STUDY REPORT SYNOPSIS

RANS – Retrospective FASENRA SEA + NP Study

Retrospective, Observational Study in Patients with Severe Eosinophilic Asthma and Nasal Polyps treated by FASENRA®

Milestones:	Final Results Tables: 30 November 2022 / 15 December 2022 / 26 January 2023 Final Study Report: 01 February 2023
Phase of development:	Not applicable
Sponsor:	AstraZeneca
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This study was performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice, including the archiving of essential documents.

Background/rationale:

Asthma is a chronic inflammatory disease estimated to affect 339 million people globally, with up to 10% having severe asthma. Among severe asthma patients, one of the most common comorbidities is chronic rhinosinusitis with nasal polyps (NPs), which is characterized by persistent inflammation of the mucous membrane lining the nasal passages and sinuses accompanied by NPs (benign growths). The prevalence of NPs among severe asthma patients ranges from 3% to 44% based on severe asthma registries that highlight regional variation in the overlapping population. The combination of severe asthma and NP provides significant treatment challenges and substantial disease burden, and the treatment of comorbid patients has become an area of focus for novel, targeted therapeutics.

The Phase IIIb, ANDHI study (CCI) showed benralizumab reduced asthma exacerbations and improved health-related quality of life (HRQoL), asthma control, and lung function in patients with severe eosinophilic asthma (SEA) and NPs. Notably, clinically meaningful improvements in Sino-nasal Outcome Test-22 (SNOT-22) total score were seen in the SEA + NP population beginning at early timepoints (4 weeks after first dose of benralizumab) and persisting over a 6-month period. Recent real world evidence studies in Italy (2 studies; n = 10 and n = 34) and the United States

(1 study; n = 23) have shown SEA + NP patients treated with benralizumab for at least 4 months had significant improvements in both NP and asthma clinical outcomes.

High-level results from the OSTRO Phase III study (CCI) showed that benralizumab compared with placebo demonstrated a statistically significant improvement in the size of NPs and in degree of nasal blockage in patients with NPs. Benralizumab demonstrated a statistically significant improvement in the endoscopic total nasal polyp score (NPS) and the nasal blockage score compared to placebo in patients with severe bilateral NPs who were still symptomatic despite continued treatment with standard of care (intranasal corticosteroids and history of systemic corticosteroids [SCS] use and/or NP surgery).

Notably, patients with asthma who had a history of frequent asthma exacerbations (≥ 2 exacerbations in the year prior to enrolment, irrespective of asthma medications) were rare in OSTRO (6.2% of the comorbid asthma OSTRO population and 4.1% of the overall OSTRO population). Therefore, the SEA population was likely under-represented.

In light of the increasing importance of comorbidities in driving choice for biologics in severe asthma, there is a knowledge gap in understanding SEA patients with comorbid NPs for whom the decision to start biologics was based on the presence of severe, uncontrolled asthma. This retrospective, observational study described the population of patients with SEA + NP who have been prescribed benralizumab and assessed available clinical outcomes for both NPs and asthma.

Objectives:

Primary Objective

The primary objective of the study was:

- To describe baseline demographics, clinical characteristics, and background treatments among SEA + NP patients on benralizumab

Secondary Objectives

The secondary objectives of the study were:

- To describe NPS before and after initiation of benralizumab among SEA + NP patients
- To describe patient-reported NP HRQoL before and after initiation of benralizumab among SEA + NP patients
- To describe the frequency and timing of NP surgery after initiation of benralizumab among SEA + NP patients
- To describe asthma clinical outcomes after initiation of benralizumab among SEA + NP patients
- To describe the use of SCS after initiation of benralizumab among SEA + NP patients

CCI

Study design:

This was a retrospective, multinational, observational study utilizing medical chart review among SEA + NP patients on benralizumab. The index date was defined as the day of first benralizumab dose. The pre-index (baseline) period was defined as beginning from 12 months prior to the index date. The follow-up period was defined as the time period up to 12 months after the index date. If a patient switched to another non-benralizumab biologic during the follow-up period, the study censored follow-up time was defined as the date that the patient started treatment for the non-benralizumab biologic. All measurements for the study outcomes were retrospectively collected during the baseline and follow-up periods.

Data source:

The primary data source was medical charts from hospitals or clinical centres that treated SEA + NP patients with benralizumab. Patient data including demographics, clinical characteristics, medication history, biologic treatment, and NP and asthma clinical outcomes were abstracted from patient medical charts onto a pre-approved electronic case report form. No personal identifiable data were collected. Data from all participating centres were combined into a single anonymized dataset for analysis.

Study population:

The study population was SEA + NP patients treated with benralizumab.

Inclusion criteria:

A participant was eligible for inclusion in this study if all of the following criteria applied:

1 Current or previous treatment with benralizumab for SEA
2 Physician-confirmed diagnosis and evaluation of NPs using NPS and/or SNOT-22 total score before and after first benralizumab injection
3 Patients who had follow-up period of at least 5 months from first benralizumab injection or at least 4 consecutive injections of benralizumab
4 Able to provide signed informed consent (if required based on local guidelines).

