Clinical Study Report Synopsis	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00065
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PONENTE: A Multicenter, Open-label, Phase 3b Efficacy and Safety Study of Benralizumab 30 mg Administered Subcutaneously to Reduce Oral Corticosteroid Use in Adult Patients with Severe Eosinophilic Asthma on High-Dose Inhaled Corticosteroid plus Long-acting β_2 Agonist and Chronic Oral Corticosteroid Therapy

Long-Term Follow-Up Substudy

Study dates (for Long-Term Follow-Up Substudy): First patient enrolled: 21 April 2021
Last patient last visit: 24 March 2022
The analyses presented in this report are based on a clinical data lock date of 06 May 2022.

Phase of development: Therapeutic confirmatory (IIIb)

International Co-ordinating Investigator: [redacted]

Sponsor's Responsible Medical Officer: [redacted]

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

Patients were enrolled at 63 sites in 15 countries (Argentina, Belgium, Brazil, Canada, Colombia, Denmark, France, Italy, Mexico, Poland, Spain, Sweden, Taiwan, United Kingdom, and the United States).

Publications

Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. Lancet Respir Med 2022; 10(1):47-58.

Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Adrenal function recovery after durable OCS-sparing with benralizumab in the PONENTE study. Eur Respir J 2022. doi: 10.1183/13993003.03226-2021.

Objectives and criteria for evaluation

Table S1 Objectives and Endpoints (Long-Term Follow-Up Substudy)

Objectives	Outcome Measures
Observational	
• To observe real-world clinical management of OCS dose 12 to 18 months after completion of the main PONENTE study	• Patients who achieve 100% reduction in daily OCS dose from Baseline[a] OCS dose to the end of the long-term follow-up substudy • Patients who achieve a daily OCS dose of ≤ 5 mg at the end of the long-term follow-up substudy • Patients who achieve ≥ 90%, ≥ 75%, ≥ 50%, or > 0% OCS reduction from Baseline[a] OCS dose to the end of the long-term follow-up substudy. • Change in daily OCS dose from Baseline[a] to the end of the long-term follow-up substudy
• To observe real-world clinical management of background maintenance asthma regimen	• Change in background asthma maintenance medication from Baseline[a, b] to the end of the long-term follow-up substudy
Safety	
• To observe shift in AI status in patients who had Complete AI or Partial AI at the end of the PONENTE study	• Shifts in AI status and further OCS dose changes from the main PONENTE study to the Long-Term Follow-Up Visit
• To observe asthma exacerbations in adult patients from the main PONENTE study to the Long-Term Follow-Up Visit	• Annualised asthma exacerbation rate • Percentage of patients without exacerbation
• To assess the safety and tolerability from the main PONENTE study to the Long-Term Follow-Up Visit	• Adverse events/Serious adverse events • Laboratory parameters and vital signs
• To evaluate corticosteroid toxicity from the main PONENTE study to the Long-Term Follow-Up Visit	• Glucocorticoid toxicity index

[a] The main PONENTE study Baseline.

[b] The table of objectives and outcomes in the CSP and substudy SAP erroneously stated change from EOT of the main study for this outcome. The intention was to assess change in background asthma maintenance medication from Baseline of the main study (as reflected in substudy SAP Section 3.1), and since patients were not permitted to change background medication during the main study, these timepoints should be equivalent.

AI Adrenal insufficiency; CSP Clinical Study Protocol; EOT End of Treatment; OCS Oral corticosteroid; SAP Statistical Analysis Plan.

Study design

PONENTE was an open-label and multicentre study which was designed to evaluate the efficacy and safety of benralizumab for maintaining asthma control during rapid oral

corticosteroid (OCS) tapering in approximately 600 adult patients with severe eosinophilic OCS-dependent asthma. In addition to standard enrolment and follow-up phases, the study consisted of 3 main treatment phases: the Induction Phase (Weeks 0 to 4), the OCS Reduction Phase (Week 4 to Start of Maintenance Phase), and the Maintenance Phase (approximately 24 to 32 weeks from the time the patient reached and maintained their lowest OCS dose without worsening of asthma control).

