BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761070/S020
Priority or Standard	Standard
Submit Date(s)	March 9, 2023
Received Date(s)	March 9, 2023
PDUFA Goal Date	January 9, 2024
Division/Office	Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation
Review Completion Date	January 8, 2024
Established/Proper Name	Benralizumab
(Proposed) Trade Name	Fasenra
Pharmacologic Class	Interleukin-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa)
Applicant	AstraZeneca
Dosage form	Injection
Applicant proposed Dosing Regimen	Patients 6 to 11 years (<35 kg) will receive 10 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter. Patients 6 to 11 years (≥35 kg) will receive 30 mg SC every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	Add-on maintenance treatment of patients with severe asthma aged 6 years and older, and with an eosinophilic phenotype
Recommendation on Regulatory Action	Complete response (due to facilities' inspection issues)
Recommended Indication(s)/Population(s) (if applicable)	Unchanged
Recommended Dosing Regimen	Unchanged

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CDRH=Center for Devices and Radiological Health
OBP= Office of Biotechnology Products
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
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Glossary

AAER annualized asthma exacerbation rate
ADAs anti-drug antibodies
ACQ-IA asthma control questionnaire-interviewer administered

AE	adverse event
BLA	biologics license application
CGIC	Clinician Global Impression of Change
DBL	data base lock
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
HE	higher exposure
ICS	inhaled corticosteroids
IL	interleukin
IL-5Rα	interleukin 5 receptor alpha
OCS	oral corticosteroids
OPF	Office of Process and Facilities
PFS	prefilled syringe
PK	pharmacokinetics
PMR	post marketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome.
Q4W	every 4 weeks
Q8W	every 8 weeks
SAE	serious adverse event
sBLA	supplemental biologics license application
SC	subcutaneously
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

AstraZeneca AB submitted an efficacy supplement (S-20) for biologics license application (BLA) 761070 to expand the indication for benralizumab "for the add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype" from ≥12 years of age to ≥6 years of age. Benralizumab is a humanized, afucosylated, monoclonal antibody (IgG1k) targeting the interleukin (IL)-5 receptor alpha (IL-5Rα) subunit, which is expressed on eosinophils and basophils. The primary mechanism of action is induction of apoptosis of eosinophils and basophils expressing IL-5Rα through antibody-dependent cell-mediated cytotoxicity.

Benralizumab was approved in 2017 for the "add-on maintenance treatment of patients with severe asthma aged 12 years of age and older, and with an eosinophilic phenotype". The approved dosing regimen consists of a loading dose of 30 mg subcutaneously (SC) every 4 weeks (Q4W) for the first 3 doses, followed by 30 mg SC every 8 weeks (Q8W). Both a 30 mg prefilled syringe and autoinjector are approved. The prefilled syringe is to be administered by a healthcare provider. The autoinjector may be administered by patients/caregivers.

A Pediatric Research Equity Act (PREA) Post-marketing Requirement (PMR) was issued with the original approval- *PMR 32871-1: open-label, pharmacokinetic (PK) and pharmacodynamics (PD) study of benralizumab in pediatric patients 6 to 11 years of age with a continued safety evaluation out to a minimum of 48 weeks*. This supplemental BLA (sBLA) fulfills the PMR and is seeking to expand the asthma indication to include patients ≥6 years of age, with dosing of 10 mg in patients aged 6 to 11 years who weigh < 35 kg and 30 mg in patients aged 6 to 11 years who weigh ≥ 35 kg. The proposed dosing regimen is the same as for patients ≥ 12 years of age (SC Q4W for the first 3 doses, followed by Q8W thereafter). A new 10 mg prefilled syringe (PFS) is proposed in this sBLA. As with the 30 mg prefilled syringe, the 10 mg prefilled syringe is to be administered by a healthcare provider.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Based on the high degree of similarity in severe asthma with an eosinophilic phenotype between adults/adolescents and pediatric subjects 6 to 11 years of age, consistency in the therapeutic approach, consistency of the benralizumab mechanism of action, and relevance of the clinical endpoints, efficacy in children 6 to 11 years of age was extrapolated from the efficacy demonstrated in the adequate and well-controlled studies in adults and adolescents 12 years of age and older that supported demonstration of substantial evidence of effectiveness with the initial approval.

To support this application, the Applicant conducted a single-arm, PK, PD, and long-term safety

trial (TATE) in 28 children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. Extrapolation of efficacy is supported by similar or higher PK and similar PD compared to that observed in adults and adolescents. Benralizumab exposure in children aged 6 to 11 years who weighted <35 kg and received 10 mg dose was similar to adolescents and adults receiving 30 mg (approved dose); however, patients 6 to 11 years who weighed ≥35kg and received 30 mg dose showed 62% higher median week 16 trough concentrations compared to adults and adolescents receiving the same dose. The PD response observed in the TATE trial for both dosing groups was similar to that observed in adults and adolescents.

Overall, substantial evidence of effectiveness for children 6 to 11 years of age "for add-on maintenance treatment for severe asthma, with an eosinophilic phenotype" is established based on extrapolation of the demonstrated efficacy from the adequate and well-controlled studies that provided demonstration of substantial evidence of effectiveness for the same indication in adults and adolescents aged 12 years and older, supported by similar or higher PK and similar PD in children 6 to 11 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This efficacy supplement-20 (S-20) for benralizumab proposes to expand the indication "for the add-on maintenance treatment of patients with severe asthma, and with eosinophilic phenotype" from ≥ 12 years of age to ≥ 6 years of age. To support the efficacy and safety of benralizumab for the proposed indication, the Applicant submitted data from the TATE trial, a single-arm, PK, PD, and long-term safety clinical trial in 28 children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. Completion of the TATE trial fulfils PREA PMR 32871-1. Dose was weight-based (10 mg for < 35 kg and 30 mg for ≥ 35 kg). The dosing regimen was the same as adults/adolescents (Q4W for 3 doses, then Q8W thereafter). Enrolled patients were treated for 48 weeks. PK/PD was assessed during the first 16-weeks of treatment (Part A), with continued safety assessments through Week 52 (Part B).

Substantial evidence of effectiveness for children 6 to 11 years of age "for add-on maintenance treatment for severe asthma, with an eosinophilic phenotype" is established based on extrapolation of efficacy from adequate and well-controlled studies that provided demonstration of substantial evidence of effectiveness for the same indication in adults and adolescents aged 12 years and older, supported by similar or higher PK and similar PD (peripheral eosinophil counts) in children 6 to 11 years of age obtained from the TATE trial. Efficacy extrapolation is supported by the high degree of similarity of severe asthma with an eosinophilic phenotype, consistency in the therapeutic approach, consistency of the benralizumab mechanism of action, and relevance of the clinical endpoints for children 6 to 11 years of age. Incidence of anti-drug antibodies (ADAs) and impacts of ADAs on PK and PD were similar between pediatric patients aged 6 to 11 years and adults/adolescents.

The safety profile for benralizumab in patients with severe asthma, and with an eosinophilic phenotype, is well established since its approval in 2017 and includes a warning and precaution for hypersensitivity reactions, including anaphylaxis. Common adverse reactions include headache and pharyngitis. Safety for the new patient population is partially extrapolated from the adolescent/adult pivotal clinical trials. No new safety signals were identified in the TATE trial. Exposure was similar for pediatric patients aged 6 to 11 year and weighting < 35 kg receiving the dose of 10mg, however, there was a higher exposure (HE) in pediatric patients weighting ≥35 kg, with 62% higher median week 16 trough concentrations compare to adults and adolescents receiving the same dose. The safety profile was similar for both weight-based dosing groups. Further support for safety for the HE-group, relies upon a similar safety profile for adults and adolescents in the 1-year phase 3 clinical studies (SIROCCO, CALIMA, and ZONDA) who received a higher dose (30 mg Q4W, n=896 with a similar exposure to the HE-group) compared to adults and adolescents who received the approved dosing regimen (n=1835).

The safety profile of benralizumab is well established since its approval in 2017. This would be the second approved drug targeting the IL5 pathway for pediatric patients 6 to 11 years of age, joining mepolizumab, and the first administrated Q8W. From the clinical standpoint, the Applicant has submitted adequate data to support the efficacy/safety of benralizumab for patients aged 6 to 11 years as add-on maintenance treatment for those with severe asthma, and with an eosinophilic phenotype. However, issues arose with the facilities' inspection that preclude approval during this review cycle; therefore, the application will receive a Complete Response pending resolution of the facilities issues.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. • While the majority of patients are successfully managed with inhaled corticosteroids plus a second controller and/or systemic corticosteroids (SCS), a subset of patients with severe asthma remain uncontrolled. • Patients with asthma and elevated peripheral eosinophils are at increased risk of asthma exacerbations and appear to be linked to severe asthma. • Estimates of the prevalence of severe asthma vary, depending on definitions and health-care settings, from 0·23–3·2% in the general population to 2·1–10% for children with asthma. • The burden of childhood asthma is substantial: asthma was the top reason for absence from school in the USA in 2013, accounting for 13·8 million missed school days.	Asthma is a heterogeneous disease with different underlying processes driving inflammation. While most children with persistent asthma can be managed with low to medium doses of ICS, some children continue to have exacerbations, including severe exacerbations that can be fatal, and decreased lung function, despite the use of high doses of steroids. Patients with severe asthma utilize a high proportion of healthcare resources related to office visits and hospital admissions, as well as wider societal costs of lost time at work and school.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Having another treatment option for younger patients is important given the impact of uncontrolled asthma on quality of life, anxiety, and absenteeism.
Current Treatment Options	• There are several biologic treatments indicated as add-on maintenance treatment for moderate-to-severe and severe asthma, depending on the underlying phenotype. • Currently, there are only two biologics, dupilumab and mepolizumab, that are approved for add-on maintenance treatment in patients ≥6 years of age with severe asthma, and with an eosinophilic phenotype. The other biologic approved for patients aged 6 and older is omalizumab, which is indicated for patients with moderate to severe asthma, in patients with sensitivity to a perennial aeroallergen.	While there are approved add-on maintenance therapies to treat moderate-to severe asthma with an eosinophilic phenotype, the availability of an additional treatment option in children as young as 6 years of age and with less frequent dosing will be an important option.
Benefit	• Based on the high degree of similarity for severe asthma with an eosinophilic phenotype, consistency in the therapeutic approach, consistency of the benralizumab mechanism of action, and relevance of the clinical endpoints, efficacy for patients 6 to 11 years of age can be fully extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older, supported by similar or higher PK and similar PD in children 6 to 11 years of age. • This pediatric trial was not designed to assess efficacy given the small sample size, duration, and uncontrolled design. However,	Efficacy was extrapolated to patients 6-11 years of age from the adolescent and adult trials, supported by similar or higher PK and similar PD. Benralizumab will be the second in-class (IL-5 pathway) and the fourth biologic approved as an add-on maintenance treatment for moderate-to-severe and severe asthma for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exploratory efficacy analyses were supportive.	patients 6 to 11 years of age. Benralizumab is administrated with a less frequent dosing schedule (every 8 weeks after the third dose), which would represent a clinically relevant benefit for this difficult to treat patient population.
Risk and Risk Management	• The safety profile for benralizumab is well established since its approval in 2017 and includes a warning and precaution for hypersensitivity reactions, including anaphylaxis. Common adverse reactions include headache and pharyngitis. • No new safety signals were identified in the 1-year pediatric safety study in 28 subjects. • Support for safety in the pediatric HE-group relies on a similar safety profile compared to the pediatric low dose group and a similar safety profile for adults and adolescents in the 1-year phase 3 clinical studies who received a higher dose with a similar exposure to the HE-group, compared to adults and adolescents who received the approved dosing regimen. • The surveillance facilities inspections revealed issues that could lead to deficiencies in manufacturing of the drug product.	Safety for the new patient population is mostly extrapolated from the adolescent and adult pivotal clinical trials, based on the limited safety data collected in the open-label study. The risk analysis from the limited safety data base is similar to the approved indicated population. Until the facilities issues are resolved, this Application cannot be approved.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Section 8.1.1.4.3.5 and 8.1.1.3.5 Interviewer-administered Asthma Control Questionnaire (ACQ-IA), Interviewer-administered Patient Global Impression of Change (PGIC-IA)
		☐	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	Section 8.1.1.4.3.5 and 8.1.1.3.5 Clinician Global Impression of Change (CGIC)
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		

	□	Patient preference studies (e.g., submitted studies or scientific publications)	
	□	Other: (Please specify):	
□	**Patient experience data that were not submitted in the application, but were considered in this review:**		
	□	Input informed from participation in meetings with patient stakeholders	
	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
□	**Patient experience data was not submitted as part of this application.**		

2. Therapeutic Context

2.1. Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing caused by underlying airway inflammation and airway hyper-responsiveness. It is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction. The diagnosis and management of this common condition are outlined in the NAEPP (National Asthma Education Prevention Program 2020) and GINA (Global Initiative for Asthma 2023) guidelines, which include a treatment approach of escalating daily maintenance therapy, based on a patient's symptoms, to achieve control. While the majority of patients are successfully managed with this stepwise treatment approach, a subset of patients with severe asthma remains uncontrolled despite maximal medical management. (1)

Prevalence of severe asthma varies, depending on definitions and health-care settings, from 2 to 10% in children with asthma. (2) The identification of alternative strategies to prevent asthma exacerbations in this difficult to treat group is crucial to decrease morbidity and hospitalizations. The emergence of biologic therapies for asthma targeting specific immunologic pathways has transformed the management of uncontrolled patients. Although, data in children and adolescents are scarce, there is supportive data demonstrating a high degree of similarity for severe asthma with an eosinophilic phenotype and responses to targeting therapies across the age spectrum from children to adults (3)

The emergence of biologic therapies for asthma provides opportunities for phenotype-directed approaches to asthma management. Elevated concentrations of eosinophils in the blood and airway have been identified as biomarkers for increased risk of asthma exacerbation and appears to be linked with severe asthma. (4)

2.2. Analysis of Current Treatment Options

There are several biologic treatments indicated as add-on maintenance treatment for asthma (Table 1). For this application, the Applicant is requesting to expand their indicated population to include patients aged 6 to 11 years who have severe asthma, and with eosinophilic phenotype. Currently, there are two biologics, dupilumab and mepolizumab, with the indication for add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype for children ≥ 6 years of age. The other biologic approved for asthma in patients aged 6 and older is omalizumab, which is indicated for patients with moderate to severe asthma and perennial aeroallergen sensitization.

Most development programs for biologics have demonstrated a reduction in annualized asthma exacerbation rates, an improvement in lung function, and reduction in daily OCS (oral corticosteroids) use in asthmatics who are on chronic OCS. Benralizumab will be an additional

treatment option for patients ≥ 6 years of age and will be the only biologic therapy with dosing every 8 weeks (after the third dose), compared with 2-to-4-week dosing regimens for currently approved biologics. (5).

Table 1. Current Biologic Therapeutic Options in the United States for Asthma

Product Name (Approval Year) MOA	Indication (Add-on Maintenance Treatment)	ROA	Age (years)	Dosage Form (Strengths)	Dosing
Omalizumab (2003) Anti-IgE	Moderate to severe persistent asthma in patients with +SPT or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with ICS	SC	≥ 6	AI/PFS (75mg/0.5mL) (150mg/mL) (300 mg/2mL) Powder (vial) (150mg/5mL)	75 to 375 mg SC Q2W to Q4W. depending on age, weight and serum IgE
Mepolizumab (2015) Anti-IL5	Severe asthma and with an **eosinophilic phenotype**	SC	≥ 6	AI/PFS (100mg/mL) PFS (40mg/0.4mL) Powder (vial) (100mg/mL)	6 to 11 years of age: 40 mg Q4W ≥ 12 years of age: 100 mg Q4W
Reslizumab (2016) Anti-IL5	Severe asthma with an **eosinophilic phenotype**	IV	≥ 18	100mg/10ml (10mg/mL)	3mg/kg Q4W
Benralizumab (2017) Anti-IL5	Severe asthma and with an **eosinophilic phenotype**	SC	≥ 12	AI/PFS (30mg/mL)	30 mg Q4W for the first 3 doses, followed by Q8W thereafter

Product Name (Approval Year) MOA	Indication (Add-on Maintenance Treatment)	ROA	Age (years)	Dosage Form (Strengths)	Dosing
Dupilumab (2018) Anti-IL4 Receptor α (blocks IL-4 and IL-13)	Moderate-to-severe asthma characterized by an **eosinophilic phenotype** or with oral corticosteroid dependent asthma	SC	≥ 6	AI/PFS (300mg/2mL) (200mg/1.14mL)	6–11-years of age: 300 mg Q4W for 15 to <30 kg 200 mg Q2W for ≥30 kg ≥12-years of age: 400 mg loading, then 200 mg Q2W Or 600 mg loading, then 300 mg Q2W
Tezepelumab (2021) Anti-TSLP	Severe asthma	SC	≥ 12	AI/PFS (210mg/1.91mL) Vial (210/1.91 mL)	210 mg Q4W

Source: Drugs@FDA.gov (https://www.accessdata.fda.gov/scripts/cder/daf/)
Abbreviations: AI, autoinjector; IL, interleukin; kg, kilogram; mg, milligram; MOA, mechanism of action; ROA, route of administration; PFS, prefilled syringe; SC, subcutaneously; SPT, skin prick test; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; IgE, immunoglobulin E; TSLP, thymic stromal lymphopoietin

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Benralizumab was approved for the add-on maintenance treatment of patients ≥12 years of age with severe asthma, and with an eosinophilic phenotype, on November 14, 2017. The original approval included a (b) (4) prefilled syringe to be administered by a healthcare provider. A new autoinjector presentation for home use was approved on October 3, 2019.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 summarizes topics related to the clinical development program that were discussed during key interactions between the Applicant and the FDA. Benralizumab for asthma was developed under IND 100237.

Table 2. Summary of Regulatory Activity Relevant to This sBLA

Date	Meeting Type	Comments
09/30/2013	Agreed iPSP	• Inclusion of 12 – 18-year-old patients in the adult development program. • Further pediatric studies including a subsequent PK trial, dose-ranging trial, confirmatory efficacy trial and open-label safety trial in children 5 to 11 were deferred until more efficacy and safety was obtained from the adult and adolescent population. • Plan to request a waiver for children < 5 years of age.
11/14/2017	Original Approval (PFS) and PREA PMR established	Approved for add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. PFS approved for healthcare provider administration. PREA PMR 3287-1 established to conduct open-label PK, PD study of benralizumab in pediatric patients 6 to 11 years of age with a continued safety evaluation out to a minimum of 48 weeks.
10/03/2019	Approval of AI	AI presentation approved for home administration.

Source: Clinical Review
Abbreviations: AI, autoinjector; iPSP, initial pediatric study plan; PFS, pre-filled syringe; PREA, Pediatric Research Equity Act; PMR, Post marketing Requirement

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspections were not deemed necessary for this supplement because the benralizumab program was a multicenter trial with each site enrolling a small number of subjects.

4.2. Product Quality

With this supplement, the Applicant introduced a new dosage strength of benralizumab (10mg/0.5mL) solution in a single-dose PFS. Cross-reference is made to the original BLA for the chemistry, manufacturing, and control drug substance information as there are no changes to the drug substance with this application. The data provided in the supplement support the conclusion that the proposed control strategy for the new presentation combined with in-process, release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. However, recent surveillance inspections of the drug product manufacturer, (b) (4) listed in this application, revealed significant quality concerns with the facilities. Until these issues can be resolved, the Office of Process and Facilities recommends that this application receive a Complete Response. Refer to the separate product quality reviews for additional details.

4.3. Devices and Companion Diagnostic Issues

The Applicant is proposing to add a new 10 mg/0.5 mL prefilled syringe for a dosage strength of 10 mg for pediatric patients (6 to 11 years of age) who weigh less than 35 kg. The dose for pediatric patients aged 6 to 11 who weighted ≥ 35 kg (30 mg) is already available as prefilled syringe and autoinjector as this is the same dose/presentation used for adults and adolescents ≥ 12 years of age. Device design verification and biocompatibility study results and assessments were reviewed by OBP and found to be acceptable.

