Clinical Study Report Synopsis	
Drug Substance	Benralizumab (MEDI-563)
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A Multicentre, Randomised, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to Medium to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma

Study dates: First subject enrolled: 07 Sep 2017
Last subject last visit: 30 Jan 2023
The analyses presented in this report are based on a clinical data lock date of 01 Mar 2023

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator: PPD
PPD

Sponsor's Responsible Medical Officer: PPD

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

Study centres

Patients were randomised at 79 centres in 3 countries (China, South Korea, and Philippines).

Publications

None at the time of writing this report.

Objectives and Criteria for Evaluation

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effect of benralizumab on asthma exacerbations in patients on medium- to high-dose ICS-LABA with uncontrolled asthma.	Annual asthma exacerbation rate, where an asthma exacerbation is defined by a worsening [a] of asthma requiring: • Use of systemic corticosteroids (or a temporary increase in a stable OCS background dose) for at least 3 days; a single depo-injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids • An ER/UC visit (defined as evaluation and treatment for < 24 hours in an emergency department or UC centre) due to asthma that required systemic corticosteroids for at least 3 days (as per above) • An inpatient hospitalisation due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24 hours)
Secondary	
To assess the effect of benralizumab on pulmonary function	Pre-bronchodilator FEV_1 [b]
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics (as per the ePRO)	• Asthma symptom score (total [b], daytime, and nighttime) • Rescue medication use • Home lung function (morning and evening PEF) • Nights with awakening due to asthma • ACQ-6
To assess the effect of benralizumab on other parameters associated with asthma exacerbations	Time to first asthma exacerbation and proportion of patients with ≥ 1 asthma exacerbation
To assess the effect of benralizumab on health-related quality of life	SGRQ
To assess the effect of benralizumab on ER/UC visits and hospitalisations due to asthma	Annual rate of asthma exacerbations that are associated with an ER/UC visit or a hospitalisation
To evaluate the effect of benralizumab on health care resource utilisation	Asthma specific resource utilisation

Table S1 Objectives and Endpoints

Objectives	Endpoints
To characterize the pharmacokinetics and immunogenicity of benralizumab	• Serum trough concentrations • Incidence of ADA and nAb, ADA titre
To assess the impact of benralizumab on blood eosinophil levels	Blood eosinophils
Safety	
To assess the safety and tolerability of benralizumab	• AE/SAE • Laboratory variables • ECG • Vital Signs

[a] For the purpose of the study, worsening of asthma was defined as new or increased symptoms and/or signs (examination or lung function) that could have been either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven). The ePRO device was programmed to alert both the patient and study centre when certain pre-specified worsening thresholds were crossed, including: decrease in morning peak flow ≥ 30% on at least 2 of 3 successive days compared with baseline (last 10 days of run-in), and/or a ≥50% increase in rescue medication or 1 new or additional nebulized β_2 agonist on at least 2 of 3 successive days compared with the average use for the previous week and/or nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or; an increase in total asthma symptom score (the sum of daytime [evening assessment] and nighttime [morning assessment]) of at least 2 units above the run-in average (last 10 days of run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days.

If an exacerbation event was not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator had to justify the decision for defining the event as an exacerbation. Events that were not supported by any objective assessment were deemed not to be a protocol-defined exacerbation.

[b] Key secondary efficacy endpoints.

ACQ-6 Asthma Control Questionnaire-6; ADA Anti-drug antibodies; AE Adverse event; ECG Electrocardiogram; ED Emergency department; ePRO Electronic Patient-Reported Outcomes; ER Emergency room; FEV_1 Forced expiratory volume in 1 second; ICS-LABA Inhaled corticosteroid plus long-acting β_2 agonist; nAb Neutralising antibodies; OCS Oral corticosteroid; PEF Peak expiratory flow; SAE Serious adverse event; SGRQ St. George's Respiratory Questionnaire; UC Urgent care.

