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Human Medicines 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/P46/075

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

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1. Introduction

On 13-Oct-2023, the MAH submitted a non-interventional, post-marketing surveillance trial for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The study was not a paediatric study per se but included paediatric patients ≥12 or ≥6 years old.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CIGE025EKR03 "*Post-marketing Surveillance of Xolair® 150mg/1ml Liquid in pre-filled syringe, Xolair® 150mg Powder for solution for injection in patients with Severe allergic asthma and Chronic Spontaneous Urticaria*" is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Xolair (omalizumab) is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human immunoglobulin E (IgE) and prevents binding of IgE to the high affinity FcεRI receptor, thereby reducing the amount of free IgE that is available to trigger the allergic cascade. Xolair 150mg/1ml solution for injection in pre-filled syringe, Xolair 75mg/0.5ml solution for injection in pre-filled syringe and Xolair 150mg Powder for solution for injection were used in the present study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CIGE025EKR03: "Post-marketing Surveillance of Xolair 150mg/1ml Liquid in pre-filled syringe, Xolair 150mg Powder for solution for injection in patients with Severe allergic asthma and Chronic Spontaneous Urticaria"

2.3.2. Clinical study

CHMP comment:

Since this is a p46 procedure for a non-interventional study that is not part of the EU RMP, only the paediatric data are assessed.

Clinical study number and title

Study CIGE025EKR03: "Post-marketing Surveillance of Xolair® 150mg/1ml Liquid in pre-filled syringe, Xolair® 150mg Powder for solution for injection in patients with Severe allergic asthma and Chronic Spontaneous Urticaria"

Description

Study CIGE025EKR03 was a multi-center, post-marketing surveillance non-interventional study conducted for 12 weeks, with at least 10% of patients followed up to 24 weeks in domestic multi-centers. CIGE025EKR03 was conducted in Korea to evaluate the safety and effectiveness of Xolair (Xolair 150mg/1ml solution for injection in pre-filled syringe, Xolair 75mg/0.5ml solution for injection in pre-filled syringe, Xolair 150mg Powder for solution for injection) in patients with Severe allergic asthma and Chronic Spontaneous urticaria in routine clinical practice. It also aimed to evaluate the basic information of subjects (age, sex, pregnancy, inpatient/outpatient and concomitant diseases etc.) and whether the administration information (reason and period of administration, dosage and concomitant medications etc.) of Xolair affects the safety and effectiveness.

Methods

Study participants

Overall, a total of 641 patients (631 patients with chronic idiopathic urticaria CIU, **including 8 paediatric patients**, and 10 severe allergic asthma patients with no paediatric patients) who were given prescription for Xolair for the indications mentioned in the approved Korean product label, were included in the safety analysis and 456 were included in the efficacy analysis.

Inclusion criteria

Patients with CSU aged 12 and above treated with Xolair per the approved label

Patients with severe allergic asthma aged 6 and above given prescription for Xolair for the indications mentioned in the currently approved product label

Patients who signed the informed consent (Patients aged 18 and below, legal representative will signed the informed consent) after listening to clear explanation of the objective and nature of the study and then participated in it

Exclusion criteria

Patients with CSU aged under 12 years

Patients with severe allergic asthma aged under 6 years

Patients with contraindications for the administration of Xolair mentioned in the approved product label

- Patients with contraindications (hypersensitivity to this drug or any ingredient of this drug) for Xolair
- Patients with contraindications (myocardial infarction or myocardial infarction history) for Xolair

Patients participating in other clinical trial

Treatments

The total duration of treatment (mean ± SD) was 17.08±10.67 weeks, the total administered dose was 764.98±412.31 mg, the total number of doses was 4.68±2.33 times, and the mean dosing interval was 4.65±1.36 weeks. The mean (mean ± SD) total and single doses at 4 weeks were 203.99±83.06 mg/4 weeks and 164.04±37.91 mg/dose, respectively.

