CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761070Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Lydia Gilbert-McClain, MD, FCCP, Deputy Division Director, DPARP Badrul Chowdhury, MD, PhD, Division Director, DPARP and Curtis Rosebraugh, MD, MPH, Office Director, ODEII
Subject	Division Director Summary Review
NDA/BLA # Supplement #	761070
Applicant Name	AstraZeneca
Date of Submission	November 16, 2016
PDUFA Goal Date	November 16, 2017
Proprietary Name / Established (USAN) Name	FASENRA/Benralizumab
Dosage Forms / Strength	Solution for injection/30 mg/mL
Proposed Indication(s)	Add on maintenance treatment for patients with severe asthma 18 years of age and older and with an eosinophilic phenotype
Action/Recommended Action for NME:	*Approval*
Approved/Recommended Indication/Population	Add on maintenance treatment for patients with severe asthma 12 years of age and older and with an eosinophilic phenotype

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sofia Chaudhry, MD
CDTL	Lydia Gilbert-McClain, MD
Statistical Review	Yu (Jade) Wang, PhD, Yongman Kim, PhD
Pharmacology Toxicology Review	Carol Galvis, PhD, Timothy Robison PhD
CMC Review/OBP Review	Jennifer Swisher, PH.D., Sarah Kennett, Ph.D, Kathleen Clouse, Ph.D
Microbiology Review	Maria Jose Lopez-Barragan, Candace Gomez-Broughton
Clinical Pharmacology Review	Suryanarayana Sista, PhD, Yunzhao Ren, MD, PhD, Jingyu Yu, PhD, Anshu Marathe, PhD, Ping Ji, PhD
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OND=Office of New Drugs; OPDP=Office of Prescription Drug Promotion (OPDP); DMEPA=Division of Medication Error Prevention and Analysis; OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Patients with severe asthma represent a small subset of asthmatic patients at particular risk for increased morbidity and mortality. Two other IL-5 targeting therapies have been approved in past two years targeting patients with severe asthma and an eosinophilic phenotype. Asthma with eosinophilic phenotype is a serious condition with chronic morbidity, including frequent exacerbations which often require hospital or emergency department care. In addition to high dose inhaled corticosteroids, these patients are often on systemic corticosteroids. Due to the undesirable effects of long-term systemic corticosteroid use, alternate treatments for these patients that could limit or eliminate systemic corticosteroid use would be a therapeutic advantage.

The efficacy and safety of benralizumab in this patient population was evaluated in three pivotal phase 3 trials including two exacerbation trials and one oral corticosteroid reduction trial. All were well-controlled and adequately designed to assess the efficacy of benralizumab in the severe asthma population. Both exacerbation studies demonstrate statistically significant and clinically meaningful improvements in exacerbations for patients receiving benralizumab beyond that provided by high dose ICS/LABA therapy. In addition, for patients requiring OCS to control their asthma, benralizumab therapy allowed a larger percentage of patients to reduce their OCS dose. All three trials also demonstrate numeric improvements in FEV_1 compared with placebo. An increased treatment benefit is consistently seen in patients with higher baseline peripheral blood eosinophil counts. While efficacy was not conclusively demonstrated in the adolescent population, a sufficiently powered study to demonstrate a treatment benefit would be impractical to conduct given the rarity of this severe asthma phenotype. There are no age-related differences in the PK and PD and the course of the disease is the same in adults and children. There are no safety concerns to offset the potential efficacy of benralizumab in adolescent patients, so it is reasonable to approve the product in patients 12 years of age and older.

In addition to the standard safety assessments the program also included an assessment of safety concerns of special interest with biologics including infections, malignancy, hypersensitivity events, and immunogenicity. No safety concerns have been identified that would warrant unique warnings/precautions for Benralizumab. A fairly high level (~ 13 – 15%) of anti-drug antibody (ADA) was observed in the clinical development program which was associated with a decrease in PK and an increase in eosinophil counts; however, there was no decrease in the efficacy response in ADA positive subjects and the elevated ADA levels were not associated with any safety concerns.

The benefit-risk assessment favors approval of Benralizumab in patients 12 years of age and older given the serious nature of the disease, and as Benralizumab may provide an alternative to those patients who do not tolerate the other drug in the class approved by the FDA for patients 12 years of age and older (i.e. mepolizumab).

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. Episodic increases in symptoms are referred to as asthma exacerbations. The disease 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 leading to	Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma patient population with severe disease continues to experience significant morbidity and the potential for mortality from this condition

	chronic symptoms despite current standard of care treatment. While many exacerbations may be managed as outpatient with the use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death. • Severe uncontrolled asthma is estimated to account for approximately 5% of all patients with asthma. While there are no specific guidelines to identify patients with severe asthma and an eosinophilic phenotype, the estimated prevalence is thought to be 3% or less.	
Current treatment options	There are two other IL-5 targeting therapies approved for the treatment of patients with severe asthma and an eosinophilic phenotype.	While there are two approved therapies treating this specific subset of asthma patients, the availability of additional treatment options for those unable to tolerate existing treatments is preferable. Further, only one of the currently approved therapies is approved for patients 12 - 17 years of age.
Benefit	Reduction in annual rate of asthma exacerbations Reduction in hospitalization due to exacerbations Reduction in oral corticosteroid use (in patients on oral corticosteroids to control their severe asthma) Improvement in lung function (FEV1) Improvement in Asthma Control Questionnaire (ACQ) and The Asthma Quality of Life Questionnaire (AQLQ)	
Risk	No increased risks in adverse events of interest such as anaphylaxis, opportunistic infections, or malignancy were seen in the controlled trials. Hypersensitivity reactions (including urticaria, angioedema, rash) occurred in the controlled trials and one case of anaphylaxis was reported in the open label extension studies	The program does not show any safety concerns that would offset the efficacy findings
Risk Management	No REMS is proposed	The risks of hypersensitivity reactions and anti-drug antibody formation as well as the reported common adverse reactions (headache, pyrexia, pharyngitis) with benralizumab can be managed through routine pharmacovigilance and product labeling.

2. Background

Asthma is a chronic inflammatory disorder of the airways affecting children and adults of all ages. It is one of the most common chronic diseases worldwide and globally an estimated 300 million individuals are affected by asthma. In the United States, the prevalence of asthma among adults is 7.4% and 8.6% among children according to 2014 data from the Centers for Disease Control and Prevention (CDC). Multiple cell types in the inflammatory cascade (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) are involved in the

pathogenesis of asthma. Eosinophilic inflammation of the airways plays a central role in the pathogenesis of asthma. IL-5 is the main cytokine involved in the regulation of blood and tissue eosinophils.

Several classes of products are available for use in patients with persistent asthma. These include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agents (LABAs), and fixed dose combination of ICS/LABAs, leukotriene modifying drugs, methylxanthines, and the long-acting anticholinergic Spiriva (tiotropium) Respimat. In addition, 3 monoclonal antibodies are also approved. These include one monoclonal antibody to IgE (omalizumab) and two monoclonal antibodies that target the Il-5 pathway (i.e. mepolizumab and reslizumab).

Severe asthma has been defined as asthma that requires treatment with medium-to high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy.[1] About 3 to 5 percent of asthma patients have severe persistent asthma. Xolair is approved for patients with moderate to severe persistent asthma and a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. The two currently approved anti-IL 5 monoclonal antibodies -mepolizumab, and reslizumab has so far been limited to severe asthma with an eosinophilic phenotype. The eosinophilic phenotype or "eosinophilic asthma" has been described as associated with elevated blood and sputum eosinophil counts. A consensus definition of "eosinophilic asthma" has not been defined in the scientific community and while the academic community is unified in the overall characterization of this asthma phenotype (i.e. severe asthma that is difficult to control despite maximum therapy) a specific cut-off for elevated blood, or sputum eosinophil levels as a criterion has not been established. For the benralizumab development program, AstraZeneca used a proprietary mathematical algorithm defined as the ELEN index to predict sputum eosinophils ≥ 2% as one of the criteria to select patients for their dose-ranging study that would inform dose selection for the phase 3 program. For the phase 3 program they used a blood eosinophil cut-off of 300/µL to enroll patients in the pivotal exacerbation studies.

Regulatory Interactions between the Agency and AstraZeneca

The Division and AstraZeneca had the typical milestone meetings regarding the development program for benralizumab for asthma. The Division met with AstraZeneca on Feb 13, 2013 for an End-of -Phase 2 (EOP2) meeting where the dose selection and other design elements of the phase 3 program were discussed. The points raised at the EOP2 meeting were as follows: AstraZeneca proposed to use the 30 mg dose based on the observed data and potential for PK variability and increased immunogenicity with lower doses. The PD model for dose selection was discussed. FDA noted that the use of the PD modeling data was acceptable but risky and that the acceptability of choosing a higher dose to overcome immunogenicity concerns would be dependent on the safety profile of the product and recommended further dose exploration or the evaluation of more than one dose in phase 3. The FDA also recommended evaluation of patients with a range of peripheral blood eosinophil counts and AstraZeneca proposed to stratify enrollment based on eosinophil "high" and 'low" patients in a 2:1 ratio using 300/µL as the cutoff with the primary efficacy analysis conducted in the eosinophil "high" population.

[1] Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014; **43**: 343 -373

The FDA found the proposal to be acceptable. AstraZeneca also met with the Agency in a Type C meeting September 8, 2014 for further discussions on the phase 3 program. AstraZeneca's proposal to rely on data from SIROCCO and CALIMA to support registration in a severe asthma population was discussed. The FDA reminded AstraZeneca of the recommendation to evaluate the full spectrum of asthma severity but noted that targeting more severe patients may be acceptable if the program provides sufficient information to inform the selection of appropriate patients and the risk-benefit was favorable for the targeted patient population. AstraZeneca also met with the Agency in a type C meeting (May 22, 2014) (b) (4) the pre-filled syringe (PFS) is proposed for marketing with this BLA submission. AstraZeneca met with the Division on September 20, 2016 for a pre-BLA meeting where the content and format of the BLA was discussed. The strategy to pool data from SIROCCO and CALIMA was discussed and found to be reasonable. The plan for descriptive analyses for adverse events was deemed acceptable. Regarding the labeling FDA noted that data documenting a treatment's impact on exacerbation-related ER visits and/or hospitalizations are clinically meaningful and appropriate for inclusion in the package insert. The Agency also commented that inclusion of data such as exacerbation history and baseline eosinophil levels as independent predictors of treatment benefit in the package insert would be a review issue.

3. CMC/Device

Benralizumab is a humanized monoclonal antibody (IgG1/κ-class) selective for interleukin-5 receptor alpha subunit (IL-5Rα). Benralizumab is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa. The drug product FASENRA (benralizumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection in a single-dose prefilled syringe (PFS). Each PFS delivers 1 mL containing 30 mg benralizumab, L-histidine (1.4 mg); L-histidine hydrochloride monohydrate (2.3 mg); polysorbate 20 (0.06 mg); α,α-trehalose dihydrate (95 mg); and Water for Injection, USP.

The prefilled syringe (b) (4) (PFS (b) (4)) is the primary container closure system for the drug product. (b) (4) This is a marketed device that has been used with other FDA-approved products. (b) (4) None of the accessories are in contact with the drug product solution or the fluid path of the delivery system. The secondary container closure system consists of a tray insert that is placed into a paperboard carton.

The drug substance, (b) (4) are manufactured by AstraZeneca Pharmaceuticals LP Manufacturing Center, Frederick, MD, and the drug product manufacturing, labeling, and packaging is done at (b) (4)

The submitted data support an expiry of 24 months for the drug product when stored at 2 to 8^0C.

There are no approvability issues regarding the manufacturing of the drug product and drug substance. A leachable study is needed to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under recommended conditions. This evaluation does not preclude approval of the application and can be conducted as a post-marketing commitment. There are no outstanding manufacturing site inspection issues.

4. Nonclinical Pharmacology/Toxicology

The Il-5 receptor is expressed on the surface of eosinophils and basophils. In an in vitro setting the absence of fucose in the Fc domain of benralizumab facilitates binding to FcγRIII receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). Treatment with benralizumab caused a reduction in both eosinophils and basophils.

The toxicity profile of benralizumab was evaluated in cynomolgus monkeys in a 39-week toxicity study. Consistent with benralizumab's mechanism of action, eosinophil levels were decreased in treated animals at all dose levels. No drug-related histopathology findings were observed. Male and female fertility parameters were unaffected in sexually mature animals in the 39-week toxicity study. There was also no evidence of maternal toxicity in pregnant cynomolgus monkeys receiving benralizumab subcutaneously during the period of organogenesis and thorough gestation. Placental transfer was demonstrated by measuring benralizumab levels in the serum of infants exposed *in utero.* Infants exposed *in utero* to benralizumab had decreased eosinophil levels which increased gradually over time. No effects were observed in infant growth, or neurological development. Benralizumab was not teratogenic in cynomolgus monkeys. AstraZeneca did not conduct rodent carcinogenicity studies. The applicant submitted a carcinogenicity risk assessment during the development of benralizumab and the Agency's Executive Carcinogenicity Assessment Committee (ECAC) agreed that the rodent carcinogenicity studies would not be required for benralizumab. Considerations leading to this conclusion were that there no proliferative or pre-neoplastic lesion identified in cynomolgus monkeys after treatment for up to 39 weeks and benralizumab does not bind to murine IL-5Rα; therefore, a 2-year study in rodents was not feasible.