Study Design

This was a randomised, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy and safety of a fixed 30 mg dose of benralizumab administered subcutaneously (SC) for patients with a history of asthma exacerbations and uncontrolled asthma receiving medium- to high-dose inhaled corticosteroid plus long-acting β_2 agonist (ICS-LABA) with or without oral corticosteroids (OCS) and additional asthma controllers. Approximately 666 patients were expected to be randomised in the study with at least 70% of patients to be from China. The randomisation was stratified by country (China [including mainland China and Taiwan], South Korea, or Philippines)/region, age group (adult or adolescent), and peripheral blood eosinophil count at Visit 1 (< 300 or ≥ 300/μL). Patients were stratified in about a 2:1 ratio by baseline blood eosinophil counts (≥ 300/μL and < 300/μL).

The strata closure process was as follows:

1 The eosinophil < 300/μL stratum was closed to the patients from the China when the total number of Chinese patients in the stratum reached approximately 166.
2 The eosinophil < 300/μL stratum was closed to the patients from all countries when the total number of patients in the eosinophil < 300/μL stratum reached approximately 222.
3 The whole study was closed for recruitment when the total number of patients in the eosinophil ≥ 300/μL stratum reached approximately 444, with at least 70% Chinese patients in the stratum.

All the patients were randomised in a 1:1 ratio to receive either placebo or benralizumab every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W).

After initial enrolment and confirmation of entry criteria, patients proceeded to the run-in period of a minimum 4 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Patients who met eligibility criteria were randomised to a 48-week treatment period. Patients were maintained on their currently prescribed medium- to high-dose ICS-LABA therapy and other asthma controllers, without change, from Visit 1 until the end of the study. A follow-up visit was conducted at Week 56.

Target Population and Sample Size

This study included female and male participants 12 to 75 years of age with a history of physician diagnosed asthma requiring treatment with medium- to high-dose inhaled corticosteroids (ICS) (> 250μg fluticasone propionate dry powder formulation equivalents total daily dose) and a long-acting β_2 agonist (LABA), for at least 6 months prior to Visit 1. Patients were required to have had at least 2 documented asthma exacerbations in the 12 months prior to the date of informed consent, during the treatment of medium- to high-dose ICS-LABA, that required use of a systemic corticosteroid or a temporary increase from the patient's usual maintenance dose of OCS. Patients were also required to have pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of < 80% predicted (< 90% predicted for patients aged 12 to 17 years) and Asthma Control Questionnaire-6 (ACQ-6) score ≥ 1.5 at Visit 2.

For the primary endpoint of annual asthma exacerbation rate, approximately 222 adult and adolescent patients with baseline blood eosinophil counts ≥ 300/μL per treatment arm (approximately 444 in total) needed to be randomised to achieve approximately 90% power of [redacted] Because a 2:1 ratio was used for patients with baseline blood eosinophil counts > 300/μL and < 300/μL, the study also

randomised approximately 111 patients/arm (approximately 222 patients total) with baseline blood eosinophil counts < 300/µL.

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

Patients confirmed to be eligible were randomised to either benralizumab 30 mg Q8W or placebo. Both benralizumab and placebo were provided in an accessorised pre-filled syringe.

CCI [redacted]

Duration of Treatment

This study consisted of a 48-week treatment period, with the last dose administered at Week 40.

Statistical Methods

Analyses of the primary and secondary efficacy endpoints included all data captured during the 48-week double-blind treatment period. This included data regardless of whether study treatment was prematurely discontinued or delayed, and/or irrespective of Clinical Study Protocol adherence, unless the patient withdrew consent/assent to study participation. Analyses of safety endpoints included all data captured during the on-study period, defined as the period from first dose of investigational product (IP) administration to the conclusion of the Follow-up Visit (Week 56), inclusive.

To account for multiplicity, a hierarchical testing strategy was applied to the 2-sided hypotheses testing for the primary (annual asthma exacerbation rate) and 2 key secondary endpoints (the change from baseline at Week 48 in pre-bronchodilator FEV_1 and total asthma symptom score) for patients with baseline blood eosinophil counts ≥ 300/µL.

