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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/P46/074

Note

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

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1. Introduction

On 28 July 2023, the MAH submitted a completed paediatric study 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 "Special drug use observational study of Xolair in patients with severe to most severe seasonal allergic rhinitis aged ≥12 years and <18 years whose symptoms were inadequately controlled despite to conventional therapies (CIGE025F1401)" is a stand alone study. Study F1301 included a smaller number of patients in the age group of ≥ 12 years and < 18 years (especially ≥ 12 years and < 15 years) compared with other age groups. Therefore, as part of pharmacovigilance activities specified in the Japan Risk Management Plan of Xolair, a post-marketing surveillance was to be conducted to evaluate the safety and efficacy of Xolair in patients with seasonal allergic rhinitis, a newly approved indication, aged ≥ 12 years and < 18 years (especially ≥ 12 years and < 15 years) (only patients with severe to most severe symptoms who had not respond adequately to conventional therapy).

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 is available as 75 mg and 150 mg powder vial and solvent for solution for subcutaneous injection (lyophilized formulation) and as 75 mg and 150 mg solution for subcutaneous injection in pre-filled syringe. The initial dose of Xolair varied between 375 and 600 mg in patients treated every 2 weeks and between 150 mg and 600 mg in patients treated every 4 weeks.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CIGE025F1401: "Special drug use observational study of Xolair in patients with severe to most severe seasonal allergic rhinitis aged ≥12 years and <18 years whose symptoms were inadequately controlled despite to conventional therapies"

2.3.2. Clinical study

Clinical study number and title

Study CIGE025F1401: Special drug use observational study of Xolair in patients with severe to most severe seasonal allergic rhinitis aged ≥ 12 years and < 18 years whose symptoms were inadequately controlled despite to conventional therapies.

Description

Study CIGE025F1401 was an open-label, multicenter, uncontrolled, single-arm special drug use trial using a central registration system in patients with severe to most severe seasonal allergic rhinitis aged ≥12 years and <18 years whose symptoms were inadequately controlled despite to conventional therapies and were then administered Xolair.

The observation period was of 24 weeks, with Day 1 defined as the start date of Xolair treatment. Because of the duration of Xolair treatment depended on the pollen dispersal situation and other factors, patients who completed or discontinued Xolair treatment before the visit at 24 weeks after the start of treatment, were followed up to 30 days after their last dose of Xolair.

Methods

Study participants

The study population included 50 paediatric patients (aged ≥ 12–< 18 years) diagnosed with severe to most severe seasonal allergic rhinitis symptoms, inadequately controlled despite conventional therapy.

Inclusion criteria

1. Patients who used Xolair in accordance with the instructions of Japan package insert

2. Patients aged ≥ 12 years and < 18 years at the start of Xolair

3. Patients who used Xolair for the following indication: ☐ Indication: seasonal allergic rhinitis (only patients with severe to most severe symptoms whose symptoms were inadequately controlled despite to conventional therapy)

4. Patients having provided written consent to participate in this study before the start of Xolair in the relevant pollen season, in person and from their legally acceptable representative (legal representative)

Exclusion criteria

1. Patients with a history of hypersensitivity to any of the Xolair ingredients

Treatments

The investigator treated patients in accordance with the Japan package insert.

Table 1: Xolair administration (safety analysis population)

