

Office of Clinical Pharmacology Review

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Submissions Date:	11/16/2016
Submission Type:	Standard 505(b)(1)
Proposed Brand Name:	FASENRA
Generic Name:	Benralizumab
Applicant:	AstraZeneca AB
Route of Administration:	Subcutaneous injection
Dosage Form and strength:	30 mg/mL solution in a single-dose prefilled syringe
Proposed Dosing Regimen:	30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter
Proposed Indication(s):	an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
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1. EXECUTIVE SUMMARY

AstraZeneca AB submitted BLA 761070 under a 351 (a) pathway seeking the marketing approval for benralizumab for the indication of add-on maintenance treatment for patients with severe asthma aged 18 years and older with an eosinophilic phenotype. Benralizumab is a humanized afucosylated, monoclonal antibody binding with human interleukin-5 receptor alpha subunit (IL-5R α). The proposed dosing regimen is 30 mg subcutaneous injection (SC) every 4 weeks for the first 3 doses (Q4W x 3), followed by 30 mg subcutaneous injection once every 8 weeks (Q8W) thereafter. The proposed dosage form is 30 mg/mL solution in a single-dose prefilled syringe.

The efficacy and safety of benralizumab in asthma patients was supported by two pivotal Phase 3 randomized, double-blind, parallel group trials in asthma patients (D3250C00017 and D3250C00018). A total of 10 completed clinical studies (2 Phase 1 studies, 3 Phase 2 studies, and 5 Phase 3 studies) in patients with asthma, assessed the pharmacokinetics (PK) and pharmacodynamics (PD) of benralizumab. At the proposed dosing regimen of 30 mg SC Q8 following a loading dose of 30 mg SC Q4 x 3 doses, the PK steady-state was reached at Week 24.

From a clinical pharmacology perspective, the proposed dosing regimen of benralizumab 30 mg SC Q8 following a loading dose of 30 mg SC Q4 x 3 doses, for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype, is appropriate. The PK and PD of benralizumab in adolescent patients were also evaluated in the pivotal phase 3 studies. The PK in adolescent patients was comparable with that in adults. The observed mean steady state trough concentrations ($C_{\text{trough,ss}}$) were overlapping in adolescent patients with that in adult patients. The PD effect, i.e., the magnitude of reduction in peripheral blood eosinophil counts (median reduction) in adolescent patients were also comparable with that in adults.

The clinical pharmacology review mainly focuses on appropriateness of dosing regimen selection and adolescent subgroup.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology II and Pharmacometrics have reviewed BLA 761070. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations
Supportive evidence of effectiveness	<p>The reduction in annual asthma exacerbation rate in pivotal Phase 3 studies provides primary evidence of effectiveness.</p> <p>The PK and PD (blood eosinophil counts) of benralizumab in adults and adolescent patients with severe asthma and eosinophilic phenotype provide supportive evidence for effectiveness.</p>
General dosing instructions	<p>From a Clinical Pharmacology perspective, the proposed 30 mg Q4W x 3 + Q8W dosing regimen is acceptable to be used as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.</p> <p>The PK and PD of benralizumab was also evaluated in adolescent patients. Benralizumab PK in adolescent patients</p>

Review Issues	Recommendations
	was comparable with that in adults based on observed mean $C_{trough,ss}$ values. The magnitude of reduction in peripheral blood eosinophil counts in adolescents were comparable to that in adults.
Dosing in patient subgroups	No separate dosing or dosing regimen is recommended in any patient subgroups due to intrinsic (e.g., age and body weight) and extrinsic factors.
Bridge between the “to-be-marketed” and clinical trial formulations	<p>Three Drug Product formulation process changes occurred during the clinical development program. Formulations using Processes 1 & 2 Drug Products were used in Phase 1 and 2 studies. Formulations using Process 3 Drug Products, which is the same as the commercial to-be-marketed products in the primary package, were used in all Phase 3 studies.</p> <p>Processes 1 and 2 and Processes 2 and 3 were bridged analytically.</p>

1.2 Post-Marketing Requirements and Commitments

None.

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2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Benralizumab is a humanized, afucosylated, interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (mAb; immunoglobulin G 1 [IgG], kappa [IgG1κ]).

The following is a summary of the clinical pharmacokinetics of benralizumab:

Absorption:	The estimated absolute bioavailability from population pharmacokinetic (PopPK) modelling is 58%. The relative bioavailability based on administration site (abdomen, thigh, or upper arm) are similar, and there were no clinically relevant differences.
Distribution:	The estimated central and peripheral volumes of distribution for benralizumab were 3.23 L and 2.45 L, respectively.
Elimination:	From PopPK modelling, the estimated benralizumab clearance (CL) was 2.91 L/day. The half-life of elimination ($t_{1/2}$) of benralizumab was approximately 15 days in asthma patients.
Metabolism:	The sponsor did not conduct metabolism studies for benralizumab since monoclonal antibodies are catabolized by proteolytic enzymes following cellular uptake and not via typical drug metabolizing enzymes such as cytochrome P450.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant proposes that benralizumab be administered subcutaneously at a dose of 30 mg every 4 weeks for the first 3 doses followed by subsequent doses administered every 8 weeks. This proposed dosing regimen was evaluated in the pivotal phase 3 studies.

Two dosing regimens, 30 mg Q4W (Q4W regimen) and 30 mg Q4W x 3 + Q8W (Q8W regimen), were evaluated in two pivotal Phase 3 studies. The observed mean $C_{trough,ss}$ of Q8W regimen was approximately 20% that of Q4W regimen. However, both regimens substantially reduced peripheral blood eosinophil counts in asthma patients compared to placebo. The magnitude of eosinophil count reduction was maintained for least 8 weeks following discontinuation of treatment, with a median peripheral blood eosinophil counts from both dosing regimens of zero (0) at steady state. There were no clinically meaningful differences of mean peripheral blood eosinophil counts between two dosing regimens at steady state.

There was no noticeable exposure-response relationship between median observed benralizumab $C_{trough,ss}$ and the Phase 3 primary efficacy endpoint (asthma exacerbation rate, AER). The exposure-response curve was generally flat for asthma exacerbation across a range of more than 6-fold (<212 ng/mL to ≥ 1250 ng/mL) median observed $C_{trough,ss}$. Similarly, there was no noticeable exposure-response relationship between $C_{average,ss}$ and Phase 3 secondary efficacy endpoint (forced expiratory volume at 1 second (FEV₁) change from baseline at the end of treatment). The exposure-response curve was generally flat for FEV₁ change from baseline at end of trial (EOT) across a range of 10-fold (200 ng/mL to 2000 ng/mL) $C_{average,ss}$.

Therefore, the lack of noticeable exposure-response relationship support the proposed dosing regimen with longer dosing interval (for further details see [section 3.3.2](#))

2.2.2 Therapeutic individualization

No therapeutic individualization of benralizumab is recommended. The factors of interest from an individualization perspective are (a) body weight and (b) adolescents, as described below.

2.2.2.1 Fixed Dose vs Body Weight Based Dosing:

Body weight was identified as a significant covariate in the PopPK analysis. Benralizumab CL increased with body weight. However, the effect of body weight on benralizumab PD and efficacy as assessed by evaluating the observed blood eosinophil and FEV₁ responses showed that blood eosinophil depletion and FEV₁ improvement were independent of body weight in the 30 mg Q8W group.

Therefore, based on the pharmacokinetic and efficacy data discussed above, the proposed fixed dosing of 30 mg SC given Q8W following an initial 3 doses given Q4W is considered to be appropriate and no alternative dose or dosing regimen for different body weight subgroups is recommended.

2.2.2.2 Adolescents:

Benralizumab PK in adolescent patients from Phase 3 studies, D3250C00017 and D3250C00018 was comparable with that in adults based on observed mean C_{trough,ss} values.

The inhibition effect benralizumab on peripheral blood eosinophil counts in adolescents were similar to that in adults. The overall anti-drug antibody (ADA) incidence in adolescent patients was 9% (4/46), 4% (1/24), and 24% (9/38) in placebo, 30 mg Q4W, and 30mg Q4W×3 + Q8W treatment groups, respectively.

For further details, see [section 3.3.3](#).

2.2.3 Immunogenicity

In the Phase 3 asthma exacerbation studies, ADA-positive responses were observed with a prevalence of approximately 12% to 15% of patients treated with benralizumab and an incidence of approximately 10% to 14%. The corresponding prevalence and incidence in patients treated with placebo were approximately 3% to 5% and 2% to 3%, respectively. Among benralizumab-treated patients who had ADA-positive responses, the majority had a persistent ADA-positive response and were also neutralizing antibody (nAb)-positive as assessed by a ligand-binding neutralizing antibody assay (LBA).

Median ADA titers increased through Week 24 or Week 32, and remained constant thereafter. No differences in ADA status, nAb status, ADA kinetics, or ADA titers were observed based on baseline eosinophils (≥ 300 cell/ μ L compared with all eosinophil counts).

Patients who developed ADA during the course of treatment tended to have lower steady-state serum trough benralizumab concentrations (C_{trough,ss}) across both dose regimens.

For both the benralizumab 30 mg Q4W and Q8W groups, a slight increase of median eosinophil counts and higher variability was observed in ADA-positive patients as compared with ADA-negative patients beginning at Week 24.

There was no indication of an effect of ADA-positive status on annual asthma exacerbation rate (crude rate), mean change from baseline by EOT in FEV₁, or change from baseline by the EOT in total asthma symptom score, regardless of the nature of the ADA response or dosing regimen. There was no indication of an effect of ADA-positive status on the overall incidence of treatment-emergent adverse events (TEAEs) or serious adverse events (SAEs) and there was no observed association between hypersensitivity TEAEs and ADA.

For further details, see section [3.3.5](#).

2.3 Outstanding Issues

None.

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2.4 Summary of Labeling Recommendations

In general the applicant proposed labeling statements are acceptable. However, the Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

Label Section	Recommendation
12.2 Pharmacodynamics	<ul style="list-style-type: none">• (b) (4) (b) (4) To be consistent with the approved labels of other IL5 antagonists (mepolizumab and reslizumab), results from phase 3 study(ies) are preferred here.• Delete section (b) (4) (b) (4) Deletion is consistent with the approved labels of other IL5 antagonists.
12.3 Pharmacokinetics	<ul style="list-style-type: none">• Clarify the dose proportional range to be between 20 to 200 mg, and not (b) (4) to (b) (4) mg, since Study MI-CP220 did not show dose linearity between (b) (4) mg and (b) (4) mg.• Specify that the PK parameters presented in this section are based on data from three different formulations.

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3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

3.1.1 Background of the disease and available therapies:

Asthma comprises a number of distinct phenotypes, mainly eosinophilic and noneosinophilic asthma, based on the cell profile of induced sputum samples. Response to asthma treatments may be different based on the different types of inflammation. Severe asthma is treated with medium to high-dose inhaled corticosteroids (ICS) and an additional second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled. Some serious asthmas remain uncontrolled despite this therapy. Patients who remain uncontrolled continue to suffer symptoms, frequent exacerbations, and compromised quality of life.

The National Heart, Lung, and Blood Institute recommends a step-wise intensification of a daily maintenance regimen primarily centered around ICS and leukotriene receptor antagonists (LTRAs), with the addition of long-acting β_2 agonists (LABAs) in patients with more severe asthma as an approach to anti-inflammatory controller therapy in asthma (Figure 1).

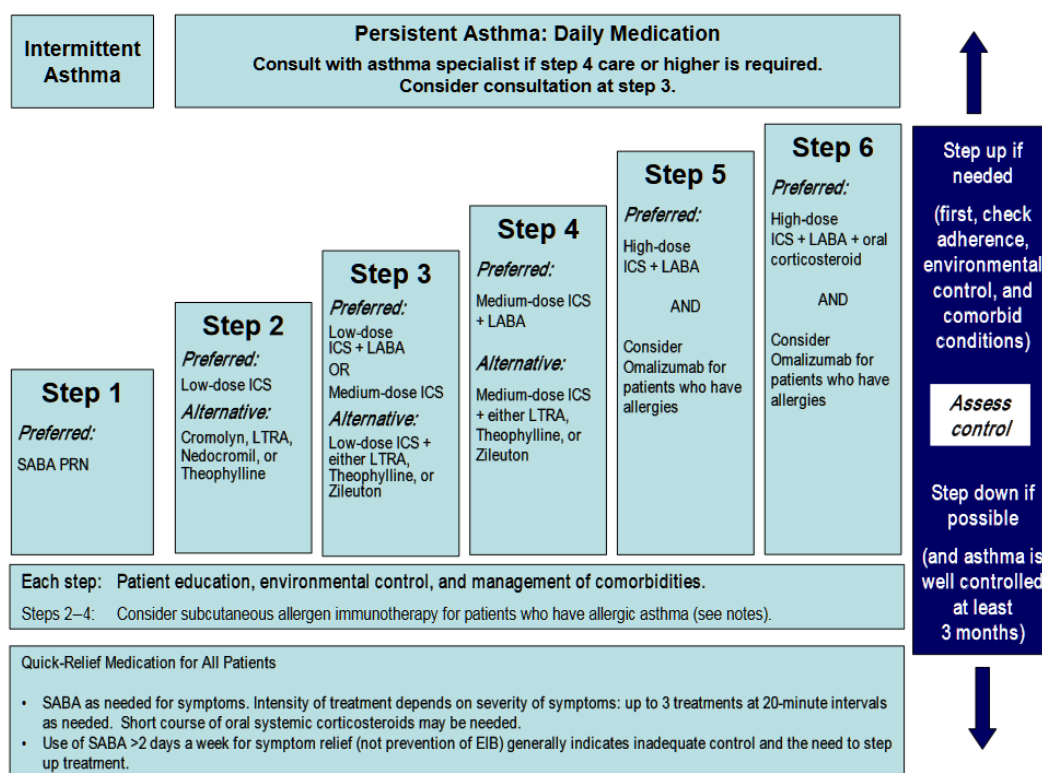


Figure 1 Stepwise Approach For Managing Asthma In Patients 12 Years of Age

(Source: National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel Report 3, Guidelines for the Diagnosis and Management of Asthma. at: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>.)

Three monoclonal antibodies (mAbs), omalizumab, mepolizumab, and reslizumab, are currently available for use as add-on treatment for severe asthma.

Omalizumab binds to immunoglobulin E (IgE) and prevents binding of IgE to FcεRI (high-affinity IgE receptor), thereby reducing the amount of free IgE that is available to trigger the allergic cascade, decreasing multiple markers of airway inflammation, including eosinophils.

Mepolizumab is an interleukin-5 (IL-5) antagonist. It inhibits the bioactivity of IL-5 by blocking the binding of IL-5 to the alpha chain of the IL-5R complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and leading to reduced production and survival of eosinophils.

Reslizumab is an IL-5 antagonist. Reslizumab binds specifically to IL-5 and interferes with IL-5 binding to its cell-surface receptor. It binds human IL-5 blocking its biological function resulting in reduction of the survival and activity of eosinophils.

3.1.2 Background of Benralizumab:

Benralizumab offers a different mechanism of action (MOA) (*see section 3.2.1*) that delivers rapid, direct, and nearly complete eosinophil depletion, early and sustained efficacy responses, and therefore offers a different choice among the currently available therapies for severe asthma with an eosinophilic phenotype.

The clinical development program for Benralizumab comprises of 12 studies: 2 Phase 1 studies, 3 Phase 2 studies, and 7 Phase 3 studies. Five of the Phase 3 studies contained PK and PD data. Of the remaining 2 Phase 3 studies, 1 study (BORA [D3250C00021]) is an ongoing safety extension study. (b) (4)

(b) (4) A total of 3873 asthma patients were randomized in these 12 studies. None of the studies were conducted in healthy volunteers. These studies provide information supporting proof-of-concept as well as the definitive efficacy and safety of benralizumab in the target population as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients.

The regulatory history regarding these communications is summarized below:

Dates	Event	Key Communication Topics
13 Feb 2013	EOP2	<ul style="list-style-type: none">Clarification from Sponsor regarding modeling conducted in support of their recommended dose of 30 mgAgency recommendation to include more than one dose in the pivotal efficacy trials
22 May 2014	Type C WRO	<ul style="list-style-type: none">Bridging strategy between AI and PFS
20 Sep 2016	Pre-BLA Type B	<ul style="list-style-type: none">Adequacy of population modelling approach to evaluate bioavailability and covariate effects

3.2 General Pharmacological and Pharmacokinetic Characteristics

The PK and PD parameters of benralizumab were assessed from a total of 10 completed clinical studies (2 Phase 1, 3 Phase 2, and 5 Phase 3 studies) that were conducted in patients with asthma. Population PK characteristics were assessed in pooled data from these studies and exposure-response characteristics were assessed using pooled data from Phase 3 studies, SIROCCO and CALIMA.

3.2.1 Mechanism of Action:

Benralizumab binds to the alpha subunit of the human interleukin-5 receptor (IL-5R α) with high affinity (16 pM) and specificity. In humans, the IL-5R is expressed exclusively on the surface of eosinophils and basophils. Benralizumab binds to IL-5R α on eosinophils and basophils, and the absence of fucose in the Fc domain of benralizumab results in high affinity for human Fc γ RIIIa, the main activating Fc γ receptor (Fc γ R) expressed on the immune effector cells, natural killer (NK) cells and macrophages. The higher affinity for Fc γ RIIIa results in the recruitment and activation of NK cells and macrophages leading to apoptosis of eosinophils and basophils through enhanced antibody-dependent cell-mediated cytotoxicity (ADCC), the principal MOA of benralizumab (Figure 2). Benralizumab's MOA induces direct and nearly complete depletion of eosinophils in the lung tissue, sputum, blood, and bone marrow. The enhanced ADCC activity of benralizumab results in the rapid depletion of eosinophils, which in the blood has been demonstrated to be within 24 hours following dosing with benralizumab. The enhanced ADCC MOA of benralizumab also results in depletion of circulating basophils.

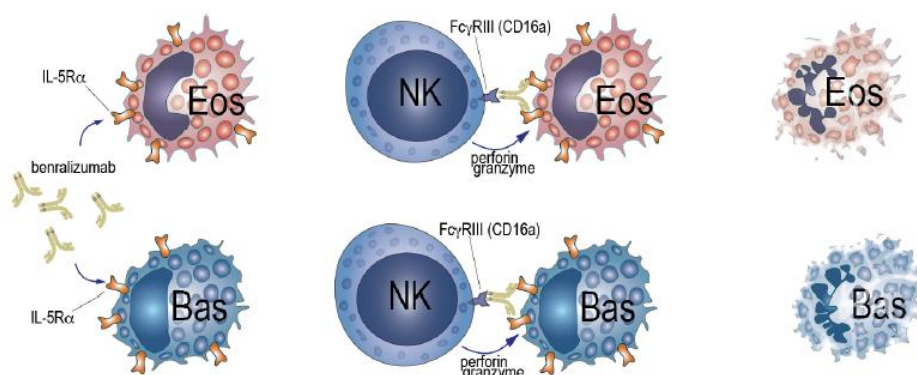


Figure 2 Target Cell Depletion By Benralizumab Through Enhanced ADCC

3.2.2 Pharmacokinetics

A total of 10 completed clinical studies (2 Phase 1 studies, 3 Phase 2 studies, and 5 Phase 3 studies) conducted in patients with asthma assessed the PK and PD of benralizumab. The PK data from Phase 1 and 2 studies were generated from Processes 1 & 2 Drug Products, respectively. The PK data from Phase 3 studies were generated from the Process 3 Drug Products, same as commercial products in the primary package.

A summary of population PK analysis are shown below:

3.2.2.1 Absorption, distribution, biotransformation, and elimination

The absorption half-life of benralizumab is 3.6 days following SC administration, and the absolute bioavailability (F) is 58%. The relative bioavailabilities based on administration site (abdomen, thigh, or upper arm) are similar, and there were no clinically relevant differences.

Based on PopPK, for a 70 kg individual, the central (V_c) and peripheral (V_p) volume of distribution of benralizumab are 3.2 L and 2.5 L, respectively. Benralizumab is a humanized IgG1 mAb that is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue. Benralizumab exhibited linear pharmacokinetics and there was no evidence of a target receptor-mediated clearance pathway. The estimated CL for benralizumab is 2.91 L/d. The elimination half-life is approximately 15 days following SC administration.

3.2.2.2 Drug-drug interactions

The sponsor did not conduct any formal drug-drug interaction studies. IL-5R α is not expressed on hepatocytes and other than IL-5 and the eosinophil chemokines eotaxin-1 and eotaxin-2, treatment with benralizumab has no identified effect on other circulating cytokines. From PopPK analysis, benralizumab CL was not influenced by commonly used small molecule drugs (montelukast, paracetamol, proton pump inhibitors, macrolides, and theophylline/aminophylline). Taken together, these data suggest that the potential risk of interactions between benralizumab and other drugs is low.

3.2.2.3 Special populations

PopPK analysis did not identify age, gender, race, liver function markers, creatinine clearance (CLCR), and commonly used small molecule drugs as having clinically relevant impact on benralizumab CL. Body weight and anti-drug antibody (ADA) were the only identified PK covariates for benralizumab. From the correlation, the power parameter (exponent) of body weight on CL, V_c , and V_p were 0.831, 0.815, and 0.563, respectively. The presence of ADA increased benralizumab CL by 121%.

3.2.2.3.1 Elderly patients (≥ 65 years old)

Based on PopPK analysis, age did not affect benralizumab clearance.

3.2.2.3.2 Gender, Race

Gender and race did not have any effect on benralizumab clearance.

3.2.2.3.3 Renal impairment

Formal studies were not conducted to investigate the effect of renal impairment on benralizumab pharmacokinetics. Based on PopPK analysis, benralizumab clearance was comparable in subjects with CLCR values between 30 and 80 mL/min and patients with normal renal function. Data in subjects with CLCR values < 30 mL/min is limited. However, benralizumab is not cleared renally.

3.2.2.3.4 Hepatic impairment

IgG monoclonal antibodies are cleared by proteolytic enzymes and not primarily cleared via the hepatic pathway; change in hepatic function is not expected to influence benralizumab clearance. The Sponsor did not conduct any formal clinical studies to investigate the effect of hepatic impairment on benralizumab. Based on PopPK analysis, baseline hepatic function biomarkers (alanine aminotransferase, aspartate aminotransferase, and bilirubin) had no clinically relevant effect on benralizumab clearance.

3.2.2.3.5 Paediatric

The PK of benralizumab in adolescents aged 12 to 17 years was consistent with that in adults. Benralizumab was not studied in children in the age group of 5-11 years.

3.2.3 Pharmacodynamics

Findings from human biomaterial studies showed that benralizumab binds to IL-5R α with high affinity on the surface of human eosinophils and basophils, and also selectively binds to eosinophils in a mixed leukocyte population. Benralizumab induced eosinophil and basophil apoptosis in the presence of NK cells with no associated increase in the concentrations of ECP and EDN, which provides evidence that benralizumab does not induce eosinophil activation or necrosis.

Findings from Phase 1 and Phase 2 studies show that benralizumab treatment (IV doses ranging from 0.0003 to 3.0 mg/kg or SC doses ranging from 2 to 200 mg) rapidly depleted peripheral blood eosinophils. Within 24 hours of dosing, mean peripheral blood eosinophil counts were typically depleted by $\geq 95\%$, however, this depletion was reversible, and the majority of eosinophil counts returned to approximately baseline levels within 6 months after cessation of repeated SC benralizumab dosing.

Benralizumab also depleted peripheral blood basophils to a lesser extent.. Dosing with benralizumab resulted in reduced NK cells following the first dose, after which NK cells trended towards baseline levels. However, no clinically meaningful trends were associated with NK cell effects.

The first post-treatment assessment at 4 weeks in the overall population as well as in adolescents in the Phase 3 studies confirmed the expected pharmacodynamic effect of eosinophil reduction.

The serum concentrations of eosinophil cationic protein (ECP) and eosinophilic-derived neurotoxin (EDN) were reduced by benralizumab treatment, demonstrating *in vivo* that eosinophil depletion by enhanced ADCC does not result in eosinophil degranulation or necrosis. Consistent with the reduction of eosinophils, dosing with benralizumab also resulted in sustained, increased serum levels of IL-5 and eotaxin-1/CCL11, as these cells are primary targets of IL-5 and eotaxin-1. Other asthma-associated biomarkers such as exhaled nitric oxide or total serum IgE levels were, however, not influenced by benralizumab suggesting that these biomarkers are not regulated by eosinophils.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The two dosing regimens, 30 mg Q4W or 30 mg Q4Wx3 + Q8W, evaluated in the two Phase 3 studies (D3250C00017 and D3250C00018) substantially reduced peripheral blood eosinophil counts in asthma patients compared to placebo. The magnitude of eosinophil count reduction was maintained for least for 8 weeks following discontinuation of treatment (see [Figure 11](#)). At steady state, the median peripheral blood eosinophil counts from both dosing regimens were 0 (see [Table 2](#)). There were no clinical meaningful differences in mean peripheral blood eosinophil counts between two dosing regimens at steady state.

Study schematics for D3250C00017 (SCIROCCO) and D3250C00018 (CALIMA) are shown in [Figure 3](#).

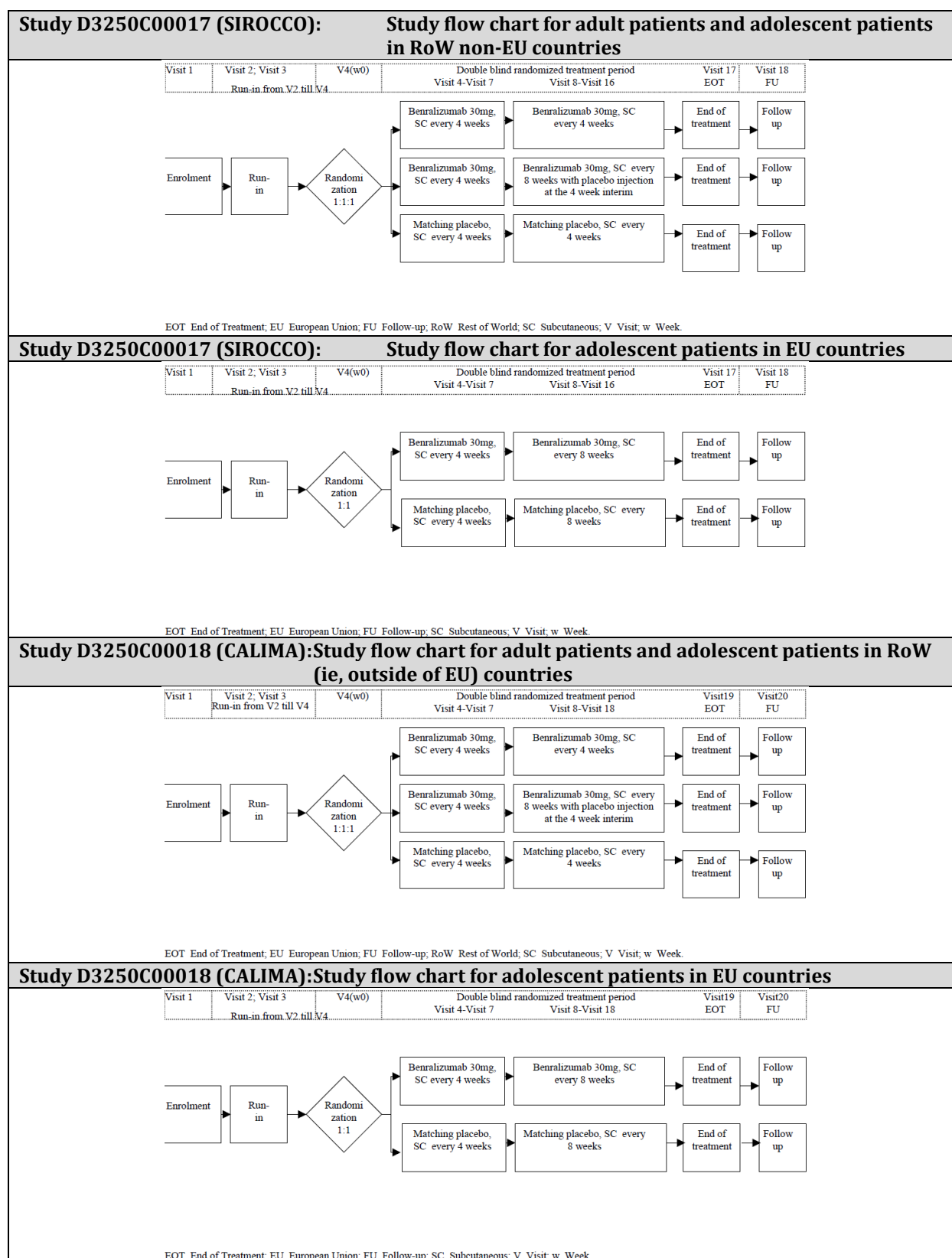


Figure 3 Schematic for Studies D3250C00017 and D3250C00018

(Source eCTD for BLA 761070, Module 5.3.5.1, CSRs for Studies D3250C00017, Figures 1 and 2, Pages 28 and 29; D3250C00018, Figures 1 and 2, Pages 29 and 30)

Study D3250C00017 (SIROCCO):

Pharmacokinetics:

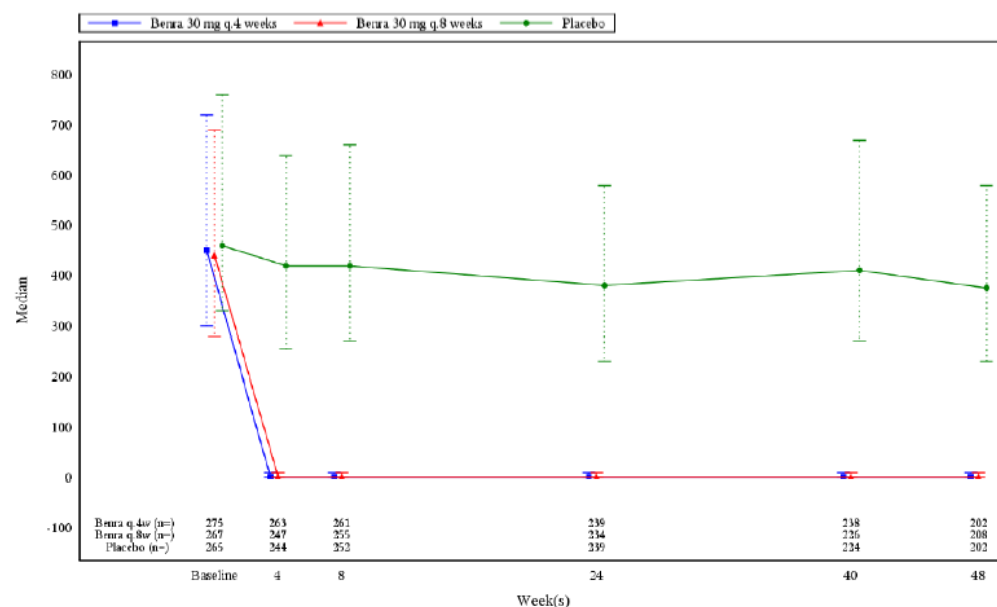
In Study D3250C00017, PK steady-state for the benralizumab 30 mg Q4W group was reached at Week 8. Patients in the benralizumab 30 mg Q8W group received treatment Q4W for the first 3 doses, followed by Q8W thereafter. The PK steady-state for the benralizumab 30 mg Q8W group was reached at Week 24. Steady-state serum C_{trough} was consistently higher beginning at Week 16 through the last common dosing time at Week 40 in the benralizumab 30 mg Q4W group (1024.26 to 967.15 ng/mL, respectively) compared with the benralizumab 30 mg Q8W group (250.84 to 157.22 ng/mL, respectively). The geometric mean benralizumab serum concentration at Week 56 was 51.7 ng/mL and 6.66 ng/mL for the benralizumab 30 mg Q4W and Q8W groups, respectively.

The PK in adolescents was slightly higher than in adults, but individual PK exposure substantially overlapped between the 2 populations. In the benralizumab 30 mg Q8W group, PK was generally comparable between adolescents and adults beginning at Week 24. The median benralizumab serum C_{trough} ranged from 190.00 to 303.50 ng/mL in adolescents, and from 238.00 to 278.00 ng/mL in adults.

Blood Eosinophils:

Mean baseline blood eosinophil counts were similar across groups. In patients with a baseline blood eosinophil count $\geq 300/\mu\text{L}$, both benralizumab 30 mg Q4W and Q8W demonstrated near complete depletion of eosinophils at Week 4 (-95.5% and -90.6%) that were maintained through Week 48 (-95.9% and -92.2%).

There was no reduction in blood eosinophils in the placebo group during the study. Both benralizumab 30 mg Q4W and Q8W demonstrated greater reductions in LS mean percent change from baseline in blood eosinophil counts compared with placebo at Week 4 (-98.28% and -94.10%, respectively; both $p < 0.001$) and at Week 48 (-102.2% and -99.59%, respectively; both $p < 0.001$). The results are shown in [Figure 4](#).



Error bars represent upper and lower quartiles.

Benra Benralizumab.

Figure 4 Median Blood Eosinophil Counts (Cells/mL) Over Time - Line Plot (Full Analysis Set, Baseline Blood Eosinophils $\geq 300/\mu\text{L}$)

(Source: CSR for Study D3250C00017, Figure 15, Page 173)

Similar results were observed for patients with blood baseline eosinophil counts <300/ μ L.

Study D3250C00018 (CALIMA):

Pharmacokinetics:

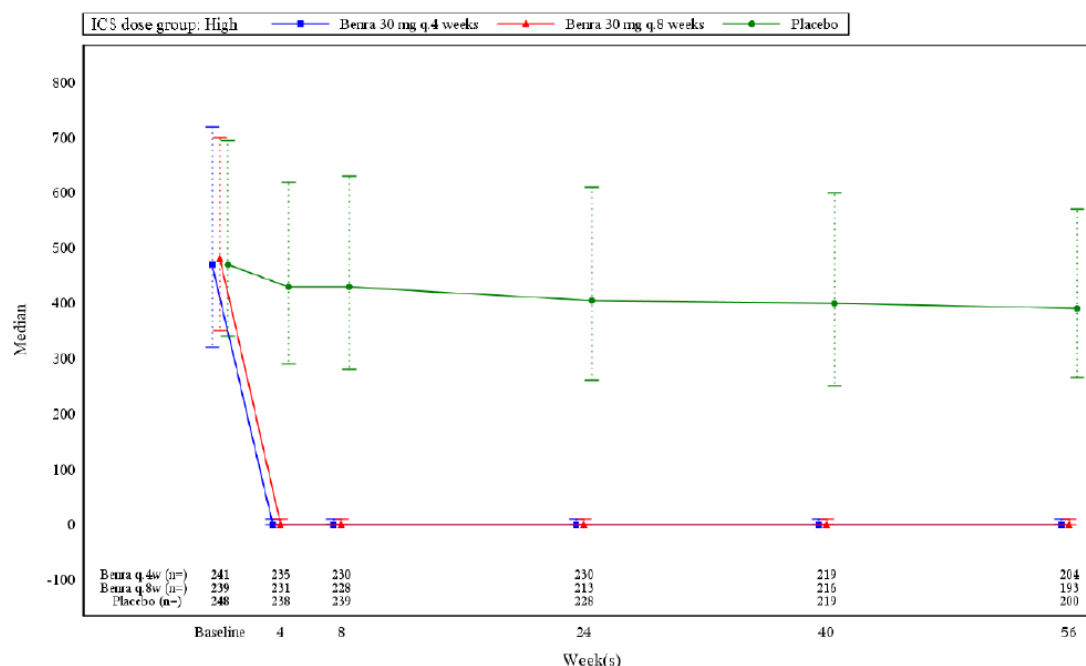
In Study D3250C00018, PK steady-state for the benralizumab 30 mg Q4W group was reached at Week 8. Patients in the benralizumab 30 mg Q8W group received treatment Q4W for the first 3 doses, followed by Q8W thereafter. The PK steady-state for the benralizumab 30 mg Q8W group was reached at Week 24. Steady-state serum C_{trough} was consistently higher beginning at Week 16 through the last common dosing time at Week 48 in the benralizumab 30 mg Q4W group (923.03 to 853.14 ng/mL, respectively) compared with the benralizumab 30 mg Q8W group (246.62 to 186.50 ng/mL, respectively). The geometric mean benralizumab serum concentration at Week 60 was 53.6 ng/mL and 18.6 ng/mL for the benralizumab 30 mg Q4W and Q8W groups, respectively.

The PK in adolescents was slightly higher than in adults, but individual PK exposure substantially overlapped between the 2 populations. In the benralizumab 30 mg Q8W group, PK was generally comparable between adolescents and adults beginning at Week 24. The median benralizumab serum C_{trough} ranged from 180.50 to 368.00 ng/mL in adolescents, and from 241.00 to 287.00 ng/mL in adults.

Blood Eosinophils:

Mean baseline blood eosinophil counts were similar across groups. In patients with a baseline blood eosinophil count $\geq 300/\mu$ L who were taking high dose ICS, both benralizumab 30 mg Q4W and Q8W demonstrated near complete depletion of eosinophils at Week 4 (-96.3% and -97.0%) that were maintained through Week 56 (-94.0% and -92.2%).

There was no reduction in blood eosinophils in the placebo group during the study. Both benralizumab 30 mg Q4W and Q8W demonstrated greater reductions in LS mean percent change from baseline in blood eosinophil counts compared with placebo at Week 4 (-104.2% and -105.0%, respectively; both $p < 0.001$) and at Week 56 (-112.3% and -106.8%, respectively; both $p < 0.001$). The results are shown in [Figure 5](#).



Error bars represent upper and lower quartiles.

Benra Benralizumab; ICS Inhaled corticosteroids; n Number of patients with data at that visit.

Figure 5 Median Blood Eosinophil Counts (Cells/mL) Over Time - Line Plot (Full Analysis Set, Baseline Blood Eosinophils $\geq 300/\text{mL}$, High-Dose Inhaled Corticosteroids (ICS))

(Source: CSR for Study D3250C00018, Figure 16, Page 175)

Similar results were observed for patients taking medium-dose ICS and for patients with blood baseline eosinophil counts $< 300/\mu\text{L}$.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen of 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter is appropriate as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype, based on the assessment of PK, PD, efficacy and safety measurements.

3.3.2.1 Benralizumab Dose Selection

PKPD modeling approach was utilized to select the appropriate dose to be evaluated in Phase 3 studies. Following subcutaneous administration, benralizumab PK was described by a two-compartment model with first-order elimination from the central compartment, and first-order absorption from the dosing compartment. The structure of the final PKPD model is shown in [Figure 6](#).