Primary Efficacy Endpoint

The primary efficacy endpoint was the annual asthma exacerbation rate (annualised exacerbation rate). The primary analysis compared the annual asthma exacerbation rates of the benralizumab and placebo groups in patients with baseline blood eosinophil counts ≥ 300/µL.

The annual exacerbation rates were compared between the benralizumab and placebo groups using a negative binomial model. The response variable in the model was the number of asthma exacerbations experienced by a patient over the 48-week treatment period. The model included covariates of treatment group, region (China/Non-China), number of exacerbations in the year before the study, and the use of maintenance OCS (yes/no). The logarithm of the follow-up time (for the definition of follow-up time, see Section 3.2 of the Statistical Analysis

Plan; Appendix 16.1.9) was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.

The negative binomial model was used to perform the hypothesis testing. 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. In addition, the annual exacerbation rate (both crude and model-estimated rates) and the corresponding 95% CI (for model-estimated rates only) within each treatment group and the absolute difference between treatment groups with the corresponding 95% CI were presented.

Key Secondary Efficacy Endpoints

All secondary efficacy endpoints were analysed in patients with baseline blood eosinophil counts ≥ 300/μL and < 300/μL, with formal statistical analyses conducted in the baseline blood eosinophil count ≥ 300/μL group.

For the multiplicity protected key secondary endpoints (pre-bronchodilator FEV_1 and total asthma symptom score), additional formal statistical analyses were conducted in the baseline blood eosinophil count < 300/μL group and by further baseline eosinophil count categories.

Pre-bronchodilator FEV_1

Change from baseline in pre-bronchodilator FEV_1 at Week 48 in the baseline blood eosinophil count ≥ 300/μL group was a multiplicity-protected key secondary endpoint. Change from baseline in pre-bronchodilator FEV_1 at Week 48 in the baseline blood eosinophil count ≥ 300/μL group was compared between the benralizumab and placebo groups using mixed-effects model for repeated measures (MMRM) analysis on patients with a baseline pre-bronchodilator FEV_1 assessment and at least 1 post-baseline pre-bronchodilator FEV_1 assessment.

The dependent variable was the change from baseline in pre-bronchodilator FEV_1 at each post-baseline protocol-specified visit (up to and including the end-of-treatment visit). Treatment group was fitted as the explanatory variable, region (China/Non-China), the use of maintenance OCS (yes/no), visit, and treatment*visit interaction as fixed effects factors, and baseline pre-bronchodilator FEV_1 as a continuous covariate. The variance-covariance matrix was assumed to be "unstructured". If the model did not converge, then the "Toeplitz", "first-order autoregressive", "compound symmetric", "variance components" variance-covariance matrix was used sequentially instead.

Total Asthma Symptom Score

Change from baseline at Week 48 in total asthma symptom score in the baseline blood eosinophil count ≥ 300/μL group was a multiplicity protected key secondary endpoint. Asthma symptoms during nighttime and daytime were recorded by the patient each morning

and evening in the Asthma Daily Diary. Symptoms were recorded using a scale of 0-3, where 0 indicated no asthma symptoms. Asthma symptom daytime score (recorded in the evening), nighttime score (recorded in the morning of the next calendar day), and total score were calculated and presented separately. The total score was calculated by taking the sum of the daytime score recorded in the evening and the nighttime score recorded the following morning.

Change from baseline in total asthma symptom score (key secondary endpoint), as well as daytime score and nighttime score (other secondary endpoints), were each summarised and analysed using the same MMRM, as described for the change from baseline in pre-bronchodilator FEV_1 endpoint, separately for patients with baseline blood eosinophil count ≥ 300/μL and < 300/μL. Each bi-weekly period of the 48 weeks used for bi-weekly mean calculation replaced visit in the model specification as for pre-bronchodilator FEV_1.