An information request was sent to the Applicant regarding the proposed prescribing information for their PFS product, specifically, limiting the dosage of 10mg to be administrated to patients only by healthcare providers. The Applicant stated the rationale for limiting administration of the PFS to healthcare providers was that in the phase 3 study (TATE), administration of benralizumab was solely given by healthcare provider. The 30 mg PFS is also limited to healthcare provider administration.

A CDRH review was requested to provide feedback whether the needle length in the autoinjector and prefilled syringe would allow for reliable administration of the product subcutaneously (and not intramuscularly) in patients 6 to 11 years of age. CDRH requested additional information from the Applicant to support the use of the prefilled syringe and

autoinjector in patients 6 to 11 years of age. The Applicant noted the prefilled syringe nominal needle length is 12.7 mm (10.7 mm – 13.7 mm), which is standard for injectable biologics for pediatric asthma (6 years and older). They referenced omalizumab, mepolizumab, and dupilumab, which have the same nominal needle length (12.7 mm) for their prefilled syringes approved for use in patients 6 years and older. They also noted that the pre-filled syringe is only for administration by a healthcare provider who will determine the appropriate injection depth for subcutaneous injection. Prefilled syringes are also administered at a < 90-degree angle to accommodate subcutaneous injection. For the autoinjector, the nominal needle length is 6 mm. Design verification testing results for the autoinjector needle injection depth yielded a range of 6.2 mm – 6.6 mm, with an average 6.4 mm. The mean skin plus subcutaneous tissue depth of patients 2 to 13 years of age is reported to be 4.89 to 7.98 mm for the arm, thigh, and abdomen injection sites (6). Autoinjectors are administered at 90-degree angle. The 6 mm nominal needle length is the same as other approved autoinjectors for use in pediatric patients down to 2 years of age (pegfilgrastim-cbqv; biosimilar to neulasta, adalimumab-aaty; biosimilar to humira, adalimumab-aqvh; biosimilar to humira). Overall, we agree this supports the subcutaneous administration of the 10 mg and 30 mg prefilled syringe and 30 mg autoinjector in patients 6 to 11 years of age.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology or toxicology studies were provided in the current supplement that proposes to extend treatment down to patients 6 years of age. All nonclinical studies were reviewed with the original BLA submission. The Applicant's nonclinical program included studies with juvenile monkeys that provide adequate nonclinical support for treatment down to patients 6 years of age.

6. Clinical Pharmacology

6.1. Executive Summary

Benralizumab is a humanized, afucosylated IgG1 kappa monoclonal antibody that targets IL-5Rα. The IL-5Rα is expressed on the surface of eosinophils and basophils. Binding of benralizumab to IL-5Rα leads to apoptosis of cells through antibody-dependent cell-mediated cytotoxicity (ADCC). Benralizumab was originally approved in 2017 for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. At the time of approval, a post-marketing requirement (PMR 3287-1) was established to conduct a PK and PD study in pediatric patients aged 6 to 11 years. The current supplement intends to fulfill PMR 3287-1 and provide data supporting extension of the indication for patients aged 6 to 11 years. The approved and proposed dosage regimens are summarized below:

Table 3. Approved and Proposed Dosage Regimens for Benralizumab

Age Group	**Approved Dosage Regimen**
Adults and adolescents 12 years and older	• Administer by subcutaneous injection • Recommended dose is 30 mg Q4W for the first 3 doses, followed by Q8W thereafter
Age Group	**Proposed Dosage Regimen**
6 to 11 years, ≥ 35 kg	• Administer by subcutaneous injection • Recommended dose is 30 mg Q4W for the first 3 doses, followed by once Q8W thereafter
6 to 11 years, < 35 kg	• Administer by subcutaneous injection • Recommended dose is 10 mg Q4W for the first 3 doses, followed by once Q8W thereafter

Source: Approved and proposed labeling for FASENRA [benralizumab]

This supplement was supported by data from one 48-week, open-label, phase 3, PK, PD, and safety study in pediatric patients with severe eosinophilic asthma (D3250C00025, the TATE Study). The study enrolled and treated 30 pediatric patients 6 to 14 years of age, including 28 patients 6 to 11 years of age (overall median [range] age = 9.0 [6, 13] years). The study enrolled 15 subjects weighing < 35 kg (median [range] = 27.3 [20.3, 34.2] kg), and 15 subjects weighing ≥ 35 kg (median [range] = 48.0 [35.0, 77.7] kg). The Applicant also submitted a population PK report, a bioanalytical method validation addendum, and in-study bioanalytical reports for quantitation of PK, PD, and anti-drug antibodies (ADAs).

PK results from the TATE study indicate that benralizumab exposures in pediatric patients aged 6 to 11 years and weighing < 35 kg who received a dose of 10 mg had comparable drug exposure to adult and adolescent patients receiving the approved 30 mg dose following the same dosing regimen. Pediatric patients 6 to 11 years and weighing ≥ 35 kg who received a dose of 30 mg had higher exposure to benralizumab, with median trough concentrations at Week 16 62% higher than that in adults and adolescents receiving the same dose and dosing regimen.

Despite this, trough concentrations in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg fell within those observed in adults and adolescents who received 30 mg Q4W for the entirety of the 1-year phase 3 studies (SIROCCO, CALIMA and ZONDA; in contrast to Q4W x 3 doses and Q8W thereafter, referred to hereafter as Q8W). Median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W were 2.2-fold and 2.6-fold greater, respectively, than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. Median trough concentrations in adults and adolescents on the 30 mg Q4W regimen are also 1.6- to 1.9-fold greater than that assumed in adolescent patients weighing < 35 kg who would receive a dose of 30 mg irrespective of weight.

PD results based on changes in peripheral blood eosinophil counts indicated that the magnitude of blood eosinophil reduction from baseline was similar between pediatric patients 6 to 11 years of age and adults and adolescents, irrespective of weight group. The incidence of treatment-emergent anti-drug antibodies (ADAs) in the TATE study was 14.3% (4/28). The presence of ADAs is associated with lower trough benralizumab concentrations and impairment of blood eosinophil reduction. However, no evidence of an association of ADA status with safety was observed. Immunogenicity results were consistent with observations in adults and adolescents.

An inspection request consult sent to the Office of Study Integrity and Surveillance (OSIS) was declined as it was determined that an inspection is not needed for the bioanalytical site due to conduct of a remote regulatory assessment at that site in April 2022. No objectionable conditions with respect to PK sample analysis were reported. Refer to the Inspection Report Review by Adanma Oji in DARRTS dated July 31, 2023.

Recommendation: The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology information submitted under BLA 761070/S-020 and finds the BLA approvable, pending resolution of the CMC manufacturing site inspection issues in a subsequent review cycle.

Post-marketing requirement/Post-marketing commitment: None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following information is derived from the approved labeling for Fasenra (benralizumab):

Pharmacodynamics

Following subcutaneous administration of benralizumab at the recommended dose, blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/µL. This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period.

Clinical Pharmacokinetics

The pharmacokinetics of benralizumab was approximately dose-proportional in patients with asthma following subcutaneous administration over a dose range of 20 to 200 mg.

Following subcutaneous administration to patients with asthma, the absorption half-life was approximately 3.5 days. The estimated absolute bioavailability was approximately 59% and there was no clinically relevant difference in relative bioavailability in the administration to the abdomen, thigh, or arm.

The central and peripheral volume of distribution was 3.1 L and 2.5 L, respectively for a 70 kg individual. Benralizumab exhibited linear pharmacokinetics and no evidence of target receptor-mediated clearance pathway. The estimated typical systemic clearance was 0.29 L/d for a subject weighing 70 kg. Following subcutaneous administration, the elimination half-life was approximately 15.5 days.

The following information is derived from data submitted in the present sBLA:

PK in Pediatric Patients

Benralizumab PK following subcutaneous administration of 10 or 30 mg in patients 6 to 11 years old with severe asthma and with an eosinophilic phenotype was investigated in the initial 16-week treatment phase in an open-label trial. Among pediatric patients aged 6 to 11 years weighing < 35 kg who received 10 mg, the median trough concentration at Week 16 was similar to that of adults and adolescents who received 30 mg. Among pediatric patients aged 6 to 11 years weighing ≥ 35 kg who received 30 mg, the median trough concentration at Week 16 was 62% higher relative to adults and adolescents receiving the same dose, due to lower body weight in pediatric patients.

PD in Pediatric Patients

In a 48-week trial with patients 6 to 11 years who had severe asthma and with an eosinophilic phenotype, the magnitude of blood eosinophil reduction was similar to that observed in adults and adolescents. Median blood eosinophil levels at baseline were 400 and 340 cells/µL in patients weighing < 35 kg and ≥ 35 kg, respectively. Across all post-dose time points, median eosinophil counts reduced to 10 to 20 cells/µL in patients weighing < 35 kg, and to 20 to 30 cells/µL in patients weighing ≥ 35 kg. Blood eosinophil reduction was observed at the first time point, 4 weeks following the first dose, and was maintained throughout the treatment period.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed a weight-based dosing regimen in pediatric patients aged 6 to 11 years. A 10 mg dose is proposed for patients weighing < 35 kg, while a 30 mg dose is proposed for patients weighing ≥ 35 kg.

In the TATE study, Week 16 benralizumab trough concentrations were comparable in pediatric patients aged 6 to 11 years and weighing < 35 kg who received 10 mg Q8W and in adults and adolescents receiving the approved dosage of 30 mg Q8W. Week 16 benralizumab trough concentrations in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg who received 30 mg Q8W was 62% higher than that in adults and adolescents receiving the same dosage of 30 mg Q8W.

Although benralizumab exposure in pediatric patients weighing ≥ 35 kg was higher than that in adults and adolescents following the same dose and dosing regimen, concentrations in pediatric patients were lower than those in adults and adolescents receiving the 30 mg dose at the more frequent Q4W regimen. Median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W in prior phase 3 studies were 2.2-fold and 2.6-fold greater, respectively, than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. The observed median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W are also 1.6-fold and 1.9-fold greater, respectively, than that assumed in adolescent subjects weighing < 35 kg who may receive 30 mg Q8W under the current approved regimen.

Therapeutic Individualization

Body weight was identified as a significant allometric covariate affecting benralizumab clearance in population PK analysis (i.e., higher clearance with higher body weight leading to lower exposure in patients with higher body weight). The current approved Fasenra labeling notes that the PK of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population PK analysis, given that the difference of body weight between adults and adolescents is generally small. In addition, the observed reduction in blood eosinophil counts from baseline was similar between adolescents and adults following the same dose and dosing regimen.

A weight-based dosing regimen was implemented in the TATE study, including a dose of 10 mg for pediatric patients weighing < 35 kg, and a dose of 30 mg for pediatric patients weighing ≥ 35 kg. The doses evaluated in the TATE study are the same as those proposed for marketing. No additional therapeutic individualization has been proposed.

Outstanding Issues

From a clinical pharmacology perspective, there are no outstanding issues that would preclude approval of this BLA supplement.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant submitted data from one newly conducted clinical trial to support the use of benralizumab in pediatric patients 6 to 11 years of age. The TATE study was an open-label, parallel-group, PK, PD, and safety study conducted in pediatric subjects with severe eosinophilic asthma (peripheral blood eosinophil count of at least 150 cells/µL at baseline). Subjects entered a 48-week treatment period that was comprised of two parts:

Part A: 16-week treatment period to evaluate PK, PD, and safety
Part B: 32-week treatment period to evaluate safety.

In each cohort, benralizumab was administered SC every 4 weeks (Q4W) for the first three doses, and then every 8 weeks (Q8W) thereafter. Subjects were stratified by weight, < 35 kg or ≥ 35 kg, and allocated to receive benralizumab at a dose of 10 or 30 mg, respectively. The study enrolled 28 subjects aged 6 to 11 years, comprised of 15 subjects with body weight < 35 kg and 13 subjects with body weight ≥ 35 kg. For additional details on the design of the TATE study, refer to Section 15.3.1.

For subjects aged 6 to 11 years (6 to 11 years PK set), the median [range] age was 9 [6, 11] years. Among the 15 subjects with body weight < 35 kg who received the 10 mg dose, the median [range] body weight = 27.3 [20.3, 34.2] kg. For the 13 subjects with body weight ≥ 35 kg who received the 30 mg dose, the median [range] body weight = 48.0 [35.0, 77.7] kg.

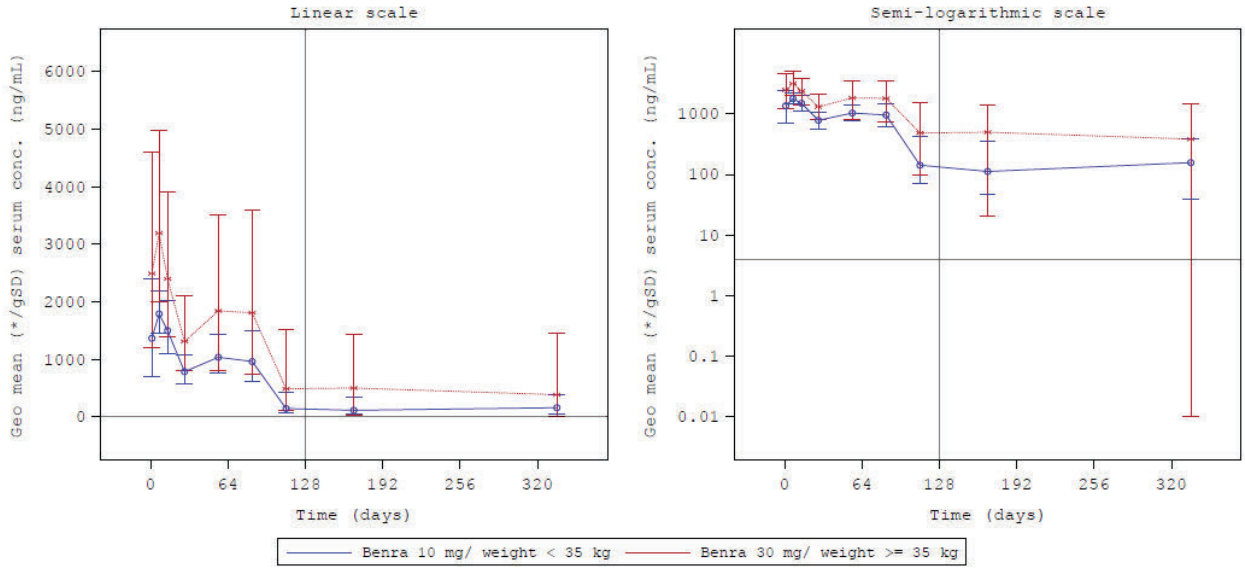
The distribution of baseline peripheral eosinophil counts was comparable across weight groups. Among patients aged 6 to 11 years, the median [range] eosinophil count was 400 [150, 1020] cells/µL for subjects weighing < 35 kg, and 340 [150, 1520] cells/µL for subjects weighing ≥ 35 kg.

Pharmacokinetics

In the TATE study, PK was evaluated as a primary objective. PK samples were collected pre-dose on Days 0, 28 (Week 4), 56 (Week 8), 112 (Week 16), and 168 (Week 24). Additional PK samples were collected on Days 1, 7, 14, 84, and 336 (Week 48).

Geometric mean concentration time profiles in pediatric patients 6 to 11 years of age throughout the 48-week treatment period are shown in Figure 1, separated by dose group. For all subjects, maximum serum concentrations of benralizumab were observed on Day 7. In both dose groups, trough concentrations declined beginning on Day 112 due to the switch in dosing frequency from Q4W to Q8W. Trough concentrations remain consistent from Day 112 through the remainder of the treatment period, indicating that benralizumab concentrations are at steady state when patients are transitioned from Q4W to Q8W dosing. Subjects weighing ≥ 35 kg who received a dose of 30 mg had higher mean benralizumab plasma concentrations at all time points relative to subjects weighing < 35 kg who received a dose of 10 mg.

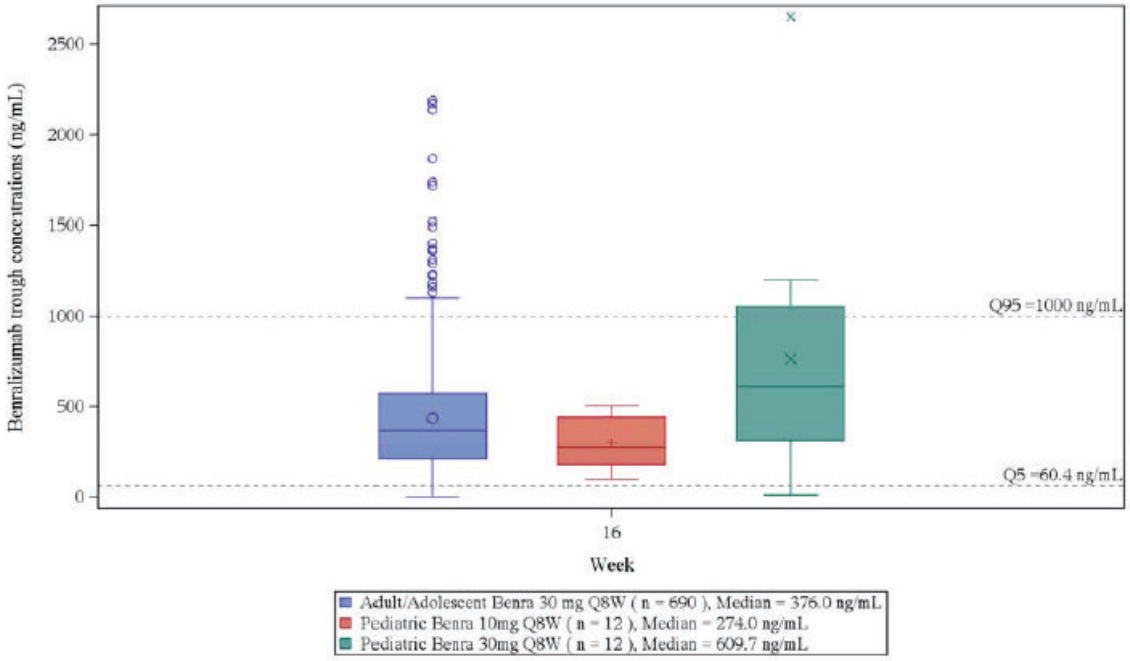
Figure 1. Geometric Mean (+/- SD) Serum Benralizumab Concentration Versus Time Profiles in Pediatric Patients 6 to 11 Years of Age by Dose Group in the Linear (Left) and Semi-Logarithmic (Right) Scales



Source: Figure 4, Clinical Study Report for TATE Study
Note: The lower limit of quantitation (LLOQ) = 3.86 ng/mL and is represented by the horizontal line

Trough concentrations at Week 16 for pediatric patients aged 6 to 11 years in each weight group was compared to observed Week 16 trough concentrations for adults and adolescents aged ≥ 12 years receiving the approved dosage of 30 mg Q8W (Figure 2 and Table 4). Data in adults and adolescents were derived from phase 2 and phase 3 studies submitted to support approval of the original BLA for benralizumab, including SIROCCO (D3250C00017), CALIMA (D3250C00018), and ZONDA (D3250C00020). Anti-drug antibodies (ADAs) to benralizumab are known to impact the PK of benralizumab. Therefore Week 16 trough concentrations were compared only amongst subjects negative for ADAs.

Figure 2. Boxplots of Week 16 Benralizumab Trough Concentrations by Age and Dose Group in ADA-Negative Subjects



Source: Figure 1, Response to Clinical Pharmacology IR, BLA 761070 SDN 990
Note: Q5 and Q95 were defined based on adult and adolescent C_{trough} at Week 16. Individual concentrations below LLOQ (3.86 ng/mL) are set to LLOQ for plotting purposes. Subjects who were ADA-positive at any timepoint were excluded.
Abbreviations: Q5, 5th percentile; Q95, 95th percentile

Table 4. Summary Statistics of Week 16 Benralizumab Trough Concentrations in ADA-Negative Adult and Pediatric Subjects

PK parameter	Summary statistic	Adult/Adolescent Benra 30 mg Q8W (N=774)	Pediatric Benra 10 mg Q8W (N=12)	Pediatric Benra 30 mg Q8W (N=12)
Ctrough (ng/mL)	n	690	12	12
	n<LLOQ (%) (a)	0	0	0
	Geometric Mean	315.31	266.80	447.38
	Geometric CV (%)	130.91	58.53	260.81
	Geometric SD	2.72	1.72	4.19
	Arithmetic Mean	435.15	301.40	763.87
	SD	313.19	142.49	698.34
	Median (Min, Max)	376.00 (1.93, 2190.00)	273.96 (96.09, 502.33)	609.72 (9.02, 2650.97)

Source: Table 1, Response to Clinical Pharmacology IR, BLA 761070 SDN 990
Note: Subjects who were ADA-positive at any timepoint were excluded.

