Clinical Study Report

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An Open-label Study to Evaluate the Pharmacokinetics and Pharmacodynamics and Long-term Safety of Benralizumab Administered Subcutaneously in Children with Severe Eosinophilic Asthma

Study dates: First patient enrolled: 21 November 2019
Last patient last visit: 12 September 2022
The analyses presented in this report are based on a clinical data lock date of 19 October 2022.

Phase of development: Phase III

International Co-ordinating Investigator: PPD
St. Louis, Missouri 63110.

Sponsor's Responsible Medical Officer: PPD, AstraZeneca
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This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study centres

This study was performed in 17 sites in the United States and Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Objectives and Endpoints

Objectives	Estimand description / Endpoints
Primary	
To evaluate the PK of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma.	• Clearance. • Area under concentration time curve to Day 28 (AUC_{0-28}). • Maximum serum concentration (C_{max}). • Terminal phase elimination half-life ($t_{1/2}$). • Time to reach C_{max} (T_{max}).
To evaluate the PD of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma.	Change from baseline in peripheral blood eosinophil count at Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B).
Secondary	
To characterize the PK of benralizumab.	Body weight-adjusted clearance.
To evaluate the immunogenicity of benralizumab.	Presence of anti-benralizumab antibodies.
To evaluate the effect of benralizumab on pulmonary function.	Change from baseline in pre-dose (when applicable), pre-bronchodilator, FEV_1 measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B).
To assess the effect of benralizumab on asthma symptoms and other asthma control metrics.	• Change from baseline in ACQ-IA score, measured at screening and Weeks 1, 2, 4, 8, 12, and 16 (Part A), and Weeks 24, 32, 40 and 48, and at follow-up (Part B). • PGIC-IA, measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD/WD visit, and CGIC measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B) and at the DXD/WD visit.
Safety	
To assess the safety and tolerability of benralizumab.	Adverse events, vital signs, and collection of clinical chemistry/haematology parameters and urinalysis.
Exploratory	
To evaluate exacerbations experienced.	Annualized asthma exacerbation rate.

ACQ-IA, interviewer-administered asthma control questionnaire; CGIC, clinician global impression of change; DXD, early discontinuation; FEV_1, forced expiratory volume in one second; PD, pharmacodynamics; PGIC-IA, interviewer-administered patient global impression of change; PK, pharmacodynamics; SC, subcutaneously; WD, early withdrawal.

Study design

This was an open-label, parallel group study designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and long-term safety of benralizumab in children from 6 to 11 years of age with severe eosinophilic asthma, which would also include up to 3 additional Japanese patients aged 12 to 14 years in an additional cohort.

The study was conducted in 2 parts:

- Part A, which consisted of 16 weeks of treatment to evaluate the PK, PD, and safety of benralizumab.
- Part B, which consisted of 32 weeks of continued treatment to evaluate the safety of benralizumab.

Thirty evaluable patients aged 6 to 11 years were stratified by body weight (<35 kg/≥35 kg) and distributed across 2 cohorts at screening, with a minimum of 8 patients in each stratum. An additional cohort was included with up to 3 Japanese patients aged 12 to 14 years.

Staggered inclusion occurred for patients aged 6 to 11 years, in which 4 patients with a body weight <35 kg and 4 patients with a body weight ≥35 kg completed Part A prior to progressing into Part B.

Results for Parts A and B of this study are included in this report.

Target population and sample size

The study aimed to recruit children aged 6 to 11 years old, or 6 to 14 years old (in Japan), with an established diagnosis of severe eosinophilic asthma, according to regional guidelines, for at least 12 months prior to Visit 1. Patients had to have a previously confirmed history of 2 or more exacerbations requiring treatment with systemic corticosteroids and/or hospitalization in the 12 months prior to Visit 1, despite the use of inhaled corticosteroids (ICS), or a persistent need for oral corticosteroid maintenance treatment to maintain asthma control, for at least 3 of the last 12 months prior to Visit 1, despite the use of ICS. The study aimed to recruit 30 evaluable patients aged 6 to 11 years with at least 8 patients in each cohort.

Patients with a diagnosis of severe eosinophilic asthma (including a peripheral blood eosinophil count of ≥150 cells/μL at Visit 1) and a well-documented requirement for regular treatment with ICS were enrolled in the study. Additionally, patients had to have current treatment with at least one additional controller medication, such as inhaled long-acting β2 agonists, leukotriene receptor antagonist, long-acting anti-muscarinic agent (LAMA), or theophylline, since at least 3 months prior to Visit 1. Patients also had to have a forced expiratory volume in one second (FEV_1) at Visit 1 or 2 (prior to first dose of study treatment) of FEV_1 ≤110% predicted normal, or, FEV_1/Forced Vital Capacity (FVC) ratio ≤0.8.

