17 December 2015
EMA/3780/2016
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

International non-proprietary name: omalizumab

Procedure No. EMEA/H/C/000606/P46 047

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Introduction

On Aug 15 2015, the MAH submitted the study CIGE025AIN01 including pediatric subjects for Xolair, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

Study CIGE025AIN01 was an open-label, noncomparative, clinical decision based post marketing surveillance study that evaluated the efficacy and safety of omalizumab in patients with severe asthma.

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.

A short critical expert overview has been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study CIGE025AIN01 is a stand alone study.

1.2. Information on the pharmaceutical formulation used in the study

Xolair, as approved in India was used in this study.

1.3. Clinical aspects

1.3.1. Introduction

Study CIGE025AIN01 (last patient last visit on 28-Dec-2014) was an open-label, post marketing surveillance study that evaluated the efficacy and safety of omalizumab in patients with severe asthma. This study was conducted at 27 centers across India, and enrolled male and female patients ≥12 and ≤75 years of age.

1.3.2. Clinical study CIGE025AIN01

Description

Methods

Objective(s)

The purpose of this study was to evaluate the effect in asthma control and if any reduction in medication requirement occurred in patients having inadequately controlled moderate-to-severe persistent allergic asthma (GINA (Global Initiative for Asthma), Stage IV) treated with omalizumab (Xolair®).

Primary objectives

- Evaluation of clinically significant asthma exacerbations in patients with severe persistent allergic asthma at the end of 16, 28 and 52 weeks.

Secondary objectives

- Reduction in OCS use in patients at baseline and 16, 28 and 52 weeks.
- Number of days missed in work or college, at baseline and 16, 28 and 52 weeks.
- Use of other asthma maintenance medication / rescue medication at baseline and 16, 28 and 52 weeks.
- Worsening of asthma symptoms i.e. hospitalization, emergency room visits and unscheduled doctor visits, at 16, 28 and 52 weeks.
- Lung function tests (FEV1, FVC and FEV1/FVC) at screening, 16, 28 and 52 weeks.
- Improvement in Asthma Control Score Questionnaire (ACQ) (all visits).

Study design

This was a multi-center, open-label, non-comparative, clinical decision based postmarketing surveillance (PMS) study. Selection of patients for the study was at discretion of treating physician which was based on the inclusion & exclusion criterion.

The potential patients were screened 2 weeks prior to initiation of treatment, and during this period tests like spirometry, Serum IgE, serum allergy test, physical examination, pregnancy test (for female patients), Asthma Control Score Questionnaire (ACQ-5) were conducted. Patients inform written consent was obtained before the screening process. Patient's were given a patient diary where he/she was required to fill his/her day-to-day details like whether he has taken medicine (morning and evening, what dose?, did he require any rescue medication, if yes which one did he take, at what dosage?, Did he miss day at work or college?, did he had any exacerbation? Was he hospitalized? Physician's/attending clinician's later asked them about these details during filling up data in CRF.

At the end of the 16 week period, patients were evaluated for primary and secondary outcomes. Those patients who responded to omalizumab therapy at week 16 were included in the next phase, which continued to week 28. Patients who responded at 28 weeks based on primary and secondary outcome continued to receive the same dose of omalizumab until week 52.

CHMP comment:

It is unclear from the clinical study report how the primary endpoint is evaluated. Two weeks before entrance in the study seems to be a short period of historical baseline data to be able to make efficacy conclusions in a 52 week long study.

Study population /Sample size

A total of 127 patients enrolled in this trial. Ninety-four patients completed 16 weeks follow-up, 54 patients completed 28 weeks follow up, and 39 completed 52 weeks follow up. The primary reason for early discontinuation at 16 weeks was withdrawal of informed consent. More male patients enrolled than females (61% vs 39%) and the mean age was 48.39 years. Seven pediatric patients enrolled in this trial (5 males and 2 females), ranging in age from 12-17 years old.

Results

Efficacy results

Asthma exacerbations during study period (no., % of pts.)

		Asthma Exacerbations		Chi-square test (McNemar)	
	N	*No.*	*%*	χ^2	'p'
Baseline	*117*	52	44.44	-	-
Week 16	*92*	8	8.70	42.959	<0.0001
Week 52	*38*	1	2.63	60.136	<0.0001

Asthma exacerbations : Defined as any one out of: 2 out of 3 consecutive night awakening; OR ≥20% drop in PEF in 2 out of 3 days; OR >50% increase in use of rescue medication in 2 out of 3 days.