		Safety Analysis population N=46 (%)	
		Patients treated every 2 weeks N=9	Patients treated every 4 weeks N=37
Xolair Treatment Duration *1 (days)	Number of patients	9	37
	Mean ± SD	75.2 (33.42)	71.9 (21.90)
	Median [min-max]	85.0	83.0
	Q1-Q3	56.0-98.0	56.0-88.0
	Minimum-Maximum	14-114	28-105
	Total duration of exposure *2 (PY)	1.9	7.3
Total duration of Xolair administration – n (%)	≤ 4 weeks	1 (11.1)	4 (10.8)
	> 4–≤8 weeks	2 (22.2)	9 (24.3)
	>8–≤12 weeks	1 (11.1)	12 (32.4)
	>12 weeks	5 (55.6)	12 (32.4)
Category of initial dose of Xolair- n (%)	75 mg	0	0
	150 mg	0	8 (21.6)
	225 mg	0	0
	300 mg	0	17 (45.9)
	375 mg	2 (22.2)	0
	450 mg	2 (22.2)	5 (13.5)
	525 mg	1 (11.1)	0
	600 mg	4 (44.4)	7 (18.9)
	Other	0	0
Total number of Xolair doses (times)	Number of patients	9	37
	Mean ± SD	4.9 ±2.15	2.4±0.69
	Median [min-max]	6.0 [4.0-6.0]	[2.0-3.0]
	Q1-Q3	4.0-6.0	2.0-3.0
Category of total number of doses – n (%)	1 time	1 (11.1)	4 (10.8)
	2 times	1 (11.1)	13 (35.1)
	3 times	0	20 (54.1)
	4 times	1 (11.1)	0
	5 times	6 (66.7)	0
Cumulative dose of Xolair (mg)	Number of patients		
	Mean ± SD	2575.0(1392.05)	855.4 (487.17)
	Median [min-max]	2625.0	900.0
	Q1-Q3	1500.0-3600.0	450.0-900.0
	Minimum-maximum	450-4200	150-1800
Mean dosing interval of Xolair (days)*3	Number of patients	8	33
	Mean ± SD	16.30 (2.933)	30.65 (3.825)
	Median (Min-Max)	14.68	28.00
	Q1-Q3	14.00-19.00	28.00-32.50
	Minimum-maximum	14.0-21.0	27.0-42.0

Source: [Table 10-5] Clinical Study Report

*1 The total duration of treatment with Xolair was calculated as follows:

Patients treated every 2 weeks: duration of treatment with Xolair (days)= date of the last dose of Xolair-date of the first dose of Xolair+14

Patients treated every 4 weeks: Duration of treatment with Xolair (days)= date of the last dose of Xolair – date of the first dose of Xolair + 28

*2 Total duration of exposure (PY)= sum of duration of treatment with Xolair (days) for all patients / 365.25

*3 The mean dosing interval of Xolair was calculated as follows, and patients who received at least 2 doses were included:

Mean dosing interval of Xolair (days) = sum of each dosing interval of Xolair/ total number of doses of Xolair-1

The dosing interval of Xolair in each patient was defined as the date of Dose +n=1- date of Dose n

PY= patient year

Objective(s)

Outcomes/endpoints

Table 2: Research objectives and endpoints

Objective	Endpoint
Primary objective • To evaluate the safety of Xolair administered in clinical setting to patients with seasonal allergic rhinitis aged ≥ 12 years and < 18 years for up to 24 weeks	Primary endpoint • Proportions of patients with the following events: ○ Adverse events ○ Serious adverse events ○ Adverse events leading to discontinuation of Xolair treatment ○ Adverse drug reactions ○ Serious adverse drug reactions ○ Adverse drug reactions leading to discontinuation of Xolair treatment
Secondary objective • To evaluate the efficacy of Xolair administered in clinical setting to patients with seasonal allergic rhinitis aged ≥ 12 years and < 18 years	Secondary endpoints • Overall improvement rate of disease by physicians at the last visit • Disease severity of seasonal allergic rhinitis at each visit • Individual symptom severity of seasonal allergic rhinitis at each visit ○ Sneezing ○ Nasal discharge ○ Nasal obstruction ○ Difficulty in daily activity

Sample size

Although there are many patients with seasonal allergic rhinitis in Japan, the target number of patients was set at 30 in consideration of the target patient population of Xolair being patients with severe to most severe seasonal allergic rhinitis not responding adequately to conventional therapy, as well as the actual number of enrolled paediatric patients and the registration period in the special drug use investigations for the other approved indications such as bronchial asthma.

Randomisation and blinding (masking)

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

Statistical Methods

Due to the nature of this non-interventional study, all statistical analyses were solely descriptive. In general, data used for analyses were information before Xolair treatment and protocol-specified data during the observation period (including the follow-up period), except for the outcome and date of outcome of adverse events. All statistical analyses were performed by Novartis Pharma K. K. and EPS Corporation using SAS version 9.4 or higher.

Results

Participant flow

A total of 50 paediatric patients were enrolled in 16 sites and had their registration confirmed (registration form received and confirmed) and CRF locked. Of these patients, 4 patients did not meet the inclusion/exclusion criteria and were excluded from the safety and efficacy analysis.

