Clinical Study Report Synopsis	
Drug Substance	Benralizumab (MEDI-563)
Study Code	D3250C00045
Edition Number	1.0 (Final CSR Synopsis)
Date	12 May 2020
EudraCT Number	2017-001040-35
NCT Number	NCT03170271

A Multicenter, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase IIIb Study to Evaluate the Safety and Efficacy of Benralizumab 30 mg sc in Patients with Severe Asthma Uncontrolled on Standard of Care Treatment (ANDHI)

CLINICAL STUDY REPORT SYNOPSIS PRESENTING RESULTS OF THE DOUBLE-BLIND PERIOD OF THE ANDHI STUDY

Study dates:
First subject enrolled: 07 July 2017
Last subject last visit: 12 September 2019
The analyses presented in this synopsis are based on a database lock date of 07 October 2019.

Phase of development:
Therapeutic confirmatory (III)

International Co-ordinating Investigator:
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

This synopsis presents results of the double-blind period of the ANDHI study.

Study Center(s)

This study was performed at 221 centers in 14 countries in Europe and North America.

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Efficacy	To determine the effect of benralizumab on the rate of asthma exacerbations	The annualized rate of asthma exacerbations (treatment period 24 weeks)
Secondary	Efficacy	To determine the effect of benralizumab on patient-reported disease specific quality of life **(key secondary efficacy objective)**	The change from baseline (Visit 4) in SGRQ to the EOT (Day 168/Week 24)
Secondary	Efficacy	To determine the effect of benralizumab on lung function	The change from baseline (Visit 4) in FEV_1 over the treatment period (up to and including Day 168/Week 24)
Secondary	Efficacy	To determine the effect of benralizumab on patient-reported asthma control	The change from baseline (Visit 4) in ACQ-6 to the EOT (Day 168/Week 24)
Secondary	Efficacy	To determine the effect of benralizumab on time to first asthma exacerbation	Time to first asthma exacerbation (treatment period 24 weeks)
Secondary	Efficacy	To determine the effect of benralizumab on lung function at home	The change from run-in baseline morning PEF to the EOT (Day 168/Week 24)
Secondary	Efficacy	To determine the effect of benralizumab general quality of life and health status	The change from baseline (Visit 4) Social Functioning SF-36v2 to the EOT (Day 168/Week 24)
Secondary	Efficacy	To evaluate patient impression of overall asthma severity (PGI-S)	The change from baseline (Visit 4) in PGI-S to the EOT (Day 168/Week 24)

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	Efficacy	To evaluate patient impression of change in the overall asthma status from baseline as reported by the patient (PGI-C) and clinician (CGI-C)	The degree of change reported by the patient (PGI-C) and clinician (CGI-C) expressed as a proportion of each of the 7 possible responses to the EOT (Day 168/Week 24)
Secondary	Efficacy	To determine the effect of benralizumab on the patient's predominant symptoms (PSIA)	The degree of change reported by the patient in their predominant symptom to the EOT (Day 168/Week 24). (Endpoint updated) [a]
Secondary	Efficacy	To determine the effect of benralizumab on disease specific health related quality of life in patients with doctor diagnosed chronic sinusitis with nasal polyposis	The change from baseline (Visit 3) in the SNOT-22 score to the EOT (Day 168/Week 24)
Secondary	Safety	To assess the safety and tolerability of benralizumab	Adverse events, laboratory variables, physical examination
Exploratory	Efficacy	To determine the effect of eosinophil depletion with benralizumab on: • Biomarker components of known asthma inflammatory pathways or airway remodeling (including periostin, DPP4, YKL-40 and MMPs)[b] • Biomarker surrogates of eosinophilic inflammation/activation (including, eosinophil granule proteins)[b]	The change from baseline (Visit 4) in circulating biomarkers to each pre-specified scheduled assessment during the treatment period[b]
Exploratory	Efficacy	To determine the effect of benralizumab on the patient's level of asthma control based on standard asthma guidance recommendations	The proportion of patients with well-controlled asthma based on composite diary measures, over time[c]

[a] Main analysis of PSIA data was changed due to error in ePRO device programming resulting in responses related to changes in patient asthma symptoms being excluded from the PSIA questionnaire.

[b] Results of the biomarker analyses will be reported separately from this clinical study report.

