Clinical Study Report (CSR) Synopsis

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Utilisation of Benralizumab in the Clinical Practise in Severe Eosinophilic Asthma Patients in Switzerland (BEEPS)

A multicentre, single arm, non-interventional, observational, prospective study to assess demographic characteristics, burden of disease and short-term patient reported outcomes on symptom relief in severe eosinophilic asthma patients aged older than 18 qualifying for treatment with benralizumab in Switzerland

Milestones:	First Study Subject In:	21 January 2019
	Last Study Subject Last Visit:	04 January 2023
	The analyses presented in this report are based on two abstracts submitted and presented at two scientific congresses in 2023. No publications were available at the time of writing this report.	
Phase of Development:	Non-interventional, observational real-world study (post-approval)	
Sponsor:	AstraZeneca AG	
Author:	[redacted]	

This study was performed in compliance with Good Clinical Practice (GCP) and Good Pharmacoepidemiology Practice (GPP), including the archiving of essential documents.

This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca (AZ) and opportunity to object.

Background and rationale

Asthma is a chronic inflammatory disease of the airways that is estimated to affect more than 315 million people worldwide, with approximately 5-10% having severe or uncontrolled asthma, resulting in a significant burden to healthcare systems and society. Patients typically have respiratory symptoms including wheeze, shortness of breath, chest tightness and cough, together with variable expiratory airflow limitation. Eosinophilic inflammation is present in approximately 50% of asthma patients and is furthermore associated with disease severity, greater frequency of exacerbations, and decreased lung function.

According to international ATS/ERS guidelines on the definition of severe asthma, patients currently rely on the use of high-dosage inhaled corticosteroids (ICS) in combination with bronchodilators, such as long-acting β2-agonists (LABA), as a standard of care treatment to control their disease, some additionally relying on oral corticosteroids (OCS) to manage their symptoms. Severe uncontrolled asthma is difficult-to-treat and a potentially fatal form of the disease, where patients experience frequent exacerbations every year and have significant limitations on lung function and quality of life.

Benralizumab is a humanised, afucosylated, monoclonal antibody against the IL-5 receptor (IL-5R) α subunit that induces direct, rapid, and near-complete depletion of eosinophils in blood, airway tissue, and bone marrow through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). This apoptotic process involves natural killer cells responsible for the controlled eosinophilic elimination. In the two pivotal phase 3 trials SIROCCO and CALIMA, benralizumab was well tolerated, significantly reduced asthma exacerbations by up to 51%, and improved lung function as well as disease control in patients with severe, uncontrolled asthma and blood eosinophil count of ≥ 300 cells/μL blood, receiving both ICS and LABA.

The rapid and near-complete depletion of eosinophils with benralizumab suggests fast symptom relief as well as potentially reducing OCS doses in patients with severe, eosinophilic asthma improving patient compliance and having a significant impact on long term healthcare costs. Demonstrating a rapid clinical benefit for patients can reduce uncertainty of patients and physicians, as the treatment advantage can be demonstrated early in the clinical reality outside of stratified trials, which saves cost and optimises patient management. The long-term follow up visit after 56 weeks, however, will demonstrate whether the early benefits are maintained over time.

Objectives

This observational study does not test a specific hypothesis. BEEPS describes the utility of patient reported outcomes (PRO) as a simple, pragmatic, and sensitive tool to assess early treatment response of benralizumab to document the level of asthma control after 1 to 16 weeks post-treatment initiation. Moreover, the percentage of patients reducing their OCS dose will be evaluated after 4, 8, and 16 weeks of treatment with benralizumab. The objective is to evaluate rapid clinical benefit for patients who are potentially eligible for referral for therapy with benralizumab. PRO comprises of the weekly Asthma Control Questionnaire, five-question version (ACQ-5), Patient Global Impression of Change as well as Severity (PGI-C and PGI-S) and an electronic asthma daily diary (eDiary) to assess lung function including peak expiratory flow (PEF). Both PRO will deliver data to support patient management for a better disease control in severe asthma patients under benralizumab treatment to estimate the level of diagnostic measures and disease burden. These results will complement the data obtained from randomised trials in a non-randomised pragmatic real-world setting. Early documented patient reported symptom relief parameters can support the communication between patient and treating physician in an objective and structured manner. To determine the long-term sustainability of the above-mentioned PRO and the utility of eDiary and PEF, assessment of the patients' status at 56 weeks after benralizumab initiation will be performed.