Exclusion criteria:

A participant was not eligible for inclusion in this study if any of the following criteria applied:

1 Patient was on any other biologic during the 12 months prior to treatment with benralizumab
2 Previously or currently received any other biologic for the treatment of asthma or NPs in a clinical trial. This exclusion criteria did not apply to patients that received biologic treatment from open-label one-arm interventional studies that provided biologic treatment as part of standard of care (according to approved labelling in that country).

Statistical methods:

All analyses were descriptive in nature. Continuous variables were summarized by providing the number of patients (or number of events), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were summarized by providing frequency counts and percentages. Asthma exacerbation rates and 95% confidence intervals (CIs) were calculated using a negative binomial model. Median time to first NP surgery and SCS use during the follow-up period were calculated using Kaplan-Meier methods. Tables and graphs were constructed to enable visualization of these summary statistics. For all longitudinal series of assessments (ie, NPS, SNOT-22 total score,

Asthma Control Questionnaire-6 [ACQ-6], Asthma Control Test [ACT], and Asthma Quality of Life Questionnaire for 12 years and older [AQLQ(S)+12]), the baseline was derived as the latest existing and non-missing assessment prior to or on the index date. Description of asthma and NP endpoints during the pre-index versus post-index were implemented. Mean change from baseline (95% CI) was provided for patients who had both pre-index and follow-up measures of total NPS or SNOT-22. In addition, proportion of patients with clinically meaningful improvement in NPS, SNOT-22, ACQ-6, and ACT was reported. CCI

Only measures from patients indicated as having clean data at database lock were used in the statistical outputs and this report. Patient measures not declared clean or with no data were reflected as missing within that analysis. The clean data from patients with a mixture of clean and non-clean measures were used in the analysis (ie, non-clean data were excluded at the record level). Percentages were based on the number of patients with data, where applicable.

Results:

The study enrolled 233 patients in Spain, France, Italy, United States, and Japan. The majority of patients were female (53.6%), white (75.1%), and the mean age was 56.0 years (range: 21 to 90). During the follow-up period, 33.5% of patients received benralizumab treatment at the clinical centre and 12.4% of patients received benralizumab treatment at home for a median total duration of exposure of 361.5 days. Treatment location was not captured for 54.1% of patients.

Primary endpoints: pre-index (baseline) period (up to 12 months prior to the first benralizumab dose):

The majority of patients had key disease-related comorbidities of asthma (83.7%) and NPs (66.1%) reported in the pre-index period. Other frequently reported disease-related comorbidities were chronic sinusitis (16.3%), allergic rhinitis (13.3%), and rhinitis (7.7%). The most frequently reported oral corticosteroids (OCS)-related comorbidity was osteoporosis (7.3%). The mean age at diagnosis was 40.2 years for patients with reported asthma and 43.3 years for patients with reported rhinitis or NPs. The median time since first appearance of NP symptoms was 7.0 years. Few patients (10.3%) had NP surgery during the pre-index period.

Disease-related treatments during the pre-index period were reported for less than half of the patients (45.9%): most commonly prednisone (30.0%) and methylprednisolone (5.6%).

The use of OCS for asthma-related treatments during the pre-index period was reported as maintenance therapy for 3.0% of patients and as rescue therapy for 37.3% of patients. The use of OCS for NP-related treatments during the pre-index period was reported for 6.9% of patients. During the pre-index period, SCS use for any condition was reported for 47.2% of patients: 40.8% for asthma and 7.3% for NPs.

The baseline ACQ-6 score was reported by 33.0% of patients (n = 77) with a mean ACQ-6 score of 1.61 (possible range: 0 [totally controlled] to 6 [severely uncontrolled]). Of these patients with available baseline scores, 42.9% had well-controlled asthma, 9.1% had partly-controlled asthma, and 48.1% had uncontrolled asthma.

The baseline ACT score was reported by 63.5% of patients (n = 148) with a mean ACT score of 15.0 (possible range: 5 [poorly controlled] to 25 [well-controlled]). Of these patients with available baseline scores, 22.3% had well-controlled asthma and 77.7% had asthma that was not well-controlled.

The baseline AQLQ(S)+12 score was reported by 24.9% of patients (n = 58) with a mean AQLQ(S)+12 score of 4.04 (possible range: 1 [severe impairment] to 7 [no impairment]).

Asthma exacerbations during the pre-index period were reported for 50.9% of patients (n = 115): 46.1% of these patients had 1 exacerbation, 25.2% had 2 exacerbations, 17.4% had 3 exacerbations, and 11.3% had ≥ 4 exacerbations during the 12-month period. The pre-index period annualised exacerbation rate was 1.17 (95% CI: 0.96, 1.41) per patient per year. Exacerbations that led to an asthma-related emergency room (ER) or urgent care visit were reported for 16.8% of patients (n = 38). Exacerbations that led to an asthma-related hospitalization were reported for 4.4% of patients (n = 10) with a median hospital stay of 9.0 days. Exacerbations that led to treatment with SCS treatment were reported for 6.2% of patients (n = 14).