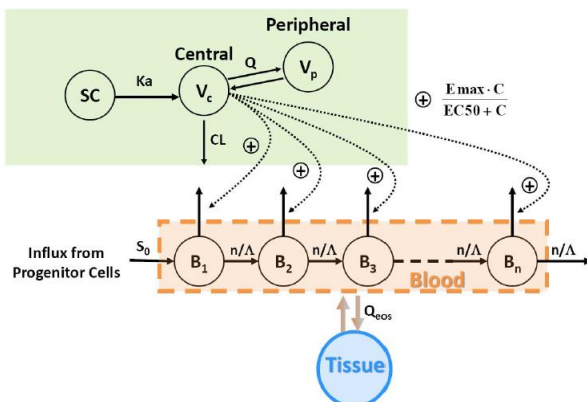
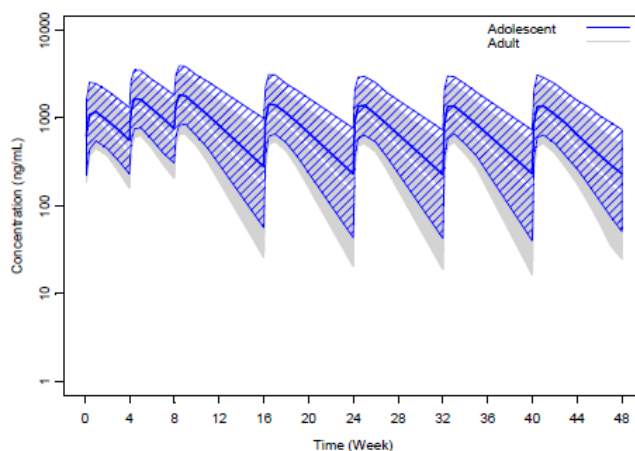


Figure 6 PKPD Model of Benralizumab in Humans

(Source: EOP2 meeting-bg-materials.pdf, Figure 12.3.3.1-1, Page 201)

Benralizumab exposure in adolescents (12-17 years old) was simulated using the full PopPK model. The simulation dataset included 1200 virtual adolescent patients with their body weights reflecting the overall weight distribution in this age range (12-17 years). Stochastic simulations were performed to obtain steady-state benralizumab exposures following multiple 20 mg Q8W SC administrations with an extra dose at Week 4 ([Figure 7](#)). Based on the simulations, adolescents with body weights at or greater than 35 kg were predicted to have slightly higher steady-state drug exposure than adults. However, there was substantial overlap in exposure between adolescents and adults.



Solid line: median; Shaded area: region between the 5th and 95th percentiles

Figure 7 Comparison of Predicted Benralizumab PK Exposure in Adults and Adolescence Subjects with Body Weight over 35 kg Following 20 mg Q8W Dosing

(Source: EOP2 meeting-bg-materials.pdf, Figure 12.3.3.1-1, Page 201)

For a discussion of the benefit:risk of benralizumab dose/dosing regimen selection from an efficacy and safety perspective, refer to the clinical review by the medical officer Dr. Sofia Chaudhry and Biometrics reviewer Dr. Yu Wang. A discussion on benralizumab dosing regimen selection from a Clinical Pharmacology perspective follows:

3.3.2.1.1 Phase 2 dose ranging study results and doses selection for Phase 3 studies

The proposed dose for marketing of 30 mg Q4W×3 + Q8W via SC route was supported by a Phase 2b dose-ranging study, MI-CP220. Study MI-CP220 was a randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of multiple-dose SC administration of benralizumab (2, 20, or 100 mg Q4W×3 + Q8W) in adult subjects with uncontrolled asthma requiring medium-dose ICS. In this study, eligible subjects were classified and stratified as having an eosinophilic or non-eosinophilic phenotype, using a proprietary mathematical algorithm to predict sputum eosinophils $\geq 2\%$ (ELEN Index) together with elevated baseline fraction of exhaled nitric oxide (FeNO). Approximately 80 patients were enrolled in each treatment arm. The last dose was given on Week 40 and the primary endpoint was annual asthma exacerbation rate (AER) from Week 1 to Week 52.

The AER results of Study MI-CP220 demonstrated a dose-response trend, in which lower dose (2 mg) did not reduce AER in patients with non-eosinophilic phenotype (rate ratio = 109%) whereas 20 mg and 100 mg reduced AER by 36% and 41% with the effective size of 100 mg reached statistical significance ([Table 1](#)).

Table 1 Summary of Annual Asthma Exacerbation Rate in mITT Population in Study MI-CP220

Parameter	EOS+				EOS-	
	Placebo N = 80	Benralizumab			Placebo N = 142	Benralizumab 100 mg N = 140
		2 mg N = 81	20 mg N = 81	100 mg N = 82		
Rate	0.57	0.65	0.37	0.34	0.56	0.43
80% CI of rate	(0.46, 0.70)	(0.53, 0.78)	(0.29, 0.48)	(0.26, 0.45)	(0.48, 0.65)	(0.36, 0.52)
RR	---	1.09	0.64	0.59	---	0.78
80% CI of RR	---	(0.74, 1.59)	(0.42, 0.97)	(0.40, 0.89)	---	(0.58, 1.05)
P-value	---	0.781	0.173	0.096	---	0.284

CI = confidence interval; ELEN Index = proprietary mathematical algorithm to predict elevated sputum eosinophils $\geq 2\%$; EOS- = ELEN Index negative and FeNO < 50 ppb; EOS+ = ELEN Index positive and/or FeNO ≥ 50 ppb; FeNO = fraction of exhaled nitric oxide; mITT = modified intent-to-treat; RR = rate ratio

Note, $p < 0.169$ was considered statistically significant

(Source: CSR MI-CP220, page 101, Table 11.4.1.1-1)

The dose-response relationship was also observed in reduction of peripheral blood eosinophil counts. The baseline mean peripheral blood eosinophil counts were 247, 415, 358, and 249 cells/ μ L in placebo, 2 mg, 20 mg, and 100 mg treatment group, respectively. At Week 40, the mean eosinophil counts were reduced to 213 ($\downarrow 14\%$), 180 ($\downarrow 57\%$), 88 ($\downarrow 75\%$), and 59 ($\downarrow 76\%$) in placebo, 2 mg, 20 mg, and 100 mg treatment group, respectively.

An exposure-response model on AER was explored based on benralizumab trough concentrations at steady state and efficacy results from Study MI-CP220. The model estimated that 30 mg via SC route to be the ED₉₀ dose following Q4W×3 + Q8W dosing regimen ([Figure 8](#)). The EC₉₀ dose was expected to

maximize therapeutic efficacy while reducing the impact of steady-state PK variability on efficacy outcome.

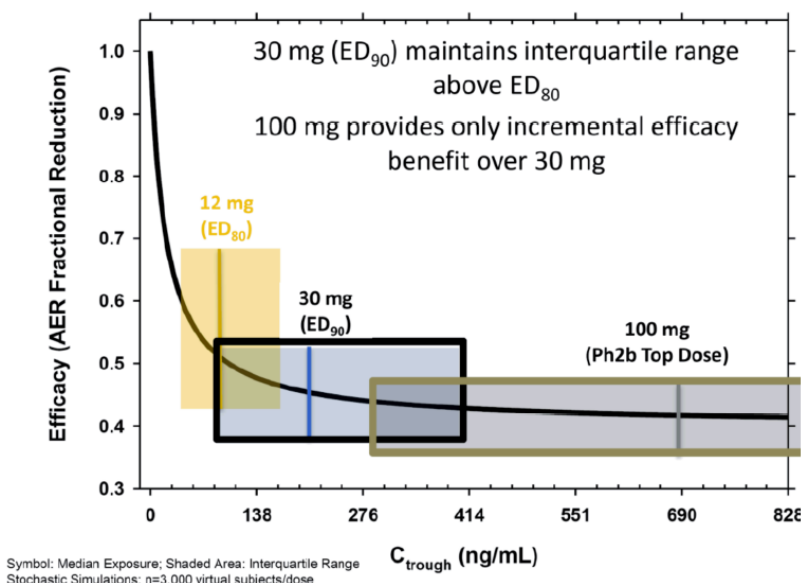


Figure 8 Simulated Exposure-Response for Supporting 30 mg SC Q4wx3 + Q8w as the EC₉₀ Dose for Reducing AER in Patients With Baseline Eosinophil Count ≥ 300 Cells/μL

(Source: Exposure-response Modeling Report, Figure 12, Page 45)

At the end of Phase 2 meeting, while agreeing to the dose selection process in principle, the Agency advised the Sponsor to evaluate more than one dose in the pivotal trials. Based on this advice, in addition to 30 mg Q8W regimen (with an extra dose at Week 4), a higher dose of 30 mg Q4W was also selected for evaluation in the primary registration studies to ascertain if higher serum trough levels would decrease the immunogenic profile of benralizumab and potentially improve efficacy in subjects with low PK exposure.

3.3.2.1.2 Are there differences in pharmacokinetics between two dosing regimens (i.e. 30 mg Q4W and 30 mg Q4W×3 + Q8W) investigated in pivotal Phase 3 Studies (Study D3250C00017 and Study D3250C00018)?

The pharmacokinetics of benralizumab are identical between two dosing regimens (i.e. Q4W and Q4W×3 + Q8W) before Week 16 as the dose and dosing interval are identical between two dosing regimens. Beginning Week 16, Q4W regimen delivers dose twice every 8 weeks whereas Q8W regimen delivers dose once every 8 weeks (Figure 9). Due to the relative short elimination half-life (~15 days), the steady state is reached after the third dose following Q4W regimen and the second dose following Q8W regimen. Since there is little accumulation at the steady state following both dosing regimen, the exposure (AUC_τ) of Q8W regimen is expected to be only half the value of Q4W regimen. The observed mean C_{trough,ss} of Q8W regimen was approximately 20% of Q4W regimen (Figure 10). The Phase 3 PK sampling scheme was not able to capture the difference of C_{max} between two dosing regimen. Based on PK parameters obtained from population PK analysis, simulation estimates that the C_{max} of Q8W regimen is approximately 80% that of Q4W regimen (Figure 9).

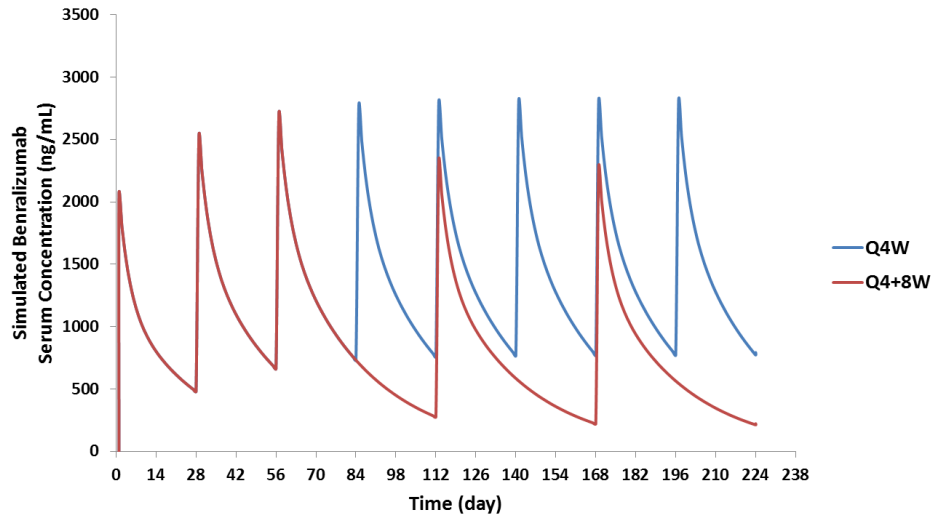


Figure 9 Simulated PK-Time Profile Following Either 30 mg Q4W (Blue) or 30 mg Q4Wx3 + Q8W (Red)

(Source: Reviewer analysis based on Sponsor's typical values of PK parameters estimated from 2-compartment population PK model)

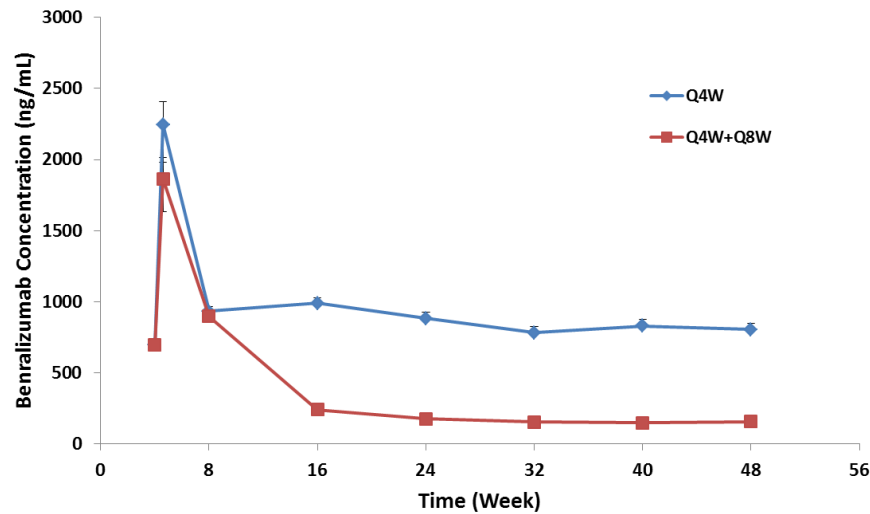


Figure 10 Observed PK-Time Profile Following Either 30 mg Q4W (Blue, N=814) or 30 mg Q4Wx3 + Q8W (Red, N=790) (Study D3250C00017 and Study D3250C00018 Combined)

Error bars represent standard error. BLQ values were imputed with $\frac{1}{2}$ LLOQ value (1.93 ng/mL).

(Source: Reviewer analysis based on pkdata_17FEB2017.xpt)

3.3.2.1.3 Does exposure-response analysis support the proposed dosing-regimen?

There was no noticeable exposure-response relationship between individual median observed $C_{trough,ss}$ and primary efficacy endpoint (asthma exacerbation rate, AER) in phase 3 studies. The exposure-response curve was generally flat for asthma exacerbation across a range of more than 6-fold (<212 ng/mL to ≥ 1250 ng/mL) median observed $C_{trough,ss}$.

Similarly, there is no noticeable exposure-response relationship between $C_{average,ss}$ and Phase 3 secondary efficacy endpoint (FEV₁ change from baseline at the end of treatment). The exposure-response curve was generally flat for FEV₁ change from baseline at EOT across a range of 10-fold (200 ng/mL to 2000 ng/mL) $C_{average,ss}$.

Therefore, the lack of noticeable exposure-response relationship supports the proposed dosing regimen with longer dosing interval of 8 weeks between doses following the initial 3 doses administered in 4 week intervals.

3.3.2.1.4 What is the difference on peripheral blood eosinophil counts between two dosing regimens (i.e. 30 mg Q4W and 30 mg Q4W×3 + Q8W) investigated in pivotal Phase 3 Studies?

Both dosing regimens substantially reduced peripheral blood eosinophil counts in asthma patients compared to placebo in the two Phase 3 studies (D3250C00017 and D3250C00018). The magnitude of eosinophil count reduction could be maintained steadily at least for 8 weeks after discontinuation of the treatment (Figure 11). The median peripheral blood eosinophil counts from both dosing regimens were zero(0) at steady state (Table 2). There were no clinical meaningful differences of mean peripheral blood eosinophil counts between two dosing regimens at steady state.

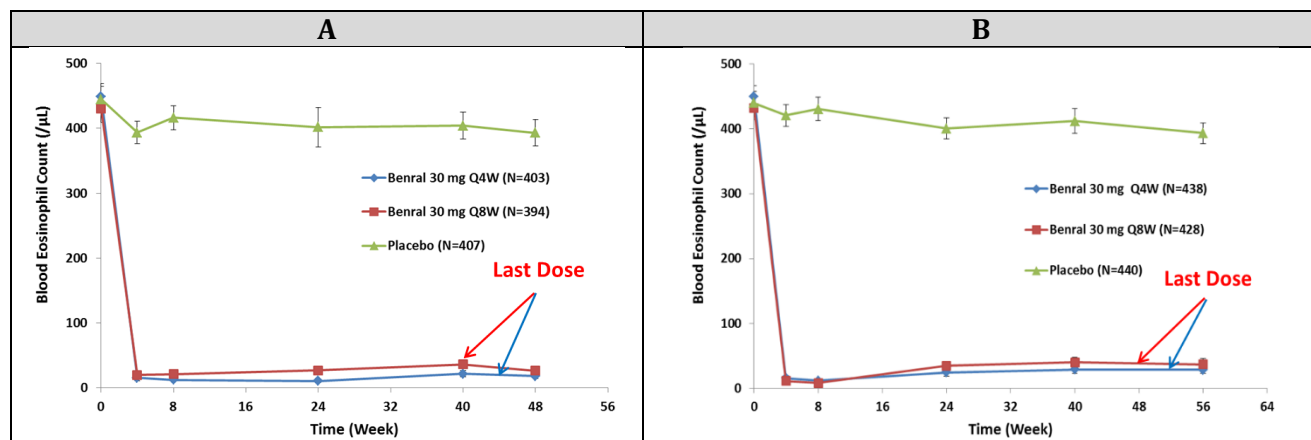


Figure 11 Peripheral Blood Eosinophil Count-Time Profiles Following Either 30 mg Q4W (Blue) or 30 mg Q4W×3 + Q8W (Red) from Study D3250C00017 (A) and Study D3250C00018 (B)

In Study D3250C00017, patients received the last dose of benralizumab on Week 44 and Week 40 in Q4W and Q4W×3 + Q8W treatment arms, respectively; In Study D3250C00018, patients received the last dose of benralizumab on Week 52 and Week 48 in Q4W and Q4W×3 + Q8W treatment arms, respectively; Error bars represent standard error.

(Source: Reviewer analysis based on RSLB.xpt)

Table 2 **Peripheral Blood Eosinophil Counts (/μL) at Steady State Following Benralizumab Treatment in Study D3250C00017 and Study D3250C00018**

Study D3250C00017				
Dosing Regimen	Counts Parameter	Week 24	Week 40	Week 48
Q4W*	Mean* (SE)	10.8 (2.21)	21.9 (4.91)	18.3 (3.91)
	Proportion of 0	64%	62%	63%
Q4W×3 + Q8W*	Mean* (SE)	26.9 (4.97)	36.2 (6.41)	26.4 (4.64)
	Proportion of 0	58%	58%	60%
Study D3250C00018				
Dosing Regimen	Counts Parameter	Week 24	Week 40	Week 56
Q4W*	Mean* (SE)	24.8 (5.81)	29.1 (5.96)	28.8 (5.90)
	Proportion of 0	61%	62%	59%
Q4W×3 + Q8W*	Mean* (SE)	34.8 (7.41)	40.2 (8.09)	37.0 (8.87)
	Proportion of 0	61%	61%	62%

(Source: Reviewer's analysis from RSLB.xpt)

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No, an alternative dose or dosing regimen is not required for subpopulation based on the intrinsic factors such as weight, age, gender, race, ethnicity, hepatic and renal impairment. The fixed 30 mg dose given once every 8 weeks following the first 3 doses given every 4 weeks is appropriate.

3.3.3.1 Body Weight:

Body weight was identified as a significant covariate in the population pharmacokinetic analysis. Benralizumab CL increased with body weight similar to other therapeutic mAb. The effect of body weight was near allometric for benralizumab, with a power parameter estimate of 0.831 (90% CI: 0.770, 0.891).

The effect of body weight on benralizumab PD and efficacy as assessed by evaluating the observed blood eosinophil and FEV₁ responses in patients with large and extremely large body weights (Studies SIRROCO and CALIMA), showed that patients with the top quartile body weight (≥89 kg) had blood eosinophil depletion and FEV₁ improvement to a similar extent as other patients in the 30 mg Q8W group (Figure 12). Blood eosinophil counts depletion throughout the study period and similar benralizumab FEV₁ improvements relative to placebo treatment were observed even in patients with extremely large body weights (≥115 kg, 95th percentile) in the same body weight range (Figure 13).

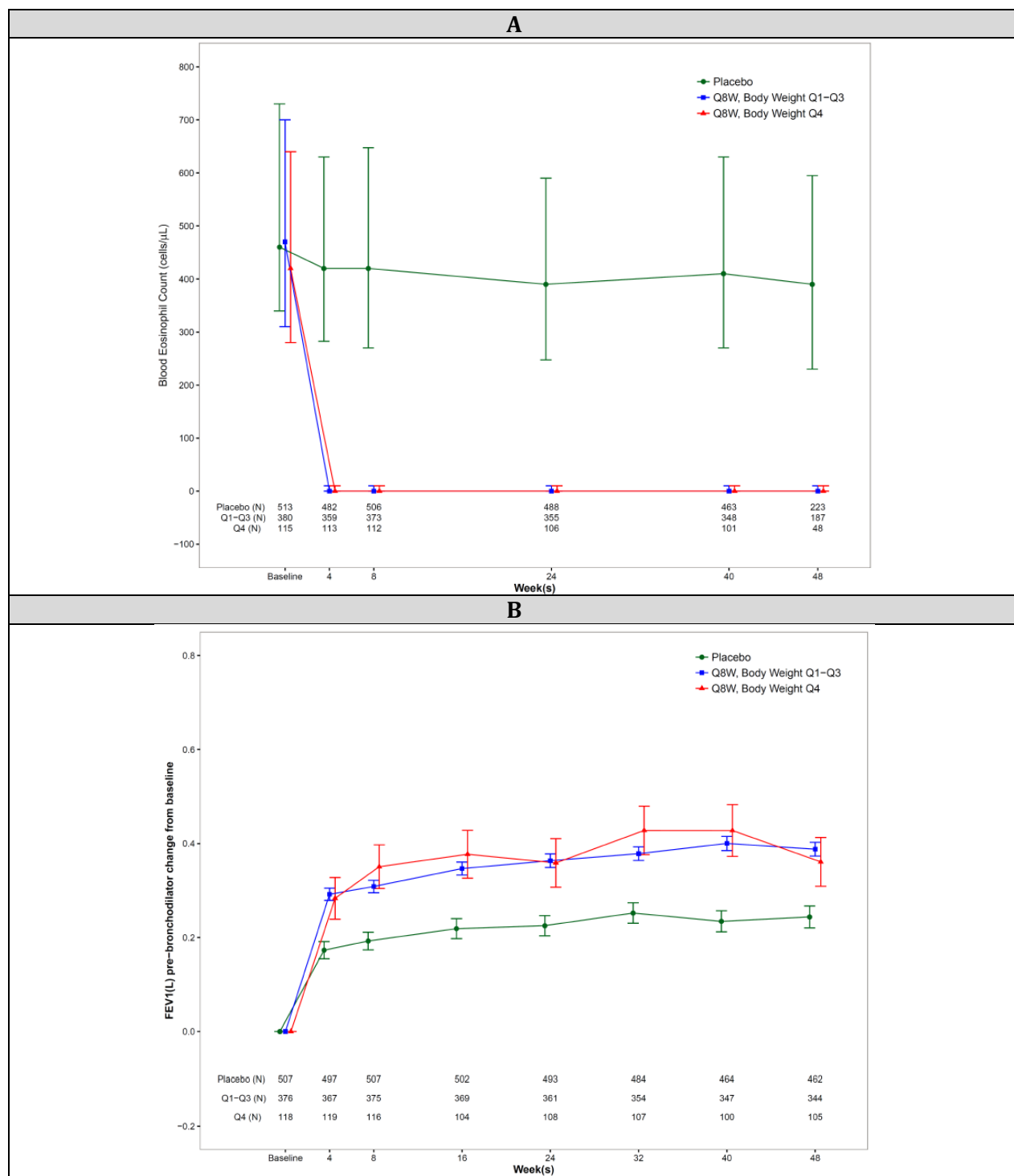


Figure 12 Effect of Body Weight on Blood Eosinophil Response or on Change in Forced Expiratory Volume in 1 Second in Patients With Top Quartile Body Weight (High Inhaled Corticosteroids, Eosinophils ≥ 300 Cells/ μ L, 30 mg Q8W Benralizumab)

(Source: Summary of Clinical Pharmacology, Figure 36, Page 142-143)

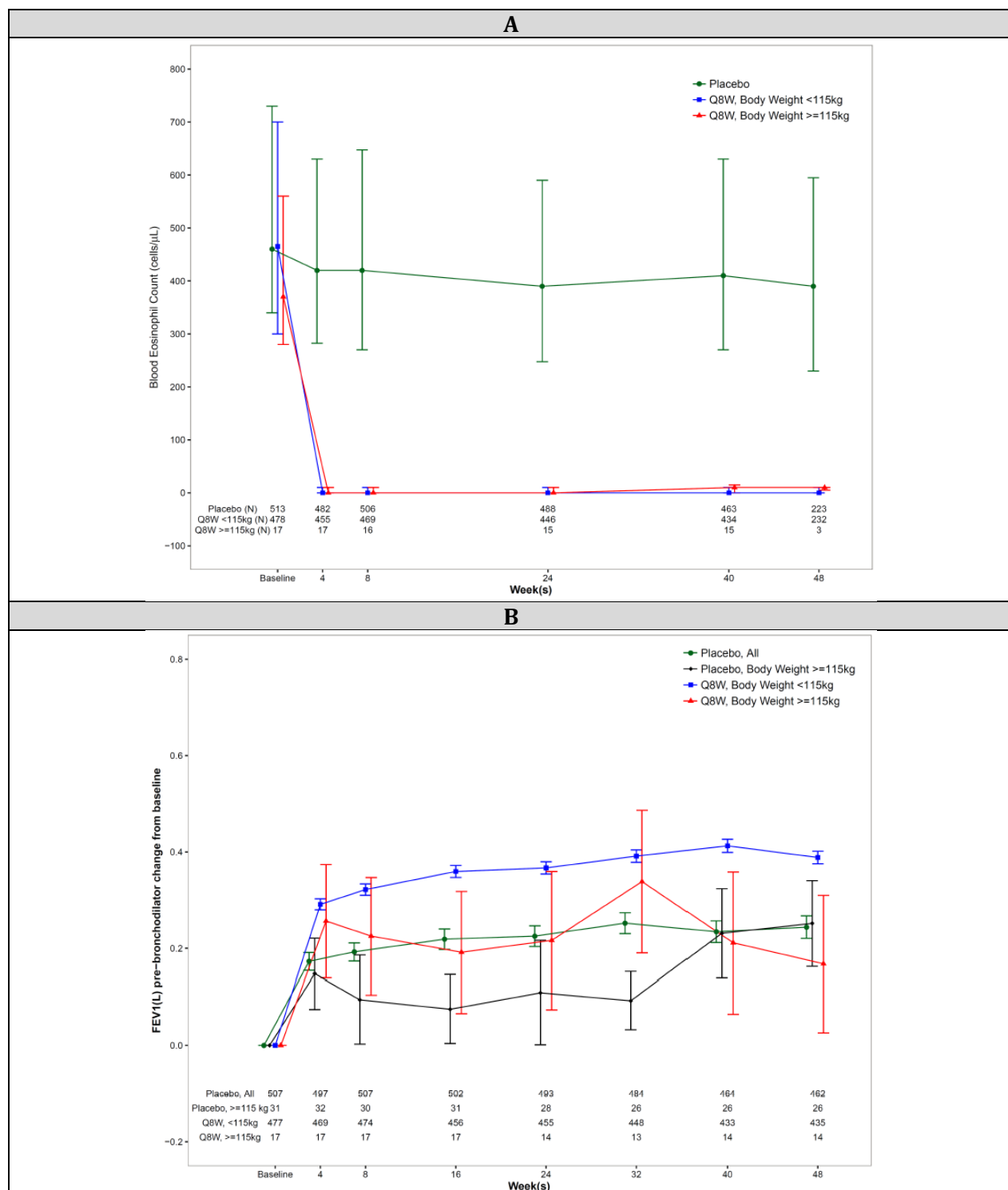


Figure 13 Effect of Body Weight on Blood Eosinophil Response or on Change in Forced Expiratory Volume in 1 Second in Patients With Extremely Large Body Weight (High Inhaled Corticosteroids, Eosinophils \geq 300 Cells/ μ L, 30 mg Q8W Benralizumab)

(Source: Summary of Clinical Pharmacology, Figure 37, Page 144-145)

Since the 30 mg Q8W dosing regimen was on the plateau portion of the exposure-response curve, large body weight had no impact on blood eosinophil depletion or efficacy.

Therefore, based on the pharmacokinetic and efficacy data discussed above, the proposed fixed dosing of 30 mg SC given Q8W following an initial 3 doses given Q4W is considered to be appropriate and no alternative dose or dosing regimen for different body weight subgroups is necessary.

3.3.3.2 Adolescents

3.3.3.2.1 Benralizumab PK characteristics in adolescents

Benralizumab PK in adolescent patients was comparable to that in adult patients.

In Study D3250C00017, of the 53 evaluable adolescent patients, 50 completed the study (9, 18, and 23 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively), and 28 had PK data (12 and 16 in the benralizumab 30 mg Q4W, Q8W groups, respectively) available for assessment. In Study D3250C00018, of the 55 evaluable adolescent patients, 45 completed the study (9, 8, and 18 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively), and 29 had PK data (10 and 19 in the benralizumab 30 mg Q4W, Q8W groups, respectively) available for assessment.

For both dosing regimens in Studies D3250C00017 and D3250C00018, the mean C_{trough} of benralizumab overlapped between adolescents and adult patients. (Figure 14)

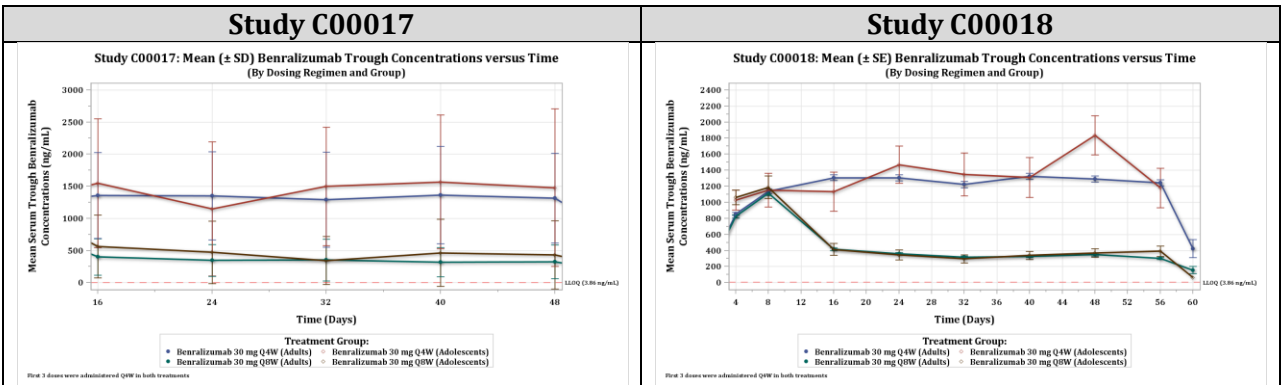


Figure 14 Mean (±SD) (Study C00017) and Mean (±SE) (Study C00018) Benralizumab Trough Concentration versus Time (by Dosing Regimen and Group)

(Source: Reviewer’s analysis)

3.3.3.2.2 Benralizumab PD characteristics in adolescents

The inhibition effect benralizumab on peripheral blood eosinophil counts in adolescents were similar to adults.

Similar to the results in adults, both dosing regimens (i.e. 30 mg Q4W and 30 mg Q4W×3 + Q8W) substantially reduced peripheral blood eosinophil counts in adolescent patients compared to placebo (Figure 15) in both studies (D3250C00017 and D3250C00018). Although the mean of peripheral blood eosinophil counts in Study D3250C00018 fluctuated with a wider range due to relatively higher inter-subject variability, the median peripheral blood eosinophil counts from both dosing regimens were kept no great than 10 from Week 4 to Week 56 (Table 3).

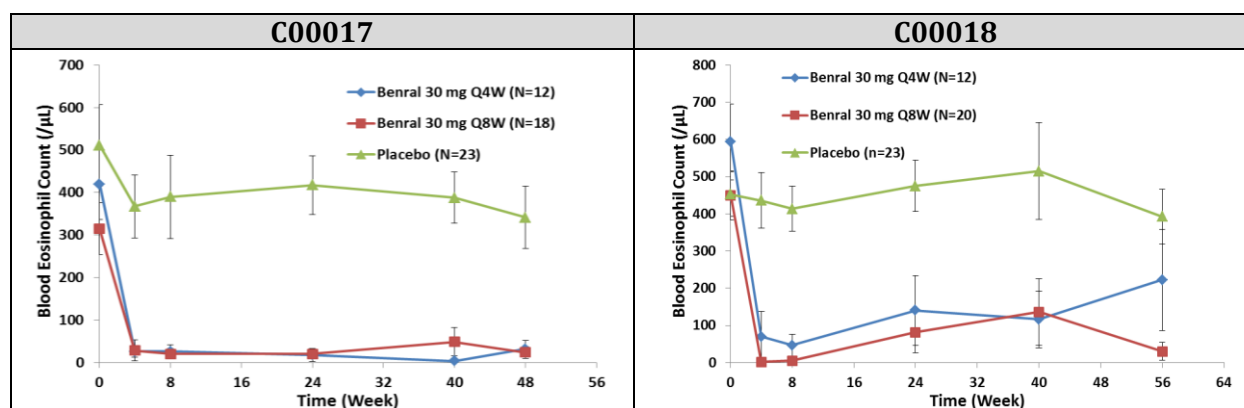


Figure 15 Peripheral Blood Eosinophil Count-Time Profiles in Adolescent Patients Following Either 30 mg Q4W (Blue) or 30 mg Q4Wx3 + Q8W (Red) from Study D3250C00017 and Study D3250C00018 . Error Bars Represent Standard Error

(Source: Reviewer analysis based on RSLB.xpt)

Table 3 Median Peripheral Blood Eosinophil Counts (/μL) in Adolescent Patients in Study D3250C00017 and Study D3250C00018

Study	Treatment Arm	Week 24	Week 40	Week 48/56*
D3250C00017	Q4W	0 (n=10)	0 (n=8)	0 (n=9)
	Q4Wx3 + Q8W	0 (n=17)	5 (n=16)	0 (n=16)
D3250C00018	Q4W	0 (n=9)	5 (n=10)	10 (n=9)
	Q4Wx3 + Q8W	0 (n=18)	0 (n=20)	0 (n=16)

* Week 48 for Study D3250C00017 and Week 56 for Study D3250C00018

(Source: Reviewer's analysis from RSLB.xpt)

3.3.3.2.3 Immunogenicity in adolescents

The overall ADA incidence in adolescent patients was 9% (4/46), 4% (1/24), and 24% (9/38) in placebo, 30 mg Q4W, and 30mg Q4Wx3 + Q8W treatment groups, respectively. However, the relative wide differences of ADA incidence between different treatment groups could possibly be explained by the small sample size in adolescents.

3.3.3.3 Age and Gender and Race:

In the Population PK analysis, age, gender and race had no impact on benralizumab CL.

3.3.3.4 Renal Impairment:

Due to size restriction of glomerular filtration in healthy kidneys, benralizumab, a monoclonal antibody with a molecular weight of 147 kDa is not expected to have substantial renal clearance. The sponsor did not conduct a formal renal impairment study.

Benralizumab CL in patients with varying degrees of renal impairment were comparable to patients with normal CLCR ([Figure 16](#)).

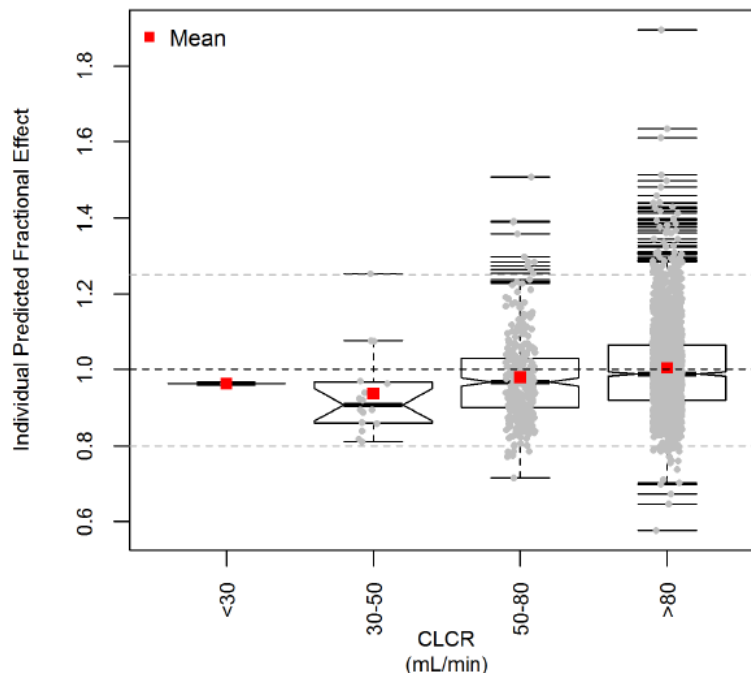


Figure 16 Individual Predictions of the Fractional Effect of CLCR on CL Grouped By CLCR Values Associated With Levels of Renal Function

(Source: Population-PK report, Figure 4, Page 61)

No dose adjustment is recommended for patients with renal impairment.

3.3.3.5 Hepatic Impairment:

Monoclonal antibodies are catabolized primarily by non-specific cellular uptake and subsequent lysosomal degradation not restricted to hepatic tissue. Hepatic function is not expected to substantially impact the elimination of benralizumab and a hepatic impairment study was not conducted by the Sponsor. Based on population pharmacokinetic analysis, baseline hepatic function biomarkers (ALT, AST, and bilirubin) had no clinically relevant effect on benralizumab clearance. Dose adjustment in patients with hepatic impairment is not recommended.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No formal drug-drug interaction studies were conducted in this submission. Direct drug-drug interactions are not expected based on the Cytochrome P450s or transporters since benralizumab is a monoclonal antibody. The primary elimination pathway for benralizumab is clearance by the reticuloendothelial system, similar to that of endogenous IgG. Currently there is no information in the literature to suggest that IL-5R α is expressed on hepatocytes or that aspects of hepatocyte biology or CYP activity are regulated by IL-5.

Population PK analysis showed that commonly used small molecule drugs (montelukast, paracetamol (acetaminophen), proton pump inhibitors, macrolides, and theophylline/aminophylline) had no effect on the clearance of benralizumab.

Food-drug interactions are not anticipated or applicable since benralizumab is administered by the SC route.

3.3.5 What was the incidence (rate) of the formation of the anti-drug antibodies (ADAs), and were there any effects of ADA on the PK, safety and efficacy of benralizumab?

3.3.5.1 What is the incidence of the formation of the ADA, including the rate of pre-existing antibodies, the rate of ADA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

In the benralizumab clinical program, observations that generally were ADA positive had an increased probability of being below limit of quantitation (BLQ) (412 of 1103 (37.4%) ADA-positive samples had BLQ PK versus 635 of 14050 (4.5%) ADA-negative samples that had BLQ PK). The distribution of plasma or serum sample ADA status by study is provided in [Table 4](#).

