STUDY REPORT SYNOPSIS

Benralizumab Patient Access Programme Study: Retrospective, observational study in UK severe asthma centres to describe patient characteristics, treatment patterns and outcomes

Milestones:

Milestone	Planed date	Actual date
Protocol submission (BPAP I)	Q1 2019	Q2 2019
Ethics submission with supporting documents (BPAP I)	Q2 2019	Q2 2019
Centre recruitment contracting & set up (BPAP I)	Q3 2019	Q2 2019
eCRF, DMP, SAP (BPAP I)	Q1 2019	Q3 2019
Data extraction 1 (BPAP I)	Q3 2019	Q4 2019
Interim analysis 1 (BPAP I)	Q4 2019	Q4 2019
Data extraction 2 (BPAP I)	Q1 2020	Q1 2020
Final database lock (BPAP I)	Q2 2020	Q2 2020
Final data analysis (BPAP I)	Q2 2020	Q3 2020
Clinical study report 1(BPAP I)	Q2 2020	Q1 2021
Protocol amendment (BPAP II)	Q4 2020	Q2 2021
Ethics amendment submission to extend the follow up period (BPAP II)	Q1 2021	Q1 2021
Final database lock (BPAP II)	Q4 2021	Q3 2022
Final analysis (BPAP II)	Q4 2021	Q3 2023
Clinical study report – extension update (BPAP II)	Q1 2021	Q3 2023

Phase of development: N/A

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

BACKGROUND/RATIONALE:

Asthma is a heterogeneous disease usually characterised by chronic airway inflammation. It is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation (GINA 2018).

The American Thoracic Society and the European Respiratory Society define severe asthma as asthma that requires either of the following treatment protocols to prevent asthma from becoming uncontrolled, or asthma that remains uncontrolled despite use of these protocols (Chung et al. 2014; GINA 2018):

- treatment guideline–suggested medications for Global Initiative for Asthma (GINA) steps 4–5 (high-dose inhaled corticosteroids [ICS] and long-acting beta-agonist [LABA] or leukotriene modifier/theophylline) within the previous year, or
- systemic corticosteroids for greater than 50% of the previous year.

AstraZeneca was granted a European marketing authorisation in January 2018 for benralizumab (brand name: Fasenra) (European Medicines Agency 2018). Benralizumab is indicated as an add-on maintenance treatment in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose ICS plus LABA.

In England, benralizumab is recommended as an option for treating severe eosinophilic asthma that is inadequately controlled in adults despite maintenance therapy with high-dose ICS and LABA, only if:

- the blood eosinophil count has been recorded as 300 cells/µL or more and the person has had ≥4 exacerbations needing systemic corticosteroids in the previous 12 months, or has had continuous maintenance oral corticosteroids (mOCS) of at least the equivalent of prednisolone 5 mg per day over the previous 6 months (that is, are eligible for mepolizumab), or
- the blood eosinophil count has been recorded as 400 cells/µL or more with ≥3 exacerbations needing systemic corticosteroids in the past 12 months (that is, the person is eligible for reslizumab), and
- the patient has agreed to and followed the optimised standard treatment plan.

Benralizumab has been reimbursed in England and Wales from July 2019 and in Scotland from December 2019. As of September 2020, over 2,000 patients were receiving benralizumab for treatment of their severe eosinophilic asthma in England and Wales.

The patients treated through the Benralizumab Patient Access Programme (BPAP) and in the first year after reimbursement provide valuable data for early benralizumab utilisation and associated clinical outcomes.

Despite the demonstration of benralizumab's efficacy in severe eosinophilic asthma patients in clinical trials, it is imperative to generate real-world evidence to understand and describe 12-month benralizumab clinical outcomes, treatment patterns and in-depth description of the patients treated with benralizumab in severe asthma centres. Early utilisation and outcome data have provided clinicians and payers with evidence of benralizumab use and associated clinical outcomes outside a clinical trial setting. Real-world clinical outcomes following 1 year of treatment with benralizumab in the UK have been previously described in the BPAP study.