Other Secondary Efficacy Endpoints

Proportion of Patients with ≥ 1 Asthma Exacerbation

The proportion of patients with ≥ 1 asthma exacerbation during the 48-week treatment period in the benralizumab group was compared with the proportion in the placebo group in patients with baseline blood eosinophil count ≥ 300/μL using a Cochran-Mantel-Haenszel test controlling for region (China/Non-China), number of exacerbations in the previous year (2, ≥3 exacerbations), and the use of maintenance OCS (yes/no). The number and percentage of patients with ≥ 1 asthma exacerbation were also summarised by treatment group.

Time to First Asthma Exacerbation

A Cox proportional hazard model was fitted to data for time to first asthma exacerbation with the covariates of treatment group, region (China/Non-China), number of exacerbations in the previous year, and the use of maintenance OCS (yes/no) for patients with baseline blood eosinophil count ≥ 300/μL.

Asthma Exacerbations Associated with Emergency Room/Urgent Care Visit or Hospitalisation

Annual rate of asthma exacerbations associated with an emergency room (ER)/urgent care (UC) visit or a hospitalisation were analysed using a similar negative binomial model as outlined for the primary efficacy endpoint. The time to first asthma exacerbation that was associated with an ER/UC visit or a hospitalisation was analysed similarly as the time to first asthma exacerbation using a Cox proportional hazard model.

Patient Reported Outcome Variables

Patient reported outcome variables included asthma symptoms (total, daytime, and nighttime), rescue medication use, nights with awakening due to asthma, home peak expiratory flow (PEF), ACQ-6, and St. George's Respiratory Questionnaire (SGRQ).

Safety Analysis Methods

Adverse events (AEs) were summarised by means of counts summaries separately for the on-study, on-treatment, and post-treatment periods. Adverse events, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of IP were summarised by System Organ Class and Preferred Term (PT) assigned to the event by Medical Dictionary for Regulatory Activities. All AEs were listed for each patient, regardless of treatment period. All summaries were presented by treatment group. Other safety data, including laboratory values, vital signs, and electrocardiogram (ECG), were also summarized descriptively for both treatment groups.

Analysis Sets

Full Analysis Set

All patients who were randomised and received any IP were included in the full analysis set (FAS), irrespective of their protocol adherence and continued participation in the study. Patients were analysed according to their randomised treatment, irrespective of whether or not they prematurely discontinued IP, according to the intent-to-treat (ITT) principle. Patients who withdrew consent (and assent when applicable) to participate in the study were included up to the date of their study termination.

All efficacy analyses were performed using an ITT approach based on the FAS. For consistency, demographic and baseline characteristics were presented using the FAS.

Safety Analysis Set

All patients who received any IP were included in the safety analysis set. Patients were classified according to the treatment they actually received. A patient who had on 1 or several occasions received active treatment was classified as active. All safety and anti-drug antibody (ADA) analyses were based on this analysis set.

Pharmacokinetic Analysis Set

All patients who received benralizumab and had at least 1 measurable serum pharmacokinetic (PK) observation post first dose from PK blood samples that were assumed not to be affected by factors such as protocol deviations were included in the PK analysis set. All PK summaries were based on this analysis set.

Study Population

In the Overall Study Population, of the 1300 patients enrolled, 695 were randomised. All randomised patients received study treatment: 348 patients received benralizumab 30 mg, and 347 patients received placebo. Of the 695 patients randomised, 643 patients (92.5%) completed study treatment, and 52 patients (7.5%) discontinued treatment. The proportions of patients who discontinued treatment were similar between groups. The most frequent reason

for discontinuation of study treatment overall was patient decision (5.2%). In the Overall Study Population, a total of 101 patients (14.5%) reported ≥ 1 important protocol deviation. The profile of important protocol deviations was similar between groups and was considered not to impact the interpretation of the study results. A total of 1 patient (0.3%) in the benralizumab group and 5 patients (1.4%) in the placebo group reported ≥ 1 important protocol deviation that was considered to be coronavirus disease 2019 (COVID-19) related. The number and type of COVID-19-related important protocol deviations did not raise any concerns about the overall conduct and quality of the study.