Investigational product: dosage, mode of administration and batch numbers

The investigational product was benralizumab (formerly referred to as MEDI-563). Benralizumab was administered SC as a single injection. See Table S2 for dosage details.

Table S2 Benralizumab Dosage per Cohort

Cohort	Benralizumab dosage Part A	Benralizumab dosage Part B
Six to 11 years old (body weight was <35 kg at screening)	CCI mg benralizumab on Day 0 and Weeks 4, 8, and 16	CCI mg benralizumab on Weeks 24, 32, and 40
Six to 11 years old (body weight was ≥35 kg at screening)	CCI mg benralizumab on Day 0 and Weeks 4, 8, and 16	CCI mg benralizumab on Weeks 24, 32, and 40
Japanese patients aged 12 to 14 years	CCI mg benralizumab on Day 0 and Weeks 4, 8, and 16	CCI mg benralizumab on Weeks 24, 32, and 40

Duration of treatment

The total planned duration of the study treatment for all patients was approximately 56 weeks and included a screening period of up to 28 days, a treatment period of 48 weeks, and a safety follow-up visit at Week 52.

Statistical methods

No formal statistical hypotheses were tested in this study. Data were interpreted through descriptive statistics.

Study population

A total of 39 patients aged 6 to 11 years were enrolled, 11 of which were screening failures. The remaining 28 patients were assigned to study treatment: 15 patients were stratified in the <35 kg weight cohort and, therefore, received CCI mg benralizumab treatment and 13 patients were stratified in the ≥35 kg weight cohort and received CCI mg benralizumab treatment. All 28 (100.0%) patients aged 6 to 11 years who were assigned to study treatment completed the study treatment and the study.

A total of 13 patients aged 6 to 14 years from Japan were enrolled, 2 of which were screening failures. The remaining 11 patients (out of which 9 were included in the 6 to 11 years cohort) were assigned to study treatment: 8 patients were stratified in the <35 kg weight cohort and, therefore, received CCI mg benralizumab treatment and 3 patients were given CCI mg benralizumab (1 patient was stratified by weight to the ≥35 kg weight cohort and the other 2 patients received CCI mg benralizumab because they were 12 to 14 years of age).

Of the 11 patients dosed, a total of 10 (90.9%) patients aged 6 to 14 years from Japan completed the study treatment and 1 (9.1%) patient aged 13 years at enrolment and in the

≥35 kg weight cohort discontinued study treatment early due to the patient's decision and was withdrawn from the study by a parent/guardian decision.

Primary Endpoints Results

Pharmacokinetic results

Patients aged 6 to 11 years

Following the first SC injection of benralizumab on Day 0, maximal serum concentrations of benralizumab were achieved by Day 7 in patients in both weight cohorts. Geometric mean maximal serum concentrations were 1788.30 ng/mL in the <35 kg weight cohort (patients in this cohort received [redacted] mg benralizumab) and 3193.43 ng/mL in the ≥35 kg weight cohort (patients in this cohort received [redacted] mg benralizumab). Following the first 2 doses given every 4 weeks, the serum concentration profiles of serum benralizumab demonstrated a trend for decline in concentrations in both dose cohorts due to the every 8-week dosing schedule thereafter. Higher serum benralizumab concentrations were observed in patients in the ≥35 kg weight cohort at all time points compared to those in patients in the <35 kg weight cohort. A decline in serum benralizumab trough concentrations after Day 112 was observed for patients in both weight cohorts.

Patients aged 6 to 14 years from Japan

Patients from Japan aged 6 to 14 years also reached peak serum concentration of benralizumab (T_{max}) by Day 7. Maximal serum concentrations were higher in the ≥35 kg weight cohort: geometric mean concentration=1791.91 ng/mL in the <35 kg weight cohort and 3292.61 ng/mL in the ≥35 kg weight cohort. Similar trends for serum benralizumab concentrations as non-Japanese patients were observed for patients in both Japanese weight cohorts. Due to the switch from every 4 weeks to every 8 weeks dosing, a decline in serum benralizumab trough concentrations after Day 112 was also observed for patients in both Japanese weight cohorts.

Overall patients

Other benralizumab PK parameters (clearance, body weight adjusted clearance, and terminal phase elimination half-life [$t_{1/2}$]) were derived by a population PK analysis approach. These parameters are presented in a separate population PK analysis report.

Pharmacodynamic results

Patients aged 6 to 11 years

Blood eosinophil values in the safety analysis set showed near-complete depletion from baseline in both weight cohorts at all post-dose time points (Weeks 4 to 48): for the <35 kg weight cohort, median blood eosinophil values fell from 400.0 cells/µL to 10.0 to

20.0 cells/µL and for the ≥35 kg weight cohort, median blood eosinophil values fell from 340.0 cells/µL to 20.0 to 30.0 cells/µL.