Longer-term data on utilisation and clinical outcomes in real-world settings are also important to demonstrate the impact of benralizumab on patients' asthma outcomes. Currently, long-term clinical outcomes and utilisation are unknown.

Hence, this study represents an amendment of the original BPAP study to generate longer-term insights into patients' treatment experience and associated outcomes in patients prescribed benralizumab under the BPAP and post reimbursement. The study also explored treatment persistence and adherence levels over the observation period. There are two components: increased follow-up from 12 months to 24 months and an increased number of study participants from 200 to 300. An additional 100 patients were planned to be recruited from up to five new centres, which was dependent on the number of eligible patients. The rationale for recruiting additional centres was to increase geographic and centre diversity to better understand clinical practices and clinical outcomes.

The overall goal of this study is to provide key, real-world evidence to support benralizumab in the UK, specifically to:

- describe the severe eosinophilic asthma patient population initiating benralizumab therapy
- describe treatment patterns and treatment duration in patients initiated on benralizumab
- assess clinical outcomes (e.g. reduction in exacerbations, changes in lung function) and changes in background OCS therapy use
- describe patient-reported outcomes by way of routinely used validated questionnaires
- describe adherence and persistence to benralizumab therapy and describe reasons for discontinuation

Since the continued use of benralizumab in patients with severe eosinophilic asthma after 12 months is dependent on demonstrating evidence of clinically meaningful reduction of either asthma exacerbations or OCS use, there is a continued need for observational studies to describe clinical outcomes associated with benralizumab beyond a 12-month period. In addition to providing evidence on the clinical effect of benralizumab use in severe eosinophilic asthma, there is a need to understand the patient population initiating, and continuing on, benralizumab therapy in the UK to assess both current and future needs and understand the long-term effect of benralizumab.

This was a descriptive, single-arm study and no *a priori* hypotheses were tested**.**

OBJECTIVES

The primary objectives of the study were:

- To describe baseline demographic and clinical characteristics of patients with severe eosinophilic asthma enrolled in the BPAP
- To describe background treatment patterns of patients with severe eosinophilic asthma at baseline and after benralizumab initiation

The secondary objectives of the study were:

- To describe clinical outcomes after initiation of benralizumab therapy in patients with severe eosinophilic asthma treated with benralizumab at 12 and 24 months.
- To describe patients' adherence to benralizumab, persistence and discontinuation rates and reasons for discontinuation at 12 and 24 months

Exploratory objectives of the study were:

- To describe clinical outcomes among a subset of patients switching from any approved severe asthma biologic to benralizumab at 12 and 24 months
- To identify responders/non-responders to benralizumab at 12 and 24 months and describe their characteristics
- To describe and characterise patients experiencing early improvement in clinical outcomes and asthma control (at 4, 8 and 16 weeks after initiation of benralizumab)
- To explore whether early response to therapy at 4 -16 weeks predicts long-term response in key clinical outcomes

In addition, *post-hoc* analyses were conducted independent from the initial study protocol:

- Analyses to describe the rates of response to benralizumab (responders, super responders, non-responders and patients achieving remission)
- Post-hoc analyses to explore the association between baseline clinical characteristics and clinical remission status

- Subgroup analyses in specific outcomes:
    - outcomes (including exacerbations, OCS use) for patients who discontinued benralizumab due to lack of efficacy at point of discontinuation
    - change in the patient-reported asthma score among patients stratified by baseline FeNO count of <50 ppm and ≥50 ppm
    - outcomes in patients previously treated with mepolizumab
- Description of baseline antineutrophil cytoplasmic antibodies test results.

STUDY DESIGN

This study was conducted as a retrospective medical record review at eight National Health Service (NHS) asthma centres. The eight NHS trusts were selected based on their participation in the BPAP and had trust-level agreement from their local Research and Development department prior to participation in the study. There was no change to the management of patients for the purposes of any part of this study.