Objective(s)

The primary objective of this non-interventional study was to evaluate the safety of Xolair in patients with chronic idiopathic urticaria and severe allergic asthma under routine clinical practice.

The secondary objective was to assess effectiveness of Xolair in these patients in routine clinical practice.

Outcomes/endpoints

The safety primary endpoint was based on AEs, SAEs, adverse drug reactions (ADR), and serious ADRs.

For CIU patients, the efficacy endpoint was based on improvement of weekly itch severity scores at week 12 and 24 (if applicable). For severe allergic asthma patients, the efficacy endpoint was assessed by the degree of improvement in general condition at Week 12 and 24 (as applicable, as not all patients would have continued treatment up to 24 weeks) including Korean Asthma Control Test (K-ACT) which is applicable only for patients over 12 years old).

An overall effectiveness evaluation was done for all patients by the investigators.

Sample size

Under Article 6 (4) of the Standard for Re-evaluation of New Drugs, etc. (MFDS Notice No. 2017-95, Nov.21, 2017), the study drug requires at least 600 subjects for re-examination. Long-term users were determined as ≥10% of all subjects. Patients with chronic spontaneous urticaria involved children (≥12 years old) and adults, and patients with severe allergic asthma involved children (≥6 years old) and adults.

Randomisation and blinding (masking)

This was a non-randomized study. Blinding/masking methods were not applicable.

Statistical Methods

Continuous variables were presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum), and categorical data were presented using frequency and percentage. Unless specified otherwise, the significance level was 5% for a two-sided test. All p-values were presented up to 4 decimal places, and values having decimal places, such as mean, standard deviation, and percentage, were presented up to 2 decimal place.

Results

Participant flow

Out of the 8 paediatric subjects in the Safety Analysis Set, one subject was excluded from effectiveness evaluation due to "effectiveness evaluation missing, final effectiveness evaluation missing, or final effectiveness not assessable", leaving 7 subjects in the Effectiveness Analysis Set. Of these subjects, 7 attended the second (12 weeks±4 weeks) assessment, and 4 subjects the third (16-28 weeks) assessment.

Recruitment

Study CIGE025EKR03 was a multi-center study. The investigators enrolled sequentially all the cases where Xolair was administered for the first time to patients with CIU aged 12 and above or patients with severe allergic asthma aged 6 and above in routine clinical practice.

Baseline data

Table 1: Baseline Characteristics on the Paediatric Subjects

	Safety Analysis Set (N=8) n (%)		
	Chronic idiopathic Urticaria (N=8)	Severe allergic asthma (N=0)	Total (N=8)
Age			
Number of patients	8	0	8
Mean±SD	16.25±1.49	NA	16.25±1.49
Median (Min~Max)	17.00 (13.00~17.00)	NA	17.00 (13.00~17.00)

	Chronic idiopathic Urticaria (N=8)	Severe allergic asthma (N=0)	Total (N=8)
Age group			
Number of patients	8	0	8
6 years ~ under 12 years old	0	NA	0
12 years ~ under 18 years old	8 (100.00)	NA	8 (100.00)
Gender			
Number of patients	8	0	8
Men	3 (37.50)	NA	3 (37.50)
Woman	5 (62.50)	NA	5 (62.50)
Height(cm)			
Number of patients	8	0	8
Mean±SD	164.13±7.14	NA	164.13±7.14
Median (Min~Max)	162.50 (155.00~178.00)	NA	162.50 (155.00~178.00)
Weight(kg)			
Number of patients	8	0	8
Mean±SD	56.75±10.38	NA	56.75±10.38
Median (Min~Max)	54.00 (48.00~80.00)	NA	54.00 (48.00~80.00)

SD=Standard Deviation, Min=Minimum, Max=Maximum

The percentages were calculated using the number of subjects per item as the denominator.

Number analysed

Please refer to heading "Participant flow".