[c] The outcome measure documented in the CSP (the proportion of time that the patient's asthma is well controlled based on composite diary measures) was updated in the SAP to be the proportion of patients with well-controlled asthma based on composite measures, over time.

ACQ-6, Asthma Control Questionnaire 6; CGI-C, clinician global impression of change; CSP, clinical study protocol; DPP4, dipeptidyl peptidase-4; EOT, End of Treatment; FEV_1, forced expiratory volume in first second; MMP, matrix metalloproteinase; SGRQ, Saint George Respiratory Questionnaire; PEF, peak expiratory flow; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; PSIA, Predominant Symptom and Impairment Assessment; SAP, statistical analysis plan; SF-36v2, Short Form 36-item Health Survey, version 2; SNOT 22, Sino-Nasal Outcome Test Item 22; YKL-40, Tyrosine (Y), lysine (K), leucine (L)-40 (inflammatory glycoprotein).

Study Design

This was a Phase IIIb, randomized, double-blind, placebo-controlled, parallel group study designed to evaluate the efficacy and safety of repeat dosing of benralizumab 30 mg administered subcutaneously (sc) versus placebo on top of standard of care asthma therapy in patients with severe uncontrolled asthma.

On completion of the 24-week double-blind period of the ANDHI study, eligible patients had the option to enter a 56-week open-label ANDHI in-Practice (AiP) sub-study, in which concomitant asthma therapies were tapered as directed by the protocol in those patients who achieved and maintained asthma control. The results of the sub-study will be reported as an addendum to this clinical study report (CSR). Patients who did not enter the open-label AiP sub-study, completed the final safety assessment at follow-up (Visit 12); the follow-up visit could be waived for patients who enrolled in the AiP sub-study.

For the double-blind period of the study, patients with peripheral blood eosinophil counts ≥ 150 cells/μL were planned to be randomized in a 2:1 ratio, using an integrated voice recognition system/integrated web recognition system (IVRS/IWRS), to receive benralizumab 30 mg sc or matched placebo for 24 weeks.

All patients were to have had ≥ 2 asthma exacerbations while on maintenance inhaled corticosteroids (ICS) plus another asthma controller that required treatment with systemic corticosteroids (intramuscular, intravenous, or oral) in the 12 months prior to Visit 1. A target goal was to recruit a minimum of 40% of patients with ≥ 3 asthma exacerbations.

After enrollment at Visit 1, eligible patients entered an up to 42-day screening/run-in period. Patients who met eligibility criteria were randomized on Visit 4 (Day 0/Week 0) to receive either benralizumab or placebo at Visit 4, Visit 6 (Day 28/Week 4), Visit 7 (Day 56/Week 8), and Visit 9 (Day 112/Week 16), with the End of Treatment (EOT) Visit 11 at Day 168 (Week 24). The initial dose of benralizumab was followed by a single loading dose of benralizumab 30 mg sc or placebo at Visit 6 (Day 28/Week 4).

Target Subject Population and Sample Size

Male and female patients with severe uncontrolled asthma (described in study design section above) and peripheral blood eosinophil counts of ≥ 150 cells/μL (with major subgroups of 150 to 300 cells/μL plus clinical features and ≥ 300 cells/μL) were to be enrolled.

The total estimated number of patients to be randomized for the double-blind period was updated by protocol amendment from approximately 800 with 1:1 randomization ratio (benralizumab:placebo) to approximately 630 with a 2:1 randomization (benralizumab:placebo) to mitigate early challenges in recruiting sufficient numbers of appropriately severe eosinophilic asthma patients to the study. The change preserved the number of patients receiving active benralizumab treatment and reduced the number of patients exposed to placebo, while retaining statistical power to detect a treatment difference for both asthma exacerbation reduction and Saint George Respiratory Questionnaire (SGRQ) improvement. Previous benralizumab Phase III asthma exacerbation studies indicated that an annual placebo rate of 1.25, a 40% reduction in exacerbation rate for the benralizumab group, and a common negative binomial shape dispersion parameter of 1.2 may be expected. Results from previous studies also indicated that a greater than 4-point difference between treatment groups in the change from baseline SGRQ score may be expected, given improvements in related patient-reported outcomes (PROs) seen in the exacerbation studies as well as the results from mepolizumab pivotal studies. A difference of 5 points and a common standard deviation of 19 points was assumed. Under these assumptions, a 630-patient study randomized to benralizumab or placebo in a ratio of 2:1 (ie, 420 benralizumab-treated and 210 placebo-treated patients) has approximately 91% power with respect to the primary endpoint (assessed over a 24-week period) and 87% power with respect to the key secondary endpoint (assuming a 2-sided significance level in both cases).