5. Clinical Pharmacology/Biopharmaceutics

AstraZeneca submitted results from a comprehensive clinical pharmacology program that included studies to assess pharmacokinetics (PK) and pharmacodynamics (PD). PD response (blood eosinophil depletion) was evaluated in a 12-week phase 2 study and in a 12-month dose-ranging study in asthmatics. The data from these studies provided support for the dose and dosing regimens evaluated in the phase 3 studies. From the phase 2 data, all benralizumab dosage groups demonstrated complete or near complete depletion of median blood eosinophil

levels. In the two phase 3 exacerbation studies, blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/µLin the 2 dosing regimens evaluated (i.e. 30 mg administered subcutaneously (SC) every 4 weeks for 3 doses followed by 30 mg SC every 8 weeks (Q8W dosing regimen), and 30 mg SC every 4 weeks (Q4W dosing regimen). This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period. Both dosing regimens depleted and maintained the low peripheral blood eosinophil counts to a similar magnitude compared to placebo. Following discontinuation of treatment in the two phase 3 exacerbation trials, the magnitude of eosinophil count reduction was maintained for at least 8 weeks with a median peripheral blood eosinophil count of 0 cells/µL in both dosing regimens (see Figures 1 and 2). The eosinophil counts started to return beyond 8 weeks post treatment in both studies (data from CALIMA depicted in Figure 3). The magnitude of reduction in the peripheral blood eosinophil counts was similar in adults and adolescents 12 to 17 year olds in the phase 3 trials. Base on the phase 3 data, there was no noticeable exposure-response relationship between median observed benralizumab steady-state trough concentrations and clinical efficacy (i.e. asthma exacerbation rate, FEV_1). At the proposed Q8W dosing regimen, the PK steady-state was reached at the third Q8W dose. The proposed Q8W dosing regimen is supported by the clinical pharmacology data.

Figures 1 and 2: Blood eosinophil count time profile following Q4W or Q8W dosing in the phase 3 trials: SIROCCO (Figure 1) CALIMA (Figure 2)

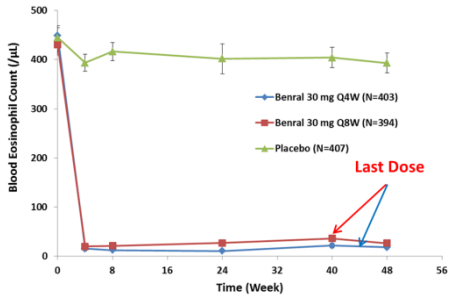


Figure1

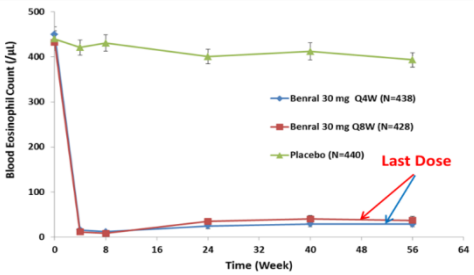
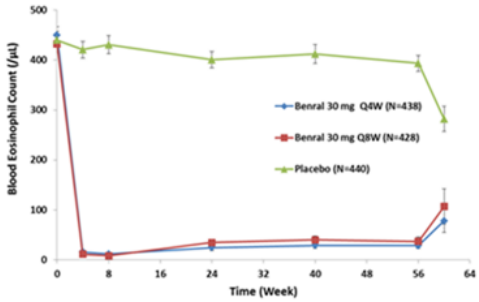


Figure 2

Source: Clinical pharmacology reviewer Dr. Yunzhao Ren

Figure 3: Blood eosinophil count time profile beyond 56 weeks (at week 60) in CALIMA



Source: Clinical pharmacology reviewer Dr. Yunzhao Ren

The pharmacokinetics of benralizumab showed dose linearity and dose proportionality between 20 to 200 mg. The estimated absolute bioavailability from population pharmacokinetic (PopPK) modelling is 58% and the relative bioavailability based on administration site (abdomen, thigh, our upper arm) is similar. From PopPK modelling, the estimated clearance of benralizumab is 0.29L/day and the half-life of elimination ($t_{1/2}$) was approximately 15 days following subcutaneous administration. Like other monoclonal antibodies, benralizumab is catabolized by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissues. Hepatic function does not influence the metabolism of Benralizumab and the potential for drug-drug interaction potential is low. The PK in adolescents 12 to 17 years of age was comparable to that in adults based on observed mean steady state trough concentrations ($C_{trough, ss}$). The PK of Benralizumab was not significantly impacted by race, ethnicity, age, or gender.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues. AstraZeneca proposed acceptable testing for the bulk drug product and the product packaged in the commercial presentation.

7. Clinical/Statistical-Efficacy

Overview of the Clinical Program

The submitted data from the clinical program are adequate to evaluate the efficacy of benralizumab for patients with severe asthma in a specified phenotype as proposed by AstraZeneca. Patients enrolled in the phase 3 studies had asthma severity based on exacerbation history, asthma medication use, and eosinophil counts. Baseline blood eosinophil count was defined as the result from Visit 1 or 3 (screening) from local laboratories and used to stratify patients at randomization. Subsequent hematology measurements for eosinophil and basophil counts were done by a central laboratory.

The patient population in the two exacerbation studies SIROCCO and CALIMA was generally balanced across the treatment groups based on demographic variables, disease characteristics, disease status. Subjects were fairly evenly distributed across the treatment arms/regimens except that there was a greater number of adolescents in the Q8W regimen compared to the Q4W regimen because the European Union only allowed randomization to the Q8W arm or placebo for adolescents, whereas, in the rest of the world adolescents were recruited into the Q4W, Q8W, or placebo arms.

The two exacerbation trials evaluated patients 12 to 75 years of age with moderate to severe asthma and a history of exacerbations who remain symptomatic despite using high-dose ICS/LABAs with or without OCS or additional controller medications. This degree of asthma

severity is consistent with asthma patients who are in NAEPP[2] steps 5 and 6 of therapeutic intervention. As per prior agreement with the Agency, patients enrolled in these trials were stratified based on having a high eosinophil count (i.e. ≥300 cells/µL) or low eosinophil count (< 300 cells/µl) at baseline. The oral corticosteroid reduction study (ZONDA) enrolled patients who in addition to high dose ICS/LABA also required OCS for asthma control. For these patients a lower eosinophil level (> 150 cells/µL) was used for study eligibility. Given the know suppressant effects of OCS on blood eosinophil levels, the eosinophil entry criterion for the OCS reduction study is reasonable. The clinical data to support dose selection for the phase 3 program came from the 52-week dose-ranging exacerbation study (MI-CP-220). Study BORA and MELTEMI are safety extension studies that were ongoing at the time of the BLA submission and safety information from those studies was included in the 120 safety day update (data cut-off point was October 21, 2016). Selected characteristics of the relevant studies that form the basis of review and regulatory decision for this application are shown in Table 1.

Table 1: Clinical trials

ID **Year** ***Study #****	**Study Characteristics** **-Patient age** **-Patient characteristics** **-Study design objectives** **-study duration**	**Treatment groups**	**N**	**Efficacy Variables**	**Regions and Countries**
MI-CP-220 12/10 -8/13	-≥ 18 years of age -moderate to severe asthma -R, DB, PC, phase 2b dose-ranging - 52 weeks	-2 mg SC Q 4wk x 3→Q8 wk -20 mg SC Q 4wk x 3→ Q 8wk -100 mg SC Q 4 wk x 3→ Q 8 wk - placebo	609	1^0: exacerbation rate 2^0: ACQ, FEV_1	95 centers in 10 countries: United States, Argentina, Brazil, Bulgaria, Canada, Columbia, Mexico, Peru, Poland
SIROCCO/017§ 9/13 -4/16 *Study 1*	-≥ 12 years of age -Moderate to severe asthma -R, DB, PC, phase 3 -48 weeks	- 30 mg SC Q 4wk→ Q 8 wk - 30 mg SC Q 4 wk - Placebo SC	1205[1]	1^0: exacerbation rate 2^0: ACQ, AQLQ, FEV_1	286 centers in 17 countries: United States, Australia, Brazil. Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russian Federation South Africa, South Korea, Spain, Turkey, United Kingdom, Vietnam
CALIMA/018 8/13 -3/16 *Study 2*	-≥ 12 years of age -Moderate to severe asthma -R, DB, PC, phase 3 -56 weeks	- 30 mg SC Q 4wk→ Q 8 wk (Q8W) - 30 mg SC Q 4 wk (Q4W) - Placebo SC	1306[2]	1^0: exacerbation rate 2^0: ACQ, AQLQ, FEV_1	242 centers in 11 countries: United States, Argentina, Canada, Chile, Germany, Japan, Philippines, Poland, Romania, Sweden, Ukraine
ZONDA/020 8/13 -3/16	-≥ 18 years of age -severe asthma requiring oral	-30 mg SC Q 4wk→ Q 8 wk (Q8W)	220	1^0: OCS reduction 2^0: exacerbations,	64 centers in 12 countries: United

[2] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and management of Asthma, 2007. Available at: http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines

ID Year *Study #**§	Study Characteristics -Patient age -Patient characteristics -Study design objectives -study duration	Treatment groups	N	Efficacy Variables	Regions and Countries
Study 3	corticosteroids and baseline eosinophil count ≥ 150 cells/µL R,DB, PC, phase 3 -28 weeks	- 30 mg SC Q 4 wk (Q4W) - Placebo SC		FEV_1, ACQ, AQLQ	States, Argentina, Bulgaria, Canada, Chile, France, Germany, Poland, South Korea, Spain, Turkey, Ukraine
BISE/032 2/15 -10/15	-≥ 18 years -mild to moderate persistent asthma -R, DB, PC -12 weeks	30 mg Q 4 week (Q4W) Placebo	211	1^0: FEV_1	52 centers in 6 countries: United States, Canada, Germany, Hungary, Poland, Slovakia
BORA (ongoing)	≥12 years and older -Patients who complete SIROCCO, CALIMA, or ZONDA R DB -56 weeks	30 mg SC Q 8 weeks 30 mg SC Q 4 weeks	2133[3]	Long-term safety	See above
MELTEMI (ongoing)	≥ 12 years and older - Patients who complete SIROCCO, CALIMA, or ZONDA and 16 weeks in BORA OL -until Benralizumab is marketed	30 mg SC Q 8 weeks 30 mg SC Q 4 weeks	345[4]	Long-term safety	See above
§The investigational number for the phase 3 studies begins with D3250C000 followed by two digits. For example, SIROCCO is D3250C00017. In the table and throughout the review the phase 3 studies will be identified by the last 3 numbers (i.e. study 017 for SIROCCO). ID = AstraZeneca's study acronym and number *Study #** =study number as identified in the package insert R, DB, PC = randomized, double-blind, placebo-controlled OL = open label					
1= > 18 years: n = 11152; 12 -17 years: n = 53 2=> 18 years: n = 1251; 12-17 years: n =55 3=Number completing treatment on investigational product 4=Number of subjects at time of data cut-off for BLA submission					

Some key characteristics of the patient population enrolled in the phase 3 studies are shown in Table 2.

Table 2: Selected Characteristics for patients (Full analysis set)[3] in the phase 3 controlled clinical studies

Characteristic	SIROCCO/017 (n = 1204)	CALIMA/018 (n = 1306)	ZONDA/020 (n =220)
Demographics/clinical characteristics			
Mean age (yr)	49	49	51
Duration of asthma, median (yr)	15	16	12
Gender (% Female)	66	62	61
BMI (mean)	29	29	30
Race (% White/Caucasian)	73	84	93
Race (% black/African-American)	4	3	2

[3] Includes both the eosinophil "high" (the primary efficacy population) and eosinophil "low" strata. The characteristics were similar in the overall population and the eosinophil 'high' population.

Characteristic	SIROCCO/017 (n = 1204)	CALIMA/018 (n = 1306)	ZONDA/020 (n =220)
Smoking history – never smoked (%)	80	78	79
Pulmonary function			
Pre-bronchodilator FEV_1 % predicted	57	58	60
Post-bronchodilator FEV_1/FVC ratio, mean	66	65	62
Reversibility, mean %ΔFEV1 post SABA	26	27	24
Eosinophil and exacerbation history			
Baseline mean blood eosinophil count (cells/μL)	472	472	575
Mean number of exacerbations in previous year	3	3	3
% patients with ≥ 2 exacerbations in previous year	62	66	29
% patients with ≥ 3 exacerbations in previous year	18	21	16%
Background treatments for asthma (% of patient)			
Mean ICS total daily dose (μg) [min. max]	899 [125,3000]	873 [12.5*,4750]	1154 [100,5000]
ICS/LABA	95%	86%	90%
LAMA	8%	8%	29%
LTRA	36%	28%	37%
Xanthine derivatives	15%	12%	15%
Oral corticosteroids (OCS) mean mg	16% (15 mg)	9% (11 mg)**	100% (14.7 mg)#

Data source: Case study reports: D3250C00017, Dc250C00018, And D3250C00020.
mean dose of OCS at optimization
*out-of-range minimum due to site data entry error
** Summary statistics for the high ICS+ high eosinophil group

Design and Conduct of the Studies

Dose-Ranging Study MI-CP-220:

The dose selection for the benralizumab phase 3 studies is based on a dose response model using PK and PD data and clinical data. The clinical data are from a 52-week dose-ranging study MI-CP-220. MI-CP-220 was a randomized, double-blind, placebo-controlled study evaluating 2 mg, 20 mg, and 100 mg of benralizumab administered SC in patients 18 years of age and older with moderate to severe asthma on medium or high-dose ICS plus a LABA and a history of ≥ 2 exacerbations in the prior year. Subjects in this dose-ranging trial were classified and stratified as having an eosinophilic phenotype (EOS+) defined as ELEN Index[4] positive and/or FeNO ≥ 50 ppb, or a non-eosinophilic phenotype (EOS-) defined as both ELEN Index negative and FENO < 50 ppb during the 3-week screening/run-in period.

[4] The ELEN Index is a proprietary mathematical algorithm to predict sputum eosinophils ≥ 2%. It was developed using multivariate statistical modelling of baseline sputum and blood data from a phase 2a clinical study (MI-CP138) that evaluated the efficacy of a humanized anti-IL9 monoclonal on late asthmatic response induced by allergen inhalation in adults with atopic asthma and validated using 2 independent datasets. In the ELEN Index, 2 predictor variables, the ratio of blood eosinophils (E) to lymphocytes (L) and the ratio of blood eosinophils (E) to neutrophils (N) were used to classify subjects as having either < 2% or ≥ 2% sputum eosinophils with the need for sputum collection. D.B. Khatry et al. A simple Index Utilizing Peripheral Blood Leukocytes predicts Sputum Eosinophilic and Non-Eosinophilic Asthma Phenotypes. C33 Cytokines And Asthma Mediators/Thematic Poster Session/Tuesday May 20/San Diego Convention Center/ *Am J Respir Crit Care Med* 189;2014:A34257

Subjects were also stratified by baseline ICS status (approx. 60% of subjects were on medium-dose ICS vs at least 40% of subjects on high-dose ICS). Study treatment was administered every 4 weeks for the first 3 doses followed by every 8 weeks thereafter (Q8W dosing regimen). The primary endpoint in this study was the annual exacerbation rate (AER) in the eosinophilic phenotype + subset. Data from this study was used in an exposure-response model on AER to explore the most appropriate dose(s) for benralizumab for the phase 3 studies.

