NOVARTIS

## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Omalizumab

## Trial Indication(s)

Seasonal allergic rhinitis

## Protocol Number

CIGE025F1401

## Protocol Title

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

## Clinical Trial Phase

Phase IV

## Phase of Drug Development

Approval

## Study Start/End Dates

Study Start Date: January 27, 2021 (Actual)
Primary Completion Date: November 03, 2022 (Actual)
Study Completion Date: November 03, 2022 (Actual)

## Reason for Termination

Not applicable

## Study Design/Methodology

This was a multicenter, uncontrolled, open-label, special drug use investigation 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 used Xolair. The study was conducted in accordance with the Good Post marketing Study Practice (GPSP) Ordinance and the protocol of the study.

The observation period was to last for up to 24 weeks, with Day 1 defined as the start date of Xolair treatment.
It should be noted that, because 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 until the date of last dose of Xolair + 30 days, and the results were recorded in the CRF.

## Centers

Japan(16)

## Objectives:

The research objective was to evaluate the safety and efficacy of Xolair by collecting data in clinical setting 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 used Xolair.

## Test Product (s), Dose(s), and Mode(s) of Administration

- Xolair for S. C. Injection 75 mg
- Xolair for S. C. Injection 150 mg
- Xolair for S. C. Injection 75 mg syringe
- Xolair for S. C. Injection 150 mg syringe

NOVARTIS

## Statistical Methods

All statistical analyses of data in this study were descriptive. Data used for analyses were, as a general rule, 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.

## Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Patients who used Xolair in accordance with the instructions of 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 therapies)
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

NOVARTIS

## Participant Flow Table

**Table 10-1 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 |

**Table 10-6 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) |

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 10-7 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) |

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.

NOVARTIS

# Baseline Characteristics

**Table 10-2 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) |

NOVARTIS

| Background factor | Safety analysis population N = 46 |
|---|---|
| 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) |

| Background factor | Safety analysis population N = 46 |
|---|---|
| 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 |

* 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.

## Primary Outcome Result(s)

Please see the safety section to see results regarding proportion of patients with Adverse Events, Serious Adverse Events, Adverse Drug Reactions and Serious Adverse Drug reactions. There were no adverse events leading to discontinuation of Xolair.

## Secondary Outcome Result(s)

The global assessment of improvement at the last evaluation was "notably improved" in 52.2% (24/46 patients) and "moderately improved" in 41.3% (19/46 patients) in the efficacy analysis population, showing that patients in whom Xolair was effective (moderately improved or better) accounted for 93.5%.
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.

NOVARTIS

***Overall improvement rate of disease by physicians***

**Table 10-10 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) | |

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.

NOVARTIS

**Table 10-11 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) | |

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.

NOVARTIS

***Disease severity of seasonal allergic rhinitis***

**Table 10-12 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 |

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.

NOVARTIS

## ***Individual symptom severity of seasonal allergic rhinitis***

**Table 10-13 Severity of each seasonal allergic rhinitis symptom (efficacy analysis population)**

| Evaluation timepoint | | Breakdown of symptoms | Severity of symptom n (%) 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) |

NOVARTIS

| Evaluation timepoint | | Breakdown of symptoms | Severity of symptom n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 4+ | 3+ | 2+ | 1+ | - | Unknown |
| 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 | - | - | - | - | - | - |

| Evaluation timepoint | | Breakdown of symptoms | Severity of symptom n (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 4+ | 3+ | 2+ | 1+ | - | Unknown |
| 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) |

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.

## Other Pre-Specified Outcome Result(s)

No data identified.

## Post-Hoc Outcome Result(s)

No data identified.

## Safety Results

The incidence of adverse events was 4.3% (2/46 patients), and events reported were seasonal allergy and injection site pain in 1 patient each.
The incidence of adverse drug reactions in this study was 2.2% (1/46 patients), and the reported event was injection site pain (16-year-old male patient). The adverse drug reaction observed in this study is listed in the Japan package insert and the incidence was also within the range specified in the Japan package insert (1% to < 5%).
No patients with special backgrounds (pregnant women, patients with renal impairment, and patients with hepatic impairment) were enrolled in this study.

***Adverse Events:***

**Table 10-8 Occurrence of adverse events (by SOC and PT) (safety analysis population)**

| SOC<br>PT | Safety analysis population<br>N=46<br>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.

***Adverse drug reactions:***

**Table 10-9 Occurrence of adverse drug reactions (by SOC and PT) (safety analysis population)**

| SOC<br>PT | Safety analysis population<br>N=46<br>n (%) |
|---|---|
| Total | 1 (2.2) |
| General disorders and administration site conditions | 1 (2.2) |
| Injection site pain | 1 (2.2) |

Source: Table AE_T001-2

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.

## All-Cause Mortality

There was no death in this study

## Serious Adverse Events

No serious adverse events or adverse drug reactions were observed.

## Other Relevant Findings

Not applicable

## Conclusion:

The Japan package insert has already included a precaution on the adverse drug reaction reported in this study in patients with seasonal allergic rhinitis aged ≥ 12 years and < 18 years, and there was no notable difference in the incidence of adverse drug reactions compared to the clinical study (Study CIGE025F1301). Since there were no new safety or efficacy concerns, no additional measures are considered necessary at present.

## Date of Clinical Trial Report

30 May 2023