Abstract

Title

A regulatory post-marketing surveillance (rPMS) of Xolair® (Xolair Inj., Xolair Prefilled Syringe Inj.) for Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

Date

15 Jul. 2025

Rationale and background

In Korea, Xolair® was first approved in 2007 as a treatment for allergic asthma in the form of Xolair Injection, followed by the addition of the indication for chronic spontaneous urticaria and the development of Xolair Prefilled Syringe injections. Furthermore, in 2020, Xolair® became the first biologic agent to be reimbursed for patients with severe allergic asthma, leading to its wider use in the treatment of allergic diseases. On 16 April 2021, the indication was expanded to include add-on maintenance treatment in adult patients aged 18 years and older with chronic rhinosinusitis with nasal polyps (CRSwNP) who are inadequately controlled with conventional therapy (intranasal corticosteroids, INCS) based on the results of the clinical trials POLYP I and II. This study was conducted to determine the post-marketing safety and effectiveness of Xolair® in patients with CRSwNP as a new indication under routine clinical practice in Korea.

This was a multicenter, single-arm, open-label, post-marketing surveillance study conducted in accordance with the requirements of the Ministry of Food and Drug Safety (MFDS). As a condition of approval for the additional indication, the MFDS granted a re-examination period of 4 years from 16 April 2021 to 15 April 2025. The objective of this study was not to test a scientific hypothesis, but to describe the incidence of all potential adverse events (AEs), serious adverse events (SAEs), and unexpected AEs not listed in the local labeling in Korean patients under routine clinical practice in accordance with the approved label in Korea. Therefore, this study involved patients who received at least one dose of Xolair® for the treatment of CRSwNP in accordance with the currently approved label in Korea.

Research question and objectives

Primary objective

- To evaluate the safety of Xolair® as an add-on maintenance therapy to adult patients (≥18 years of age) with CRSwNP and who are not adequately controlled with conventional therapy (INCS) under routine clinical practice

Secondary objectives

- To evaluate the effectiveness of Xolair® as an add-on maintenance therapy to adult patients (≥18 years of age) with CRSwNP and who are not adequately controlled with conventional therapy (INCS) under routine clinical practice
- To identify subject baseline characteristics and treatment information that may affect the safety and effectiveness of Xolair®

Study design

This was a 24-week, prospective, open-label, multicenter, single-arm, observational, post-marketing surveillance study under routine clinical practice, without any mandatory treatments, visits, or assessments. The study design was approved by the Korean health authorities.
The investigators collected safety data and evaluated effectiveness for up to 24 weeks after administration of Xolair® in patients who were prescribed the drug. However, subjects who received Xolair® for 12 weeks or more were defined as long-term users, and their results are presented separately. Xolair® was prescribed in accordance with the approved label. Decisions regarding the treatment method for subjects were made based on the approved indications within the real-world practice setting and regardless of whether the subject was enrolled in the study. No additional diagnostic or monitoring procedures were required for this surveillance other than the procedures in the routine care settings. An epidemiological method was used for the analysis of the collected data.

Patients were required to sign a consent form for data collection. Participants were not required to provide consent for taking the drug as its administration was determined prior to study participation and

was part of routine clinical care.

The study was conducted through complete enumeration. All patients for whom an informed consent form (ICF) was obtained by the investigator and who had initiated or were receiving Xolair® after the start date of the study were enrolled sequentially.

Setting and study population

Novartis has signed agreements with hospitals and investigators. The investigators enrolled all patients who provided informed consent for observation and met all of the eligibility criteria for this study after its initiation at the institution. The investigator provided an informed consent form and obtained the subject's signature.

Participation in this study and the collection and use of the corresponding data were documented by the site staff at or prior to the site visit following subject consent, as required by local requirements. A copy of the signed informed consent form was provided to the patient and the original was retained.

For this study, baseline was defined as the time point of the first data collection after the subject's consent to the study, and data were collected prospectively from baseline.

Subjects who met all the inclusion criteria and did not meet any of the exclusion criteria were enrolled, and rescreening was not permitted.