Exacerbation studies; SIROCCO/ study 017 and CALIMA/study 018

The two exacerbation studies SIROCCO/ study 017 and CALIMA/ study 018 were conducted in adults and adolescents (ages 12 to 75 years) who had uncontrolled asthma (i.e. still symptomatic despite using high-dose ICS plus LABA with or without OCS or additional controller medications and a history of at least 2 asthma exacerbations in the previous year. CALIMA/study 018 was expanded to include patients on medium dose ICS/LABA.[5] Both exacerbation studies were randomized, double-blind, parallel group, placebo-controlled in design. In both studies, an enrichment strategy to enroll subjects in a 2:1 ratio for the high eosinophil high stratum (eosinophil counts ≥ 300 cells/ μL) versus the low eosinophil stratum (eosinophil count < 300 cells/μL) was used. Eligible subjects were randomized with stratification by geographical region, age group (adult or adolescent) and baseline blood eosinophil count (≥ 300/μL or < 300/μL). Baseline blood eosinophil count was obtained with routine CBC counts at local laboratories and subsequent eosinophil measurements were obtained from central laboratories.

In both studies 2 dosing regimens were evaluated: benralizumab 30 mg SC once every 4 weeks x 3 doses followed by once every 8 weeks (Q8W dosing regimen), or Benralizumab 30 mg once every 4 weeks (Q4W dosing regimen). Subjects were randomized 1:1:1 to the active treatment regimens or placebo. After the first 3 doses, patients randomized to the 8-week regimen received placebo at Visit 8 (dose 4) with active drug administered at Visit 9 (dose 5) and then every second treatment visit thereafter; placebo injections were administered at the 4-week interim treatment visits in order to maintain the blind. The double-blind treatment period was 48 weeks in length with the last dose of benralizumab or placebo administered at Week 44 and the end of treatment visit on Week 48 in SIROCCO/study 017. The double-blind treatment period was 56 weeks in CALIMA/study 018.

The primary efficacy endpoint and multiplicity adjustment for statistical calculations was based on the eosinophil high population. The primary efficacy endpoint in both exacerbation studies was the annual exacerbation rate. Secondary endpoints included time to first exacerbation, exacerbation leading to ER visits and hospitalizations, lung function (FEV_1) and patient reported outcomes (ACQ and AQLQ).

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5 (b) (4) the CALIMA trial following a re-design of that trial to allow for inclusion of subjects using medium-dose ICS/LABAs with or without OCS or additional controller medications.

Oral corticosteroid reduction (OCS) study; ZONDA/study 020

Study 020 (ZONDA) was conducted in adult patients 18 to 75 years of age with severe asthma who required treatment with high-dose ICS/LABAs and chronic OCS therapy with or without additional controller medications. This study evaluated the same two dosing regimens (Q4W and Q8W) that were studied in SIROCCO and CALIMA compared with placebo. All patients were required to be treated with OCS of 7.5 to 40 mg for at least 6 months prior to enrollment and to be on a stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization. Patients were required to have at least 1 exacerbation in the previous 12 months. The study included an 8 week run-or or OCS dose optimization period, a 28-week treatment period, and an 8-week follow-up period. Eligible subjects were randomized 1:1:1 to the treatment arms with the last dose of investigational product administered at Week 24, and end-of-treatment visit at Week 28. The primary endpoint was the percent reduction from baseline in the final OCS dose while maintaining asthma control. The study was designed such that OCS reduction could occur between Week 4 to Week 24 following a dose titration schedule. Secondary endpoints included lung function (FEV_1), patient reported outcomes using the ACQ and the AQLQ, and exacerbations.

Lung function study; BISE/study 032

BISE/study 032 was a dedicated lung function study conducted in patients 18 years of age and older with mild to moderate persistent asthma. The study was conducted to address the Agency's recommendation to evaluate the full spectrum of asthma severity in the benralizumab program. Only one dose of benralizumab 30 mg Q4W was studied compared to placebo. The treatment duration was 12 weeks. The primary efficacy endpoint was the change from baseline in pre-bronchodilator FEV_1 at Week 12.

Efficacy Results and Conclusion

The submitted data from the clinical program are adequate to support efficacy of benralizumab. The proposed dosing regimen is 30 mg SC Q4 x 3 doses then Q8W (Q8W dosing regimen) for patients with severe asthma in a specified target population. The clinical data from the phase 3 program support this dosing strategy. (b) (4) Based on the mechanism of action of benralizumab, it is reasonable to consider that this biologic will be an effective therapeutic agent in asthma patients with increased eosinophilic burden (i.e. eosinophilic inflammation). The Agency has previously accepted the term "eosinophilic phenotype" as part of the qualifying language in the indication statement for other anti-IL 5 products. The patient population was selected with enrichment criteria geared towards ensuring that patients with increased eosinophilic inflammation were enrolled (i.e. high eosinophil blood levels and other criteria suggestive of difficult to control asthma such as frequent exacerbations despite being on high dose ICS/LABAs and other controllers +/- oral corticosteroids). While the data do support a greater benefit in patients with high(er) eosinophil counts, and more frequent exacerbations, the overall data suggest efficacy (albeit to a lesser degree) in all comers. The

statistical team conducted several sensitivity analyses (including a tipping point analysis) to evaluate the robustness of the efficacy findings and these all support the efficacy of benralizumab. The two dosing regimens evaluated 30 mg Q4W and 30 mg Q8W are both effective. There does not appear to be any efficacy or safety advantage of the Q4W dosing regimen over the Q8W dosing regimen.

Dose and dosing Schedule

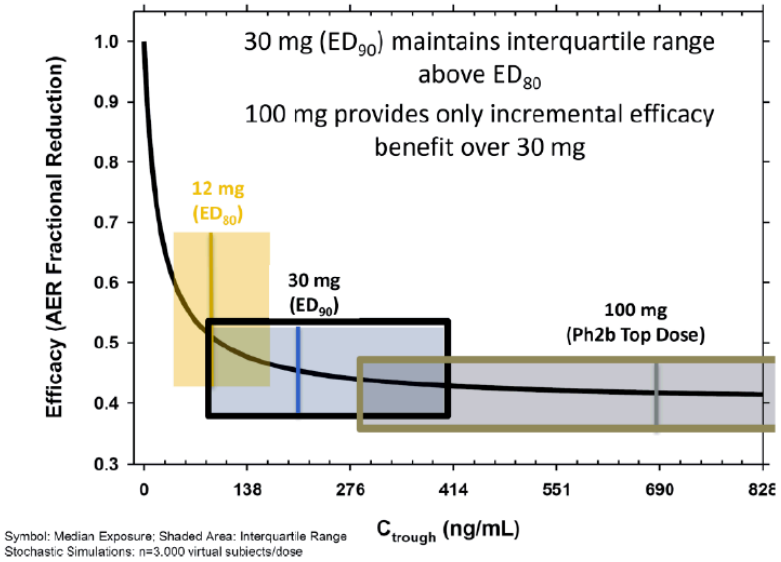
The proposed dose and dosing regimen of benralizumab 30 mg Q4W x 3 doses followed by 30 mg SC Q8W is supported by the submitted data. The dose selection for the benralizumab phase 3 studies is based on a dose response model using PK and PD data and clinical data that came from the 52-week dose-ranging study MI-CP-220 described above. The study demonstrated a dose-response trend in which the lowest dose (2 mg) did not reduce the annual exacerbation rate (AER) in patients with non-eosinophilic phenotype (RR = 109%) whereas both the 20 mg and the 100 mg dose reduced AER by 36% and 41%. The results are shown in Table 3.

Table 3: Annual Asthma Exacerbation Rate in mITT Population

Parameter	EOS +				EOS -	
	Placebo N = 80	Benralizumab				
		2 mg N = 81	20 mg N = 81	100 mg N = 82	Placebo N = 142	Benralizumab 100 mg N = 140
Rate (80% CI	0.57 (0.46,0.70)	0.65 (0.53,0.78)	0.37 (0.29,0.48)	0.34 (0.26,0.45)	0.56 (0.48,0.65)	0.43 (0.36,0.52)
RR (80% CI)	-----	1.09 (0.74,1.59)	0.64 (0.42,0.97)	0.59 (0.40,0.89)		0.78 (0.58,1.05)
EOS+ = ELEN index positive and/or FeNO ≥ 50 ppb EOS - = ELEN Index negative and FeNO < 50 ppb FeNO= fraction of exhaled nitric oxide *Data source: CSR M-CP220, page 101, Table 11.4.1.1-1*						

A dose response relationship was also observed in reduction of peripheral blood eosinophil counts with a 14%, 57%, 75% and 76% reduction in mean eosinophil counts from baseline at Week 40 [i.e. the last dose of study treatment administered] in the placebo, 2 mg, 20 mg, and 100 mg treatment groups respectively. The reduction in eosinophil count was similar in 20 mg and 100 mg treatment group. An exposure-response model estimated that 30 mg SC was the estimated effective dose that gave 90% inhibition (ED_{90}) for asthma exacerbation rate following the Q4W x 3 doses + Q8W dosing regimen. The 30 mg Q8W dosing regimen was expected to maximize therapeutic efficacy (residing at the efficacy plateau of asthma exacerbation rate, pre-bronchodilator FEV_1, and ACQ responses) while reducing the impact of steady-state PK variability on the efficacy outcome (Figure 4). No dose-limiting safety issues were identified in the study. The inclusion of the more frequent regimen of 30 mg Q4W in the phase 3 studies was to ascertain if higher serum trough levels would decrease the immunogenic profile of benralizumab and potentially improve efficacy in subjects with low PK exposure.

Figure 4: A priori simulated exposure-response for the 30 mg Q8W regimen as the optimal phase 3 dose 9baseline blood eosinophil count ≥ 300/µL



Source: Summary of Clinical Efficacy Figure 22 page 168 (181)

Exacerbation effects

The primary endpoint for studies SIROCCO/study 017 and CALIMA/study 018 was the annual asthma exacerbation rate. An asthma exacerbation was defined by a worsening of asthma symptoms requiring: a) use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids; b) an emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department (ED) or urgent care center) due to asthma that required systemic corticosteroids (as per above), or c) an inpatient hospitalization due to asthma. Statistically significant reductions in the annual asthma exacerbation rates were seen in both exacerbation studies for both dosing regimens of benralizumab compared to placebo in the eosinophil high stratum, and in the overall population (both eosinophil high and eosinophil low strata). The treatment effect in the eosinophil low stratum trended in a direction favoring benralizumab. Exacerbations requiring hospitalizations and emergency room visits were decreased in both studies but reach nominal statistical significance in only one of the studies (SIROCCO) for one comparison (benralizumab Q8W vs. placebo). Exacerbations requiring hospitalizations were numerically lower in one study (CALIMA).

The marginal method was used to estimate the exacerbation rate by calculating the predicted rate for each subject with model estimated parameter values and the subject's own covariate values and then averaging these predictions for each treatment group to provide the estimate for each arm. Although this is a relatively new method, the FDA statistical review team agreed

with AstraZeneca to use this approach. The FDA statistical team confirmed that this approach represents a more appropriate estimate of the annual exacerbation rates (in terms of alignment with the crude rates) compared to a model based approach. In the model based approach, the mean values of covariates in the study are calculated first and then the model- estimated parameter values are used to calculate the annual exacerbation rates. The exacerbation results using both methods are presented in Dr. Yu (Jade) Wang's statistical review. Table 4 shows the exacerbation results for both studies using the marginal method which is the method that is reflected in the product label. Of note, estimation of treatment effect in the form of rate ratios of benralizumab arms versus the placebo, as a parameter built into the negative binomial model, will not be affected by either of the two approaches described above. Across the two studies, benralizumab had a demonstrable benefit on reducing asthma exacerbations.

Table 4: Exacerbation Results Studies SIROCCO/017 and CALIMA/018*

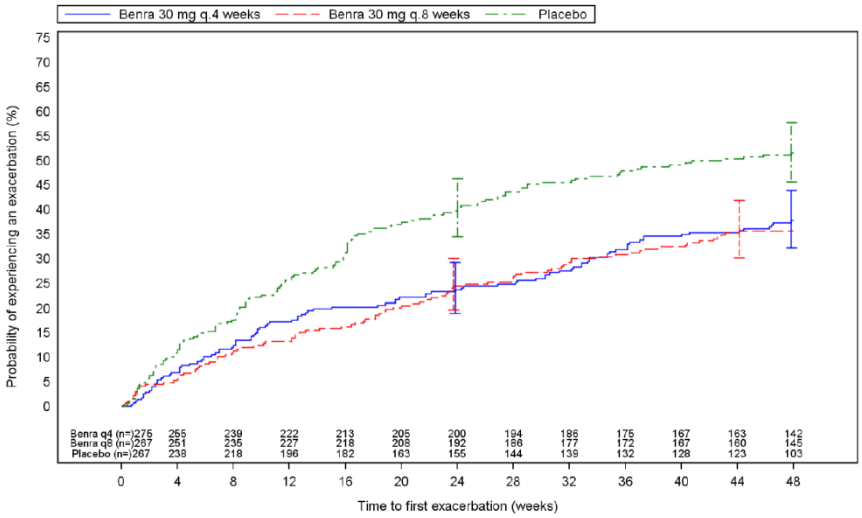
Study	**Treatment (n)**	**Exacerbations**		
		Mean Rate (95% CI)	Rate diff (95% CI)	Rate ratio (95% CI) p-value
Exacerbations (all exacerbations)				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.74 (0.59,0.92)	-0.78 (-1.08,-0.47)	0.49 (0.37,0.64) p < 0.001
	Benra 30 mg Q4W (n= 275)	0.83 (0.68, 1.02)	-0.69 (-1.00,-0.38)	0.55 (0.42, 0.71) p<0.001
	Placebo (n = 267)	1.52 (1.27,1.81)	---	---
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.73 (0.58, 0.90)	-0.29 (-0.53,-0.05)	0.72 (0.54,0.95) P=0.019
	Benra 30 mg Q4W (n = 241)	0.65 (0.52,0.81)	-0.36 (-0.59,, -0.13)	0.64 (0.49,0.85) p=0.002
	Placebo (n = 248)	1.01 (0.84,1.22)	-----	----
Exacerbations requiring hospitalization/emergency room visit				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.09 (0.05,0.16)	-0.16 ((-0.26, -0.06)	0.37 (0.20,0.67) P<0.001
	Benra 30 mg Q4W (n = 275)	0.15 (0.10, 0.24)	-0.10 (-0.21,0.01)	0.61 (0.37,1.01) p =0.053
	Placebo (n 267)	0.25 (0.17,0.38)	----	----
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.12 (0.08,0.19)	0.02 (-0.05,0.09)	1.23 (0.64,2.35) p=0.538
	Benra 30 mg Q4W (n = 241)	0.09 (0.06,0.15)	-0.01 (-0.07,0.06)	0.93 (0.48,1.82) p=0.837
	Placebo (n = 248)	0.10 (0.06,0.15)	----	----
Exacerbations requiring hospitalization				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.07 (0.03,0.14)	-0.07 (-0.16,0.01)	0.48 (0.22,1.03) p =0.06
	Benra 30 mg Q4W (n = 275)	0.09 (0.04,0.18)	-0.05 (-0.14,0.03)	0.62 (0.31,1.27) p=0.192
	Placebo (n = 267)	0.14 (0.07,0.27)	----	----
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.07 (0.04,0.13)	0.02 (-0.03,0.08)	1.48 (0.65,3.37) p=0.356