Patients were randomized to benralizumab or placebo as described above, and according to the following stratification factors:

- Previous exacerbations (2 exacerbations in 12 months prior to Visit 1; ≥ 3 exacerbations in 12 months prior to Visit 1).
- Maintenance oral corticosteroids (OCS) use (use, nonuse).
- Region (North America/Rest of World).

Investigational Product and Comparator(S): Dosage, Mode of Administration and Batch Numbers

Benralizumab 30 mg/mL solution for sc injection in an accessorized pre-filled syringe, 1 mL fill volume CCI [redacted] matching placebo solution for sc injection in an accessorized pre-filled syringe, 1 mL fill volume CCI [redacted] manufactured by MedImmune.

Duration of Treatment

After enrollment, eligible patients entered a screening/run-in period (of up to 42 days). Patients who met eligibility criteria entered a 24-week treatment period and received 30 mg benralizumab or placebo on Day 0, Day 28 (± 3 days), Day 56 (± 3 days), and Day 112

(± 3 days). An EOT Visit was conducted at Day 168 (+ 7 days) and a follow-up visit was conducted at Day 182 (± 7 days).

The total planned treatment duration for each patient in the double-blind period was 24 weeks (defined as the time from randomization to the date of the EOT visit [Week 24]). The total planned study duration for the double-blind period, including the run-in and double-blind study periods, was a maximum of 32 weeks.

On completion of the 24-week double-blind period, eligible patients had the option to enroll in the 56-week open-label AiP sub-study. In these cases, the follow-up visit could have been waived.

Patients who transitioned into the open-label AiP sub-study prior to the follow-up Visit 12, received the first open-label dose of benralizumab at Visit 13 on Day 168 and completed the EOS Visit 27 at Week 80. As noted above, data from the AiP sub-study will be reported as an addendum to this CSR after the final patient has completed the AiP sub-study.

Statistical Methods

Analysis of the primary efficacy endpoint was performed for the Full analysis set, which included all patients who were randomized and received any IP, who were included irrespective of their protocol adherence, and continued participation in the study. Patients were analyzed according to their randomized treatment, irrespective of whether they had prematurely discontinued, according to the intention-to-treat principle.

Analyses of secondary efficacy endpoints were performed for the Full analysis set with the exception of the change from baseline in Sino-Nasal Outcome Test Item 22 (SNOT-22) total score and SNOT-22 responder status, which were analyzed for the Chronic rhinosinusitis with nasal polyposis sub-study analysis set. This analysis set included patients who had doctor diagnosed chronic rhinosinusitis and nasal polyposis in their medical history, who had signed the informed consent to participate in the sub-study, and who had received at least 1 dose of IP.

Analyses of safety endpoints were performed for the Safety analysis set, which included all patients randomized who had received any IP. Patients were classified according to the treatment they actually received.

<u>Primary Efficacy Endpoint Analysis</u>

The annualized rate of asthma exacerbations was analyzed by comparison of exacerbation rate on benralizumab with exacerbation rate on placebo using a negative binomial model with covariates of treatment group, region (North America/Rest of World), number of exacerbations in previous year (count, as a continuous variable), and maintenance OCS use at baseline (yes/no). If the number of exacerbations was missing, it was imputed as the

randomization stratification value. The estimated treatment effect (ie, the rate ratio of benralizumab versus placebo), corresponding 95% confidence interval (CI), and 2-sided p-value for the rate ratio were presented.

The analysis was repeated for the following:

- Modification of primary endpoint: Exacerbations associated with hospitalization and/or emergency room visit.
- Patients with screening blood eosinophil count ≥ 150 to < 300 cells/μL and ≥ 300 cells/μL.
- Patients with screening blood eosinophil count ≥ 150 to < 400 cells/μL and ≥ 400 cells/μL.
- Patients with screening blood eosinophil count ≥ 150 to < 500 cells/μL and ≥ 500 cells/μL.

As a sensitivity analysis, the primary analysis was repeated where the time at risk (included in the model as an offset variable) excluded any time during which a patient was having an exacerbation (plus 7 days during which time any further exacerbation was not considered as a separate event).