Table 4 Summary of ADA Status

Study Phase	CP158 1	CP166 1	CP186 2	CP197 2a	CP220 ^a 2b	SIROCCO 3	CALIMA 3	BISE 3	Total >LLOQ PK Conc. ^b	Total BLQ PK Conc. ^c	Total
N	539	126	270	146	2210	5213	6444	205	14106	1047	15153
ADA positive	30	7	9	9	255	307	470	16	691	412	1103
ADA negative or missing	509	119	261	137	1955	4906	5974	189	13415	635	14050

^a PK data for the 2 mg Q4W SC dose from Study CP220 were initially included in the analysis data file for evaluation in base model development. These data were later excluded from the population PK analysis due to low and variable PK observations and are not reported here.

^b Total number of samples analyzed for ADA that had PK concentration above the LLOQ

^c Total number of samples analyzed for ADA that had PK concentration BLQ

ADA Anti-drug antibodies; BLQ Below limit of quantification; Conc. Concentration; LLOQ Lower limit of quantification; N Number of subjects; PK Pharmacokinetic.

(Source: Population-PK-report, Table 8, page 35)

An integrated analysis was performed using pooled data from 2 Phase 3 studies (D3250C00017 and D3250C00018). Approximately 9 to 10 blood samples were scheduled to be collected from each subject for ADA analysis during one-year period of treatment. The pre-existing ADA incidence was approximately 2% and was consistent across placebo arm and active treatment arms at baseline ([Table 5](#)). The overall ADA incidence in two active treatment arms were similar, with 13.1% and 14.9% in 30 mg Q4W arm and 30mg Q4W×3 + Q8W arm, respectively. Approximately two thirds of the ADA-positive patients were consistently ADA-positive, which is defined as positive at ≥ 2 post-baseline assessments or positive at last post-baseline assessment. In addition, approximately 70-80% of ADA-positive patients were also positive on the neutralizing antibody.

Table 5 Summary of Anti-Drug Antibody Responses* from Study D3250C00017 and D3250C00018

ADA Category	30 mg Q4W	30mg Q4W×3 + Q8W	Placebo
Pre-Existing ADA Incidence	1.9% (16/840)	2.0% (16/820)	1.9% (16/847)
ADA Incidence (total)	13.1% (110/840)	14.9% (122/820)	4.0% (34/847)
Persistent ADA Incidence [#]	8.0% (67/840)	9.9% (81/820)	2.7% (23/847)
Neutralizing Antibody Incidence	8.9% (75/840)	12.0% (98/820)	2.2% (19/847)

*Incidence rate (n/N), N represents the number of patients with at least one ADA result. And n represents the number of patients with at least one result of the specified category.

[#]Persistently positive is defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment.

(Source: eCTD for BLA 761070, Module 5.3.5.3, Adapted from Integrated Summary of Immunogenicity.pdf, Table 13, page 71)

3.3.5.2 Does immunogenicity affect the PK of Benralizumab?

Presence of ADA reduced benralizumab serum concentration and increased drug clearance. Sponsor's PK validation report demonstrated that anti-benralizumab antibody (goat anti-benralizumab antibody) significantly interfered with the measurement of serum benralizumab concentrations- 10 ng/mL anti-benralizumab antibody reduced benralizumab concentration value by 49.4% at lower quality control (LQC) level; 1000 ng/mL anti-benralizumab antibody reduced benralizumab concentration value by 60.3% and 57.2% at LQC and higher quality control(HQC) level, respectively.

Therefore the significant effect of ADA on benralizumab PK is expected. The geometric mean C_{trough} value from ADA-positive PK samples from patients in 30mg Q4W×3 + Q8W treatment arm in 2 Phase 3 studies was only 5% of the mean C_{trough} value from ADA-negative PK samples ([Figure 17A](#)). The C_{trough} comparison result was also similar in patients receiving 3mg Q4W treatment. In addition, benralizumab CL was compared in 316 patients having both ADA-positive and ADA-negative periods in pooled population PK dataset. The median benralizumab CL increased 2.3-fold when ADA-negative results switched to ADA-positive status in those patients ([Figure 17B](#)).

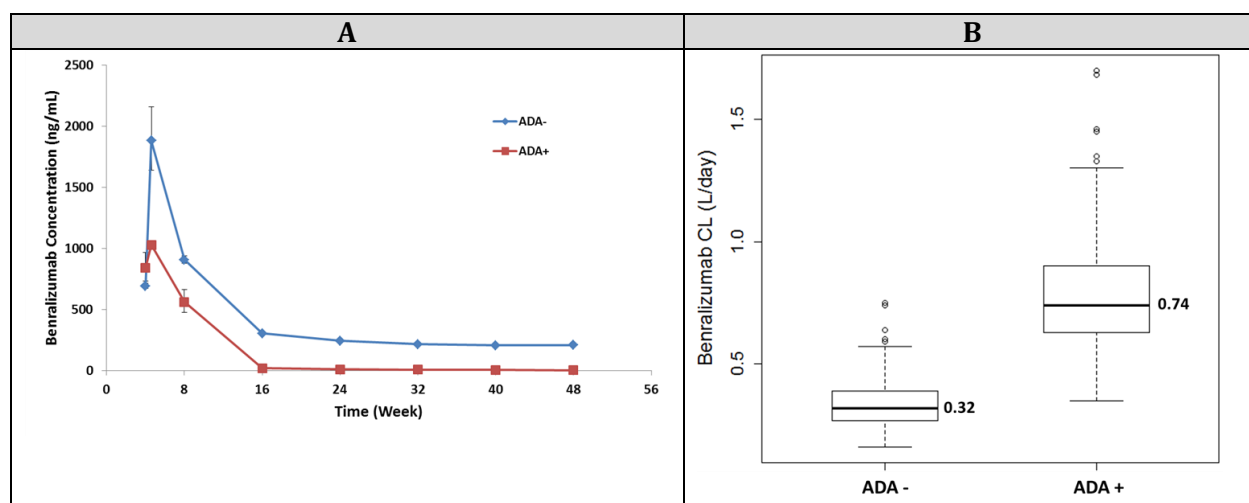


Figure 17 ADA's effect on Benralizumab PK: (A) Mean PK Profile Comparison Between ADA-Positive PK Samples and ADA-Negative PK Samples from Patients in 30mg Q4Wx3 + Q8W treatment Arm in Study D3250C00017 and Study D3250C00018. BLQ Values Were Imputed With $\frac{1}{2}$ LOQ (1.93 ng/mL); (B) Benralizumab CL Comparison in 316 Subjects Between Their ADA-Negative Period and ADA-Positive Period. Subjects Were From Pooled Population PK Dataset With Criteria That They Must Have Both ADA-Positive and ADA-Negative Periods During the Treatment

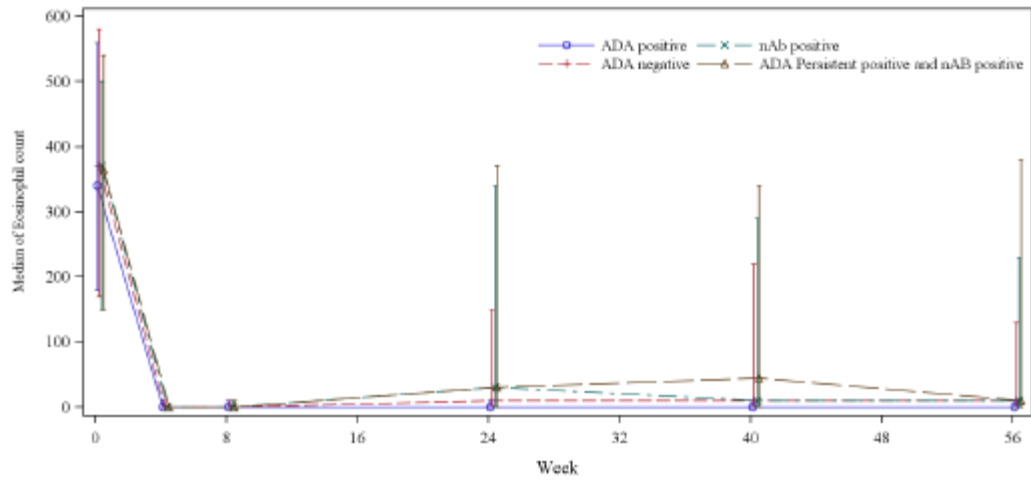
(Source: Reviewer's analysis)

3.3.5.2 Does immunogenicity affect the PD of Benralizumab?

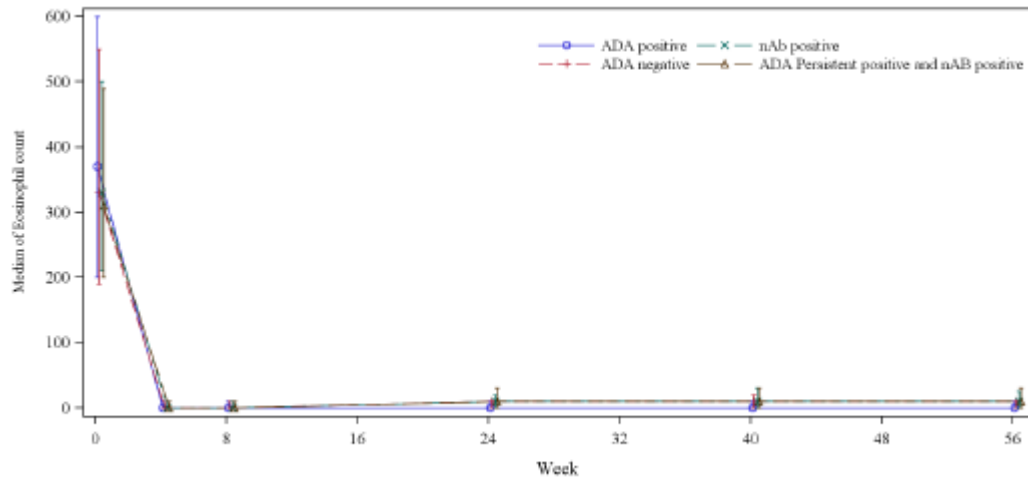
Presence of ADA slightly impaired drug's reduction effect on peripheral blood eosinophil counts.

Peripheral blood eosinophil counts from patients in two active treatment arms from two Phase 3 Studies (D3250C00017 and D3250C00018) to characterize the ADA's effect on PD were evaluated. Mean blood eosinophil counts summarized from accompanying ADA-negative samples were kept below $50/\mu\text{L}$ after Week 4 for both treatments in two studies ([Figure 18](#)). For ADA-positive samples, a slight increase in median eosinophil counts and large variability were observed.

Study D3250C00018



Benralizumab 30 mg Q8W group



Benralizumab 30 mg Q4W

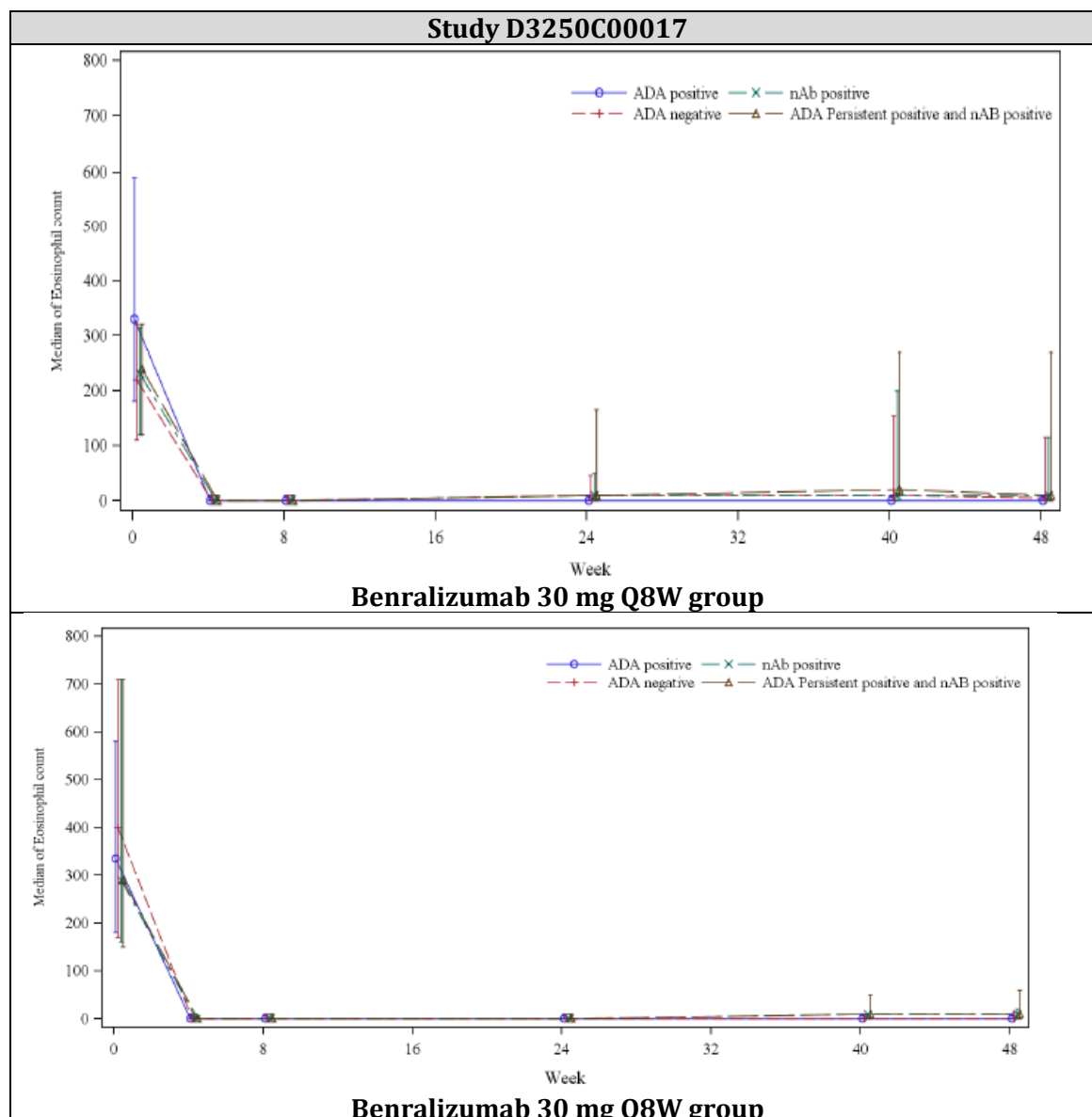


Figure 18 ADA's Effect on Peripheral Blood Eosinophil Counts. Eosinophil Counts Were Pooled From Patients in Two Active Treatment Arms (Q4W and Q4Wx3 + Q8W) From Phase 3 Study D3250C00017 and Study D3250C00018. Blood Samples Were Classified By Accompanying ADA

(Source: eCTD for BLA 761070, Module 5.3.5.1, CSR for Study C00018, Figures 22-23, pp 275-276, and CSR for Study C00017, Figures 22-23, pp 273-274)

3.3.5.3 What is the impact of ADA on clinical efficacy?

There was no indication that ADA-positive status could result in an impairment of efficacy. There was no increase of annual asthma exacerbation rate (crude rate) in ADA-positive patients. The annual asthma exacerbation in ADA-positive patients did not increase compared to ADA-negative patients in both active treatment arms from the two Phase 3 Studies D3250C00017 and D3250C00018 (Table 6). In addition, for ADA categories of ADA titer >median of the maximum titer, persistently ADA-positive, neutralizing Ab-positive, and persistently ADA-positive and nAb-positive, annual asthma exacerbation rates were similar compared with ADA-negative patients for both active treatment arms.

Table 6 Annual Asthma Exacerbation Rates (Crude Rates) by ADA Category from Study D3250C00017 and D3250C00018

ADA Category	n	Benra 30 mg Q4W (N=841)			n	Benra 30 mg Q8W (N=822)			n	Placebo (N=847)		
		Total number of exacer.	Total follow up time (yrs)	Rate		Total number of exacer.	Total follow up time (yrs)	Rate		Total number of exacer.	Total follow up time (yrs)	Rate
Negative	730	566	703.0	0.81	698	466	659.4	0.71	813	967	786.9	1.23
Positive	110	63	108.6	0.58	122	85	120.5	0.71	34	46	32.9	1.40
ADA titre >median	51	27	51.3	0.53	48	21	47.5	0.44	15	19	14.6	1.30
Persistently positive	67	37	66.9	0.55	81	49	79.4	0.62	23	28	21.9	1.28
nAb positive	75	37	74.1	0.50	98	74	96.1	0.77	19	24	18.9	1.27
ADA persistently positive and nAb positive	60	28	59.6	0.47	76	46	76.4	0.62	15	21	14.6	1.44

(Source: eCTD for BLA 761070, Module 5.3.5.3, Integrated Summary of Immunogenicity.pdf, Table 22, page 100)

3.3.5.4 What is the impact of ADA on clinical safety?

There was no indication of an effect of ADA-positive status on overall TEAE and SAE reporting.

The percentages of ADA-positive patients reporting TEAEs and SAEs were similar to the percentages of ADA-negative patients in both active treatment groups from the two Phase 3 Studies D3250C00017 and D3250C00018 (Table 7).

Table 7 Summary of Adverse Events Incidence* by ADA Responses from Study D3250C00017 and D3250C00018

Safety	ADA Status	30 mg Q4W	30mg Q4W×3 + Q8W	Placebo
Patients with any AE	ADA+	77% (85/110)	76% (93/122)	77% (26/34)
	ADA-	73% (536/730)	73 (510/698)	78% (635/813)
Patients with SAE	ADA+	11% (12/110)	15% (12/122)	12% (4/34)
	ADA-	12% (85/730)	12% (80/698)	14% (115/813)
Patients with Hypersensitivity	ADA+	3.6% (4/110)	4.1% (5/122)	2.9% (1/34)
	ADA-	3.0% (22/730)	2.9% (20/698)	3.4% (28/813)

* Incidence rate (n/N)

(Source: eCTD for BLA 761070, Module 5.3.5.3, Adapted from Integrated Summary of Immunogenicity.pdf, Table 1.8.2, page 505; Table 1.8.6, page 802; Table 1.8.21, page 1461)

Hypersensitivity TEAE incidence was either comparable between ADA-positive (3.6%) and ADA-negative patients (3.0%) in 30 mg Q4W treatment arm, or higher in ADA-positive patients (4.1%) compared to ADA-negative patients (2.9%) in 30mg Q4W×3 + Q8W treatment arm. However, the comparable hypersensitivity TEAE incidence (3.4%) observed in ADA-negative patients from placebo arm made interpretation of those observations difficult.

3.3.6 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No bioequivalency study was conducted since the clinical and commercial drug products (Process 3) are identical in formulation and primary container closure system. The differences in the clinical and commercial presentations is that the syringe accessories differ only in the color of the extended finger flange and plunger rod and the logo on the plunger rod. The composition of benralizumab drug product is shown in [Table 8](#).

Table 8 Composition of Benralizumab SC Drug Product

Ingredient	Concentration	Unit Formula per 30 mg syringe	Purpose	Quality Standard
<i>Active Ingredient</i>				
Benralizumab	30 mg/mL	30 mg	Active	In-house Reference Standard
<i>Excipients</i>				
L-Histidine	9 mM	1.4 mg	(b) (4)	USP/NF; Ph. Eur.; JP
L-Histidine hydrochloride monohydrate	11 mM	2.3 mg		Ph. Eur.; JP
α,α-trehalose dihydrate	0.25 M	95 mg		USP/NF; Ph. Eur.; JP
Polysorbate 20 (b) (4)	0.006% w/v	0.06 mg		USP/NF; Ph. Eur.; JP
Water for Injection	Not applicable	Approximately (b) (4) mg		USP/NF; Ph. Eur.; JP

JP = Japanese Pharmacopoeia; Ph. Eur. = European Pharmacopoeia; USP/NF = United States Pharmacopoeia/National Formulary

(Source: Module 2.3.P, Drug Product, Table 2.3.P.1-1, page 1)

Three Drug Product formulation process changes occurred during the clinical development program. Processes 1 and 2 Drug Products were used in the Phase 1 and 2 studies, respectively. The drug product used in the Phase 2b study MI-CP220 was manufactured using the Process 2 method.

(b) (4) The protein concentration was (b) (4) mg/mL for the process 2 material compared to 30 mg/mL for the Process 3 material ([Table 9](#)).

Findings from Study MI-CP220 were used in an exposure-response model to determine the dose to be evaluated in the pivotal Phase 3 trials. The three Drug Product formulation processes were supported by analytical comparability testing. (Please see the Product Quality Review from Dr. Jennifer Swisher) . No direct PK comparisons were made between formulations using these different processes.

Cross-study PK comparison based on formulations for the three processes used in the Benralizumab BLA program show the following:

1. The half-life of elimination for Benralizumab was ~19 days following Process 1 and Process 2 material.

2. The T_{max} value of 7 days was similar for Process 1 and Process 2 material. In both Phase 3 studies, C00017 and C00018, PK samples were collected on Day 7, close to the timepoint assessed with the earlier formulation.
3. The concentration on Day 7, Week 4 for studies, C00017 and C00018, was in the same range of C_{max} observed with the Process 2 formulation.

There appears to be no marked PK difference between the formulations from these three processes.

Table 9 Benralizumab Drug Product Development Summary

	Process 1	Process 1b	Process 2	Process 3 Clinical	Process 3 Commercial
Dosage form	(b) (4)			Liquid in APFS	
Protein concentration				30 mg/mL	
Formulation				20 mM histidine/ histidine hydrochloride, 0.25 M trehalose dihydrate, 0.006% w/v PS-20, pH 6.0	
Nominal volume				1.0 mL	
Primary container				(b) (4) (b) (4) 1 mL long syringe, 29-gauge thin wall needle, (b) (4) rigid needle shield	
Primary closure				(b) (4) plunger stopper (b) (4)	
Secondary packaging component or accessory				(b) (4) needle safety shield, extended finger flange, and plunger rod	

APFS = accessorized prefilled syringe; PS = polysorbate

(Source: Module 3.2.P.2, Pharmaceutical-Development-Drug-Product-30-mg, Table P.2.2.1.1-1, page 2)

4. APPENDICES

Tabular Listing of All Studies Providing Clinical Pharmacology Data

Study	Design Control type	Treatment	Study objective and primary endpoint	Number of subjects randomised/completed study/completed treatment
Phase 1				
MI-CP158	DE/OL	Benra IV Single-dose: 0.0003 mg/kg, 0.003 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg	Safety: AEs, SAEs, laboratory evaluations, vital signs, ECGs, ADA response, CRP, IL-6, and FACS	44/39 ^b
MI-CP166	RD/DB/DE/PC	Cohort 1: Single-IV dose Benra 1.0 mg/kg, Placebo Cohort 2: Multiple SC (3) doses (Q4W for 8 weeks) Benra: 100 mg, 200 mg, Placebo	PD: eosinophil counts in airway mucosal biopsies Safety: AEs, SAEs, laboratories evaluations, CRP, ECP, EDN, IL- 5, IL-6, tryptase, vital signs, and ECGs	27/26/27
Phase 2				
MI-CP186	RD/DB/PC	Single IV dose Benra: 0.3 mg/kg, 1.0 mg/kg Placebo	Efficacy: proportion of patients with asthma exacerbations (relapsed or de novo) at Week 12	110/103 ^b
MI-CP197	RD/DB/DE/PC	Multiple (3) SC doses: Q4W for 8 weeks Benra: 25 mg, 100 mg, 200 mg Placebo	Safety: AEs, SAEs, laboratory evaluations, ECGs, vital signs	25/24 ^b
MI-CP-220	RD/DB/DR/PC	Multiple SC doses: Q4W for 3 doses, Q8W for next 4 doses) Benra: 2 mg, 20 mg, 100 mg Placebo	Efficacy: Annual exacerbation rate	609/521 ^b
Phase 3 (WINDWARD programme)				
(b) (4)				
D3250C00017 (SIROCCO)	RD/DB/PC 48-week treatment period	Multiple SC doses Benra: 30 mg, Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter	Efficacy, Safety, PK/ADA Annual exacerbation rate	N=1205 ^a ≥300/μL: 809 <300/μL: 395 Benra (≥300/μL) Q4W: 276/247/244 ^{c,d} Q8W: 267/240/240 ^{c,d} Placebo (≥300/μL): 267/241/235 ^{c,d} Adults randomised: 1151 ≥300/μL: 779 <300/μL: 372 Adolescents randomised: 53 ≥300/μL: 30 <300/μL: 23
D3250C00018 (CALIMA)	RD/DB/PC 56-week treatment period	Multiple SC doses Benra: 30 mg, Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter	Efficacy, Safety, PK/ADA Annual exacerbation rate	N=1306 ≥300/μL: 875 <300/μL: 431 Benra (≥300/μL) Q4W: 288/265/264 ^{c,d} Q8W: 290/262/259 ^{c,d} Placebo (≥300/μL): 297/273/267 ^{c,d} Adults randomised: HD ICS/LABA: ≥300/μL: 712; <300/μL: 353 MD ICS/LABA: ≥300/μL: 125; <300/μL: 61 Adolescents randomised: 55 HD ICS/LABA: ≥300/μL: 16; <300/μL: 10 MD ICS/LABA: ≥300/μL: 22; <300/μL: 7

D3250C00020 (ZONDA)	RD/DB/PC 28-week treatment period	Multiple SC doses Benra:30 mg, Placebo 2 dosing regimens: Q4W throughout the treatment period, Q4W for the first 3 doses and then Q8W thereafter	OCS reduction,Efficacy, Safety, PK/ADA Percentage reduction in final OCS dose compared with baseline while maintaining asthma control	N=220/209/207 ^{a,d} Benra: Q4W: 72/68/68 Q8W: 73/69/67 Placebo: 75/72/72 ≥300/μL: 187/177/179
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^a AstraZeneca and MedImmune-sponsored studies only. For KHK-sponsored studies, see Module 5.2.

^b Blinded data only will be included from this study (AEs, SAEs, and AEs by Investigator's assessment of causality) as study is ongoing.

^c Number completed study is number of patients who completed the study. Some patients withdrew from treatment but completed all study visits and assessments.

^d Number completed treatment is number of patients who completed treatment on investigational product.

^e One patient was randomised but not treated.

^f Study is ongoing and will not be included in the BLA.

^g Not available at this time as study is ongoing.

^h Completed treatment numbers are not provided.

ADA Anti-drug antibodies; AE: Adverse event; APFS Accessorised pre-filled syringe; BD Bronchodilator; Benra Benralizumab; BLA Biologic License Application; CRP C-reactive protein; DB Double blind; DE Dose escalation; DR Dose ranging; ECG Electrocardiogram; ECP Eosinophil cationic protein; EDN Eosinophil-derived neurotoxin; FACS Fluorescence-activated cell sorting; FEV₁ Forced expiratory volume in 1 second; HD High-dose; ICS Inhaled corticosteroids; IL Interleukin; IV Intravenous; LABA Long-acting β₂ agonist; MD Medium-dose; NA Not available; OCS Oral corticosteroid; OL Open label; PC Placebo controlled; PD Pharmacodynamic; PK Pharmacokinetic; Q4W Every 4 weeks; Q8W Every 8 weeks; RD Randomised; SAE Serious adverse event; SC Subcutaneous; UC Uncontrolled.

List of Clinical Pharmacology Reports for Assessment of Population Pharmacokinetics

See [section 4.2.1](#), Table 4.2.1-1 for a list of clinical studies included in the population PK analysis.

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4.1 Appendix - Individual Study Review

4.1.1 Study MI-CP158: Dose-Escalation in Subjects with Mild Asthma

Study:	MI-CP158
Study Title:	<i>A Multicenter, Open-label, Single Administration, Sequential Dose Escalation of BIW-8405/MEDI-563 in Subjects with Mild Asthma</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To investigate the safety of administration of benralizumab in increasing doses to male and female adult subjects with mild asthma (atopic). <p>Secondary:</p> <ul style="list-style-type: none"> To assess the pharmacological activity of benralizumab when administered in increasing doses to adult subjects with mild asthma (atopic). The activity of benralizumab was measured by the elimination of eosinophils in the peripheral circulation, change from baseline in fractional exhaled nitric oxide (FeNO), and change from baseline in ECP (serum). To assess the pharmacokinetics (PK) of benralizumab when administered to adult subjects with mild asthma (atopic).
Study Design:	<p>This was a Phase 1, multicenter, open-label, single administration, sequential dose-escalation study of benralizumab in adult male and female subjects, aged 18-45 years, with mild atopic asthma. The study was originally designed to evaluate the safety and tolerability of single intravenous (IV) doses of benralizumab (0.03-3.0 mg/kg) in 30 subjects (6 subjects per cohort) with a follow up period of 58 days.</p> <p>Preliminary data from Cohort 1 (0.03 mg/kg) indicated longer than expected persistence of peripheral blood eosinophil depletion activity of benralizumab. Therefore, the study protocol was amended to extend the follow-up period to 84 days (for subjects in Cohorts 3-5) and add long-term follow-up of subjects in Cohorts 3-5 with a low eosinophil count (defined as < 70% of baseline value, in which baseline value equaled the mean of eosinophil levels measured at Visit 1 and Visit 2) at Day 84. Subjects in the long term follow-up period were to be followed monthly for 6 months and every 3 months thereafter for a maximum of 1 year after the end of the study, until the eosinophil count reached ≥ 100 eosinophils/mm³ OR $\geq 70\%$ of baseline value at any follow up visit. The protocol was further amended to find the minimal effective dose of benralizumab that provoked a mean reduction (< 50%) of the eosinophil count in peripheral blood.</p> <p>Cohort 6 (0.003 mg/kg) was added following the completion of Cohort 5 (3.0 mg/kg), and Cohort 7 (0.0003 mg/kg) was added after the minimal effective dose that provoked a mean reduction (< 50%) of eosinophil count in peripheral blood was not found in Days 1-7 in Cohort 6 (0.003 mg/kg). A total of 6 subjects each were entered into Cohorts 6 and 7. A further amendment was added to the protocol to extend the infusion period to 30 minutes (for 3 subjects added to Cohort 4 [1.0 mg/kg] and the remaining 2 subjects in Cohort 5) after 2 of 4 subjects in Cohort 5 reported a constellation of treatment-emergent adverse events (TEAEs, i.e., nausea, fever, and chills) following administration of benralizumab. Therefore, a total of 45 subjects were planned in this study to receive single IV doses of benralizumab ranging from 0.0003-3.0 mg/kg.</p> <p>Benralizumab administration occurred on Day 0. Subjects in Cohorts 1 and 2 were followed from Days 0-58, and subjects in Cohorts 3-7 were followed from Days 0-84. Follow-up visits were also scheduled for any subject in Cohorts 3-7 with a low eosinophil count (defined as < 70% of baseline value, in which baseline value equals the mean of eosinophil levels measured at Visit 1 and Visit 2) at Visit 12 (Day 84). These subjects were followed monthly for 6 months and every 3 months thereafter. The follow-up</p>

	<p>continued until the eosinophil count reached ≥ 100 eosinophils/mm³ OR $\geq 70\%$ of baseline value at any follow-up visit. The maximum follow-up was 1 year after each subject completed participation in the study. Subjects in Cohort 1 and 2 with low eosinophil counts on Day 58 were followed at the discretion of the principal investigator with agreement of the medical monitor.</p> <p>The formulation used in this study were manufactured using Process 1 material.</p>
Study Population:	<p>The subjects in this study were male and female, aged 18-45 years, in good general health other than mild (intermittent or persistent) asthma consistent with the definition proposed by the 2002 Expert Panel report of the National Asthma Education and Prevention Program (NAEPP, 2002).</p> <p>A total of 44 subjects were entered into the study at 3 sites in the USA. Of the 5 subjects who did not complete the study, 2 subjects (Subjects 02035 and 02036 in the 0.0003 mg/kg dose group) were lost to follow-up and 3 subjects (Subject 01010 in the 0.1 mg/kg dose group, Subject 01021 in the 1.0 mg/kg dose group, and Subject 02022 in the 3.0 mg/kg dose group) withdrew consent. In addition, no subject died or withdrew from the study due to an AE.</p>
PK Data Analysis:	<p>The mean age of the subject population was 24.7 years (18-41 years), and the majority (61.4%) of subjects were female. Most subjects were White (93.2%) and Non-Hispanic (88.6%). Mean BMI ranged from 22.815-25.887 kg/m², with all but 4 subjects having a BMI > 15 kg/m² and < 30 kg/m².</p> <p>Baseline disease characteristics were similar between dose groups. Subjects in this study had mild (intermittent or persistent) asthma as determined by the investigator. The screening FEV₁ values were consistent with a mild asthmatic population. All subjects in the study had a PC₂₀ ≤ 8 mg/mL at screening. Mean peripheral blood eosinophil counts at baseline ranged from 0.155-0.381 $\times 10^3$ cells/μL.</p> <p>Blood samples for plasma benralizumab concentration measurements were collected from subjects pre- and post-belimumab administration according to the schedule below.</p> <ul style="list-style-type: none"> Immediately prior to dosing, and at 2, 30 60 minutes, and 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 336, 672, 1392 and 2016 hours post-administration. <p>Plasma samples for Study MI-CP158 were analyzed using a validated enzyme-linked immunosorbent assay (ELISA) with a lower limit of quantitation (LLOQ) of approximately 10 ng/mL</p> <p>Pharmacokinetic analyses were performed by the Sponsor using WinNonLin®, SAS®, S-Plus, or relevant other software. Concentration-time data for individual subjects were analyzed by non-compartmental methods. Pharmacokinetic parameters were summarized using descriptive statistics (mean, standard deviation, maximum, median, minimum, percent coefficient of variation) at each dose level. The following PK parameters were determined from the plasma concentration-time data:</p> <p style="text-align: center;">C_{max}, T_{max}, λ_z, $t_{1/2}$, AUC_{last}, AUC_{inf}, $AUC\%_{Extrap}$, CL, and V_z.</p>
Results:	<p>Mean (\pm SD) plasma benralizumab concentration-time profiles are shown in Figure 4.1.1-1.</p>

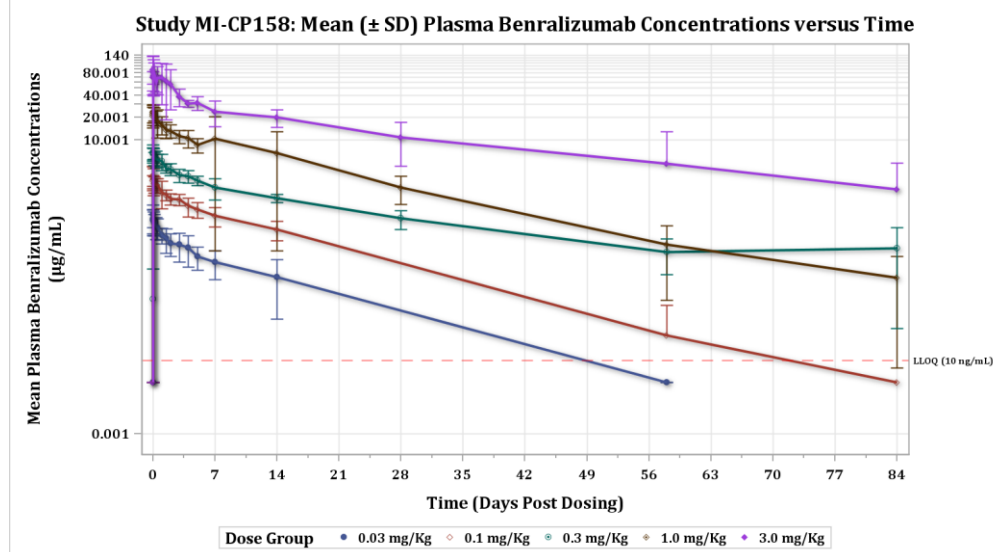


Figure 4.1.1-1: Mean (\pm SD) Plasma Benralizumab Concentrations Following Single IV Administration at Doses Ranging From 0.03-3.0 mg/kg in Subjects With Mild (Intermittent Or Persistent) Asthma

(Source: Reviewer generated plot)

Mean (\pm SD) PK parameters following single IV administration are summarized in Table 4.1.1-1.

Serum belimumab concentration-time profiles were multiphasic following single IV administration of 240 mg belimumab. The mean (%CV) C_{max} and $AUC_{0-\infty}$ values were 88 $\mu\text{g/mL}$ (20.0) and 1080 $\text{day}\cdot\mu\text{g/mL}$ (32.1), respectively. Mean Belimumab CL was 3.2 mL/day/kg , while mean $t_{1/2,term}$ was 18.2 days.

Mean plasma benralizumab concentrations declined in a bi-exponential manner, with an initial rapid decrease followed by a prolonged elimination phase. Plasma benralizumab concentrations at the 0.0003 and 0.003 mg/kg dose levels were below the LOQ. A summary of PK parameters are presented in Table 4.1.1-1. At doses of 0.03-3.0 mg/kg the mean C_{max} ranged from 0.98-82.20 $\mu\text{g/mL}$ while mean AUC_{inf} ranged from 5.19-774.8 $\mu\text{g}\cdot\text{d/mL}$, indicating dose proportionality. Mean CL ranged from 3.63-6.68 mL/kg/d , with a mean elimination $t_{1/2}$ ranging from 7.32-18.6 days. Mean V_{ss} ranged from 51.5-92.7 mL/kg .

Table 4.1.1-1: Mean (\pm SD) PK Parameters Following A Single Dose Of Belimumab at 240 mg Given As 1-hour IV Infusion or at 2x120, 240 or 200 mg Given As SC Injection In Healthy Subjects

PK Parameters	Mean (CV%)						
	Benralizumab Dose Groups						
	0.0003 mg/kg N = 5	0.003 mg/kg N = 6	0.03 mg/kg N = 6	0.1 mg/kg N = 6	0.3 mg/kg N = 6	1.0 mg/kg N = 9	3.0 mg/kg N = 6
T _{max} (days)	< LOQ	< LOQ	0.0078 (213.6789)	0.0180 (111.8862)	0.0802 (159.1841)	0.5440 (113.1127)	0.0172 (99.3829)
C _{max} (μ g/mL)	< LOQ	< LOQ	0.9833 (31.7814)	3.4667 (33.3752)	7.5833 (19.4775)	23.1111 (37.2495)	82.2000 (22.3725)
AUC _(0-T) (μ g \cdot day/mL)	< LOQ	< LOQ	3.7127 (41.2749)	18.3882 (23.6222)	71.6823 (16.5713)	171.8594 (23.1601)	767.3088 (13.8265)
AUC infinity (μ g \cdot day/mL)	< LOQ	< LOQ	5.1825 (41.7791)	26.0222 (19.854)	79.2655 (21.7951)	184.5271 (18.4946)	774.8306 (14.1721)
AUC extrapolated	< LOQ	< LOQ	28.2267 (19.9506)	27.6520 (64.4262)	8.7895 (67.935)	7.4710 (136.9640)	0.9366 (81.0422)
CL	< LOQ	< LOQ	6.6825 (38.9434)	3.9997 (24.2000)	3.9112 (18.0819)	3.6267 (78.0763)	3.9350 (14.2345)
T _{1/2} (days)	< LOQ	< LOQ	7.2547 (27.7476)	12.7845 (31.6942)	18.6068 (22.4876)	11.6802 (36.6428)	15.6368 (17.9352)
V _{ss} (mL/kg)	< LOQ	< LOQ	65.1077 (42.2333)	67.4952 (42.0243)	92.7155 (13.3224)	51.5067 (87.5464)	70.7916 (25.6386)

AUC = area under the plasma concentration-time curve; CL = clearance; C_{max} = maximal drug concentration observed in plasma; CV = coefficient of variation; LOQ = limit of quantification; T_{max} = time to reach maximum concentration; T_{1/2} = terminal elimination half-life; V_{ss} = volume of distribution at steady state.