	Benra 30 mg Q4W (n = 241)	0.05 (0.03,0.10)	0.00 (-0.04,0.05)	1.02 (0.42,2.49) p=0.970
	Placebo (n = 248)	0.05 (0.03,0.09)	----	----

*Baseline blood eosinophil counts ≥300/µL and on high-dose ICS

In both studies, treatment with benralizumab (both treatment regimens) delayed the time to first exacerbation compared to placebo. In SIROCCO the longer time to first exacerbation was indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.63, 95% CI [0.49, 0.82] for benralizumab 30 mgQ4W and 0.60 [0.46, 0.78] for benralizumab 30 mg Q8W, both nominal p <0.001).

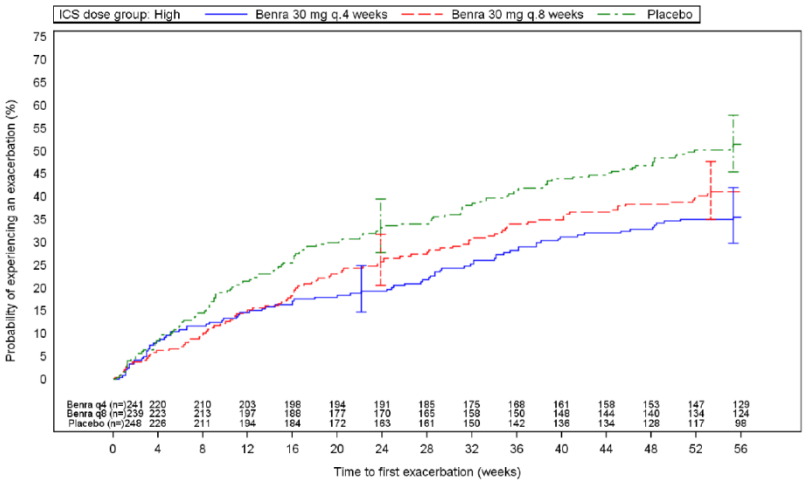
Figure 5: Time to first asthma exacerbation, Kaplan-Meier cumulative incidence curve (full analysis set, baseline blood eosinophils ≥ 300/µL (SIROCCO/study 017)



Source: D3250C0017 CSR Figure 6 page 123

In CALIMA the time to first asthma exacerbation was longer for both benralizumab 30 mg Q4W and Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.61, 95% CI [0.46,0.80], nominal p <0.001, and 0.73, 95% CI [0.55, 0.95], nominal p ≤ 0.018.

Figure 6: Figure 3: Time to first asthma exacerbation, Kaplan-Meier cumulative incidence curve (full analysis set, baseline blood eosinophils ≥ 300/µL (CALIMA/study 018)



Source: D3250C0018 CSR Figure 7 page 122

Asthma exacerbation rate was also evaluated in the oral corticosteroid reduction study ZONDA. Because the definition of an asthma exacerbation incorporates oral corticosteroid use, the relevant exacerbation outcome in an OCS reduction study would be exacerbations requiring hospitalizations and emergency room visits. In the OCS reduction study, the number of asthma exacerbation events associated with ER visit or hospitalization over 28 weeks was lower in both benralizumab 30 mg Q4W and Q8W regimens compared with placebo (5, 1, and 14 respectively). Both benralizumab 30 mg Q4W and Q8W reduced the annual rate of asthma exacerbations associate with ER visit or hospitalization over 28 weeks compared with placebo as shown in Table 5.

Table 5: Annualized asthma exacerbation rate ratio associated with ER visits or hospitalization over 28 weeks in ZONDA

Treatment (n)	Number of events	Mean rate[1] (95% CI)	Rate diff (95% CI)	Rate ratio (95% CI)
Benra 30 mg Q 8W (n= 73)	1	0.02 (0.00,0.18)	-0.30 (-0.53,-0.07)	0.07 (0.01,0.63)
Benra 30 mg Q 4 W (=72)	5	0.14 (0.05,0.38)	-0.18 (-0.45,0.09)	0.44 (0.13,1.49)
Placebo (n=75)	14	0.32 (0.16,0.65)	--	---

Source: D3250C00020 Clinical Study Report Table 11.2.4.6 page 382

[1]Mean rate based on marginal method as in Table 4 above

Oral Corticosteroid Reduction

The primary endpoint in ZONDA/study 020 was the percent reduction from baseline of the final OCS dose during Weeks 24 to 28 while maintaining asthma control. In this study asthma control was assessed by the investigator based on a subject's FEV_1, PEF, nighttime awakenings, short-acting bronchodilator rescue use, or any other symptoms that would require an increase in OCS dose. The mean and median optimized (baseline) OCS doses were 14.7 mg and 10.0 mg and were similar across treatment groups. The majority of subjects had eosinophil levels ≥ 300/μL at baseline. Treatment with benralizumab resulted in a significant reduction in OCS use compared to treatment with placebo. The median percent reduction in daily OCS dose from baseline was 75% in patients receiving benralizumab 30 mg Q8W, or 30 mg Q4W compared to 25% in subjects receiving placebo (both p <0.001). Results are shown in Table 6.

Table 6: Percent reduction from baseline in daily OCS dose at Week 28

	Benralizumab 30 mg Q4W (n = 72)	**Benralizumab Q8W (n = 73)**	**Placebo (n=75)**
Wilcoxon rank-sum test (primary analysis)			
Baseline daily OCS dose (mg) , mean (SD)	15.78 (8.83)	14.28 (7.76)	14.15 (6.35)
Final daily OCS dose at Week 28 (mg), mean (SD)	8.25 (10.80)	6.36 (6.88)	11.25 (8.47)
Median percent reduction from baseline	75	75	25
Hodges-Lehmann estimate for difference in % reduction from baseline Benra vs. placebo (95% CI)	33.30 (16.70, 50.00) p-value <0.001	37.50 (20.80, 50.00) p-value < 0.001	--
Proportional odds model (sensitivity analysis) – probability by category N (%)			
90% to 100% reduction	24 (33.3)	27 (37.0)	9 (12.0)
75% to <90% reduction	14 (19.4)	10 (13.7)	6 (8.0)
50% to <75% reduction	10 (13.9)	11 (15.1)	13 (17.3)
>0% to <50% reduction	7 (9.7)	10 (13.7)	12 (16.0)
No change or increase	17 (23.6)	15 (20.5)	35 (46.7)
Odds ratio (95% CI)	4.09 (2.22, 7.57) p <0.001	4.12 (4.12 (2.22, 7.63) p < 0.001	

Source: D3250C00020 Clinical Study Report Table 18 page 97 -98

Lung Function effects

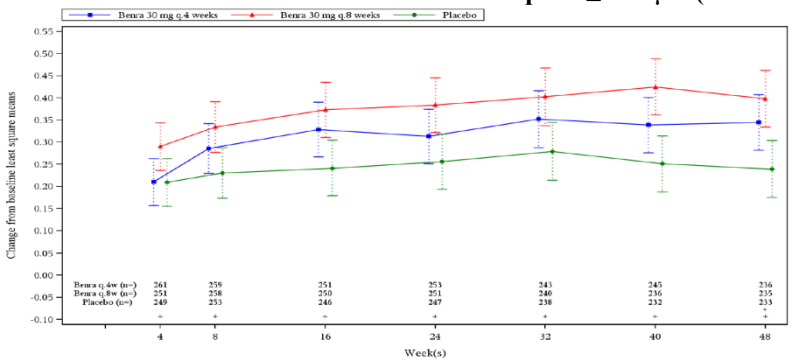
Change from baseline in mean pre-bronchodilator FEV_1 at end of treatment was assessed in both exacerbation trials and the OCS reduction trial as a secondary endpoint and as a primary endpoint in a 12-week lung function study in mild to moderate asthmatics (BISE). An improvement in lung function was seen with benralizumab treatment in the two treatment regimens in the exacerbation and OCS reduction studies. Only one dosing regimen (30 mg Q4W) was evaluated in the 12-week lung function study. The lung function results are shown in Table 7. Only data from the 30 mg Q8W dosing regimen in the pivotal phase 3 trials are shown. The 30 mg Q4W dosing regimen (in the pivotal phase 3 trials) had similar results.

Table 7: Change from baseline in mean pre-bronchodilator FEV_1 (L) at end of treatment

Trial	**Difference from placebo in mean change from pre-bronchodilator baseline FEV_1 (L) (95% CI)**
SIROCCO/study 017 (Q8W vs. placebo)	0.16 (0.07,0.25)
CALIMA/study 018 (Q8W vs. placebo)	0.12 (0.03, 0.20)
ZONDA/study 020 (Q8W vs. placebo)	0.11 (-0.33,0.26)
BISE/study032 (Q4W vs. placebo)	0.08 (0.00, 0.15)

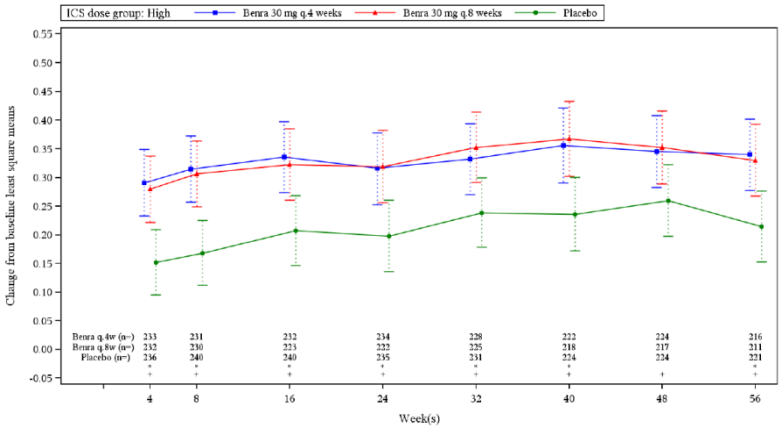
The mean change from baseline in pre-bronchodilator FEV_1 (L) for SIROCCO and CALIMA are is shown in Figures 4 and 5 below.

Figure 7: Change from baseline in pre-bronchodilator FEV_1 (L) by time point (full analysis set, baseline blood eosinophils ≥ 300/µL (SIROCCO)



Source: D3250C00017 Clinical study report Figure 8 pg 130

Figure 8: Change from baseline in pre-bronchodilator FEV1 (L) by time point (full analysis set, baseline blood eosinophils ≥ 300/µL (CALIMA)



Source: D3250C00018 Clinical study report Figure 9 pg 129

Patient reported outcome measures

Both the asthma control questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ) were used in this program. Both instruments are commonly used in asthma and have well defined measurement properties and are listed in well-recognized asthma treatment guidelines. AstraZeneca also looked at other patient reported outcome measures; i.e. the EQ-5D-5L (EuroQol 5 dimensions-5 levels) and the WPAI +CIQ (Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions) however, these instruments are less well known and are not universally used in asthma assessments. Subjects recorded asthma symptoms in a daily dairy (day and night symptoms) and AstraZeneca captured this in an asthma symptom score. As the information captured in such a dairy will already be captured in the well-known and accepted ACQ, the asthma symptom score as calculated by AstraZeneca will not be discussed further.

ACQ is a questionnaire that measures the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. The 7 items that make up

the ACQ include 5 items of self-administered questions (breathlessness, nocturnal waking due to asthma, and asthma symptoms upon waking, activity limitation, and wheeze); 1 item of self-administered rescue bronchodilator use, and 1 item of FEV_1 measurement completed by clinical staff. In this program the ACQ-6 was used – i.e. the FEV_1 measurement was excluded. This is reasonable since FEV_1 was being analyzed separately as a key secondary endpoint. Questions on the ACQ are scored on a 7-point scale from 0 (totally controlled) to 6 (severely uncontrolled); thus a decrease in score indicates improvement. A change in score of 0.5 is considered to be the minimum clinically important difference (MCID). The shortened version (ACQ-6 [and sometimes ACQ-5] have been used in clinical programs and use the same minimum cut off for clinical significance. To be confident that a patient has uncontrolled asthma the optimal cut-point on the ACQ score is 1.5 (positive predictive value = 88)[6]

The AQLQ is a disease specific health-related instrument that measures physical and emotional impact of disease. There are 32 questions in the AQLQ grouped in 4 domains – symptoms, activity limitation, emotional function, and environmental stimuli. Each of the 32 questions is scored on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment); thus an increase in score indicates improvement. The recall period for the AQLQ is 2 weeks. A change in score on 0.5 on the 7-point scale is considered the minimum clinically important difference (MCID). The AQLQ (S) +12 is the standardized version of the AQLQ for use in adolescents and adults 12 years of age and older. ACQ and AQLQ results at the end of treatment for SIROCCO, CALIMA, and ZONDA are shown in table 8 (data for the Q8W regimen only are shown). Mean baseline scores for the ACQ-6 and AQLQ were similar across treatment arms.

