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Committee for Medicinal Products for Human Use (CHMP)

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/P46/073

Note

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

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1. Introduction

On 5 January 2022, the MAH submitted a non-interventional post-marketing surveillance trial in China 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

The MAH stated that Study No. CIGE025A2455, Post Approval Safety Study (PASS) for s.c. injection 150 mg Xolair® (Omalizumab) in Chinese Patients (≥ 6 years) with Moderate to Severe Allergic Asthma was a regulatory requirement for all newly approved drugs by the Chinese Health Authority (HA) – Chinese Medical Products Administration (NMPA), the purpose of which was to monitor safety for a defined period of 5 years in real word setting.

2.2. Information on the pharmaceutical formulation used in the study

Xolair for s.c. injection 150 mg was used in the present study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- CIGE025A2455, "Post Approval Safety Study (PASS) for s.c. injection 150mg Xolair® (omalizumab) in Chinese Patients (≥ 6 years) with Moderate to Severe Allergic Asthma".

2.3.2. Clinical study

CIGE025A2455 is a Non-interventional post-marketing surveillance trial in China to gather safety and efficacy data on China patients with moderate to severe allergic asthma.

Description

Methods

Objective(s)

The primary objective of this non-interventional study was to evaluate the safety of omalizumab in a real world setting in Chinese moderate to severe allergic asthma patients (≥6 years) over 24 weeks observation period.

The primary end-point was the incidence of AEs and SAEs over 24 weeks of omalizumab treatment.

The secondary objective was to evaluate the effectiveness of omalizumab, treatment patters, incidence of Adverse events of special interest (AESI) and treatment discontinuation with omalizumab due to AEs and SAEs in moderate to severe allergic asthma (AA) patients during a 24- weeks observation period.

The secondary end-points were:

☐ Response to treatment as measured by Investigator's and patient's Global Evaluation of Treatment Effectiveness (GETE) at Weeks 16 and 24.

☐ Patient's health-related quality of life as measured by Mini Asthma Quality of Life Questionnaire (mini-AQLQ) and the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) at Weeks 16 and 24.

☐ Rate of asthma exacerbations over Weeks 16 and 24. An asthma exacerbation is defined as a worsening of asthma symptoms requiring additional systemic steroid therapy, hospitalization due to asthma, emergency visit due to asthma, unscheduled visit due to asthma, or absence from school/work including housework due to asthma.

☐ Treatment patterns and medical healthcare use captured in case report forms (CRFs) (e.g., patient characteristics, dosage and dates administration of omalizumab use, treatment status of asthma, treatment for asthma exacerbation, concomitant medication, comorbidities, number of hospitalizations, emergency visits and unscheduled visits within one year prior to Day 1) at Day 1 and Week 24.

☐ Incidence of AEs of special interest including anaphylaxis over 24 weeks during omalizumab therapy: o Important identified risks: anaphylaxis/anaphylactoid reactions and Churg-Strauss syndrome/hyper eosinophilic syndrome o Important potential risks: arterial thromboembolic events and malignant neoplasms

☐ Incidence and reasons of discontinuation/withdrawal at Weeks 16 and 24.

Study design

Study CIGE025A2455, non-interventional, multi-center, post approval safety study (PASS), was designed as per China Health Authority requirement to collect safety, effectiveness, treatment patterns and other clinical information in patients with moderate-to-severe AA receiving omalizumab in a real-world clinical setting in mainland China. This was a single arm study with no comparison groups and an observation period of 24 weeks.

Study population /Sample size

1528 patients were included, of which 316 paediatric patients were 6 to <18 years old (including 191 paediatric patients 6 to <12 years old).

Key inclusion criteria were:

1. Male or female adult, adolescent and paediatric patients (≥ 6 years old).

2. Patients with moderate-to-severe AA to be commenced on omalizumab whose symptoms were inadequately controlled with ICS plus a long-acting inhaled β2-agonist.

3. Patients who signed informed consent form. For patients aged 6 to <18 years, whose parent, or legal representative signed the written informed consent prior to initiation of any study procedures.

Key exclusion criteria were:

1. Contraindications according to locally approved label: hypersensitivity to the active substance or to any of the excipients.

2. Participation with any investigational clinical trial within 30 days prior to enrolment.

3. Previous treatment with omalizumab, within 1 year prior to enrolment.

Treatments

The commercially available drug omalizumab (marketed as Xolair®) was prescribed by the investigators under actual clinical practice while adhering to the product information in China. The actual dosage was recorded as per the local prescribing information according to the approved dosing tables.

The observation period was set to 24 weeks.

Outcomes/endpoints

The key safety assessment was AEs, SAEs and AEs of special interest (AESI) including type, severity and duration. AEs of special interest (AESI) were identified based on the following definitions:

☐ Important identified risks: anaphylaxis/anaphylactoid reactions and Churg-Strauss syndrome/hypereosinophilic syndrome

☐ Important potential risks: arterial thromboembolic events and malignant neoplasms

Due to the nature of this non-interventional trial, all statistical analyses were solely descriptive

Assessor's comment:

The reported study was conducted to evaluate safety and efficacy of Xolair (150 mg, subcutaneous injection) in clinical use in patients in China with moderate to severe allergic asthma.

The study was a non-interventional post-marketing surveillance trial with an observation period of 24 weeks and included 1528 patients, among them 316 paediatric patients (191 in the age group 6-12 years old).