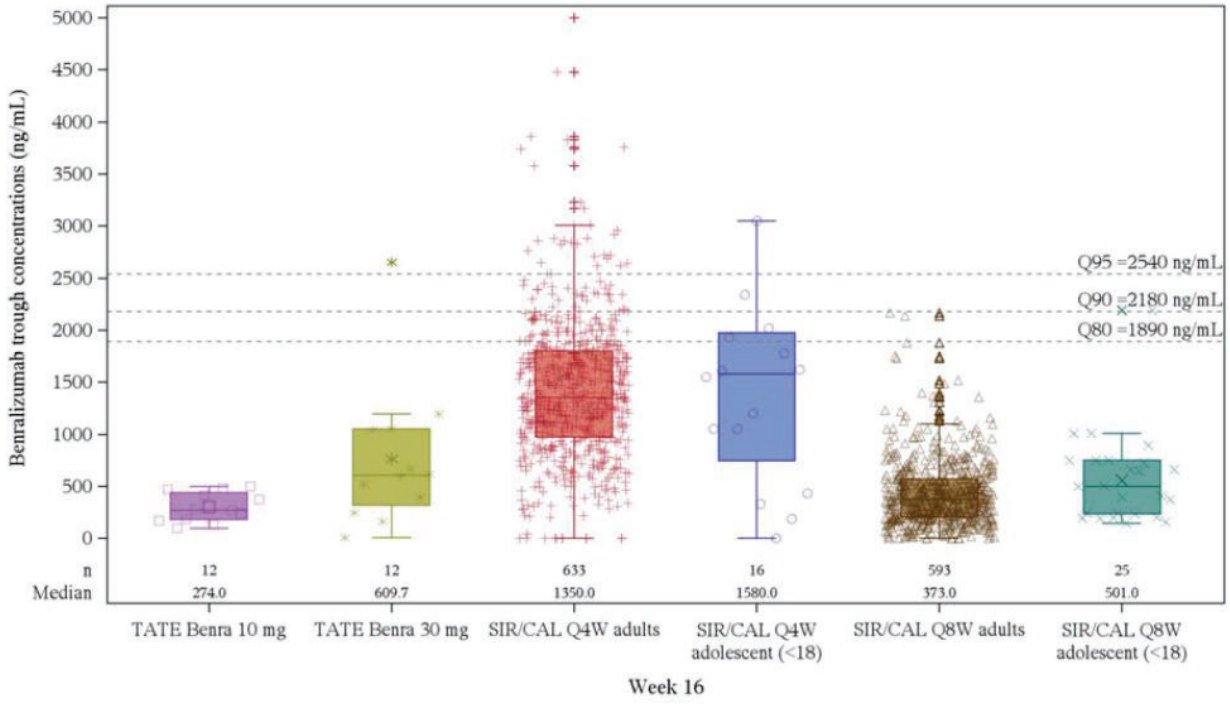
Week 16 benralizumab mean/median trough concentrations were comparable in pediatric patients aged 6 to 11 years and weighing < 35 kg who received 10 mg Q8W and in adults and adolescents receiving the approved dosage of 30 mg Q8W. Median trough concentrations in pediatric patients receiving 10 mg were 27% lower relative to adults and adolescents receiving 30 mg. However, all ADA-negative pediatric patients in this group had trough concentrations that fell within the reference range defined by the 5^{th} and 95^{th} percentiles derived from data in adults and adolescents.

In contrast, Week 16 benralizumab median trough concentrations in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg who received 30 mg Q8W was 62% higher than that in adults and adolescents receiving the same dosage of 30 mg Q8W. Among ADA-negative pediatric subjects in the 30 mg dose group, 5/12 (41.7%) had trough concentrations that fell outside of the adult/adolescent reference range.

The proposed maintenance dosage for pediatric patients aged 6 to 11 years and weighing ≥ 35 kg is 30 mg Q8W, the same as that evaluated in the TATE study. PK results indicated that benralizumab median trough concentrations at Week 16 were 62% higher relative to that in adults and adolescents aged 12 years and older who received the same dosage. The data are sufficient to support extrapolation of efficacy in pediatric patients based on achieving equivalent or higher benralizumab exposures to that in adults/adolescents.

In phase 3 studies supporting approval of the original BLA, SIROCCO, CALIMA, and ZONDA, a proportion of adult (all trials) and adolescent (SIROCCO and CALIMA only) subjects were randomized to receive 30 mg benralizumab at a higher dosing frequency of Q4W throughout the treatment period, in contrast to the approved regimen consisting of receiving the initial three doses Q4W followed by a transition to Q8W dosing. To support safety in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg, Week 16 trough concentrations of benralizumab were examined in ADA-negative adult and adolescent subjects enrolled in studies SIROCCO and CALIMA. Boxplots of Week 16 trough concentrations across dose and age groups by study are shown in Figure 3.

Figure 3. Boxplots of Week 16 Benralizumab Trough Concentrations by Age and Dose Group in ADA-Negative Adult, Adolescent, and Pediatric Subjects



Source: Figure 1, November 8, 2023 Response, BLA 761070 SDN 1066
Note: The horizontal reference lines represent quantiles from pooled Week 16 plasma concentration data in studies SIROCCO and CALIMA among subjects receiving the 30 mg Q4W regimen. TATE Benra 10 mg = pediatric subjects aged 6 to 11 years and weighing < 35 kg. TATE Benra 30 mg = pediatric subjects aged 6 to 11 years and weighing ≥ 35 kg.
Abbreviations: Q80, 80th percentile; Q90, 90th percentile; Q95, 95th percentile; SIR/CAL, SIROCCO/CALIMA

Median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W in SIROCCO and CALIMA were 2.2-fold and 2.6-fold greater, respectively, than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. In ZONDA, the median trough concentration at Week 16 across all adults (regardless of ADA status) was 1530 ng/mL, which is about 2.5-fold greater than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. Thus, controlled safety data in adults and adolescents who received 30 mg Q4W may support the safe use of 30 mg Q8W benralizumab in pediatric patients 6 to 11 years of age weighing ≥ 35 kg.

Per the current approved dosage regimen for benralizumab, all adolescent patients aged 12 years and older will receive 30 mg Q8W irrespective of weight. Thus, adolescents with body weight < 35 kg would receive a dose of 30 mg. As shown in Table 4 and Figure 3, the observed Week 16 median trough concentration in ADA-negative pediatric patients aged 6 to 11 years and weighing < 35 kg is 274 ng/mL. Assuming dose proportionality (the current approved labeling for Fasenra indicates dose proportionality from 20 to 200 mg), the estimated Week 16 trough concentration if these subjects received a 30 mg dose is 822 ng/mL (274*3). This assumed value is 1.3-fold greater than the observed median for pediatric patients weighing ≥ 35 kg (610 ng/mL) and 2.2-fold greater than the observed median for adults/adolescents receiving 30 mg Q8W (376 ng/mL). However, this estimated median trough concentration still falls below the observed median trough concentration in adults and adolescents who received

30 mg Q4W. The observed median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W are 1.6-fold and 1.9-fold greater, respectively, than that assumed in adolescent subjects weighing < 35 kg who receive 30 mg Q8W.

Review of safety data in adult and adolescent subjects who received 30 mg Q4W is deferred to the clinical review. Refer to Section 8 for additional discussion on safety.

Pharmacodynamics

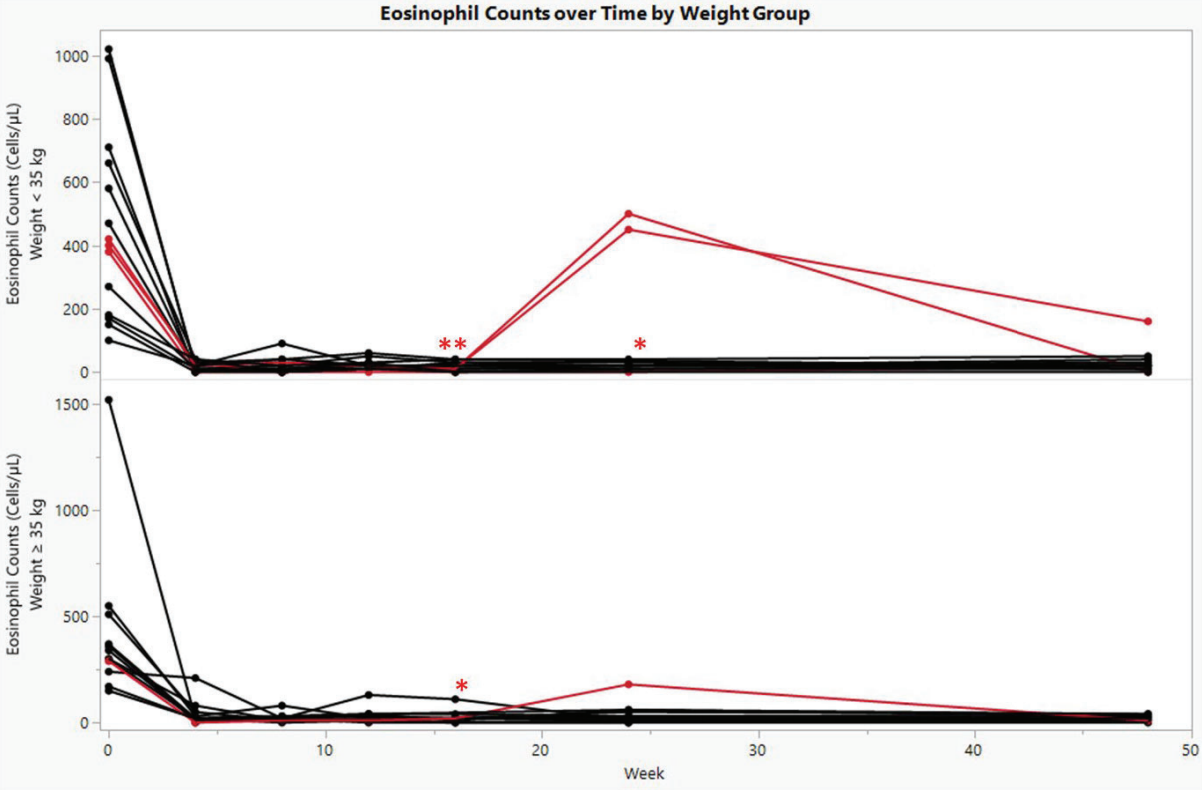
In the TATE study, PD was assessed as a primary objective based on measurements of peripheral blood eosinophil counts over time. PD analysis was conducted as part of the standard hematology assessment (complete blood count [CBC] with differential). Samples were collected at baseline and post-dose at Weeks 4, 8, 12, 16, 24, and 48.

Individual eosinophil counts over time by weight group are shown in Figure 4. In both weight groups, eosinophils were nearly ablated, observed beginning at the first post-dose time point (Week 4). Pediatric patients weighing < 35 kg had a median eosinophil count of 400 cells/µL at baseline, which was reduced to a median value of 10 to 20 cells/µL across all post-dose time points. Pediatric patients weighing ≥ 35 kg had a median eosinophil count of 340 cells/µL at baseline, which was reduced to a median value of 20 to 30 cells/µL across all post-dose time points.

Per the approved labeling for Fasenra, it is noted that in phase 3 studies SIROCCO and CALIMA conducted at the approved dose, blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/µL beginning at the first observed time point (4 weeks of treatment) and maintained throughout the treatment period.

The data thus indicate that observed reductions in peripheral blood eosinophils from baseline are comparable between pediatric patients aged 6 to 11 years and adults and adolescents.

Figure 4. Eosinophil Counts Over Time in Pediatric Patients 6 to 11 Years of Age by Weight Group



Source: Reviewer-generated plot using adlb dataset
Note: Individual data are shown. Time profiles in red represent individual subjects that developed anti-drug antibodies (ADAs) during the treatment period. Asterisks represent the time points of first ADA detection.

The impact of immunogenicity on eosinophil counts will be discussed in the following section on immunogenicity.

Immunogenicity

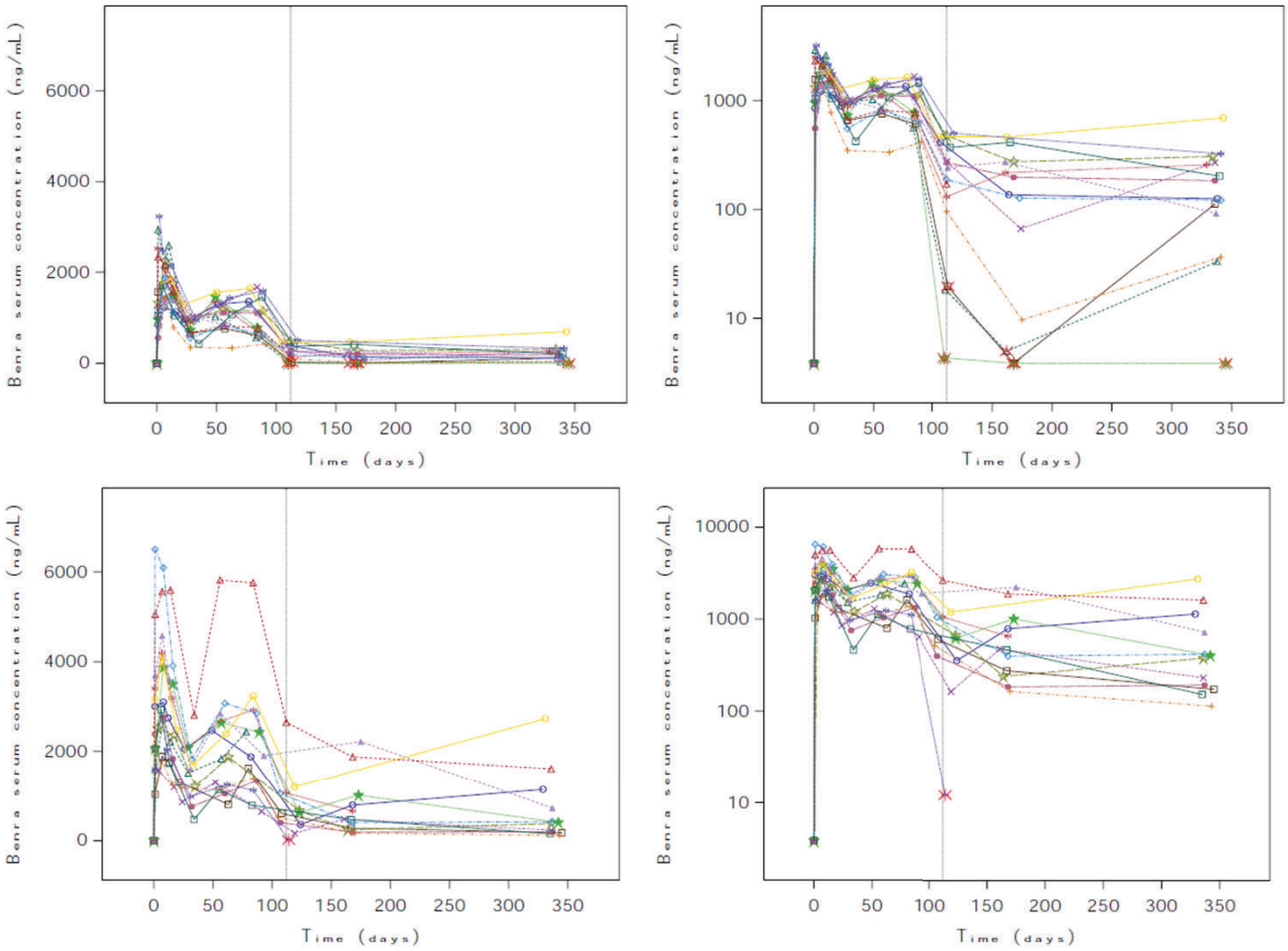
In the TATE study, immunogenicity was assessed as a secondary objective. Samples for assessment of ADAs were collected pre-dose on Day 0 and Weeks 8, 16, and 24. An additional sample was collected at Week 48.

Out of 28 subjects, 4 (14.3%) developed ADAs to benralizumab. This includes 3 subjects with body weight < 35 kg, and one subject with body weight ≥ 35 kg. All subjects were also positive for neutralizing antibodies (nAbs). Seroconversion occurred at either Week 16 (n = 3) or Week 24 (n = 1). For 3 out of 4 subjects, ADAs were transient. In these three subjects, ADA titers were relatively low, with titers ≤ 1:200. One subject with body weight < 35 kg was noted to have a positive ADA response at Weeks 16, 24, and 48. ADA titers in this subject were greater than in subjects with transient ADAs, with titers up to 1:3200 observed at Weeks 24 and 48. Per the current approved labeling for Fasenra, treatment-emergent ADAs developed in 13% of patients treated with the recommended dosing regimen during the 48- to 56-week treatment period. Thus, the incidence of ADAs is consistent between pediatric patients 6 to 11 years of age and adults and adolescents.

Impact of Immunogenicity on PK

Individual concentration-time profiles factoring in the effect of ADAs are shown in Figure 5. Despite the low incidence of developing ADAs to benralizumab, ADAs appear to impact observed benralizumab concentrations. Subjects positive for ADAs (indicated by the red asterisks) have lower trough concentrations relative to subjects who did not develop ADAs. In addition, data in two subjects indicates a rebound in benralizumab concentrations after seroconverting back to an ADA-negative status. Median benralizumab trough concentrations at Week 16 by ADA status are shown in Table 5. Based on limited available data, median trough concentrations at Week 16 were 93 to 98% lower in ADA-positive subjects relative to ADA-negative subjects.

Figure 5. Individual Concentration-Time Profiles and ADA Status in Pediatric Patients Weighing < 35 kg (Top) or ≥ 35 kg (Bottom) in the Linear (Left) or Semi-Logarithmic (Right) Scales



Source: Figures 14.2.1.1 and 14.2.1.2, Clinical Study Report for TATE Study
Note: Plots on the top show data in pediatric patients 6 to 11 years of age weighing < 35 kg who received a 10 mg dose.Plots on the bottom show data in pediatric patients 6 to 11 years of age weighing ≥ 35 kg who received a 30 mg dose. Concentrations in plots at the left panels are in linear scale. Concentrations in plots at the right panels are in log scale. Red asterisks indicate ADA positive time points for individual subjects.

Table 5. Median (Range) Benralizumab Concentrations (ng/mL) at Week 16 in Pediatric Patients Aged 6 to 11 Years by ADA Status

	N	Weight < 35 kg 10 mg	N	Weight ≥ 35 kg 30 mg
ADA-Negative	12	274 (96.1, 502)	12	610 (9.02, 2651)
ADA-Positive	3	18.3 (4.32, 19.6)	1	12.3

Source: Table 1, Response to Clinical Pharmacology IR, BLA 761070 SDN 990; and Table 14.2.1.1, Clinical Study Report for TATE Study
Note: ADA-positive refers to subjects who developed ADAs at any time point. Note that in 3 out of 4 pediatric subjects, ADAs developed beginning at Week 16. One subject with body weight < 35 kg did not develop ADAs until Week 24.

Per the approved labeling for Fasenra, anti-benralizumab antibodies were associated with increased clearance of benralizumab (lower exposure). In the original clinical pharmacology review for benralizumab, the geometric mean C_{trough} value from ADA-positive subjects in phase 3 was 5% of that from ADA-negative subjects (refer to clinical pharmacology review in DARRTS dated July 17, 2017, reference ID 4125440). This behavior is consistent with observations in pediatric patients 6 to 11 years of age.