Table 3: Patient composition (registration-confirmed patients)

Analysis population	n
Patient with registered in this study	50
Patients with locked CRF	50
Patients excluded from safety analysis	4
Patients who violated the inclusion or exclusion criteria	4
Safety analysis population	46
Patients excluded from efficacy analysis	4
Patients who violated the inclusion or exclusion criteria	4
Efficacy analysis population	46

Source: Table AS_T001

Table 4: Disposition of patients who completed or discontinued Xolair treatment (safety analysis population)

Completion or discontinuation of Xolair treatment/reason for completion or discontinuation of Xolair treatment	Safety analysis population N = 46 n (%)
Completion or discontinuation of Xolair treatment	46 (100)
Reason for completion or discontinuation of Xolair treatment	
Achievement of the treatment goal	43 (93.5)
Failure to visit	2 (4.3)
Inadequate response	1 (2.2)

Source: Table DS_T001

The reasons for completion or discontinuation of Xolair treatment were shown in descending order of the number of patients and then in order of description in the CRF.

Table 5: Disposition of patients who completed or discontinued the study (safety analysis population)

Completion or discontinuation of the study	Safety analysis population N = 46 n (%)
Completed	37 (80.4)
Discontinued	9 (19.6)

Source: Table DS_T002

Among patients in whom treatment with Xolair was ongoing and patients in whom treatment with Xolair was completed or discontinued, patients who completed the 30-day follow-up period (date of last observation – date of the last dose of Xolair ≥ 30) were defined as patients who completed the study, and other patients were defined as patients who discontinued the study.

Recruitment

Table 6: Course of the study

Milestone	Planned or actual date
Start of study	2 October 2020
Start of data collection (FPFV)	27 January 2021
End of recruitment period (LPFV)	13 May 2022
End of observation of the last patient (LPLV)	03 November 2022
End of study (database lock date)	22 February 2023
Approval of Final Study Report of post-marketing surveillance results	30 May 2023

Baseline data

Table 7: Demographic and disease characteristics (safety analysis population)

Background factor	Safety analysis population N = 46
Sex - n (%)	
Male	35 (76.1)
Female	11 (23.9)
Age (years)	
Number of patients	46
Mean (SD)	14.1 (1.48)
Median	14.0
Minimum - maximum	12 - 17
Age category - n (%)	
≥ 12 years and < 15 years	26 (56.5)
≥ 15 years and < 18 years	20 (43.5)
Causative antigen* -n (%)	
Japanese cedar	46 (100)
Japanese alder	12 (26.1)
Japanese cypress	38 (82.6)
Japanese white birch	11 (23.9)
Poaceae	16 (34.8)
Ragweed	12 (26.1)
Japanese mugwort	9 (19.6)
Japanese hop	0
Other (pollen)	0
Other (other than pollen)	26 (56.5)
Duration of disease (weeks)	
Number of patients	46
Mean (SD)	112.03 (147.437)
Median	50.36
Minimum - maximum	1.0 - 634.0
Disease duration category - n (%)	
< 12 weeks	13 (28.3)
≥ 12 weeks and < 24 weeks	4 (8.7)
≥ 24 weeks and < 52 weeks	7 (15.2)
≥ 52 weeks and < 104 weeks	8 (17.4)
≥ 104 weeks	14 (30.4)
Disease type - n (%)	
Sneezing/rhinorrhea type	10 (21.7)
Nasal obstruction type	7 (15.2)
Complete type	26 (56.5)
Unknown/not recorded	3 (6.5)
History of treatment with omalizumab for seasonal allergic rhinitis - n (%)	
No	32 (69.6)
Yes	14 (30.4)

Complications - n (%)	
No	19 (41.3)
Yes	27 (58.7)
Prior medications for seasonal allergic rhinitis** - n (%)	
No	0
Yes	46 (100)
Concomitant drugs (at the start of treatment with Xolair) - n (%)	
No	0
Yes	46 (100)
Surgical therapy - n (%)	
No	46 (100)
Yes	0
Pregnancy - n (%)	
No	11 (100)
Yes	0
Month of start of Xolair treatment - n (%)	
January	6 (13.0)
February	27 (58.7)
March or later	13 (28.3)
Severity of seasonal allergic rhinitis at the first visit - n (%)	
Most severe	17 (37.0)
Severe	21 (45.7)
Moderate	7 (15.2)
Mild	1 (2.2)
No symptom	0
Unknown	0

Source: Table DM_T001

* Patients with multiple causative antigens were counted for each reason.