Primary objective

- To evaluate the overall change after 8 weeks of treatment with benralizumab in ACQ-5 score

Secondary objectives

- To assess the percentage of patients on OCS who were able to successfully reduce their OCS dose after 16 and 56 weeks of treatment with benralizumab
- Percentage of patients on OCS who were able to successfully reduce their OCS dose after 4 and 8 weeks of treatment with benralizumab
- Median OCS dose reduction at 4, 8, 16 and 56 weeks of treatment with benralizumab
- To evaluate the overall change after 1, 2, 4, 16 and 56 weeks of treatment with benralizumab in ACQ-5 score
- To determine the proportion of patients with a total score improvement of ≥ 0.5 in ACQ-5 after 1, 2, 4, 8, 16 and 56 weeks of treatment with benralizumab
- To assess change from baseline after 1, 2, 4, 8, and 16 weeks in PGI-C and after 1, 2, 4, 8, 16 and 56 in PGI-S in asthma
- To describe asthma disease history, past treatment status and current medication at baseline of severe asthma patients

Exploratory objectives

- To assess the changes in PEF after 1, 2, 4, 8, 16 and 56 weeks of treatment with benralizumab
- Assess weekly trend in PEF changes over study period
- To assess the pre- and postbronchodilator changes in FEV1 and FVC after 8 and 16 and 56 weeks of treatment with benralizumab
- To assess background medication status after 56 weeks
- To assess the proportion of patients experiencing at least one severe exacerbation
- To assess the improvement of nasal polyposis relevant health status (taste and smell)
- To assess the persistence of patients utilizing the eDiary and PEF measurements over 56 weeks

Study design

This is a multicentre, single arm, non-interventional observational, prospective study including patients older than 18 years, who qualify for the treatment with benralizumab according to label in participating specialist centres focusing on severe asthma in Switzerland. The decision by the physician to start benralizumab is made independently from study inclusion and patient informed consent. Patients who meet the study criteria will be enrolled and, as outlined in the current Summary of Product Characteristics (SmPC), are planned to receive a total of four subcutaneously (s.c.) applied doses of 30 mg benralizumab, at weeks 0 (baseline), 4, 8, and 16. A long time follow-up visit to assess the sustainability of achieved changes will be done after 56 weeks (Figure 1). No study drug will be provided, all patients will be on commercial drug. Additional study visits are scheduled at week 1 and 2 to obtain the paper based ACQ-5, PGI-C and PGI-S questionnaire. Alternatively, these two visits can also be done remotely via phone calls.