Table 8: ACQ-6 and AQLQ (s) + results for SIROCCO, CALIMA, and ZONDA (Baseline eosinophil count ≥ 300/μL)

	Benralizumab 30 mg Q8W	**Placebo**
ACQ-6 responder analysis at ≥ 0.5 threshold at end of treatment		
	Benralizumab 30 mg Q8W	**Placebo**
SIROCCO Benra vs placebo, odds ratio (95% CI)	60%	57% 1.55 (1.09,2.19)
CALIMA Benra vs. placebo, odds ratio (95% CI)	63%	59% 1.16 (0.80,1.68)
ZONDA Benra vs. placebo, odds ratio (95% CI)	63%	54.7% 1.66(0.83, 3.34)
AQLQ (S) +12 responder analysis at ≥0.5 threshold at end of treatment		
	Benralizumab 30 mg Q 8W	**Placebo**
SIROCCO Benra vs. placebo, odds ratio (95% CI)	57%	49% 1.42 (0.99,2.02)
CALIMA Benra vs. placebo, odds ratio (95% CI)	60%	59% 1.03 (0.70,1.51)
ZONDA	60%	52.0%

[6] Elizabeth F. Juniper et al. Identifying "well-controlled" and 'not well-controlled" asthma using the Asthma Control Questionnaire. *Respiratory Medicine* (2006) **100**, 616-621

Benra vs. placebo, odds ratio (95% CI)		1.78 (0.88, 3.61)

Effect of Eosinophil count and exacerbation history (potential predictors of efficacy)

Reduction in exacerbation rates were observed irrespective of baseline peripheral eosinophil counts; however, patients with a baseline blood eosinophil count ≥ 300/µL showed greater response than those with counts < 300/µL. There was also a trend for a greater exacerbation response in subjects with a history of 3 or more exacerbations within the 12 months prior to randomization to benralizumab in the SIROCCO and CALIMA trials. Lung function improvement was also numerically better in subjects with higher eosinophil counts and more frequent prior exacerbation history.

AstraZeneca explored various eosinophil cut-off points to assess the interaction between treatment effect and baseline blood eosinophil count. The studies were not powered nor designed to test these interactions and no definitive conclusions should be drawn from these exploratory analyses. That said, there was no clear threshold that determined benefit when evaluating by baseline blood eosinophil count categories and efficacy was observed across all baseline blood eosinophil categories with a greater treatment effect observed in subjects with higher baseline blood eosinophil levels than those with lower baseline blood eosinophil levels. This trend was also evident for change from baseline in pre-bronchodilator FEV_1.

Table 9: Exacerbation rate and pre-bronchodilator FEV_1 by baseline blood eosinophil counts < 300 µL and ≥300µL (Integrated SIROCCO/CALIMA)

	Rate difference	**95% CI**
Annual asthma exacerbation rate: Rate ratio		
Eosinophil count < 300/µL		
Benra 30 mg Q8W (n =256)	0.73	(0.57,0.94)
Benra 30 mg Q4W (n = 240)	0.68	(0.53,0.87)
Placebo (n = 262)		
Eosinophil count ≥300/µL		
Benra 30 mg Q8W (n =506)	0.58	(0.48,0.70)
Benra 30 mg Q4W (n = 516)	0.59	(0.49,0.72)
Placebo (n = 515)		
Pre-bronchodilator FEV_1 (L) change from baseline at Week 48: Difference in LS means		
Eosinophil count < 300/µL		
Benra 30 mg Q8W (n =250)	0.044	(-0.031,0.120)
Benra 30 mg Q4W (n = 234)	-0.001	(-0.078,0.076)
Placebo (n = 254)		
Eosinophil count ≥300/µL		
Benra 30 mg Q8W (n =502)	0.128	(0.064,0.191)
Benra 30 mg Q4W (n = 509)	0.094	(0.031,0.157)
Placebo (n = 505)		

Data source: Summary of Clinical Efficacy 2.7.3 Table 26 page 140 (181)

Subgroup population analysis

Efficacy data were analyzed based on the typical subgroups such as gender, age, ethnicity, and geographical regions. In the pediatric population (12 to 17 years) the point estimate favored placebo in both exacerbation trials. However the confidence intervals were wide for both estimates. The statistical review team commented that the current efficacy does not provide

substantial evidence of a clinically meaningful benefit of benralizumab in children 12 to 17 years of age. It is important to keep in mind the small sample size and the fact that these studies were not powered for efficacy in this age range. That said, the interaction tests across the two exacerbation trials on age subgroup were not statistically significant. Furthermore, the inherent type I error inflation with conducting multiple post hoc subgroup analyses must be considered. That said, in view of the robust efficacy in the overall population and the biologic plausibility that benralizumab would be expected to have the same effect in children 12 to 17 years of age, the subgroup analysis would not on its own determine whether benralizumab should be approved in children 12 to 17 years of age or not (see Pediatric Section). The Forest plots for exacerbation and FEV_1 subgroup analysis (age) are shown below copied from Dr. Yu (Jade) Wang's statistical review.

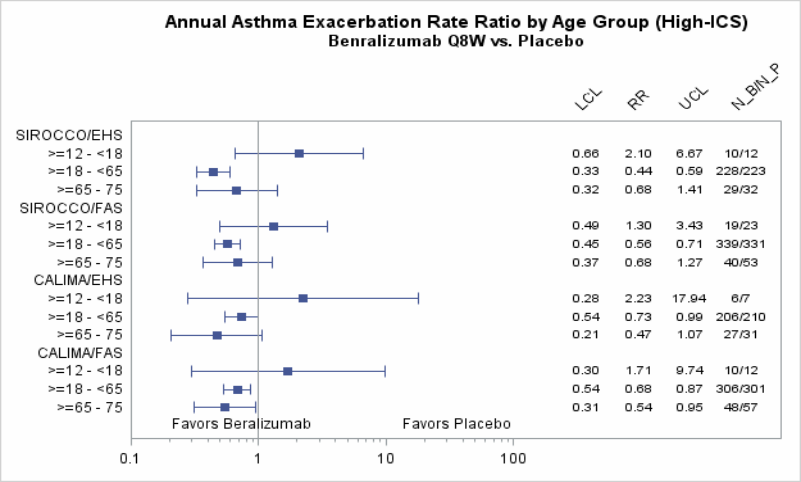


Figure 9: Annual asthma exacerbation rate ratio

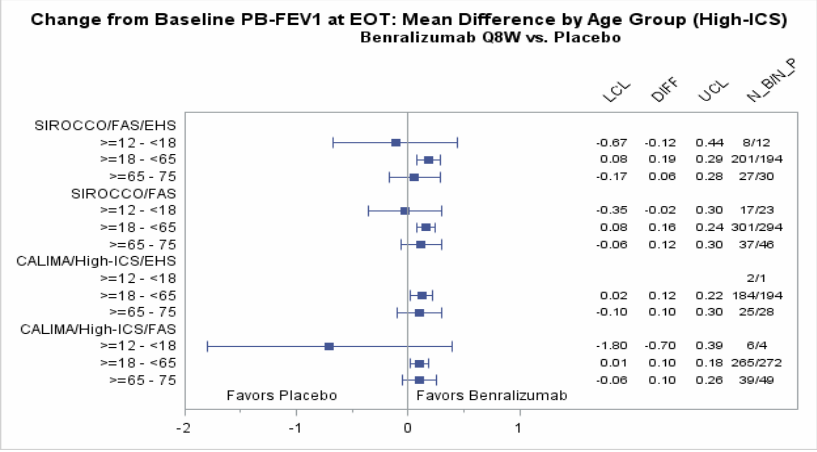


Figure 10: Change from baseline in pre-bronchodilator FEV_1 mean difference by age group

8. Safety

Safety database

The safety assessment of benralizumab for asthma is based on the studies shown in Table 1. Most of the safety data are from the placebo-controlled exacerbation trials SIROCCO and CALIMA. As a reminder these trials had slightly different duration (48 weeks for SIROCCO and 56 weeks for CALIMA). The Agency agreed to use the pooled safety data out to 48 weeks to inform the safety information for labeling. A total of 2511 subjects were randomized in the two exacerbation studies of whom 822 subjects received benralizumab 30 mg SC Q8W and 841 received benralizumab 30 mg SC Q4W. A total of 1,387 subjects received benralizumab for ≥ 48 weeks. Across the phase 2 and 3 program, a total of 3,882 subjects with asthma received at least 1 dose of benralizumab. Safety information from the long-term open extension studies BORA and MELTI was provided in the 120-day safety update (database lock date October 21, 2016) and provided safety data on an additional 1279 subjects from the two exacerbation trials (637 on benralizumab 30 mg Q4W, and 642 on Benralizumab 30 mg Q8W). Safety data from subjects previously enrolled in ZONDA and subjects previously on placebo and rolled over to active treatment in the long-term extension were also provided in the 120-day safety update. The safety database is adequate to evaluate the safety of benralizumab.

Safety findings and Conclusion

The submitted data support the safety of benralizumab at the proposed dose of 30 mg SC Q8W for the treatment of asthma. AstraZeneca conducted a comprehensive safety analysis of the data that included the safety assessments typically done in clinical development programs such as evaluation of deaths, serious adverse events (SAEs), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, urinalysis, and ECGs. All laboratory assessments were performed at a central laboratory. Given that the product is a biologic for injection, events of special interest were allergic reactions including anaphylaxis, local injection site reactions, infections, malignancy, and immunogenicity.

Deaths, SAEs, dropouts, discontinuations

There were 15 deaths in the asthma clinical studies; 4 were reported on placebo, 5 in the benralizumab Q8W arm, and 6 in the benralizumab Q4W arm. In 7 of the cases, the causes of death were cardiovascular (including stroke and MI) and in 6 of these cases the patients had underlying cardiovascular co-morbidities and risk factors for heart disease and stroke. There was one report of sudden cardiac death in a 51 year old female with no prior medical or surgical history beyond the use of lansoprazole. There was one death due to pancytopenia but the patient had a history of pancreatic insufficiency following pancreatic resection [for chronic pancreatitis] with resultant pancreatic insufficiency, prior asbestos exposure and underlying cardiovascular disease for which he was receiving amiodarone. Amiodarone has been reported to cause aplastic anemia. The other 7 deaths were pulmonary embolism (1 case – placebo), neoplasm of the colon (1 case – placebo), pneumonia (1 case - benralizumab Q8W), opioid overdose (1 case – benralizumab Q8W); road traffic accident (1 case – benralizumab Q4); suicide (1 case – benralizumab Q4W), and asthma (1 case – benralizumab Q4). There is no pattern to the deaths and none of the deaths in the program appear to be related to benralizumab. An independent adjudication committee assessed all cases of death.

Serious adverse events (SAEs)[7] occurred with comparable frequencies between benralizumab and placebo treatment groups with a slightly higher frequency in the placebo treatment groups (11.2% in benralizumab 30 mg Q8W, 10.9% in benralizumab 30 mg Q4W, 13.6% in placebo). The majority of the SAEs were related to respiratory disorders with asthma being the most frequent disorder followed by pneumonia. The frequency of these events were similar across the treatment groups but with a trend towards a higher incidence in the placebo group. In the pooled safety database for SIROCCO/CALIMA the percentage of patients with a serious asthma event was 6.4 in the placebo group compared to 5.1 in both benralizumab treatment arms. Pneumonia was reported in less than 1% of patients across all treatment arms.

Dropouts and discontinuations due to adverse events occurred more frequently in patients receiving benralizumab (2.1% in benralizumab-treated patients vs. 0.9% in placebo) in the SIROCCO/CALIMA trials. There was no pattern observed or single preferred term that accounted for the differences between groups in patients who discontinued due to adverse events.

Common adverse events[8]:
Common adverse events were typical of those seen in asthma development programs and were reported in 73% of patients exposed to benralizumab in the 2 exacerbation trials compared to 77% exposed to placebo. Common adverse events reported included nasopharyngitis (16% in Benralizumab Q4W, 15% in Benralizumab Q8W, vs 16% in placebo), asthma (14% in benralizumab Q4W, 11% in benralizumab Q8W, vs 17% in placebo, upper respiratory tract infection (9% in Benralizumab Q4W, 8% in benralizumab Q8W, vs 9% in placebo. Headache (8%), pyrexia (3%) and pharyngitis (4%) were reported with higher frequency (≥3%) in the benralizumab treatment arms[9] compared to placebo (6%, 2%, and 2% respectively). When looking at the safety data out to 56 weeks, arthralgias were reported more frequently in the benralizumab Q8W treatment arm (4%) compared to 2 % in the Benralizumab Q4W and placebo arms and cough was reported in 3% of the benralizumab treatment arms compared to 2% in placebo.

Laboratory findings and ECGs, vital signs
Other than the expected reduction in blood eosinophil counts, there were no clinically meaningful effects on hematologic parameters. There were no signals in the clinical chemistry, or urinalysis. ECGs were performed as part of a routine assessment and were done in a sub-study in 201 patients in the SIROCCO trial. No safety concerns were found with the ECG findings. Vital signs (pulse, temperature, blood pressure, and respiratory rate) were obtained at baseline and at every clinic visit and other than vital sign abnormalities related to adverse events discussed elsewhere, there were no clinically meaningful changes in vital signs.

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[7] Defined as in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threating adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death form the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect.
[8] Data presented rounded to nearest whole number and represent the pooled database out to 56 weeks. The pooled database out to 48 weeks was previously agreed upon to be used in the label. When the 48 week database is used, arthralgia and cough fall off as common AEs meeting the threshold for the label.
[9] Data represents both benra Q4W and Q8W treatment arms except as otherwise noted.

Adverse events of interest

- *Hypersensitivity reactions*

Hypersensitivity reactions including urticaria, urticarial rash, and anaphylaxis have been reported with biologics. The clinical program used the accepted definition of anaphylaxis.[10] There were two events of anaphylaxis in the same patient in the controlled clinical trials however the patient had a history of peanut allergy and in both instances the investigator attributed the event to the patient's underlying food allergy. Neither event was temporally related to benralizumab exposure. The patient subsequently received additional benralizumab doses without difficulty. There was one case of anaphylaxis reported in the 120-day safety update. The event occurred in a patient who developed nausea and vomiting and loss of consciousness 25 minutes following administration of benralizumab. Epinephrine was administered and the patient recovered. The patient had a normal tryptase level but this was drawn almost 2 hours after the event. The histamine level was reported to be elevated. With the grouping of hypersensitivity terms together (urticaria, urticaria popular, and rash) the incidence of hypersensitivity reactions was 3% in the benralizumab and placebo treatment group in the exacerbation trials.