(Source: eCTD for BLA 761070, Module 5.3.3.2, PK Report for Study MI-CP158, Table 11.4.2.1-1, page 77)

Eosinophils in Peripheral Blood:

Mean (\pm SD) peripheral blood eosinophil suppression presented in Figure 4.1.1-2 shows that eosinophil suppression was observed at all levels, with persistent suppression at 0.003 mg/kg dose and higher. Median peripheral blood eosinophil counts remained < 100 cells/ μ L up to Day 3 (median 50 cells/ μ L; range 0-70 cells/ μ L) in the lowest dose group (0.0003 mg/kg) and at least 84 days (median 0 cells/ μ L; range 0-220 cells/ μ L) in the highest dose groups (0.3-3.0 mg/kg). One day after dosing (Day 1), the mean peripheral blood eosinophil counts were decreased by >9% across all dose groups (Table 4.1.1-2), with persistent decreases of >95% observed throughout the study at doses of 0.1 mg/kg and higher.

Study MI-CP158: Reductions in Mean Peripheral Blood Eosinophil Count (1000 cells per Microliter) Over Visits

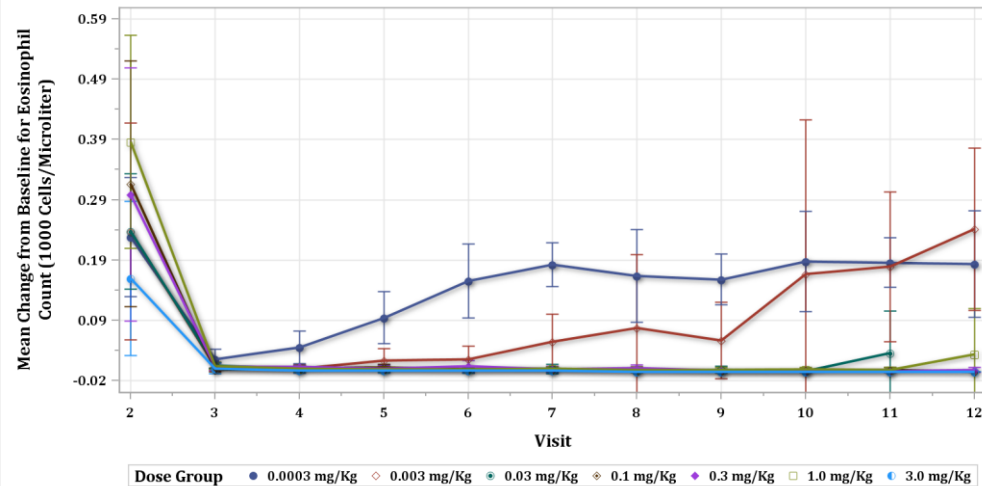


Figure 4.1.1-2: Mean (\pm SD) Reductions in Peripheral Blood Eosinophil Count (1000 Cells Per Microliter) Following Single-Dose IV Administration Of Benralizumab

(Source: Reviewer generated plot)

Table 4.1.1-2: Summary of Percent Change from Baseline for Peripheral Blood Eosinophil Counts

Visit	Benralizumab Dose Groups							Total N = 44
	0.0003 mg/kg N = 5	0.003 mg/kg N = 6	0.03 mg/kg N = 6	0.1 mg/kg N = 6	0.3 mg/kg N = 6	1.0 mg/kg N = 9	3.0 mg/kg N = 6	
Day 0 (Baseline)								
Mean ($\times 10^3$ cells/ μ L)	0.224	0.233	0.235	0.310	0.297	0.381	0.155	0.271
Day 1								
Mean % Change	- 89.4%	- 96.7%	- 95.1%	- 99.4%	- 95.6%	- 96.8%	- 97.7%	- 96.0%
Day 2								
Mean % Change	- 81.9%	- 98.7%	- 97.3%	- 98.6%	- 95.0%	- 98.6%	- 99.1%	- 96.1%
Day 3								
Mean % Change	- 59.8%	- 92.3%	- 97.4%	- 97.1%	- 95.4%	- 99.4%	- 99.5%	- 92.8%
Day 4								
Mean % Change	- 31.3%	- 92.7%	- 99.2%	- 97.2%	- 92.7%	- 98.6%	- 99.1%	- 89.1%
Day 5								
Mean % Change	- 28.1%	- 79.7%	- 97.8%	- 97.6%	- 97.5%	- 98.1%	- 99.1%	- 88.7%
Day 7								
Mean % Change	- 29.1%	- 75.4%	-100%	- 97.7%	- 95.7%	- 99.1%	-100%	- 87.5%
Day 14								
Mean % Change	- 26.7%	- 80.8%	- 98.6%	- 99.4%	- 99.6%	- 99.4%	-100%	- 88.6%
Day 28								
Mean % Change	- 15.8%	- 41.9%	- 99.5%	- 99.1%	-100%	- 98.7%	-100%	- 82.1%
Day 58								
Mean % Change	- 27.4%	- 36.1%	- 84.6%	- 99.1%	-100%	- 98.9%	-100%	- 81.4%
Day 84								
Mean % Change	- 16.5%	3.8%	NA	-100%	- 98.5%	- 95.8%	-100%	- 68.5%

NA = not available

(Source: eCTD for BLA 761070, Module 5.3.3.2, PK Report for Study MI-CP158, Table 11.4.2.3-1, page 82)

Mean change from baseline for peripheral blood eosinophil counts across all dose groups is shown in Figure 4.1.1-3.

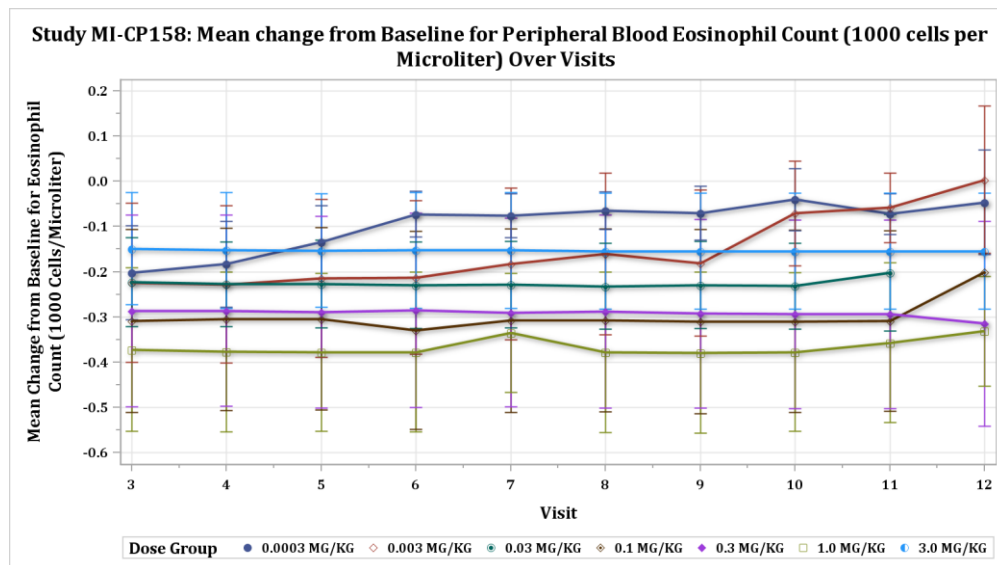


Figure 4.1.1-3: Mean (\pm SD) Change From Baseline in Peripheral Blood Eosinophil Count (1000 Cells Per Microliter) Following Single-Dose IV Administration of Benralizumab

(Source: Reviewer generated plot)

An arbitrary number of ≥ 100 eosinophils/ mm^3 OR $\geq 70\%$ of baseline value by 12 months post final scheduled visit was defined for eosinophil recovery in this study. Thirty-one of 44 subjects (70.5%) across the dose groups had their peripheral blood eosinophil count

recover to ≥ 100 eosinophils/ mm^3 or $\geq 70\%$ of baseline value at the final scheduled visit or any follow-up visit thereafter. Mean time to eosinophil recovery was 5.8 days post-dose for the 0.0003 mg/kg dose group, 39.7 days post-dose for the 0.003 mg/kg dose group, 98.8 days post-dose for the 0.03 mg/kg dose group, 114.3 days post-dose of the 0.1 mg/kg dose group, 250.3 days post-dose for the 0.3 mg/kg dose group, 178.3 days post-dose for the 1.0 mg/kg dose group, and 190.6 days post-dose for the 3.0 mg/kg dose group.

Fractional Exhaled Nitric Oxide:

As seen in Figure 4.1.1-4, following single IV dose administration of benralizumab at all dose levels, there was no apparent change in mean fractional exhaled nitric oxide (FeNO) indicating no association between peripheral blood eosinophil suppression and FeNO at the doses tested.

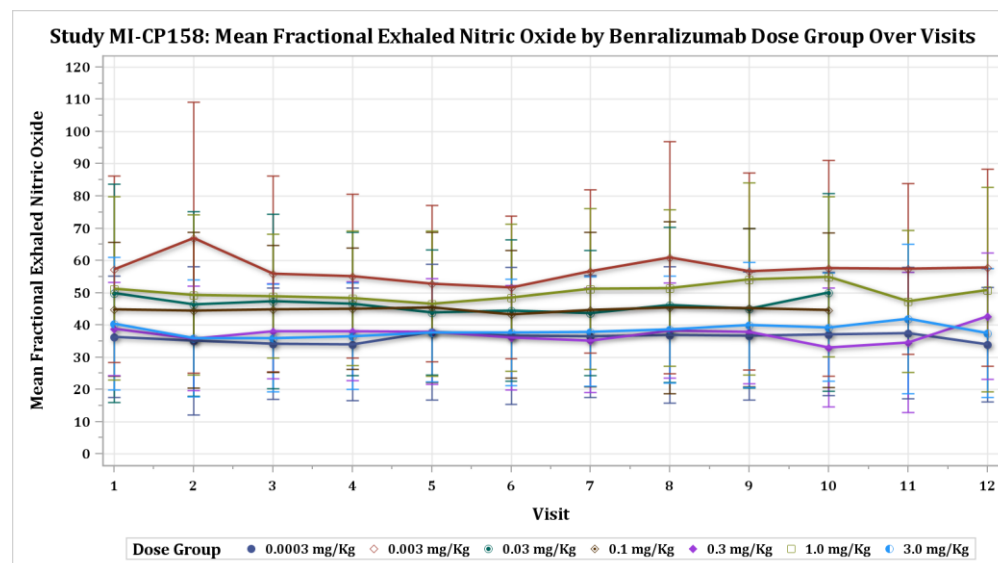


Figure 4.1.1-4: Mean (\pm SD) Fractional Exhaled Nitric Oxide by Benralizumab Dose Group Following Single-Dose IV Administration of Benralizumab

(Source: Reviewer generated plot)

Eosinophil Cationic Protein:

Reductions in mean serum ECP levels were observed following single IV administration of benralizumab at all dose levels (Figure 4.1.1-5). In general, the reduction in mean serum ECP correlated with the peripheral blood eosinophil suppression observed across dose groups.

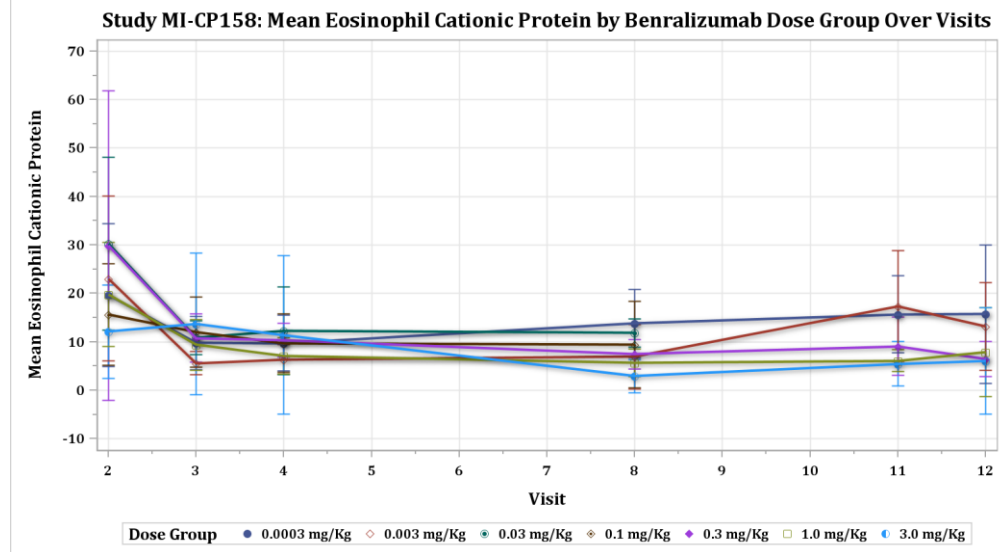


Figure 4.1.1-5: Mean (± SD) Eosinophil Cationic Protein by Benralizumab Dose Group Following Single-Dose IV Administration of Benralizumab

(Source: Reviewer generated plot)

Immunogenicity:

Seven (7) of 37 subjects (18.9%) had quantifiable anti-benralizumab antibodies some time during the course of the study. This includes one subject each in the 0.1 and 0.3 mg/kg dose groups, 3 subjects in the 1.0 mg/kg dose group, and 2 subjects in the 3.0 mg/kg dose group. There appeared to be no relationship between the presence of anti-benralizumab antibody titers and the occurrence of TEAEs in these subjects.

Safety:

The most frequently reported TEAEs (incidence > 15%) were decreased white blood cell count (15 subjects, 34.1%); nasopharyngitis (12 subjects, 27.3%); increased blood CPK and headache (11 subjects each, 25.0%); increased CRP and decreased neutrophil count (10 subjects each, 22.7%); protein in the urine (9 subjects, 20.5%); and nasal congestion (7 subjects, 15.9%). There was no apparent increase in the incidence of TEAEs with increasing doses of benralizumab.

Conclusions:

- Mean plasma benralizumab concentrations declined in a bi-exponential manner, with an initial rapid decrease followed by a prolonged elimination phase. Mean elimination half-life ranged from 1-3 weeks.
- Pharmacological activity as evidenced by reduced peripheral blood eosinophil counts and serum ECP levels, were observed at all dose levels (0.0003 – 3.0 mg/kg) evaluated in this study.
- There was no effect by benralizumab on FeNO levels or other clinical outcomes at the doses tested.
- Anti-benralizumab antibodies were observed in 7 of 37 subjects (18.9%) tested.

4.1.2 Study MI-CP166: Safety, Tolerability and Effects in Subjects with Mild Asthma

Study:	MI-CP166
Study Title:	<i>A Phase 1, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability and Effects of Benralizumab, a Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, on Airway Eosinophils in Adults with Asthma</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of benralizumab in adults with asthma To evaluate the effects of benralizumab on eosinophil counts in airway mucosal biopsies 28 days after completion of dosing in adults with asthma <p>Secondary:</p> <ul style="list-style-type: none"> To evaluate the pharmacokinetics (PK) of benralizumab in adults with asthma To evaluate the immunogenicity (IM) of benralizumab in adults with asthma <p>Exploratory:</p> <ul style="list-style-type: none"> To evaluate the effects of benralizumab on disease activity To evaluate the effects of benralizumab on inflammatory cells and proteins in mucosal biopsies, including eosinophils in mucosal biopsies To evaluate the effects of benralizumab on inflammatory cells and proteins in induced sputum To evaluate the effects of benralizumab on eosinophils and eosinophil precursors in bone marrow in adults with asthma To evaluate the effects of benralizumab on peripheral blood levels of eosinophil- and basophil-derived proteins and cytokines in adults with asthma To evaluate the effects of benralizumab on peripheral blood eosinophil and basophil counts To evaluate downstream effects of benralizumab on messenger ribonucleic acid (mRNA) levels in whole blood, using microarray analyses To explore single-nucleotide-polymorphisms and microsatellite or short tandem repeat analyses for genes associated with asthma in whole blood deoxyribonucleic acid (DNA), if such analyses were warranted based on other exploratory analyses in adults with asthma
Study Design:	<p>This was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, and effects of single intravenous (1.0 mg/kg) and multiple subcutaneous (100 and 200 mg) administrations of benralizumab on airway eosinophils in adults with asthma who have $\geq 2.5\%$ eosinophils in sputum.</p> <p>The study was conducted in 2 cohorts of subjects. Each cohort was to have 12 subjects, to be expanded to 15 subjects if eligible subjects were already in screening at the time 12 subjects had been randomized into the dose cohort. The 12 subjects in Cohort 1 were to be randomized in a 2:1 ratio to receive a single IV dose of benralizumab (1.0 mg/kg) or placebo, with 8 subjects receiving benralizumab and 4 subjects receiving placebo. The 12 subjects in Cohort 2 were randomized in a 1:1:1 ratio to receive 1 of 2 doses of benralizumab (100 or 200 mg) or placebo as an SC injection once every 4 weeks for 8 weeks (Day 0, Day 28, and Day 56). The study flow diagram is shown below:</p>

	<p style="text-align: center;">Subjects with Asthma ($\geq 2.5\%$ eosinophils in sputum) N=24</p> <p>Cohort 1 (N=12): Single IV dose of MEDI-563 1.0 mg/kg (N=8) or Placebo (N=4)</p> <p>Cohort 2 (N=12): Multiple SC doses of MEDI-563 [100 mg (N=4) or 200 mg (N=4)] or Placebo (N=4)</p> <p> Dosing Airway biopsy </p> <p>* Optional airway biopsy IV = intravenous; MEDI-563 = benralizumab; N = number; SC = subcutaneous</p> <p>The formulation used in this study were manufactured using Process 1b material.</p>
Study Population:	<p>The subjects in this study were adults between ages of 18-65 years, with asthma who had $\geq 2.5\%$ eosinophils in sputum.</p> <p>A total of 27 subjects (13 subjects in Cohort 1; 14 subjects in Cohort 2) participated in the study.</p>
PK Data Analysis:	<p>The following PK parameters were calculated using non-compartmental analysis:</p> <ul style="list-style-type: none"> • maximum observed serum concentration (C_{max}) of benralizumab, • time to the maximum observed serum concentration (t_{max}) • area under the concentration-time curve from time 0 to infinity (AUC_{inf}) • terminal half-life ($t_{1/2}$) • systemic clearance (CL) after IV infusion • apparent clearance (CL/F) after SC injection • steady-state volume of distribution (V_{ss}) after IV infusion • SC bioavailability (F) <p>Following each dose of investigational product in Cohort 2, the non-compartmental PK parameters included C_{max} and pre-dose trough concentration (C_{trough}). Descriptive statistics of these non-compartmental parameters by dose cohort were also generated.</p> <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay that employed MSD technology with a LLOQ of 3.86 ng/mL.</p>
Results:	<p>Mean (\pm SD) plasma benralizumab concentration-time profiles are shown in Figure 4.1.2-1.</p>

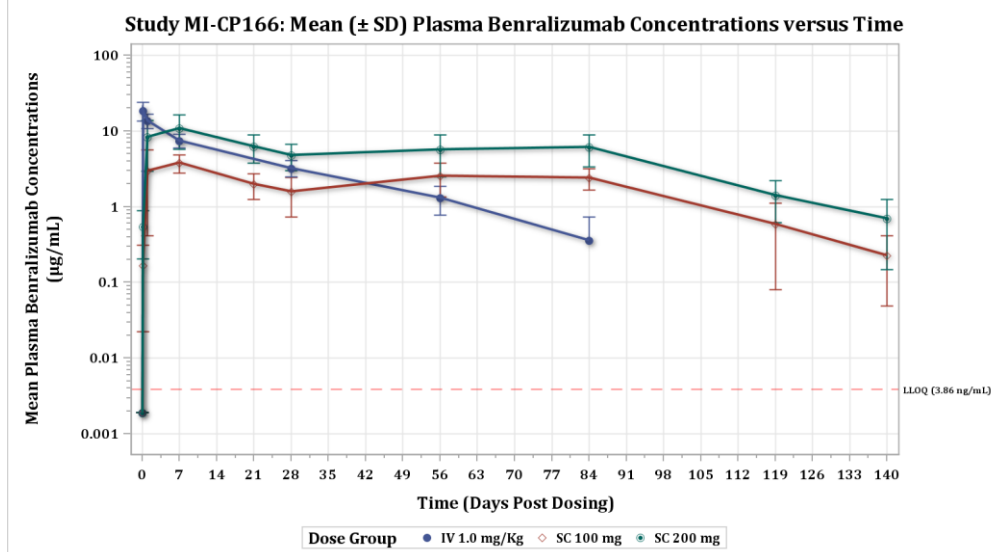


Figure 4.1.2-1: Mean (\pm SD) Benralizumab Plasma Concentrations Following Single IV or Multiple SC Doses

(Source: Reviewer generated plot)

Mean (\pm SD) PK parameters following single IV administration are summarized in Table 4.1.2-1.

The mean C_{max} and AUC_{inf} were 18.8 $\mu\text{g/mL}$ and 282 $\mu\text{g}\cdot\text{d/mL}$, respectively, following a single IV infusion of 1.0 mg/kg benralizumab. The corresponding mean CL and steady-state volume of distribution (V_{ss}) were 3.69 mL/kg/d and 97.0 mL/kg, respectively. The mean $t_{1/2}$ of benralizumab was approximately 20 days.

The PK exposure (C_{max} and AUC_{inf} following the first dose, and C_{trough} on Day 56) was slightly more than dose-proportional following multiple-dose SC administrations of benralizumab at 100 and 200 mg. The mean CL/F after SC administration was 898 and 657 mL/d for the 100 and 200 mg doses, respectively. The mean PK $t_{1/2}$ of the two SC doses were similar and close to that after single IV infusion. The small sample size and PK inter-individual variability of each SC dose group may have contributed towards the slight dose-nonlinearity after SC administrations. The SC bioavailability (F), ranging from 38% to 45% may have been underestimated in this study due to the limited PK sampling schedule following the first SC dose.

Table 4.1.2-1: Mean (\pm SD) PK Parameters Following Single IV or Multiple SC Doses

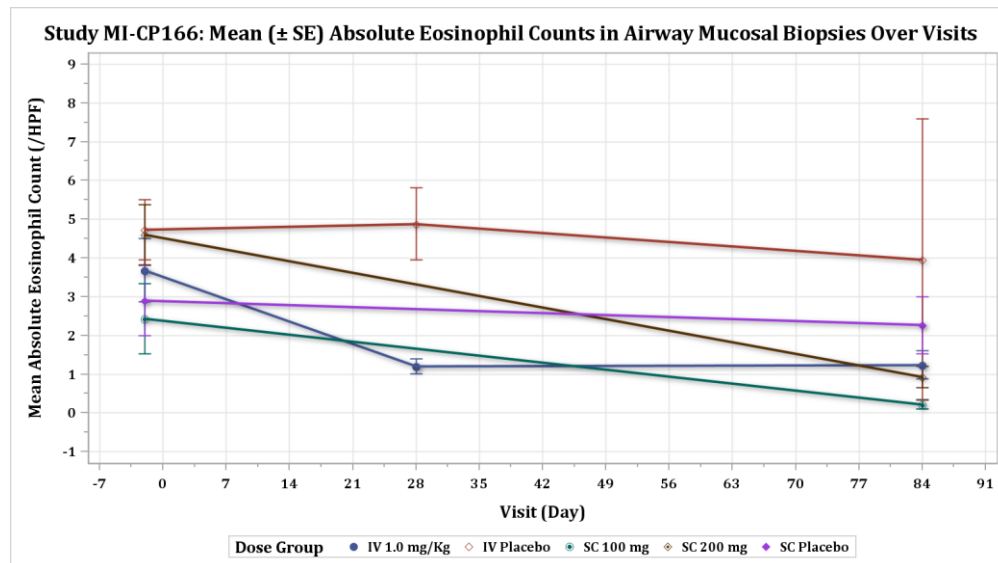
Pharmacokinetic Parameters	Benralizumab Dose Groups ^a		
	Cohort 1 (IV)	Cohort 2 (SC)	
	Benralizumab 1.0 mg/kg N = 8	Benralizumab 100 mg N = 4	Benralizumab 200 mg N = 5
T _{max} (days)	0.083 (0.083 - 0.083)	7 (1 - 7)	7 (7 - 7)
C _{max} (μ g/mL)	18.8 (5.34)	4.43 (1.78)	11.0 (5.26)
AUC _{inf} (μ g•d/mL)	282 (61.1)	127 (62.9)	347 (132)
CL (mL/kg/d)	3.69 (0.748)	NA	NA
CL/F (mL/d)	NA	898 (300)	657 (280)
T _{1/2} ^b (days)	19.7 (5.13)	19.1 (2.43)	18.8 (6.74)
C _{trough} (μ g/mL)	NA	2.57 (1.23)	7.05 (2.04)
F	NA	37.9	45.2

Source: eCTD for BLA 761070, Module 5.3.3.2, PK Report for Study MI-CP166, Table 11.4.5-1, page 161

Eosinophil Counts in Airway Mucosal Biopsies:

Following administration of 1.0 mg/kg IV benralizumab, mean absolute eosinophil counts (/HPF) in airway mucosa had decreased by 43.35% compared to a 40.48% increase in the IV placebo group through Day 28 (Figure 4.1.2-2). As shown in Table 4.1.2-2, these changes, were not statistically significant using two-sided ttest ($p=0.085$) or two-sided Wilcoxon rank-sum test ($p=0.284$).

Following administration of 100 and 200 mg SC benralizumab, mean absolute eosinophil counts (/HPF) in airway mucosa had decreased by 73.95% and 88.40%, respectively (81.98% in the total SC benralizumab group), compared to a 2.44% increase in the SC placebo group through Day 84 (Figure 4.1.2-2). As shown in Table 4.1.2-2, these changes were statistically significant using two-sided t-test ($p=0.039$), but not with two-sided Wilcoxon rank-sum test ($p=0.059$).

**Figure 4.1.2-2: Mean (\pm SE) Absolute Eosinophil Counts in Airway Mucosal Biopsies Following 1.0 mg/kg IV, 100 mg SC and 200 mg SC Administration of Benralizumab**

(Source: Reviewer generated plot)

Table 4.1.2-2: Percent Change from Baseline of Absolute Eosinophil Counts in Airway Mucosal Biopsies

VISIT		COHORT1: PLACEBO IV (N=5)	COHORT1: MEDI-563 IV 1 MG/KG (N=8)	COHORT2: PLACEBO SC (N=5)	COHORT2: MEDI-563 SC 100 MG (N=4)	COHORT2: MEDI-563 SC 200 MG (N=5)	COHORT2: MEDI-563 SC TOTAL (N=9)
DAY 28	N	5	8	NA	NA	NA	NA
	MEAN	40.48	-43.35	NA	NA	NA	NA
	SD	110.09	50.86	NA	NA	NA	NA
	MEDIAN	19.58	-61.89	NA	NA	NA	NA
	MIN - MAX	(-92.5-201.3)	(-91.2-30.5)	NA	NA	NA	NA
	P-VALUE [1] P-VALUE [2]		0.085 0.284				
DAY 84	N	1	5	5	4	5	9
	MEAN	-37.14	-40.18	2.44	-73.95	-88.40	-81.98
	SD	NA	68.79	103.95	49.34	11.35	32.18
	MEDIAN	-37.14	-59.26	-46.67	-97.90	-88.87	-95.81
	MIN - MAX	(-37.1--37.1)	(-96.9-75.4)	(-98.9-146.8)	(-100.0--0.0)	(-100.0--72.7)	(-100.0--0.0)
	P-VALUE [1] P-VALUE [2]						0.039 0.059

[1] P-VALUE REPRESENTS COMPARISON OF MEAN PERCENT CHANGE FROM BASELINE BETWEEN COMBINED PLACEBO AND COMBINED MEDI-563 TREATMENT GROUPS WITHIN EACH COHORT USING T-TEST.
[2] P-VALUE REPRESENTS COMPARISON OF PERCENT CHANGE FROM BASELINE BETWEEN PLACEBO AND MEDI-563 TREATMENT GROUPS WITHIN EACH COHORT USING WILCOXON RANK-SUM TEST.

Source: eCTD for BLA 761070, Module 5.3.3.2, PK Report for Study MI-CP166, Table 14.2.1.1.1.3, page 277

Peripheral blood eosinophil suppression:

Following single-dose IV administration of 1.0 mg/kg benralizumab through Day 84, peripheral blood eosinophil suppression was observed. By Day 1, the mean percent change from baseline in peripheral blood eosinophil counts (10^3 cells/ μ L) was 100%. In contrast, no suppression of peripheral blood eosinophil counts was observed in the IV placebo group. Peripheral blood eosinophil suppression was also observed following multiple-dose SC administration of 100 and 200 mg benralizumab through Day 140. Mean percent change from baseline in peripheral blood eosinophil counts of 100% were observed throughout the study. No suppression of peripheral blood eosinophil counts was observed in the SC placebo group.

Mean change from baseline for peripheral blood eosinophil counts across all dose groups is shown in Figure 4.1.2-3.

An arbitrary number of ≥ 100 eosinophils/ mm^3 OR $\geq 70\%$ of baseline value by 12 months post final scheduled visit was defined for eosinophil recovery in this study. At the final scheduled visit, the subjects had their peripheral blood eosinophil count recover to at least 100 eosinophils/ mm^3 OR within 70% of their baseline value.

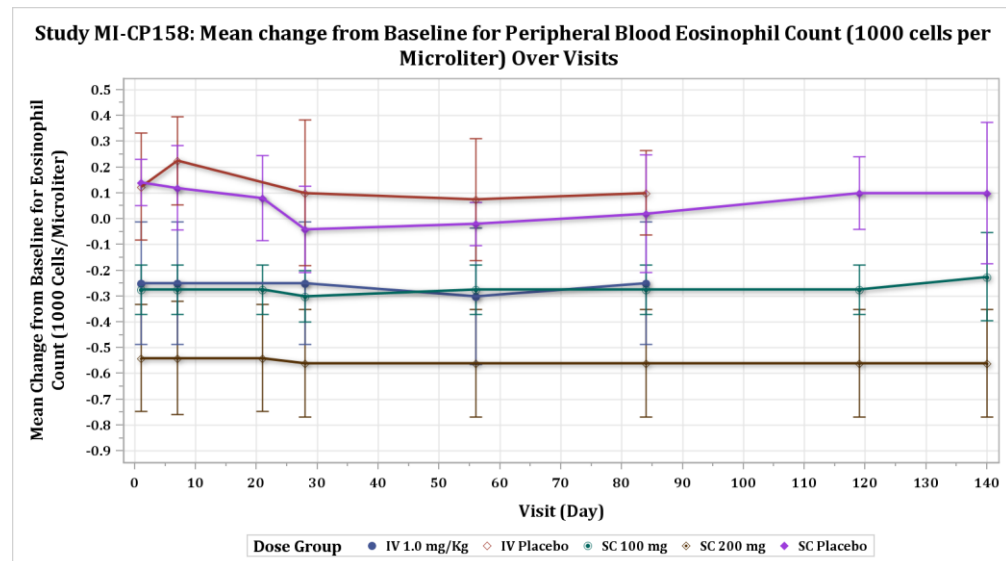


Figure 4.1.2-3: Mean (\pm SD) Change from Baseline in Peripheral Blood Eosinophil Count (1000 cells per microliter) Following 1.0 mg/kg IV, 100 mg SC and 200 mg SC Administration of Benralizumab

(Source: Reviewer generated plot)

Eosinophil Cationic Protein:

Following single-dose IV administration of 1.0 mg/kg benralizumab from Day 1 through the last scheduled visit (Day 84), mean reductions in serum ECP levels from baseline ranging from 5.1 µg/L to 9.4 µg/L were observed, compared to mean reductions ranging from 0.3 µg/L to 18.6 µg/L for the IV placebo group during the same period (Figure 4.1.2-4).

Following multiple-dose SC administration of benralizumab from Day 1 through the last scheduled visit (Day 140), mean reductions in serum ECP levels from baseline ranging from 9.5 µg/L to 18.0 µg/L and 29.6 µg/L to 37.2 µg/L were observed. For the 100 mg and 200 mg dose groups, respectively. Mean increases in serum ECP levels from baseline were observed for the SC placebo group during the same period (Figure 4.1.2-4).

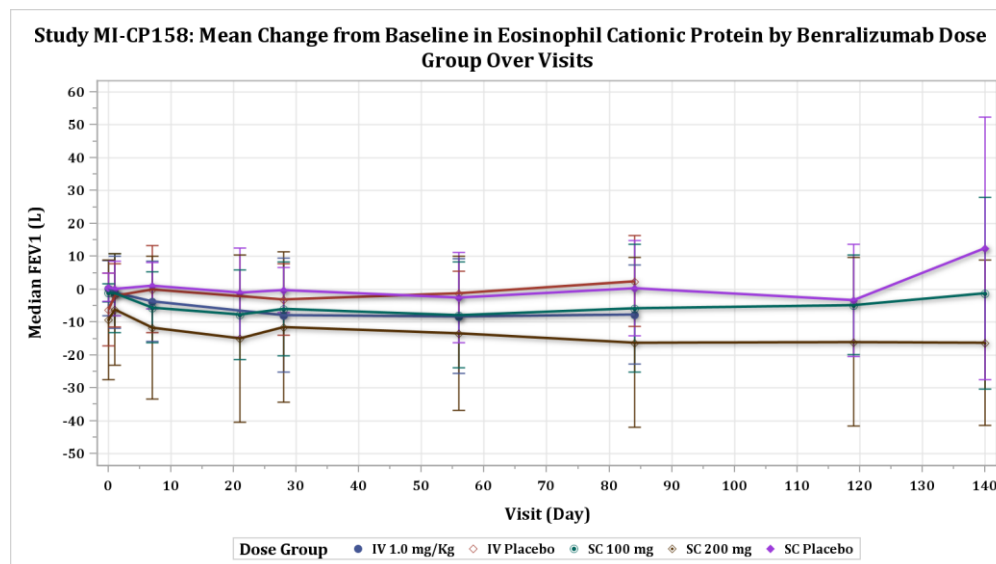


Figure 4.1.2-4: Mean (± SD) Eosinophil Cationic Protein by Benralizumab Dose Group Following 1.0 mg/kg IV, 100 mg SC and 200 mg SC Administration of Benralizumab

(Source: Reviewer generated plot)

Fractional Exhaled Nitric Oxide:

As seen in Figure 4.1.2-5, there were no differences between the IV placebo group and 1.0 mg/kg IV benralizumab group on the median change from baseline to Day 84 in exhaled nitric oxide (eNO). For the benralizumab SC administration, subjects in the 100 mg group had a relatively large decrease from baseline to Day 140 in eNO compared to the other SC treatment groups (SC placebo or 200 mg SC benralizumab). Given the small size of the study and the variability of baseline characteristics among the treatment groups, these findings are difficult to interpret.

Study MI-CP158: Mean Change from baseline in Fractional Exhaled Nitric Oxide by Benralizumab Dose Group Over Visits

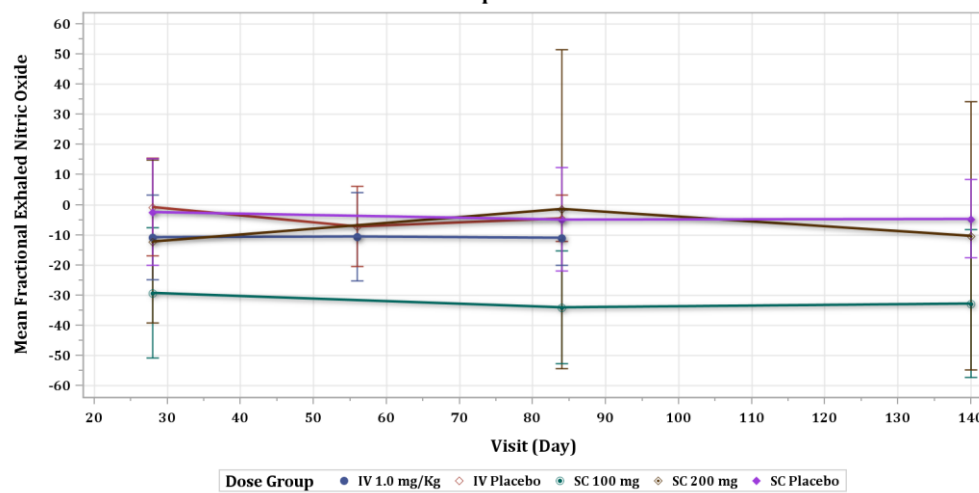


Figure 4.1.2-5: Mean (\pm SD) Fractional Exhaled Nitric Oxide by Benralizumab Dose Group Following 1.0 mg/kg IV, 100 mg SC and 200 mg SC Administration of Benralizumab

(Source: Reviewer generated plot)

Eosinophil Derived Neurotoxins, IL-5, and IL-6:

Mean percent reductions in serum eosinophil derived neurotoxins (EDN), mean percent increases in serum IL-5 and IL-6 levels following IV administration of 1.0 mg/kg and SC administration of 100 mg and 200 mg benralizumab compared to corresponding placebo treatments is shown in Table 4.1.2-3.

Table 4.1.2-3 Mean Percent Changes in Serum EDN, IL-5 and IL-6

PD Marker	Intravenous		Subcutaneous		
	1.0 mg/kg	Placebo	100 mg	200 mg	Placebo
EDN	↓ 36.80% - 90.23%	Relatively close to baseline	↓ 45.82% - 90.00%	↓ 61.51% - 97.23%	Relatively close to baseline
IL-5	↑ 176.19% - 281.67%	Small mean percent changes	↑ 0.00% - 58.33%	↑ 185.64% - 414.87%	Relatively close to baseline
IL-6	↑ 5.89% - 43.50%	Small mean percent changes	↑ 5.15% - 98.08%	↑ 8.63% - 48.53%	Relatively close to baseline

Immunogenicity:

Anti-drug antibodies were detected in 2 of 8 subjects (25%) treated with IV benralizumab and in 1 of 9 subjects (11%) treated with SC benralizumab. Plasma concentrations of benralizumab were decreased in subjects who had ADA titers of ≥ 400 post-dose only.