** Prior medications for seasonal allergic rhinitis: Prior medications used in the pollen season were tabulated regardless of whether they were used in the relevant pollen season or past pollen seasons.

Table 8: Prior medications for seasonal allergic rhinitis before treatment with Xolair (safety analysis population)

	Safety analysis population N = 46 n (%)
Prior medications for seasonal allergic rhinitis	
Yes	46 (100)
Breakdown of drugs	
Relevant pollen season	46 (100)
Chemical mediator receptor antagonists	43 (93.5)
Oral	43 (93.5)
Corticosteroids	38 (82.6)
Oral	1 (2.2)
Nasal	38 (82.6)
Allergen immunotherapy	16 (34.8)
Other	1 (2.2)
Past pollen seasons	31 (67.4)
Chemical mediator receptor antagonists	21 (45.7)
Oral	21 (45.7)
Other	1 (2.2)
Corticosteroids	23 (50.0)
Nasal	23 (50.0)
Nasal vasoconstrictors	1 (2.2)
Biological preparations	14 (30.4)
No	0

Source: Table PM_T001

Table 9: Concomitant drugs and therapies during treatment with Xolair (safety analysis population)

	Safety analysis population N = 46 n (%)
Concomitant drugs*	
No	0
Yes	46 (100)
Breakdown of concomitant drugs	
Chemical mediator release inhibitors	1 (2.2)
Ophthalmic solution	1 (2.2)
Chemical mediator receptor antagonists	46 (100)
Oral	46 (100)
Ophthalmic solution	12 (26.1)
Other	1 (2.2)
Corticosteroids	42 (91.3)
Oral	1 (2.2)
Nasal	42 (91.3)
Ophthalmic solution	1 (2.2)
Other	3 (6.5)
Allergen immunotherapy	21 (45.7)
Other	4 (8.7)
Surgical therapy for seasonal allergic rhinitis	
No	46 (100)
Yes	0

Source: Table CM_T001

* Concomitant drugs: Tabulated regardless of reason for use

Number analysed

Please refer to table under heading "Participant flow".

Efficacy results

In the efficacy analysis population (46 patients), the median (minimum to maximum) duration of the efficacy analysis period was 71.0 (18 to 131) days.

Table 10: Global assessment of improvement (efficacy analysis population)

Evaluation timepoint			n (%)	(95% CI)
Efficacy analysis population	(N=46)			
Last evaluation	(m=46)	Effective	43 (93.5)	(82.1, 98.6)
		Global assessment of improvement		
		Notably improved	24 (52.2)	
		Moderately improved	19 (41.3)	
		Slightly improved	1 (2.2)	
		No change	1 (2.2)	
		Worsened	0	
		Indeterminate	1 (2.2)	

Source: Table CGI_T001_1-1
N = Number of patients analyzed for efficacy, m = number of patients evaluated
Effective: "remarkably improved" + "moderately improved."
The denominator was the number of patients evaluated at the last evaluation.
95% CI were calculated by the Clopper-Pearson method.

Table 11: Global assessment of improvement (patients who completed the study in the efficacy analysis population)

Evaluation timepoint			n (%)	(95% CI)
Efficacy analysis population	(N=37)			
Last evaluation	(m=37)	Effective	34 (91.9)	(78.1, 98.3)
		Global assessment of improvement		
		Notably improved	20 (54.1)	
		Moderately improved	14 (37.8)	
		Slightly improved	1 (2.7)	
		No change	1 (2.7)	
		Worsened	0	
		Indeterminate	1 (2.7)	

Source: Table CGI_T001_1-2
N = Number of patients analyzed for efficacy, m = number of patients evaluated
Effective: "remarkably improved" + "moderately improved."
The denominator was the number of patients evaluated at the last evaluation.
95% CI were calculated by the Clopper-Pearson method.