Of the 695 patients randomised, all were included in the safety analysis set and the FAS, and 345 patients in the benralizumab group were included in the PK analysis set. In the China Subpopulation, of the 536 patients randomised, all were included in the safety analysis set and the FAS, and 265 were included in the PK analysis set.

In the Overall Study Population, demographic characteristics were balanced between groups, and the study population was representative of the intended target population. All patients in the FAS were Asian, and no patients were Hispanic or Latino. The majority of patients in the FAS were female (61.6%). The mean age was 51.1 years PPD One patient (0.1%) was an adolescent (ie, ≥ 12 to < 18 years of age); this participant from the PPD was in the < 300/μL baseline blood eosinophil group and received benralizumab. The remaining patients were adults, of whom 100 (14.4%) were ≥ 65 to 75 years. There were no patients < 12 years or > 75 years enrolled in this study, in agreement with the inclusion criteria of the study. The mean weight was 64.666 kg PPD and the mean body mass index was 24.468 kg/m^2 PPD

The median baseline blood eosinophil count was 370.0 cells/μL. Patients were stratified at about a 2:1 ratio (baseline blood eosinophil counts ≥ 300/μL to < 300/μL), and the demographic and patient characteristics for all patients in the FAS with baseline blood eosinophil counts ≥ 300/μL and < 300/μL were generally similar to the demographic and patient characteristics of the FAS overall. The demographic and patient characteristics were similar between the Overall Study Population and China Subpopulation.

The profiles of baseline lung function, baseline respiratory disease characteristics, and concomitant medication use were similar between groups and reflective of the protocol-intended patient population having a history of asthma exacerbations and uncontrolled asthma, and the profile of baseline lung function and respiratory disease characteristics for all patients in the FAS with baseline blood eosinophil counts ≥ 300/μL and < 300/μL were generally similar to the profile of the FAS overall. The profile of baseline lung function and respiratory disease characteristics at study entry was similar between the Overall Study Population and China Subpopulation.

In the Overall Study Population, the percentage of patients on maintenance asthma medication at baseline was similar between groups. In the FAS, 695 patients (100%) were taking ICS, and 694 patients (99.9%) were taking LABA. A total of 398 patients (57.3%) were taking additional maintenance treatment in addition to ICS-LABA (ie, at least 1 of the following maintenance asthma medications: OCS, long-acting anti-muscarinics (LAMAs), leukotriene receptor antagonists (LTRA), Xanthine derivatives, LABA/LAMA) at baseline. A total of 692 patients (99.6%) were taking their ICS-LABA as a fixed-dose combination device, with 2 patients taking ICS and LABA in separate inhalers and 1 patient taking only ICS. A total of 67 patients (9.6%) were taking OCS. A total of 47 patients (6.8%) were taking LAMA, 347 patients (49.9%) were taking LTRA, and 78 patients (16.5%) were taking xanthine derivatives. The total daily dose of ICS and OCS taken at baseline were similar between groups. Maintenance asthma medication use for all patients in the FAS with baseline blood eosinophil counts ≥ 300/μL and < 300/μL was similar to maintenance asthma medication use in the FAS overall. The profile of maintenance asthma medication use at baseline was similar between the Overall Study Population and China Subpopulation.

Summary of Efficacy Results

Benralizumab 30 mg Q8W achieved statistical significance for the primary endpoint, annual asthma exacerbation rate, as well as the 2 key secondary endpoints, change from baseline in FEV_1 and change from baseline in total asthma symptom score. Benralizumab demonstrated a statistically significant and clinically meaningful reduction in annual asthma exacerbation rate over 48 weeks compared with placebo (rate ratio of 0.26 [ie, 74% reduction], 95% CI [0.19, 0.36]; $p < 0.0001$) in patients with baseline blood eosinophil counts ≥ 300/μL. Benralizumab demonstrated a clinically meaningful and statistically significantly greater improvement (ie, least squares [LS] mean change from baseline) compared with placebo at Week 48 in pre-bronchodilator FEV_1 (LS mean difference: 0.25 L, 95% CI [0.17, 0.34]; $p < 0.0001$) and a statistically significantly greater improvement compared with placebo at Week 48 in total asthma symptom score (LS mean difference: -0.25 units, 95% CI [-0.45, -0.05]; $p = 0.0126$) in patients with baseline blood eosinophil counts ≥ 300/μL. In the China Subpopulation, benralizumab demonstrated a similar magnitude of improvement over placebo for the primary and key secondary endpoints.