- *Infections*

A signal for opportunistic infections was not observed in the benralizumab program. There were 2 cases of herpes zoster but these were confounded by concomitant immunosuppressant medication use (methotrexate, systemic steroids). Given the role of eosinophils in the defense against helminthic parasitic infections patients with known helminthic infections were excluded from the program. There were two reports of positive *strongyloides* serology in the program but in neither case was there a worsening of infection with the use of benralizumab. Pneumonia (bacterial), influenza, and appendicitis were the most commonly reported infections. The incidence of these events was < 1% and was similar across the benralizumab treatment arms and placebo.

- *Malignancy*

There was no imbalance in malignancy events in the controlled clinical trials. In the 120-day safety update there was a report of three lymphoma cases but the case narratives suggest that these patients already had other underlying risk factors for lymphoma and it is unlikely that benralizumab is implicated in these events.

- *Immunogenicity*

Immunogenicity is a potential for all therapeutic proteins and the development of anti-drug-antibodies (ADA) can result with treatment. In the exacerbation trials treatment-emergent ADA developed in 13 – 15% of patients in the benralizumab treatment groups compared with 4% in the placebo treatment group. The majority of the ADA positive patients (12%) had neutralizing antibodies. Compared to antibody negative patients, patients with positive ADA

[10] Sampson, HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report-second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J allergy clin Immunology* **2006;** 117:391-397

had increased clearance of benralizumab and increased blood eosinophil levels however there was no observed effect on efficacy or safety.

- *Cardiac safety*

There was no *a priori* cardiac safety concern with this product however, in addition to the adjudicating of the cases of death; the independent adjudication committee evaluated all investigator reported cases of non-fatal MI and non-fatal stroke (hemorrhagic, ischemic, and embolic). There was no imbalance between benralizumab treatment and placebo for MACE events.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not convened for this application. Benralizumab is the third product targeting the IL-5 pathway for the treatment of asthma. The general issues about the appropriate population, the role of eosinophils in determining treatment, the risk-balance considerations for biologics such as this anti-IL 5 for asthma have all been discussed before at AC meetings. Benralizumab did not present any new safety concerns that would warrant discussion at an AC meeting.

10. Pediatrics

The agreed upon pediatric study plan (PSP) for benralizumab consisted of the inclusion of 12 – 17 year old patients in the adult development program, deferral of studies in children (b) (4) to 11 years of age, and a plan to request a waiver for children (b) (4) years of age.[11] AstraZeneca included 108 adolescents 12 to 17 years of age in the 2 exacerbation trials. These patients were required to have a history of 2 or more exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator $FEV_1 < 90\%$) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller medications. Although the point estimate for efficacy in subgroup analysis favored placebo, the similar PK and PD between adolescents and adults, the fact that the studies were not powered for efficacy in the 12 to 17 year olds, and the knowledge that the disease characteristics are similar in adults and pediatric patients can allow for extrapolation of efficacy from the adults to the pediatric population.[12] The overall safety profile of benralizumab is favorable and there were no safety concerns in patients 12 to 17 years of age. Taken together, these observations support extending the indication to patients 12 years of age and older.

[11] IND 100,237 Advice 9/30/2013

[12] "Under PREA (section 505B*a) (2) (B) of the FD&C act), if the course of disease and the effects of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be extrapolated from adult data." *Guidance for Industry and Review Staff – Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*

The application was presented at the Pediatric Review Committee (PeRC) meeting on August 2nd, 2017. The committee agreed that the PREA requirements for the 12 to 17 year olds had been fulfilled and agreed with the Division's recommendation to extend the indication to adolescents 12 to 17 years of age. The applicant will be asked to conduct PK and safety studies in children 6[13] to 11 years of age to support the PREA requirements in that age group. These studies will be conducted as post-marketing required (PMR) studies under PREA. The PREA requirement for studies in children less than 6 years of age is waived because studies would be impossible or highly impracticable (because the number of patients in this age group would be very small).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

Application integrity Policy (AIP)
Review of the application did not raise concerns of any wrongful acts that would lead to questions about the reliability of the data.

Exclusivity and patent issues
There are no exclusivity and patent issues of concern with this application

Office of Scientific Investigations (OSI) audits
The Division of Clinical Compliance evaluation in the Office of Scientific Investigations (OSI) conducted an inspection as part of a routine audit. Two clinical sites from the 2 large exacerbation trials were selected for inspection. There were no irregularities identified during the OSI audit that would impact data integrity

Financial disclosure
AstraZeneca submitted acceptable financial disclosure statements. Two investigators had disclosable financial interest in AstraZeneca. These investigators recruited a small sample of the total study populations and were not large enough to alter the outcome of any study. In addition, the multi-center nature of the study makes it unlikely that the financial interest could have influenced or biased the results of these studies in any way.

Other Good Clinical Practice (GCP) issues:
All studies were conducted in accordance with acceptable good clinical practice standards and adhered to regulatory requirements for clinical trials conduct

12. Labeling

[13] Although AstraZeneca's initial iPSP was a planned request for waiver in children (b) (4) to match the PREA requirement for the currently approved anti-IL product mepolizumab.

The product label was reviewed by the Division, OSE/DMEP, DRISK, and OPDP. Various changes to different sections of the label were done to reflect the data accurately, remove extraneous information, and to streamline the label to communicate the findings of the clinical program and the risk benefit accurately to healthcare providers. At this time the labeling negotiations are still ongoing but most of the labeling issues have been resolved and the label is close to being final.

- Proprietary name
  The proposed proprietary name FASENRA was reviewed and has been approved by DMEPA.

- Physician labeling
  Major labeling issues addressed during labeling negotiations include:
  Indication and usage: AstraZeneca's original proposal was for patients 18 years of age and older. The program included 108 pediatric patients 12 to 17 years of age. They were required to have the same entry criteria as the adult population. The point estimate for exacerbation benefit did not favor the 12 to 17 year old age group in subgroup analysis but the confidence intervals were very wide. The studies were not powered for efficacy in the 12 to 17 year olds and the PK and PD effects of benralizumab were comparable to that in the adult population. Therefore the Division supported AstraZeneca's subsequent justification to modify the indication to extend the age range to include adolescents 12 years of age and older
  Dosage and administration: AstraZeneca proposed a dosing regimen of q8W dosing. The dosing schedule proposed is for 30 mg SC every 4 weeks for the first 3 doses followed by 30 mg every 8 weeks. This is the dosing strategy that was studied in the phase 3 program and it is acceptable.
  Efficacy information: Exacerbation effects, lung function effects, and patient reported outcomes based on the ACQ and the AQLQ will be described in the label. Section 14 of the label was substantially revised from what AstraZeneca proposed initially with the removal of (b) (4) discussion in section. Also the dose-ranging study MI-CP-220 and the dedicated 12-week lung function study were added to section 14.
  Safety: The most notable change was the addition of the term "anaphylaxis" to the other terms in the hypersensitivity warning. Although no cases of anaphylaxis related to benralizumab was seen in the controlled trials, the case seen in the 120-day safety update is convincing and as a monoclonal antibody benralizumab is expected to cause anaphylaxis in some patients.

- Patient labeling and Medication Guide
  The product will not have a medication guide. Benralizumab will have patient counselling information and the patient information was reviewed by the patient labeling team. AstraZeneca has incorporated the recommendations

- Carton and immediate container labels
  These were reviewed by the various disciplines and found to be acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

The proposed regulatory action for this BLA is approval for patients 12 years of age and older.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

REMS will not be required for this application. The information necessary to use Benralizumab safely and effectively can be adequately provided through the prescribing information and patient labeling

- Recommendation for other Postmarketing Requirements and Commitments

AstraZeneca will conduct post-marketing required studies to support the PREA requirements for pediatric patients 6 to 11 years of age. AstraZeneca will also commit to perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions as a post-marketing commitment (PMC).

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/s/

LYDIA I GILBERT MCCLAIN
11/06/2017

BADRUL A CHOWDHURY
11/06/2017

CURTIS J ROSEBRAUGH
11/06/2017

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Badrul A. Chowdhury, MD, PhD, Division Director and Lydia Gilbert-McClain, MD, FCCP, Deputy Division Director, DPARP
Subject	Division Director Summary Review
NDA/BLA # Supplement #	761070
Applicant Name	AstraZeneca
Date of Submission	November 16, 2016
PDUFA Goal Date	November 16, 2017
Proprietary Name / Established (USAN) Name	FASENRA/Benralizumab
Dosage Forms / Strength	Solution for injection/30 mg/mL
Proposed Indication(s)	Add on maintenance treatment for patients with severe asthma 18 years of age and older and with an eosinophilic phenotype
Action/Recommended Action for NME:	*Approval*
Approved/Recommended Indication/Population	Add on maintenance treatment for patients with severe asthma 12 years of age and older and with an eosinophilic phenotype

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sofia Chaudhry, MD
CDTL	Lydia Gilbert-McClain, MD
Statistical Review	Yu (Jade) Wang, PhD, Youngman Kim, PhD
Pharmacology Toxicology Review	Carol Galvis, PhD, Timothy Robison PhD
CMC Review/OBP Review	Jennifer Swisher, PH.D., Sarah Kennett, Ph.D, Kathleen Clouse, Ph.D
Microbiology Review	Maria Jose Lopez-Barragan, Candace Gomez-Broughton
Clinical Pharmacology Review	Suryanarayana Sista, PhD, Yunzhao Ren, MD, PhD, Jingyu Yu, PhD, Anshu Marathe, PhD, Ping Ji, PhD
OPDP	Kyle Snyder, PharmD
OSI	CDR LaKisha Williams
OSE/DMEPA	Teresa McMillan, PharmD, Sarah K. Vee, PharmD, Matthew Barlow, RN, BSN, QuynhNhu Nguyen, MS, Lubna Merchant, PharmD

OND=Office of New Drugs; OPDP=Office of Prescription Drug Promotion (OPDP); DMEPA=Division of Medication Error Prevention and Analysis; OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology

1. Benefit-Risk Assessment

Patients with severe asthma represent a small subset of asthmatic patients at particular risk for increased morbidity and mortality. Two other IL-5 targeting therapies have been approved in past two years targeting patients with severe asthma and an eosinophilic phenotype. Asthma with eosinophilic phenotype is a serious condition with chronic morbidity, including frequent exacerbations which often require hospital or emergency department care. In addition to high dose inhaled corticosteroids, these patients are often on systemic corticosteroids. Due to the undesirable effects of long-term systemic corticosteroid use, alternate treatments for these patients that could limit or eliminate systemic corticosteroid use would be a therapeutic advantage.

The efficacy and safety of benralizumab in this patient population was evaluated in three pivotal phase 3 trials including two exacerbation trials and one oral corticosteroid reduction trial. All were well-controlled and adequately designed to assess the efficacy of benralizumab in the severe asthma population. Both exacerbation studies demonstrate statistically significant and clinically meaningful improvements in exacerbations for patients receiving benralizumab beyond that provided by high dose ICS/LABA therapy. In addition, for patients requiring OCS to control their asthma, benralizumab therapy allowed a larger percentage of patients to reduce their OCS dose. All three trials also demonstrate numeric improvements in FEV_1 compared with placebo. An increased treatment benefit is consistently seen in patients with higher baseline peripheral blood eosinophil counts. While efficacy was not conclusively demonstrated in the adolescent population, a sufficiently powered study to demonstrate a treatment benefit would be impractical to conduct given the rarity of this severe asthma phenotype. There are no age-related differences in the PK and PD and the course of the disease is the same in adults and children. There are no safety concerns to offset the potential efficacy of benralizumab in adolescent patients, so it is reasonable to approve the product in patients 12 years of age and older.

In addition to the standard safety assessments the program also included an assessment of safety concerns of special interest with biologics including infections, malignancy, hypersensitivity events, and immunogenicity. No safety concerns have been identified that would warrant unique warnings/precautions for Benralizumab. A fairly high level (~ 13 – 15%) of anti-drug antibody (ADA) was observed in the clinical development program which was associated with a decrease in PK and an increase in eosinophil counts; however, there was no decrease in the efficacy response in ADA positive subjects and the elevated ADA levels were not associated with any safety concerns.

The benefit-risk assessment favors approval of Benralizumab in patients 12 years of age and older given the serious nature of the disease, and as Benralizumab may provide an alternative to those patients who do not tolerate the other drug in the class approved by the FDA for patients 12 years of age and older (i.e. mepolizumab).

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. Episodic increases in symptoms are referred to as asthma exacerbations. The disease 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 leading to chronic symptoms despite current standard of care treatment. While many exacerbations may be	Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma patient population with severe disease continues to experience significant morbidity and the potential for mortality from this condition

	managed as outpatient with the use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death. • Severe uncontrolled asthma is estimated to account for approximately 5% of all patients with asthma. While there are no specific guidelines to identify patients with severe asthma and an eosinophilic phenotype, the estimated prevalence is thought to be 3% or less.	
Current treatment options	There are two other IL-5 targeting therapies approved for the treatment of patients with severe asthma and an eosinophilic phenotype.	While there are two approved therapies treating this specific subset of asthma patients, the availability of additional treatment options for those unable to tolerate existing treatments is preferable. Further, only one of the currently approved therapies is approved for patients 12 - 17 years of age.
Benefit	Reduction in annual rate of asthma exacerbations Reduction in hospitalization due to exacerbations Reduction in oral corticosteroid use (in patients on oral corticosteroids to control their severe asthma) Improvement in lung function (FEV1) Improvement in Asthma Control Questionnaire (ACQ) and The Asthma Quality of Life Questionnaire (AQLQ)	
Risk	No increased risks in adverse events of interest such as anaphylaxis, opportunistic infections, or malignancy were seen in the controlled trials. Hypersensitivity reactions (including urticaria, angioedema, rash) occurred in the controlled trials and one case of anaphylaxis was reported in the open label extension studies	The program does not show any safety concerns that would offset the efficacy findings
Risk Management	No REMS is proposed	The risks of hypersensitivity reactions and anti-drug antibody formation as well as the reported common adverse reactions (headache, pyrexia, pharyngitis) with benralizumab can be managed through routine pharmacovigilance and product labeling.