Patients who completed the PONENTE study End of Treatment (EOT) Visit were invited to participate in a long-term follow-up substudy that included a single additional visit that occurred approximately 12 to 18 months after completion of the main study. The current Clinical Study Report (CSR) Addendum presents the results of this long-term follow-up substudy. The substudy was designed to observe changes in the OCS dose and other background asthma therapy, to assess the amount of recovery from adrenal insufficiency (AI), and to assess glucocorticoid toxicity by means of the glucocorticoid toxicity index (GTI), after the Maintenance Phase and in a real-world setting.

Target subject population and sample size

The main PONENTE study included male and female patients ≥ 18 years of age who had OCS-dependent asthma with peripheral blood eosinophil count of ≥ 150 cells/μL at Visit 1 or a documented eosinophil count of ≥ 300 cells/μL in the past 12 months.

The substudy was not formally powered; all patients from the main study meeting all inclusion criteria and no exclusion criteria of the substudy were eligible to enrol.

Investigational product and comparator: dosage, mode of administration and batch numbers

Patients were treated according to healthcare provider discretion during the substudy, and therefore, no investigational product (IP; ie, benralizumab) was provided by the sponsor. Between the EOT Visit of the main PONENTE study and the Long-Term Follow-Up Visit, any changes in the maintenance asthma regimen were allowed. Benralizumab and other biologic usage as prescribed in clinical practice, including start and stop dates, were reported by patients as concomitant medications.

Duration of treatment

As noted above, there was no sponsor-provided IP in this substudy. Duration of biologic and benralizumab treatment during the substudy were calculated based on the start and stop dates reported by the patients. The Long-Term Follow-Up Visit occurred approximately 12 to 18 months after completion of the main PONENTE study.

Statistical methods

The substudy database lock (DBL) was performed after the final patient of the substudy completed the PONENTE Long-Term Follow-Up Visit.

Within this CSR Addendum, "Baseline" always refers to Baseline of the main PONENTE study.

Changes in OCS dose from Baseline of the main study to the end of the OCS Reduction Phase, to the end of the Maintenance Phase (ie, EOT Visit), and to the Long-Term Follow-Up Visit were summarised using descriptive statistics in tables. Percentages of patients achieving 100% reduction in OCS daily dose, a ≤ 5 mg daily dose, and other pre-specified percentage reductions in OCS daily dose were also reported with nominal 95% confidence intervals (CIs) derived using the exact Clopper-Pearson method at these timepoints.

Change in inhaled corticosteroid (ICS) dose from Baseline of the main study to the Long-Term Follow-Up Visit was summarised. Percentages of patients achieving ICS category reductions (Supra High Dose to High Dose, Supra High Dose to Medium Dose, Supra High Dose to Low Dose, High Dose to Medium Dose, High Dose to Low Dose, or Medium Dose to Low Dose) or discontinuation of any other controller medication (specifically long-acting β2 agonists [LABAs], long-acting muscarinic antagonists [LAMAs], leukotriene receptor antagonists [LTRAs], and xanthine) were reported with nominal 95% CIs derived using the exact Clopper-Pearson method. Similar increases in ICS dose categories and in use of additional controller medications were also reported. A shift table presented changes in ICS categories from Baseline to the Long-Term Follow-Up Visit.

Safety analyses used all available data, including data from unscheduled visits and repeated measurements. Change from Baseline at the Long-Term Follow-Up Visit was calculated for relevant measurements, including laboratory data and vital signs.

Adverse events (AEs) were summarised by means of descriptive statistics and qualitative summaries. Adverse events were summarised for the Substudy On-Study Period, defined as from the date of informed consent for the substudy to the last available visit or contact for a patient. Any AEs occurring after the main study EOT Visit but prior to date of substudy informed consent were recorded as medical history.

The results of all morning cortisol, additional cortisol, repeat cortisol, and adrenocorticotropic hormone (ACTH) stimulation tests were tabulated. In order for pathways through the AI testing schematic from the initial morning cortisol test to the Long-Term Follow-Up Visit to be evaluated, patients' AI status (Normal, Partial AI, or Complete AI) at each stage was also tabulated. Shift in patients' AI status from initial morning cortisol test to the Long-Term Follow-Up Visit, from the end of the OCS Reduction Phase to the Long-Term Follow-Up Visit, and from the end of the Maintenance Phase (EOT Visit) to the Long-Term Follow-Up

Visit were summarised. A logistic regression model was developed to identify factors potentially predictive of long-term AI.