Table 12: Severity of seasonal allergic rhinitis (efficacy analysis population)

Evaluation timepoint		Severity n (%)					
		Most severe	Severe	Moderate	Mild	No symptom	Unknown
Efficacy analysis population	(N=46)						
Baseline	(m=46)	17 (37.0)	21 (45.7)	7 (15.2)	1 (2.2)	0	0
Week 2	(m=9)	1 (11.1)	2 (22.2)	1 (11.1)	5 (55.6)	0	0
Week 4	(m=42)	1 (2.4)	10 (23.8)	11 (26.2)	18 (42.9)	2 (4.8)	0
Week 6	(m=7)	1 (14.3)	1 (14.3)	1 (14.3)	4 (57.1)	0	0
Week 8	(m=23)	0	2 (8.7)	9 (39.1)	12 (52.2)	0	0
Week 10	(m=6)	1 (16.7)	0	2 (33.3)	3 (50.0)	0	0
Week 12	(m=5)	0	0	2 (40.0)	3 (60.0)	0	0
Week 14	(m=1)	0	0	1 (100)	0	0	0
Week 16	(m=0)	-	-	-	-	-	-
Week 18	(m=0)	-	-	-	-	-	-
Week 20	(m=0)	-	-	-	-	-	-
Week 22	(m=0)	-	-	-	-	-	-
Week 24	(m=0)	-	-	-	-	-	-
Day of last evaluation	(m=45)	0	6 (13.3)	13 (28.9)	25 (55.6)	1 (2.2)	0

Source: Table CGI_T002_1-1

N = Number of patients analyzed for efficacy, m = number of patients evaluated at each evaluation timepoint

The denominator was the number of patients evaluated at each evaluation timepoint.

The severity of seasonal allergic rhinitis comprehensively assessed by physicians was severe or higher in 82.7% of the patients in the efficacy analysis population at baseline. However, this proportion decreased over time, and the severity was moderate or lower in 86.7% of the patients at the last evaluation. Similarly, nasal symptoms (sneezing, nasal discharge, and nasal obstruction) and difficulty in daily activities tended to improve continuously after baseline.

The investigator assessed the severity of each seasonal allergic rhinitis symptom (sneezing, nasal discharge, nasal obstruction, difficulty in daily activity) at each visit (with or without Xolair administration) in accordance with the criteria in the Practical Guideline for the Management of Allergic Rhinitis in Japan (2016), using "4+," "3+," "2+," "1+," or "−," and recorded the assessment in the CRF.

Table 13: Severity of each seasonal allergic rhinitis symptom

Severity	4+	3+	2+	1+	–
Sneezing	≥ 21 times	20 to 11 times	10 to 6 times	5 to 1 time	Less than 1+
Nasal discharge	≥ 21 times	20 to 11 times	10 to 6 times	5 to 1 time	Less than 1+
Nasal obstruction	Complete obstruction all day	Very severe nasal obstruction with mouth breathing for a long time per day	Severe nasal obstruction, with mouth breathing sometimes per day	No mouth breathing but with nasal obstruction	Less than 1+
Difficulty in daily activity	No activities	Too severe to do activities	Between 3+ and 1+	Almost no difficulty	Less than 1+

Difficulty in daily activities: difficulty in activities such as work, study, housework, sleep, and going out

Table 14: Severity of each seasonal allergic rhinitis symptom (efficacy analysis population)