Key Secondary Efficacy Analysis

In consideration of multiplicity, a hierarchical testing strategy was used in which change from baseline in Saint George Respiratory Questionnaire (SGRQ) total score at the EOT visit was tested for statistical significance at the 2-sided 5% level only if the primary endpoint was statistically significant at the 2-sided 5% level. Change from baseline in SGRQ total score at the EOT visit was compared between the benralizumab group and placebo group using a restricted maximum likelihood based on a mixed-effect model for repeated measures (MMRM) analysis. Treatment group was fitted as the explanatory variable, with region (North America/Rest of World), number of exacerbations in previous year, maintenance OCS use at baseline (yes/no), visit, and treatment × visit interaction as fixed effects, and baseline SGRQ total score as a covariate. The variance-covariance matrix was assumed to be unstructured.

Change from baseline in SGRQ domain scores (symptoms, activity, and impacts) during the 24-week treatment period was analyzed using a similar MMRM model as described above.

The SGRQ total score responder status (improvement, ie, change from baseline in total score ≤ -4-points) at Weeks 4, 12, and EOT was analyzed using a logistic regression model with covariates of treatment, region (North America/Rest of World), number of exacerbations in previous year, maintenance OCS use at baseline (yes/no), and baseline SGRQ total score.

Other Secondary Efficacy Analyses

The same MMRM method as described for the key secondary efficacy analysis was used for the analysis of change from baseline in:

- Pre-bronchodilator (pre-BD) forced expiratory volume in first second (FEV_1).
- Asthma Control Questionnaire 6 (ACQ-6).
- Peak expiratory flow (PEF) assessment at home.
- Short Form 36-item Health Survey, version 2 (SF-36v2) subscale and component summary scores.
- Predominant Symptom and Impairment Assessment (PSIA) severity score for each of the patient's top 3 ranked symptoms and impairments, and the average severity score of each patient's top 3 ranked symptoms and impairments. This analysis was also repeated as a post hoc analysis where the average PSIA score was calculated if any of the top 3 ranked symptoms/impairments were available.
- The SNOT-22 total score and for the patient subgroup with baseline SNOT-22 total score of > 30.

Baseline values were included in the model, where applicable. The analysis of change from baseline in pre-BD FEV_1 also included age and gender in the model.

A logistic regression model, as described above, was used for the analysis of the following:

- SF-36v2 responder status based on subscale and component summary scores at EOT and responder threshold values.
- Asthma control responder status based on ACQ-6 at EOT.
- Patient improvement status (improvement, important improvement) based on patient global impression of severity (PGI-S) at EOT. Baseline PGI-S response was included in the model.
- Responder status (much improved and very much improved) clinician global impression of change (CGI-C) and patient global impression of change (PGI-C) at EOT.
- Improvement status at Week 20 based on PSIA for the top ranked symptom/impairment and for the combined response (based on the 3 top ranked symptoms/impairments only if all 3 were available) at Week 20.
- The SNOT-22 responder status based on SNOT-22 total score at EOT and for patients with SNOT-22 total score of > 30 at baseline.

Time to first asthma exacerbation was analyzed as a supportive efficacy variable to the primary objective to explore the extent that treatment with benralizumab delayed the time to first exacerbation compared to placebo. A Cox proportional hazard model was fitted to data with the same covariates as described for the primary endpoint analysis. The model included the Efron method for handling ties (TIES = EFRON), and the CIs for hazard ratios were

calculated using profile-likelihood confidence limits (RL = PL). Results were summarized as hazard ratios, 95% CI and p-values.

As part of the PSIA analysis, the number and proportion of patients recording an improvement in their top ranked symptom/impairment were summarized by treatment group at Week 20 and included the 95% CIs for the proportions of patients, calculated using the exact Clopper-Pearson formula. The analysis was repeated for the second and third top ranked symptoms/impairments, and for the combined response based on the 3 top ranked symptoms and impairments.

Safety Analyses

Safety variables were summarized descriptively.