The number of asthma exacerbations, number of patients with at least 1 exacerbation, number of patients with exactly 0, 1, 2, or > 2 exacerbations, number of exacerbations per patient, number of exacerbations requiring hospitalisation, number of exacerbations requiring emergency room (ER) visits, number of exacerbations requiring OCS use, and number of exacerbations requiring systemic corticosteroid use were summarised. The annualised rate of asthma exacerbations during the substudy, and in corresponding patients from the main study, were summarized for the periods of Baseline to the end of the OCS Reduction Phase, Baseline to the end of the Maintenance Phase (EOT Visit), and Baseline to the Long-Term Follow-Up Visit, using mean, 95% CI, and dispersion based on the negative binomial distribution, adjusting for study period (main study or substudy).

A subset of 8 items from the composite GTI were assessed in PONENTE: body mass index, glucose tolerance (glycosylated haemoglobin), blood pressure, low-density lipoprotein, steroid myopathy, skin toxicity, neuropsychiatric toxicity, and infection. Glucocorticoid toxicity index and each of these 8 items were summarised over time from the start of the main study to the end of the substudy, including Baseline of the main study, the initial morning cortisol test during the OCS Reduction Phase, the end of the Maintenance Phase (EOT Visit), and the Long-Term Follow-Up Visit. Statistical correlation between GTI and change in cumulative OCS dose at the Long-Term Follow-Up Visit were analysed graphically.

Study population

- The majority of patients in the Biologic analysis set (ie, those with ≥ 50% exposure to any biologic) were also in the Benralizumab analysis set (ie, those with ≥ 50% exposure to benralizumab). Totals of 195, 78, and 69 patients were included in the Long-Term Follow-Up, Biologic, and Benralizumab analysis sets, respectively.
- The demographic and baseline characteristics of the substudy population were similar to those of the main study population.
- Any AE or reported medical history event that occurred after the main study EOT Visit but prior to the date of substudy informed consent was recorded as medical history. The most common medical history conditions reported in the Long-Term Follow-Up analysis set were asthma (16.9% of patients), rhinitis allergic (2.6%), and gastrooesophageal reflux disease (2.1%).

Summary of efficacy results

The observational outcomes of the substudy support the following conclusions regarding real-world clinical management of OCS dose and background maintenance asthma medication

approximately 12 to 18 months after completion of the EOT Visit in the main PONENTE study:

- Reductions from baseline in daily OCS dose at the end of the Maintenance Phase (EOT Visit) of the main study were generally maintained at the Long-Term Follow-Up Visit.
  - In the Long-Term Follow-Up analysis set:
    - Most patients (89.7%) reduced their daily OCS dose by some amount (> 0% reduction) at the Long-Term Follow-Up Visit, which was similar to the proportion of patients with > 0% reduction at the end of the Maintenance Phase (91.3%).
    - 88.2% of patients achieved ≥ 50% reduction in daily OCS dose at the Long-Term Follow-Up Visit, which was similar to the proportion of patients with 50% reduction at the end of the Maintenance Phase (89.2%).
    - 70.8% of patients achieved 100% reduction in daily OCS dose at the Long-Term Follow-Up Visit, which was similar to the proportion of patients with 100% reduction at the end of the Maintenance Phase (66.7%).
    - 90.8% of patients achieved a daily OCS dose of ≤ 5 mg at the Long-Term Follow-Up Visit, which was similar to the proportion of patients who achieved a daily OCS dose of ≤ 5 mg at the end of the Maintenance Phase (94.9%).
    - The mean (standard deviation [SD]) daily OCS dose was 1.96 (4.248) mg at the Long-Term Follow-Up Visit, which was a mean (SD) change from Baseline of -10.01 (8.859) mg and of comparable magnitude to the change from Baseline observed at the end of the Maintenance Phase (-10.19 [8.274] mg).
  - Similar patterns of results for reductions in daily OCS dose were observed in the Benralizumab analysis set and the Biologic analysis set, ie, among patients in the Long-Term Follow-Up analysis set with ≥50% exposure to benralizumab or to any biologic treatment for asthma, respectively, from the end of the Maintenance Phase of the main study to the Long-Term Follow-Up Visit.
- Little change in background asthma maintenance medication was observed from Baseline to the end of the long-term follow-up substudy.
  - In each analysis set, the median change from Baseline in ICS dose at the Long-Term Follow-Up Visit was 0.00 µg.
  - Few changes in ICS dose category or discontinuations or increases in the use of any additional controller medication (LABA, LAMA, LTRA, or xanthine) were observed in any analysis set.