			Severity of symptom n (%)					
Evaluation timepoint		**Breakdown of symptoms**	**4+**	**3+**	**2+**	**1+**	**-**	**Unknown**
Efficacy analysis population	(N=46)							
Baseline	(m=46)	Sneezing	17 (37.0)	18 (39.1)	5 (10.9)	5 (10.9)	1 (2.2)	0
		Nasal discharge	21 (45.7)	13 (28.3)	11 (23.9)	1 (2.2)	0	0
		Nasal obstruction	15 (32.6)	17 (37.0)	13 (28.3)	1 (2.2)	0	0
		Difficulty in daily activity	10 (21.7)	11 (23.9)	18 (39.1)	2 (4.3)	1 (2.2)	4 (8.7)
Week 2	(m=9)	Sneezing	1 (11.1)	1 (11.1)	2 (22.2)	5 (55.6)	0	0
		Nasal discharge	1 (11.1)	1 (11.1)	2 (22.2)	5 (55.6)	0	0
		Nasal obstruction	1 (11.1)	1 (11.1)	1 (11.1)	5 (55.6)	1 (11.1)	0
		Difficulty in daily activity	0	0	1 (11.1)	6 (66.7)	1 (11.1)	1 (11.1)
Week 4	(m=42)	Sneezing	3 (7.1)	5 (11.9)	11 (26.2)	20 (47.6)	3 (7.1)	0
		Nasal discharge	3 (7.1)	11 (26.2)	6 (14.3)	19 (45.2)	3 (7.1)	0
		Nasal obstruction	2 (4.8)	6 (14.3)	12 (28.6)	16 (38.1)	6 (14.3)	0
		Difficulty in daily activity	1 (2.4)	5 (11.9)	7 (16.7)	19 (45.2)	6 (14.3)	4 (9.5)
Week 6	(m=7)	Sneezing	1 (14.3)	1 (14.3)	1 (14.3)	4 (57.1)	0	0
		Nasal discharge	1 (14.3)	1 (14.3)	1 (14.3)	4 (57.1)	0	0
		Nasal obstruction	0	2 (28.6)	0	1 (14.3)	4 (57.1)	0
		Difficulty in daily activity	1 (14.3)	0	1 (14.3)	3 (42.9)	1 (14.3)	1 (14.3)
Week 8	(m=23)	Sneezing	2 (8.7)	0	6 (26.1)	13 (56.5)	2 (8.7)	0
		Nasal discharge	1 (4.3)	2 (8.7)	7 (30.4)	12 (52.2)	1 (4.3)	0
		Nasal obstruction	1 (4.3)	1 (4.3)	7 (30.4)	11 (47.8)	3 (13.0)	0
		Difficulty in daily activity	0	1 (4.3)	2 (8.7)	11 (47.8)	4 (17.4)	5 (21.7)

Week 10	(m=6)	Sneezing	0	0	2 (33.3)	4 (66.7)	0	0
		Nasal discharge	0	1 (16.7)	1 (16.7)	4 (66.7)	0	0
		Nasal obstruction	0	0	2 (33.3)	3 (50.0)	1 (16.7)	0
		Difficulty in daily activity	0	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)
Week 12	(m=5)	Sneezing	0	0	3 (60.0)	2 (40.0)	0	0
		Nasal discharge	0	0	3 (60.0)	2 (40.0)	0	0
		Nasal obstruction	0	1 (20.0)	0	2 (40.0)	2 (40.0)	0
		Difficulty in daily activity	0	0	1 (20.0)	3 (60.0)	1 (20.0)	0
Week 14	(m=1)	Sneezing	0	0	1 (100)	0	0	0
		Nasal discharge	0	0	1 (100)	0	0	0
		Nasal obstruction	0	0	1 (100)	0	0	0
		Difficulty in daily activity	0	0	1 (100)	0	0	0
Week 16	(m=0)	Sneezing	-	-	-	-	-	-
		Nasal discharge	-	-	-	-	-	-
		Nasal obstruction	-	-	-	-	-	-
		Difficulty in daily activity	-	-	-	-	-	-
Week 18	(m=0)	Sneezing	-	-	-	-	-	-
		Nasal discharge	-	-	-	-	-	-
		Nasal obstruction	-	-	-	-	-	-
		Difficulty in daily activity	-	-	-	-	-	-
Week 20	(m=0)	Sneezing	-	-	-	-	-	-
		Nasal discharge	-	-	-	-	-	-
		Nasal obstruction	-	-	-	-	-	-
		Difficulty in daily activity	-	-	-	-	-	-
Week 22	(m=0)	Sneezing	-	-	-	-	-	-
		Nasal discharge	-	-	-	-	-	-
		Nasal obstruction	-	-	-	-	-	-
		Difficulty in daily activity	-	-	-	-	-	-
Week 24	(m=0)	Sneezing	-	-	-	-	-	-
		Nasal discharge	-	-	-	-	-	-
		Nasal obstruction	-	-	-	-	-	-
		Difficulty in daily activity	-	-	-	-	-	-
Day of last evaluation	(m=45)	Sneezing	1 (2.2)	3 (6.7)	15 (33.3)	23 (51.1)	3 (6.7)	0
		Nasal discharge	1 (2.2)	7 (15.6)	13 (28.9)	20 (44.4)	4 (8.9)	0
		Nasal obstruction	2 (4.4)	4 (8.9)	10 (22.2)	19 (42.2)	10 (22.2)	0
		Difficulty in daily activity	1 (2.2)	4 (8.9)	6 (13.3)	22 (48.9)	7 (15.6)	5 (11.1)