Results

Recruitment/ Number analysed

Among the 1528 enrolled patients, 690 patients (45.2%) completed the treatment, 71 patients (4.6%) withdrew from the study with the main reason of lost to follow-up (2.3%). 744 patients (48.7%) discontinued treatment on or before Week 16. The main reason for discontinuation/withdrawal of treatment before Week 16 was symptom improvement.

There were 316 patients aged under 18 enrolled in the trial, amongst them, 191 patients in the 6 to <12 years old range. There were 146 (46.2%) completers (84 (44%) of the 6 to <12 years range) The main reasons for discontinuation were symptom improvement: 75 (23.7%) for the <18 years old, and 48 (25.1%) for the 6 to <12 years range.

Assessor's comment:

The clinical overview describes the results from the whole study as well as for the paediatric population separately. For this P-46 procedure the assessor chooses to focus on the paediatric results.

Demographic characteristics of paediatric population

Regarding the paediatric patients, 215 of them were male and 101 females. The median age of the paediatric patients was 10 years old (youngest 6, oldest, 17) and all had a history of allergic asthma, 280 moderate and 36 severe.

Efficacy results

GETE
At Week 16, 86-1% of the patients were assessed as responders by the investigators and 82.1% by the patients. More than half of the patients had good response (56.3% based on the investigator's GETE; 54.6% based on the patient's GETE). At Week 24, 86.3% of the patients were assessed as responders by the investigators and 84% as assessed by the patients. More than half of the patients had good response (55.4% based on the investigator's GETE as well as the patient's GETE).

P-AQLQ
The PAQLQ contains 23 items that children with asthma have identified as troublesome in their daily lives. PAQLQ domains include: activity limitation, emotional function, symptoms, and overall.

For patients <18 years old, the mean (SD) change of PAQLQ scores from baseline of the overall domain was 0.95 (0.97) at Week 16 and 1.13 (1.03) at Week 24.

For patients of 12 to <18 years old, the mean (SD) change of PAQLQ scores from baseline of the overall domain was 1.05 (1.02) at Week 16 and 1.24 (1.07) at Week 24.

Asthma exacerbation
During pre-treatment, the mean (SD) of annualized number of asthma exacerbation events was 0.3 (0.89) times. At Weeks 16 and 24, the mean (SD) of number of annualized asthma exacerbation events was 0.197(1.0367) times and 0.152 (0.7790) times, respectively.

Spirometry results
At Week 16, the mean (SD) change from baseline in FEV1 was 0.081(0.2272), the % predicted FEV1 mean (SD) change from baseline was 0.355 (9.6295), for FVC, 0.043(0.2383) %, and for FEV1/FVC, 2.023(5.5793). The PEF mean (SD) change from baseline was 0.391(0.6659).

At Week 24, mean (SD) change from baseline in FEV1 was 0.184 (0.3137), the % predicted FEV1 mean (SD) change from baseline was 1,401 (12.6463), for FVC, 0,187(0.3702) %, and for FEV1/FVC, 1,370 (5.6054). The PEF mean (SD) change from baseline was 0.527 (0,7589).

Assessor's comment:

The efficacy results for the paediatric population are in line with previous results for this age group there are no results that impact the already established efficacy.

Safety results

There were 74 adverse events reported for 49 (15.5%) of the patients, with mild severity for 44 AEs (27 patients), moderate severity for 24 AEs (20 patients), and severe for 6 AEs (2 patients).

Most commonly reported AEs by SOC in ≥2% of patients were infections and infestations (6.3%), with mainly upper respiratory tract infection (3.5% of the patients) and skin and subcutaneous tissue disorders (2.5%), with erythema, urticaria or pruritus being reported for 0.6% of the patients.

There were 6 AEs reported in 5 patients leading to treatment discontinuation, including gastroenteritis, upper respiratory infection, nausea and headache, pyrexia, and finally myalgia

There were 12 SAEs reported in 8 (2.5%) patients, among them, 4 SAEs were reported in three patients for asthma exacerbation: One 06-year- old male patient with one mild bronchial asthma exacerbation One 15-year- old male patient with one moderate bronchial asthma exacerbation One 16-year-old female

patient with 2 severe allergic asthma exacerbations The other reported SAEs included one 16-year-old female patient with mild cardiac palpitation, one 6-year-old male patient with moderate hydrocele, one 16-year old male patient with moderate colitis ulcerative, one 15 year old male with mild abnormal hepatic function and one 9 year old male patient with moderate bacterial gastroenteritis (which was the only one leading to treatment discontinuation).

All reported SAEs were assessed as not related to treatment. No AESI and no death were reported in the paediatric population.

Assessor's comment:

The AEs reported for the paediatric population was in line with previous results in this age group and with the known safety profile for Xolair.

2.3.3. Discussion on clinical aspects

As the submitted study, CIGE025A2455, was an open-label, single armed study there are limitations to the evaluation of efficacy and safety. In addition, it is stated by the MAH that the actual number of patients was lower than the study size estimation due to the impact of COVID-19.

However, in the study, including 316 paediatric patients, there are no findings questioning the previously confirmed positive benefit-risk balance in the paediatric population previously concluded. The effect recorded seems as expected for the product and the reported AEs for the peadiatric population were in line with the known safety profile of Xolair and with previous results in this population.

3. CHMP overall conclusion and recommendation

Study CIGE025A2455 included 316 children receiving omalizumab. The results, both efficacy and safety, are in line with the known profile of Xolair and the benefit-risk balance is deemed unchanged.

☒ Fulfilled:

No regulatory action required.