Consistent with the results for the primary efficacy endpoint, annual asthma exacerbation rate, a lower proportion of patients in the benralizumab group had ≥1 asthma exacerbation over 48 weeks compared with the placebo group (nominal $p <0.0001$), and the time to first asthma exacerbation was longer for the benralizumab group compared with the placebo group (nominal $p < 0.0001$). Although the annual rate of asthma exacerbations associated with an ER/UC visit or hospitalisation over 48 weeks was low in both groups, benralizumab demonstrated a reduction in the annual rate of asthma exacerbations associated with an ER/UC visit or hospitalisation over 48 weeks compared with placebo (nominal $p = 0.0222$).

Consistent with the results for the key secondary efficacy endpoint, pre-bronchodilator FEV_1, benralizumab demonstrated greater improvements in morning and evening PEF over 48 weeks compared with placebo (nominal p <0.0001 for both).

Consistent with the results for the key secondary efficacy endpoint, total asthma symptom score, benralizumab demonstrated a greater improvement compared with placebo in ACQ-6 at Week 4 (the first post-baseline time point for ACQ-6 assessment) that was maintained through Week 48 (nominal $p < 0.05$ for all visits). Benralizumab demonstrated a greater improvement (ie, LS mean change from baseline) at Week 48 compared with placebo in ACQ-6 score (LS mean difference: -0.43 units; nominal $p < 0.0001$), as well as a higher ACQ-6 responder rate in the benralizumab group compared with the placebo group (74.6% and 57.4%, respectively; odds ratio: 2.53; 95% CI [1.67, 3.83]; nominal $p < 0.0001$). The results in the China Subpopulation were consistent with those observed in the Overall Study Population.

Benralizumab also improved health-related quality of life in the Overall Study Population, with a greater improvement compared with placebo in SGRQ total score at Week 8 (the first post-baseline time point for SGRQ assessment) that was maintained through Week 48 (nominal $p < 0.05$ for all visits). Benralizumab demonstrated a greater improvement (ie, LS mean change from baseline) at Week 48 compared with placebo in SGRQ total score (LS mean difference: -9.19 units, 95% CI [-12.79, -5.60]; nominal $p < 0.0001$), as well as a higher SGRQ responder rate compared with placebo (73.3% and 58.6%, respectively; odds ratio: 2.24; 95% CI [1.49, 3.37]; nominal $p = 0.0001$). The results in the China Subpopulation were consistent with those observed in the Overall Study Population.

The benralizumab group generally had a lower or similar incidence of most asthma-related healthcare encounter types over the treatment period compared with the placebo group. Improvements in asthma-specific resource utilisation in the Overall Study Population were similar between the benralizumab and placebo groups.

Efficacy was observed across all baseline blood eosinophil count categories and baseline blood eosinophil cumulative count categories for benralizumab 30 mg Q8W. For annual asthma exacerbation rate and pre-bronchodilator FEV_1, a generally greater treatment effect was observed in patients with higher baseline blood eosinophil levels than in those with lower baseline blood eosinophil levels. For total asthma symptom score, the treatment effect of benralizumab was generally similar in patients across baseline blood eosinophil levels. There were also numerically greater treatment effects in ACQ-6 score and SGRQ total score in patients with baseline blood eosinophil counts $\geq 300/\mu L$ compared to patients with baseline blood eosinophil counts $< 300/\mu L$. The results in the China Subpopulation were consistent with those observed in the Overall Study Population.