Patients aged 6 to 14 years from Japan

Blood eosinophil values in the safety analysis set showed near-complete depletion from baseline in both weight cohorts at all post-dose time points (Weeks 4 to 48): for the <35 kg weight cohort, median blood eosinophil values fell from 435.0 cells/µL to 5.0 to 20.0 cells/µL and for the ≥35 kg weight cohort, median blood eosinophil values fell from 430.0 cells/µL to 5.0 to 20.0 cells/µL.

Pharmacokinetic/pharmacodynamic relationships

Benralizumab systemic exposure achieved by both doses (benralizumab CCI mg and CCI mg) resulted in similar near-complete eosinophil depletion. A similar PD effect of near-complete eosinophil depletion was observed from the first post-dose time point onwards in patients in both weight cohorts.

Secondary Endpoints Results

Immunogenicity results

In the overall study population, the anti-drug antibody (ADA) prevalence was of 14.3%, with 4 patients (3 in the <35 kg weight cohort and 1 in the ≥35 kg weight cohort) having at least 1 ADA positive response throughout all time points. The ADA incidence was the same (14.3%) as the ADA prevalence as none of the patients were baseline ADA positive. Thus, all the ADA responses were treatment-induced. All the ADA-positive patients were also positive for neutralizing antibodies (nAb).

Overall, 3 (10.7%) patients (2 in the <35 kg weight cohort and 1 in the ≥35 kg weight cohort) had ADA transiently positive responses. One (3.6%) patient in the <35 kg weight cohort had ADA persistently positive results.

Data on the effect of ADA on PK and PD (blood eosinophils) were limited due to the small number of ADA positive patients. However, there was a decrease in the PK of benralizumab in association with the ADA positive time points and an increase in the blood eosinophil levels at or near the ADA positive time points.

Data do not demonstrate any apparent differences in the safety profile of patients who had ADA-positive results compared to that in patients who had ADA-negative results; however, the number of ADA positive patients was small. Additionally, no consistent pattern was observed for any AEs reported in patients with ADA positive results and no SAEs were reported by any of these patients.

The number of patients in the various ADA categories was small, so caution should be taken when interpreting these data.

Effect of benralizumab in pulmonary function results

Patients aged 6 to 11 years

Increases in mean FEV_1 were observed in patients aged 6 to 11 years in the <35 kg weight cohort during Weeks 24 and 48 (mean FEV_1 changes from baseline [n; standard deviation (SD)]=0.068 L [14; 0.2650] and 0.003 L [15; 0.3412], respectively) which were numerically lower than the mean FEV_1 increases observed in patients aged 6 to 11 years in the ≥35 kg weight cohort throughout all time points (mean FEV_1 changes from baseline [n; SD] ranged from 0.043 L [10; 0.1804] to 0.425 L [12; 0.4395]), except for Week 16 (mean FEV_1 change from baseline [n; SD]= -0.119 L [7; 0.2435]). A more favourable lung function at baseline in the <35 kg weight cohort may account for these differences, with the ≥35 weight cohort potentially having more room for improvement.

Patients aged 6 to 14 years from Japan

Trends in the Japanese group of patients aged 6 to 14 years were similar, but the number of patients were more limited (8 patients received [redacted] mg benralizumab and 3 patients received [redacted] mg benralizumab).

Effect of benralizumab on asthma symptoms results

Patients aged 6 to 11 years

Patients aged 6 to 11 years in both weight cohorts showed a decrease in mean Interviewer-administered asthma control questionnaire (ACQ-IA) scores throughout all time points compared to baseline. The mean score decreases were numerically larger in patients in the ≥35 kg weight cohort, who also had less-controlled asthma ACQ-IA scores at baseline and thus greater room for improvement.

Overall, most (>50.0%) patients showed an improvement in ACQ-IA score results from Week 12 to Week 52 (change from baseline ≤ -0.5) compared to baseline values, whereas most (>50.0%) patients did not show meaningful improvement in ACQ-IA score (changes from baseline > -0.5) from Week 1 to Week 4.

For patients aged 6 to 11 years, results in both Investigator-reported clinician global impression of change (CGIC) and patient-reported Interviewer-administered patient global impression of change (PGIC-IA) questionnaires agreed that more patients had improved and very much improved health status from start of treatment to Week 48 compared to start of treatment up to Week 16. The overall responses from Week 16 throughout Week 48 were

favourable, showing a higher percentage of patients with improved health status since start of treatment compared to those with no change or worsened health status.

