, Italy, Netherlands, Switzerland, UK and USA to assess the efficacy of multiple doses of omalizumab (Xolair®) in cystic fibrosis (CF) complicated by allergic bronchopulmonary aspergillosis (ABPA).

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

2. Scientific discussion

2.1. Information on the development program

The study CIGE025ABR01 is a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

Xolair, as approved was used in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has completed study CIGE025A2437 (last patient last visit on 12-Jul-2010). This is an exploratory, randomized, double-blind, placebo controlled study to assess the efficacy of multiple doses of omalizumab (Xolair®) CF complicated by ABPA. This study was conducted in eight countries (Belgium, Germany, Ireland, Italy, Netherlands, Switzerland, UK and USA) and enrolled 14 male and female patients aged 13 to 42 years with CF complicated by ABPA. Patients were randomized to omalizumab or placebo in a ratio of 2;1 and treated for 26 weeks, followed by an open-label treatment period of 26 weeks. The study was terminated early due to a lack of recruitment of suitable patients.

ABPA is a severe complication in children, adolescents and adults with CF. Colonization of the respiratory tract by fungi, commonly Aspergillus fumigatus, leads to sensitization to fungal antigens, accompanied by a Th2 immune response and the production of high levels of specific IgE. The consequent inflammatory and obstructive bronchopulmonary injury can accelerate clinical deterioration in CF. Because of the probable role of IgE in the pathophysiology of ABPA, omalizumab has been empirically employed in treatment, resulting in a growing number of clinical anecdotes that have primarily been positive, consistent with the measurable onset of activity in clinical trials of asthma shortly after dosing begins (Van der Ent, 2007). Thus, CIGE025A2437 was planned to explore whether

the utility of omalizumab in ABPA could be demonstrated in a standardized fashion, i.e. in a controlled clinical study for proof of efficacy.

2.3.2. Clinical study CIGE025A2437

Methods

Objectives

Primary objective

- To assess the efficacy of omalizumab in adolescent and adult patients with CF complicated by chronic or acute ABPA
  - As measured by the proportion of patients who required rescue with corticosteroids following 6 months of study treatment.
  - As measured by time to deviation from the protocol prescribed steroid tapering regime.
- To explore the safety and tolerability of higher doses of omalizumab in this patient population

Secondary Objectives:

- To assess the ABPA exacerbation rates during the treatment periods
- To assess the changes in FEV1 from baseline, measured after 3 and 6 months of study treatment, and in particular the changes between FEV1 measured before and after the first dose in both the blinded and open label treatment periods
- To assess the proportion of patients responding to omalizumab treatment, where responder was defined by a reduction in systemic corticosteroid dose of 50% or more compared to baseline
- To measure the time to steroid free state
- To assess the change from baseline over time in the average dose of rescue corticosteroid
- To assess the proportion of patients in each treatment group (omalizumab/placebo)
- responding to omalizumab whose steroid dose had reduced to 5 mg following 6 months of treatment
- To measure the number of steps needed to reduce the steroid dose to zero (or to 5 mg or less) following 6 months of treatment
- To measure immunogenicity (anti-omalizumab antibodies)
- To measure PK/PD: total omalizumab levels, free & total IgE

Study design

An exploratory, randomized, double-blind, placebo controlled study.

Study population /Sample size

The study population consisted of male and female adolescents and adult CF patients (as diagnosed by gene profiling and/or sweat test) who had been diagnosed with ABPA according to the Cystic Fibrosis Foundation Concensus Conference Guidelines.

A total of 14 patients (9 patients in omalizumab, 5 patients in placebo) were enrolled into this study before the study was terminated. Of these 14 patients, seven (four in the omalizumab group and three in the placebo group) completed the double blinded period and entered the open label period. Only three patients completed the full study.

The patients received omalizumab according to the dosing table based on baseline serum IgE and body weight or matched placebo during double blinded period. During the open label period, all patients received omalizumab. In the age group 12 to <18 years, one patient (Center/Subject ID: 4/5109, 13 years old, male, Caucasian) was enrolled into this study and randomized to omalizumab. This patient discontinued the study during the double blind period due to “Unsatisfactory therapeutic effect”. No patients aged 6 to <12 years were enrolled into this study.

Statistical analysis

Not applied.

Results

Efficacy results

Only one paediatric subject was included (13 years old, male, Caucasian) was enrolled into this study and randomized to omalizumab. This patient discontinued the study during the double blind period due to “Unsatisfactory therapeutic effect”.

Safety results

Injection site reactions were the only reported AEs in the single paediatric patient that were judged as suspected to be related to the study drug.

3. Discussion on clinical aspects

Study CIGE025A2437 was an exploratory, randomized, double-blind, placebo controlled study to assess the efficacy of multiple doses of omalizumab (Xolair®) CF complicated by ABPA. One single paediatric patient was included. This patient withdrew from the study due to insufficient efficacy and experienced mild to moderate injection site reactions. The presented data does not change the benefit risk for omalizumab in the paediatric approved indications. No changes are warranted in the SmPC.

4. Rapporteur’s overall conclusion and recommendation

The study report for Study CIGE025A2437 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.