Safety:

The most frequently reported TEAEs in the 1.0 mg/kg IV benralizumab group were nasopharyngitis (2/8, 25.0%) and headache (2/8, 25.0%); there were no TEAEs in the IV placebo group that were reported in more than one subject. All TEAEs in the IV placebo and 1.0 mg/kg IV benralizumab groups were mild or moderate in severity.

The most frequently reported TEAE in the 100 mg SC benralizumab group was nasopharyngitis (2/4, 50.0%); there were no TEAEs in the 200 mg SC benralizumab group that were reported in more than one subject. The most frequently reported TEAE in the SC placebo group was nasopharyngitis (4/5, 80.0%). The majority of TEAEs in the

	SC placebo and total SC benralizumab groups were mild or moderate in severity. One subject in the 100 mg SC benralizumab group had 5 severe TEAEs (2 events of wheezing, pyrexia, chest discomfort, and cough), and one subject in the 200 mg SC benralizumab group had one severe TEAE (hyperthyroidism).
Conclusions:	<ul style="list-style-type: none"> • Benralizumab administered as a single 1.0 mg/kg IV dose or as multiple SC doses of either 100 or 200 mg resulted in decreased mucosal airway eosinophils 28 days after completion of dosing compared to placebo. • Benralizumab administered as a single 1.0 mg/kg IV dose or as multiple SC doses of either 100 or 200 mg resulted in persistent peripheral blood eosinophil suppression. All subjects who had at least 12 months follow-up after their last scheduled visit had their peripheral blood eosinophil count recover to at least 100 eosinophils/mm³ OR to at least 70% of their baseline value. • Benralizumab PK was dose-proportional in the 1.0 mg/kg IV dose investigated. The mean half-life was approximately 20 days. Benralizumab PK was slightly more than dose-proportional in the 100 and 200 mg SC doses investigated. The mean half-life of both SC doses was approximately 19 days. • Anti-drug antibodies were detected in 2 of 8 subjects (25%) treated with IV benralizumab and in 1 of 9 subjects (11%) treated with SC benralizumab. Plasma concentrations of benralizumab were decreased in subjects who had ADA titers of ≥ 400 post-dose only.

APPEARS THIS WAY ON ORIGINAL

4.1.3 Study MI-CP186: Safety, Tolerability and Effects in Subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation

Study:	MI-CP186
Study Title:	<i>A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Intravenously Administered MEDI-563, A Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, on Asthma Control Following Acute Exacerbations in Adults</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the effect of two intravenous (IV) dose regimens of benralizumab (0.3 and 1.0 mg/kg) on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation <p>Secondary:</p> <ul style="list-style-type: none"> Assess the safety profile of benralizumab in this subject population Evaluate the effect of benralizumab on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 4 Evaluate the effect of benralizumab on the proportion of subjects with asthma exacerbations (relapse or de novo) at Week 24 Evaluate the effect of benralizumab on asthma control using the Asthma Control Questionnaire (ACQ) Evaluate the effect of benralizumab on variability of airflow obstruction using forced expiratory volume in 1 second (FEV1) at the study sites and peak expiratory flow (PEF) at home Evaluate the effect of benralizumab on the need to use concomitant controller or rescue medications Evaluate the effect of benralizumab on physician evaluation of subject status Evaluate the effect of benralizumab on health-related quality of life using the Asthma Quality of Life Questionnaire Evaluate the effect of benralizumab on healthcare resource utilization and economics Assess the pharmacokinetics (PK) and immunogenicity (IM) of benralizumab
Study Design:	<p>This was a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the effect of two IV dose regimens of benralizumab (0.3 and 1.0 mg/kg) on the proportion of asthma exacerbations (relapse and de novo) at Week 12 in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation.</p> <p>During the first step (Step 1), subjects were randomized in a 1:1 ratio to Treatment Arms I (0.3 mg/kg benralizumab or II (1.0 mg/kg benralizumab), and in the second step (Step 2) subjects were randomized in each treatment arm in a 2:1 ratio to receive a single IV dose of benralizumab or placebo. Prior to being randomized into a treatment arm, subjects were stratified by baseline eosinophil levels (> 450 eosinophils/mm³ vs ≤ 450 eosinophils/mm³) in peripheral blood analyzed at site local laboratories.</p> <p>Investigational product (benralizumab or placebo) was administered on Day 0 (within 7 days of meeting eligibility criteria. The subject's FEV₁ was to be $\geq 30\%$ predicted prior to administration of the investigational product.</p> <p>Investigational product was administered as a single IV infusion over a period of at least 30 minutes. If the subject weighed ≥ 130 kg, the infusion time was increased to at least 60</p>

	<p>minutes. Subjects were followed for a total of 24 weeks after administration of the investigational product; however, the last 12 weeks of follow-up only included telephone contacts with the subject for evaluation of asthma exacerbations.</p> <p>The study flow diagram is shown below:</p> <p>108 Adult Subjects Meeting the Following Eligibility Criteria</p> <ul style="list-style-type: none">• Have an asthma exacerbation lasting ≥ 2 hours prior to arrival to the urgent healthcare setting;• Receive treatment by EMS or in an urgent healthcare setting for ≥ 1 hour;• Have a FEV₁ not more than 70% predicted after 1 hour of treatment;• Show no further deterioration in FEV₁ or PEF ($> 25\%$), arterial blood gases, consciousness, or signs of impending ventilatory failure since arrival to the urgent healthcare facility; and• FEV₁ must be $\geq 30\%$ predicted prior to receiving investigational product on Study Day 0. <p>STRATIFY</p> <p>Baseline Eosinophil Levels in Peripheral Blood (>450 eosinophils/mm³ vs. ≤ 450 eosinophils/mm³)</p> <p>RANDOMIZE</p> <p>Step 1: (1:1)</p> <p>Treatment Arm I (N=54)</p> <p>Treatment Arm II (N=54)</p> <p>Study Day Step 2: (2:1)</p> <p>0 7 28 42 63 84 112 140 168</p> <p>0.3 mg/kg MEDI-563 (N=36)</p> <p>Placebo (N=18)</p> <p>1.0 mg/kg MEDI-563 (N=36)</p> <p>Placebo (N=18)</p> <p><i>Study Days 28, 63, 112, 140, and 168 are phone contacts only</i></p>
Study Population:	<p>The subjects in this study were adults between ages of 18-60 years, with a physician-diagnosed asthma with duration of ≥ 2 years by medical chart or subject report and an asthma exacerbation requiring urgent care in the year prior to screening.</p> <p>The study was conducted in USA and Canada. Of the 110 subjects participating in the study, 103 completed. Baseline demographic characteristics were generally similar between the placebo and benralizumab dose groups. The median age of the subject population was 37.0 years (19-60 years), and most subjects were female, not Hispanic or Latino, and Black/African American.</p>
PK Data Analysis:	<p>The following PK parameters were calculated using non-compartmental analysis:</p> <ul style="list-style-type: none">• Maximum observed serum concentration, C_{max}, were direct observations from the serum concentration vs. time data.• Area under the concentration-time curve from dosing to last measurable time point (AUC_{last}) was calculated using log/linear trapezoidal method• Area under the serum concentration-time curve from time 0 to infinity (AUC_{inf}) was estimated as the sum of corresponding AUC_{last} and C_{last}/λ_z values: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$• Terminal half-life (t_{1/2}) was calculated as $t_{1/2} = \frac{\ln(2)}{\lambda_z}$, where λ_z was the first-order terminal rate constant estimated via linear regression of the terminal log-linear decay phase.• Systemic clearance (CL) was calculated as: $CL = \frac{Dose}{AUC_{inf}}$• Steady state volume of distribution, V_{ss}, after IV infusion was calculated as: V_{ss} = MRT*CL, where MRT is the Mean Residence Time and CL is systemic clearance• Volume of distribution of the central compartment, V_c, after IV infusion was calculated as: V_c = Dose/C_{max} <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay</p>

	that employed MSD technology with a LLOQ of 3.86 ng/mL.
Results:	<p>Mean (\pm SD) plasma benralizumab concentration-time profiles are shown in Figure 4.1.3-1.</p> <p>Note: Error bars represent standard deviation of the mean d = day; LLOQ = lower limit of quantification (shown by dashed line); n = number.</p> <p>Figure 4.1.3-1: Mean (\pmSD) Serum Concentration-Time Profiles of Benralizumab in Adult Asthmatic Subjects (Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP186, Figure 5.2-1, page 4100)</p> <p>Mean (\pm SD) PK parameters in asthmatic subjects are summarized in Table 4.1.3-1.</p> <p>The PK exposure (C_{\max} and AUC) increased approximately in a dose proportional manner following a single IV administration of benralizumab. Only 2 subjects received 0.1 mg dose of benralizumab, and the individual CL was 4.59 and 6.06 mL/kg/d. The mean CL values were 4.92 (\pm1.96) and 3.97 (\pm1.02) mL/kg/d for 0.3 and 1.0 mg/kg dose groups, respectively. The mean V_{ss} was 71.8 (\pm23.2) mL/kg [0.3 mg/kg] and 64.0 (\pm15.1) mL/kg [1.0 mg/kg]. The volume of central compartment, V_c was close to the serum volume. The peripheral distribution volume as estimated by the difference between V_{ss} and V_c, was approximately 25 mL/kg, suggesting restricted extravascular distribution of benralizumab upon IV dosing. The mean terminal PK half-lives were 11.5 and 13.2 days in subjects receiving 0.3 and 1.0 mg/kg benralizumab, respectively.</p> <p>The PK inter-individual variability was modest following a single IV administration. In subjects receiving a 0.3 mg/kg dose, the inter-individual variability (%CV) were 25.2% and 26.9% for C_{\max} and AUC_{inf}, respectively. For subjects in the 1.0 mg/kg group, the inter-individual variability was 24.3% CV for C_{\max}, and 24.5% CV for AUC_{inf}.</p>

Table 4.1.3-1: Mean (\pm SD) PK Parameters in Asthmatic Subjects

Dose (mg/kg)	n	C _{max} (μg/mL)	AUC _{last} (μg*d/mL)	AUC _{inf} (μg*d/mL)	CL (mL/kg/d)	t _{1/2} (d)	V _c (mL/kg)	V _{ss} (mL/kg)
0.1	2	1.79	17.8	19.1	5.33	10.6	58.0	82.9
0.3	34	7.03 (1.78)	65.7 (18.5)	67.1 (18.0)	4.92 (1.96)	11.5 (3.14)	46.4 (17.0)	71.8 (23.2)
1.0	36	26.7 (6.49)	263 (64.1)	268 (65.7)	3.97 (1.02)	13.2 (2.39)	39.8 (10.3)	64.0 (15.1)

Parameters are shown as mean (standard deviation); parameter values are rounded to 3 significant figures; n = number; C_{max}: maximum observed concentration postdose; AUC_{last}: area under the concentration-time curve from dosing to last measurable timepoint; AUC_{inf}: area under the concentration-time curve extrapolated to infinity postdose; CL: systemic clearance; t_{1/2}: elimination half-life; V_c: volume of distribution of the central compartment; V_{ss}: steady state volume of distribution

(Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP186, Table 5.3-1, page 4101)

Asthma Exacerbation:

Overall, there was no difference between the combined benralizumab group and placebo group on the primary endpoint of proportion of subjects with at least one asthma exacerbation (unadjudicated or adjudicated) at 12 weeks. The proportion of subjects with asthma exacerbations (nonadjudicated and adjudicated) at Week 12 was 38.9% in the placebo group and 33.3% in the combined benralizumab group (Figure 4.1.3-2). Additionally, the proportion of subjects with asthma exacerbations (nonadjudicated and adjudicated) at Week 4 and 24 were 22.2% and 47.2%, respectively in the placebo group and 16.7% and 43.1%, respectively in the combined benralizumab group; these differences were not statistically significant. Similar results were seen with severe asthma exacerbations (ie, those that resulted in hospitalization).

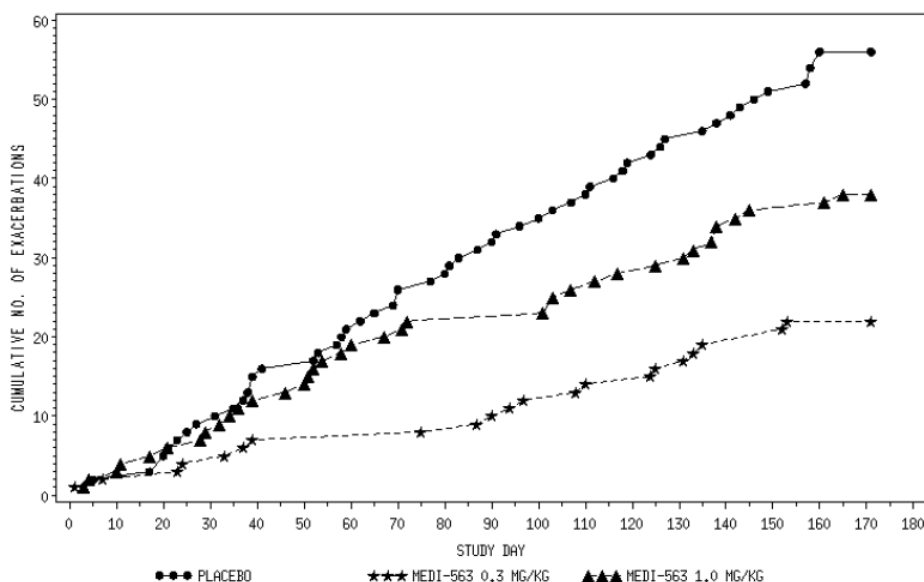


Figure 4.1.3-2: Cumulative Adjudicated Asthma Exacerbations Over Time (Evaluable Population)

(Source: eCTD for BLA 761070, Module 5.3.5.1, CSR for Study MI-CP166, Figure 11.4.1.1-1, page 112)

When analyzing the rate of asthma exacerbations, as opposed to the proportion of asthma exacerbations, there was a statistically significant effect of benralizumab on the overall adjudicated asthma exacerbations and the adjudicated severe asthma exacerbations (ie, those that resulted in hospitalization). Subjects in the combined benralizumab group had a statistically significantly lower weighted adjudicated asthma exacerbation rate (1.82 exacerbations per year, 95% confidence interval [CI]: 1.24-2.59 exacerbations per year; p

= 0.007) compared to the placebo group (3.59 exacerbations per year, 95% CI: 2.44-5.10 exacerbations per year), with only the 0.3 mg/kg benralizumab group showing statistical significance (1.05 exacerbations per year, 95% CI: 0.48-1.99 exacerbations per year; p = 0.001).

Subjects in the combined benralizumab group had a statistically significantly lower weighted adjudicated severe asthma exacerbation rate (0.65 exacerbations per year, 95% CI: 0.32-1.16 exacerbations per year; p = 0.022) compared to the placebo group (1.62 exacerbations per year, 95% CI: 0.89-2.72 exacerbations per year), with only the 0.3 mg/kg benralizumab group showing statistical significance (0.35 exacerbations per year, 95% CI: 0.07-1.02 exacerbations per year; p = 0.016). Results are shown in Figure 4.1.3-3 and Table 4.1.3-2.

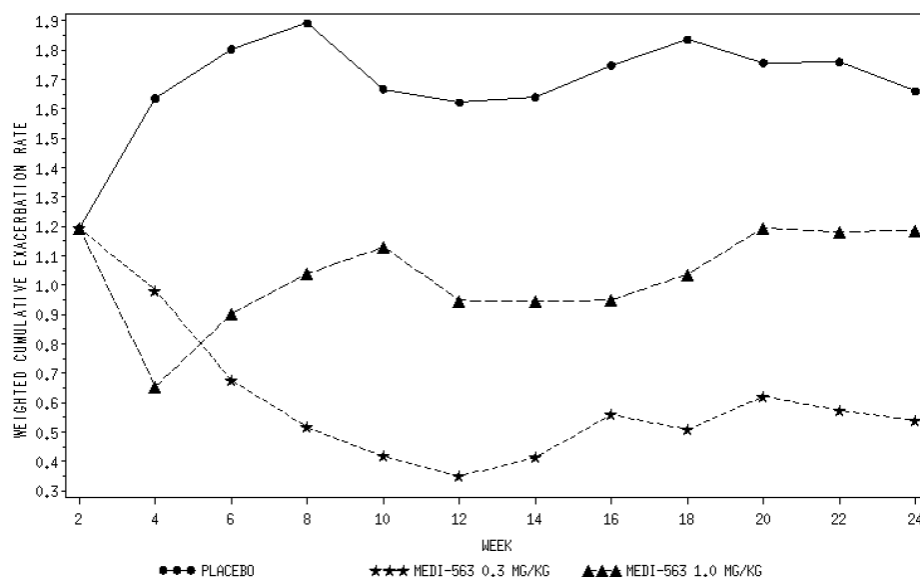


Figure 4.1.3-3: Weighted Cumulative Severe Adjudicated Asthma Exacerbation Rate Over Time (Evaluable Population)

(Source eCTD for BLA 761070, Module 5.3.5.1, CSR for Study MI-CP166, Figure 11.4.1.2.2-2, page 116)

Table 4.1.3-2: Post-Hoc - Weighted Severe Asthma Exacerbation Rate Through Day 84 Evaluable Population (Adjudicated Severe Asthma Exacerbation)

TREATMENT GROUP	RATE (95% CI) [1]	P-VALUE [2]
PLACEBO (N=36)	1.62 (0.89, 2.72)	
MEDI-563 0.3 MG/KG (N=36)	0.35 (0.07, 1.02)	0.016
MEDI-563 1.0 MG/KG (N=36)	0.95 (0.41, 1.87)	0.225
MEDI-563 TOTAL (N=72)	0.65 (0.32, 1.16)	0.022

[1] RATE = TOTAL NUMBER OF EXACERBATION IN EACH GROUP / TOTAL DURATION OF PERSON-YEAR FOLLOW-UP IN EACH GROUP; 95% CI IS THE EXACT 95% POISSON CONFIDENCE INTERVAL.

[2] FROM PAIRWISE POISSON REGRESSION.

(Source: eCTD for BLA 761070, Module 5.3.5.1, CSR for Study MI-CP166, Table 13-3, page 445)

PD Markers:

After treatment with benralizumab, median peripheral blood eosinophil counts were $0.00 \times 10^3/\mu\text{L}$ in the combined benralizumab groups, while median peripheral blood eosinophil counts were $\geq 0.200 \times 10^3/\mu\text{L}$ in the placebo group. Similar trends were seen with ECP and EDN levels, and eotaxin. After treatment, mean levels of ECP and EDN decreased by 15.5 to 18.6 $\mu\text{g/L}$ and 9.90 to 22.36 ng/mL, respectively in the combined benralizumab group, while these levels increased in the placebo group by 2.0 to 4.6 $\mu\text{g/L}$ and 4.75 to 11.27

	<p>ng/mL, respectively. After treatment, mean levels of serum eotaxin levels increased by 61.1 to 17.3 ng/mL in the combined benralizumab group and by 17.0 to 2.1 ng/mL in the placebo group. There did not appear to be any differences between the benralizumab groups in peripheral blood eosinophils, ECP, EDN, and eotaxin.</p> <p><u>Immunogenicity:</u> There were 9.2% (6/65 subjects) of benralizumab subjects and no placebo subjects who were considered ADA positive after baseline (titer ≥ 50). There did not appear to be a relationship between the ADA titers and the peripheral blood eosinophil levels on Day 84, however many subjects received oral corticosteroids at baseline and throughout the study, and subjects were not followed for eosinophil recovery. There were no TEAEs consistent with immune complex disease (defined as Type 3 hypersensitivity reactions) in subjects with ADA.</p> <p>There were 5 subjects with high titers (≥ 400) of ADA who appeared to have a lower terminal PK than in others receiving the same dose. However, the impact of ADA was only observed at low PK levels, and there was no apparent correlation with any safety or efficacy parameters.</p> <p><u>Safety:</u> The pattern and type of TEAEs reported in this study are similar to what has been observed in previous studies with benralizumab using the IV formulation, and there were no new or unexpected safety findings. There were no clinically important safety differences between the placebo group and the combined benralizumab treatment groups with regard to overall pattern of TEAEs or TSEAEs. There were also no differences between groups in the frequency of treatment-emergent infections. The frequency of treatment-related TEAEs and of acute TEAEs was higher in the combined benralizumab group than the placebo group. There were no deaths in this study and one subject (0.3 mg/kg benralizumab) discontinued the investigational product due to the occurrence of a cluster of TEAEs (pyrexia, infusion site rash, infusion site edema, wheezing, and blood pressure decreased).</p>
Conclusions:	<ul style="list-style-type: none"> • The primary endpoint of the study was not met as the proportion of subjects with at least one asthma exacerbation (non-adjudicated or adjudicated) at Week 12 was similar between the placebo and combined benralizumab groups • There was an effect of benralizumab on reducing the rate of adjudicated asthma exacerbations and adjudicated severe asthma exacerbations. Statistical significance was achieved with the combined treatment group and 0.3 mg/kg benralizumab group when compared to the placebo group, but not the 1.0 mg/kg benralizumab group • Peripheral blood eosinophil, basophil, ECP, and EDN levels decreased in the combined benralizumab group through the last scheduled visit (Day 84). Similar reductions in these measurements of eosinophilic inflammation were achieved in both the 0.3 mg/kg and 1.0 mg/kg treatment groups individually, indicating that although the 1.0 mg/kg group was not significantly different than placebo when examining the rate of asthma exacerbations, there is a similar PD effect for both benralizumab dose levels • Following single IV administration of benralizumab, the PK exposure increased approximately dose proportionally in the dose range investigated • A total of 6 of 65 subjects (9.2%) in the combined benralizumab group had positive ADA following treatment with benralizumab. Serum concentrations of benralizumab were reduced in 5 subjects. Peripheral blood eosinophil levels were not altered in subjects with positive ADA and there were no AEs consistent with immune complex disease (defined as Type 3 hypersensitivity reactions) in subjects with ADA.

	<ul style="list-style-type: none">• The safety profile of benralizumab (following single doses of 0.3 or 1.0 mg/kg in adult subjects who required an urgent healthcare visit for treatment of an acute asthma exacerbation) supports further clinical development• Subjects treated with a single dose of 0.3 or 1.0 mg/kg had higher frequencies of treatment-related and acute TEAEs compared to subjects in the placebo group• Decreases in median WBC counts and ANC were observed following treatment with benralizumab.
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4.1.4 Study MI-CP197: Safety, Tolerability Pharmacokinetics, and Immunogenicity of multiple SC doses of benralizumab in adult subjects with asthma

Study:	MI-CP197
Study Title:	<i>A Phase 2a, Randomized, Double-blind, Placebo-controlled, Dose-escalation Study to Evaluate the Safety and Tolerability of Multiple-dose Subcutaneous Administration of MEDI-563, a Humanized Anti-interleukin-5 Receptor Alpha Monoclonal Antibody, in Adults with Asthma</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of escalating multiple SC doses of benralizumab in adult subjects with asthma <p>Secondary:</p> <ul style="list-style-type: none"> Assess the pharmacokinetics (PK) of benralizumab Assess the immunogenicity (IM) of benralizumab in this subject population <p>Exploratory:</p> <ul style="list-style-type: none"> Assess the effect of benralizumab on pulmonary function Assess the effect of benralizumab on peripheral blood levels of eosinophils and basophils in adults with asthma Assess the effect of benralizumab on eosinophil and inflammatory biomarkers, including eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil-derived neurotoxin (EDN), eotaxin, IL-5, and C-reactive protein (CRP) Assess the effect of benralizumab on total serum IgE and IgE fluorescence enzyme immunoassay (FEIA) for common aeroallergens Assess the effect of benralizumab on asthma control, short-acting β_2-agonist use, asthma symptom scores, health-related quality of life, and asthma exacerbations Assess the effect of benralizumab on total nasal symptom scores
Study Design:	<p>This was a Phase 2a, randomized, double-blind, placebo-controlled, dose-escalation, multicenter study evaluating the safety, tolerability, PK, and IM of multiple SC doses of benralizumab in adult subjects with asthma.</p> <p>This study was a randomized, double-blind, placebo-controlled, dose-escalation study of multiple SC doses of benralizumab (25, 100, or 200 mg) or placebo. A total of 24 subjects were to be randomized in a 3:1 ratio to receive SC benralizumab (25, 100, or 200 mg) or SC placebo every 4 weeks (on Days 0, 28, and 56) for a total of 8 weeks. In each dose cohort, 6 subjects were to receive benralizumab and 2 subjects were to receive placebo. The investigational product (benralizumab or placebo) was administered on Days 0, 28, and 56. The number of SC injections administered on each treatment day was dependent on the dose cohort. Subjects in the 25 mg dose cohort received one SC injection each treatment day, subjects in the 100 mg dose cohort received two SC injections each treatment day, and subjects in the 200 mg dose cohort received 4 SC injections each treatment day. Subjects were to be followed for 105 days after their last SC injection (through Day 161).</p> <p>Subjects were to be in the study for approximately 175 days (up to 14 days for screening, 56 days of treatment, and 105 days of follow-up).</p> <p>Any subject whose eosinophil count in peripheral blood had not returned to at least 20% of the baseline value at the End of Study (Day 161)/Early Discontinuation visit was to be asked to return to the study site every other month thereafter until the eosinophil count had returned to at least 20% of the baseline value.</p> <p>The study flow diagram is shown below:</p>

	<p>Dose Cohort 1: 25 mg SC, N=8 (6 MEDI-563/2 Placebo)</p> <p>Dose Cohort 2: 100 mg SC, N=8 (6 MEDI-563/2 Placebo)</p> <p>Dose Cohort 3: 200 mg SC, N=8 (6 MEDI-563/2 Placebo)</p> <p>↑ Administration of investigational product (MEDI-563 or placebo)</p> <p>↗ Dosing at each next higher dose cohort commenced after all 8 subjects from the previous lower dose cohort had been followed through the Study Day 35 evaluations with an acceptable safety profile.</p> <p>* Subjects whose eosinophil counts did not return to 20% of baseline value were to return every other month until eosinophil counts return to 20% of baseline value.</p> <p>The formulation used in this study were manufactured using Process 1b material.</p>
Study Population:	<p>A total of 25 subjects participated in the study at 6 sites in the USA. Subjects received benralizumab (25, 100, or 200 mg) or placebo as SC injections. Of the 25 subjects enrolled in the study, 24 (96.0%) completed the study. One subject in the 25 mg group was withdrawn from the study because of a protocol violation (did not meet eligibility criteria). The median age of the subject population was 44.0 years (range 27-69 years), and the majority of subjects were female (14/25 subjects; 56.0%). Most subjects were White (80.0%) and not Hispanic (92.0%). Subjects in the study had a diagnosis of asthma of ≥ 1 year duration based on their medical and asthma history.</p>
PK Data Analysis:	<p>Following the first dose of investigational product in each of the dose cohorts, the non-compartmental PK parameters included, but were not limited to maximum observed serum concentration of benralizumab (C_{max}), area under the concentration-time curve (AUC), half-life (time for concentration [of drug] to decrease by 50% [$t_{1/2}$]) and systemic clearance (CL). Following each dose of investigational product in each dose cohort, the non-compartmental PK parameters included C_{max} and pre-dose trough serum concentrations.</p> <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay that employed MSD technology with a LLOQ of 3.86 ng/mL.</p>
Results:	<p>Mean (\pm SD) plasma benralizumab concentration-time profiles are shown in Figure 4.1.4-1.</p>

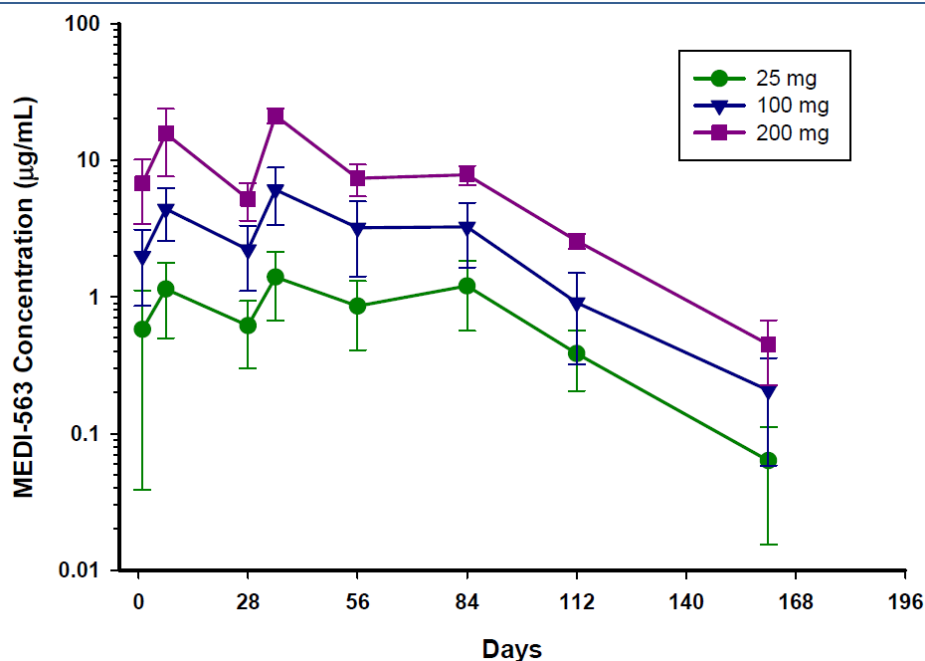


Figure 4.1.4-1: Mean (\pm SD) Serum Concentration-Time Profiles of Benralizumab Following Multiple SC Doses of 25, 100, and 200 mg, Safety Population

(Source: eCTD for BLA 761070, Module 5.3.5.1, CSR for Study MI-CP197, Figure 11.4.1.1-1, page 106)

Mean (\pm SD) PK parameters in asthmatic subjects are summarized in Table 4.1.4-1.

Following the first dose of benralizumab, C_{max} were generally achieved at 7 days across all 3 dose levels. Mean C_{max} after the first dose and the overall AUC increased in an approximately dose-proportional manner in the 25-100 mg dose range. However the PK exposure was more than dose-proportional when the dose increased from 100 to 200 mg. In all cohorts the PK steady-state was achieved following the third dose, as the pre-dose serum benralizumab concentrations on Day 56 were similar to those observed on Day 84. The trough concentrations (Section 14, Table 24.1) at steady-state appeared dose-proportional in the 25-200 mg dose range. In addition, the mean PK half-life of benralizumab (17.2-18.6 days) was similar across the 3 dose levels. Thus, the apparent PK nonlinearity in C_{max} following the first dose and overall AUC may be likely due to the limited sample scheme which did not allow the capturing of full benralizumab PK profiles (i.e., the true C_{max} could have been missed). The dose-proportional steady-state trough concentrations and similar elimination half lives across all dose levels suggested that benralizumab PK was linear with dose in the 25-200 mg dose range investigated.

Table 4.1.4-1: Summary of Benralizumab PK Parameters, Safety Population

Pharmacokinetic Parameters	Benralizumab Dose Groups ^a		
	25 mg N=7	100 mg N=6	200 mg N=6
T _{max} (days)	7.00 (7.00-28.00)	7.00 (1.00-7.00)	7.00 (7.00-7.00)
C _{max} (µg/mL)	1.152 (0.615)	4.127 (1.775)	15.637 (8.062)
AUC _{0-inf} (µg•day/mL)	118.335 (69.640)	405.868 (205.856)	1,157.013 (86.444)
t _{1/2} (days)	17.163 (2.368)	18.610 (3.905)	18.315 (3.484)

AUC_{0-inf} = area under the concentration-time curve from 0 to infinity; C_{max} = maximum observed concentration; N = number of subjects in the Safety Population; t_{1/2} = half-life; T_{max} = time to maximum observed concentration

^a All parameters are shown as mean (standard deviation [SD]), except T_{max} which is shown as median (range).

(Source: eCTD for BLA 761070, Module 5.3.5.1, CSR for Study MI-CP197, Table 11.4.1.1-1, page 107)

Immunogenicity:

Quantifiable antidrug antibodies (ADA) were found in 4 of 19 benralizumab subjects (21.1 %) and no placebo subjects at some time during the course of the study. There was one subject each in the 25 mg (maximum titer 3,200) and 100 mg (maximum titer 50) dose groups, and 2 subjects in the 200 mg (maximum titer 200 and 800) dose group.

There appeared to be an effect of ADA on PK and PD. Subjects with ADA titers of ≥ 200 had a decrease in benralizumab serum concentrations at the time the antibodies were detected when compared with subjects in the same dose cohort. The Sponsor did not include these subjects in the calculation of PK parameters. Subjects with ADA titers of ≥ 800 had eosinophil recovery by Day 161 which was earlier than most subjects who received benralizumab.

There were no hypersensitivity reactions or AEs consistent with immune complex disease (defined as Type 3 hypersensitivity reactions) in subjects with ADA. One subject in the 25 mg group had AEs of increased troponin 1 (mild) and decreased white blood count (WBC) count (moderate) on Day 56. Both AEs were considered resolved prior to the last scheduled visit (Day 161). The relationship of these laboratory changes to ADA in this subject is unlikely.

PD Markers:

Multiple-dose SC treatment with benralizumab administered at doses of 25, 100, and 200 mg had an effect on eosinophil and inflammatory biomarkers, including ECP, EDN, eotaxin, and IL-5.

There were baseline differences among the benralizumab groups. Levels of eosinophils and inflammatory biomarkers were higher in the 25 mg group than the placebo group and the other benralizumab groups. Peripheral blood eosinophil suppression was observed following SC administration of benralizumab at all dose levels through the last scheduled visit (Day 161). No suppression of peripheral blood eosinophils was observed in the placebo group. Persistent decreases of > 70.0% were observed throughout the study.