Impact of Immunogenicity on PD

Individual time profiles for blood eosinophils factoring in the effect of ADAs are shown in Figure 4. In 3 out of 4 ADA-positive subjects, impairment of blood eosinophil reduction was observed after ADA detection. No apparent impact to blood eosinophils was observed in one ADA-positive subject with ADAs detected at Week 24. It is possible that the impact of immunogenicity on eosinophils was missed in this subject since the next eosinophil measurement was not taken until Week 48.

The approved labeling for Fasenra indicates that anti-benralizumab antibodies were associated with increased blood eosinophil levels compared to antibody-negative patients. Thus, the impacts on PD observed in pediatric patients aged 6 to 11 years is consistent with prior observations in adults and adolescents.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The submission includes data from one clinical trial, the TATE study, to support the use of benralizumab in pediatric patients aged 6 to 11 years. The TATE study was conducted in an open-label manner. As a result, the primary objectives of the study were to evaluate PK, PD, and safety. Evaluations of clinical outcomes were secondary objectives based on measures of pulmonary function, asthma symptoms, and other asthma control metrics. Refer to Section 8 for assessment of efficacy in the TATE study.

Efficacy in pediatric patients aged 6 to 11 years was extrapolated based on demonstrating similar or higher benralizumab exposures compared to that of adults and adolescents receiving the approved dose of 30 mg. Similar drug exposure as in adults and adolescents was achieved in pediatric patients aged 6 to 11 years and weighing < 35 kg who received a dose of 10 mg. Patients 6 to 11 years and weighing ≥ 35 kg who received a dose of 30 mg had higher drug exposure, with median Week 16 trough concentrations about 1.6-fold greater than that in adults and adolescents.

The magnitude of peripheral blood eosinophil reduction was also found to be similar between pediatric patients 6 to 11 years of age and adults and adolescents, irrespective of weight group. PD results provide additional supportive evidence of effectiveness.

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

Week 16 benralizumab trough concentrations were comparable in pediatric patients aged 6 to 11 years and weighing < 35 kg who received 10 mg Q8W and in adults and adolescents receiving the approved dosage of 30 mg Q8W. Week 16 benralizumab trough concentrations in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg who received 30 mg Q8W was approximately 62% higher than that in adults and adolescents receiving the same dosage of 30 mg Q8W.

Although benralizumab exposure in pediatric patients weighing ≥ 35 kg was higher than that in adults and adolescents at the same dose, concentrations in pediatric patients were lower than those in adults and adolescents receiving the 30 mg dose at the more frequent Q4W regimen in phase 3 trials SIROCCO and CALIMA. Median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W in prior phase 3 studies were 2.2-fold and 2.6-fold greater, respectively, than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. The observed median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W are also 1.6-fold and 1.9-fold greater, respectively, than that assumed in adolescent subjects weighing < 35 kg who may receive 30 mg Q8W.

Thus, controlled safety data in adults and adolescents who received 30 mg Q4W may support the safe use of 30 mg Q8W benralizumab in pediatric patients 6 to 11 years of age weighing ≥ 35 kg as well as in adolescents aged 12 to < 18 years and weighing < 35 kg who would still receive a 30 mg dose, consistent with the approved dosing regimen. Review of safety data in adult and adolescent subjects who received 30 mg Q4W is deferred to the clinical review. Refer to Section 8 for additional discussion on safety.

From a clinical pharmacology perspective, the proposed dosage regimens are appropriate for the general patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Per the approved labeling for Fasenra, the PK of benralizumab is not affected by age, gender, race, mild and moderate renal impairment, and baseline hepatic function biomarkers (ALT, AST, and bilirubin).

Population PK analysis identified body weight as a significant covariate affecting the clearance of benralizumab with a near allometric effect (i.e., higher clearance with higher body weight leading to lower exposure in patients with higher body weight). The Fasenra labeling notes that the PK of benralizumab in adolescents 12 to 17 years of age were consistent with adults based on population PK analysis and the reduction in blood eosinophil counts was similar to that observed in adults following the same treatment.

A weight-based dosing regimen was implemented in the TATE study, including a dose of 10 mg for pediatric patients weighing < 35 kg, and a dose of 30 mg for pediatric patients weighing ≥ 35 kg. The doses evaluated in the TATE study are the same as those proposed for marketing.

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

Benralizumab is administered via SC injection. Therefore, there are no clinically relevant food-drug interactions. Per the current approved labeling for Fasenra, no formal drug interaction studies have been conducted with benralizumab. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of benralizumab. There is no evidence of IL-5Rα expression on hepatocytes and eosinophil depletion does not produce chronic systemic alterations of proinflammatory cytokines. The labeling also indicated that based on population analysis, commonly co-administered medications had no effect on benralizumab clearance in patients with asthma. No new data was submitted in this sBLA regarding drug-drug interactions

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The sources of clinical data used in this review are summarized in Table 6 below.

Table 6 Clinical Trials Relevant to This sBLA

Trial Identity	Trial Design	Regimen (mg)	Study Endpoints	Treatment Duration	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Phase 3 Studies to Support Efficacy and Safety							
TATE Study D3250 C00025	Open label, single arm	**Part A:** • (<35kg) 10mg SC Q4W x 3 and Q8W thereafter • (≥35kg) 30mg SC Q4W x 3 and Q8W thereafter	Safety, PK, PD	16 weeks	39 screened 28 treated 15 patients <35kg 13 patients ≥ 35kg	6 to < 11 years of age*	17 sites US and Japan
		Part B: Same doses	Safety	32 weeks			

Source: TATE clinical study report (CSR), section 9 p25
Note: *Two additional subjects aged 12-14 years were enrolled in the study from Japan
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetic; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous

7.2. Review Strategy

This supplement review contains one trial (TATE) evaluating PK, PD, and safety endpoints in subjects 6 to 11 years of age. The clinical review was conducted by one primary clinical reviewer and one statistical reviewer. Efficacy was evaluated under the original BLA (approved Nov 2017) for ages 12 years and older. TATE was not designed or powered to detect significant

changes in the clinical assessments, but the trial had secondary efficacy endpoints and exploratory patient reported outcome endpoints that are briefly discussed in Section 8.1.1.3.4 and 8.1.1.4.3.

TATE included two patients enrolled in sites in Japan who were 13 years of age. Those patients were excluded from the safety review tables and labeling given that their age is not within the range of the new proposed indication. The safety data for these two patients was reviewed and comments are included where applicable.

For the evaluation of safety, the primary clinical reviewer analyzed data from TATE using JMP, JMP Clinical, and Analysis Studio. The safety results presented in Section 8.1.1.4.4 represent the primary clinical reviewer's own analyses.

Additionally, Internal FDA Subject Matter Expert (SME) Team assisted in the independent production of tables through commonly used clinical data review tools, including production of specialized tables. This service included review of tables provided by the Applicant with an in-depth assessment of the clinical data.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. TATE Trial (Study D3250C00025)

8.1.1.1. Administrative Information

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

Study Dates: First patient enrolled: November 21, 2019; last patient last visit: September 12, 2022

Study Sites: This study was performed at 17 sites in the United States and Japan.

Study Report Date: February 21, 2023

8.1.1.2. Objectives

Primary Objectives

To evaluate the PK of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma.

To evaluate the PD of benralizumab administered SC in children from 6 to 11 years of age with severe eosinophilic asthma.

Secondary Objectives

To characterize the PK of benralizumab.

To evaluate the immunogenicity of benralizumab.

To evaluate the effect of benralizumab on pulmonary function.

To assess the effect of benralizumab on asthma symptoms and other asthma control metrics.

Safety Objective

To assess the safety and tolerability of benralizumab

Exploratory Objective

To evaluate exacerbations experienced

8.1.1.3. Study Design

8.1.1.3.1. Trial Design

This is an open-label, parallel group (two weight-based treatment groups) study designed to evaluate the PK and PD, and long-term safety of benralizumab administered SC in children from 6 to 11 years of age with severe asthma, and with an eosinophilic phenotype. Following

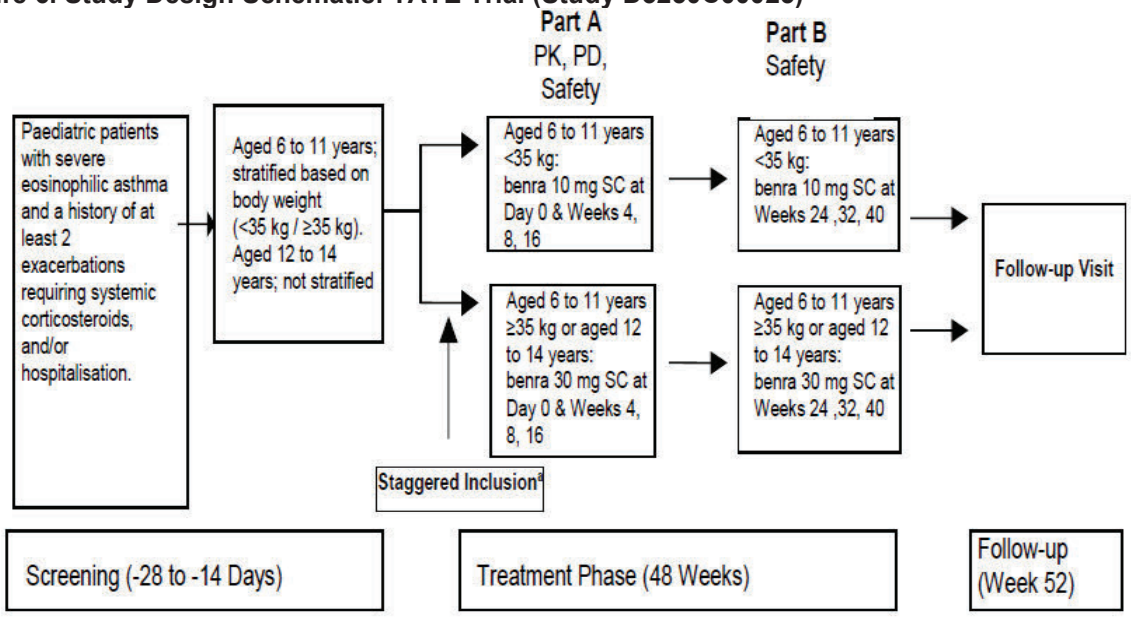
informed consent, subject aged 6 to 11 years of age were stratified by body weight at screening (<35 kg/ ≥35 kg). Patients with a body weight <35 kg at screening received 10 mg administered by SC injection. Patients with body weight ≥35 kg at screening received 30 mg administered by SC injection. All subjects received doses Q4W x 3 doses, followed by Q8W through Week 40.

The study was conducted in 2 parts, Part A and Part B. Part A consisted of 16 weeks of treatment to evaluate the PK and PD, and safety of benralizumab. Part B consisted of 32 weeks of continued treatment to evaluate the safety of benralizumab. All study data was summarized together.

After initial enrollment and confirmation of entry criteria, patients entered a screening period of up to 28 days. Patients who met eligibility criteria entered the 48-week treatment period. Patients were maintained on their currently prescribed asthma maintenance therapy(ies) without change, from enrollment through screening, and through the treatment period.

The total duration of the study for most patients was up to 56 weeks and included a screening period of up to 28 days, a treatment period of 48 weeks, and a safety follow-up visit at Week 52. A schematic of the trial design and table of the trial assessments are shown below in Figure 6 and Table 7.

Figure 6. Study Design Schematic: TATE Trial (Study D3250C00025)



[a] After the first 4 patients in each weight group have completed Part A (after evaluation of the PK and safety from Part A in these patients by the safety review committee), the remaining patients within the weight group will enter the treatment phase.

Source: TATE Trial protocol, figure 1, p344

Table 7. Schedule of Assessments

	Part A – PK, PD, Safety									Part B- Safety					DXD/ WD
Visit Visit windows	1 SCRN Days −28 to -14	2	3 +1 day	4 ±3 day	5 ±4 day	6 ±7 day	7 ±7 day	8 ±7 day	9 ±7 day	10 ±7 day	11 ±7 days	12 ±7 days	13 EOT ±7 day	14 F/U ±7 day	
Week	-	0	0	1	2	4	8	12	16	24	32	40	48	52	-
Day	-	0	1	7	14	28	56	84	112	168	224	280	336	362	-
Written informed consent/assent	X														
Inclusion/ exclusion criteria	X	X													
ACQ-IA	X	X		X	X	X	X	X	X	X	X	X	X	X	X
PGIC-IA									X	X	X		X		X
CGIC									X	X	X		X		X
Body weight and height	X								X	X			X		X
Patient stratification	X														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/surgical history	X	X													
12-lead ECG	X								X				X		X
Complete PE (pre-dose)	X	X							X				X		X
Brief PE (pre-dose)						X	X	X		X	X	X			
FEV_1	X	X				X	X	X	X	X			X		X
Clinical chemistry assessments	X[a]	[a]				X	X	X	X	X			X		X
Haematology (CBC + differential)	X[a]	[a]				X	X	X	X	X			X		X
Serology (hepatitis B, C, HIV)	X														
Urinalysis	X					X	X	X	X	X			X		X
Pregnancy test	X	X[b]				X[b]	X[b]	X	X[b]	X[b]	X[b]	X[b]	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Asthma exacerbation			X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sampling		X[b]	X	X	X	X[b]	X[b]	X	X[b]	X[b]			X		X
ADA sampling		X[b]					X[b]		X[b]	X[b]			X		X
Single-dose IP injections		X				X	X		X	X	X	X			

[a] The screening clinical chemistry/haematology samples at Visit 1 (Day -28 to Day -14) will constitute baseline values provided that Visit 2 (Day 0) is done ≤ 28 days after Visit 1. If so, no safety laboratory samples will need to be collected at Visit 2.

[b] To be performed before IP is administered at these visits.

Abbreviations: ACQ-IA interviewer-administered asthma control questionnaire, ADA anti-drug antibody(ies), CBC complete blood count, CGIC clinician global impression of change, DXD early discontinuation, ECG electrocardiogram, exam examination, EOT end of treatment, FEV_1 forced expiratory volume in 1 second, F/U follow-up, HIV human immunodeficiency virus, IP investigational product, PD pharmacodynamics, PE physical examination, PGIC-IA interviewer administered patient global impression of change, PK pharmacokinetics, SCRN screening, std standard, WD early withdrawal.

Source: TATE Trial protocol, Table 1, p337-339

8.1.1.3.2. Trial Population

The study population included pediatric subjects aged 6 to 11 years of age (≥ 15 kg) with a diagnosis of severe asthma and a peripheral blood eosinophil count ≥ 150 cells/µL, with either a previously confirmed history of ≥2 exacerbations requiring treatment with systemic steroids and/or hospitalizations in the last 12 months or the need for oral corticosteroid maintenance therapy for at least 3 of the last 12 months.

Key inclusion criteria

- Severe asthma for at least 12 months
- Previously confirmed history of ≥2 exacerbations requiring treatment with systemic steroids and or hospitalizations in the last 12 months or a persistent need for oral corticosteroid maintenance treatment to maintain asthma control for at least 3 of the last 12 months.
- Peripheral blood eosinophil count ≥ 150 cells/µL
- Requirement for regular treatment with medium or high dose ICS and at least 1 additional controller medication (long-acting beta-agonist (LABA), leukotriene receptor antagonist, long-acting anti-muscarinic agent, theophylline) for at least 3 months
- FEV1 (forced expiratory volume in 1 second) ≤110% predicted normal, or, FEV1/Forced Vital Capacity (FVC) ratio ≤0.8.

Key exclusion criteria:

- Life-threatening asthma (e.g. requiring intubation)
- History of pulmonary disease other than asthma
- Malignant disease
- History of anaphylaxis to biologics
- Cardiac conditions, hepatitis, HIV, helminth parasitic infection within 24 weeks, abnormal liver test (≥1.5 times the ULN)
- Immunosuppressive therapy (methotrexate, cyclosporine, IM long-acting depot corticosteroid) within 3 months. Chronic maintenance corticosteroid for the treatment of asthma was allowed
- Ig or blood products within 30 days
- Marketed or investigational biologic within 4 months or 5 half-lives
- Receipt of live attenuated vaccines within 30 days
- Two subjects aged 13-years-old (weight ≥35 kg) from Japan were included in the study. Both patients were required to have the same inclusion criteria than younger patients to enroll the study and received the 30mg dose.

8.1.1.3.3. Treatment

Patients with a body weight <35 kg at screening received the following regimen of benralizumab: 10 mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by 10 mg at Weeks 24, 32, and 40 (Part B). Patients with a body weight ≥35 kg at

screening received the following regimen of benralizumab: 30 mg administered by SC injection at Day 0 and Weeks 4, 8, and 16 (Part A), followed by 30 mg at Weeks 24, 32, and 40 (Part B).

8.1.1.3.4. Study Endpoints

Primary Endpoints:

PK endpoints:

- Clearance.
- Area under concentration time curve to Day 28 (AUC0-28).
- Maximum serum concentration (Cmax).
- Terminal phase elimination half-life (t1/2).
- Time to reach Cmax (Tmax).

PD: Change from baseline in peripheral blood eosinophil count at Weeks 4, 8, 12 and 16 (Part A), and Weeks 24 and 48 (Part B).

Secondary Endpoints:

- Body weight-adjusted clearance**.**
- Presence of anti-benralizumab antibodies.
- Change from baseline in pre-dose (when applicable), pre-bronchodilator, FEV1 measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B).
- Change from baseline in ACQ-IA score, measured at screening and Weeks 1, 2, 4, 8, 12, and 16 (Part A), and Weeks 24, 32, 40 and 48, and at follow-up (Part B).
- PGIC-IA, measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B), and at the DXD (early discontinuation)/WD (early withdrawal) visit, and CGIC measured at Week 16 (Part A), Weeks 24, 32 and 48 (Part B) and at the DXD/WD visit.

Safety Endpoints:

Adverse events, vital signs, and collection of clinical chemistry/hematology parameters and urinalysis.

Exploratory Endpoints:

Annualized asthma exacerbation rate (AAER)

8.1.1.3.5. Efficacy Measurements

Annualized Asthma Exacerbation Rate (AAER)

An asthma exacerbation was defined by a worsening of asthma requiring the use of systemic corticosteroids (or an increase in oral steroid dose for those already on systemic corticosteroids) and/or an emergency department (ED) visit requiring the use of systemic corticosteroids and/or an in-patient hospitalization due to asthma.

Exacerbations experienced during the treatment period were summarized descriptively for each treatment/weight group, including the number of exacerbations associated with an emergency room visit or hospitalization.

For the production of summary statistics, the AAER was calculated using the time-based risk approach: AAER = 365.25*Total number of exacerbations /Total duration of at-risk treatment period (days)

Forced Expiratory Volume in 1 Second (FEV1)

Lung function (FEV1) at the study center was measured by spirometry using the site's own

equipment. Spirometry was performed by the investigator or authorized delegate, according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.

Multiple forced expiratory efforts (at least 3 but no more than 8) were performed for each center spirometry session and the 2 best efforts that meet the ATS/ERS acceptability and reproducibility criteria was recorded in the eCRF.

FEV1 was measured at Weeks 4, 8, 12, and 16 (Part A), and Weeks 24 and 48 (Part B).

Asthma Control Questionnaire-Interviewer Administered (ACQ-IA)

The Asthma Control Questionnarie-7 (ACQ-7) is a questionnaire designed to measure the adequacy of asthma control and change in asthma control. The questionnaire includes 7 items and requires a 1-week recall (for items on symptoms and rescue inhaler use). The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment) for six questions regarding symptoms and rescue use. The seventh component is the measured FEV1 percentage.

An interviewer-administered version of the ACQ, was developed for use with children aged ≥6 years (ACQ-IA), will be used in this study with the omission of item 7. The only difference between the ACQ-IA and the ACQ is the mode of administration. The ACQ-IA is administered by trained individuals according to standardized instructions to help the child understand concepts like "during the last week" and the 7-point scale. The estimated threshold indicating poor asthma control is an ACQ-IA score ≥1.25 in patients ages 6 to 17 years.