Responder rate after 16 weeks (no., % of pts.)

Responder (16 wks.)	*No.*	*% (n=94)*
Responder	**91**	**96.81**
Responder criteria		
1. A change of 0.5 on the ACQ score or 2 points on ACT from baseline	57	60.64
2. Global assessment by physician & patient	77	81.91
3. Reduced requirement of OCS compared to baseline	62	65.96
4. Lesser number of days missed at work or college compared to baseline	57	60.64
5. Decrease in requirement of asthma medication & rescue medication compared to baseline	67	71.28
6. Decrease incidence of exacerbations as compared to baseline	66	70.21
7. Decrease incidence of unscheduled hospitalization as compared to baseline	47	50.00

The number of patients having asthma exacerbations decreased from 44.44% at baseline to 8.70% after 16 weeks (p<0.0001) and to 2.63% at the end of the 52 weeks (p<0.0001). At baseline 52 exacerbations were reported out of 117 patients. Improvement in exacerbations was observed in 44 (84.62%) patients after 16 weeks and 51 (98.08%) patients after 52 weeks. Patients were considered responders at 16 weeks if they met 7 pre-defined responder criteria. Out of the 94 patients who were evaluated at 16 weeks, 91 patients responded to omalizumab therapy (96.81% response rate) based on meeting these responder criteria. The number of days of missed college/work due to asthma exacerbations was reduced from 45.30% of patients at baseline to 5.43% of patients at week 16 and this was further reduced to 2.63% of patients at 52 weeks after starting omalizumab therapy.

The mean ACQ composite score reduced significantly (p=0.0001) from 12.87 (5.19) at baseline to 9.07 (5.30) after 16 weeks, a reduction in 40.10% from baseline. Further therapy with omalizumab reduced the mean ACQ score to 5.59 (5.64), a reduction by 63.10% after 52 weeks (p<0.0001).

Overall reduction in OCS use with omalizumab therapy was observed in 70.93% patients at week 16 and 82.56% patients at 52 weeks.

CHMP comment:

A significant effect was seen in the primary endpoint in this open study. However, only patients responding on treatment continued in the study after week 16 and week 28. The mean ACQ score was reduced and there were trends towards response in the secondary endpoints but no p-values are given. It is doubtful if it is possible to draw any efficacy conclusions from this study since it seems that the historic period for comparison is only two weeks. At least this is unclear because of scarce information from the MAH.

Safety results

A total of 21 (16.54%) patients developed AEs, which included 2 patients suffering from SAEs (one patient was hospitalized due to chest pain and another patient suffered diarrhea) while taking omalizumab. In both events, the causality was reported as "Not-Assessable" and the outcome of these events were "Improving Condition."

Fourteen (11.02%) patients each had cough and dyspnea. All these events were non-serious and causality for 22 patients was reported as "Not Suspected" and "Not Suspected/Not assessable" for 6 patients. Eleven (8.66%) patients had asthma exacerbations that were nonserious (causality for 8 of these patients was not suspected, 2 were not assessable/not suspected and 1 remaining was not assessable).

No patients reported AEs that met the criteria of AESI.

CHMP comment:

No new or unexpected safety events were identified.

Pediatric summary

As noted above, 7 pediatric patients were enrolled in this trial, ranging in age from 12-17 years. There was no separate analysis of pediatric patients in this study. According to the study database, one patient suffered 3 AEs during the study. These events were rhinitis, breathlessness, and cough. Rhinitis resolved after 6 days and breathlessness and cough were continuing at the time the patient completed the trial. None of these events were serious and no further details were provided.

CHMP comment:

No separate analyses or listing of the paediatric patients could be found by the CHMP in the clinical study report.

1.3.3. Discussion on clinical aspects

Study CIGE025AIN01 was an open-label, noncomparative, post marketing study performed in India. There was no separate analysis of the seven pediatric patients in the study. This is a weakness of the submitted material. Moreover, the clinical study report was very short and detailed information about the study was lacking. However, no unexpected findings were noted. The effect

of omalizumab (Xolair®) in patients with asthma was as expected and no unexpected safety issues occurred.

2. CHMP overall conclusion and recommendation

Overall conclusion

The study report 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.