Subject Population

- A total of 660 patients were randomized in the double-blind period of the study and 616 patients (93.3%) completed the study period.
- Demographic and key baseline disease characteristics were generally balanced across both benralizumab and placebo groups, and the study population was representative of the intended target population.
  - The majority of patients in the Full analysis set were White (85.9%), female (60.8%), and not Hispanic or Latino (86.9%). The mean age was 52.8 years PPD ; 46.2% of patients were ≥ 50 to < 65 years, 34.5% were < 50 years, and the remaining 19.4% were ≥ 65 years.
  - The mean number of exacerbations experienced by patients within the 12 months before study entry was 3.2. A total of 51.4% randomized patients had ≥ 3 asthma exacerbations in the last 12 months prior to Visit 1. Mean pre-BD percent-predicted normal FEV_1 was 54.7%. A higher proportion of placebo patients were in the adult onset age group (≥ 18 years at asthma diagnosis) compared to benralizumab patients (77.3% versus 70.9%, respectively).
- Patient-reported outcome assessments and diary data recorded at baseline were in line with those expected in a severe asthma population and were generally balanced between treatment groups. Overall, the mean SGRQ total score was 57.66 units, ACQ-6 total score was 3.05 units, total asthma symptom score was 2.23 units, and total rescue medication use (number of times used) was 2.38. Mean SNOT-22 total score (for patients included in the Chronic rhinosinusitis with nasal polyposis sub-study analysis set) was 50.2 units.
- Demographic and disease characteristics were generally balanced for randomized patients by screening eosinophil blood count categories ≥ 150 to < 300 cells/µL and ≥ 300 cells/µL with the exception of the following:
  - A higher proportion of all patients in the ≥ 150 to < 300 cells/µL category had ≥ 3 exacerbations in the previous 12 months compared to the ≥ 300 cells/µL category (56.2% versus 49.4%, respectively).

  - For benralizumab versus placebo comparisons:
    - In both eosinophil count categories, more placebo patients had an adult onset of their asthma (74.6% and 68.2%, respectively, in the ≥ 150 to < 300 cells/µL category, and 78.2% and 72.0%, respectively, in the ≥ 300 cells/µL category).
    - In the ≥ 150 to < 300 cells/µL category, more benralizumab patients compared to placebo patients had ≥ 3 exacerbations in the 12 months prior to enrollment (59.7% and 49.2%, respectively) and had used maintenance OCS at baseline (21.7% and 12.7%, respectively).
- Overall mean compliance was high (99.4%) and similar for both treatment groups (range 50%–100%).

Summary of Efficacy Results

The primary and key secondary endpoints (comparison of the annualized rate of asthma exacerbations over 24 weeks and change in SGRQ total score from baseline to EOT, respectively) were tested sequentially according to the hierarchical testing strategy, and both demonstrated statistically significant improvements for benralizumab compared to placebo ($p < 0.0001$ for both endpoints). The study met other secondary efficacy measures as evidenced by improvements in FEV_1, ACQ-6, and SNOT-22 (in those patients with a medical history of nasal polyps). Patient and clinician impression of change in disease status and predominant symptoms favored benralizumab. Benralizumab treatment effects were observed at the earliest time points assessed in most of the secondary endpoints, and were sustained throughout the treatment period.

All reported p-values stated below are nominal (ie, not adjusted for multiplicity) and only the primary and key secondary endpoint analyses were multiplicity protected in the testing procedure.

- Benralizumab treatment resulted in a statistically significantly lower (49%) annualized asthma exacerbation rate compared to placebo (rate ratio estimate: 0.51; 95% CI: 0.39, 0.65; $p < 0.0001$). Time to first asthma exacerbation was also delayed for benralizumab, as indicated by a lower risk of having an asthma exacerbation compared to placebo (hazard ratio: 0.52; 95% CI: 0.40, 0.67; $p < 0.0001$).
  - The rate of exacerbations associated with hospitalization and/or an emergency room visit for benralizumab-treated patients was reduced by 35% relative to placebo (rate ratio estimate: 0.65; 95% CI: 0.38, 1.11; $p = 0.1158$.
  - Improvements in the exacerbation rate relative to placebo were primarily driven by patients with higher levels of eosinophils at study entry (59% reduction; $p < 0.0001$, in patients with ≥ 300 cells/µL compared to a 15% reduction; $p = 0.5214$, in patients with ≥ 150 to < 300 cells/µL).
- Benralizumab provided significantly greater improvements in SGRQ total score from baseline at Week 24 compared to placebo (-8.11 units; 95% CI: -11.41, -4.82;

p < 0.0001). The magnitude of improvement over placebo was evident from Week 4, the first post-baseline assessment (-7.78 units; 95% CI: -10.59, -4.97; p < 0.0001).