The questions include:

1. In general, during the past week, how much of the time did you wheeze?
2. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day?
3. In general, during the past week, how limited were you in your activities because of your asthma?
4. In general, during the past week, how much shortness of breath did you experience because of your asthma?
5. In general, during the past week, how much of the time did you wheeze?
6. On average, during the past week, how many puffs/inhalations of short-acting bronchodilator have you used each day?

The ACQ-IA (Interview Administered) has a multi-dimensional construct assessing symptoms (5 items administered by clinic staff to the child using the interviewer administer format), rescue bronchodilator use (query to child or parent), and FEV1% (1 item) completed by clinic staff. The ACQ-IA will be administered to subjects for whom an appropriate translation is available.

Interviewer-administered Patient Global Impression of Change (PGIC-IA)

The Patient Global Impression of Change (PGIC) question captures the patient's overall evaluation of response to treatment.

The patient is asked to report the degree to which they have changed since entering the treatment period using a 7-point scale ('Much Better', to 'About the same', to 'Much worse').

The questions include:

Since beginning treatment at this clinic, how would you describe the change (if any) in activity, limitations, symptoms, emotions and overall quality of life, related to your painful condition? (Select only ONE).

1. No change (or condition is worse)
2. Almost the same, hardly any change at all
3. A little better, but no noticeable change
4. Somewhat better, but the change has not made any real difference
5. Moderately better, and a slight but noticeable change
6. Better, and a definite improvement that has made a real and worthwhile difference
7. A great deal better, and a considerable improvement that has made all the difference

Clinician Global Impression of Change (CGIC)

This questionnaire captures the patient's overall evaluation of response to treatment from the perspective of the clinician.

The clinician is asked to report the degree to which they perceive the patient has changed since entering the treatment period using a 7-point scale ('Much Better', to 'About the same', to 'Much worse').

8.1.1.3.6. Safety Assessments

Safety monitoring included recording of treatment emergent adverse events (TEAEs), asthma exacerbation, physical exams, vital signs (temperature, heart rate, blood pressure (BP), respiratory rate(RR)), clinical laboratory tests (hematology, chemistry, liver function tests, coagulation, serology hepatitis B,C, HIV, urinalysis, pregnancy), 12-lead electrocardiogram (ECG), FEV1, and anti-drug antibodies (ADA) according to the schedule in Table 7.

8.1.1.3.7. Quality of Life Assessments

As outlined in Section 8.1.1.3.5, Quality of Life data was obtained using ACQ-IA score at baseline and at weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, and 52 weeks.

8.1.1.3.8. Statistical Analysis Plan

The clinical development program of benralizumab to support expanding the indication for add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype, from 12 years of age to 6 years of age consisted of a single uncontrolled open-label trial (TATE) in 28 children. TATE was a PK/PD study conducted as part of an extrapolation strategy to support the use of benralizumab in this age group and indication. Assessment of PK/PD and safety were the primary endpoints of the study; statistical analysis plan and analysis results regarding the PK/PD endpoints were reviewed under the Clinical Pharmacology review in Section 6 and will not be repeated here.

With the small sample size and uncontrolled design, this study provided limited clinical outcome measure data and was not designed to detect significant changes in the clinical assessments. All clinical outcome analyses were based on the safety set, which was defined as all subjects (aged 6 to 11-years-old) who received any dose of benralizumab. Only descriptive analyses were conducted.

This section will describe aspects of the statistical analysis plan (SAP) on sample size determination, analysis population, and summary statistics used for selected efficacy endpoints.

Sample Size

No formal sample size calculation was performed. The sample size was not based on any statistical considerations. This study was designed to evaluate the safety and efficacy of open label treatment with benralizumab.

Analysis Populations

The Safety Population included all subjects who received any study drug (i.e., any exposure to open-label benralizumab).

Analysis of Efficacy

All efficacy analyses were conducted on the Safety Population which consisted of all subjects aged 6 to 11 years-old who received any dose of benralizumab.

All efficacy endpoints were analyzed descriptively, and the summary statistics were presented.

No interim analysis was planned for this study.

All data listings were sorted by site, subject number, and included the subject's age, sex, and race.

8.1.1.3.9. Compliance With Good Clinical Practices

A statement of compliance with Good Clinical Practice is in the Clinical Study Report.

8.1.1.3.10. Financial Disclosure

The Applicant has adequately disclosed that there were no financial interests with any of the clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators (see Appendix 15.2).

8.1.1.4. Study Results

8.1.1.4.1. Protocol Amendments

The original clinical study report was approved on June 22, 2018. There was a total of 4 amendments. The first amendment on July 22, 2019, changed the stratification by body weight <40kg/≥40 kg to stratification by body weight <35kg/≥35 kg. The dose of (b) (4) mg to be administered to patients in the lower weight stratum (previously <40kg) was changed to 10 mg for the updated lower weight stratum of < 35 kg. Body weight stratification was changed (b) (4) The 10 mg dose in the 6–11-year-old pediatric patients weighing <35 kg was chosen to prevent higher exposure of benralizumab to these patients.

Minor administrative amendments were made before database lock (DBL) and were determined to not affect the interpretation of the study results. No subjects were enrolled prior to this amendment, first patient was enrolled into the study on November 21, 2019.

8.1.1.4.2. Protocol Violations/Deviations

Important protocol deviations were reported in a total of 6 (21%) patients. The most frequently reported category of protocol deviations was “eligibility and entry criteria”, with a total of 2 (7%) patients reporting important deviations in this category (1 patient in the ≥35 kg weight cohort and 1 in the <35 kg weight cohort).

One patient (≥35 kg) had an important protocol deviation in the ‘inclusion criteria’ category. This patient did not meet inclusion criterion 6, which stated that patients had to have well-documented regular treatment with ICS prior to enrollment. This protocol deviation was detected approximately 17 months after the patient was screened (after DBL and the patient was confirmed to be eligible as per the review that was completed post DBL).

8.1.1.4.3. Review of Efficacy

8.1.1.4.3.1. Patient Disposition

A total of 39 patients aged 6 to 11 years were enrolled, 11 of which were screen failures. The remaining 28 patients were assigned to study treatment: 15 patients were stratified in the <35 kg weight cohort and received 10 mg benralizumab and 13 patients were stratified in the ≥35 kg weight cohort and received 30 mg benralizumab. All 28 (100%) patients aged 6 to 11 years assigned to study treatment completed the study treatment and the study. All 28 subjects were included in the safety population.

8.1.1.4.3.2. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics are summarized in Table 8. The population enrolled had higher male proportion (68%), majority Asian (32%; likely due to several sites being located in Japan), higher eosinophilic population (68% ≥300 cells/uL), were on ICS at baseline (97%) but no patients were on oral corticosteroids (OCS) at baseline. Sixty percent of patients were between 9-10 years of age and 39% of patients were 6 to 8 years old. The mean age was 8.8 years.

Overall, patients aged 6 to 11 years had a mean baseline peripheral eosinophil count of 469 cells/µL (min=150 cells/µL, max=1520 cells/µL).

There were 2 female patients aged 13 years from Japan. Both patients were Asian, had higher eosinophilic population of ≥300 cells/uL and were on inhaled ICS at baseline. These patients had a mean baseline peripheral eosinophil count of 498 cells/µL (min=170 cells/µL, max=1020 cells/µL).

Table 8. TATE Trial (Study D3250c00025), Demographics and Other Baseline Characteristics of the Safety Population

	Benralizumab 10 mg (N=15)	Benralizumab 30 mg (N=13)	Total (N=28)
Age			
ean (SD)	8.3 (2.02)	9.3 (1.55)	8.8 (1.86)
edian (Min, Max)	9.0 (6, 11)	9.0 (6, 11)	9.0 (6, 11)
Sex			
F	4 (26.7)	5 (38.5)	9 (32.1)
M	11 (73.3)	8 (61.5)	19 (67.9)
Race			
ASIAN	8 (53.3)	1 (7.7)	9 (32.1)
BLACK OR AFRICAN AMERICAN	3 (20.0)	5 (38.5)	8 (28.6)
OTHER	0	3 (23.1)	3 (10.7)
HISPANIC	0	2 (15.4)	2 (7.1)
UNKNOWN, NOT REPORTED	0	1 (7.7)	1 (3.6)
WHITE	4 (26.7)	4 (30.8)	8 (28.6)
Ethnicity			
HISPANIC OR LATINO	1 (6.7)	5 (38.5)	6 (21.4)
NOT HISPANIC OR LATINO	14 (93.3)	8 (61.5)	22 (78.6)
Weigh (kg)			
Mean (SD)	27.5 (3.9)	50.52 (12.3)	38.2 (14.5)
Median (Min, Max)	27.3 (20.3, 34.2)	48 (35,77.7)	33.8 (20.3,77.7)
Body Mass Index (kg/m^2)			
Mean (SD)	16.7 (2.32)	26.3 (4.20)	21.1 (5.87)
Median (Min, Max)	16.4 (14.2, 23.4)	25.5 (18.1, 34.8)	18.3 (14.2, 34.8)
Body Mass Index (kg/m^2) Group			
Normal (<=25)	15 (100.0)	5 (38.5)	20 (71.4)
Obese (>30-35)	0	3 (23.1)	3 (10.7)

	Benralizumab 10 mg (N=15)	Benralizumab 30 mg (N=13)	Total (N=28)
Overweight (>25-30)	0	5 (38.5)	5 (17.9)
Baseline Blood Eosinophil Count (cells/uL) **Mean (SD)** **Median (Min, Max)**	 464.0 (283.01) 400.0 (150, 1020)	 474.6 (392.08) 340.0 (150, 1520)	 468.9 (331.49) 375.0 (150, 1520)
Baseline Blood Eosinophil Count (cells/uL)			
>=150-<300 cells/uL	5 (33.3)	4 (30.8)	9 (32.1)
>=300 cells/uL	10 (66.7)	9 (69.2)	19 (67.9)
Age at Asthma Diagnosis **Mean (SD)** **Median (Min, Max)**	 1.9 (1.58) 2.0 (0, 5)	 2.8 (1.92) 2.0 (0, 6)	 2.3 (1.76) 2.0 (0, 6)
Number of Exacerbations Within 12 Months **Mean (SD)** **Median (Min, Max)**	 3.7 (3.35) 2.0 (2, 15)	 2.5 (0.97) 2.0 (2, 5)	 3.2 (2.57) 2.0 (2, 15)
Number of Exacerbations Within 12 Months			
2	8 (53.3)	9 (69.2)	17 (60.7)
3	1 (6.7)	2 (15.4)	3 (10.7)
4	4 (26.7)	1 (7.7)	5 (17.9)
>4	2 (13.3)	1 (7.7)	3 (10.7)
Baseline ACQ-IA Score **Mean (SD)** **Median (Min, Max)**	 1.3 (0.92) 1.3 (0, 2.83)	 2.1 (1.19) 1.7 (0.67, 4.5)	 1.6 (1.12) 1.3 (0, 4.5)
ICS as Maintenance Medication at Baseline	15 (100.0)	12 (92.3)	27 (96.4)
ICS Total Daily Dose (ug) at Baseline [a,b] **Mean (SD)** **Median (Min, Max)**	 481.0 (272.1) 460.0 (200, 909.1)	 719.4 (362.5) 704.5 (230, 1534.1)	 595.4 (334.7) 500.0 (200, 1534.1)
OCS as Maintenance Medication at Baseline	0	0	0
OCS Total Daily Dose (mg) at Baseline	0	0	0
LABA as Maintenance Medication at Baseline	14 (93.3)	11 (84.6)	25 (89.3)
ICS/LABA as Maintenance Medication at Baseline	14 (93.3)	11 (84.6)	25 (89.3)
LABA/LAMA as Maintenance Medication at Baseline	15 (100.0)	13 (100.0)	28 (100.0)
LAMA as Maintenance Medication at Baseline	0	4 (30.8)	4 (14.3)
LTRA as Maintenance Medication at Baseline	9 (60.0)	7 (53.8)	16 (57.1)
Xanthan Derivatives as Maintenance Medication at Baseline	2 (13.3)	0	2 (7.1)
Other Asthma Medications as Maintenance Medication at Baseline	1 (6.7)	0	1 (3.6)

	Benralizumab 10 mg (N=15)	Benralizumab 30 mg (N=13)	Total (N=28)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.
Age - Dataset: Demographics; Filter: None; Row Variable 1: AGE (Age)
Sex - Dataset: Demographics; Filter: None; Row Variable 1: SEX (Sex)
Race - Dataset: Demographics; Filter: None; Row Variable 1: RACE (Race); Row Variable 2: RACEOTH (Other Race Specification)
Ethnicity - Dataset: Demographics; Filter: None; Row Variable 1: ETHNIC (Ethnicity)
Body Mass Index (kg/m^2) - Dataset: Demographics; Filter: None; Row Variable 1: BMIBL (Baseline Body Mass Index)
Body Mass Index (kg/m^2) Group - Dataset: Demographics; Filter: None; Row Variable 1: BMIGRP (Baseline BMI Group)
Baseline Blood Eosinophil Count (cells/uL) - Dataset: Demographics; Filter: None; Row Variable 1: EOSCNBL (Eosinophil Baseline in Conventional Units)
Baseline Blood Eosinophil Count (cells/uL) Category - Dataset: Demographics; Filter: None; Row Variable 1: EOSGRP (Eosinophil Baseline Group in Conventional Units)
Age at Asthma Diagnosis - Dataset: Demographics; Filter: None; Row Variable 1: AGEON (Age at Onset of Asthma (Years) (N))
Age Group at Asthma Diagnosis - Dataset: Demographics; Filter: None; Row Variable 1: ADAGEGRP (Age Group at Asthma Diagnosis)
Number of Exacerbations Within 12 Months Prior to Informed Consent - Dataset: Demographics; Filter: None; Row Variable 1: FAXDPNO (Number of Exacerbations Prev 12 Months)
Number of Exacerbations Within 12 Months Prior to Informed Consent: Grouped - Dataset: Demographics; Filter: None; Row Variable 1: FAXDPGP (No Exacerb in Prev 12 Mo GRP)
Baseline ACQ-IA Score - Dataset: Questionnaires; Filter: ABLFL = 'Y', PARAM = 'ACQ-IA Score'; Row Variable 1: AVAL (Analysis Value)
ICS as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL04FL = 'Y'.
ICS Total Daily Dose (ug) at Baseline - Dataset: Concomitant Medications (Modified); Filter: None; Row Variable 1: CMFPTDSM (FP Equivalent Total Daily Dose Sum)
OCS as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL05FL = 'Y'.
OCS Total Daily Dose (mg) at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL05FL = 'Y'.
LABA as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL07FL = 'Y'.
ICS/LABA as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL15FL = 'Y'.
LABA/LAMA as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y'.
LAMA as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL09FL = 'Y'.
LTRA as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL10FL = 'Y'.
Xanthan Derivatives as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ABLFL = 'Y', ANL11FL = 'Y'.
Other Asthma Medications as Maintenance Medication at Baseline - Dataset: Concomitant Medications; Filter: ANL12FL = 'Y', ABLFL = 'Y'.
SD = Standard Deviation.
a ICS doses were converted to their Fluticasone Propionate equivalent for this summary. ICS may be taken in a separate inhaler or as part of combination ICS-LABA therapy. ICS total daily dose is the sum of doses at baseline across multiple inhalers.
b Filters used to generate the modified Concomitant Medications dataset are ABLFL = 'Y' and ANL04FL = 'Y'. The sum of the resulting baseline ICS and LABA doses were summed for each patient.

8.1.1.4.3.3. Primary Endpoints

PK and PD were the primary endpoints and are discussed in the Clinical Pharmacology Section 6.

8.1.1.4.3.4. Statistical Issues

No statistical issues were identified in this single-arm trial, which was assessed with descriptive statistics and comparisons to baseline and to the adequate and well-controlled adolescent and adult study.

8.1.1.4.3.5. Secondary Endpoints: PK, Immunogenicity, Change from Baseline in Forced Expiratory Volume (FEV1) and Patient Reported Outcomes (PRO).

PK/Immunogenicity

Secondary PK assessments and immunogenicity endpoints results are discussed in the Clinical Pharmacology Section 6.

FEV1

The trend in FEV1 was improvement for both dose groups, although the change in FEV1 from baseline in the 10 mg dose group was variable, likely due to the smaller margin for increase as the baseline %predicated FEV1 was 94%, as shown in Table 9. Overall, the mean change in FEV1 for both dosing groups at Week 24 was 90 mL and after the 48-week treatment period was 191 mL which is similar to the mean change in FEV1 in the adolescent and adult studies which ranged from 112 mL at Week 28 to 159 mL at Week 48.

Table 9. FEV1 (L) by Timepoint, Summary Statistics (TATE Safety Analysis)

	Benralizumab 10 mg (N=15)	Benralizumab 30 mg (N=13)	Total (N=28)
FEV1 (L) Baseline, Mean (SD), N	1.54 (0.36), N=15	1.69 (0.42), N=12	1.61 (0.39)
FEV1 (%predicted) Baseline, Mean (SD), N	94 (17), N=15	83 (20), N=12	89 (19)
FEV1 (L), Week 24, Mean (SD), N	1.62 (0.37), N=14	1.76 (0.43), N=12	1.69 (0.40)
Change from baseline, N	0.07 (0.27), N=14	0.11 (0.41), N=11	0.09 (0.33)
FEV (L), Week 48, Mean (SD), N	1.54 (0.44), N=15	2.06 (0.47), N=13	1.78 (0.52)
Change from baseline, N	0.003 (0.341), N=15	0.425 (0.440), N=12	0.191 (0.44)

Source: CSR, Table 14.1.15.1, pg 225; Table 14.2.3.2.1, pgs 353 - 355

PROs

There was an overall improvement on ACQ-IA responses. Mean ACQ-IA (total score 0-6, with 6 being poorly controlled) was 1.26 for the 10 mg dose group and 2.09 for 30 mg dose group. The ACQ-IA decreased by 0.56 (score of 0.69) for 10 mg and by 1.36 (score of 0.65) for 30 mg dose group.

Results in both Investigator-reported CGIC and patient-reported PGIC-IA questionnaires agreed that more patients had improved and very much improved health status from start of treatment to week 48 compared to up to week 16. The overall responses from week 16 throughout week 48 were favorable, showing a higher percentage of patients with improved health status since start of treatment compared to those with no change or worsened health status.

8.1.1.4.3.6. Exploratory Endpoint: Annualized Asthma Exacerbation Rate

Subjects were required to have to have ≥2 exacerbations requiring treatment with systemic steroids and or hospitalizations in 12 months prior to enrollment. The total of exacerbations per patient per treatment year was 3.2 in the preceding 12 months prior to enrollment. Over the treatment period, the number of exacerbations decreased to 1.61. In addition, half (14/28) of the subjects reported no exacerbations over the 48-week treatment period.

8.1.1.4.3.7. Assessment of Efficacy Across Trials

Efficacy in children 6 to 11 years of age is extrapolated from efficacy demonstrated in adequate and well-controlled studies in adults and adolescents 12 years of age and older. Extrapolation is supported by the high degree of similarity for severe asthma with an eosinophilic phenotype, consistency in the therapeutic approach and consistency of the benralizumab mechanism of action. Incidence of anti-drug antibodies (ADAs) and impacts of ADAs on PK and PD were similar between pediatric patients aged 6 to 11 years and adults/adolescents. Extrapolation of efficacy in patients aged 6 to 11 years is further supported by similar or higher drug exposure and similar PD (peripheral eosinophils) in patients aged 6 to 11 years.

To support this application, the Applicant conducted a single-arm, PK, PD, and long-term safety trial (TATE) in 28 children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. Blood eosinophil values in the safety analysis set showed near-complete depletion from baseline in both weight cohorts at all post-dose time points (week 4 to 48: for the <35 kg weight cohort, median blood eosinophil values fell from 435.0 cells/µL to 5.0 to 20.0 cells/µL and for the ≥35 kg weight cohort, median blood eosinophil values fell from 430.0 cells/µL to 5.0 to 20.0 cells/µL).