Data collection and analysis were performed on patients who had enrolled in the AstraZeneca BPAP.

Data were collected retrospectively, with a focus on obtaining data at the following timepoints:

- baseline (12-month period prior to benralizumab first dose)
- index date (day of first benralizumab dose)
- follow-up period (time after first dose of benralizumab)
    - data collected up to 24 months after first benralizumab dose
    - clinical outcome assessment at 16, 24 and 48 and 100 weeks after benralizumab initiation.

DATA SOURCE

The study involved retrospective review of participant medical records and no personally identifiable data were collected.

Data collectors extracted anonymised-coded data from the paper and/or electronic medical records of patients included in the study. Data were recorded in an electronic case report form (eCRF) and securely transmitted to the third-party vendor for analysis. Data from all participating centres were combined into a single dataset for analysis.

STUDY POPULATION

This study included a total of 276 patients with severe eosinophilic asthma.

Inclusion criteria: Patients who met the following criteria were considered for participation in the study:

- patients enrolled in the BPAP between April 2018 and May 2019
- Patients initiated on benralizumab outside of the BPAP by October 30, 2019.
- patients who had at least one benralizumab injection and with at least 3 months of follow-up data from the time of enrolment into the BPAP
- where data collection was conducted by a third-party vendor, patients must have been able and willing to give informed consent to participate in the study[1].

Exclusion criteria:

- currently receiving benralizumab or any other biologic drug for the treatment of asthma in a clinical trial
- refused or unable to provide informed consent where the third-party vendor was designated to collect the data.

STATISTICAL METHODS

All analyses were descriptive in nature. The distributions of continuous variables were examined using histograms or tests as appropriate. Variables were summarised by providing the measure of central tendency — mean and median, as well as associated measures of variability — standard deviation (SD), interquartile range (IQR; Q1 and Q3) and range (minimum and maximum). For healthcare resource utilisation (HRU), the mean (SD) for the total population is reported. Least-square means, nominal p-values and 95% confidence interval (CI) were included as appropriate. CI was calculated using the Clopper-Pearson method. Categorical variables were summarised by providing frequencies and proportions.

[1] None of the data collection was performed by a third-party vendor (all conducted by members of the direct care team). Hence, consent was not a requirement, although three sites obtained consent for their patients.

Statistical analyses were carried out using Stata (StataCorp LLC), R statistical software (R Foundation for Statistical Computing) and Microsoft Excel.

KEY RESULTS

Baseline demographics and clinical characteristics

A total of 276 patients met the eligibility criteria and were included in the study.

The mean (SD) age of all patient at asthma onset and at start of benralizumab treatment was 31.4 (18.5) and 50.9 (14.3) years, respectively. A total of 75% (104/138; missing = 138) of patients had adult (≥ 18 years) onset asthma. A total of 62% (171/276) of patients were female, 53% (138/258) were obese and 67% (160/240) were reported as non-smokers. A total of 81% (222/273) of patients had a baseline peak eosinophil count of ≥300 cells/µL, with a median (IQR) baseline peak eosinophil count of 500 (300–800) cells/µL.

During the baseline period patients had an annual exacerbation rate of 5.3 (95% CI 4.8–5.7) exacerbations. The mean (SD) FeNO count in the overall study population (N=276) was 78.8 (61.8) ppb. A total of 63% (174/276) of patients were receiving mOCS at baseline (dosage ≥5 mg/day), and among such patients the range of mOCS daily dosage was [redacted] mg/day; 24% (66/276) of the whole study cohort received a daily dose of >10 mg/day. The median daily mOCS dose was 10 (5–20) mg/day.