Inclusion criteria
1) Adults aged ≥18 years
2) Patients with CRSwNP who are not adequately controlled with conventional therapy (INCS)
3) Patients prescribed or receiving Xolair® as per the locally approved label information
4) Patients who provide written informed consent to participate in the study

Exclusion criteria
1) Patients who do not agree on the participation in the study
2) Patients participating in another clinical trial
3) Contraindications listed in the locally approved label information of Xolair®
   - Patients with hypersensitivity to the active ingredient or any other components of Xolair®
   - Patients with myocardial infarction or history of myocardial infarction (for prefilled syringes only)

Variables

Site information
1) Site information: name of site, department, investigator, contract date

Basic information on subjects
1) Inclusion/exclusion criteria: whether ICF was signed, date of signature, inclusion/exclusion criteria
2) Subject number
3) Demographic data: year of birth, sex, height (cm), body weight (kg)

Information on CRSwNP
1) Diagnosis, date of diagnosis, disease duration (days)
2) History of INCS use in relation to CRSwNP (name of drug, dosing start date, dosing end date, daily dose)
3) Treatment history other than INCS use in relation to CRSwNP (presence or absence of treatment history, name of surgery or drug, date of treatment)
4) Presence or absence of asthma and aspirin sensitivity (asthma with aspirin sensitivity/asthma without aspirin sensitivity/no asthma)
5) Smoking status
6) IgE levels
7) Sino-nasal outcome test-22 (SNOT-22) score

Medical history
1) Presence or absence of disease, diagnosis, disease classification (renal impairment, hepatic impairment, other), severity, date of diagnosis, date of resolution (whether it is ongoing or not)

Concomitant treatment
1) Concomitant medications: Whether concomitant medication was used, name of medication (brand name), dosing start date and end date, whether medication is ongoing, dosage, route of administration, purpose (treatment of CRSwNP/treatment of underlying disease/treatment of

AE/prophylaxis/other)
2) Concomitant therapy: Whether a concomitant therapy was used, name of therapy, therapy start date and end date, whether therapy is ongoing, purpose (treatment of CRSwNP/treatment of underlying disease/treatment of AE/prophylaxis/other)

Xolair® administration status
1) Xolair® batch number
2) Purpose of administration (to prevent post-operative recurrence of nasal polyps/to relieve CRSwNP symptoms/to reduce the size of nasal polyps/other)
3) Dosing date
4) Dose administered
5) Reason for treatment discontinuation (AE onset/subject failed to return/other)

Safety evaluation data
1) Adverse events

Effectiveness evaluation data
1) Change from baseline in SNOT-22 at Week 12 and Week 24

End of study data
1) Date of end of study
2) Reason for withdrawal (lost to follow-up/death/withdrawal of consent/investigator's decision/other)

Data sources

This study used data derived from assessments conducted in accordance with the investigator's routine medical practice and standard of care. Records from routine medical documents will be used as source data. They include, but are not limited to, electronic and paper-based patient medical charts, hospital discharge files, drug prescription files, and investigator letters. Subject demographics and characteristics of disease and prior treatments were retrospectively collected. Other variables of interest were collected prospectively where possible. Only available data were collected in the case report form (CRF) in this non-interventional study.

Study size

Based on previous CRSwNP studies and statistical calculation of the primary objective, the sample size for this study was set at 100 subjects.

Data analysis

Safety analysis:

The number, incidence, and frequency of subjects who experienced adverse events (AEs)/adverse drug reactions (ADRs), serious adverse events (SAEs)/serious adverse drug reactions (SADRs), unexpected AEs (UAEs)/ADRs (UADRs), and serious unexpected AEs (SUAEs)/ADRs (SUADRs) were presented along with 95% Wald or Clopper-Pearson confidence intervals for the incidence rates. The number, incidence, and frequency of subjects who experienced AEs/ADRs, SAEs/SADRs, UAEs/UADRs, and SUAEs/SUADRs were summarized according to the system organ class (SOC) and preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA). The list of individual subjects with ADRs, SAEs and unexpected AEs is provided with details including the name of the AE, SOC, PT, date of onset and date of resolution, severity, seriousness and seriousness criteria, causality to Lucentis, action taken, outcome, and expectedness. The number and incidence of subjects who experienced AEs were summarized according to the severity, causality, actions taken, and outcomes of the events, based on the SOC and PT of the MedDRA. In the final report, additional analyses were performed to identify subject characteristics associated with AEs.

Effectiveness analysis:

Descriptive statistics were presented to summarize the changes from baseline in SNOT-22 scores at Weeks 12 and 24. In the final report, additional analyses were conducted to assess subject characteristics associated with the changes from baseline in SNOT-22 scores at Weeks 12 and 24.

Results and discussion

This PMS was performed to investigate and identify AEs and factors affecting the safety and effectiveness that may not have been identified during the development of Xolair® in patients with CRSwNP, the newly approved indication, under routine clinical practice in Korea, and to incorporate

them into the label according to the Guidelines on Re-examination of New Drugs, etc.