Although the TATE trial was not designed to assess efficacy given the small sample size and uncontrolled design, efficacy outcomes were included. The effect of benralizumab on pulmonary function was evaluated as a secondary endpoint. The trend in FEV1 was improvement for both dose groups, although the change in FEV1 from baseline in the 10 mg dose group was variable, likely due to the smaller margin for increase as the baseline %predicated FEV1 was 94% compared to 83% for the 30 mg dose group.

Exacerbations were assessed as an exploratory endpoint. The total of exacerbations per patient per treatment year was 3.2 in the preceding 12 months prior to enrollment. Over the treatment period, the number of exacerbations decreased to 1.61. In addition, half (14/28) of the subjects reported no exacerbations over the 48-week treatment period.

The effect of benralizumab on asthma symptoms and other asthma control metrics relative to baseline was overall favorable as assessed via ACQ-IA, CGIC and PGIC-IA.

Overall, substantial evidence of effectiveness for children 6 to 11 years of age for add-on maintenance treatment for severe asthma, with an eosinophilic phenotype is established based on extrapolation of efficacy from adequate and well-controlled studies that supported substantial evidence of effectiveness for the same indication in adults and adolescents aged 12 years and older, supported by similar or higher PK and similar PD in children 6 to 11 years of age. Although the single-arm, PK, PD, and long-term safety trial (TATE) in 28 children 6 to 11 years of age with severe asthma with an eosinophilic phenotype was not designed to assess efficacy, efficacy outcomes including lung function, asthma exacerbation and symptoms were generally supportive.

8.1.1.4.4. Review of Safety

8.1.1.4.4.1. Safety Review Approach

The study was conducted in 2 parts, Part A and Part B. Part A consisted of 16 weeks of treatment to evaluate the PK and PD, and safety of benralizumab. Part B consisted of 32 weeks of continued treatment to evaluate the safety of benralizumab. The safety review included Part A and Part B. All study data was summarized together.

The safety review for the higher exposure group (≥ 35 kg receiving 30 mg) in the TATE trial was compared with the safety results from the adolescent and adult pivotal clinical trials (SIROCCO, CALIMA and ZONDA) by reviewing the original asthma clinical review submitted in 2017, which included patients who received 30mg of benralizumab Q4W and had similar exposure than the HE-group in the TATE study.

8.1.1.4.4.2. Review of the Safety Database

Overall Exposure

All 28 patients enrolled in the study completed the 48-week on-treatment period. One patient's Week 16 dose was delayed and given to the patient four weeks later.

Adequacy of the Safety Database:

Overall, the safety database is of sufficient size and duration to assess the safety of the proposed pediatric dose given the previous safety database for the approved adolescent and adult asthma indication.

8.1.1.4.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data integrity or submission quality issues that hinder the safety review of this sBLA were identified.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols. Adverse events (AEs) and serious adverse events (SAEs) were captured from signing of informed consent through the treatment period and including the follow-up period (Week 52).

AE were classified into system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

The Applicant's coding of verbatim terms to preferred terms was appropriate. Adverse events of special interest included hypersensitivity, injection site reactions, helminth infections, and malignancy.

Routine Clinical Tests

Safety assessments consisted of routine reporting of all adverse events, serious adverse events, relationship to the drug, concomitant medications, and pregnancies. Participants also underwent regular monitoring of bloodwork (hematology, chemistry, urine analysis), vital signs and physical exams. A 12-lead electrocardiogram was obtained at Visit 1, during Exit Visit of Part A (Visit 9), during week 14 of Part B, and during DXD/WD. Blood samples were also obtained regularly to assess for immunogenicity.

8.1.1.4.4.4. Safety Results

Deaths

There were no deaths in either Part A or Part B of the study.

Serious Adverse Events

A total of 3 SAEs of asthma exacerbation, which were considered not related to study treatment by the Investigator. All SAEs resolved.

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

Dropouts and/or Discontinuations Due to Adverse Effects

There were no study discontinuations or dropouts due to AEs during Part A or Part B.

Adverse Reactions

Given the absence of a placebo group in TATE Trial, it is difficult to assess relatedness of events to medication use. Generally, events were mostly singular and balanced between

treatment arms. A review of all AEs in TATE Trial did not reveal any new safety concerns compared to the safety profile established based on studies conducted in adults and adolescents. Common AEs (occurring in ≥2 subjects by system organ class and treatment group) reported are summarized in Table 10. Overall, the common adverse events for pediatric patients are similar to that observed in patients aged 12 years and older which include AEs of upper respiratory infections and headache. Risk difference between the two weight groups was conducted due to the higher exposure in the ≥ 35 kg group. With the exception of cough, there AEs were lower in the higher exposure ≥ 35 kg group.

No marked differences were observed in the adverse events reported in the 2 older patients from Japan and the overall study population (data not shown).

Table 10. TATE Trial (Study D3250c00025): Summary of on Study AEs Affecting ≥ 10% of Any Population for Subjects Ages 6-11

System Organ Class - Preferred Term	Benralizumab 10mg/ weight < 35 kg (N=15) n (%)	Benralizumab 30mg/ weight >= 35 kg (N=13) n (%)	Risk Difference RD (95% CI)	Forest Plot
Infections and infestations	**12 (80.0)**	**6 (46.2)**	33.85 (0.02, 67.67)	
Nasopharyngitis	4 (26.7)	1 (7.7)	18.97 (-7.68, 45.63)	
Viral upper respiratory tract infection	2 (13.3)	2 (15.4)	-2.05 (-28.14, 24.04)	
Sinusitis	2 (13.3)	0 (0.0)	13.33 (-3.87, 30.54)	
Covid-19	1 (6.7)	2 (15.4)	-8.72 (-32.04, 14.61)	
General disorders and administration site conditions	**6 (40.0)**	**1 (7.7)**	32.31 (3.59, 61.02)	
Pyrexia	3 (20.0)	1 (7.7)	12.31 (-12.58, 37.20)	
Gastrointestinal disorders	**4 (26.7)**	**2 (15.4)**	11.28 (-18.48, 41.04)	
Constipation	2 (13.3)	0 (0.0)	13.33 (-3.87, 30.54)	
Vomiting	2 (13.3)	0 (0.0)	13.33 (-3.87, 30.54)	
Injury, poisoning and procedural complications	**3 (20.0)**	**0 (0.0)**	20.00 (-0.24, 40.24)	
Skin and subcutaneous tissue disorders	**3 (20.0)**	**3 (23.1)**	-3.08 (-33.64, 27.49)	
Immune system disorders	**2 (13.3)**	**1 (7.7)**	5.64 (-16.85, 28.13)	

System Organ Class - Preferred Term	Benralizumab 10mg/ weight < 35 kg (N=15) n (%)	Benralizumab 30mg/ weight >= 35 kg (N=13) n (%)	Risk Difference RD (95% CI)	Forest Plot
Musculoskeletal and connective tissue disorders	**2 (13.3)**	**0 (0.0)**	13.33 (-3.87, 30.54)	
Pain in extremity	2 (13.3)	0 (0.0)	13.33 (-3.87, 30.54)	
Nervous system disorders	**2 (13.3)**	**1 (7.7)**	5.64 (-16.85, 28.13)	
Headache	2 (13.3)	1 (7.7)	5.64 (-16.85, 28.13)	
Respiratory, thoracic, and mediastinal disorders	**2 (13.3)**	**5 (38.5)**	-25.13 (-56.68, 6.42)	
Asthma	1 (6.7)	2 (15.4)	-8.72 (-32.04, 14.61)	
Cough	0 (0.0)	3 (23.1)	-23.08 (-45.98, -0.17)	

Source: OCS Analysis Studio, Safety Explorer.
Note: Filters: TRT01A = "Benralizumab 10 mg SC" and AGEGR1 = ">=6 - <12" and SAFFL = "Y" (Benra 10mg/ weight < 35 kg Ages 6-11); TRT01A = "Benralizumab 30 mg SC" and AGEGR1 = ">=6 - <12" and SAFFL = "Y" (Benra 30mg/ weight >= 35 kg Ages 6-11); ONSTDFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 10%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Immunogenicity

No subjects reported positive ADA results at baseline. In the overall study population, the anti-drug antibody (ADA) prevalence was of 14.3%, with 4 patients (3 in the <35 kg weight cohort and 1 in the ≥35 kg weight cohort) having at least 1 ADA positive response throughout all time points. All the ADA-positive patients were also positive for neutralizing antibodies (nAb). See Appendix Section 15.3.1 for additional information.

8.1.1.4.4.4.1. Analysis of Submission-Specific Safety Issues

Adverse events of special interest included systemic (allergic and nonallergic) reactions, local injection site reactions, helminth infections and malignancies. There were no helminth infections or malignancy reported in the study. No anaphylaxis adverse events were reported. No trends were observed for hypersensitivity AEs in any weight cohort or age group. Three

adverse events of urticaria were reported (1 in the < 35 kg and 2 in the ≤ 35 kg group). All 3 resolved within 1-3 days. Two cases of atopic dermatitis were reported (1 in each dose group) and were mild.

Exposure for patients who were < 35 kg and received 10 mg Q4W x 3 doses, then Q8W was similar to adults and adolescents who received 30 mg with the same dosing regimen. Subjects who weighted ≥ 35 kg and received 30 mg showed 62% higher median week 16 trough concentrations compare to adults and adolescents receiving the same dosage. No new safety signals were identified in the TATE trial and the safety profile for the 10 mg dose group was similar to the 30 mg dose group. Further safety support was conducted for the high exposure group by reviewing the safety profile reported in the 1-year phase 3 well controlled clinical studies (SIROCCO, CALIMA and ZONDA) where 896 patients received a higher dose (30 mg Q4W) compared to the approved dose of benralizumab (30 mg Q4W x 3 doses, then Q8W). The safety profile in these trials for the 30 mg Q4W dose group was similar to the approved benralizumab dose group for ≥ 12 years of age (n=1835). See review for the original asthma approval from 2017.

8.1.1.4.4.4.2. Safety Analyses by Demographic Subgroups

Safety analysis by demographic subgroup was not conducted due to the small study size.

8.1.1.4.4.5. Safety in the Post-market Setting

No new safety concerns have been identified based on post-marketing experience since benralizumab was approved for patients > 12 years of age in 2017.

8.1.1.4.4.6. Integrated Assessment of Safety

Based on the high degree of similarity for severe asthma, with an eosinophilic phenotype, response to treatment and the consistency of the benralizumab mechanism of action between adults and the target pediatric population, the safety for the new patient population is partially extrapolated from the adolescent and adult pivotal clinical trials.

The safety experience based on the TATE trial was limited to 28 subjects. There were no new safety concerns identified in TATE Trial that alter the risk-benefit profile of benralizumab for the population 6 to 11 years of age. The frequency and type of AEs were consistent with previous studies in adults and adolescents. There were no deaths, SAEs, or investigator confirmed AESIs reported during the study. No subjects discontinued the study due to TEAEs. The most commonly reported TEAE was nasopharyngitis and most TEAEs were mild or moderate in severity. No clinically meaningful changes in laboratory values were described during this trial.

Benralizumab exposure in children aged 6 to 11 years who weight <35 kg and received 10 mg Q4W x 3 doses, then Q8W was similar to adolescents and adults receiving 30 mg at the same dosing regimen (approved dosage). However, patients 6 to 11 years who weighed ≥35kg and received 30 mg showed 62% higher median week 16 trough concentrations compare to adults and adolescents receiving the same dose. Support for safety for the higher exposure group relies upon similar safety in the TATE trial for the 10 mg and 30 mg dose group and safety from

the adolescent and adult pivotal clinical trials (SIROCCO, CALIMA and ZONDA; original asthma clinical review, 2017) which included 896 patients who received 30mg of benralizumab Q4W for 1-year and had similar exposure to the higher exposure group in the TATE study.

8.2. Conclusions and Recommendations

This efficacy supplement-20 (S-20) for benralizumab proposes to expand the indication "for the add-on maintenance treatment of patients with severe asthma, and with eosinophilic phenotype" from ≥ 12 years of age to ≥ 6 years of age. To support the efficacy and safety of benralizumab for the proposed indication, the Applicant submitted data from the TATE trial, a single-arm, PK, PD, and long-term safety clinical trial in 28 children 6 to 11 years of age with severe asthma with an eosinophilic phenotype. Completion of the TATE trial fulfils PREA PMR 32871-1. Dose was weight-based (10 mg for < 35 kg and 30 mg for ≥ 35 kg). The dosing regimen was the same as adults/adolescents (Q4W for 3 doses, then Q8W thereafter). Enrolled patients were treated for 48 weeks. PK/PD was assessed during the first 16-weeks of treatment (Part A), with continued safety assessments through Week 52 (Part B).

Substantial evidence of effectiveness for children 6 to 11 years of age "for add-on maintenance treatment for severe asthma, with an eosinophilic phenotype" is established based on extrapolation of efficacy from adequate and well-controlled studies that provided demonstration of substantial evidence of effectiveness for the same indication in adults and adolescents aged 12 years and older, supported by similar or higher PK and similar PD (peripheral eosinophil counts) in children 6 to 11 years of age obtained from the TATE trial. Efficacy extrapolation is supported by the high degree of similarity of severe asthma with an eosinophilic phenotype, consistency in the therapeutic approach, consistency of the benralizumab mechanism of action, and relevance of the clinical endpoints for children 6 to 11 years of age. Incidence of anti-drug antibodies (ADAs) and impacts of ADAs on PK and PD were similar between pediatric patients aged 6 to 11 years and adults/adolescents.

The safety profile for benralizumab in patients with severe asthma, and with an eosinophilic phenotype, is well established since its approval in 2017 and includes a warning and precaution for hypersensitivity reactions, including anaphylaxis. Common adverse reactions include headache and pharyngitis. Safety for the new patient population is partially extrapolated from the adolescent/adult pivotal clinical trials. No new safety signals were identified in the TATE trial. Exposure was similar for pediatric patients aged 6 to 11 year and weighting < 35 kg receiving the dose of 10mg, however, there was a higher exposure (HE) in pediatric patients weighting ≥35 kg, with 62% higher median week 16 trough concentrations compare to adults and adolescents receiving the same dose. The safety profile was similar for both weight-based dosing groups. Further support for safety for the HE-group, relies upon a similar safety profile for adults and adolescents in the 1-year phase 3 clinical studies (SIROCCO, CALIMA, and ZONDA) who received a higher dose (30 mg Q4W, n=896 with a similar exposure to the HE-group) compared to adults and adolescents who received the approved dosing regimen (n=1835).

The safety profile of benralizumab is well established since its approval in 2017. This would be the second approved drug targeting the IL5 pathway for pediatric patients 6 to 11 years of age, joining mepolizumab, and the first administrated Q8W. From the clinical standpoint, the Applicant has submitted adequate data to support the efficacy/safety of benralizumab for patients aged 6 to 11 years as add-on maintenance treatment for those with severe asthma, and with an eosinophilic phenotype. However, issues arose with the facilities' inspection that preclude approval during this review cycle; therefore, the application will receive a Complete Response pending resolution of the facilities issues.

9. Advisory Committee Meeting and Other External Consultations

As benralizumab is approved for the same indication in adolescents and adults and there were no safety or efficacy concerns identified for this pediatric program, no advisory committee meeting was required.

10. Pediatrics

The Applicant submitted data from TATE Trial (Study D3250C00025) to fulfill the requirements of the Pediatric Research Equity Act (PREA) Post-Marketing Requirement (PMR) (3287-1) that was issued for children 6 to 11 years of age. The requirement of studies in ages 0 to 5 years were waived at the time of the adolescent and adult approval because necessary studies are impossible or highly impracticable as severe asthma with eosinophilic phenotype is unlikely to exist in sufficient numbers to allow for a study to be conducted.

On October 24, 2023, the Pediatric Review Committee (PeRC) reviewed TATE Trial (Study D3250C00025) and agreed that this clinical trial fulfilled the outstanding PMR (3287-1). Approval of the pediatric indication (extending age of use down to 6 years of age) was also endorsed.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The supplement proposes to expand the indication to include pediatric patients 6 to 11 years of age based on extrapolation of efficacy from adult and adolescents, and additional pharmacokinetic and pharmacodynamic data from a 48-week trial with pediatric patients aged 6 to 11 years of age. Refer to the Labeling Information Requests dated October 31, and December 8, 2023, for the labeling revisions conveyed to the Applicant. The Applicant incorporated our revisions, and the agreed upon labeling is dated December 14, 2023.

Table 11. Labeling Recommendations

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)[2]**
INDICATIONS AND USAGE	The supplement proposed to expand the indication by adding the patient population of pediatric patients 6 to 11 years of age. The previous indication was for pediatric patients 12 years and older. There was a minor revision to the indication statement because the previous language separated the two qualifiers: severe asthma and eosinophilic phenotype. The modified indication also aligns with other asthma labels. The following is the new indication by expanding the patient population to include pediatric patients 6 to 11 years of age: *FASENRA is indicated for the add-on maintenance treatment of patients aged 6 years and older with severe asthma, and with an eosinophilic phenotype [see Use in Specific Populations (8.4), Clinical Studies (14)].*
2 DOSAGE AND ADMINISTRATION	• The recommended dosage for adult and pediatric patients 12 years and older is 30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter. There were safety concerns with the higher exposure of FASENRA in pediatric patients 12 years and older who weigh less than 35 kg and receive 30 mg based on age. However, the Applicant addressed this concern by noting that no new safety information has been identified from clinical studies or post-marketing data that would warrant a change to the established dosing recommendation for adolescents and stated the

	exposure is similar for adolescents weighing < 35 kg receiving 30 mg Q4W x 3 doses, then Q8W compared to the Q4W x 1 year dosing in SIROCCO and CALIMA in adolescents and adults. The Division agreed with this rationale. As such, the dosage for pediatric patients 12 years and older is not based on weight and remains at 30 mg every 4 weeks, then every 8 weeks thereafter, and the dosage for pediatric patients 6 to 11 years of age is based on weight. • Subsection 2.1 is updated with the addition of Table 1 that provides the recommended dosage of FASENRA based on weight for the new patient population, pediatric patients 6 to 11 years of age. • Subsection 2.3 was updated because of the addition of a new presentation; 10 mg/0.5 mL prefilled syringe. Figure 1 depicts the two FASENRA Prefilled Syringes and identifying characteristics of the two different strengths to help prescribers check labels on the FASENRA carton and prefilled syringes to ensure the correct 10 mg or 30 mg prefilled syringe is used.
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	N/A
6 ADVERSE REACTIONS	Reformatted to provide headings and subheadings to separate the safety information for *Adult and Adolescent Patients 12 Years of Age and Older* from *Pediatric Patients 6 to 11 Years of Age*. Added a summary of safety for the pediatric patients 6 to 11 years of age.
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS	Updated **8.4 Pediatric Use** subsection to include the pediatric use statement with information that supports the use in pediatric patients 6 to 11 years of age.
10 OVERDOSAGE	N/A
12 CLINICAL PHARMACOLOGY	• **12.2 Pharmacodynamic** subsection was updated with results of the magnitude of blood eosinophil reduction

	from the 48-week trial with patients 6 to 11 years of age. • **12.3 Pharmacokinetics** subsection updated with the addition of pharmacokinetic data for *Pediatric Patients* from the 48-week trial with pediatric patients 6 to 11 years of age.
13 NONCLINICAL TOXICOLOGY	No changes were made as this supplement did not include new nonclinical pharmacology or toxicology studies.
14 CLINICAL STUDIES	• [redacted] (b) (4) language was removed based on 21CFR 201.57(c)(3)(ii): [redacted] (b) (4) The first paragraph summarizing the clinical trials is revised to align with the deletion of the [redacted] (b) (4) information. • Updated trial numbers with trial names. • Patient population in the clinical trials was updated to specify 'adult' for clarity since this supplement expanded the indication to include pediatric patients 6 to 11 years of age.
17 PATIENT COUNSELING INFORMATION	N/A
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	**Section 3 DOSAGE FORMS AND STRENGTHS:** reformatted and addition of new 10 mg/0.5 mL presentation. **Section 11 DESCRIPTION:** updated with pH information. **Section 16 HOW SUPPLIED/STORAGE AND HANDLING**: updated the description of the prefilled syringes with different colors for the plunger rod.