A total of 41% of patients in the total study cohort (n=113) received one (88% [n=99]) or more (12% [n=14]) biologic treatment(s) in the 1 year prior to benralizumab initiation (biologic-experienced patients). Mepolizumab was the most commonly prescribed biologic (n=86), followed by reslizumab (n=17) and omalizumab (n=13). The mean (SD) duration of treatment with mepolizumab, reslizumab and omalizumab was 210.5 (95.0), 166.4 (108.3) and 198.5 (107.5) days, respectively.

Clinical outcomes

At 12 and 24 months' post-benralizumab initiation, 86.2% (95% CI: 81.6.%–89.8%) and 75.7% (95% CI 70.2.%–80.4%) of patients, respectively, remained on benralizumab. Results reported here are for the whole study sample (regardless of treatment persistence) unless otherwise specified.

After 48 weeks the annual exacerbation rate (95% CI) was 1.2 (1.0–1.5), and after 100 weeks it was 1.4 (1.2–1.6). At the 48-week and 100-week follow-up timepoint (following benralizumab treatment), 46% (127/275) and 28% (77/273) of patients were exacerbation-free since index, respectively.

The annual rate of exacerbation (95% CI) leading to an A&E visit was 1.2 (0.9–1.5) at baseline, and the annualised rate of exacerbation leading to an A&E visit (95% CI) was 0.4 (0.3–0.5) and 0.3 (0.2–0.3) at 48 and 100 weeks' post-benralizumab initiation, respectively.

The proportion of patients on mOCS for asthma (dose of ≥5 mg/day) decreased from 63% (174/276) during baseline to 37% (102/273) at 48 weeks and 34% (92/271) at 100 weeks. In the 174 patients receiving mOCS for asthma at baseline, 52% (89/172) were receiving mOCS at 48 weeks and 47% (80/170) at 100 weeks' post-benralizumab initiation.

A total of 17% (n=44/257) of patients included in the study reported at baseline an ACQ score of <1.5 (indicating their asthma was partially controlled or well controlled); the proportion of patients reporting the same score (<1.5) was 36% (n=70/195) and 51% (80/156) at 48 and 100 weeks' post-benralizumab initiation, respectively. Over half of the patients showed an improvement of ≥0.5 units from baseline (the minimum clinically important difference); 60% (114/190) at 48 weeks and 70% (105/150) at 100 weeks.

From a baseline mean (SD) FeNO count of 78.8 (61.8, n=203), the mean (SD) FeNO count at the 48- and 100-week follow-up timepoints was 54.9 (49.6, n=173) and 52.0 (50.3, n=45), respectively.

STUDY LIMITATIONS

Some study limitations should be considered. The interpretation of data collected retrospectively is dependent on the completeness and quality of the medical records and the reliability of the abstraction of data from the medical records. However, source data verification was employed to identify and correct abstraction errors. An appreciable proportion (59%) of patients were recruited from a single centre, however this was representative of the pattern of participation in the BPAP and a real-world reflection of patients' treatment patterns. This was primarily a descriptive study and no adjustments to control for confounding were carried out. Finally, the results from the study may be impacted by the COVID-19 pandemic, particularly at observation points that occurred during the pandemic (e.g. 100 weeks).

CONCLUSIONS

The baseline clinical characteristics are indicative of a group of patients with a high frequency of exacerbations who received high doses of mOCS with evidence of relatively high levels of eosinophilic airway inflammation, as reflected in the ≥400 cells/μL EOS count and FeNO count of ≥50 ppb); this was also reflected in a high burden on healthcare resource use. In

addition, 83% of patients included in the study reported that their asthma was not well-controlled at baseline.

Overall, the clinical outcomes for the extended follow-up of 2 years following the treatment of severe eosinophilic asthma with benralizumab suggest a sustained improvement in all clinical outcome measures, including reduced exacerbations, reduced mOCS use, improved asthma control (ACQ-6), and asthma-related quality of life [AQLQ]). The results of this study provide additional, longer term real-world evidence relating to benralizumab for the treatment of severe asthma and may support clinicians to make more informed, evidence-based treatment decisions.