2. Background

Asthma is a chronic inflammatory disorder of the airways affecting children and adults of all ages. It is one of the most common chronic diseases worldwide and globally an estimated 300 million individuals are affected by asthma. In the United States, the prevalence of asthma among adults is 7.4% and 8.6% among children according to 2014 data from the Centers for Disease Control and Prevention (CDC). Multiple cell types in the inflammatory cascade (e.g. mast cells, eosinophils, neutrophils, macrophages, lymphocytes) are involved in the pathogenesis of asthma. Eosinophilic inflammation of the airways plays a central role in the

pathogenesis of asthma. IL-5 is the main cytokine involved in the regulation of blood and tissue eosinophils.

Several classes of products are available for use in patients with persistent asthma. These include inhaled corticosteroids (ICS), inhaled long-acting beta-adrenergic agents (LABAs), and fixed dose combination of ICS/LABAs, leukotriene modifying drugs, methylxanthines, and the long-acting anticholinergic Spiriva (tiotropium) Respimat. In addition, 3 monoclonal antibodies are also approved. These include one monoclonal antibody to IgE (omalizumab) and two monoclonal antibodies that target the Il-5 pathway (i.e. mepolizumab and reslizumab).

Severe asthma has been defined as asthma that requires treatment with medium-to high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming uncontrolled, or that remains uncontrolled despite this therapy.[1] About 3 to 5 percent of asthma patients have severe persistent asthma. Xolair is approved for patients with moderate to severe persistent asthma and a positive skin test or *in vitro* reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. The two currently approved anti-IL 5 monoclonal antibodies -mepolizumab, and reslizumab has so far been limited to severe asthma with an eosinophilic phenotype. The eosinophilic phenotype or "eosinophilic asthma" has been described as associated with elevated blood and sputum eosinophil counts. A consensus definition of "eosinophilic asthma" has not been defined in the scientific community and while the academic community is unified in the overall characterization of this asthma phenotype (i.e. severe asthma that is difficult to control despite maximum therapy) a specific cut-off for elevated blood, or sputum eosinophil levels as a criterion has not been established. For the benralizumab development program, AstraZeneca used a proprietary mathematical algorithm defined as the ELEN index to predict sputum eosinophils $\geq$ 2% as one of the criteria to select patients for their dose-ranging study that would inform dose selection for the phase 3 program. For the phase 3 program they used a blood eosinophil cut-off of 300/µL to enroll patients in the pivotal exacerbation studies.

Regulatory Interactions between the Agency and AstraZeneca

The Division and AstraZeneca had the typical milestone meetings regarding the development program for benralizumab for asthma. The Division met with AstraZeneca on Feb 13, 2013 for an End-of -Phase 2 (EOP2) meeting where the dose selection and other design elements of the phase 3 program were discussed. The points raised at the EOP2 meeting were as follows: AstraZeneca proposed to use the 30 mg dose based on the observed data and potential for PK variability and increased immunogenicity with lower doses. The PD model for dose selection was discussed. FDA noted that the use of the PD modeling data was acceptable but risky and that the acceptability of choosing a higher dose to overcome immunogenicity concerns would be dependent on the safety profile of the product and recommended further dose exploration or the evaluation of more than one dose in phase 3. The FDA also recommended evaluation of patients with a range of peripheral blood eosinophil counts and AstraZeneca proposed to stratify enrollment based on eosinophil "high" and 'low" patients in a 2:1 ratio using 300/µL as the cutoff with the primary efficacy analysis conducted in the eosinophil "high" population. The FDA found the proposal to be acceptable. AstraZeneca also met with the Agency in a

[1] Chung KF et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* 2014; **43**: 343 -373

Type C meeting September 8, 2014 for further discussions on the phase 3 program. AstraZeneca's proposal to rely on data from SIROCCO and CALIMA to support registration in a severe asthma population was discussed. The FDA reminded AstraZeneca of the recommendation to evaluate the full spectrum of asthma severity but noted that targeting more severe patients may be acceptable if the program provides sufficient information to inform the selection of appropriate patients and the risk-benefit was favorable for the targeted patient population. AstraZeneca also met with the Agency in a type C meeting (May 22, 2014) (b) (4) the pre-filled syringe (PFS) is proposed for marketing with this BLA submission. AstraZeneca met with the Division on September 20, 2016 for a pre-BLA meeting where the content and format of the BLA was discussed. The strategy to pool data from SIROCCO and CALIMA was discussed and found to be reasonable. The plan for descriptive analyses for adverse events was deemed acceptable. Regarding the labeling FDA noted that data documenting a treatment's impact on exacerbation-related ER visits and/or hospitalizations are clinically meaningful and appropriate for inclusion in the package insert. The Agency also commented that inclusion of data such as exacerbation history and baseline eosinophil levels as independent predictors of treatment benefit in the package insert would be a review issue.

3. CMC/Device

Benralizumab is a humanized monoclonal antibody (IgG1/κ-class) selective for interleukin-5 receptor alpha subunit (IL-5Rα). Benralizumab is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology. Benralizumab has a molecular weight of approximately 150 kDa. The drug product FASENRA (benralizumab) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for subcutaneous injection in a single-dose prefilled syringe (PFS). Each PFS delivers 1 mL containing 30 mg benralizumab, L-histidine (1.4 mg); L-histidine hydrochloride monohydrate (2.3 mg); polysorbate 20 (0.06 mg); α,α-trehalose dihydrate (95 mg); and Water for Injection, USP.

The prefilled syringe (b) (4) (PFS (b) (4) is the primary container closure system for the drug product. (b) (4) This is a marketed device that has been used with other FDA-approved products. (b) (4) None of the accessories are in contact with the drug product solution or the fluid path of the delivery system. The secondary container closure system consists of a tray insert that is placed into a paperboard carton.

The drug substance, (b) (4) are manufactured by AstraZeneca Pharmaceuticals LP Manufacturing Center, Frederick, MD, and the drug product manufacturing, labeling, and packaging is done at (b) (4)

The submitted data support an expiry of 24 months for the drug product when stored at 2 to 8^0C.

There are no approvability issues regarding the manufacturing of the drug product and drug substance. A leachable study is needed to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under recommended conditions. This evaluation does not preclude approval of the application and can be conducted as a post-marketing commitment. There are no outstanding manufacturing site inspection issues.

4. Nonclinical Pharmacology/Toxicology

The Il-5 receptor is expressed on the surface of eosinophils and basophils. In an in vitro setting the absence of fucose in the Fc domain of benralizumab facilitates binding to FcγRIII receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). Treatment with benralizumab caused a reduction in both eosinophils and basophils.

The toxicity profile of benralizumab was evaluated in cynomolgus monkeys in a 39-week toxicity study. Consistent with benralizumab's mechanism of action, eosinophil levels were decreased in treated animals at all dose levels. No drug-related histopathology findings were observed. Male and female fertility parameters were unaffected in sexually mature animals in the 39-week toxicity study. There was also no evidence of maternal toxicity in pregnant cynomolgus monkeys receiving benralizumab subcutaneously during the period of organogenesis and thorough gestation. Placental transfer was demonstrated by measuring benralizumab levels in the serum of infants exposed *in utero.* Infants exposed *in utero* to benralizumab had decreased eosinophil levels which increased gradually over time. No effects were observed in infant growth, or neurological development. Benralizumab was not teratogenic in cynomolgus monkeys. AstraZeneca did not conduct rodent carcinogenicity studies. The applicant submitted a carcinogenicity risk assessment during the development of benralizumab and the Agency's Executive Carcinogenicity Assessment Committee (ECAC) agreed that the rodent carcinogenicity studies would not be required for benralizumab. Considerations leading to this conclusion were that there no proliferative or pre-neoplastic lesion identified in cynomolgus monkeys after treatment for up to 39 weeks and benralizumab does not bind to murine IL-5Rα; therefore, a 2-year study in rodents was not feasible.

5. Clinical Pharmacology/Biopharmaceutics

AstraZeneca submitted results from a comprehensive clinical pharmacology program that included studies to assess pharmacokinetics (PK) and pharmacodynamics (PD). PD response (blood eosinophil depletion) was evaluated in a 12-week phase 2 study and in a 12-month dose-ranging study in asthmatics. The data from these studies provided support for the dose and dosing regimens evaluated in the phase 3 studies. From the phase 2 data, all benralizumab dosage groups demonstrated complete or near complete depletion of median blood eosinophil levels. In the two phase 3 exacerbation studies, blood eosinophils were reduced to a median absolute blood eosinophil count of 0 cells/μLin the 2 dosing regimens evaluated (i.e. 30 mg

administered subcutaneously (SC) every 4 weeks for 3 doses followed by 30 mg SC every 8 weeks (Q8W dosing regimen), and 30 mg SC every 4 weeks (Q4W dosing regimen). This magnitude of reduction was seen at the first observed time point, 4 weeks of treatment, and was maintained throughout the treatment period. Both dosing regimens depleted and maintained the low peripheral blood eosinophil counts to a similar magnitude compared to placebo. Following discontinuation of treatment in the two phase 3 exacerbation trials, the magnitude of eosinophil count reduction was maintained for at least 8 weeks with a median peripheral blood eosinophil count of 0 cells/µL in both dosing regimens (see Figures 1 and 2). The eosinophil counts started to return beyond 8 weeks post treatment in both studies (data from CALIMA depicted in Figure 3). The magnitude of reduction in the peripheral blood eosinophil counts was similar in adults and adolescents 12 to 17 year olds in the phase 3 trials. Base on the phase 3 data, there was no noticeable exposure-response relationship between median observed benralizumab steady-state trough concentrations and clinical efficacy (i.e. asthma exacerbation rate, FEV_1). At the proposed Q8W dosing regimen, the PK steady-state was reached at the third Q8W dose. The proposed Q8W dosing regimen is supported by the clinical pharmacology data.

Figures 1 and 2: Blood eosinophil count time profile following Q4W or Q8W dosing in the phase 3 trials: SIROCCO (Figure 1) CALIMA (Figure 2)

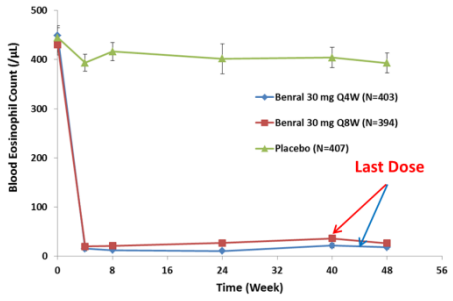


Figure1

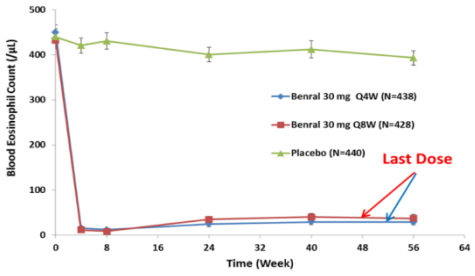
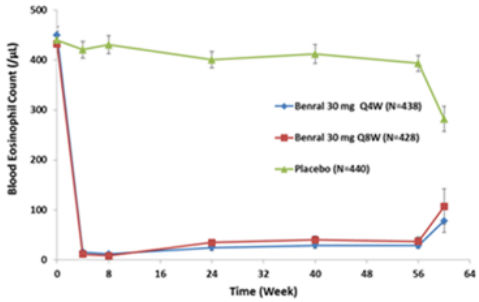


Figure 2

Source: Clinical pharmacology reviewer Dr. Yunzhao Ren

Figure 3: Blood eosinophil count time profile beyond 56 weeks (at week 60) in CALIMA



Source: Clinical pharmacology reviewer Dr. Yunzhao Ren

The pharmacokinetics of benralizumab showed dose linearity and dose proportionality between 20 to 200 mg. The estimated absolute bioavailability from population pharmacokinetic (PopPK) modelling is 58% and the relative bioavailability based on

administration site (abdomen, thigh, our upper arm) is similar. From PopPK modelling, the estimated clearance of benralizumab is 0.29L/day and the half-life of elimination ($t_{1/2}$) was approximately 15 days following subcutaneous administration. Like other monoclonal antibodies, benralizumab is catabolized by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissues. Hepatic function does not influence the metabolism of Benralizumab and the potential for drug-drug interaction potential is low. The PK in adolescents 12 to 17 years of age was comparable to that in adults based on observed mean steady state trough concentrations ($C_{trough, ss}$). The PK of Benralizumab was not significantly impacted by race, ethnicity, age, or gender.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues. AstraZeneca proposed acceptable testing for the bulk drug product and the product packaged in the commercial presentation.

7. Clinical/Statistical-Efficacy

Overview of the Clinical Program

The submitted data from the clinical program are adequate to evaluate the efficacy of benralizumab for patients with severe asthma in a specified phenotype as proposed by AstraZeneca. Patients enrolled in the phase 3 studies had asthma severity based on exacerbation history, asthma medication use, and eosinophil counts. Baseline blood eosinophil count was defined as the result from Visit 1 or 3 (screening) from local laboratories and used to stratify patients at randomization. Subsequent hematology measurements for eosinophil and basophil counts were done by a central laboratory.

The patient population in the two exacerbation studies SIROCCO and CALIMA was generally balanced across the treatment groups based on demographic variables, disease characteristics, disease status. Subjects were fairly evenly distributed across the treatment arms/regimens except that there was a greater number of adolescents in the Q8W regimen compared to the Q4W regimen because the European Union only allowed randomization to the Q8W arm or placebo for adolescents, whereas, in the rest of the world adolescents were recruited into the Q4W, Q8W, or placebo arms.