Source: Labeling Discussion Comments dated October 31, and December 8, 2023. Final labeling is dated December 14, 2023

12. Risk Evaluation and Mitigation Strategies

Given the favorable safety profile of benralizumab for 6- to 11-year-olds, there are no additional risk management strategies required.

13. Post marketing Requirements and Commitment

None.

14. Division Director (Clinical) Comments

Based on the reviews completed by the clinical, statistical, clinical pharmacology, and nonclinical review teams, this sBLA supports Approval of benralizumab for the add-on maintenance treatment of patients with severe asthma, and with an eosinophilic phenotype, to include children 6-11 years of age, with the proposed dosing of 10 mg in patients aged 6 to 11 years who weigh < 35 kg and 30 mg in patients aged 6 to 11 years who weigh ≥ 35 kg, administered subcutaneously Q4 weeks for the first 3 doses, then Q8 weeks for subsequent doses. However, recent surveillance inspections of the drug product manufacturer, (b) (4) revealed significant quality concerns with the facilities. Due to the manufacturing deficiencies, the Office of Process and Facilities reports that the application cannot be approved at this time. As a result, the recommended action is to issue a **Complete Response**.

This supplement was supported by data from one 48-week, open-label, phase 3, PK, PD, and safety study in pediatric patients with severe eosinophilic asthma (TATE Study). The study enrolled and treated 30 pediatric patients 6 to 14 years of age, including 28 patients 6 to 11 years of age. The study enrolled 15 subjects weighing < 35 kg and 15 subjects weighing ≥ 35 kg. Subjects entered a 48-week treatment period that was comprised of two parts:

Part A: 16-week treatment period to evaluate PK, PD, and safety
Part B: 32-week treatment period to evaluate safety.

PK results from the TATE Study demonstrate that benralizumab exposures in pediatric patients aged 6 to 11 years and weighing < 35 kg who received a dose of 10 mg had comparable drug exposure to adult and adolescent patients receiving the approved 30 mg dose following the same dosing regimen. Pediatric patients 6 to 11 years and weighing ≥ 35 kg who received a dose of 30 mg had higher exposure to benralizumab, with median trough concentrations at Week 16 62% higher than that in adults and adolescents receiving the same dose and dosing regimen. Despite this higher exposure, trough concentrations in pediatric patients aged 6 to 11 years and weighing ≥ 35 kg and receiving a dose of 30 mg fell within those observed in adults and adolescents who received 30 mg Q4W for the entirety of 1-year, phase 3 studies (SIROCCO, CALIMA and ZONDA) in the benralizumab development program. Median trough concentrations at Week 16 in adults and adolescents who received 30 mg Q4W were 2.2-fold and 2.6-fold greater, respectively, than that in pediatric patients 6 to 11 years of age receiving 30 mg Q8W. A similar safety profile was observed for adults and adolescents in SIROCCO, CALIMA, and ZONDA who received a higher dose (30 mg Q4W, n=896) compared to adults and adolescents who received the approved dosing regimen (n=1835), supporting safety of the 30 mg dose in children 6-11 years of age weighing ≥ 35 kg.

PD results based on changes in peripheral blood eosinophil counts indicated that the magnitude of blood eosinophil reduction from baseline was similar between pediatric patients 6 to 11

years of age and adults and adolescents, irrespective of weight group. The incidence of treatment-emergent anti-drug antibodies (ADAs) in the TATE study was 14.3% (4/28). The presence of ADAs is associated with lower trough benralizumab concentrations and impairment of blood eosinophil reduction. However, no evidence of an association of ADA status with safety was observed. Immunogenicity results were consistent with observations in adults and adolescents.

Substantial evidence of effectiveness for expansion of the asthma indication to children 6 to 11 years of age is provided by full extrapolation of efficacy from the adequate and well-controlled studies that provided support for approval of the indication in adults and adolescents aged 12 years and older, with PK matching based on the TATE study. Full efficacy extrapolation is supported by the high degree of similarity of severe asthma with an eosinophilic phenotype across the age spectrum (children to adults) and consistency of the benralizumab mechanism of action, as demonstrated by PD responses. Safety is demonstrated based on extrapolation of safety data from the adolescent and adult trials, with limited safety data obtained from the TATE Study identifying no new safety signals.

With this supplement, the Applicant introduced a new dosage strength of benralizumab (10mg/0.5mL) solution in a single-dose PFS. Review of the new dosage strength by the Office of Biotechnology Products and the PFS device and needle length by the Center for Devices and Radiologic Health identified no areas of concern and both groups recommended approval.

Overall, based on the data submitted with this sBLA, the risk-benefit is favorable, and I agree with the recommendation for Approval to expand the benralizumab indication to include children 6-11 years of age as add-on maintenance treatment for those with severe asthma, and with an eosinophilic phenotype; this recommendation is based on the reviews from the clinical, statistical, clinical pharmacology, and nonclinical review teams. Approval of benralizumab in the 6-11 age group with severe asthma with an eosinophilic phenotype would add another treatment option for this population with high morbidity; in addition, it offers the potential benefit of less frequent, Q8 week, dosing. However, the recommended regulatory action at this time is for a **Complete Response**, requiring resolution of manufacturing deficiencies before the application can be approved.

15. Appendices

15.1. References

(1) Ross KR,*et. al*. Severe asthma during childhood and adolescence: A longitudinal study. J Allergy Clin Immunol. 2020 Jan;145(1):140-146.e9. doi: 10.1016/j.jaci.2019.09.030. Epub 2019 Oct 14. PMID: 31622688.
(2) Pijnenburg MW, Fleming L. Advances in understanding and reducing the burden of severe asthma in children. Lancet Respir Med. 2020 Oct;8(10):1032-1044. doi: 10.1016/S2213-2600(20)30399-4. Epub 2020 Sep 7. PMID: 32910897.
(3) Daniel J Jackson, *et al.* Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet 2022; 400: 502–11. PMID: 35964610; PMCID: PMC9623810.
(4) Jackson DJ, *et al*; US National Institute of Allergy and Infectious Disease's Inner City Asthma Consortium. Mepolizumab for urban children with exacerbation-prone eosinophilic asthma in the USA (MUPPITS-2): a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet. 2022 Aug 13;400(10351):502-511. doi: 10.1016/S0140-6736(22)01198-9. PMID: 35964610; PMCID: PMC9623810.
(5) Martin Alonso A, Saglani S. Mechanisms Mediating Pediatric Severe Asthma and Potential Novel Therapies. Front Pediatr. 2017 Jul 5;5:154. doi: 10.3389/fped.2017.00154. PMID: 28725641; PMCID: PMC5497140.
(6) Lo Presti D, Ingegnosi C, Strauss K. Skin and subcutaneous thickness at injecting sites in children with diabetes: ultrasound findings and recommendations for giving injection. Pediatr Diabetes. 2012 Nov;13(7):525-33. doi: 10.1111/j.1399-5448.2012.00865. Epub 2012 May 14. PMID: 22583390.

15.2. Financial Disclosure

The financial disclosure checklist for the clinical trial submitted to this sBLA is provided below.

Covered Clinical Study (Name and/or Number): TATE Trial/D3250C00025

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 93		
Number of investigators who are Sponsor employees (including both full-time and part-time		

<table>
<tr><td colspan="3">employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
Significant payments of other sorts: 0
Proprietary interest in the product tested held by investigator: 0
Significant equity interest held by investigator in S
Sponsor of covered study: 0</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
</table>

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. TATE Study

To support the use of benralizumab in pediatric patients aged 6 to 11 years, the Applicant conducted study D3250C00025 (TATE study), an open-label, parallel-group study to evaluate the PK, PD, and long-term safety of benralizumab in pediatric subjects with severe eosinophilic asthma. The primary objectives of the study were to evaluate the PK and PD of benralizumab following SC administration in pediatric subjects with severe eosinophilic asthma. PD assessments were based on the change from baseline in peripheral blood eosinophil count.

Secondary objectives included evaluations of immunogenicity and effects on pulmonary function and asthma symptoms.

Study Design

Study D3250C00025 was designed as an open-label, parallel-group, multicenter study in pediatric subjects aged 6 to 14 years with severe eosinophilic asthma (n = 30). The study enrolled 28 subjects aged 6 to 11 years, and 2 Japanese subjects aged 12 to 14 years. All subjects had a peripheral blood eosinophil count of at least 150 cells/µL at baseline. Subjects were stratified by weight (< 35 kg or ≥ 35 kg) and allocated to receive either 10 or 30 mg benralizumab based on weight stratum. The 2 Japanese subjects aged 12 to 14 years received the 30 mg dose without being stratified. Subjects entered a 48-week treatment period that was comprised of two parts as follows:

Part A: 16-week treatment period to evaluate PK, PD, and safety
Part B: 32-week treatment period to evaluate safety

In each cohort, benralizumab was administered SC every 4 weeks (Q4W) for the first three doses, and then every 8 weeks (Q8W) thereafter. The dosing regimens evaluated in study D3250C00025 are the proposed pediatric dosing regimens:

6 to 11 years weighing < 35 kg: 10 mg
6 to 11 years weighing ≥ 35 kg: 30 mg

All treatments were administered into the upper arm, thighs, or abdomen. The site of injection was rotated such that subjects received injections at a different anatomical site at each treatment visit. The study schema is shown in Figure 6.

Noteworthy Inclusion and Exclusion Criteria

Inclusion Criteria

Patient had to be 6 to 11 years of age inclusive (6 to 14 years of age inclusive in Japan), at the time of signing the informed consent form
Diagnosis of severe asthma for at least 12 months prior to Visit 1
Eosinophilic airway inflammation that was related to asthma characterized as eosinophilic in nature as indicated by peripheral blood eosinophil count of ≥ 150 cells/µL at Visit 1
A well-documented requirement for regular treatment with inhaled corticosteroids (ICS)
Current treatment with at least one additional controlled medication, such as inhaled long-acting beta-agonist (LABA), since at least 3 months prior to Visit 1.
Body weight ≥ 15 kg

Exclusion Criteria

Use of immunosuppressive medication within 3 months prior to Visit 1. Chronic maintenance corticosteroids for the treatment of asthma were allowed.
Receipt of immunoglobulin or blood products within 30 days prior to Visit 1
Receipt of any marketed or investigational biologic within 4 months or 5 half-lives, whichever was longer, prior to Visit 1

Initiation of new allergen immunotherapy was not allowed within 30 days prior to Visit 1.
Current use of any oral or ophthalmic non-selective β-adrenergic antagonist.
Alanine aminotransferase (ALT) of aspartate aminotransferase (AST) level ≥ 1.5x the upper limit of normal confirmed during the screening period.

The subject's usual pre-study ICS and/or oral corticosteroid formulations, doses and regimens, and any other additional asthma controlled has to be continued throughout the screening and treatment periods.

Subject Disposition and Demographics

A total of 30 subjects were enrolled in the study, including 28 subjects aged 6 to 11 years and 2 Japanese subjects aged 12 to 14 years. For subjects aged 6 to 11 years, the median [range] age was 9 [6, 11] years. Among the 28 subjects aged 6 to 11 years, 15 were stratified to the < 35 kg weight category (median [range] = 27.3 [20.3, 34.2] kg) and received the 10 mg dose. The remaining 13 were stratified to the ≥ 35 kg weight category (median [range] = 48.0 [35.0, 77.7] kg) and received the 30 mg dose. Out of 30 subjects, 29 (96.7%) completed the study, including all 28 subjects aged 6 to 11 years. One Japanese subject aged 13 years was withdrawn from the study prematurely due to parent/guardian decision.

For those subjects aged 6 to 11 years and weighing < 35 kg (n = 15), most were male (n = 11, 73.3%), Asian (n = 8, 53.3%), and not of Hispanic or Latino ethnicity (n = 14, 93.3%). For subjects aged 6 to 11 years and weighing ≥ 35 kg (n = 13), most were male (n = 8, 61.5%), Black or African American (n = 38.5%), and not of Hispanic or Latino ethnicity (n = 8, 6.5%). The distribution of baseline peripheral eosinophil counts was also comparable across weight groups. Among patients aged 6 to 11 years, the median [range] eosinophil count was 400 [150, 1020] for subjects weighing < 35 kg, and 340 [150, 1520] for subjects weighing ≥ 35 kg.

PK, PD and ADA Sample Collection

Blood samples for PK were collected on Days 0, 1, 7, 14, 28, 56, 84, 112, 168, and 336. Samples were collected pre-dose on Days 0, 28, 56, 112, and 168, and at any time of day on the remaining time points.

Serum samples for assessment of immunogenicity were collected pre-dose on Days 0, 56, 112, and 168. Another sample was collected on Day 336.

Peripheral blood eosinophil counts were assessed as a PD marker. Eosinophil counts were measured as part of the standard hematology assessment (complete blood count [CBC] with differential). Samples to conduct this assessment were collected at Screening/Baseline, and post-dose on Days 28, 56, 84, 112, 168, and 336.

PK, PD and ADA Analysis

The PK analysis set included all subjects who received at least one dose of benralizumab and from whom PK blood samples were not assumed to be affected by factors such as protocol

violations and who had at least one quantifiable serum PK observation post-first benralizumab dose. All enrolled subjects were included in the PK analysis set.

PK parameters were determined using non-compartmental analysis of the first dose benralizumab serum concentration-time profile. Serum concentrations and PK parameters were summarized by treatment/weight group using descriptive statistics. Serum concentration data associated with positive anti-drug antibody (ADA) status were flagged and excluded from summary statistics and mean profiles.

Population PK modeling was also used to characterize the PK of benralizumab. A previously developed population PK model using data from patients with severe asthma was amended as needed using a Bayesian approach to characterize benralizumab PK in pediatric subjects. The effect of covariates, including age, sex, race, baseline eosinophil count, body weight, and ADA status, were also evaluated in the population PK model. For additional details on the population PK methodology and analysis, refer to the Pharmacometrics Review in Section 15.3.3.

Assessment of PD was one of the primary objectives of study D3250C00025 based on change in peripheral blood eosinophil counts. Values and changes from baseline at each visit were summarized using descriptive statistics for each treatment/weight group. Data were summarized based on the safety analysis set, which was comprised of all subjects who received at least one dose of benralizumab.

Assessment of immunogenicity was a secondary objective in study D3250C00025. All listings and summaries were based on the safety analysis set. ADA-positive samples were further tested for the presence of neutralizing antibodies (nAbs). The number and percentage of patients who developed ADAs to benralizumab were determined for each of the following categories:

Positive ADA at any time (ADA prevalence)
Treatment-emergent ADA positive (ADA incidence), defined as either treatment-induced or treatment-boosted ADA-positive
Positive ADA at both baseline and at least one post-baseline measurement
Positive ADA at baseline only
Persistently positive ADA, defined as having at least two post-baseline ADA-positive measurements within at least 16 weeks between the first and last positive measurements
Transiently positive ADA, defined as having at least one post-baseline ADA-positive measurement and not fulfilling conditions for persistently positive
NAb positive at baseline and/or post-baseline (nAb prevalence)
Treatment-induced nAb-positive (nAb incidence)

In addition to the above, hypersensitivity AEs reported during the treatment period were presented by preferred term and ADA status. The effect of ADAs on PK, PD, safety, and efficacy was evaluated.

Exclusions

All enrolled subjects were included in the PK analysis set.

Some subjects were excluded from summary statistics determined for $AUC_{0\text{-}28d}$, which was determined based on benralizumab concentration data after the first dose (samples collected at Days 1, 7, 14, and 28). The exclusions included 5 subjects in the < 35 kg weight group (dose of 10 mg), and 3 subjects in the ≥ 35 kg weight group (dose of 30 mg). Subjects were excluded because the last sample was collected more than 10% prior to the scheduled Day 28 visit. It was presumed that the AUC estimated via non-compartmental analysis would be underestimated.

15.3.2. Bioanalytical Methods

PK Bioanalytical Method (ICD 561)

For study D3250C00025 (TATE study), benralizumab concentrations were quantified in human serum samples using Method ICD 561 – An Electrochemiluminescent (ECL) Method for the Quantitation of Benralizumab in Human Serum (b) (4)). This method used to quantitate benralizumab concentrations is the same as that used on samples from previously submitted phase 3 studies supporting approval of the original BLA. A validation report (Project RCNO2) was provided with the original submission for BLA 761070 (submitted November 16, 2016) and determined to be acceptable (refer to Clinical Pharmacology Review in DARRTS dated July 17, 2017).

The assay uses a sandwich format with capture and detection antibodies recognizing two distinct epitopes on benralizumab. Benralizumab is captured using a biotinylated anti-benralizumab monoclonal antibody bound to a streptavidin coated Meso Scale Discovery (MSD) plate. The captured benralizumab is detected using a sulfo-TAG labeled anti-benralizumab antibody that recognizes a different epitope from the capture antibody. An ECL signal is generated following application of an electrical current to activate ruthenium on the detection antibody. The ECL signal is proportional to the amount of sandwich complex present in the well. The linear range of the assay is 3.86 to 1250 ng/mL, and the minimum required dilution (MRD) is 1:50.

To support the use of Method ICD 561 to samples from study D3250C00025, the Applicant submitted an addendum to the method validation report to evaluate the selectivity of the method in pediatric human serum (Project RCNO11): Addendum 9 – Selectivity in Pediatric Human Serum (issue date: January 20, 2023). The following was determined:

Analysis using the original assay diluent, Blocker Casein in PBS, produced unacceptable results in human pediatric serum samples spiked with 4.83 ng/mL benralizumab, with most samples falling outside acceptance criteria of within 20% of the theoretical value.

Further analysis with unspiked matrix blank controls yielded higher than usual responses. All samples were within 20% of the theoretical values when analyzed at the high QC level (1000 ng/mL).

Analyses were re-conducted using a different assay diluent, Scytek SuperBlock. Results met the criteria for demonstrating specificity and selectivity in pediatric human serum with no evidence of interference with blank matrix

At the 4.83 ng/mL level, 8/10 (80%) samples were within 20% of the theoretical value
At the 1000 ng/mL level, 9/10 (90%) samples were within 20% of the theoretical value

Based on the results from Project RCNO11, Method ICD 561 used in study D3250C00025 was updated to use the Scytek SuperBlock assay diluent (Version 1.02).

Table 12. Method Performance in Study D3250C00025 (TATE)

Assay passing rate	• **25/26 runs met the method acceptance criteria** • **One run was rejected due to unacceptable quality control samples**	**Yes**
Standard curve performance	• Except for masked samples, all standard curve samples across all runs fell within ± 20% of the nominal value (± 25% for the LLOQ) • For two runs, the LLOQ calibration standard (3.86 ng/mL) was excluded from calculations due to unacceptable quantitation. For these runs, the LLOQ was raised to the next calibration standard (7.72 ng/mL) • Cumulative accuracy (% bias) range: -5.2 to 5.6% • Cumulative precision (% CV): ≤ 3.7%	Yes
QC performance	• Across all passing runs, QC performance met acceptance criteria based on at least 2/3 of the total QCs and at least 50% at each concentration level falling within ± 20% of the nominal values • Cumulative accuracy (% bias) range: -2.7 to -0.2% • Cumulative precision (% CV): ≤ 10.4% • Percent total error (%TE): ≤ 13.0%	Yes
Method reproducibility	• Incurred sample reanalysis was performed for 36/257 samples (14.0%). • 32/36 samples (88.9%) met acceptance criteria based on percent difference ≤ 30% of the mean.	Yes
Repeat analysis	Sample analysis was repeated for the following reasons: • Original result was above the ULOQ • A diluted sample quantitated below the LLOQ that was raised due to the deletion of a calibration standard	Yes

Assay passing rate	• **25/26 runs met the method acceptance criteria** • **One run was rejected due to unacceptable quality control samples**	**Yes**
	• Replicate analysis CV was unacceptable For all samples in run 16RNCY and one sample in run 13RNCY, samples were reanalyzed as part of an investigation. The investigation was initiated as more than one-half of samples selected for incurred sample reanalysis to support these runs failed to meet acceptance criteria.	
Study sample analysis/ stability	All samples were stored at -80 °C until analysis. Samples were stored for a maximum of 456 days between sample collection and analysis. All samples were received between (b) (4); and analyzed between (b) (4). All samples were analyzed within the established stability of 1379 days at -80 °C.	

