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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/P46/063

## Note

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

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Introduction

In February 2018, the MAH submitted a completed paediatric study for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Novartis has completed a study CIGE025AMX02 (last patient last visit on 08-Jan-2016) entitled“Multi-center, Open-label, Randomized, Parallel-group Study to Evaluate the Efficacy and Safety of Omalizumab in a 12-Month Period, in Patients with Severe IgEmediated Asthma Inadequately Controlled with High Doses of Corticosteroids (MEXIC Study).” This study was conducted in Mexico and was prematurely terminated after 129 patients aged 6 to 55 years with severe IgE mediated asthma inadequately controlled with high doses ICS were randomized.

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

# 1. Scientific discussion

## *1.1. Information on the development program*

CIGE025AMX02 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:

- Study CIGE025AMX02 was a Multi-center, Open-label, Randomized, Parallel-group Study to Evaluate the Efficacy and Safety of Omalizumab in a 12-Month Period, in Patients with Severe IgE-mediated Asthma Inadequately Controlled with High Doses of Corticosteroids (MEXIC Study). The (last patient last visit was 08-Jan-2016).

### 1.3.2. Clinical study

CIGE025AMX02

### Description

Study CIGE025AMX02 was a multi-center, open-label, randomized, parallel-group study to evaluate the efficacy and safety of omalizumab in a 12-Month Period, in patients with severe IgE-mediated asthma inadequately controlled with high doses of corticosteroids. The purpose of the study was to assess if the treatment with omalizumab during 12 months is efficacious and safe for reducing the use of ICS.

## Methods

### *Objective(s)*

The primary objective of the study was to evaluate the efficacy of omalizumab in severe IgE-mediated asthma, inadequately controlled with high doses of corticosteroids, assessed by the proportion of patients able to reduce the baseline dose of budesonide by at least 50%.

In addition there were a number of secondary objectives i.e. to evaluate:

- reduction in clinically significant asthma exacerbation episodes;
- frequency of hospital admission due to asthma exacerbation;
- need for oral or systemic corticosteroid for asthma treatment;
- number of the days missed in school or work due to asthma exacerbation episodes;
- control of asthma symptoms;
- impact in quality of life;
- safety and tolerability during a 12-month treatment period.

### *Study design*

The study comprised of 4 phases, a run-in phase, a stable-steroid phase, a steroid dose reduction phase and an extension phase. After the Screening visit, eligible patients entered a 4-week run-in phase. During the 4-week run-in phase, adult patients received budesonide 800 µg and formoterol 24 µg (budesonide/formoterol) and pediatric patients received budesonide 400 µg and formoterol 12 µg every 24 hours. During the 16-week stable-steroid phase, adult and pediatric patients were randomized to one of two treatment groups in a 1:1 ratio:

- Budesonide and formoterol every 12 hours and omalizumab s.c. injection every 2 or 4 weeks.
- Budesonide and formoterol every 12 hours.

During the 8-week steroid dose-reduction phase, the dose of budesonide was reduced by 25% of baseline dose depending on disease control, until subjects reached a 100% reduction of baseline dose, however, formoterol dosages were not modified during the study. If the patient´s asthma symptoms are not controlled following the dose reduction, the last effective dose was maintained (minimal effective dose) until the next visit, where the Investigator decided the dosages (reduced or increased in ±25%) to achieve clinical control of asthma. Clinical control of asthma was defined according to the GINA 2012. During the 28-week extension phase, the minimal effective dose was maintained. However, dose adjustments were allowed for safety reasons. Patients received the protocol-determined omalizumab subcutaneous injection dose according to the IgE level and body weight every 2 or 4 weeks following the specific administration instructions as per the prescribing information.

***CHMP Comment:***

The rationale behind the study objective is not fully understood as Xolair was used to taper off the dose of ICS. Xolair is approved for use in patients inadequately controlled with high doses of corticosteroids and is not intended to replace ICS treatment. LABA treatment without ICS is not recommended in GINA guidelines and it is not understood how an adequate evaluation of secondary parameters could be made considering the variation in ISC dose.

***Study population***

The original sample size planned to enroll approximately a total of 138 to be randomized in a 1:1 ratio to the treatment groups. However the study was terminated with 129 randomized patients.

***CHMP Comment:***

The study was prematurely discontinued by the Sponsor for reasons related to data management handling.