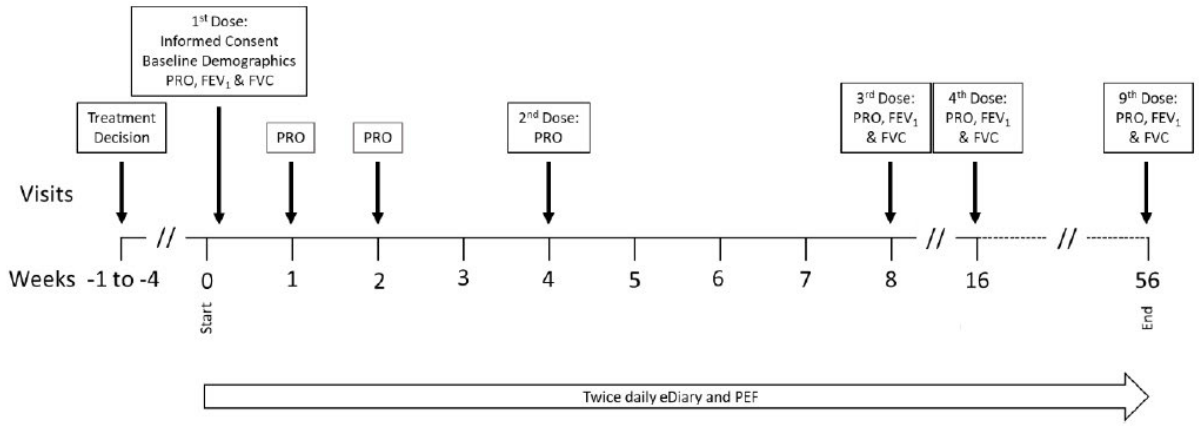

Figure 1: BEEPS study design. FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; PEF: Peak expiratory flow; PRO: Patient reported outcome

Data source

Site staff will collect all necessary information from the patients' medical record to determine eligibility for enrolment. Consecutively, adult patients with a diagnosis of asthma will be screened and those with severe asthma (GINA step 4/5) and within the Swiss label will be invited to participate, consented and enrolled. For each enrolled patient, the physician will document data from medical records or conducting interviews at each study visit. In addition, the patient will be asked to provide prospectively PRO data on asthma control via ACQ-5 and eDiary including PEF as well as adherence to asthma medication.

Study population

The study recruited 73 male and female patients aged ≥ 18 years with severe, eosinophilic asthma who met all inclusion criteria and none of the exclusion criteria. 13 specialist centres across Switzerland participated in the study. In Switzerland, the label for benralizumab defines the eligible patients as eosinophilic (≥ 300 cells/µL blood) with 2 or more exacerbations in the last 12 months and in high ICS plus LABA maintenance treatment.

Inclusion criteria

Subject eligible for enrolment in the study and treatment for benralizumab according to the specific Swiss label must meet all the following criteria:

- Male or female patients older than 18 years with physician's confirmed diagnosis of severe, uncontrolled asthma according to ATS/ERS guidelines
- Asthma requiring high-dose ICS plus LABA as maintenance treatment
- Minimum of 2 exacerbations in the last 12 months
- Documented peripheral blood eosinophil count ≥ 300 cells/µL blood
- Provision of signed written informed consent form (ICF) indicating that they understand the purpose of the study and procedures required for participation in the study
- Patients must be able and willing to read and comprehend written instructions and comprehend and complete the questionnaires required by the protocol (ACQ-5, PGI-C and PGI-S)

Exclusion criteria

Subjects meeting any of the following criteria will not be eligible to participate in the study:

- Documented lung diseases other than asthma, e.g. COPD, and not within reimbursed label, e.g pregnancy or lactation
- Currently enrolled in an interventional clinical study in parallel, except:
  - Patients being in parallel documented in a national asthma registry
  - Patients having completed any other clinical trial including those with biologic treatment
- An acute or chronic condition that, in the investigator's opinion, would limit the patients' ability to complete questionnaires or participate in this study or impact the interpretations of results

Statistical methods

This study is descriptive in nature with no pre-specified hypotheses, therefore there is no definition of sequential testing procedures necessary. All outcome will be presented using descriptive summaries and estimates with nominal 95% confidence intervals (CI), any p-values presented to be interpreted descriptively with $p<0.05$ being significant (two-sided). The analyses will be performed in the full analysis set (FAS). All enrolled patients who received at least one dose of benralizumab will be included in the FAS, irrespective of their protocol adherence and continued participation in the study according to the Intention-to-Treat (ITT) principle. Patients who withdraw from the study will be included up to the date of their study termination.

Results

Baseline demographics and clinical characteristics are reported in Table 1. Out of 73 patients included in the study, 61.6% were women. Age varied from 19 to 83 (mean: 53.8 years. Over half of patients (60.3%) were overweight or obese (BMI ≥25). Mean ACQ-5 score at baseline was 2.76, corresponding to uncontrolled asthma. On average, patients had 3.65 exacerbations in the 12 months prior to enrolment.