Asthma- and NP-related hospitalizations during the pre-index period were reported for 6.4% and 0.4% of patients (n = 15 and n = 1), respectively. The mean annualised rate for asthma- and NP-related hospitalization were 0.10 and 0.01 per patient per year, respectively.

Asthma- and NP-related intensive care unit (ICU) stays during the pre-index period were reported for 0.9% and 0.0% of patients (n = 2 and n = 0), respectively. The mean annualised rate for asthma- and NP-related ICU stays were 0.02 and 0.00 per patient per year, respectively.

Asthma- and NP-related ER visits during the pre-index period were reported for 10.3% and 1.3% of patients (n = 24 and n = 3), respectively. The mean annualised rate for asthma- and NP-related ER visits were 0.19 and 0.02 per patient per year, respectively.

Asthma- and NP-related outpatient visits during the pre-index period were reported for 39.1% and 24.0% of patients (n = 91 and n = 56), respectively. The mean annualised rate for asthma- and NP-related outpatient visits were 1.57 and 0.81 per patient per year, respectively.

Secondary endpoints: follow-up period (up to 12 months after the first benralizumab dose):

The mean total NPS at baseline and during the 12-month follow-up period was 3.8 (SD = 2.35; n = 91) and 3.0 (SD = 2.08; n = 63), respectively, with a mean change from baseline of -1.2 (95% CI: -1.69, -0.63; n = 57), indicating a reduction in the bilateral NP burden following benralizumab treatment. Overall during the 12-month follow-up period, 49.1% of these patients were NPS responders with clinically meaningful improvement in NPS (change from baseline to follow-up of total NPS score ≤ -1). CCI

The mean SNOT-22 total score at baseline and during the 12-month follow-up period was 47.5 (SD = 22.58; n = 161) and 28.9 (SD = 21.06; n = 114), respectively, with a mean change from baseline of -19.8 (95% CI: -23.63, -15.90; n = 105), indicating an improvement in NP HRQoL. Overall during the 12-month follow-up period, 67.6% of these patients were SNOT-22 responders with clinically meaningful improvement in SNOT-22 (change from baseline to follow-up total score ≤ -8.9). CCI

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Few patients (6.0%) had NP surgery during the follow-up period.

Asthma exacerbations during the follow-up period were reported for 13.7% of patients: 74.2% of these patients had 1 exacerbation, 19.4% had 2 exacerbations, 3.2% had 3 exacerbations, and 3.2% had ≥ 4 exacerbations during the 12-month period. The annualised exacerbation rate was significant lower ($p < 0.0001$) during the follow-up period compared to the pre-index period (0.19 versus 1.17 per patient per year).

The mean ACQ-6 score for patients during the 12-month follow-up period was 0.84 with a mean change from baseline of -0.78 (95% CI: -1.12, -0.44; n = 53), indicating an improvement in asthma control. During the 12-month follow-up period, 67.2% had well-controlled asthma (ACQ-6 ≤ 0.75), 8.6% had partly controlled asthma (0.75 < ACQ-6 < 1.5), 24.1% had uncontrolled asthma (ACQ-6 ≥ 1.5), and 56.6% of these patients were ACQ-6 responders.

The mean ACT score for patients during the 12-month follow-up period was 22.0, with a mean change from baseline of 7.2 (95% CI: 6.19, 8.13; n = 106), indicating an improvement in asthma control. During the 12-month follow-up period, 80.5% had well-controlled asthma (ACT ≥ 20), 19.5% had uncontrolled asthma (ACT ≤ 19), and 81.1% of these patients were ACT responders.

The mean AQLQ(S)+12 score for patients during the 12-month follow-up period was 5.27, with a mean change from baseline of 1.14 (95% CI: 0.80, 1.47; n = 44), indicating an improvement in asthma-related HRQoL. During the 12-month follow-up period, 79.5% of these patients were AQLQ(S)+12 responders.

Lung function improved during the 12-month follow-up period, with a mean change in forced expiratory volume in 1 second (FEV_1) from baseline of 0.42 L (95% CI: 0.32, 0.52; n = 119), indicating an improvement in FEV_1.

Concomitant SCS use for any condition was reported for 27.5% of patients: 19.3% for asthma and 6.0% for NPs. During the follow-up period, less SCS use for any condition was reported for 18.5% of patients: 12.0% for asthma and 4.7% for NPs.

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Conclusion:

Clinically significant improvements in both asthma and NP outcomes were observed during the 12 months following benralizumab initiation, supporting the clinical effects of benralizumab in patients with comorbid SEA and NPs.

Publications:

Not applicable.