Eosinophil recovery occurred in all subjects 6 months after the last scheduled visit (Day

	<p>161), with the majority of subjects (88.9%) recovering 4 months after the last scheduled visit (Day 161). Four of 18 (22.2%) benralizumab subjects who were followed through Day 161 had eosinophil recovery by Day 161. This included the 2 subjects with the highest levels of ADA (ADA titers ≥ 800), one subject with a baseline eosinophil count of $1.0 \times 10^3/\mu\text{L}$ (highest of any subject in the study), and one subject with no apparent explanation for the difference in recovery time. The remaining 14 subjects recovered during the long-term follow up period.</p> <p>There were no differences in time to recovery using the criterion of ≥ 50 eosinophils/mm^3 (equivalent of $0.05 \times 10^3/\mu\text{L}$) or $\geq 20\%$ of the baseline value. The median time to recovery for the 25, 100, and 200 mg groups was 160.5 days (range 57-219 days); 183.5 days (range 108-239 days), and 186.5 days (100-214 days), respectively using either criteria. Eosinophil recovery occurred by the 2-month post final scheduled visit for the 25 and 200 mg groups and by the 4 month post final scheduled visit for the 100 mg group.</p> <p>Reductions in ECP and EDN were observed following SC administration of benralizumab at all dose levels through Day 161. No reductions in either ECP or EDN were observed in the placebo group. By Day 7, reductions in median serum ECP and EDN levels of $\geq 65.0\%$ were observed in all benralizumab groups.</p> <p><u>Patient-Reported Outcomes:</u></p> <p>There appeared to be no effect of benralizumab on patient reported outcomes (PROs) using the ACQ-6, AQLQ(S), TNSS, and asthma symptom scores. Median changes from baseline in total asthma system scores tended to be higher in the 100 and 200 mg benralizumab groups compared to the placebo and 25 mg benralizumab groups. Median changes from baseline in TNSS tended to be slightly higher in the 200 mg benralizumab group compared to the placebo and 25 and 100 mg benralizumab groups. Given the small size of the study and the variability of baseline disease characteristics, interpretation of the asthma symptom scores and TNSS findings may be difficult.</p> <p><u>Safety:</u></p> <p>There were no deaths, no SAEs, and no TEAEs that resulted in discontinuation of benralizumab in an individual subject. The frequency of TEAEs was slightly higher in the benralizumab group compared to the placebo group, but the frequency of severe TEAEs were similar between the two groups. The most common TEAEs occurred in the Events of Infections and Infestations system organ class (SOC; 2/6 placebo subjects, 33.3%; 8/19 benralizumab subjects, 42.1%). The most frequently reported TEAEs were upper respiratory tract infections (3/19 benralizumab subjects, 15.8%; 1/6 placebo subjects, 16.7%) and asthma (3/19 benralizumab subjects, 15.8%; 0 placebo subjects). The majority of TEAEs in all subjects were mild (38%) to moderate (51%) in severity. There were 4 subjects (16%) with severe TEAEs and 5 subjects (20%) with related events. The severe TEAEs were increased blood creatine phosphokinase (CPK; placebo), procedural pain (25 mg), decreased WBC count (100 mg), and myalgia (200 mg). Treatment-related TEAEs were increased blood CPK (placebo and 25 mg), increased troponin 1 (25 mg), decreased WBC count (25 mg and 100 mg), headache (100 mg), and urticaria (25 mg).</p> <p>The most frequently reported treatment-related TEAE (incidence $\geq 10\%$) in the combined benralizumab group was decreased WBC count (0 placebo subjects; 2/19 benralizumab subjects each, 10.5%). No injection site reactions were reported during the study.</p>
Conclusions:	<ul style="list-style-type: none"> Benralizumab PK was linear with dose in the 25-200 mg dose range investigated. The mean PK half-life was approximately 17-18 days. Approximately one-fifth of subjects in this study developed ADA. Serum

	<p>concentrations of benralizumab were decreased in subjects with ADA titers \geq 200 and more rapid protocol-specified eosinophil recovery occurred in subjects who had ADA titers \geq 800. There did not appear to be a relationship between the presence of ADA to benralizumab and the occurrence of TEAEs.</p> <ul style="list-style-type: none"> • Peripheral blood eosinophil suppression was observed following SC administration of benralizumab at all dose levels, with protocol-specified eosinophil recovery within 6 months after the last scheduled study visit (Day 161). • Reductions in serum ECP and serum EDN levels and increases in serum eotaxin and serum IL-5 were observed following SC administration of benralizumab at all dose levels. • There were no differences between placebo and benralizumab on any of the exploratory endpoints of clinical activity.
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4.1.5 Study MI-CP220: Dose ranging study evaluating the efficacy and safety of multiple-dose SC administration of benralizumab (2, 20, or 100 mg) in adult subjects with uncontrolled asthma requiring medium- or high-dose inhaled corticosteroids (ICS) plus long-acting β 2 agonist (LABA)

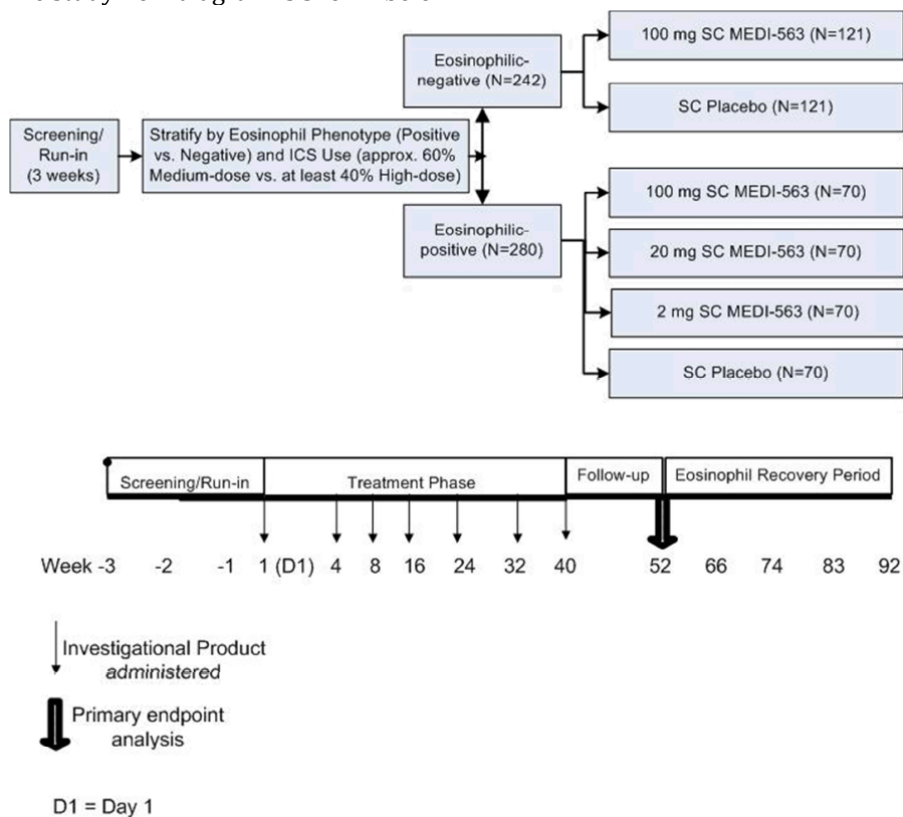
Study:	MI-CP220
Study Title:	<i>A Phase 2b, Dose-ranging Study to Evaluate the Efficacy and Safety of MEDI-563 in Adults with Uncontrolled Asthma</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the effect of multiple-dose subcutaneous (SC) administration of benralizumab on the annual asthma exacerbation rate (AER) in adult subjects with uncontrolled, suspected eosinophilic asthma <p>Secondary:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of benralizumab. To determine the optimal dose of benralizumab to be used in Phase 3 studies. To describe the immunogenicity and pharmacokinetics (PK) of benralizumab. To assess the effect of benralizumab on other assessments of clinical activity (ie, asthma control and pulmonary function). To assess the effect of benralizumab on health-related quality of life. <p>Exploratory:</p> <ul style="list-style-type: none"> To determine the effect of benralizumab on the annual AER in eosinophilic-negative adult subjects. To assess the effect of benralizumab on other parameters associated with asthma exacerbations (e.g., rate; time to first asthma exacerbation). To assess the effect of benralizumab on healthcare resource utilization and productivity. To assess the effect of benralizumab on blood and sputum biomarkers
Study Design:	<p>This was a Phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of multiple-dose SC administration of benralizumab (2, 20, or 100 mg) in adult subjects with uncontrolled asthma requiring medium-dose ICS (defined as > 250-500 μg fluticasone propionate or equivalent) or high-dose ICS (defined as > 500 μg fluticasone propionate or equivalent and/or receipt of chronic oral corticosteroids) plus LABA and having a history of ≥ 2 but ≤ 6 documented asthma exacerbations in the 12 months prior to the date informed consent was obtained that required use of a systemic corticosteroid burst.</p> <p>Eligible subjects were classified and stratified as having either an eosinophilic phenotype (EOS+), defined as ELEN Index positive and/or FeNO ≥ 50 ppb, or a non-eosinophilic phenotype (EOS-), defined as both ELEN Index negative and FeNO < 50 ppb, during the 3-week screening/run-in period. Subjects were also stratified by baseline ICS status (approximately 60% of subjects on medium-dose vs at least 40% of subjects on high-dose).</p> <p>The plan was to have approximately 100-150 study sites around the world to participate in this study, with 522 subjects comprising 280 EOS+ subjects and 242 EOS- subjects to be randomized in the study. EOS+ subjects were randomized in a 1:1:1:1 ratio to receive SC benralizumab (2, 20, or 100 mg) or placebo; EOS- subjects were randomized in a 1:1 ratio to receive SC benralizumab (100 mg) or placebo</p> <p>Investigational product was administered as two SC injections every 4 weeks (Q4W) for the first 3 doses on Weeks 1 (Day 1), 4, and 8 and then every 8 weeks (Q8W) thereafter</p>

for the last 4 doses on Weeks 16, 24, 32, and 40. After Week 40, subjects were followed an additional 12 weeks (through Week 52) for assessment of acute exacerbations. After Week 52, subjects were followed an additional 14 weeks (through Week 66) for safety including recovery of peripheral blood eosinophil count (as defined in Section 5.2.3 of the study protocol [Section 16.1.1]).

A 3-week screening/run-in period preceded administration of investigational product (benralizumab or placebo). During the 3-week screening/run-in period, subjects continued the same dose (medium- or high-dose) ICS/LABA combination product as prior to participation in the study (doses of ICS/LABA must have been stable for 30 days prior to the Week -3 screening visit). Subjects who used individual ICS and LABA inhalers prior to participation in the study switched to an ICS/LABA combination product of their choice (either fluticasone/salmeterol or budesonide/formoterol) at an equivalent dose of ICS. Subjects remained on the same dose of ICS/LABA through the Week 52 visit.

Anti-drug antibodies (ADA) were assessed at Day 1, and Weeks 4, 16, 24, 32, 40, 52, 66, 74, 83, and 92. An analysis of ADA to benralizumab was performed when 180 subjects had reached the Week 16 visit. This analysis included a blinded review of safety and ADA data.

The study flow diagram is shown below:



The formulation used in this study were manufactured using Process 2 material.

Study Population:

A total of 609 subjects who met eligibility criteria and were randomized into the study. The 609 randomized subjects comprised 324 EOS+ and 285 EOS- asthma subjects, with at least 84% of EOS+ subjects and 89% of EOS- subjects completing the study as planned. There were similar proportions of subjects who completed the study within each ELEN Index subgroup, with a higher proportion of subjects completing the study in the EOS- subgroup than in the EOS+ subgroup. Baseline demographic characteristics were generally similar between the placebo and benralizumab groups within each eosinophil

	<p>phenotype and across eosinophil phenotypes for the mITT population. The median age (range) of the subject population was 50.0 years (18 to 75 years), and most subjects were female (68.8%), White (70.6%), and not Hispanic or Latino (59.1%). Subjects had a median weight of 75.0 kg and a median body mass index of 28.0 kg/m².</p>
PK Data Analysis:	<p>Due to the limited PK sampling schedule, non-compartmental analysis was not performed. Descriptive statistics of benralizumab serum concentration data were prepared. To avoid statistical bias, PK data associated with missing doses or early withdrawal were censored for exclusion from mean calculations. Benralizumab serum concentration were summarized by dose group, eosinophil index, and ADA status using descriptive statistics that includes mean, standard deviation (SD), minimum (Min), median, maximum (Max), and percent coefficient of variation (%CV). Empirical assessments of PK dose-linearity, ADA impact, and demographic covariate effect(s) were performed based on the steady-state trough (pre-dose) benralizumab concentrations (C_{trough,ss}).</p> <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay that employed MSD technology with a LLOQ of 3.86 ng/mL.</p>
Results:	<p>The mean PK profiles of benralizumab for 2-, 20- and 100-mg treatment groups are shown in Figure 4.1.5-1.</p> <p>Figure 4.1.5-1: Mean (±SD) Serum Concentration-Time Profiles of Benralizumab in Subjects with Uncontrolled Asthma</p> <p>LLOQ=lower limit of quantitation (shown as dashed line); N = Number of Subjects. Unscheduled data and data associated with missing doses or early withdrawal were excluded from mean calculations and plotting. Error bars represent standard deviations; Arrows indicate dosing events. BLQ values are plotted at half LLOQ level. (Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP220, Figure 6.3-2, page 24)</p> <p>As shown in Figure 4.1.5-2, at the 100 mg dose level, there was no difference in PK between eosinophilic-positive and -negative asthma groups.</p>

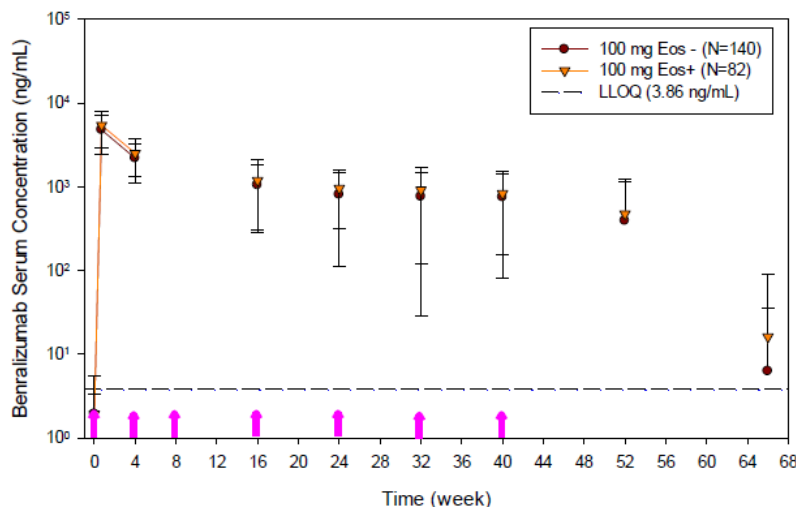


Figure 4.1.5-2: Mean (\pm SD) Serum Concentration-Time Profiles of Benralizumab in Eosinophilic-Positive and -Negative Asthma Subjects in the 100 mg Dose Group

LLOQ=lower limit of quantitation (shown as dashed line); N = Number of Subjects.

Unscheduled data and data associated with missing doses or early withdrawal were excluded from mean calculations and plotting. Error bars represent standard deviations; Arrows indicate dosing events. BLQ values are plotted at half LLOQ level.

(Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP220, Figure 6.3-1, page 23)

The week 1 (Day 6) observation corresponded to the maximum serum concentration of benralizumab following single SC administration. Other samples in the treatment phase (Weeks 1-40) were collected prior to the dose administration at a dosing visit. The apparent PK steady-state was reached at Week 16.

Impact of ADA on PK:

Approximately 10% placebo subjects had at least one serum sample that tested positive during the course of the study (presumed false-positive). In benralizumab treated subjects, the incidence of ADA decreased with increasing dose level. During the course of the study, 42% subjects in the 2 mg group tested positive for ADA (32.1% over placebo). At the top 100 mg dose, the overall ADA rate was 25.7%, or 15.8% over placebo. There was no appreciable difference in ADA incidence among eosinophilic-positive and eosinophilic-negative subjects.

The mean serum concentration-time profiles of benralizumab in ADA-positive and -negative subjects are presented in Figure 4.1.5-3. The development of ADA was associated with reduced steady-state PK exposure. The effect of ADA on PK exposure was greatest for the 2 mg dose group.

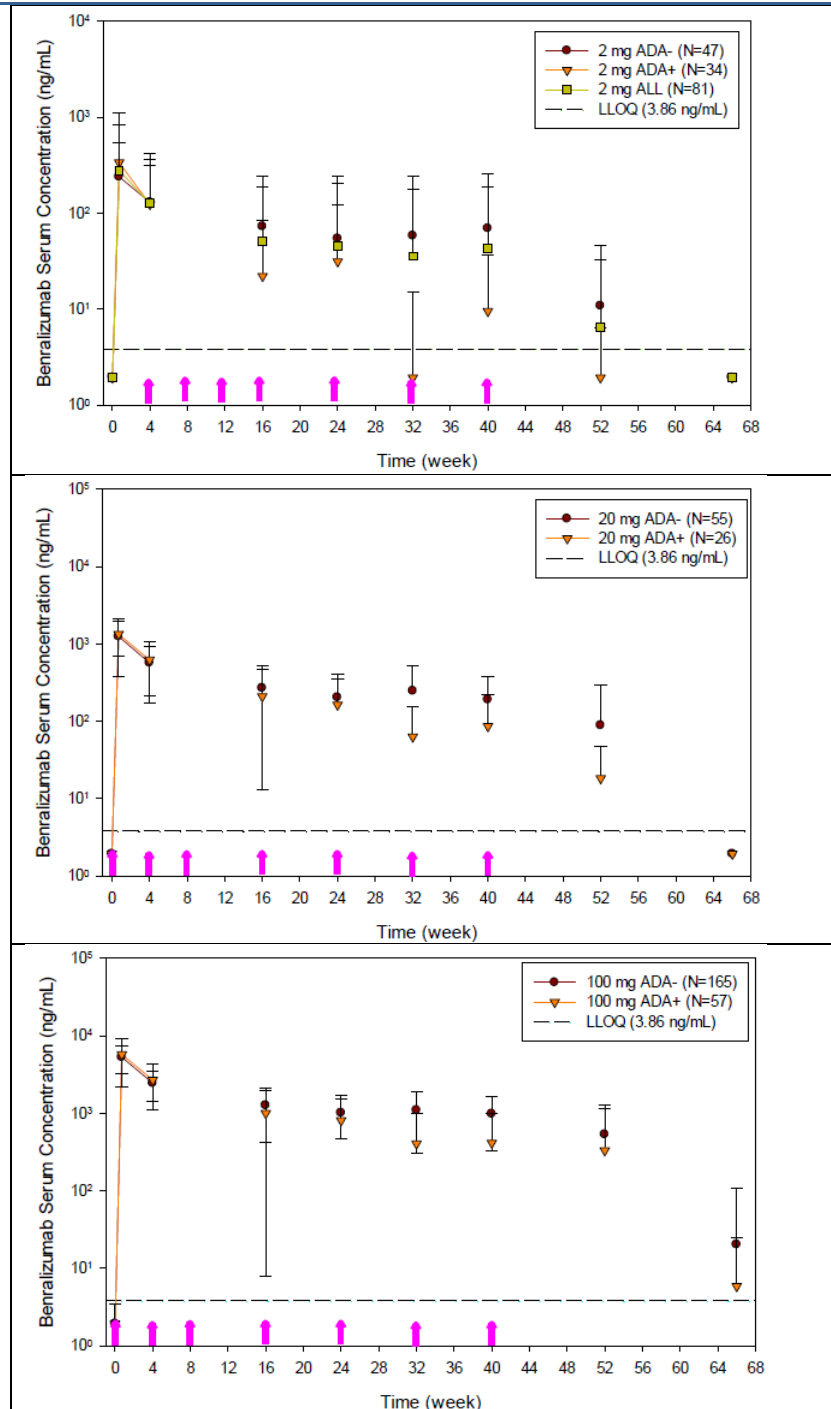


Figure 4.1.5-3: Mean (\pm SD) Serum Concentration-Time Profiles of Benralizumab in ADA-Positive and -Negative Subjects in the 2 mg, 20 mg and 100 mg Dose Groups

LLOQ=lower limit of quantitation (shown as dashed line); N = Number of Subjects.

Unscheduled data and data associated with missing doses or early withdrawal were excluded from mean calculations and plotting. Error bars represent standard deviations; Arrows indicate dosing events. BLQ values are plotted at half LLOQ level.

The upper panel shows the PK profiles for the 2 mg dose group, the middle panel for the 20 mg dose group and the lower panel for the 100 mg dose group.

(Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP220, Figure 6.4-1, 6.4-2 and 6.4-3, pp 27-29)

PK evaluations were primarily based on C_{max} following the first dose, and the steady-state trough concentrations, $C_{trough,ss}$, due to limited sampling, as shown in Table 4.1.5-1 below. Compared with ADA negative subjects, ADA positive subjects had much lower $C_{trough,ss}$ levels. The impact of ADA was more pronounced as the dose decreased. The mean $C_{trough,ss}$ in ADA(+) subjects was 83% lower than in ADA(-) subjects at 2 mg dose level, 42% lower at 20 mg, and 52% at 100 mg.

Table 4.1.5-1: Summary of Benralizumab Steady-State Mean PK Summary Statistics

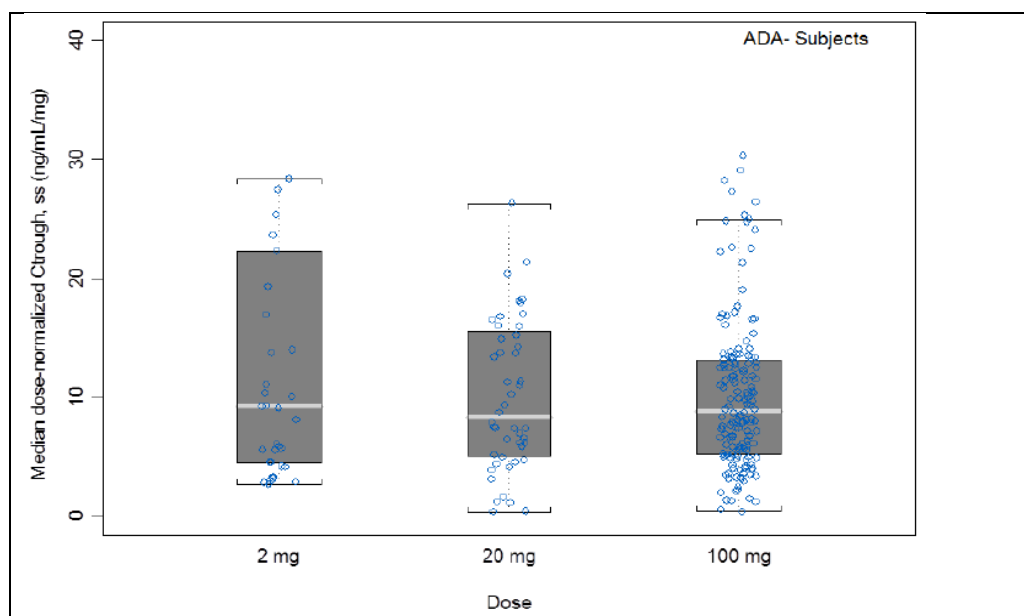
Week	2mg			20mg			100mg		
	ADA Neg	ADA Pos	All	ADA Neg	ADA Pos	All	ADA Neg	ADA Pos	All
16	72.6 (170)	22.0 (62.9)	51.1 (137)	269 (256)	209 (260)	249 (257)	1200 (811)	806 (758)	1100 (815)
24	54.3 (190)	31.3 (91.0)	45.1 (157)	203 (209)	163 (185)	190 (201)	992 (638)	499 (660)	862 (678)
32	58.2 (184)	3.39 (13.1)	35.6 (143)	247 (283)	62.8 (93.2)	183 (250)	974 (782)	392 (489)	820 (760)
40	69.4 (189)	9.49 (26.6)	42.5 (144)	191 (191)	85.8 (136)	150 (178)	916 (674)	405 (503)	777 (671)
$C_{trough,ss}$	53.9 (169)	8.87 (28.9)	34.7 (131)	212 (187)	124 (154)	182 (180)	1010 (643)	489 (573)	869 (665)
$C_{trough,ss,D}$	27.0 (84.4)	4.43 (14.5)	17.3 (65.3)	10.6 (9.37)	6.20 (7.69)	9.10 (9.02)	10.1 (6.43)	4.89 (5.73)	8.69 (6.65)

Parameters are shown as mean (standard deviation).

$C_{trough,ss}$: steady-state trough concentrations; $C_{trough,ss,D}$: dose-normalized steady-state trough concentrations

(Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP220, Table 6.5-1, page 32)

The PK of benralizumab was dose proportional between the 20 and 100 mg dose groups (Figure 4.1.5-4).



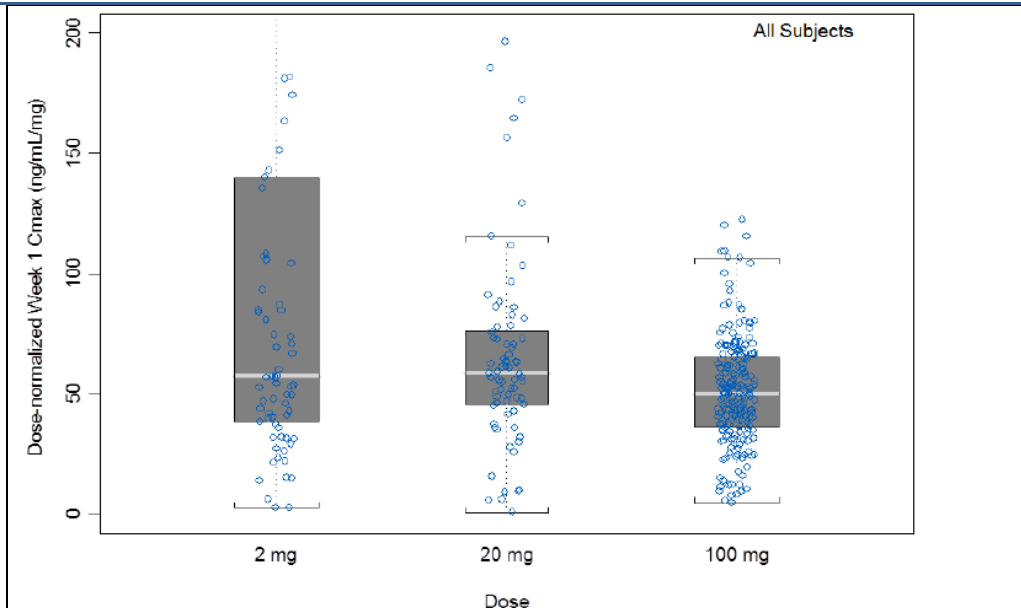


Figure 4.1.5-4: Dose Normalized $C_{trough,ss}$ In ADA(-) Subjects (Top Panel) and Dose-Normalized Week1 C_{max} in All Subjects (Bottom Panel)

(Source: eCTD for BLA 761070, Module 5.3.5.1, PK Report for Study MI-CP220, Figure 6.5-1 and 6.5-2, pp 33-34)

Efficacy:

Annual Asthma Exacerbation Rate:

There was a statistically significant 41% reduction in the annual AER in the EOS+ 100 mg benralizumab group versus the EOS+ placebo group ($p = 0.096$); a 36% reduction in the annual AER was seen in the EOS+ 20 mg benralizumab group versus the EOS+ placebo group, but this difference was not statistically significant.

When the placebo and benralizumab groups were combined across the eosinophil phenotypes and by Week -1 local peripheral blood eosinophil count (< 300 vs ≥ 300 cells/ μ L), statistically significant 57% and 43% reductions in the annual AER were seen in the 20 and 100 mg benralizumab groups, respectively, versus the placebo group in subjects who had a Week -1 local peripheral blood eosinophil count of ≥ 300 cells/ μ L ($p = 0.015$ and $p = 0.049$, respectively). For the < 300 cells/ μ L subgroup, there were no statistically significant differences in annual AER between any of the benralizumab dose groups and placebo. More robust reductions in annual AER were seen in the 20 and 100 mg benralizumab groups versus the placebo group in subjects who had a Week -1 local peripheral blood eosinophil count of ≥ 400 cells/ μ L. For the < 200 , < 300 , and < 400 cells/ μ L subgroups, there were no statistically significant differences in annual AER between any of the benralizumab dose groups and placebo.

The mean time to first asthma exacerbation through Week 52 was statistically significantly longer in both the 20 and 100 mg benralizumab groups (148.9 and 149.7 days, respectively) versus the placebo group (123.3 days) for the ≥ 300 cells/ μ L subgroup ($p = 0.033$ and $p = 0.022$, respectively).

Pulmonary Function

Statistically significant improvements from baseline in FEV1 at Week 52 were seen in the EOS+ 2, 20, and 100 mg benralizumab groups versus the EOS+ placebo group ($p = 0.140$, $p = 0.069$, and $p = 0.063$, respectively) and in the EOS- 100 mg benralizumab group versus the EOS- placebo group ($p = 0.155$).

Asthma control

Statistically significant greater improvements from baseline in ACQ-6 scores at Week 52 were seen in the EOS+ 2, 20, and 100 mg benralizumab groups versus the EOS+ placebo group ($p = 0.125$, $p = 0.074$, and $p = 0.057$, respectively) and in the EOS- 100 mg benralizumab group versus the EOS- placebo group ($p = 0.053$).

PD Effects:

Mean absolute peripheral blood eosinophils were markedly reduced across the 2, 20, and 100 mg benralizumab groups through Week 4; thereafter at Week 8, mean absolute peripheral blood eosinophil counts steadily increased in the 2 mg benralizumab group but continued to decrease or stabilize in the 20 and 100 mg benralizumab groups. Increases in mean absolute peripheral blood eosinophil counts occurred at Week 52 in the 20 mg benralizumab group and at Week 66 in the 100 mg benralizumab group. Mean absolute peripheral blood eosinophil counts were not reduced in the placebo group.

Nearly all subjects in the 2, 20, or 100 mg benralizumab groups had absolute peripheral blood eosinophil recovery to ≥ 50 cells/ μ L or $\geq 20\%$ of baseline absolute peripheral blood eosinophil level at Week 66. Statistically significant mean decreases of 33.50% and 25.56% in average absolute peripheral blood basophils by flow cytometry at Week 52 from baseline were seen in the 20 and 100 mg benralizumab groups versus the placebo group ($p < 0.001$ and $p = 0.001$, respectively); whereas, average absolute peripheral blood basophils increased by 37.09% and 28.50% in the placebo and 2 mg benralizumab groups, respectively.

Safety:

There was a higher proportion of subjects with at least one TEAE by Week 66 in the total benralizumab group than in the placebo group, with no apparent dose response between the individual benralizumab dose groups. The most frequent TEAE (incidence $> 10\%$) in the placebo group was asthma, and the most frequent TEAEs in the total benralizumab group were asthma and nasopharyngitis. Treatment-emergent adverse events that occurred at > 5 percentage point higher frequencies in the total benralizumab group than in the placebo group were nasopharyngitis and injection site erythema, with no apparent dose response between the individual benralizumab dose groups.

The majority of TEAEs, on both an event and subject basis, by Week 66 in the placebo and total benralizumab groups were mild or moderate in severity. The proportion of subjects with a severe TEAE was higher in the total benralizumab group (58/385 [15.1%]) than in the placebo group (26/221 [11.8%]), but the proportion of severe TEAEs was higher in the placebo group (56/620 events [9.0%]) than in the total benralizumab group (88/1,408 events [6.3%]). Asthma was the most frequent severe TEAE in the placebo and total benralizumab groups (14/221 [6.3%] and 21/385 [5.5%], respectively).

The investigational product-related TEAE that occurred at a > 5 percentage point higher frequency in the total benralizumab group than in the placebo group was injection site erythema. Treatment-emergent adverse events of injection site reactions occurred at a higher frequency in the individual benralizumab dose groups than the placebo group, with the most frequent TEAEs in the total benralizumab group being injection site erythema, injection site pain, and injection site pruritus.

There were no TEAEs of immune complex disease in either the placebo or total benralizumab group, and no subject in the total benralizumab group had an anaphylactic reaction related to investigational product.

No clinically important shifts or changes in hematology, chemistry, or urinalysis parameters were observed, and there were no clinically important shifts in vital signs or

	ECGs.
Conclusions:	<ul style="list-style-type: none"> • The addition of multiple SC doses of 100 mg benralizumab in subjects with uncontrolled asthma receiving medium- or high-dose ICS plus LABA met the primary endpoint of reduction in annual AER at Week 52 for subjects with an eosinophilic phenotype • The addition of multiple SC doses of 100 mg benralizumab in subjects with uncontrolled asthma receiving medium- or high-dose ICS plus LABA statistically significantly improved lung function and asthma control at Week 52 for subjects with an eosinophilic phenotype • The addition of multiple SC doses of 20 and 100 mg benralizumab in subjects with uncontrolled asthma receiving medium- or high-dose ICS plus LABA statistically significantly reduced annual AER and improved lung function and asthma control at Week 52 for subjects with Week -1 local peripheral blood eosinophil counts ≥ 300 cells/μL • Benralizumab, administered at multiple SC doses of 2, 20, or 100 mg, was adequately tolerated in subjects with uncontrolled asthma receiving medium- or high-dose ICS plus LABA.

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4.1.6 Study D3250C00017: Efficacy and safety of multiple-dose SC administration of benralizumab Added to High-dose Inhaled Corticosteroid Plus Long-acting β 2 Agonist in Patients with Uncontrolled Asthma

Study:	D3250C00017 (SIROCCO)
Study Title:	<i>A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β2 Agonist in Patients with Uncontrolled Asthma (SIROCCO)</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma <p>Secondary:</p> <ul style="list-style-type: none"> To assess the effect of 2 dosing regimens of benralizumab on pulmonary function To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics To assess the effect of 2 dosing regimens of benralizumab on other parameters associated with asthma exacerbations To assess the effect of 2 dosing regimens of benralizumab on asthma-related and general health-related quality of life To assess the effect of 2 dosing regimens of benralizumab on ER/urgent care visits and hospitalizations due to asthma To evaluate the effect of 2 dosing regimens of benralizumab on health care resource utilization and productivity loss due to asthma To evaluate the PK and immunogenicity of 2 dosing regimens of benralizumab To evaluate the overall response to treatment <p>Safety:</p> <ul style="list-style-type: none"> To assess the safety and tolerability of 2 dosing regimens of benralizumab <p>Exploratory:</p> <ul style="list-style-type: none"> To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers
Study Design:	<p>This was a multicenter, global, randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy, safety, PK, and immunogenicity of a fixed 30 mg dose of benralizumab administered SC for 48 weeks in patients with a history of asthma exacerbations and severe asthma (i.e., uncontrolled asthma despite receiving high-dose ICS-LABA with or without OCS and additional asthma controllers).</p> <p>Adult and adolescent patients in the Rest of World (RoW; i.e., countries outside of the European Union [EU]) were randomized in a 1:1:1 ratio to receive double-blind treatment of either placebo or 1 of 2 dosing regimens of benralizumab 30 mg, those being every 4 weeks (Q4W) throughout the treatment period versus every 4 weeks for the first 3 doses followed by every 8 weeks thereafter (Q8W).</p> <p>Adolescent patients in EU countries were randomized in a 1:1 ratio, to receive double-blind treatment of either placebo or benralizumab 30 mg Q8W. These patients still followed an every 4-week study visit schedule even though IP was only administered at every other visit after the first 3 monthly doses. The rationale for the different dosing regimen in adolescents in the EU was based on the Pediatric Committee at the European Medicines Agency's (PDCO)</p>

request to limit drug burden in adolescents and to study only the less frequent dose in this patient population.

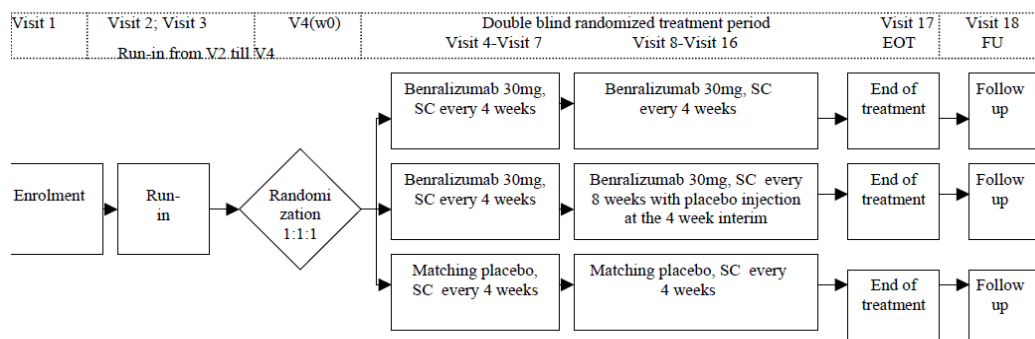
The study recruited 1205 patients stratified by age group (adult or adolescent), country (adults)/region (within EU/outside EU for adolescents) and peripheral blood eosinophil count ($\geq 300/\mu\text{L}$ or $< 300/\mu\text{L}$).

Patients who met eligibility criteria were randomized at Visit 4 (Week 0) to a 48-week treatment period. Following randomization, a patient received 48-week double-blind treatment, with the last dose of IP administered at Visit 15 (Week 40, Q8W for adolescents in EU) or Visit 16 (Week 44, Q4W for adults and adolescents in RoW). Patients were maintained on their currently prescribed high-dose ICS-LABA therapy(ies), without change, from enrolment throughout the run-in and treatment period. Patients had scheduled visits at a 4-week interval (regardless of treatment regimen) to complete protocol-specific assessments and IP administration. Patients monitored lung function at home, as well as recorded asthma symptoms and responses to questionnaires using an ePRO device throughout the 48-week treatment period.

Those patients who completed the treatment on IP and did not enter the follow-on extension study (D3250C00021; BORA) at the End of Treatment (EOT) Visit (Week 48) returned at Week 56 for a final Follow-up Visit. Patients who prematurely discontinued IP were to return to the study center and complete the procedures described for the Premature IP Discontinuation (IPD) Visit within 4 weeks (+7 days).

The study flow diagrams are shown below:

Study flow chart for adult patients and adolescent patients in RoW non-EU countries



EOT End of Treatment; EU European Union; FU Follow-up; RoW Rest of World; SC Subcutaneous; V Visit; w Week.

	<p style="text-align: center;">Study flow chart for adolescent patients in EU countries</p> <p>EOT End of Treatment; EU European Union; FU Follow-up; SC Subcutaneous; V Visit; w Week.</p> <p>The formulation used in this study were manufactured using Process 3 material.</p>
Study Population:	<p>Demographic characteristics were balanced across the groups and the study population was representative of the intended target population. The majority of patients in the FAS were White (72.6%), female (66.1%), and not Hispanic or Latino (80.9%). The mean age was 48.8 years (range: 12 to 75 years); 53 (4.4%) patients were ≥ 12 to < 18 years (i.e., adolescents), the remaining patients were adults, of whom 143 (11.9%) were ≥ 65 to 75 years. There were no patients < 12 years or > 75 years enrolled in this study. The mean weight was 77.92 kg (range: 40.0 to 194.5 kg), the mean BMI was 28.78 kg/m² (range: 14.5 to 61.7 kg/m²). Of the 53 adolescent patients in this study, fewer were in the benralizumab 30 mg Q4W group (11 patients [2.8%]) than the Q8W (19 patients [4.8%]) or placebo (23 patients [5.7%]) groups. Of the 53 evaluable adolescent patients, 50 completed the study (9, 18, and 23 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively). A total of 30 adolescents had baseline blood eosinophil counts $\geq 300/\mu\text{L}$ and therefore were eligible for the primary efficacy evaluation; of these, 27 completed the study (6, 9, and 12 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively).</p>
PK Data Analysis:	<p>During the study, PK data were collected at Weeks 0, 4 (Day 0 and Day 6), 8, 16, 24, 32, 40, 48, and 56. Pharmacokinetic samples were collected at Week 4, Day 6 for a subset of patients participating in an ECG sub-study.</p> <p>Descriptive statistics of benralizumab trough serum concentration data were prepared. Benralizumab serum concentration were summarized for the adult and adolescent groups.</p> <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay that employed MSD technology with a LLOQ of 3.86 ng/mL.</p>
Results:	<p><u>PK in Adults</u></p> <p>Due to the shorter dosing interval, steady-state C_{trough} was consistently higher beginning at Week 16 through the last common dosing time at Week 40 in the benralizumab 30 mg Q4W group (1024.26 to 967.15 ng/mL, respectively) compared with the benralizumab 30 mg Q8W group (250.84 to 157.22 ng/mL, respectively). Among patients who did not roll over into the follow-on extension study (D3250C00021; BORA), the geometric mean benralizumab serum concentration at Week 56 was 51.7 ng/mL and 6.66 ng/mL for the benralizumab 30 mg Q4W and Q8W groups, respectively.</p> <p><u>PK in Adolescents</u></p> <p>Due to the lower body weight, the PK in adolescents was slightly higher than in adults, but individual PK exposure substantially overlapped between the 2 populations. From Week 8 to Week 48, adolescents in the benralizumab 30 mg Q4W group had median benralizumab serum C_{trough} that ranged from 1125.00 to 2380.00 ng/mL; the median benralizumab serum</p>

C_{trough} was 2380.00 ng/mL at Week 48 (n=7). In adult patients in the benralizumab 30 mg Q4W group, the median benralizumab serum C_{trough} ranged from 1135.00 to 1310.00 ng/mL. In the benralizumab 30 mg Q8W group, PK was generally comparable between adolescents and adults beginning at Week 24. The median benralizumab serum C_{trough} ranged from 190.00 to 303.50 ng/mL in adolescents, and from 238.00 to 278.00 ng/mL in adults.

The mean PK profiles of benralizumab in adults and adolescents are shown in Figure 4.1.6-1.

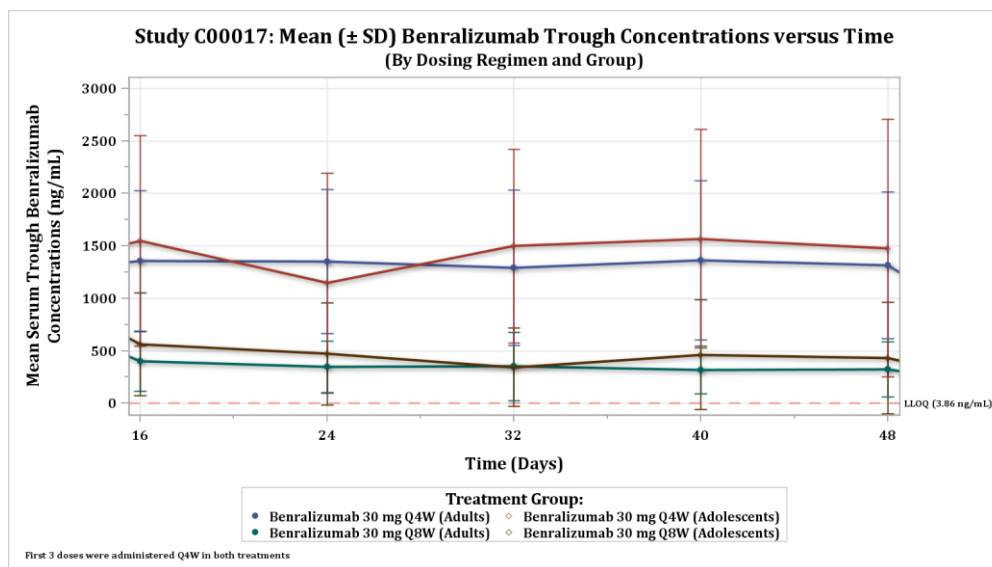


Figure 4.1.6-1: Mean (±SD) Trough Serum Concentration-Time Profiles of Benralizumab in Adults and Adolescents

(Source: Reviewer generated plot)

Immunogenicity:

A total of 126 patients tested positive for ADA responses at any timepoint (including at baseline). This included 21 patients in the placebo group, 47 patients in the benralizumab 30 mg Q4W group, and 58 patients in the benralizumab 30 mg Q8W group. In the benralizumab-treated groups, 12 patients were ADA-positive at baseline only (6 patients each in the benralizumab 30 mg Q4W and Q8W groups), 5 patients were ADA-positive at both baseline and post-baseline timepoints (2 patients in the benralizumab 30 mg Q4W group and 3 patients in the benralizumab 30 mg Q8W group), and 88 patients had ADA-positive responses at post-baseline timepoints only (39 patients in the benralizumab 30 mg Q4W group and 49 patients in the benralizumab 30 mg Q8W group).