## Results

***Recruitment / Number analysed***

A total of 93 adult and 36 paediatric patients were randomized in the study. The ITT population included 33 patients who received at least one dose of study drug and had at least one post-baseline assessment of the primary or secondary efficacy variables. The PP population included 23 patients who completed at least 12 months of treatment, had a valid assessment of the primary efficacy variable at Week 24 and no major protocol deviations. The mean (SD) age of paediatric patients in the omalizumab group was 11.1 (3.32) years and 12.4 (1.80) years in the budesonide and formoterol group. In the omalizumab group, half of the patients had persistent moderate asthma and the mean (SD) length of time since asthma diagnosis was 6.8 (3.87) years. In the budesonide and formoterol group, the majority of patients had persistent severe asthma (64.7%) and the mean (SD) length of time since asthma diagnosis was 6.5 (3.68) years. Overall, most paediatrics (93.9%) were found to have an allergic component.

***Efficacy results***

Due to premature termination of the study, follow-up efficacy data could not be verified. Primary efficacy variable included only the absolute budesonide dose at Baseline without any post-baseline results.

***Safety results***

In the paediatric population, a total of 59 AEs were reported in 11 patients in the omalizumab group and 33 AEs were reported in 7 patients in the budesonide and formoterol group, respectively as summarised in the table below.

**Table 3-1 Adverse events regardless of study drug relationship, by primary system organ class (All available safety data, Pediatric Population)**

| MedDRA organ class | Omalizumab + Budesonide and Formoterol N=11 Number of events (%) Number of patients | Budesonide and Formoterol N=7 Number of events (%) Number of patients | Total N=18 Number of events (%) Number of patients |
|---|---|---|---|
| **Total** | **59 (64.1) 11** | **33 (35.9) 7** | **92 (100) 18** |
| Respiratory, thoracic and mediastinal disorders | 14 (23.7) 8 | 13 (39.4) 2 | 27 (29.3) 10 |
| Infections and Infestations | 19 (32.2) 8 | 5 (15.2) 5 | 24 (26.1) 13 |
| Musculoskeletal and connective tissue disorders | 13 (22.0) 2 | 0 ( 0.0) 0 | 13 (14.1) 2 |
| Nervous system disorders | 4 ( 6.8) 2 | 7 (21.2) 4 | 11 (12.0) 6 |
| Gastrointestinal disorders | 2 ( 3.4) 2 | 6 (18.2) 1 | 8 ( 8.7) 3 |
| General disorders and administration site conditions | 6 (10.2) 2 | 0 ( 0.0) 0 | 6 ( 6.5) 2 |
| Eye disorders | 0 ( 0.0) 0 | 2 ( 6.1) 2 | 2 ( 2.2) 2 |
| Skin and subcutaneous tissue disorders | 1 ( 1.7) 1 | 0 ( 0.0) 0 | 1 ( 1.1) 1 |

Twenty three AEs noted in 3 patients in the omalizumab group and 1 AE noted in 1 patient in the budesonide and formoterol group were suspected to be related to study drug (Table 12-7). Adverse events suspected to be related to study drug were reported in the following primary SOCs:

- musculoskeletal and connective tissue disorders (2 patients in the omalizumab group),
- nervous system disorders (1 patient each in the omalizumab group and budesonide and formoterol group, respectively),
- general disorders and administration site conditions, gastrointestinal disorders and skin and subcutaneous tissue disorders (1 patient in each category in the omalizumab group).

***CHMP Comment:***

The MAH concludes that there we not unexpected findings in this study, although in the paediatric population there were 13 adverse events of musculoskeletal and connective tissue disorders recordings in 22 % of patients reported as related to study drug. No corresponding events were recorded in the bud/form group. Systemic lupus erythematosus (SLE) is listed in the SmPC with frequency “rare” and arthralgia, myalgia and joint swelling are listed with frequencies “not known” (indicating that no frequencies could be set based on data from controlled studies, else there are no listings from this SOC). Thus the total frequency of recordings from the SOC appears to be considerably higher than expected. Nevertheless, considering that it appears to be only two patients involved and both had a number of events listed as “pain localised” it appears to be injections site reactions incorrectly classified. This issue is not further pursued.

## 1.3.3. Discussion on clinical aspects

The rationale behind the study objective is not fully understood as Xolair was used to taper off the dose of ICS, a treatment strategy which is not in line with the GINA guideline. However, no efficacy results were retrieved from this study as it was terminated prematurely for reasons linked to data management handling. With regard to safety there were adverse events recorded with a certain unbalance between test and reference (especially musculoskeletal and connective tissue disorders). However, due to the limited number of patients firm conclusions should not be drawn.

The safety information recorded in this study does not change the benefit/risk balance for the product.

## 2. Rapporteur's overall conclusion and recommendation

The study report for Study CIGE025AMX02 has been provided as requested according to Article 46 of Regulation (EC) No1901/2006, as amended. There is no change to the benefit/risk balance for the product.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

## 3. Additional clarification requested

NA