Source: PK Bioanalytical Report for Study D3250C00025, Appendix 16.1.13

Overall, the bioanalytical performance for quantitation of benralizumab in human serum samples in study D3250C00025 (TATE) is acceptable.

PD Analysis Method

In study D3250C00025, PD was measured by evaluating changes in peripheral blood eosinophil values from baseline. Samples for analysis of peripheral blood eosinophils were collected as part of the standard hematology assessment (complete blood count [CBC] with differential).

15.3.3. Pharmacometrics Review

Review Summary

In general, the Applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in Table 13.

Table 13. Specific Comments on Applicant's Final Population PK Model

Utility of the final model			**Reviewer's Comments**
Support proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	"Among patients aged 6 to 11 years weighing <35 kg who received 10 mg, the median trough concentration at Week 16 was similar to that of adults and adolescents who received 30 mg. Among patients aged 6 to 11 years weighing ≥35 kg who received 30 mg, the median trough concentration at Week 16 was 62% higher relative to adults and adolescents receiving the same dose, due to lower body weight in pediatric patients." "Based upon the pharmacokinetic data from TATE, a subcutaneous dose of 10 mg (patients <35 kg) and subcutaneous dose of 30 mg (patients ≥35 kg) of benralizumab administered every 4 weeks for the first 3 doses, then every 8 weeks thereafter in patients aged 6 to 11 years was determined to have similar or higher exposure, respectively, to adults and adolescents administered a subcutaneous dose of 30 mg with the same dosing regimen [see Clinical Pharmacology (12.3)]. The pharmacodynamic response observed in TATE for pediatric patients aged 6 to 11 years was similar to that observed in adults and adolescents [see Clinical Pharmacology (12.2)]. "	Acceptable
	Extrinsic factor	NA	NA
Derive exposure metrics for	NA		NA

Utility of the final model		**Reviewer's Comments**
Exposure-response analyses		
Predict exposures at alternative dosing regimen	NA	NA

Source: Reviewer-generated table; proposed labeling for FASENRA [benralizumab]

Population PK Analyses

Objectives

The aim of this analysis was to characterize the population PK of benralizumab in pediatric patients (aged 6 to 13) with severe eosinophilic asthma.

The specific objectives were:

Objective 1: To compare the observed pediatric PK to projections from the existing population PK model in adult and adolescent asthma patients.
Objective 2: To describe the population PK characteristics of benralizumab, including associated interindividual variability (IIV) and residual unexplained variability (RUV) in pediatric patients with severe eosinophilic asthma.
Objective 3: To evaluate the impact of selected covariates on benralizumab PK in children.
Objective 4: To derive individual benralizumab PK parameter estimates, including CL, half-life (t1/2) and body weight (WT) adjusted CL.

Data

The data for this analysis originate from one study (TATE2). Key characteristics of the benralizumab PK analysis data set are provided in Table 14.

Table 14. Key Characteristics of the Benralizumab PK Analysis Data Set

	Benralizumab PK
Number of subjects	30
Number of samples	257
Development phase	3
Age (year) [median (min, max)]	9 (6, 13)
Weight (kg) [median (min, max)]	34.6 (20.3, 77.7)
Sex	11 females, 19 males
Subject type	pediatric patients with severe eosinophilic asthma
Race	11 Asian, 8 White, 8 Black, 3 Other
Dose levels and regimens	10 mg (<35 kg) or 30 mg (≥35 kg) at Day 0 and Weeks 4, 8, 16, 24, 32 and 40
Route of administration and formulation	SC

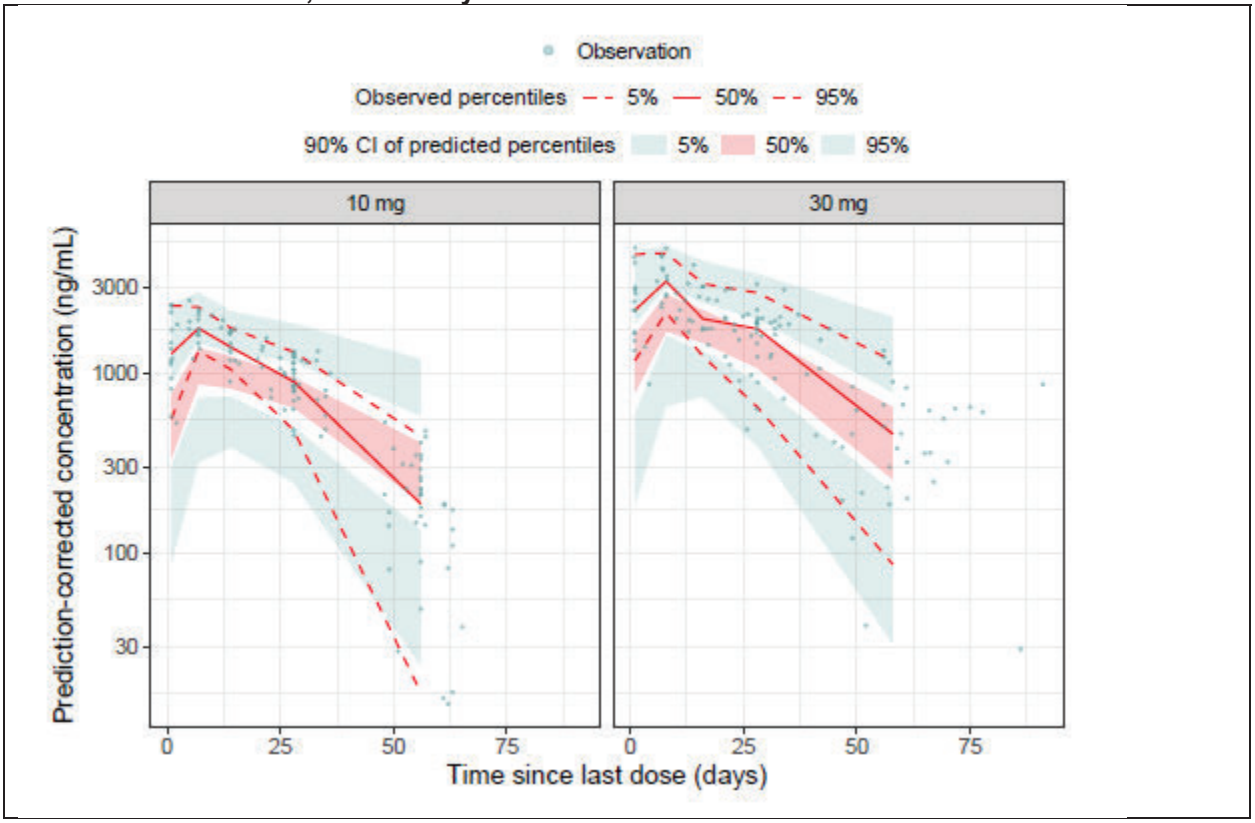
Source: Sponsor's PopPK report

Overview of model development

An existing model (referred to as the legacy model) describing the PK characteristics of benralizumab in adult and adolescent patients with asthma was evaluated first and resulted in a base model which was further evaluated with testing potential covariates. No statistically significant covariate-parameter relationships were identified. Thus, the final model was unchanged compared to the base model.

Legacy Model: An evaluation of the legacy model using the current benralizumab PK analysis data set was performed. The observed benralizumab concentrations in children with severe eosinophilic asthma were compared to projections from the legacy population PK model developed based on data in adult and adolescent patients with asthma. The resulting GOF plots showed an acceptable agreement between the observed data and the legacy model predictions at the end of the PK profile, however for earlier time points the benralizumab concentrations were underestimated (See Figure 7).

Figure 7. Prediction-Corrected Visual Predictive Check of Benralizumab PK Serum Concentrations Versus Time Since Last Dose, for the Benralizumab PK Analysis Data Set, Using the Legacy Benralizumab PK Model, Stratified by Dose Level



Source: Sponsor's report.

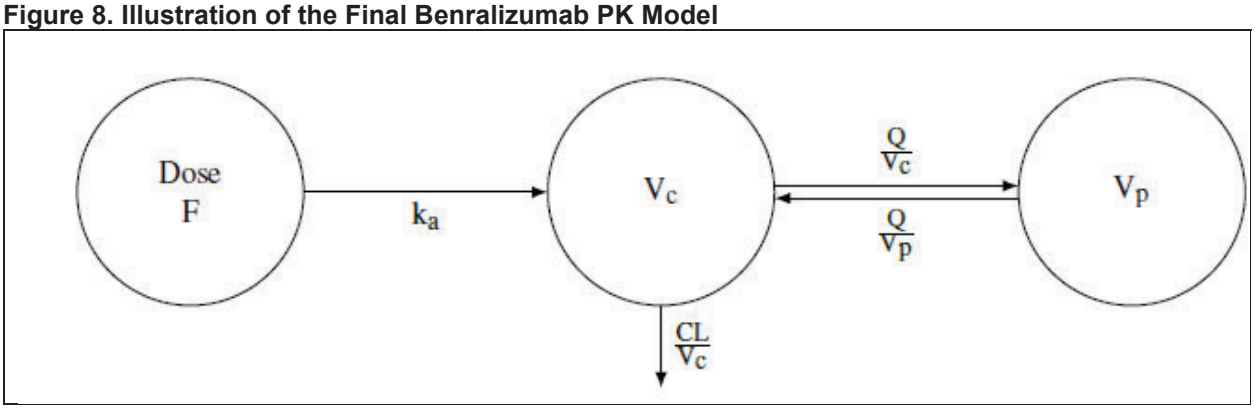
From Legacy Model to Base Model: When the parameter could be estimated with reasonable precision after removing the prior, and the corresponding model provided a better description of the observed data, the model was retained. The best performing model resulting from these evaluations was considered to be the base model.

Base/Final Model: The base model had the same characteristics as the legacy model with all parameters estimated using priors, except the following ones:

F was fixed to the value estimated in the legacy model.
As in the legacy model, IIV on Q was fixed to 8.9 % CV.
The residual unexplained variability (RUV) parameter was estimated without a prior.
CL and ka where estimated without a prior.

No statistically significant covariate-parameter relationships were identified. Thus, the base model and the final model had the same structure (See Figure 8).

Figure 8. Illustration of the Final Benralizumab PK Model



Source: Sponsor' report

Covariate Model: A search for significant exploratory covariate-parameter relationships was performed using the stepwise covariate modeling procedure. No statistically significant covariate-parameter relationships were identified.

Final Model: The final model structure is illustrated in Figure 10. The parameter estimates of the final benralizumab model are presented in Table 15. All parameters could be estimated with good precision and the final parameter estimates were relatively similar to the ones from the legacy model. In the final model, the estimated values of $t1_{/2abs}$ and allometric coefficients for the WT effect on CL, Vc and Vp were slightly different, compared to the legacy model.

Prediction-corrected visual predictive checks (pcVPCs) generally show a good agreement between the observations and the model predictions (Figure 11).

Key Model Assumptions: The PK characteristics of benralizumab are similar in adolescents/adults with asthma and in children with severe eosinophilic. The structure of the legacy model as well as priors built based on the parameter estimates from the legacy model were used for model development since available pediatric (aged 6-14) data in the TATE

study was limited and sparse. Different model might be obtained when developing from scratch based on rich data in the children with severe eosinophilic asthma.

Reviewer's Question: The Population PK (PPK) analysis was performed using the benralizumab serum concentrations collected from pediatric patients who participated in the TATE study. A previously developed PPK model in patients with severe asthma was utilized and amended as needed to characterize benralizumab PK in this pediatric patient population via a Bayesian approach. An information request was issued to clarify the rationale for using this novel approach rather than the traditional pooled analysis.

Figure 9. IR Response to Our Review Question

As stated in the seminal paper by Gisleskog et al 2002 on using prior information to stabilize population PK analyses, pooling data versus using the $PRIOR subroutine in NONMEM produces similar results for parameter and standard error estimation. This was validated in this benralizumab population PK analysis where the adult model was able to predict the pediatric concentrations of benralizumab (Figures 8 and 9, REP-2-AZ_BEN-PMX-1.pdf). This was further substantiated by the similarities demonstrated in the parameter estimates (Table 7, REP-2-AZ_BEN-PMX-1.pdf). These two aspects were considered to be important to evaluate the use of PRIOR approach as highlighted in a recent review by Chan Kwong et al 2020.

Advantages of using a PRIOR approach can be beneficial over using a pooled data approach are as follows:

1) Models built with PRIORS can be more stable or reduce the residual unexplained variability (Pérez-Ruixo at al 2011 and Cella et al 2010).

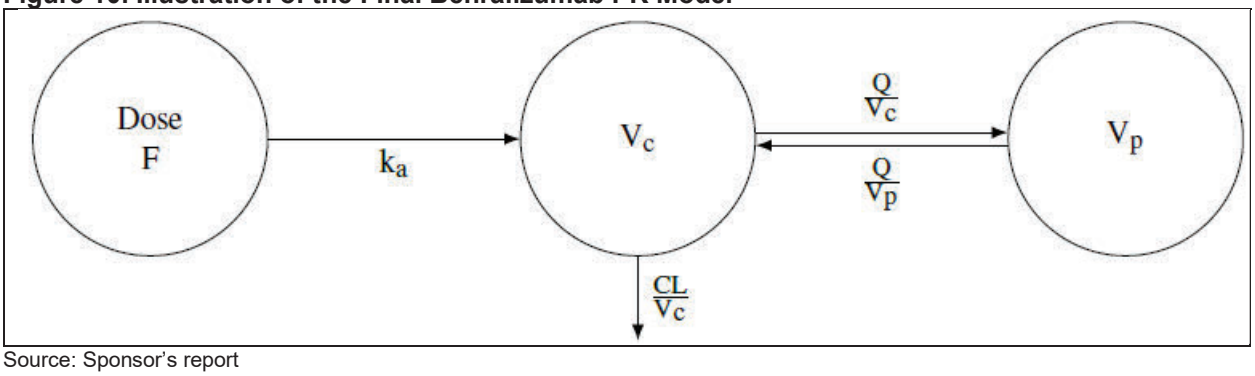
2) Using a PRIOR approach can prevent a large number of subjects and samples in the rich PRIOR study from driving the estimates of a small new dataset (Knebel et al 2013).

3) Analysis can be completed more efficiently in a single NONMEM run (Marshall et al 2006).

Source: Applicant's Response to May 5, 2023 IR, submitted May 9, 2023

Comments: Reviewers agree with Sponsor's rationale for the approach adapted in the popPK analysis. The final benralizumab PK model in pediatric patients with severe eosinophilic asthma provided a good description of the observed data, overall and in treatment, and WT subgroups.

Figure 10. Illustration of the Final Benralizumab PK Model



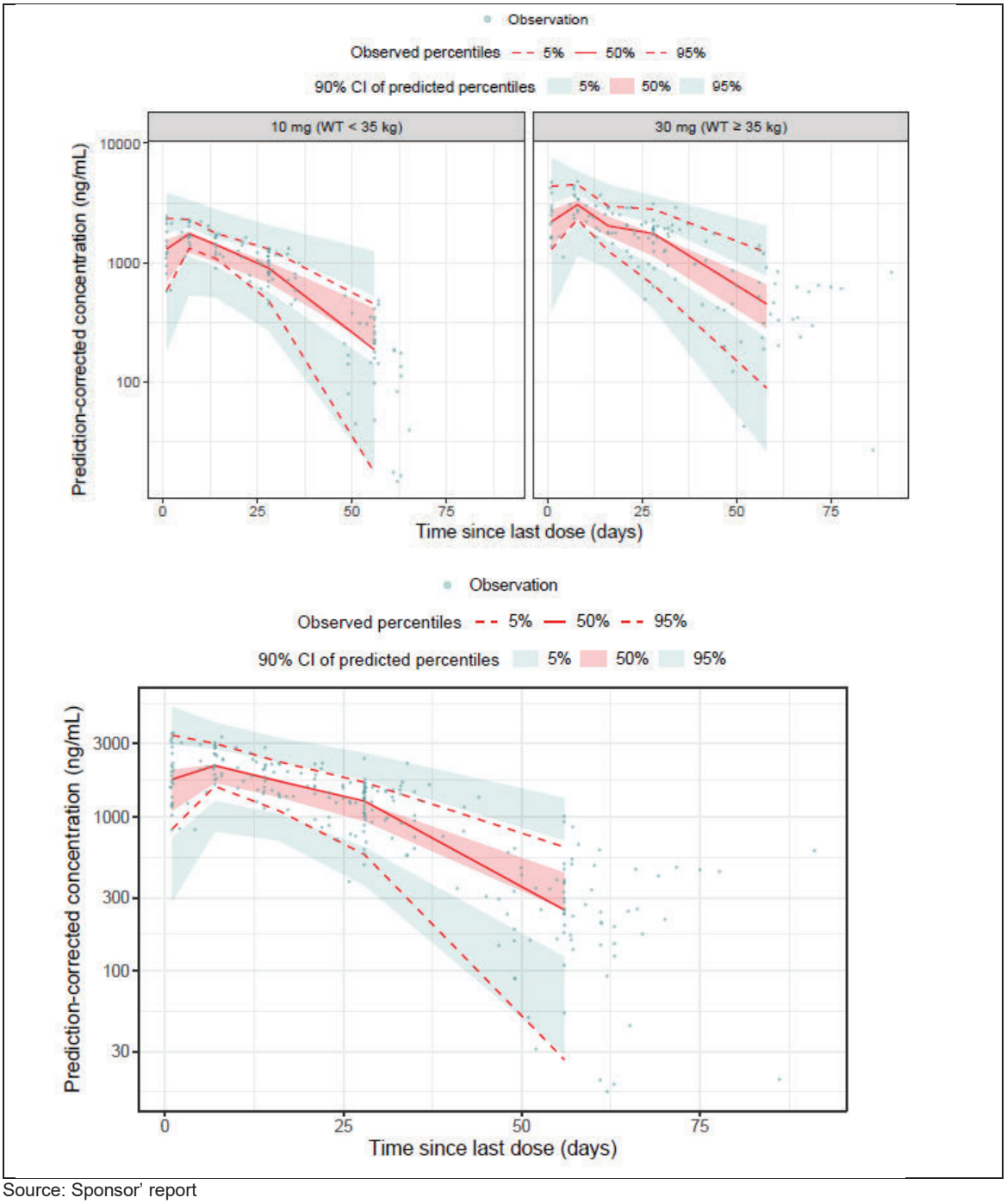
Source: Sponsor's report

Table 15. Comparison of the Parameter Estimates Between the Final Benralizumab PK Model and the Legacy Benralizumab PK Model

		Final model		Legacy model	
	Unit	Value	RSE (%)	Value	RSE (%)
CL	(L/day)	0.257	5.23	0.289	2.25
V_c	(L)	3.00	2.98	3.13	3.22
Q	(L/day)	0.699	5.14	0.739	5.09
V_p	(L)	2.40	4.00	2.52	4.44
k_a $t_{1/2abs}$	(day)	1.95	13.1	3.56	7.22
F		0.589	(FIX)	0.589	2.51
WT on CL		0.866	3.68	0.807	4.24
ADA on CL		2.34	1.50	2.24	1.52
WT on V_c		1.01	9.76	0.803	13.3
WT on V_p		0.630	13.7	0.528	20.5
IIV CL	(CV)	0.240	3.63	0.241	3.73
IIV V_c	(CV)	0.249	8.00	0.244	8.40
IIV Q	(CV)	0.0894	(FIX)	0.0894	(FIX)
IIV V_p	(CV)	0.443	5.47	0.447	5.42
IIV k_a	(CV)	0.801	4.92	0.831	5.33
IIV F	(CV)	0.173	10.9	0.171	11.3
RUV	(CV)	0.228	13.4	0.250	2.76

Source: Sponsor' report

Figure 11. Prediction-Corrected Visual Predictive Check of Benralizumab PK Serum Concentrations Versus Time Since Last Dose, for the Benralizumab PK Analysis Data Set, Using the Final Benralizumab PK Model



Source: Sponsor' report
Note: Data are presented on a semi-logarithmic scale

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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