Steady-state PK was lower in ADA-positive patients than in ADA-negative patients in both benralizumab treatment groups. Beginning at Week 40 (Q4W) or Week 24 (Q8W), a slight increase in median eosinophil counts was observed in ADA-positive categories, compared to previous post-baseline timepoints, which persisted through the EOT Visit (Week 48), with larger increases observed in patients with a maximum ADA titer greater than the median of the maximum titer in the benralizumab 30 mg Q8W group. Despite effects on PK and PD, there was no indication of an effect of ADA-positive status on efficacy.

Efficacy:

For the primary endpoint, benralizumab 30 mg Q4W and Q8W dose regimens statistically significantly reduced the annual asthma exacerbation rate over 48 weeks compared with placebo by 45% (rate ratio: 0.55 [95% CI: 0.42, 0.71]; p<0.001) and 51% (rate ratio: 0.49 [95% CI: 0.37, 0.64]; p<0.001), respectively. A lower proportion of patients had ≥1 asthma exacerbation over 48 weeks in both benralizumab 30 mg Q4W (36.4%) and Q8W (34.8%)

groups compared with placebo (50.6%) (odds ratio: 0.54 [0.37, 0.78] and 0.62 [0.43, 0.90], respectively; nominal $p \leq 0.010$). The time to first asthma exacerbation was longer for both benralizumab 30 mg Q4W and Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.63 [0.49, 0.82] and 0.60 [0.46, 0.78], respectively; both nominal $p < 0.001$). Both benralizumab 30 mg Q4W and Q8W reduced the annual rate of asthma exacerbations associated with an ER/urgent care visit or hospitalisation by 39% (nominal $p = 0.053$) and 63% (nominal $p < 0.001$), respectively, compared with placebo.

With regard to pulmonary function, both benralizumab 30 mg Q4W and Q8W dose regimens demonstrated statistically significant and clinically meaningful improvements over placebo for the key secondary endpoint of change from baseline in pre-bronchodilator FEV₁ at Week 48 (0.106 L [95% CI: 0.016, 0.196] and 0.159 L [95% CI: 0.068, 0.249], respectively; both $p \leq 0.022$), that were supported by improvements observed for the secondary endpoints of post-bronchodilator FEV₁ and morning and evening PEF. Improvements in lung function were seen from as early as Week 4 and were maintained through Week 48.

With regard to asthma symptom improvement, benralizumab 30 mg Q8W showed improvement over placebo by multiple assessments, including the key secondary endpoint of change from baseline to Week 48 in total asthma symptom score (-0.25 units [95% CI: -0.45, -0.06]; which achieved statistical significance [$p = 0.012$]) as well as for change from baseline to Week 48 for ACQ-6 (-0.29 units [95% CI: -0.48, -0.10]; nominal $p = 0.003$) and in the proportion of ACQ-6 responders (ie, patients achieving a minimally clinically important difference (MCID) of ≤ -0.5 units at the end of treatment; 60.3% vs 49.8%; odds ratio: 1.549 [95% CI: 1.094, 2.193]; nominal $p = 0.014$).

Similar to the results observed for symptom benefit, improvements in asthma-related quality of life were demonstrated for benralizumab 30 mg Q8W for change from baseline in AQLQ(S)+12 (0.30 units [95% CI: 0.10, 0.50]; nominal $p = 0.004$) and AQLQ(S)+12 responders (ie, patients achieving an MCID of ≥ 0.5 units at the end of treatment; 57.3% vs 49.1%; odds ratio: 1.417 [95% CI: 0.993, 2.023]; nominal $p = 0.055$) after 48 weeks of treatment. Improvements in AQLQ(S)+12 favoured benralizumab 30 mg Q4W over placebo for both changes from baseline (0.18 units [95% CI: -0.02, 0.37]; nominal $p = 0.081$) and AQLQ(S)+12 responders (55.3% vs 49.1%; odds ratio: 1.303 [95% CI: 0.917, 1.852]; nominal $p = 0.139$) after 48 weeks of treatment.

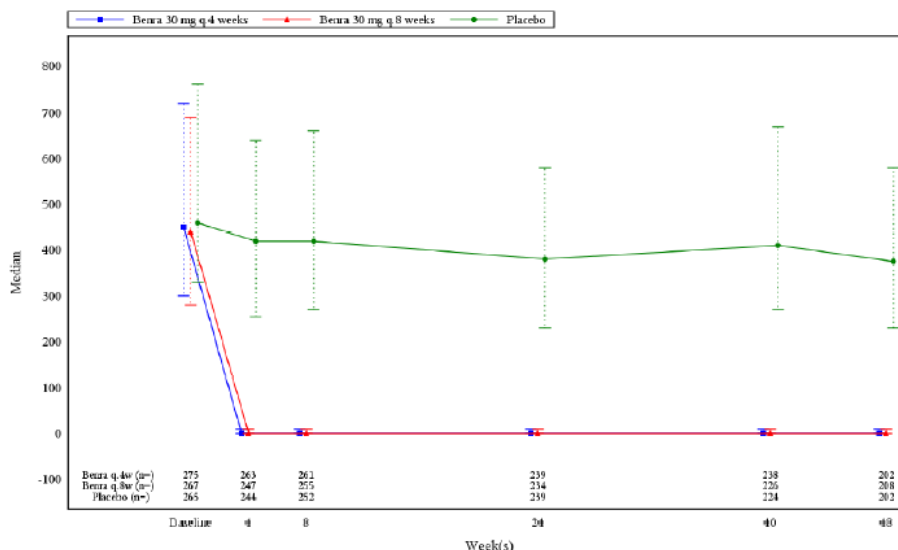
Data also showed that both baseline blood eosinophil count and the number of exacerbations in the previous 12 months (a measure of baseline severity) were clinically relevant predictors of efficacy. Efficacy was observed across all baseline blood eosinophil categories for both benralizumab 30 mg Q4W and Q8W, with a generally greater treatment effect observed in patients with higher baseline blood eosinophil levels than those with lower baseline blood eosinophil levels. This trend was most evident for annual asthma exacerbation rate and change from baseline in pre-bronchodilator FEV₁.

PD Effects:

Mean baseline blood eosinophil counts were similar across groups. In patients with a baseline blood eosinophil count $\geq 300/\mu\text{L}$, both benralizumab 30 mg Q4W and Q8W demonstrated near complete depletion of eosinophils at Week 4 (-95.5% and -90.6%) that were maintained through Week 48 (-95.9% and -92.2%) (Figure 4.6.1-2).

The marked reduction in mean eosinophil levels following dosing with benralizumab was not observed in the placebo group. Both benralizumab 30 mg Q4W and Q8W demonstrated greater reductions in least squares (LS) mean percent change from baseline in blood eosinophil counts compared with placebo at Week 4 (-98.28% [-107.3, -89.23] and -94.11% [-103.3, -84.93], respectively; both $p < 0.001$) and at Week 48 (-102.2% [-116.2, -88.16] and -

99.60% [-113.6, -85.60], respectively; both $p < 0.001$). Similar results were observed for patients with blood baseline eosinophil counts $< 300/\mu\text{L}$.



Error bars represent upper and lower quartiles.

Figure 4.1.6-2: Median Blood Eosinophil Counts (Cells/ μL) Over Time - Line Plot (Full Analysis Set, Baseline Blood Eosinophils $\geq 300/\mu\text{L}$)

(Source: eCTD for BLA 761070, Module 2.7.2, Summary of Clinical Pharmacology, Figure 31, Page 105)

Safety:

There were no appreciable differences in the safety results between the benralizumab 30 mg Q4W and Q8W dosing regimens. The overall incidence of treatment-emergent adverse events (TEAEs) during the on-treatment period was 75.3%, the incidence of which was lower in the benralizumab 30 mg Q4W and Q8W groups (72.7% and 71.3%, respectively) compared with the placebo group (76.4%). The most common TEAEs overall were asthma (15.2%), nasopharyngitis (11.6%), and upper respiratory tract infection (9.3%). The majority of TEAEs were mild or moderate in intensity and were assessed as not related to the IP by the investigator.

Six patients died during the on-study period: 2 patients each in the benralizumab 30 mg Q4W and Q8W groups, and the placebo group. None of the deaths were considered related to IP by the investigator, or sponsor.

Asthma was the most common SAE reported for 22 patients (5.5%) in the benralizumab 30 mg Q4W group, 24 patients (6.1%) in the benralizumab 30 mg Q8W group, and 31 patients (7.6 %) in the placebo group.

The incidence of TEAEs of injection site reaction was low ($< 1\%$) and the majority of injection site reactions were considered related to the IP by the investigator. All of the TEAEs of injection site reaction in the benralizumab groups were non-serious, transient in nature, and the majority were mild in intensity.

There were no clinically meaningful trends in hematology and clinical chemistry parameters, and the incidence of TEAE PTs related to hematology and clinical chemistry were low and similar across groups. There were no clinically meaningful changes in vital signs or ECGs over time and no notable differences were observed between groups. No treatment-emergent findings were identified in the ECG sub-study and the ECG assessments coincided with the benralizumab T_{max} .

Conclusions:	<ul style="list-style-type: none"> • Both benralizumab 30 mg Q4W and benralizumab 30 mg Q8W demonstrated statistically significant and clinically meaningful improvements compared with placebo for the primary endpoint, annual asthma exacerbation rate, and the key secondary endpoint, change from baseline in pre-bronchodilator FEV1 at Week 48, with statistically significant improvements demonstrated for benralizumab 30 mg Q8W compared with placebo for the key secondary endpoint, change from baseline in total asthma symptom score at Week 48. Both regimens of benralizumab showed improvements over placebo in other measures of pulmonary function, asthma control, and asthma-related quality of life after 48 weeks of treatment. Treatment benefits in pulmonary function were observed as early as Week 4 that were maintained through Week 48. • Pharmacokinetic and pharmacodynamic results were as expected during this study, with higher steady-state concentrations in the more frequent Q4W regimen compared with the Q8W regimen and near complete depletion of eosinophils for both regimens at Week 4 that were maintained through Week 48. • Benralizumab 30 mg Q4W and benralizumab 30 mg Q8W were well tolerated with no unexpected safety findings. • Positive ADA responses were observed in approximately 12% to 15% of patients in the benralizumab 30 mg Q4W and Q8W groups. In these ADA-positive patients, geometric mean concentrations of benralizumab decreased over time. Median blood eosinophil counts remained near depletion throughout the dosing cycle for both dose regimens regardless of ADA status. An exception was patients in the benralizumab 30 mg Q8W group with high ADA titers, in which median blood eosinophil counts rose from Week 24 to Week 48. Despite these changes to PK and PD parameters in ADA-positive patients, there was no indication of an effect of ADA-positive status on efficacy or safety.
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4.1.7 Study D3250C00018: Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β 2 Agonist

Study:	D3250C00018 (CALIMA)
Study Title:	<i>A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab in Asthmatic Adults and Adolescents Inadequately Controlled on Inhaled Corticosteroid Plus Long-acting β2 Agonist (CALIMA)</i>
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> To evaluate the effect of 2 dosing regimens of benralizumab on asthma exacerbations in patients on high-dose ICS-LABA with uncontrolled asthma <p>Secondary:</p> <ul style="list-style-type: none"> To assess the effect of 2 dosing regimens of benralizumab on asthma symptoms and other asthma control metrics To assess the effect of 2 dosing regimens of benralizumab on other parameters associated with asthma exacerbations To assess the effect of 2 dosing regimens of benralizumab on asthma-related and general health-related quality of life To assess the effect of 2 dosing regimens of benralizumab on ER/urgent care visits and hospitalizations due to asthma To evaluate the effect of 2 dosing regimens of benralizumab on health care resource utilization and productivity loss due to asthma To evaluate the PK and immunogenicity of 2 dosing regimens of benralizumab To evaluate the overall response to treatment <p>Safety:</p> <ul style="list-style-type: none"> To assess the safety and tolerability of 2 dosing regimens of benralizumab <p>Exploratory:</p> <ul style="list-style-type: none"> To assess the impact of 2 dosing regimens of benralizumab on blood eosinophil levels To evaluate the effect of 2 dosing regimens of benralizumab on blood biomarkers
Study Design:	<p>This was a multicenter, global, randomized, double-blind, parallel group, placebo-controlled study designed to evaluate the efficacy, safety, PK, and immunogenicity of a fixed 30 mg dose of benralizumab administered SC for 56 weeks in patients with a history of asthma exacerbations and severe asthma (ie, uncontrolled despite receiving medium- or high-dose ICS/LABA with or without OCS and additional asthma controllers). Patients on medium-dose ICS were added to this study via an Amendment.</p> <p>Adult and adolescent patients in the Rest of World (RoW; ie, countries outside of the European Union [EU]) were randomized in a 1:1:1 ratio, via an interactive web/voice response system (IWRs/IVRS), to receive double-blind treatment (double-dummy technique) of either placebo or 1 of 2 dosing regimens of benralizumab 30 mg, those being every 4 weeks (Q4W) throughout the treatment period versus Q4W for the first 3 doses followed by every 8 weeks (Q8W) thereafter. Adolescent patients were added to this study via an Amendment.</p> <p>Adolescent patients in EU countries were randomized in a 1:1 ratio, to receive double-blind treatment of either placebo or benralizumab 30 mg Q8W. These patients still followed an every 4-week study visit schedule even though IP was only administered at every other visit</p>

after the first 3 monthly doses. The rationale for the different dosing regimen in adolescents in the EU was based on the Pediatric Committee at the European Medicines Agency's (PDCO) request to limit drug burden in adolescents and to study only the less frequent dose in this patient population.

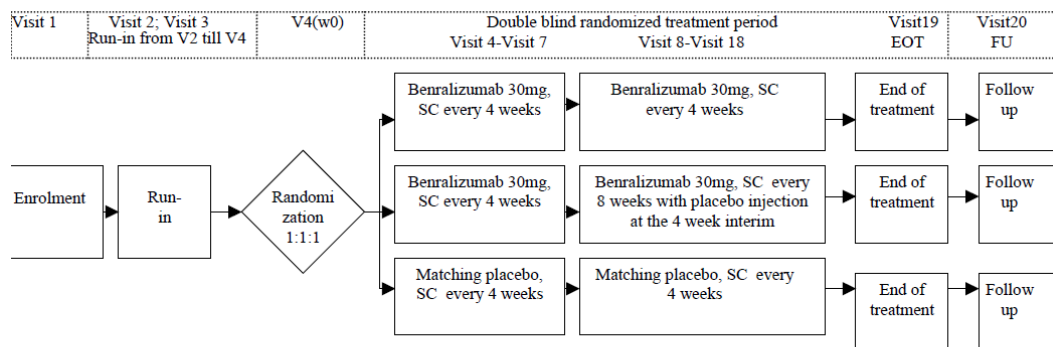
The study recruited 1306 patients stratified by ICS dose (high/medium), age group (adult or adolescent), country (adults)/region (within EU/outside EU for adolescents) and peripheral blood eosinophil count ($\geq 300/\mu\text{L}$ or $< 300/\mu\text{L}$).

Patients who met eligibility criteria were randomized at Visit 4 (Week 0) to a 56-week treatment period. Following randomization, a patient received 56-week double-blind treatment, with the last dose of IP administered at Visit 17 (Week 48, Q8W for adolescents in EU) or Visit 18 (Week 52, Q4W for adults and adolescents in RoW). Patients were maintained on their currently prescribed medium- or high-dose ICS/LABA therapy(ies), without change, from enrolment throughout the run-in and treatment period. Patients had scheduled visits at a 4-week interval (regardless of treatment regimen) to complete protocol-specific assessments and IP administration, as listed in Table 3. Patients monitored lung function at home, as well as recorded asthma symptoms and responses to questionnaires using an ePRO device throughout the 56-week treatment period.

Those patients who completed the treatment on IP and did not enter the follow-on extension study (D3250C00021; BORA) at the End of Treatment (EOT) Visit (Week 56) returned at Week 60 for a final Follow-up Visit. Patients who prematurely discontinued IP were to return to the study center and complete the procedures described for the Premature IP Discontinuation (IPD) Visit within 4 weeks (+7 days). The IPD Visit was added to this study via an Amendment.

The study flow diagrams are shown below:

Study flow chart for adult patients and adolescent patients in RoW (ie, outside of EU) countries



EOT End of Treatment; EU European Union; FU Follow-up; RoW Rest of World; SC Subcutaneous; V Visit; w Week.

	<p style="text-align: center;">Study flow chart for adolescent patients in EU countries</p> <p style="text-align: center;">EOT End of Treatment; EU European Union; FU Follow-up; SC Subcutaneous; V Visit; w Week.</p>
Study Population:	<p>The formulation used in this study were manufactured using Process 3 material.</p> <p>Demographic characteristics were balanced across the groups and the study population was representative of the intended target population. The majority of patients in the FAS were White (84.3%), female (61.8%), and not Hispanic or Latino (77.0%). The mean age was 49.2 years (range: 12 to 75 years); 55 (4.2%) patients were ≥ 12 to < 18 years (i.e., adolescents), the remaining patients were adults, of whom 177 (13.6%) 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 79.11 kg (range: 41.0 to 204.4 kg), the mean BMI was 28.77 kg/m² (range: 15.9 to 79.9 kg/m²).</p> <p>Of the 55 adolescent patients in this study, fewer were in the benralizumab 30 mg Q4W group (11 patients [2.6%]) than the Q8W (21 patients [4.8%]) or placebo (23 patients [5.2%]) groups. The difference was primarily driven by the larger pool of adolescents available for recruitment into the Q8W group as adolescents in the EU were only randomized into the Q8W or placebo arms; patients in the RoW were recruited to either the Q4W, Q8W, or placebo arms. Of the 55 evaluable adolescent patients, 45 completed the study (9, 18, and 18 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively). A total of 16 adolescents were taking high-dose ICS at baseline with blood eosinophil counts $\geq 300/\mu\text{L}$ and therefore were eligible for the primary efficacy evaluation; of these, 13 completed the study (3, 5, and 5 patients in the benralizumab 30 mg Q4W, Q8W, and placebo groups, respectively).</p>
PK Data Analysis:	<p>During the study, PK data were collected at Weeks 0, 4, 8, 16, 24, 32, 40, 48, 56, and 60.</p> <p>Descriptive statistics of benralizumab trough serum concentration data were prepared. Benralizumab serum concentration were summarized for the adult and adolescent groups.</p> <p>Plasma benralizumab concentrations were assayed using a validated ECL immunoassay that employed MSD technology with a LLOQ of 3.86 ng/mL.</p>
Results:	<p><u>PK in Adults</u></p> <p>Due to the shorter dosing interval, C_{trough} was consistently higher beginning at Week 16 through the last common dosing time at Week 48 in the benralizumab 30 mg Q4W group (923.03 to 853.14 ng/mL, respectively) compared with the benralizumab 30 mg Q8W group (246.62 to 186.50 ng/mL, respectively).</p> <p>Among patients who did not roll over into the follow-on extension study (D3250C00021; BORA) (approximately 10%), the geometric mean benralizumab serum concentration at Week 60 was 53.6 ng/mL and 18.6 ng/mL for the benralizumab 30 mg Q4W and Q8W groups, respectively.</p>

PK in Adolescents

Due to the lower body weight, the PK in adolescents was slightly higher than in adults, but individual PK exposure substantially overlapped between the 2 populations; due to the small number of adolescent patients. From Week 8 to Week 48, adolescents in the benralizumab 30 mg Q4W group had median benralizumab serum C_{trough} concentrations that ranged from 1220.00 to 1905.00 ng/mL. The median benralizumab serum C_{trough} concentration was 1905.00 ng/mL at Week 48 (n=4) and 1275.00 ng/mL at Week 56. In adult patients in the benralizumab 30 mg Q4W group, the median benralizumab serum C_{trough} concentrations ranged from 1065.00 to 1250.00 ng/mL. In the benralizumab 30 mg Q8W group, PK was generally comparable between adolescents and adults beginning at Week 24. The median benralizumab serum C_{trough} concentrations ranged from 180.50 to 368.00 ng/mL in adolescents, and from 241.00 to 287.00 ng/mL in adults.

The mean PK profiles of benralizumab in adults and adolescents are shown in Figure 4.1.7-1.

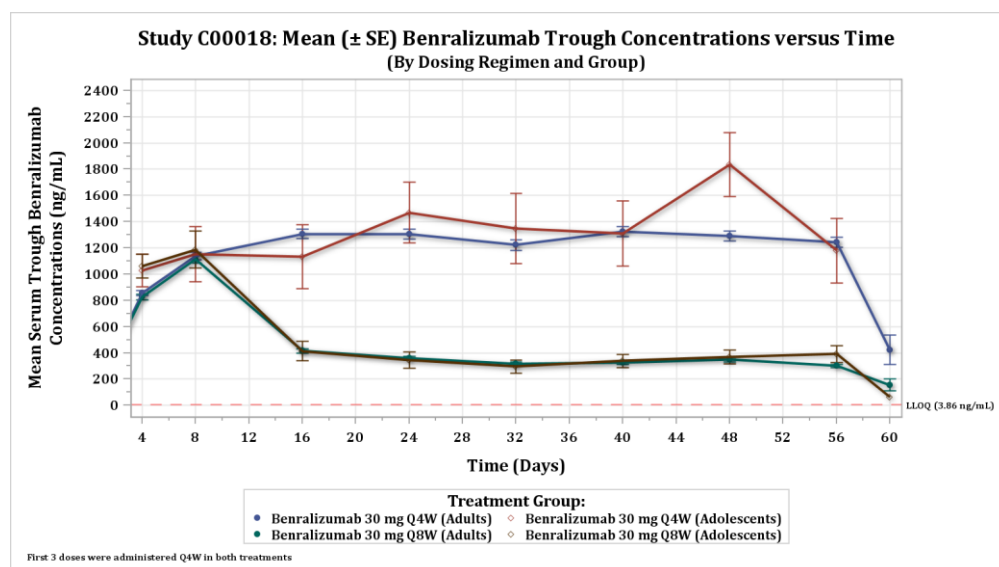


Figure 4.1.6-1: Mean (\pm SE) Trough Serum Concentration-Time Profiles of Benralizumab in Adults and Adolescents

(Source: Reviewer generated plot)

Immunogenicity:

A total of 140 patients tested positive for ADA responses at any timepoint (including at baseline). This included 13 patients in the placebo group, 63 patients in the benralizumab 30 mg Q4W group, and 64 patients in the benralizumab 30 mg Q8W group. In the benralizumab-treated groups, 5 patients were ADA-positive at baseline only (3 patients in the benralizumab 30 mg Q4W group and 2 patients in the benralizumab 30 mg Q8W group), 10 patients were ADA-positive at both baseline and post-baseline timepoints (5 patients each in the benralizumab 30 mg Q4W and Q8W groups), and 112 patients had ADA-positive responses at post-baseline timepoints only (55 patients in the benralizumab 30 mg Q4W group and 57 patients in the benralizumab 30 mg Q8W group).

In the placebo group, of the 13 patients who tested positive for ADA responses at any timepoint, none were positive at baseline only, 5 patients were positive at both baseline and post-baseline timepoints, and 8 patients had ADA-positive responses at post-baseline timepoints only.

Steady-state PK was lower in ADA-positive patients than in ADA-negative patients in both benralizumab treatment groups. Beginning at Week 24 for both the benralizumab 30 mg

Q4W and Q8W groups, a slight increase in median eosinophil counts was observed in ADA-positive categories, compared to previous post-baseline timepoints, which persisted through the EOT Visit (Week 56), with larger increases observed in patients with a maximum ADA titer greater than the median of the maximum titer in the benralizumab 30 mg Q8W group. Despite effects on PK and PD, there was no indication of an effect of ADA-positive status on efficacy.

Efficacy:

For the primary endpoint, benralizumab 30 mg Q4W and Q8W dose regimens statistically significantly reduced the annual asthma exacerbation rate over 56 weeks compared with placebo by 36% (rate ratio: 0.64 [95% CI: 0.49, 0.85]; $p=0.002$) and 28% (rate ratio: 0.72 [95% CI: 0.54, 0.95]; $p=0.019$), respectively. A lower proportion of patients had ≥ 1 asthma exacerbation over 56 weeks in both benralizumab 30 mg Q4W (34.9%) and Q8W (39.7%) regimens compared with placebo (50.8%) (odds ratio: 0.46 [95% CI: 0.31, 0.69] and 0.65 [95% CI: 0.45, 0.95], respectively; nominal $p \leq 0.023$). The time to first asthma exacerbation was longer for both benralizumab 30 mg Q4W and Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.61 [95% CI: 0.46, 0.80] and 0.73 [95% CI: 0.55, 0.95], respectively; nominal $p \leq 0.018$). The annual rate of asthma exacerbations associated with an adjudicated ER/urgent care visit or hospitalisation over 56 weeks was low and similar across groups (range of crude rates: 0.09 to 0.11).

With regard to pulmonary function, both benralizumab 30 mg Q4W and Q8W dose regimens demonstrated statistically significant and clinically meaningful improvements over placebo for the key secondary endpoint of change from baseline in pre-bronchodilator FEV₁ at Week 56 (0.125 L [95% CI: 0.037, 0.213] and 0.116 L [95% CI: 0.028, 0.204], respectively; both $p \leq 0.010$), that were supported by improvements observed for the secondary endpoints of post-bronchodilator FEV₁ and morning and evening PEF. Improvements in lung function were seen from as early as Week 4 and were maintained through Week 56.

With regard to asthma symptom improvement, both treatment regimens showed improvement over placebo by multiple assessments. Benralizumab 30 mg Q8W demonstrated consistent improvements from baseline to Week 56 compared with placebo for the key secondary endpoint of total asthma symptom score (-0.23 units [95% CI: -0.43, -0.04]; which achieved statistical significance [$p=0.019$]) and ACQ-6 (-0.25 units [95% CI: -0.44, -0.07]; nominal $p=0.008$). Improvement from baseline to Week 56 favoured benralizumab 30 mg Q4W over placebo for total asthma symptom score (-0.12 units [95% CI: -0.32, 0.07]; though not statistically significant [$p=0.224$]) and ACQ-6 (-0.19 units [95% CI: -0.38, -0.01]; nominal $p=0.043$). Improvements in asthma symptoms were seen from as early as Week 4 that were maintained through Week 56. Reductions in rescue medication use and the proportion of nights with nocturnal awakenings were similar between both benralizumab groups and placebo.

Similar to the results observed for symptom benefit, improvements in asthma-related quality of life as assessed by AQLQ(S)+12 at Week 56 were also observed for benralizumab 30 mg Q8W over placebo (0.24 units [95% CI: 0.04, 0.45]; nominal $p=0.019$), with results favouring benralizumab 30 mg Q4W over placebo (0.16 units [95% CI: -0.04, 0.37]; nominal $p=0.119$).

Data also showed that both baseline blood eosinophil count and the number of exacerbations in the previous 12 months (a measure of baseline severity) were clinically relevant predictors of efficacy. Efficacy was observed across all baseline blood eosinophil categories for both benralizumab 30 mg Q4W and Q8W, with a generally greater treatment effect observed in patients with higher baseline blood eosinophil levels than those with lower baseline blood eosinophil levels. This trend was most evident for annual asthma exacerbation rate and change from baseline in pre-bronchodilator FEV₁. When efficacy was evaluated by prior exacerbation status, generally greater treatment effects for both

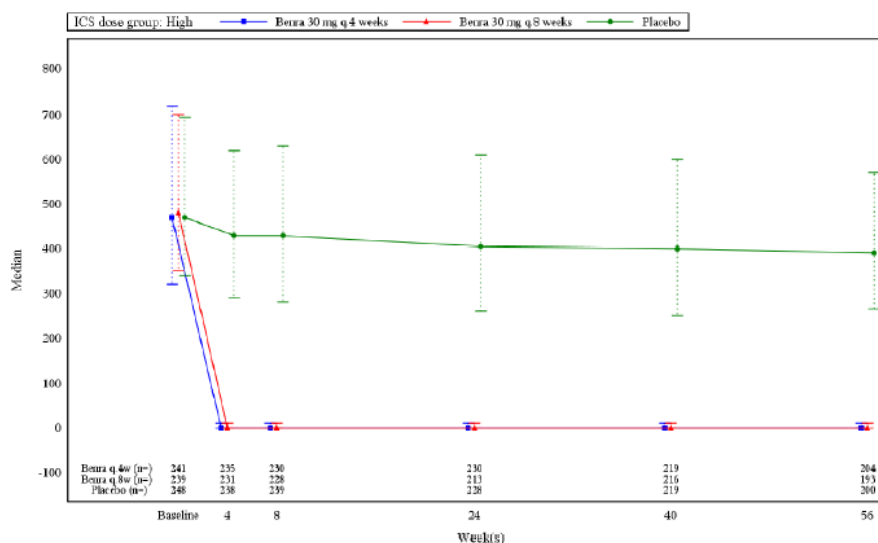
benralizumab 30 mg Q4W and Q8W compared with placebo were observed in patients with ≥ 3 exacerbations in the previous year compared with those with 2 exacerbations in the previous year for the primary and key secondary endpoints.

PD Effects:

Mean baseline blood eosinophil counts were similar across groups. In patients with a baseline blood eosinophil count $\geq 300/\mu\text{L}$ who were taking high-dose ICS, both benralizumab 30 mg Q4W and Q8W, respectively, demonstrated near complete depletion of eosinophils at Week 4 (-96.3% and -97.0%) that was maintained through Week 56 (-94.0% and -92.2%) (Table 34 and Figure 32). The marked reduction in mean peripheral blood eosinophil counts following dosing with benralizumab was not observed in the placebo group.

Both benralizumab 30 mg Q4W and Q8W demonstrated greater reductions in LS mean percent change from baseline in blood eosinophil counts compared with placebo at Week 4 (-104.2% [-114.2, -94.15] and -105.0% [-115.1, -94.96], respectively; both $p < 0.001$) and at Week 56 (-112.3% [-155.0, -69.54] and -106.8% [-149.7, -63.88], respectively; both $p < 0.001$).

Similar results were observed for patients taking medium-dose ICS and for patients with blood baseline eosinophil counts $< 300/\mu\text{L}$.



Error bars represent upper and lower quartiles.

Figure 4.1.7-2: Median Blood Eosinophil Counts (Cells/ μL) Over Time - Line Plot (Full Analysis Set, Baseline Blood Eosinophils $\geq 300/\mu\text{L}$, High-Dose ICS)

(Source: eCTD for BLA 761070, Module 2.7.2, Summary of Clinical Pharmacology, Figure 32, Page 115)

Safety:

There were no appreciable differences in the safety results between the benralizumab 30 mg Q4W and Q8W dosing regimens. The overall incidence of treatment-emergent adverse events (TEAEs) during the on-treatment period was 75.3%, the incidence of which was lower in the benralizumab 30 mg Q4W and Q8W groups (73.5% and 74.8%, respectively) compared with the placebo group (77.7%).

The most common TEAEs overall were nasopharyngitis (20.0%), asthma (13.5%), and upper respiratory tract infection (10.4%). The majority of TEAEs were mild or moderate in intensity and were assessed as not related to the IP by the investigator.

	<p>Six patients died during the on-study period: 3 patients in the benralizumab 30 mg Q4W group, 2 patients in the benralizumab 30 mg Q8W group, and 1 patient in the placebo group. None of the deaths were considered related to IP by the investigator or sponsor. Asthma was the most common SAE, reported by 21 patients (4.8%) in the benralizumab 30 mg Q4W group, 18 patients (4.2%) in the benralizumab 30 mg Q8W group, and 23 patients (5.2%) in the placebo group.</p> <p>The incidence of hypersensitivity TEAEs was similar across groups: 13 patients (3.0% each) in the benralizumab 30 mg Q4W and Q8W groups, and 17 patients (3.9%) in the placebo group. The most common TEAE of hypersensitivity was urticaria.</p> <p>The incidence of serious infections was similar across groups; the most commonly reported serious infection PT was pneumonia.</p> <p>The incidence of TEAEs of injection site reaction were low (<1%) and the majority of injection site reactions were considered related to the IP by the investigator. All of the TEAEs of injection site reaction were non-serious, transient in nature, and the majority were mild in intensity.</p> <p>There were no clinically meaningful trends in hematology and clinical chemistry parameters. There were no clinically meaningful changes in vital signs or ECGs over time and no notable differences were observed between groups.</p>
Conclusions:	<ul style="list-style-type: none"> Both benralizumab 30 mg Q4W and benralizumab 30 mg Q8W demonstrated statistically significant and clinically meaningful improvements compared with placebo for the primary endpoint, annual asthma exacerbation rate, and the key secondary endpoint, change from baseline in pre-bronchodilator FEV1 at Week 56, with statistically significant improvements demonstrated for benralizumab 30 mg Q8W compared with placebo for the key secondary endpoint, change from baseline in total asthma symptom score at Week 56. Both regimens of benralizumab showed improvements over placebo in other measures of pulmonary function, asthma control, and asthma-related quality of life after 56 weeks of treatment. Treatment benefits in pulmonary function were observed as early as Week 4 that were maintained through Week 56. Pharmacokinetic and pharmacodynamic results were as expected during this study, with higher steady-state concentrations in the more frequent Q4W regimen compared with the Q8W regimen and near complete depletion of eosinophils for both regimens at Week 4 that were maintained through Week 56. Benralizumab 30 mg Q4W and benralizumab 30 mg Q8W were well tolerated with no unexpected safety findings. Positive ADA responses were observed in approximately 15% of patients in both the benralizumab 30 mg Q4W and Q8W groups. In these ADA-positive patients, geometric mean concentrations of benralizumab decreased over time. Median blood eosinophil counts remained near depletion throughout the dosing cycle for both dose regimens regardless of ADA status. An exception was patients in the benralizumab 30 mg Q8W group with high ADA titers, in which median blood eosinophil counts rose from Week 24 to Week 56. Despite these changes to PK and PD parameters in ADA-positive patients, there was no indication of an effect of ADA-positive status on efficacy or safety.

4.2 Population PK Analysis

4.2.1 Are the PK parameters reported in the label supported by the population PK analysis submitted by the sponsor?

Yes, the PK parameters reported in the label are supported by the population PK (popPK) analysis submitted by the sponsor.

In total, 14918 non-BLQ benralizumab concentrations from 2267 asthma patients following benralizumab treatment in 9 studies (MI-CP158, MI-CP166, MI-CP186, MI-CP197, MI-CP220, D3250C00017, D3250C00018, D3250C00020, and D3250C00032) were pooled for popPK analysis. Among them, 4 studies (MI-CP158, MI-CP166, MI-CP186, and MI-CP197) enriched with intensive PK sampling schemes; and 2 pivotal Phase 3 studies (D3250C00017 and D3250C00018) contributed approximately 75% of the total PK samples. The dose and dosing regimen of collected PK data are summarized in Table 4.2.1.

Table 4.2.1 List of Clinical Studies included in Phase2-3 Population PK Analysis

Administration Route	Dose Scheme	Dose	Number of PK Samples	Proportion	Intensive PK Sampling Scheme
IV	Single Dose	0.03 mg/kg	89	0.6%	Yes
IV	Single Dose	0.1 mg/kg	92	0.6%	Yes
IV	Single Dose	0.3 mg/kg	231	1.6%	Yes
IV	Single Dose	1 mg/kg	314	2.1%	Yes
IV	Single Dose	3 mg/kg	74	0.5%	Yes
SC	Multiple Dose	20 mg ¹	425	2.8%	No
SC	Multiple Dose	25 mg ²	48	0.3%	Yes
SC	Multiple Dose	30 mg ³	12113	81%	No
SC	Multiple Dose	100 mg ³	1440	9.7%	Some
SC	Multiple Dose	200 mg ²	92	0.6%	Some

¹Dosing regimen as Q4W×3 then Q8W

²Dosing regimen as Q4W

³Dosing regimen as Q4W or Q4W×3 then Q8W

(Source: eCTD for BLA 761070; adapted from Module 5.3.3.5, Population PK Study Report.pdf, Table 3, page 23)

Due to the low and variable PK observations in asthma patients receiving the 2 mg SC dose in Study MI-CP220, 589 samples from 81 subjects were excluded from the population modeling. Drug concentration outliers for which there was no mechanistic explanation for the deviation were to be excluded from analysis (a priori outliers). Outliers based on the population PK model analysis (a posteriori outliers) were evaluated using conditional weighted residuals (CWRES) and individual weighted residuals (IWRES). Observations with |CWRES|>6 or |IWRES|>6 were flagged as outliers. PK concentrations and PK sample times were not imputed in the derived dataset.

The PK of benralizumab is dose-proportional and can be represented using a 2-compartment disposition model with first-order absorption following SC administration. The estimates of PK parameters from the final updated model are listed in Table 4.2.2. The estimated bioavailability following SC administration of benralizumab with Phase 3/commercial formulation was 59% (CV= 17%). The median terminal half-life was approximately 15 days. The estimated typical CL was as 0.291 (CV=24%) L/day. The estimated central volume was 3.13 (CV=24%). The estimated peripheral volume was 2.52 (CV=45%) L. Body

weight was identified as a significant covariate for CL with the estimated allometric power as 0.807 (90% CI=0.751, 0.864). ADA was also identified as a significant covariate for CL in which positive ADA resulted in 2.24-fold (90% CI=2.18, 2.30) increase of CL. Body weight was also identified as significant covariate for the central and peripheral volumes.