An 81% rate reduction in annual asthma exacerbation rate compared with placebo was observed in patients with ≥3 prior exacerbations, and a 68% rate reduction was observed in

patients with 2 prior exacerbations. A greater treatment effect was also observed in patients with ≥ 3 exacerbations in the previous year for pre-bronchodilator FEV_1 and total asthma symptom score compared with patients with 2 exacerbations in the previous year.

A 77% rate reduction in annual asthma exacerbation rate compared with placebo was observed in patients receiving high-dose ICS at baseline, and a 51% rate reduction was observed in patients receiving medium-dose ICS at baseline. For pre-bronchodilator FEV_1 and total asthma symptom score, the treatment effect of benralizumab was generally similar in patients receiving high- or medium-dose ICS at baseline.

Summary of Pharmacokinetic Results

Trough benralizumab serum concentrations were consistent with the overall known PK profile for benralizumab. Geometric mean (coefficient of variation %) trough benralizumab serum concentrations at Week 24 were similar between the Overall Study Population and the China Subpopulation (137.914 ng/mL [432.419%] and 133.446 ng/mL [468.191%], respectively).

Summary of Pharmacodynamic Results

In patients with a baseline blood eosinophil count ≥ 300/μL within the Overall Study Population, benralizumab treatment resulted in near complete depletion of blood eosinophils at the first timepoint assessed (Week 4) (median percent change from baseline: -93.9%) and was maintained through Week 48 (median percent change from baseline: -92.9%), consistent with the mechanism of action and results in previous asthma studies.

Results for the China Subpopulation were consistent with the Overall Study Population. The median percent depletion of blood eosinophils in the benralizumab group in Chinese patients with a baseline blood eosinophil count ≥ 300/μL was -93.3% at Week 4, and -90.5% at Week 48.

Consistent results were observed for patients with baseline blood eosinophil counts < 300 cells/μL in both populations.

Summary of Pharmacokinetic/Pharmacodynamic Relationships

Not applicable.

Summary of Pharmacogenetic Results

Not applicable.

Summary of Immunogenicity Results

Anti-drug antibody prevalence in the Overall Study Population was 16.7% in the benralizumab-treated group with an ADA incidence of 16.8%. The majority of post-baseline ADA positive patients were persistently ADA positive and the majority of ADA positive

patients were neutralising antibody (nAb)-positive. The immunogenicity profile in the China Subpopulation was consistent with the Overall Study Population.

The development of ADA reduced trough benralizumab serum concentrations at steady-state PK. The presence of ADA was associated with an increase in eosinophil counts at trough serum concentrations of benralizumab, with the greatest increase observed in those patients with the highest ADA titres.

There was no meaningful effect of ADA-positive status on efficacy, as measured in annual asthma exacerbation rate, mean change from baseline in FEV_1, and change from baseline in Total Asthma Score.

There was no meaningful effect of ADA-positive status on the overall incidence of AEs or serious adverse events (SAEs) and there was no apparent correlation between hypersensitivity AEs and ADA.

Summary of Safety Results

Overall, benralizumab 30 mg administered SC every 8 weeks was well tolerated in patients with a history of asthma exacerbations and uncontrolled asthma.

In general, the safety results were reflective of the patient population. The AE patterns in patients with baseline blood eosinophil counts ≥ 300/μL and < 300/μL were generally similar to those in all patients. The COVID-19 pandemic did not have an impact on the overall AE profile during the on-treatment period.

During the on-treatment period, AEs were reported at a numerically lower incidence in the benralizumab group (74.4%) compared with the placebo group (77.8%) during the on-treatment period. There were no AEs with outcomes of death during the study. Serious AEs were reported at a numerically lower incidence in the benralizumab group (10.3%) compared with the placebo group (15.9%), which was primarily driven by SAEs with the PT of asthma. Adverse events leading to discontinuation of IP were reported at a numerically higher incidence in the benralizumab group (2.0%) compared with the placebo group (0.3%); however, no AEs leading to discontinuation of IP by PT were reported in > 1 patient in either group. The majority of AEs were assessed as mild or moderate in intensity and the majority of AEs were assessed as not related to the IP by the Investigator.