Patients aged 6 to 14 years from Japan

Patients aged 6 to 14 years from Japan showed a decrease in mean ACQ-IA scores in both weight cohorts and throughout all time points compared to baseline, except patients in the <35 kg weight cohort at Week 24 and patients in the ≥35 kg weight cohort at Week 8 and 16.

Overall, most (>50.0%) patients showed no meaningful improvement from baseline in ACQ-IA score results (change from baseline > -0.5) from Week 1 to Week 4. More than 50.0% of patients showed an improvement in ACQ-IA score results from Week 8 to Week 52 (change from baseline ≤ -0.5) compared to baseline values.

For patients aged 6 to 14 years from Japan, results in both CGIC and PGIC-IA questionnaires agreed that by Week 48 all patients had improved health status, and overall responses from Week 16 throughout Week 48 were favourable.

Exploratory results

All patients reported at least 2 exacerbations in the year prior to trial entry in both weight cohorts. The number and proportion of patients reporting exacerbations was lower than the year prior to study entry. During the treatment period, 14 (50%) of patients aged 6 to 11 years old reported a total of 42 asthma exacerbations. Of these, 3 patients (10.7%) had at least one exacerbation requiring hospitalization, and 8 (28.6%) had at least one exacerbation requiring an emergency room urgent care visit. There were no notable differences between cohorts regarding patients reporting exacerbations during treatment.

Summary of safety results

For patients overall (aged 6 to 14 years), AEs were reported in 13 (86.7%) patients in the <35 kg weight cohort and in 11 (73.3%) patients in the ≥35 kg weight cohort. There were no meaningful patterns of AEs observed.

There were no AEs with the outcome of death or study treatment discontinuation in any weight cohort.

Of the 28 patients aged 6 to 11 years, 22 (78.6%) patients experienced 76 AEs. Of these, 3 (10.7%) patients experienced a total of 3 SAEs: one [6.7%] patient in the <35 kg cohort experienced 1 SAE and 2 [15.4%] patients in the ≥35 kg cohort experienced a total of 2 SAEs. All (11) patients from Japan, aged 6 to 14 years, experienced a total of 64 AEs. Of these, 2 (18.2%) patients (both in the ≥35 kg cohort) experienced a total of 3 SAEs.

The most frequently reported system organ class (SOC) for overall patients (aged 6 to 14 years) was infections and infestations. There were no consistent patterns observed between SOCs.

A total of 4 patients, all aged 6 to 11 years, reported AEs that were considered related to study treatment by the Investigator. These AEs were of mild intensity, and all resolved. No action on study treatment was taken for any of these AEs.

The majority of AEs reported in during the study were of mild or moderate intensity. Severe AEs were reported in 3 (10.7%) patients in the 6- to 11-year-old group and in 2 (18.2%) patients in the 6- to 14-year-old group from Japan.

One patient in the <35 kg cohort in the Japanese group experienced two mild AEs of injection site reaction. These AEs were considered of mild intensity and related to study treatment by the Investigator.

Of the 28 patients aged 6 to 11 years, 3 (10.7%) patients reported a total of 3 SAEs of asthma exacerbation, which were considered not related to study treatment by the Investigator. All SAEs resolved. Of all 11 patients in the Japanese group, 2 (18.2%) patients, both in the 12 to 14 years cohort, reported a total of 3 SAEs of asthma exacerbation which were considered not related to study treatment by the Investigator.

Overall, there were no clinically meaningful trends in safety laboratory values, vital signs, or electrocardiogram (ECG) measurements.

This study was conducted during the Coronavirus disease 2019 (COVID-19) pandemic. A total of 4 patients overall (age 6 to 14 years) reported COVID-19 related AEs during the study. None of these were serious, and all resolved. The COVID-19 pandemic did not impact the interpretation of the safety results.

Conclusion(s)

- With regard to the primary PK endpoints, overall systemic exposure to benralizumab increased from CCI mg (<35 kg weight cohort) to CCI mg (the ≥35 kg weight cohort) as expected. Maximum benralizumab concentration was reached by Day 7 in both weight cohorts.
- The expected PD effect of near-complete eosinophil depletion was seen in both weight cohorts from the first time point (Week 4) and was maintained throughout the treatment period.
- Some improvements in lung function, symptoms and other asthma control metrics were observed, most consistently in the ≥35 kg weight cohort. Of note, patients in the <35 kg weight cohort appeared to have milder disease at baseline compared to patients in the ≥35 kg weight cohort and therefore potentially had less room to show improvement.

- The incidence of ADA and nAb was consistent with that seen in previous asthma studies with benralizumab. In ADA-positive and nAb-positive patients some return towards baseline blood eosinophil values was observed. Although numbers were limited, there was no evidence of an impact of ADA on safety.
- Treatment with benralizumab was generally safe and well tolerated, with no unexpected safety findings, and the safety data were consistent with the known safety profile of benralizumab.