During the re-examination period (16 April 2021 - 15 April 2025), CRFs of 135 cases were collected from 16 different institutions. Of the 135 cases collected, 22 were excluded, comprising 2 cases of "study drug not administered," 2 cases of "safety follow-up not conducted" (also overlapping with "off-label use of the study drug"), and 20 cases of "off-label use of the study drug", resulting in 113 cases included in the Safety Analysis Set. The Safety Analysis Set included subjects whose CRFs were collected, who received at least one dose of Xolair® in accordance with the approved indications, and had at least one completed safety follow-up. This comprised of cases where the administration was considered to be within the approved indications based on the investigator's clinical judgment. Among the subjects included in the Safety Analysis Set, 63 cases who received Xolair® for 12 weeks or longer were included in the Long-term Safety Analysis Set. Among the subjects included in the Safety Analysis Set, 50 cases were included in the Effectiveness Analysis Set, excluding 63 cases not evaluated for effectiveness at Week 12 or Week 24. Of those in the Effectiveness Analysis Set, 27 cases who were evaluated for effectiveness at Week 24 were included in the Long-term Effectiveness Analysis Set.

During this re-examination period, the incidence of AEs reported among the 113 subjects in the Safety Analysis Set was 16.81% (19/113 subjects, 28 events), and the incidence of ADRs was 7.08% (8/113 subjects, 12 events). In terms of seriousness, there were no SAEs. When the AEs were analyzed by expectedness, the incidence of UAEs was 9.73% (11/113 subjects, 15 events), and the incidence of UADRs was 1.77% (2/113 subjects, 3 events).

During the re-examination period, no AEs were reported among the 9 elderly subjects (≥65 years of age), 1 patient with renal impairment, and 2 patients with hepatic impairment in the Safety Analysis Set. During the surveillance period, there were no children, pregnant women, or breastfeeding women in the Safety Analysis Set.

During this re-examination period, the incidence of AEs reported among the 63 subjects in the Long-term Safety Analysis Set was 15.87% (10/63 subjects, 12 events), and the incidence of ADRs was 4.76% (3/63 subjects, 4 events). In terms of seriousness, there were no SAEs. Based on the classification of AEs according to expectedness, the incidence of UAEs was 4.76% (3/63 subjects, 4 events), and none of these were UADRs.
During this re-examination period, there were no AEs reported among the 20 subjects who were excluded from the Safety Analysis Set due to off-label use; among the 8 subjects who switched from the Safety Analysis Set to off-label use, the incidence of AEs was 50.00% (4/8 subjects, 8 events), and the incidence of ADRs was 37.50% (3/8 subjects, 6 events). In terms of seriousness, there were no SAEs. When the AEs were analyzed by expectedness, the incidence of UAEs was 37.50% (3/8 subjects, 4 events), and the incidence of UADRs was 25.00% (2/8 subjects, 3 events).
During this re-examination period, the mean SNOT-22 scores of the 50 subjects in the Effectiveness Analysis Set were 35.20 ± 23.86 at baseline, 19.36 ± 17.75 at Week 12, and 21.37 ± 15.21 at Week 24. The mean change from baseline in SNOT-22 was -15.32 ± 20.65 at Week 12 and -13.48 ± 17.53 at Week 24.

During this re-examination period, there were no children, pregnant or breastfeeding women, or patients with renal or hepatic impairment in the Effectiveness Analysis Set.

During this re-examination period, the mean SNOT-22 scores of the 27 subjects in the Long-term Effectiveness Analysis Set were 34.85 ± 22.84 at baseline, 18.38 ± 15.84 at Week 12, and 21.37 ± 15.21 at Week 24. The mean change from baseline in SNOT-22 was -15.42 ± 20.60 at Week 12 and -13.48 ± 17.53 at Week 24.

In conclusion, there were no signals suggesting specific safety or effectiveness concerns observed for Xolair® during this re-examination period. Through this post-marketing surveillance, Xolair® will be monitored continuously to identify factors affecting its safety and effectiveness, and efforts will be made to ensure thorough safety management based on the results of this report and spontaneous reports.

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report/Record Form
CRS	Chronic Rhinosinusitis
CRSwNP	Chronic Rhinosinusitis with Nasal Polyps
ICF	Informed Consent Form
IgE	Immunoglobulin E
INCS	Intranasal Corticosteroids
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NCS	Nasal Congestion Score
PMS	Post Marketing Surveillance
PT	Preferred Term
SADR	Serious adverse drug reaction
SAE	Serious Adverse Event
SNOT-22	Sino-Nasal Outcome Test-22
SOC	System Organ Class
SUADR	Serious unexpected adverse drug reaction
SUAE	Serious unexpected adverse event
UADR	Unexpected adverse drug reaction
UAE	Unexpected adverse event
WHO	World Health Organisation