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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/P46/059

Note

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

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Introduction

On 04-jun-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 [CIGE025BFR02], entitled STELLAIR "Next Steps Toward personalized care: EvaLuating responders to XoLAIR® treatment in patients with severe allergic asthma". This study was a multicentre non-interventional study to evaluate responders to omalizumab treatment. The study included children, adolescent and adult patients with severe allergic asthma in French clinical practice.

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 CIGE025BFR02 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study<ies>

Xolair, as approved was used in this study.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted a final report for:

- Study CIGE025BFR02 (end of data collection on 30-Sept-2016)

Clinical study

CIGE025BFR02, STELLAIR "Next Steps Toward personalized care: EvaLuating responders to XoLAIR® treatment in patients with severe allergic asthma".

Description

STELLAIR was an observational retrospective study to evaluate responders to Xolair® treatment in patients with severe allergic asthma.

Methods

Objective(s)

The aim of this non interventional retrospective study was to describe, in real-life conditions, responders to omalizumab treatment at the first Xolair® efficacy assessment (after 4 to 6 months of treatment).

Primary objective: To describe, in real-life conditions, patients (adults, adolescents and children) with severe persistent allergic asthma treated for 4 to 6 months and who are responders to omalizumab treatment.

The response to omalizumab was evaluated using three definitions:

-Physician's overall evaluation according to Global Evaluation of Treatment Effectiveness (GETE) scale.

GETE is a five-point scale, where 1 = excellent (complete control of asthma), 2 = good (marked improvement), 3 = moderate (discernible, but limited improvement), 4 = poor (no appreciable change) and 5 = worsening.

The rating of symptoms control as 'excellent'/'good', or 'moderate'/'poor'/ 'worsening' allowed the patient to be respectively defined as 'responder', or 'non responder'.

-A reduction in the annual exacerbation rate: responder having a reduction of at least 40% in the annual exacerbation rate.

An asthma exacerbation was defined as a significant worsening of asthma requiring a short burst of OCS or, if the patients were treated with OCS, increased of OCS dose regimen.

-The combination of both definitions (physician's evaluation and annual exacerbation rate decrease).

The response rate was also evaluated according to blood eosinophils count per µl (EOS) measured in the year prior omalizumab initiation and was conducted in two sub-groups of interest based on EOS ≥ 300 cells per µL and < 300 cells per µL.

Secondary objectives: To describe, in real-life conditions, after 6 months of Xolair® treatment, the characteristics of patients, based on the physician's overall assessment, classified as:

Super responders (i.e. complete control of asthma),

Good responders (i.e. marked improvement of asthma),

Non responders (i.e. discernible but limited improvement in asthma, no appreciable change in asthma or worsening of asthma).

To evaluate the efficacy on:

Exacerbation and hospitalisation including emergency department presentation, daytime hospitalisation and intensive care unit visits,

Changes in the use of anti-asthmatic medications.

Study design

STELLAIR was a non-interventional, retrospective and descriptive study which evaluated secondary data obtained from medical records of patients (879 patients were included by 78 sites in France). The study design did not require any follow-up visit (routine clinical care).

Study population /Sample size

Patients who met the following inclusion / exclusion criteria were included in the study.

Inclusion criteria:

1. Outpatients, age ≥ 6 years,
2. Patients who had been treated with Xolair® for a poorly controlled severe persistent allergic asthma with dose and regimen according to the SmPC,

3. Patients with a documented value of blood eosinophilia within the last 12 months prior to Xolair® initiation,
4. Patients with a number of exacerbations recorded during 12 months prior to Xolair® initiation,
5. Patients with a documented response to Xolair® after at least 16 weeks of treatment and with exacerbation recorded.

Exclusion criteria:

1. Patients who refused the collection of their medical data,
2. Patients treated with Xolair® for another reason than a poorly controlled severe persistent allergic asthma,
3. Patients with no documented value of blood eosinophilia within the last 12 months prior to Xolair® initiation,
4. Patients with no number of exacerbations recorded during 12 months prior to Xolair® initiation,
5. Patients with no documented response to Xolair® treatment in patient-file and no recorded exacerbations.

879 patients were included by 78 sites in France. 872 severe allergic asthmatic patients treated with omalizumab were analysed (7 patients excluded from analysis: no 6 months evaluation (N=5), no maintenance asthma treatment documented before Xolair initiation (N=2)): 723 adults and 149 minors. 68 patients were between 6 and 12 years old and 81 were between 12 and 17 years old.

In the population of those below the age of 18 years, analyses were conducted in two subgroups: a group of children of [6-12 years including 68 patients (46% of the whole minor population) and a group of adolescents of [12-17] years comprising 81 patients (54% of the minor population).

Setting

The participating pulmonologists and pediatricians (hospital and community based) were asked to include all their severe allergic asthmatic patients treated with omalizumab (Xolair®) that met inclusion / exclusion criteria (45 medical records maximum per pulmonologist). The questions asked in this study were simple and short, providing information on key clinical parameters routinely explored during a consultation for severe asthma. The data collected came only from patients' medical records and were completed in an electronic case report form (e-CRF) specifically developed for the study. A corresponding database was created, this database was tested and validated prior to the study.

Statistical Methods

A total of 456 patients were required in the initial protocol to describe the proportion of patients with reduction of exacerbation annual rate and the proportion of Xolair® responders in both sub-groups based on eosinophilia counts with an absolute precision of ± 7.5 %. A precision of 7.5 % guarantees a length of the two-sided 95 % confidence intervals to be less than 15 % under hypotheses.