Summary of safety results

The safety outcomes of the substudy support the following conclusions:

- In the Long-Term Follow-Up analysis set, the mean (SD) durations of exposure to any biologic and to benralizumab were 196.8 (229.84) days and 179.6 (229.30) days, respectively, which corresponded to mean (SD) exposures of 39.3% (44.95%) and 35.7% (44.67%), respectively, of the time between the EOT Visit of the main study and the Long-Term Follow-Up Visit.
- A total of 2 AEs (both were coronavirus disease 2019 [COVID-19]) were reported during the Substudy On-Study Period; neither was serious.
  - Any AE or reported medical history event that occurred after the main study EOT Visit but prior to the date of substudy informed consent was recorded as medical history and not as an AE, which accounts for the low number of reported AEs. No safety concerns were noted among the reported medical history conditions.
- No clinically meaningful changes were observed for haematology, clinical chemistry, or vital signs.
- Among patients in the Long-Term Follow-Up analysis set, the final AI status in the AI pathway was normal for 106 patients (54.4%), Partial AI for 31 patients (15.9%), and Complete AI for 38 patients (19.5%).
  - For the subset of patients in the Long-Term Follow-Up analysis set who underwent the relevant morning cortisol testing, shifts from Partial AI or Complete AI to normal adrenal function were observed for 4 patients and 3 patients, respectively (40.0% and 15.8% of those with Partial AI or Complete AI, respectively, at the last assessment of the main PONENTE study).
  - Logistic regression did not identify reliable predictors of long-term AI status.
  - Due to the low number of patients who underwent morning cortisol testing at the Long-Term Follow-Up Visit, conclusions regarding changes in adrenal function between the last assessment of the main study and the Long-Term Follow-Up Visit should be made with caution.
- Most patients (65.1%) in the Long-Term Follow-Up analysis set did not report any asthma exacerbations after the main study EOT. The annualised exacerbation rate from Baseline to the Long-Term Follow-Up Visit was 0.23, which was lower than the annualised rates from Baseline to the end of the OCS Reduction Phase (0.53) and from Baseline to the last assessment of the main PONENTE study (0.45). Similar patterns were observed in the Benralizumab and Biologic analysis sets.
- Based on an evaluation of 8 domains of the GTI, little overall change in glucocorticoid toxicity was observed between the initial morning cortisol test, the end of the Maintenance Phase (EOT Visit), and the Long-Term Follow-Up Visit in any analysis set.

Conclusions

- Following 12 to 18 months of real-world clinical management of OCS dose after completion of the main PONENTE study, reductions in OCS use achieved in the main study were maintained through the long-term follow-up substudy.
- Little change in background asthma maintenance medication was observed from Baseline to the end of the substudy.
- There was no clear evidence that patients who had AI following OCS dose reduction consistently improved to normal AI status, nor that they continued to have worsening AI, during the substudy. Reliable predictors of long-term AI status were not identified. However, interpretation is limited by the low number of patients in the substudy who underwent the relevant cortisol testing.
- The rate of asthma exacerbations in the substudy was low.
- No unexpected safety findings were observed during the substudy.
- There were no meaningful changes from the initial morning cortisol test of the main study to the end of the substudy in corticosteroid toxicity based on an evaluation of 8 domains of the GTI; however, interpretation is limited by the length of the study and substudy.