Source: Table CGI_T003_1-1

N = Number of patients analyzed for efficacy, m = number of patients evaluated at each evaluation timepoint

The denominator was the number of patients evaluated at each evaluation timepoint.

The results of analysis considering the full-scale dispersal period of cedar pollen showed a similar tendency of improvement in severity of the disease and severity of each symptom.

Each factor that may affect the efficacy of Xolair was examined (including age, the effect on the severity of seasonal allergic rhinitis by duration of treatment with Xolair, the effect on the severity of seasonal allergic rhinitis by severity of seasonal allergic rhinitis at the first visit and between patients with and without a history of treatment with Xolair for seasonal allergic rhinitis) but no factor that greatly affects the efficacy was found in this study.

There was no notable difference in the effect on the severity of seasonal allergic rhinitis in patients who started Xolair in January or February. Since patients who started Xolair in March or later received only 1 or 2 doses, it was difficult to evaluate the effect on the severity of seasonal allergic rhinitis.

Safety results

In the safety analysis population (46 patients), the median (minimum to maximum) safety analysis period was 71.0 (18 to 131) days.

Table 15: Occurrence of adverse events (by SOC and PT) (safety analysis population)

SOC PT	Safety analysis population N=46 n (%)
Total	2 (4.3)
Immune system disorders	1 (2.2)
Seasonal allergy	1 (2.2)
General disorders and administration site conditions	1 (2.2)
Injection site pain	1 (2.2)

Source: Table AE_T001-1
Multiple episodes of an event (PT) in a patient were counted only once.
SOC is shown by internationally agreed order, and PT is shown in descending order of incidence and then in order of code.
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The patient with seasonal allergy was a 16-year-old woman who received Xolair every 2 weeks. Seasonal allergy (event verbatim, worsening of primary disease) occurred on Day 43 after the first dose of Xolair, which was resolving on Day 50 after onset. The event was reported to be mild in severity and not related to Xolair. The patient with injection site pain was a 16-year-old man who received Xolair every 2 weeks. Injection site pain occurred on Day 42 after the first dose of Xolair, which resolved on Day 44 after onset. The event was reported to be mild in severity and related to Xolair.

No serious adverse events or deaths were observed. There were no adverse events leading to discontinuation of Xolair.

2.3.3. Discussion on clinical aspects

In accordance with article 46 of regulation (EC) No 1901/2006 for paediatric studies, the MAH submitted the final study report of "Special drug use observational study of Xolair in patients with severe to most severe seasonal allergic rhinitis aged ≥ 12 years and < 18 years whose symptoms were inadequately controlled despite to conventional therapies".

The condition studied is not approved within EU/EES and as the submitted study was an uncontrolled, open-label study there are limitations to the evaluation of efficacy and safety. However, in the study, including 46 paediatric patients, there are no findings questioning the previously confirmed positive benefit-risk balance in the paediatric population previously concluded. The reported AEs for the paediatric population were in line with the known safety profile of Xolair.

3. CHMP overall conclusion and recommendation

Study CIGE025F1401 included 46 patients with severe to most severe seasonal allergic rhinitis aged ≥12 years and <18 years receiving omalizumab. Xolair is approved for the treatment of severe persistent allergic asthma, chronic Spontaneous Urticaria (CSU) / Chronic Idiopathic Urticaria (CIU) and Nasal Polyps in the EU/EEA. The indication seasonal allergic rhinitis is never applied for. The Applicant does not plan to update the summary of product characteristics (SmPC) with results from this study. This is considered reasonable due to the limited study size and the design of the study.

Overall, the safety profile of Xolair observed in the paediatric study CIGE025F1401 was consistent with the already known safety profile of Xolair.

☒ **Fulfilled:**

No regulatory action required.