During the study, the mean number of patients included per physician was higher than planned. It was decided to continue inclusions without any modification of the study timelines and selection of physicians. Overall, 872 forms were analyzed.

Results

Recruitment / Number analysed

The majority of children and adolescents were male (63.1%), with a higher proportion of male in the [6-12[years children group than in the [12-17] years adolescents group (73.5% (50 children) vs. 54.3% (44 adolescents). 89.7% in the [6-12[years group and 92.6% in the [12-17] years group had comorbidities including perennial (79.4%) and seasonal (40.4%) rhinitis, atopic dermatitis (36.8%), and food allergy (27.2%).

Omalizumab was prescribed as add-on therapy to improve asthma control in patients who had had multiple documented severe asthma exacerbations despite daily high-dose ICS, plus a LABA. At Xolair® initiation, only 3 adolescents were treated with OCS as maintenance treatment.

The mean number of exacerbations (5.7 ± 3.3 in children, 4.7 ± 4.2 in adolescents) and hospitalisations (2.3 ± 1.9 in children, 2.3 ± 2.1 in adolescents) in the 12 months before omalizumab initiation were high and confirmed the important burden of severe asthma in children and adolescents.

In minors, this severe atopic population was characterised by very high total IgE levels (mean IgE level of 1361 IU/mL). The median of the total serum IgE was the same in the two age groups (850 IU/mL). 42.3% of children were administered omalizumab every 4 weeks with a dose of 300 mg and 45.8% of adolescents every 2 weeks with a dose of 600 mg.

In the 12 months before omalizumab initiation, the distribution of EOS in severe asthmatic allergic patients was different in the adult population compared to the minor population. The median EOS was 619 cells/µL in the minor population and 308 cells/µL in the adult population. The median EOS was higher in children (700 cells/µL) than in adolescents (590 cells/µL).

73.4% (110 patients) of minors with severe allergic asthma had a blood eosinophilia count higher than or equal to 300 cells/µL.

Baseline data

Efficacy results

Primary endpoint:

Response according to physician´s global evaluation: By physician's GETE, 67.2% of adults and 77.2% of minors were responders (i.e. complete control or marked improvement of asthma) to omalizumab after 6 months of treatment. 80.9% of children aged [6-12[years and 74.1% of adolescents aged [12-17] years were responders according to GETE scale through physician's evaluation. These proportions were not different in the two age classes as their corresponding confidence intervals overlapped.

The same analysis was performed according to blood EOS count with a cut-off at 300 cells/µL. In minors, the proportion of responders was 81.8% in those with EOS ≥ 300 cells/µL (n=110, CI95% [73.3%-88.5%]) and 64.1% in those with EOS < 300 cells/µL (n=39, CI95% [47.2%-78.8%]). In subjects with EOS ≥ 300 cells/µL, 83.7% of children (n=41) and 80.3% of adolescents (n=49) were 'responders' to omalizumab treatment based on physician's global evaluation.

There was no difference in the proportion of responders in the two subgroups of blood eosinophilia within the two age classes of minors. Confidence intervals of these proportions overlapped.

Response according to annual exacerbation rate: At 6 months, 31% of the [6-12] years children and 38% of the [12-17] years adolescents had presented at least one exacerbation. The mean number of

exacerbations in patients with at least one exacerbation was at 6 months 1.8 in the youngest group and 2 in the oldest one.

The change in the annual exacerbation rate reached -69% in children of [6-12] years and -52.8% in adolescents of [12-17] years. The proportion of responders based on a reduction in the annual exacerbation rate was 85.3% (CI 95% [74.6%-92.7%]) in children and 72.8% (CI 95% [61.8%-82.1%]) in adolescents. These proportions were not different.

The proportion of responders in the two age groups of the minor population according to the number of exacerbations did not change with the cut-off of EOS count at 300 cells/µL. In minors, the response rate was 78.2% in EOS ≥ 300 cells/µL and 79.5% in EOS < 300 cells/µL.

Response according to the combined criteria: Responders to omalizumab treatment defined with the exacerbation criteria and with the physician' evaluation criteria were consistent in 67.8% of the cases in the minor population of patients. Response according to the combination of the two definitions reached 67.8% in minors (CI 95% [59.7%-75.2%]): 75% (CI 95% [63%-84.7%]) in children and 61.7% (CI 95% [50.3%-72.3%]) in adolescents.

The responders' proportion according to one or two criteria was 87.9% in minor population: 91.2% in children and 85.2% in adolescents.

There was no difference in the proportions of responders, as defined with the combined criteria, according to the studied cut-off EOS count in the two populations.

Safety results

Due to the non-interventional nature of the study with secondary data collection, there was no safety data collection performed in this study.

1.3.2. Discussion on clinical aspects

STELLAIR quantified the overlap between severe allergic asthma and severe eosinophilic asthma and demonstrated the real-world effectiveness of omalizumab, irrespective of blood eosinophilia status. STELLAIR demonstrated that omalizumab efficacy was similar in 'high EOS' and 'low EOS' severe allergic asthma subgroups.

2. Rapporteur's overall conclusion and recommendation

Overall conclusion

The study report for Study CIGE025BFR02 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.

Additional clarifications requested

Not applicable.