Efficacy results

Out of the 8 paediatric subjects in the Safety Analysis Set, one subject was excluded from effectiveness evaluation due to "effectiveness evaluation missing, final effectiveness evaluation missing, or final effectiveness not assessable", leaving 7 subjects in the Effectiveness Analysis Set. The final effectiveness was analysed by the investigator based on the effectiveness evaluation results for each diagnosis during the subject's visit.

Table 2: Effectiveness Evaluation on the Paediatric Subjects

	Effectiveness Analysis Set (N=7) n (%) Chronic idiopathic urticaria	
	Result	**Change from Baseline**
Weekly Itch Severity Score		
Baseline visit		
Number of patients	7	
Mean±SD	18.00±3.74	
Median (Min~Max)	21.00 (14.00~21.00)	
Visit 2 (12weeks±4weeks)		
Number of patients	7	7
Mean±SD	8.00±4.83	-10.00±6.83
Median (Min~Max)	7.00 (0.00~14.00)	-7.00 (-21.00~0.00)
p-value[1]		0.0082*
Visit 3 (16-28 weeks)		
Number of patients	4	4
Mean±SD	7.00±5.72	-10.50±9.04
Median (Min~Max)	7.00 (0.00~14.00)	-10.50 (-21.00~0.00)
p-value[1]		0.1027

* Statistically significant at a two-sided significance level of 5%.

[1] Paired t-test or Wilcoxon's signed rank test

At Visit 2 (12 weeks±4 weeks) and Visit 3 (16-28 weeks, if applicable) after treatment with the study drug, the investigator evaluated the final effectiveness of the study drug (Xolair®) as 'Improved', 'Unchanged', or 'Aggravated', taking into account the subject's general condition, including the effectiveness results assessed for each diagnosis during the post-treatment visits. 'Improved' and 'unchanged' were considered to indicate 'effective', while 'exacerbated' was considered to indicate 'ineffective' to analyse the effective rate of the study drug.

Table 3: Final Effectiveness Evaluation on the Paediatric Subjects

	n (%)	95% Confidence Interval
Final Effectiveness Assessment		
Number of patients	7	
Improved	6 (85.71)	
Unchanged	1 (14.29)	
Aggravated	0	
Valid/Invalid		
Number of patients	7	
Valid[1]	7 (100.00)	[59.04, 100.00]
Invalid[2]	0	[0.00, 40.96]

[1] As a result of the effectiveness assessment, it is evaluated as [Improved] or [Unchanged]
[2] As a result of the effectiveness assessment, it is evaluated as [Aggravated]

Safety results

A total of 1 AE was reported in one patient (12.50%, 95% CI [0.32, 52.65]) of the 8 paediatric patients. The related event was the ADR 'Injection site pruritus', which was a non-serious AE with mild severity, and the outcome was "recovered".

2.3.3. Discussion on clinical aspects

This procedure present final data from Study CIGE025EKR03.

Study CIGE025EKR03 was a post-marketing surveillance non-interventional study conducted to evaluate the safety and effectiveness of Xolair in patients with Severe allergic asthma and Chronic Spontaneous urticaria in routine clinical practice.

Since this is a p46 procedure and the study was not part of the EU RMP, only the paediatric data are assessed.

Eight paediatric subjects (16.25±1.49 years) were included in the study. In the paediatric population the final effectiveness result was 'improved' in 85.71% (6/7 subjects), 'unchanged' in 14.29% (1/7 subjects), and no aggravated case. A total of one non-serious AE was reported in one patient. Overall, the results were consistent with data from previous studies in this age group.

The MAH proposes no changes to the current approved EU SmPC, which is agreed.

3. CHMP overall conclusion and recommendation

The safety and effectiveness of Xolair in the paediatric subpopulation of study CIGE025EKR03 is largely in line with the previous experience of Xolair. No changes to the current approved EU SmPC are proposed.

The benefit/risk ratio for Xolair remains unchanged.

☒ **Fulfilled:**

No regulatory action required.