  - The likelihood of achieving SGRQ responder status (improvement in SGRQ total score per minimal clinically important difference [≥ 4-point decrease from baseline]) was higher for benralizumab compared to placebo throughout the treatment period from Week 4 (odds ratio: 1.79; 95% CI: 1.23, 2.61; p = 0.0025) to Week 24 (odds ratio: 1.91; 95% CI: 1.30, 2.81; p = 0.0010) demonstrating an early and sustained response to treatment.

- Benralizumab improved pulmonary function as measured by change from baseline in pre-BD FEV_1 compared to placebo, from Week 4 (LS mean difference: 0.09 L; 95% CI: 0.03, 0.15; p = 0.0041) through Week 24 (LS mean difference: 0.16 L; 95% CI: 0.09, 0.23; p < 0.0001), and improved home morning and evening PEF from Week 1 through Week 24.
- Benralizumab demonstrated early and sustained improvements from baseline in patient-reported asthma control compared to placebo, as assessed by ACQ-6, from Week 2 (LS mean difference: -0.36 units; p < 0.0001) through Week 24 (LS mean difference: -0.46 units; p < 0.0001). This treatment effect was also seen for ACQ-6 responders (improvements from baseline of at least -0.5 units) at EOT (odds ratio: 1.53; p = 0.0193).
- Subgroup analyses of overall treatment effect showed that adult onset asthma, a medical history of nasal polyposis, and OCS dependence resulted in a numerically larger treatment effect than the population average in reducing annualized exacerbation rate, irrespective of eosinophil count category. Screening eosinophil counts ≥ 150 to < 300 cells/μL and early onset asthma (< 18 years) were generally associated with a reduced treatment effect, of which the latter was most pronounced in the ≥ 150 to < 300 cells/μL sub-population.
- Consistent with the improvements noted above, further evidence of treatment benefit of benralizumab compared to placebo was seen for the majority of other PRO assessments at EOT including SF-36v2, PGI-S responders, CGI-C and PGI-C, and PSIA.
- Improvement in symptoms and impairments related to nasal polyposis was observed for benralizumab relative to placebo using the symptom-based rhinosinusitis outcome measure (SNOT-22). The SNOT-22 sub-study included a subset of 153 patients with comorbid chronic rhinosinusitis with nasal polyposis at baseline and who had provided additional consent to participate:
  - Benralizumab resulted in clinically meaningful improvements in SNOT-22 total score from baseline from Week 4 (-7.47; 95% CI: -13.16, -1.77; p = 0.0105) to Week 24 (-8.91; 95% CI: -16.42, -1.40; p = 0.0204) compared to placebo, and a higher proportion of SNOT-22 responders at EOT, defined as improvements of at least 8.9 units (odds ratio: 2.99; 95% CI: 1.43, 6.24; p = 0.0036). An even greater treatment effect was seen when these analyses were repeated in patients with an elevated baseline SNOT-22 total score > 30 units.

Summary of Safety Results

For the double-blind period, the following safety conclusions were made based on all patients in the Safety analysis set:

- Benralizumab was well tolerated in patients with severe eosinophilic asthma whose disease remained uncontrolled despite standard of care therapy(ies).
- The mean (SD) duration of exposure was 109.0 (21.58) days (range 1 to 163 days) in the benralizumab group and 110.7 (18.60) days (range 1 to 163 days) in the placebo group.
- The incidence of adverse events (AEs) during the on-treatment period was similar in both treatment groups (63.5% in the benralizumab group and 62.4% in the placebo group). The most commonly reported AEs (frequency > 5%) were consistent with the known safety profile of benralizumab. Headache, sinusitis, pyrexia, and dyspnoea were more frequently reported in the benralizumab group compared to the placebo group (benralizumab versus placebo: 8.7% versus 3.1%; 6.6% versus 5.2%; 6.1% versus 2.2%; and 5.7% versus 1.6%). Conversely, nasopharyngitis, bronchitis, and asthma (exacerbations meeting criteria for AE reporting) were more frequently reported in the placebo group (placebo versus benralizumab: 7.4% versus 7.0%; 7.9% versus 5.2%; and 6.1% versus 4.9%).
- The majority of AEs were assessed as not related to investigational product (IP) by the investigator. A numerical imbalance was noted for these AEs with a higher incidence reported in the benralizumab group (16.9%) compared to the placebo group (8.7%). However, the overall imbalance was not driven by any individual preferred terms. Headache and pyrexia were more frequently reported in the benralizumab group (each reported for 4.0% of patients) compared to the placebo group (1.7% and 0.9%, respectively).
- No AEs with an outcome of death were reported during the double-blind period.
- A numerical imbalance was noted in the incidence of serious AEs (SAEs) with a higher proportion of patients in the placebo group reporting these events than the benralizumab group (10.9% and 5.4%, respectively). However, the overall imbalance was not driven by any individual preferred terms. Four patients (0.9%) in the benralizumab group reported SAEs assessed as related to IP by the investigator (cytokine release syndrome, mydriasis, pneumonia, and urticaria). No IP related SAEs were reported in the placebo group.
- Asthma (exacerbation) and pneumonia were the most commonly reported SAEs in both the benralizumab and placebo groups, both reported at a higher incidence in the placebo group compared to the benralizumab group (2.1% versus 3.9% and 0.5% versus 0.9%, respectively). Respiratory failure (reported for 0.9% in the placebo group) was the only other SAE reported for > 1 patient in either group.
- The incidence of AEs leading to IP discontinuation was low overall with a slightly higher proportion of patients reported in the benralizumab group than the placebo group (1.4% and 0.9%, respectively). No apparent trend or pattern was noted in the incidence of these AEs. All events by PT were reported for 1 patient in either group. Four AEs, all reported in the benralizumab group, were assessed by the investigator as related to IP: cytokine release syndrome, urticaria (both SAEs, stated above), drug eruption, and eczema.

- Other AEs of potential interest:
  - The incidence of injection site reactions was low and similar in both treatment groups (0.9% and 1.3% of patients in the benralizumab and placebo groups, respectively) with the majority assessed as related to IP by the investigator. All injection site reactions were mild or moderate in intensity, non-serious, and were transient in nature.
  - The incidence of hypersensitivity AEs was similar in both treatment groups (6.8% and 6.1% of patients in the benralizumab and placebo groups, respectively). Hypersensitivity AEs assessed by the investigator as related to IP were reported in 1.2% and 0.9% of patients in the benralizumab and placebo groups, respectively. Three IP related hypersensitivity AEs reported in the benralizumab group led to IP discontinuation (urticaria [SAE], eczema, and drug eruption). No AEs of anaphylaxis were reported.
  - A total of 35.1% of patients in the benralizumab group and 41.5% of patients in the placebo group had AEs in the system organ class of Infections and infestations. The incidence of infections reported as SAEs was low for both groups (2.6% and 0.7% of patients in the placebo and benralizumab groups, respectively). Pneumonia was the most commonly reported serious infection in both groups (0.5% and 0.9% of patients in the benralizumab and placebo groups, respectively). No cases of helminth infections were reported.
  - The incidence of malignancy was low overall, with 2 skin cancers reported for benralizumab patients (1 event each of basal cell carcinoma and basosquamous carcinoma) and 1 skin cancer reported for the placebo group (malignant melanoma in situ).
- Other than a significant reduction in blood eosinophil levels, as expected based on the mechanism of action of benralizumab, there were no clinically meaningful trends in hematology or clinical chemistry parameters over time. No patients met the criteria for Hy's Law.
- There were no clinically meaningful trends in vital signs over time and no notable differences between treatment groups in vital sign parameters. None of the reported vital sign related AEs were assessed as related to IP by the investigator.

Conclusions

- The results of this study support and expand on the results of the Phase III pivotal exacerbation trials in asthma patients.
  - In severe uncontrolled asthma patients with screening blood eosinophil counts ≥ 150 cells/μL, benralizumab demonstrated a statistically significant and clinically meaningful reduction in annualized asthma exacerbation rate (49%) and disease-specific quality of life improvements. Additionally, benralizumab provided early and sustained improvements in lung function, asthma control, and patient perception of symptom severity.
  - The observed efficacy effects were more pronounced in the high blood eosinophil group (≥ 300◦cells/μL) and in patients with adult onset asthma.

- Benralizumab demonstrated an early and sustained clinically meaningful improvement in symptoms and impairments related to nasal polyposis compared to placebo in those patients with comorbid chronic rhinosinusitis with nasal polyposis at baseline, with a numerically larger treatment effect seen in patients with greater baseline impairment (baseline SNOT-22 > 30 units).
- Benralizumab was well tolerated with an overall safety profile consistent with that of previous benralizumab trials and the product label.