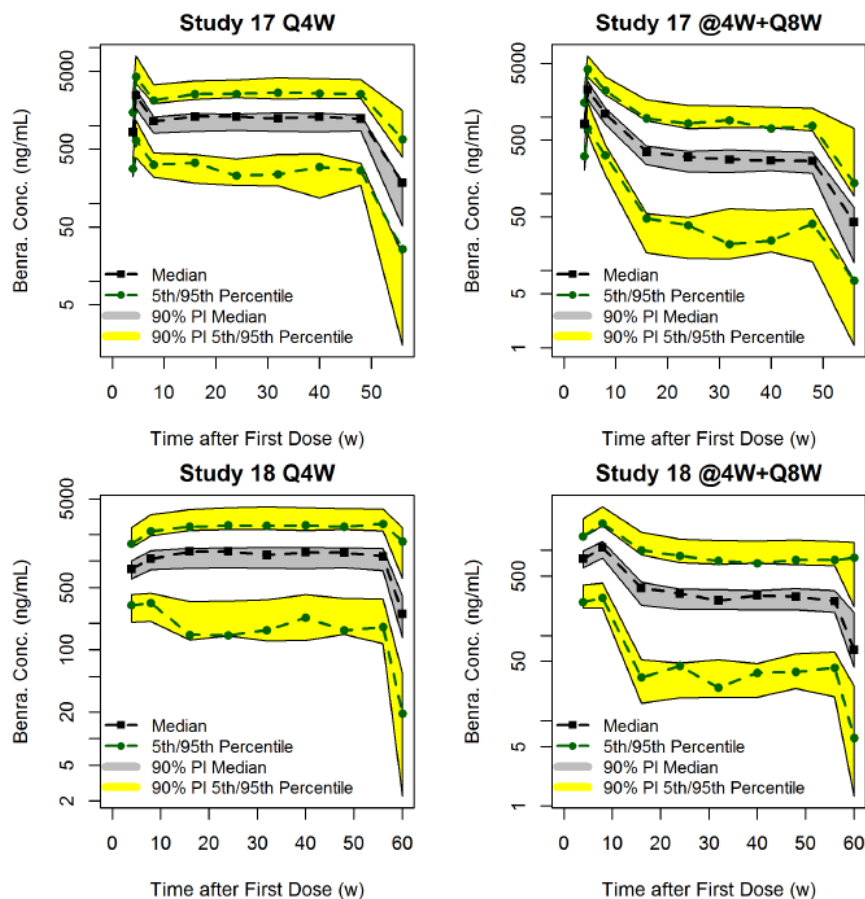
Table 4.2.2 List of PK Parameter Estimates from the Final Updated Model

Parameter	Estimate (ASE)	Transformed Estimate	Transformed 90%CI
Clearance (CL; L/day) [01]	-1.24 (0.0225)	0.291	(0.28,0.302)
Body weight on CL (power) [07]	0.807 (0.0342)	0.807	(0.751,0.864)
ADA+ on CL (fraction) [013]	0.806 (0.0152)	2.24	(2.18,2.3)
Central volume (V2; L) [02]	1.14 (0.0322)	3.13	(2.97,3.31)
Body weight on V2 (power) [08]	0.803 (0.107)	0.803	(0.627,0.979)
Inter-compartmental clearance (Q2; L/day) [03]	-0.303 (0.0509)	0.738	(0.679,0.803)
Body weight on Q2 (power) [09]	0 (0)	0	--
Peripheral volume (V3; L) [04]	0.924 (0.0444)	2.52	(2.34,2.71)
Body weight on V3 (power) [010]	0.528 (0.108)	0.528	(0.351,0.706)
Ka (half-life; Days) [05]	1.27 (0.0722)	3.54	(3.15,3.99)
Bioavailability (F1; fraction) [06]	-0.53 (0.0251)	0.589	(0.565,0.614)
Change in F1 with 200 mg SC dose (fraction) [011]	0 (0)	1	--
Bioavailability (F1; fraction) Study CP220 (fraction) [012]	-0.713 (0.0382)	0.490	(0.461,0.522)
Var(ETA-CL) (%CV)	0.0583 (0.00435)	24.2	(22.6,25.6)
Var(ETA-V2) (%CV)	0.0595 (0.01)	24.4	(20.7,27.6)
Var(ETA-Q) (%CV)	0.008 (0)	8.94	--
Var(ETA-V3) (%CV)	0.2 (0.0217)	44.7	(40.5,48.5)
Var(ETA-KA[half-life]) (%CV)	0.691 (0.0737)	83.1	(75.5,90.1)
Var(ETA-F1) (%CV)	0.0292 (0.00662)	17.1	(13.5,20)

(Source: from ppk-report-errata-list-1.pdf submitted to BLA 761070 on 3/27/2017, Table 13, page 6)

Age, sex, race, creatinine clearance, and baseline blood eosinophil count had no clinically relevant impact on benralizumab CL. The SC bioavailability from Study MI-CP220 was only 49%. However, it's unclear if this difference was due to cross-study comparison or formulation changes (there was a minor change of excipients between formulation Process 2 and Process 3). Compared to the upper arm SC injection site, the bioavailability increased 9% for the abdomen and thigh sites. The magnitudes of the estimates were not considered clinically relevant.

A visual predictive check (VPC) was performed for the final updated model. The model appeared to adequately capture the population concentration-time profile of benralizumab across studies and dosing regimens. Visual predictive check results are displayed for the 2 Phase 3 pivotal studies (Study D3250C00017 and Study D3250C00018), grouped by two different dosing regimens (Q4W and Q4W + Q8W), in Figure 4.2.1.



@4W+4W+Q8W Every 4 weeks for the first 2 doses followed by every 8 weeks; w week; @4W+Q8W Every 4 weeks for the first 3 doses followed by every 8 weeks; IV Intravenous; PI Prediction interval; Q4 Every 4 weeks; SC Subcutaneous; Study 17 SIROCCO; Study 18 CALIMA; Study 32 BISE.

Figure 4.2.1 Visual Predictive Check Of Final Updated Pharmacokinetic Model for Study D3250C00017 and Study D3250C00018. @4W+Q8W Stands For Every 4 Weeks for the First 3 Doses Followed by Every 8 Weeks.

(Source: *ppk-report-errata-list-1.pdf* submitted on 3/27/2017, Table 9, page 13)

4.2.2 What are the effects of intrinsic factors on the PK of benralizumab?

Age, sex, race, creatinine clearance, and baseline blood eosinophil count had no impact on benralizumab CL.

Body weight

Body weight was identified as the only significant intrinsic factor covariate for benralizumab CL with the estimated allometric power as 0.807 (90% CI = 0.751, 0.864) (Figure 4.2.2). Patients with body weight of 58 Kg (median body weight of 1st quartile of body weight) and 99 Kg (median body weight of 4th quartile of body weight) were estimated to have 20% decrease and 24% increase of CL/F compared to patients weighing 76 kg (median body weight of patient population), respectively. By considering the coefficient of variation of CL inter-individual variability was 24%, the dose adjustment by body weight in adults is not necessary.

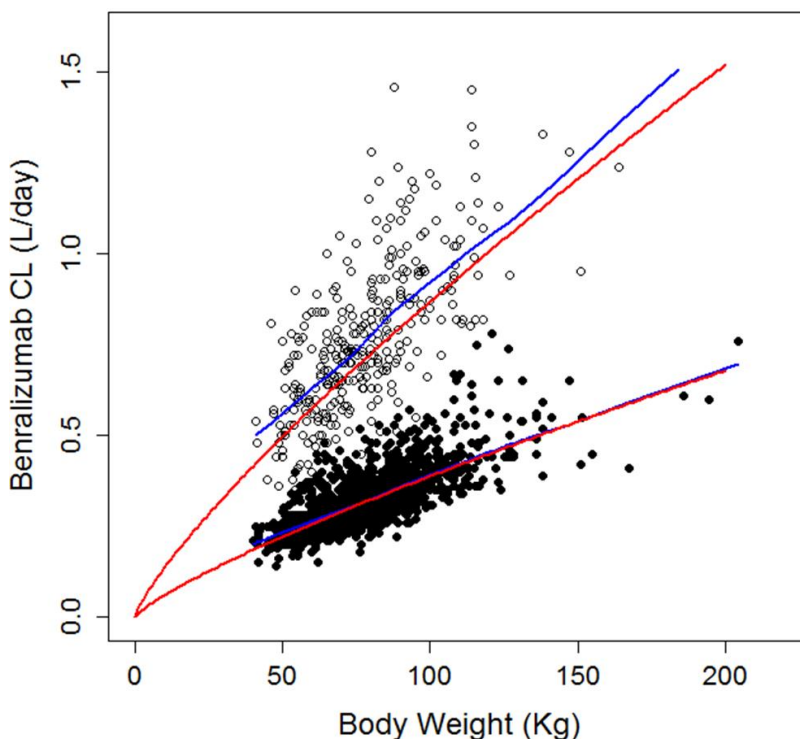


Figure 4.2.2 Scatter Plot of Benralizumab CL Over Body Weight. The Closed Circles Represent CL in Patients When Their ADA Results Were Negative. The Open Circles Represent CL in Patients When Their ADA results Were Positive. The Red Lines Represent Prediction Curves $[CL \times (Body\ Weight/70)^{0.807}]$. The Blue Lines Represent Local Smoothing Curves.

(Source: Reviewer's analysis)

- Adolescents

PK samples from 22 adolescents were included in this population PK analysis and age group was not identified as a significant covariate for CL. When the CL from ADA-negative PK samples were summarized, the median CL of adolescents was 0.255 L/day (Figure 4.2.3), which was only 18% less than that of adults (0.310 L/day). By considering that the median body weight in adolescents and adults was 56 and 76 kg, respectively, the allometric scaling model (predicted to be 22% difference) sufficiently characterize the small difference of CL between adolescents and adults.

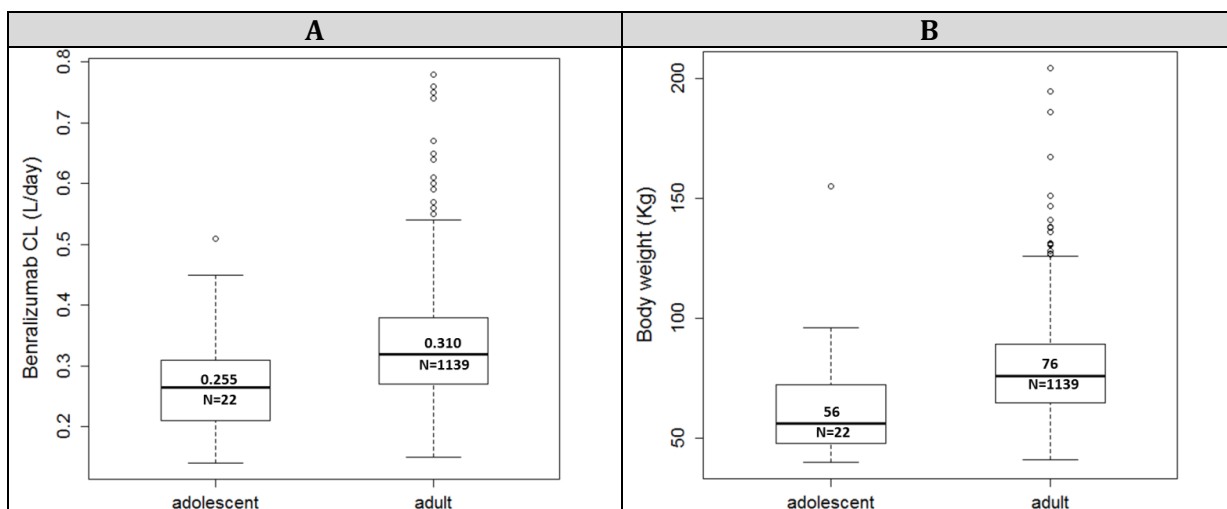


Figure 4.2.3 Box Plot of Benralizumab CL Over Age Group (A) and Body Weight Over Age Group (B). Clearance Values Were Summarized From ADA-Negative PK Samples.

(Source: Reviewer's analysis)

4.2.3 What are the effects of immunogenicity on the PK of benralizumab?

ADA was identified as a significant covariate for CL in which presence of ADA resulted in 2.24-fold (90% CI=2.18, 2.30) increase of CL (Figure 4.2.2, 4.2.4). From 316 patients with their PK samples available at both ADA-negative and ADA-positive status, the median value of CL increased from 0.32 (when ADA result is negative) to 0.74 L/day (when ADA result is positive).

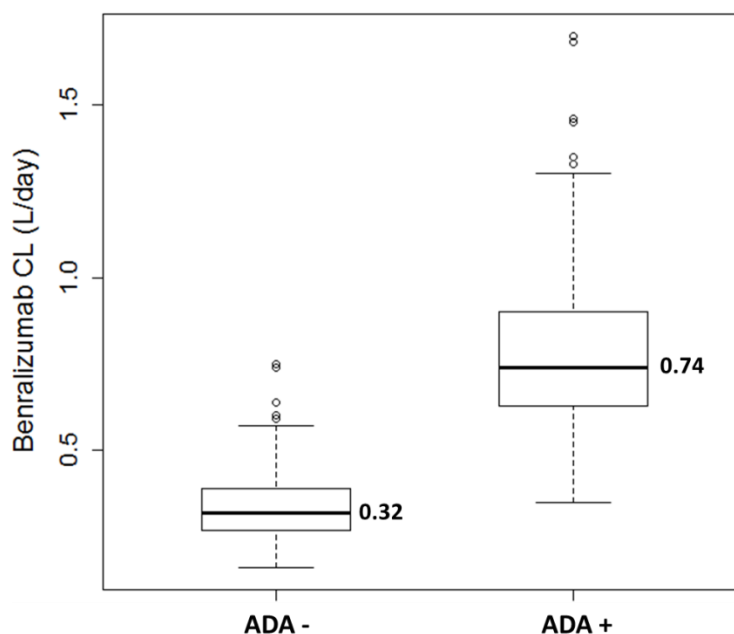


Figure 4.2.4 Box Plot of Benralizumab CL Over ADA Status. CL Values From 316 Subjects Were Compared Between Their ADA Negative Status and Positive Status.

(Source: Reviewer's analysis)

4.3 Appendix - Exposure-Response Analysis

4.3.1 Exposure-response relationship for efficacy

4.3.1.1 Is there an exposure-response relationship for asthma exacerbation rate (AER)?

There is no noticeable exposure-response relationship between individual median observed $C_{\text{trough,ss}}$ and AER. The exposure-response curve was generally flat for asthma exacerbation across a range of more than 6-fold (<212 ng/mL to ≥ 1250 ng/mL) median observed $C_{\text{trough,ss}}$.

The exposure-response analysis for AER primarily focused on the efficacy outcomes of the 2 pivotal Phase 3 studies (D3250C00017, D3250C00018). In both studies, adult and adolescent patients were randomized in a 1:1:1 ratio to receive placebo, 30 mg Q4W or 30 mg Q4×3 + Q8W dosing regimen. The patients were stratified by geographical region, age group (adult or adolescent), and peripheral blood eosinophils count (≥ 300 or <300 cells/ μL). The empirical assessment of AER was limited to those patients with at least one measurable $C_{\text{trough,ss}}$ at Weeks 16, 24, 32, 40, or 48 after receiving the first 3 doses of study medication.

Figure 4.2.5 depicts the distribution of medians of the steady-state trough concentrations by studies and dose regimens. The median observed $C_{\text{trough,ss}}$ within each dosing regimen were consistent across two studies. The median observed $C_{\text{trough,ss}}$ value following Q4W dosing regimen was about 5 times that of Q4×3 + Q8W dosing regimen.

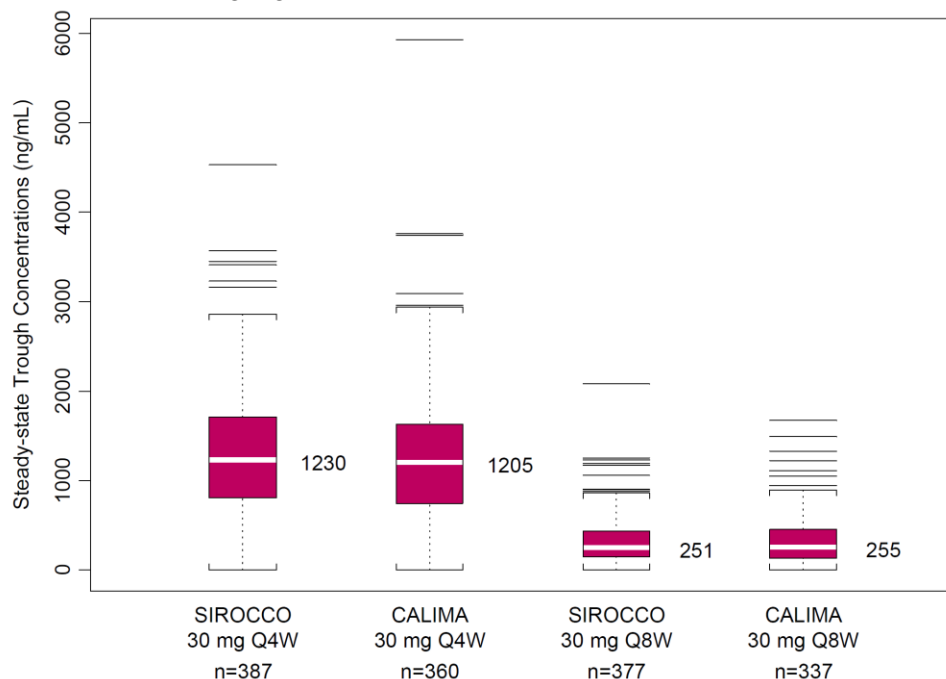


Figure 4.2.5 Median Observed $C_{\text{trough,ss}}$ by Dosing Regimen AND Studies (Including All Baseline Eosinophil Counts). SIROCCO: Study D3250C00017; CALIMA: D3250C00018.

(Source: Response-to-query-bla-fda-10-mar-2017.pdf, Page 33, Figure 5)

The final population model to characterize the asthma exacerbation events where the mean of the exacerbation events, λ , was described as follows:

$$\begin{aligned}\log(\lambda(t)) = & \beta_0 + \beta_{\text{prior exacerbation}}(\text{Number of prior exacerbation in past year}) \\ & + \beta_{\text{OCS}}I(\text{Maintenance of OCS}) + \beta_{\text{E.Europe}}I(\text{E.Europe}) \\ & + \frac{\beta_{\text{Emax}} \cdot C(t)}{C(t) + EC50} + \eta\end{aligned}$$

In the analysis of exacerbation events, the estimated EC₅₀ (103 ng/mL) was only approximately 11% of the typical C_{trough,ss} value (927 ng/mL) (Table 4.2.3). Meanwhile, the EC₉₀ (103 ng/mL) was close to the typical C_{trough,ss} value. The results indicate the exposure-response curve was flat from two pivotal Phase 3 Studies (Figure 4.2.6).

Table 4.2.3 Parameter Estimates of Final PK Exposure-AER Model in Severe Asthma Patients on high-dose ICS regardless of baseline eosinophil counts

	Point Estimate	Standard Error
β_0	-6.60	0.0921
β_{Emax}	-0.528	0.210
$\log(EC50)$	4.63	4.97
$\beta_{\text{prior exacerbation}}$	0.170	0.0174
β_{OCS}	0.266	0.0932
$\beta_{\text{E.Europe}}$	-0.365	0.0752
$\text{Var}[\eta]$	0.962	0.078

(Source: eCTD for BLA 761070, Module 5.3.3.5, Exposure-Response-Modeling-Report.pdf, page 5)

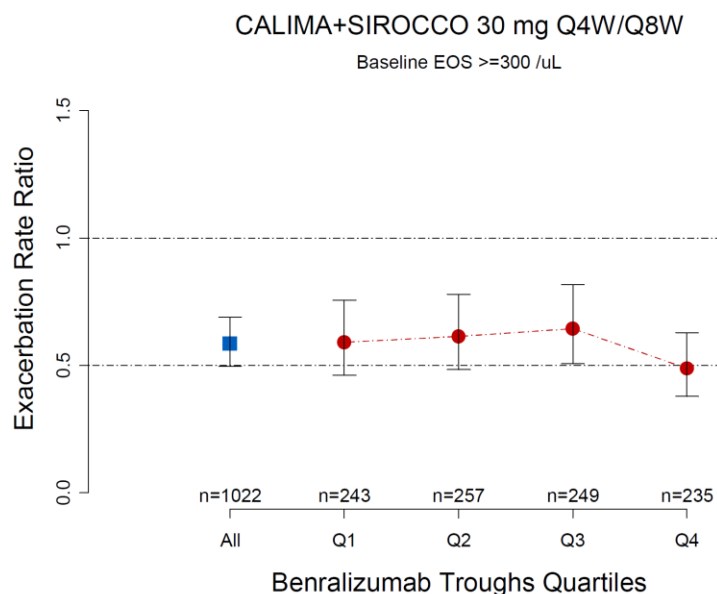


Figure 4.2.6 Relative Risk of Exacerbation by Steady-State Trough PK (C_{trough,ss}) Quartiles in Asthma Patients With Baseline Eosinophils Counts ≥300/μL in Both Study D3250C00017 (SIROCCO) and D3250C00018 (CALIMA) From Both Dosing Regimens.

(Source: Response-to-query-bla-fda-10-mar-2017.pdf, Page 3, Figure 1)

The Central/Eastern Europe region (labelled as “Eastern Europe” on source data and graphs), fewer prior exacerbations, and no maintenance OCS usage were associated with lower base asthma exacerbation rate over the study period (Table 4.2.3).

Based on population exposure-response modeling and simulations, dose regimen, presence of anti-drug antibody, and adolescent vs. adult had no impact on benralizumab efficacy, although the projected AER for adolescents via trial simulation using subgroup analysis had a wide confidence interval due to the small sample size.

During the population model development a positive blood eosinophil effect on benralizumab efficacy (E_{max}) was noted. Patients with higher baseline eosinophil counts tended to have a lower exacerbation rate ratio (i.e., larger treatment effect), although benralizumab treatment benefit was observed over the entire range of baseline eosinophil counts. The covariate effect on efficacy was only associated with a p-value of 0.048 ($\Delta OBJ=3.9$) and not found significant by likelihood ratio tests (LRT) with a more stringent acceptance criterion of $p<0.001$ (χ^2 , $df=1$). As a result, the effect of baseline eosinophil count on benralizumab E_{max} was not retained in the final exposure-response model for AER.

4.3.1.2 Is there an exposure-response relationship for FEV₁?

There is no noticeable exposure-response relationship between $C_{average,ss}$ and FEV₁ change from baseline at the end of treatment (EOT, Week 48 for Study D3250C00017 and Week 56 for Study D3250C00018). The exposure-response curve was generally flat for FEV₁ change from baseline at EOT across a range of more than 10-fold (200 ng/mL to 2000 ng/mL) $C_{average,ss}$.

Pre-bronchodilator FEV₁ data from Studies D3250C00017 and D3250C00018 were pooled and simultaneously modelled using a population approach. During the development of a population longitudinal model, the FEV₁ response in benralizumab-treated subjects is depicted in the equation below:

$$FEV_1 = FEV_{1baseline} + P_{max} \cdot (1 - e^{-k_{pbo} \cdot time}) + \frac{E_{max} \cdot [drug]}{EC_{50} + [drug]}$$

Where

$$E_{max} = \theta_1 \cdot \left(\frac{EoS_0}{380} \right)^{\theta_7} \cdot e^{\eta_1}$$

$$P_{max} = \theta_5 \cdot \left(\frac{BFEV_1}{1650} \right)^{\theta_6} + \eta_5$$

The placebo effect was characterized using an exponential function. P_{max} was assumed to be normally distributed, to allow for negative placebo effect in some subjects given the large variability in FEV₁ response.

However, $C_{average,ss}$ was not identified as a significant covariate for FEV₁ change from baseline at EOT. The estimated EC_{50} was 1.36 ng/mL (Table 4.2.4); the value was even smaller than the assay's lower limit of quantification (LLOQ=3.86 ng/mL). Indeed, the exposure-response curve for FEV₁ was flat for both dosing regimens from both studies (Figure 4.2.7). As such, information in the primary registration study data did not support the full characterization of PK exposure-response relationship for FEV₁ using the modeling approach.

Benralizumab dosing regimen, ADA, concomitant medications, and other demographic covariates had no significant impact on benralizumab efficacy. Compared with other age groups, adolescents had the strongest placebo effect (P_{\max}).

Table 4.2.4 Summary of FEV1 Parameter Estimates from an Exposure-Response Model (High-Dose ICS, All Baseline Eosinophil Counts)

OBJ	Base Model	
	228396	
Parameter (Units)	Estimate	SE
E_{\max} (mL)	92.4	9.49
EC_{50} (ng/mL)	1.36	0.247
$FEV_{1, \text{baseline}}$ (mL)	1600	12.7
k_{pbo} (d^{-1})	0.033	0.00228
P_{\max} (mL)	198	11.4
BFEV1 on P_{\max} (power)	0.619	0.125
Eos ₀ on E_{\max} (power)	0.715	0.0864
Inter-individual Variability		
ETA- E_{\max} (%CV)	120	5.39
ETA- EC_{50} (%CV)	294	26.5
ETA- P_{\max} (%CV)	34.5	0.59
ETA- k_{pbo} (%CV)	117	5.11
ETA- P_{\max} (SD, mL)	319	12.6
Residual Error		
Residual error, proportional (%CV)	9.19	0.48
Residual error, additive (SD, mL)	124	9.78

BFEV1: Baseline FEV1 (observed value)

Eos₀: Baseline blood eosinophil count (observed value)

P_{\max} : Maximum placebo effect;

k_{pbo} : Rate constant for placebo effect

(Source: eCTD for BLA 761070, Module 5.3.3.5, Exposure-Response-Modeling-Report.pdf, Table 11, page 73)

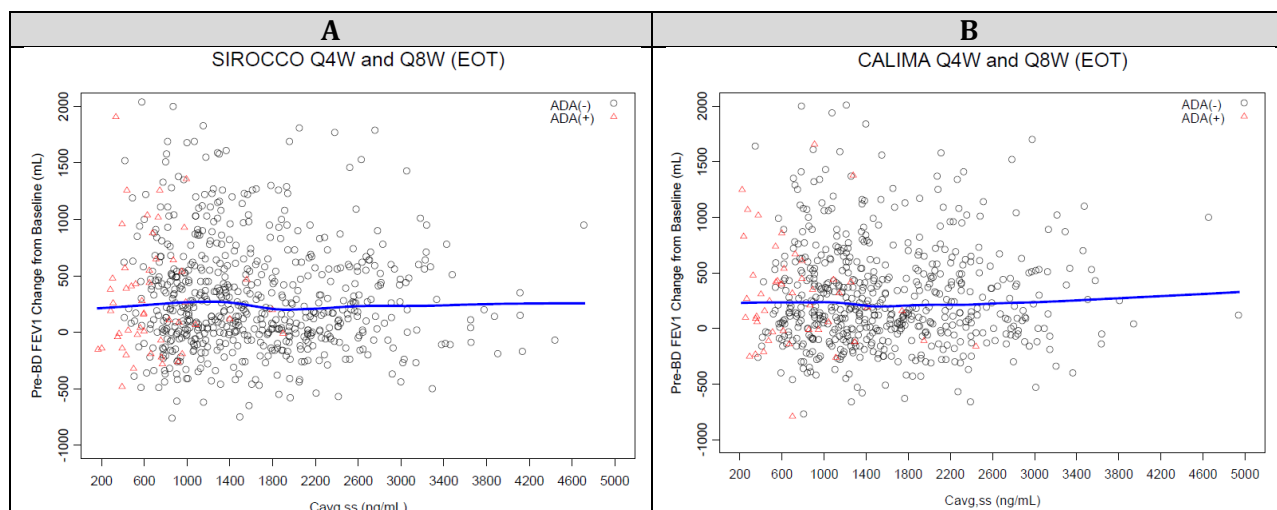


Figure 4.2.7 Empirical Correlation Of Pre-Bronchodilator FEV₁ Change From Baseline at EOT With C_{average,ss} for Pooled Two Dosing Regimens From Study D3250C00017 (A) and D3250C00018 (B)

(Source: eCTD for BLA 761070, Module 5.3.3.5, Exposure-Response-Modeling-Report.pdf, Figures 4.3 and 4.4, pp 278-279)

The estimated typical benralizumab treatment effect was 95.8 mL in patients with median baseline eosinophils counts of 380 cells/ μ L. The predicted drug effect (benralizumab efficacy) is greater in asthma patients with higher baseline eosinophil counts (Figure 4.2.8). From population longitudinal modelling, benralizumab treatment was associated with a rapid improvement of FEV₁ over placebo with an estimated half-maximum time of 7.6 days following the first dose administration. On the other hand, the onset of placebo effect was much slower, with an estimated half-life of approximately 19 days.

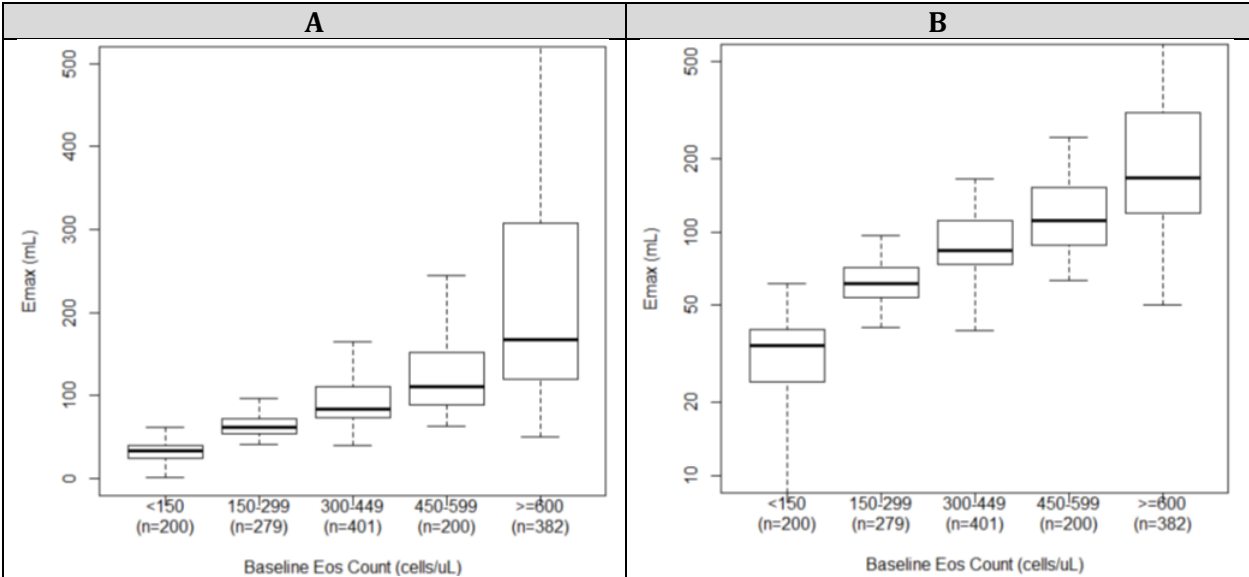


Figure 4.2.8 Effect of Baseline Eosinophil Counts on Individual Model-Predicted Benralizumab Efficacy (Emax) From Study D3250C00017 (A) and D3250C00018 (B).

(Source: *Response-to-query-bla-fda-10-mar-2017.pdf*, Figure 29, Page 102)

4.3.2 Exposure-response relationship for safety

The exposure-response relationship for safety was not evaluated.

4.4 Appendix – Summary of Bioanalytical Method Validation

4.4.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

Plasma samples from Study MI-CP158 were analyzed for benralizumab levels using a validated ELISA method with a lower limit of quantitation (LLOQ) of approximately 10 ng/mL. All other clinical studies measured benralizumab concentrations using a validated electrochemiluminescent (ECL) immunoassay that employed meso scale discovery (MSD) technology with a LLOQ of 3.86 ng/mL.

Plasma samples for Study MI-CP158 were analyzed by (b) (4). Plasma samples from Study MI-CP166, and serum samples from the Phase 2 studies (Studies MI-CP186, MI-CP197, and MI-CP220) were analyzed by MedImmune (One MedImmune Way, Gaithersburg, MD; Method CT-050094. Serum samples from the Phase 3 studies (BISE, GREGALE, CALIMA, SIROCCO, ZONDA, (b) (4)) were analyzed by (b) (4).

Bioanalytical methods used for determination of benralizumab concentrations in human biological samples is listed in Table 4.4.1-1.

Table 4.4.1-1: Bioanalytical Methods for Determination of Benralizumab Concentrations in Human Biological Samples

Method	Site	Matrix	Report No. ^a	LLOQ ng/mL	Linear range ng/mL	Study numbers
ELISA						
30423	(b) (4)	Human lithium-heparin plasma	38090_00	10	10 to 10000 ^b	MI-CP158
ECL immunoassay with MSD						
CT-050094 ^c	MedImmune	Human serum and lithium-heparin plasma	CTVR-0049	3.86	3.86 to 1250	MI-CP166 (plasma); MI-CP186, MI-CP197, MI-CP200 (serum)
ICD 561	(b) (4)	Human serum	ICD 561	3.86	3.86 to 1250	SIROCCO, CALIMA, ZONDA, GREGALE, BISE, (b) (4) BORA ^d

Note: Depending on the time the method was developed during the clinical development program, benralizumab may have been referred to as BIW-8405 or MEDI-563.

^a Refers to Method Validation Report and any subsequent amendments/addenda, located in Module 5.3.1.4.

^b For Method 30423, an ULOQ was not defined in the validation report. However, the method was tested and able to accurately recover concentrations up to 250 µg/mL and the standard curve included concentrations ranging from 10 to 10000 ng/mL.

^c Method CT-050094 was formerly CT-9618. The method number was changed when a Standard Operating Procedure database was moved to Aegis; however, the method itself was not changed.

^d BORA (D3250C00021) is an ongoing study.

ECL Electrochemiluminescent; ELISA Enzyme-linked immunosorbent assay; LLOQ Lower limit of quantitation; MSD Meso Scale Discovery; No Number; ULOQ Upper limit of quantitation

(Source: eCTD module 2.7. Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 2, Page 9)

4.4.2 What was the performance of bioanalytical methods?

The PK assay was appropriately qualified and is suitable for the quantitative determination of benralizumab in human plasma and serum.

The analytical methods conducted at (b) (4) for Study MI-CP158 were found to be selective, sensitive, precise, and accurate for the determination of benralizumab in human plasma. The limit of quantitation was 10 ng/mL, with a linear range between 10 – 10,000 ng/mL. Accuracy of the assay was 88%, 90% and 97% at the 250 µg/mL, 7.5 µg/mL and 0.2 µg/mL, respectively. The mean intra-assay precision was 4.7%, and inter-assay precision was 8.8%.

The analytical methods conducted at MedImmune for Study MI-CP166 (plasma) and studies MI-CP186, MI-CP197 and MI-CP200 (serum) were found to be selective, sensitive, precise, and accurate for the determination of benralizumab in human plasma and serum. The limit of quantitation was 3.86 ng/mL, with a measurement range of 3.86 - 1250 ng/ml for human serum or plasma diluted 1:50. The method was found to have acceptable accuracy at each of the serum QC levels, with absolute % biases ≤ 4.0 , and for the plasma QC levels, with absolute % biases ≤ 7.1 . The method was found to have acceptable intra-assay precision at each level, irrespective of the matrix in which the QCs were in. Pooled intra-assay precision data at each QC of the serum and plasma QCs showed acceptable intra-assay precision at each level with %CVs ≤ 5.0 . The inter-assay precision at each QC level was acceptable with %CVs ≤ 16.1 .

The analytical methods conducted at (b) (4) for all Phase 3 studies were found to be selective, sensitive, precise, and accurate for the determination of benralizumab in human serum. The limit of quantitation was 3.86 ng/mL, with a measurement range of 3.86 - 1250 ng/ml for human serum. Bioanalytical validation summary listing accuracy and precision are listed in Table 4.4.2-1.

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Table 4.4.2-1: Bioanalytical Method Validation Summary for Benralizumab -563 in Human Serum

(b) (4) Project Code	RCNO2			
Method ID	ICD 561			
Analyte	Benralizumab (MEDI-563)			
Minimum Required Dilution	1:50 in assay buffer			
Matrix	Human Serum			
Anticoagulant	None			
Method Description	Electrochemiluminescent			
Sample Volume (µL)	20-µL aliquot			
Sample Storage Temperature	-80 °C ± 10 °C			
Lower Limit of Quantitation (LLOQ)	3.86 ng/mL			
Upper Limit of Quantitation (ULOQ)	1250 ng/mL			
Regression, Weighting	Four-parameter logistic, 1/response ²			
Standard Curve Concentrations	0.960 (anchor) to 11250 (anchor) ng/mL			
QC Concentrations	3.86, 10.0, 100, 1000, and 1250 ng/mL			
QC Intra-assay Statistics (%) Runs 4RCNO2 and 5RCNO2	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	3.86	6.97%	5.92%
	Low	10.0	6.01%	15.7%
	Mid	100	13.9%	4.60%
	High	1000	1.99%	2.86%
	ULOQ	1250	9.78%	4.61%
QC Intra-assay Statistics (%) Runs 7RCNO2 and 8RCNO2	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	3.86	2.55%	7.31%
	Low	10.0	4.82%	6.36%
	Mid	100	5.07%	-0.486%
	High	1000	1.67%	7.63%
	ULOQ	1250	9.75%	5.49%
QC Inter-assay Statistics (%)	Level	Conc. (ng/mL)	Precision	Accuracy
	LLOQ	3.86	11.0%	8.36%
	Low	10.0	11.6%	2.98%
	Mid	100	7.44%	-1.12%
	High	1000	8.12%	6.71%
	ULOQ	1250	6.80%	9.71%
Dilutional Linearity	11,250 ng/mL diluted 50- and 500-fold			
Hook Effect	No apparent hook effect observed at concentrations up to 11,250 ng/mL			
Freeze-thaw Stability (cycles)	Six cycles thawed at room temperature			
Antibody Interference	Detection of the low QC is inhibited by 53.7% in the presence of 10.0 ng/mL ADA			
	Low QC is undetectable in the presence of 1000 ng/mL ADA			
	Detection of the high QC is not impacted by 10.0 ng/mL ADA			
	Detection of the high QC is inhibited by 73.9% in the presence of 1000 ng/mL ADA			
Antibody Specificity	No effect from R347 Control Ab IgG-1 on the quantitation of MEDI-563.			
Selectivity/Specificity	Acceptable with all unfortified selectivity sample lots meeting the acceptance criteria			
	Acceptable with eight out of ten fortified healthy human serum specificity lots meeting the acceptance criteria			
	Acceptable with all fortified asthma and COPD human serum specificity lots meeting the acceptance criteria			
Assay Robustness	Assay is robust with overall assay pass rate of 80.0%.			
Inter-laboratory Cross-validation	(b) (4) results confirm MedImmune-provided nominal concentrations.			

(Source: Method Validation Report ICD 561, Validation Summary Table, Pages 7-8)

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/s/

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