The most common AEs by PT during the on-treatment period were upper respiratory tract infection (33.3%), nasopharyngitis (7.8%), and rhinitis allergic (5.5%) in the benralizumab group, which were reported at frequencies of 33.4%, 9.5%, and 4.3%, respectively, in the placebo group. The incidence of AEs with the PT of asthma was numerically lower in the benralizumab group (2.3%) compared with the placebo group (8.9%). The incidences of the other most common AEs by PT were generally similar between groups.

The most common SAEs by PT during the on-treatment period were asthma (2.3%) and pneumonia and pneumonia bacterial (0.9% each) in the benralizumab group, which were reported at frequencies of 8.6%, 1.4%, and 0.9%, respectively, in the placebo group. The majority of SAEs that were reported during the on-treatment period were assessed as not related to the IP by the Investigator.

Based on the benralizumab mechanism of action and/or potential risks generally associated with monoclonal antibodies, AEs of interest included serious infections, helminth infections, and malignancy. The incidence of on-treatment AEs of interest and other significant AEs (ie, injection site reactions and hypersensitivity) was either generally similar between groups (serious infections, injection site reactions, hypersensitivity) or zero (helminth infections and malignancies).

In general, there were no clinically meaningful changes in other haematology, clinical chemistry, and urinalysis variables over time or shifts from baseline. There were no notable trends in AEs related to laboratory variables in either group. No new safety concerns related to vital signs, ECGs, or physical examinations were identified.

The safety profile for the China Subpopulation was generally consistent with the Overall Study Population.

Conclusions

The following overall conclusions were made in patients with a history of asthma exacerbations and uncontrolled asthma receiving medium- to high-dose ICS-LABA with or without OCS and additional asthma controllers:

- Benralizumab 30 mg Q8W demonstrated statistically significant and clinically meaningful improvements compared with placebo for the primary endpoint of annual asthma exacerbation rate and the key secondary endpoints of change from baseline in pre-bronchodilator FEV_1 and total asthma symptom score at Week 48. Benralizumab also showed improvements over placebo in other secondary measures of pulmonary function, asthma symptoms and other asthma control metrics, and health-related quality of life after 48 weeks of treatment. Treatment benefits in pulmonary function and asthma symptom control were observed as early as Week 2 and Week 4, respectively, and were maintained through Week 48. The efficacy results for the China Subpopulation were consistent with the Overall Study Population.
- Trough benralizumab serum concentrations were consistent with the overall known PK profile for benralizumab. Trough benralizumab serum concentrations at steady-state were similar between the Overall Study Population and the China Subpopulation. Benralizumab treatment resulted in near complete depletion of blood eosinophils at

Week 4, which was sustained through Week 48. Results for the China Subpopulation were consistent with the Overall Study Population.

- The incidence of ADA and nAb in patients treated with benralizumab was consistent with what has been seen in previous asthma studies, with neutralising activity detected in a majority of ADA-positive patients. No meaningful differences in ADA status, nAb status, ADA kinetics, or ADA titres were observed based on baseline blood eosinophil count status (≥ 300 cell/μL compared with all baseline blood eosinophil counts). The immunogenicity profile in the China Subpopulation was consistent with the Overall Study Population. Geometric mean benralizumab serum concentrations were lower in ADA-positive patients compared with ADA-negative patients. The presence of ADA was associated with an increase in eosinophil counts at trough serum concentrations of benralizumab, with the greatest increase observed in those patients with the highest ADA titres. Despite these changes to PK and pharmacodynamic parameters in ADA-positive patients, there was no evidence of a meaningful effect of ADA-positive status on efficacy or safety.
- Treatment with benralizumab was well tolerated with no unexpected safety findings and had a safety profile that was similar to that seen in previous asthma studies. The safety profile for the China Subpopulation was generally consistent with the Overall Study Population.
- In general, the number and type of COVID-19-related disruptions were balanced between the treatment groups and did not raise any concerns about the overall conduct and quality of the study.