Table 1: Baseline demographics and clinical characteristics. ACQ-5: Asthma control questionnaire, five-question version; BMI: Body mass index

Characteristic	
Number of patients — N	73
Female sex — N (%)	45 (61.6%)
Age [years] — mean (min; max)	53.8 ( )
BMI — N (%)	74.78 (17.05)
Normal (BMI <25)	29 (39.7%)
Overweight (BMI ≥25 and <30)	30 (41.1%)
Obese (BMI ≥30)	14 (29.2%)
Smoking status — N (%)	
Current	4 (5.5%)
Former	29 (39.7%)
Never	40 (54.8%)
Annualised exacerbation rate — mean (95% CI)	3.65 (3.18; 4.18)

ACQ-5 score — mean (SD)	2.76 (1.26)
Proportion of patients with — N (%)	
Well controlled asthma (ACQ-5 ≤ 0.75)	3 (4.1%)
Partially controlled asthma (ACQ-5 > 0.75 and ≤ 1.5)	10 (13.7%)
Uncontrolled asthma (ACQ-5 > 1.5)	60 (82.2%)
Biomarkers (last available) — mean (min; max)	
Blood eosinophil count [cells/µL]	685 ([redacted])
Total IgE [IU/mL]	346.1 ([redacted])
FeNO [ppb]	53.1 ([redacted])
History of positive allergy test — N (%)	
Positive	35 (47.9%)
Negative	23 (31.5%)
Unknown	15 (20.5%)

Study outcome analysis according to the SAP were still in progress at the time of writing this CSR synopsis. However, two abstracts have been accepted and presented at national and international congresses in 2023, covering ACQ-5 outcomes according to primary and secondary objectives:[1,2]

Out of 73 patients, 66 completed the ACQ-5 at week 8. The mean change (95% CI) from baseline ACQ-5 score was 0.34 (0.58; 0.09) at week 1, 0.58 (0.86; 0.29) at week 2, 0.68 (0.99; 0.38) at week 4, 0.95 (1.25; 0.66) at week 8, 1.22 (1.58; 0.86) at week 16 and 1.58 (1.96; 1.21) at week 56 after treatment initiation ($p<0.01$ for all timepoints). At week 8, 39 patients (59.1%) achieved a score improvement of ≥0.5, which is the minimal clinical important difference (MCID) for ACQ-5. Moreover, 34 (51.5%) and 18 (27.3%) patients achieved an ACQ-5 score of ≤1.5 (baseline: 13 [17.8%]) and ≤0.75 (baseline: 3 [4.1%]), respectively.

Conclusion

Severe eosinophilic asthma patients reported significant and clinically meaningful differences in asthma control as early as 2 weeks after first dose of benralizumab treatment, complementing the data obtained from RCT in a non-randomised pragmatic real-world Swiss setting.

Publications and abstracts

1 Schuoler C, van Iperen P, Stolz D et al. Early Improvement in Asthma Control with Benralizumab in Patients with Severe, Eosinophilic Asthma. Presented at SSC/SSCS SSP/SSTS Joint Annual Meeting 2023, Basel, Switzerland, 21 – 23 June 2023

2 Schuoler C, van Iperen P, Stolz D et al. Early Response to Benralizumab in Severe, Eosinophilic Asthma: a Real-World Study in Switzerland. Presented at ERS International Congress 2023, Milan, Italy, 09 – 13 September 2023

Submitted abstracts currently under evaluation:

- Stolz D, Schuoler C, Charbonnier F et al. Asthma Exacerbation Rate Reduction with Benralizumab − Results from the Swiss Real-World BEEPS Study. Submitted to SSP/SSTS Joint Annual Meeting 2024, Baden, Switzerland, 29 – 31 May 2024

- Stolz D, Schuoler C, Charbonnier F et al. Oral corticosteroid reductions in severe eosinophilic asthma patients treated with benralizumab: a real-world study in Switzerland. Submitted to ERS International Congress 2024, Vienna, Switzerland, 07 – 11 September 2024