The two exacerbation trials evaluated patients 12 to 75 years of age with moderate to severe asthma and a history of exacerbations who remain symptomatic despite using high-dose ICS/LABAs with or without OCS or additional controller medications. This degree of asthma severity is consistent with asthma patients who are in NAEPP[2] steps 5 and 6 of therapeutic

[2] National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3: Guidelines for the Diagnosis and management of Asthma, 2007. Available at: http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines

intervention. As per prior agreement with the Agency, patients enrolled in these trials were stratified based on having a high eosinophil count (i.e. ≥300 cells/μL) or low eosinophil count (< 300 cells/μl) at baseline. The oral corticosteroid reduction study (ZONDA) enrolled patients who in addition to high dose ICS/LABA also required OCS for asthma control. For these patients a lower eosinophil level (> 150 cells/μL) was used for study eligibility. Given the know suppressant effects of OCS on blood eosinophil levels, the eosinophil entry criterion for the OCS reduction study is reasonable. The clinical data to support dose selection for the phase 3 program came from the 52-week dose-ranging exacerbation study (MI-CP-220). Study BORA and MELTEMI are safety extension studies that were ongoing at the time of the BLA submission and safety information from those studies was included in the 120 safety day update (data cut-off point was October 21, 2016). Selected characteristics of the relevant studies that form the basis of review and regulatory decision for this application are shown in Table 1.

Table 1: Clinical trials

ID **Year** ***Study #**** **Study Characteristics** **-Patient age** **-Patient characteristics** **-Study design objectives** **-study duration**	**Treatment groups**	**N**	**Efficacy Variables**	**Regions and Countries**
MI-CP-220 12/10 -8/13 -≥ 18 years of age -moderate to severe asthma -R, DB, PC, phase 2b dose-ranging - 52 weeks	-2 mg SC Q 4wk x 3→Q8 wk -20 mg SC Q 4wk x 3→ Q 8wk -100 mg SC Q 4 wk x 3→ Q 8 wk - placebo	609	1^0: exacerbation rate 2^0: ACQ, FEV_1	95 centers in 10 countries: United States, Argentina, Brazil, Bulgaria, Canada, Columbia, Mexico, Peru, Poland
SIROCCO/017§ 9/13 -4/16 *Study 1* -≥ 12 years of age -Moderate to severe asthma -R, DB, PC, phase 3 -48 weeks	- 30 mg SC Q 4wk→ Q 8 wk - 30 mg SC Q 4 wk - Placebo SC	1205[1]	1^0: exacerbation rate 2^0: ACQ, AQLQ, FEV_1	286 centers in 17 countries: United States, Australia, Brazil. Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russian Federation South Africa, South Korea, Spain, Turkey, United Kingdom, Vietnam
CALIMA/018 8/13 -3/16 *Study 2* -≥ 12 years of age -Moderate to severe asthma -R, DB, PC, phase 3 -56 weeks	- 30 mg SC Q 4wk→ Q 8 wk (Q8W) - 30 mg SC Q 4 wk (Q4W) - Placebo SC	1306[2]	1^0: exacerbation rate 2^0: ACQ, AQLQ, FEV_1	242 centers in 11 countries: United States, Argentina, Canada, Chile, Germany, Japan, Philippines, Poland, Romania, Sweden, Ukraine
ZONDA/020 8/13 -3/16 *Study 3* -≥ 18 years of age -severe asthma requiring oral corticosteroids and baseline eosinophil count ≥ 150 cells/μL R,DB, PC, phase 3 -28 weeks	-30 mg SC Q 4wk→ Q 8 wk (Q8W) - 30 mg SC Q 4 wk (Q4W) - Placebo SC	220	1^0: OCS reduction 2^0: exacerbations, FEV_1, ACQ, AQLQ	64 centers in 12 countries: United States, Argentina, Bulgaria, Canada, Chile, France, Germany, Poland, South Korea, Spain, Turkey, Ukraine
BISE/032	-≥ 18 years 30 mg Q 4 week (Q4W)	211	1^0: FEV_1	52 centers in 6

ID Year *Study #** 	Study Characteristics -Patient age -Patient characteristics -Study design objectives -study duration	Treatment groups	N	Efficacy Variables	Regions and Countries
2/15 -10/15	-mild to moderate persistent asthma -R, DB, PC -12 weeks	Placebo			countries: United States, Canada, Germany, Hungary, Poland, Slovakia
BORA (ongoing)	≥12 years and older -Patients who complete SIROCCO, CALIMA, or ZONDA R DB -56 weeks	30 mg SC Q 8 weeks 30 mg SC Q 4 weeks	2133[3]	Long-term safety	See above
MELTEMI (ongoing)	≥ 12 years and older - Patients who complete SIROCCO, CALIMA, or ZONDA and 16 weeks in BORA OL -until Benralizumab is marketed	30 mg SC Q 8 weeks 30 mg SC Q 4 weeks	345[4]	Long-term safety	See above
§The investigational number for the phase 3 studies begins with D3250C000 followed by two digits. For example, SIROCCO is D3250C00017. In the table and throughout the review the phase 3 studies will be identified by the last 3 numbers (i.e. study 017 for SIROCCO). ID = AstraZeneca's study acronym and number *Study #** =study number as identified in the package insert R, DB, PC = randomized, double-blind, placebo-controlled OL = open label					
1= > 18 years: n = 11152; 12 -17 years: n = 53 2=> 18 years: n = 1251; 12-17 years: n =55 3=Number completing treatment on investigational product 4=Number of subjects at time of data cut-off for BLA submission					

Some key characteristics of the patient population enrolled in the phase 3 studies are shown in Table 2.

Table 2: Selected Characteristics for patients (Full analysis set)[3] in the phase 3 controlled clinical studies

Characteristic	SIROCCO/017 (n = 1204)	CALIMA/018 (n = 1306)	ZONDA/020 (n =220)
Demographics/clinical characteristics			
Mean age (yr)	49	49	51
Duration of asthma, median (yr)	15	16	12
Gender (% Female)	66	62	61
BMI (mean)	29	29	30
Race (% White/Caucasian)	73	84	93
Race (% black/African-American)	4	3	2
Smoking history – never smoked (%)	80	78	79
Pulmonary function			
Pre-bronchodilator FEV_1 % predicted	57	58	60
Post-bronchodilator FEV_1/FVC ratio, mean	66	65	62
Reversibility, mean %ΔFEV1 post SABA	26	27	24
Eosinophil and exacerbation history			

[3] Includes both the eosinophil "high" (the primary efficacy population) and eosinophil "low" strata. The characteristics were similar in the overall population and the eosinophil 'high' population.

Characteristic	SIROCCO/017 (n = 1204)	CALIMA/018 (n = 1306)	ZONDA/020 (n =220)
Baseline mean blood eosinophil count (cells/μL)	472	472	575
Mean number of exacerbations in previous year	3	3	3
% patients with ≥ 2 exacerbations in previous year	62	66	29
% patients with ≥ 3 exacerbations in previous year	18	21	16%
Background treatments for asthma (% of patient)			
Mean ICS total daily dose (μg) [min. max]	899 [125,3000]	873 [12.5*,4750]	1154 [100,5000]
ICS/LABA	95%	86%	90%
LAMA	8%	8%	29%
LTRA	36%	28%	37%
Xanthine derivatives	15%	12%	15%
Oral corticosteroids (OCS) mean mg	16% (15 mg)	9% (11 mg)**	100% (14.7 mg)#

Data source: Case study reports: D3250C00017, Dc250C00018, And D3250C00020.
mean dose of OCS at optimization
*out-of-range minimum due to site data entry error
** Summary statistics for the high ICS+ high eosinophil group

Design and Conduct of the Studies

Dose-Ranging Study MI-CP-220:

The dose selection for the benralizumab phase 3 studies is based on a dose response model using PK and PD data and clinical data. The clinical data are from a 52-week dose-ranging study MI-CP-220. MI-CP-220 was a randomized, double-blind, placebo-controlled study evaluating 2 mg, 20 mg, and 100 mg of benralizumab administered SC in patients 18 years of age and older with moderate to severe asthma on medium or high-dose ICS plus a LABA and a history of ≥ 2 exacerbations in the prior year. Subjects in this dose-ranging trial were classified and stratified as having an eosinophilic phenotype (EOS+) defined as ELEN Index[4] positive and/or FeNO ≥ 50 ppb, or a non-eosinophilic phenotype (EOS-) defined as both ELEN Index negative and FENO < 50 ppb during the 3-week screening/run-in period. Subjects were also stratified by baseline ICS status (approx. 60% of subjects were on medium-dose ICS vs at least 40% of subjects on high-dose ICS). Study treatment was administered every 4 weeks for the first 3 doses followed by every 8 weeks thereafter (Q8W dosing regimen). The primary endpoint in this study was the annual exacerbation rate (AER) in the eosinophilic phenotype + subset. Data from this study was used in an exposure-response

[4] The ELEN Index is a proprietary mathematical algorithm to predict sputum eosinophils ≥ 2%. It was developed using multivariate statistical modelling of baseline sputum and blood data from a phase 2a clinical study (MI-CP138) that evaluated the efficacy of a humanized anti-IL9 monoclonal on late asthmatic response induced by allergen inhalation in adults with atopic asthma and validated using 2 independent datasets. In the ELEN Index, 2 predictor variables, the ratio of blood eosinophils (E) to lymphocytes (L) and the ratio of blood eosinophils (E) to neutrophils (N) were used to classify subjects as having either < 2% or ≥ 2% sputum eosinophils with the need for sputum collection. D.B. Khatry et al. A simple Index Utilizing Peripheral Blood Leukocytes predicts Sputum Eosinophilic and Non-Eosinophilic Asthma Phenotypes. C33 Cytokines And Asthma Mediators/Thematic Poster Session/Tuesday May 20/San Diego Convention Center/ *Am J Respir Crit Care Med* 189;2014:A34257

model on AER to explore the most appropriate dose(s) for benralizumab for the phase 3 studies.

Exacerbation studies; SIROCCO/ study 017 and CALIMA/study 018

The two exacerbation studies SIROCCO/ study 017 and CALIMA/ study 018 were conducted in adults and adolescents (ages 12 to 75 years) who had uncontrolled asthma (i.e. still symptomatic despite using high-dose ICS plus LABA with or without OCS or additional controller medications and a history of at least 2 asthma exacerbations in the previous year. CALIMA/study 018 was expanded to include patients on medium dose ICS/LABA.[5] Both exacerbation studies were randomized, double-blind, parallel group, placebo-controlled in design. In both studies, an enrichment strategy to enroll subjects in a 2:1 ratio for the high eosinophil high stratum (eosinophil counts ≥ 300 cells/ μL) versus the low eosinophil stratum (eosinophil count < 300 cells/μL) was used. Eligible subjects were randomized with stratification by geographical region, age group (adult or adolescent) and baseline blood eosinophil count (≥ 300/μL or < 300/μL). Baseline blood eosinophil count was obtained with routine CBC counts at local laboratories and subsequent eosinophil measurements were obtained from central laboratories.

In both studies 2 dosing regimens were evaluated: benralizumab 30 mg SC once every 4 weeks x 3 doses followed by once every 8 weeks (Q8W dosing regimen), or Benralizumab 30 mg once every 4 weeks (Q4W dosing regimen). Subjects were randomized 1:1:1 to the active treatment regimens or placebo. After the first 3 doses, patients randomized to the 8-week regimen received placebo at Visit 8 (dose 4) with active drug administered at Visit 9 (dose 5) and then every second treatment visit thereafter; placebo injections were administered at the 4-week interim treatment visits in order to maintain the blind. The double-blind treatment period was 48 weeks in length with the last dose of benralizumab or placebo administered at Week 44 and the end of treatment visit on Week 48 in SIROCCO/study 017. The double-blind treatment period was 56 weeks in CALIMA/study 018.

The primary efficacy endpoint and multiplicity adjustment for statistical calculations was based on the eosinophil high population. The primary efficacy endpoint in both exacerbation studies was the annual exacerbation rate. Secondary endpoints included time to first exacerbation, exacerbation leading to ER visits and hospitalizations, lung function (FEV_1) and patient reported outcomes (ACQ and AQLQ).

Oral corticosteroid reduction (OCS) study; ZONDA/study 020

Study 020 (ZONDA) was conducted in adult patients 18 to 75 years of age with severe asthma who required treatment with high-dose ICS/LABAs and chronic OCS therapy with or without additional controller medications. This study evaluated the same two dosing regimens (Q4W

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5 (b) (4) the CALIMA trial following a re-design of that trial to allow for inclusion of subjects using medium-dose ICS/LABAs with or without OCS or additional controller medications.

and Q8W) that were studied in SIROCCO and CALIMA compared with placebo. All patients were required to be treated with OCS of 7.5 to 40 mg for at least 6 months prior to enrollment and to be on a stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization. Patients were required to have at least 1 exacerbation in the previous 12 months. The study included an 8 week run-or or OCS dose optimization period, a 28-week treatment period, and an 8-week follow-up period. Eligible subjects were randomized 1:1:1 to the treatment arms with the last dose of investigational product administered at Week 24, and end-of-treatment visit at Week 28. The primary endpoint was the percent reduction from baseline in the final OCS dose while maintaining asthma control. The study was designed such that OCS reduction could occur between Week 4 to Week 24 following a dose titration schedule. Secondary endpoints included lung function (FEV_1), patient reported outcomes using the ACQ and the AQLQ, and exacerbations.

Lung function study; BISE/study 032

BISE/study 032 was a dedicated lung function study conducted in patients 18 years of age and older with mild to moderate persistent asthma. The study was conducted to address the Agency's recommendation to evaluate the full spectrum of asthma severity in the benralizumab program. Only one dose of benralizumab 30 mg Q4W was studied compared to placebo. The treatment duration was 12 weeks. The primary efficacy endpoint was the change from baseline in pre-bronchodilator FEV_1 at Week 12.

Efficacy Results and Conclusion

The submitted data from the clinical program are adequate to support efficacy of benralizumab. The proposed dosing regimen is 30 mg SC Q4 x 3 doses then Q8W (Q8W dosing regimen) for patients with severe asthma in a specified target population. The clinical data from the phase 3 program support this dosing strategy. (b) (4) Based on the mechanism of action of benralizumab, it is reasonable to consider that this biologic will be an effective therapeutic agent in asthma patients with increased eosinophilic burden (i.e. eosinophilic inflammation). The Agency has previously accepted the term "eosinophilic phenotype" as part of the qualifying language in the indication statement for other anti-IL 5 products. The patient population was selected with enrichment criteria geared towards ensuring that patients with increased eosinophilic inflammation were enrolled (i.e. high eosinophil blood levels and other criteria suggestive of difficult to control asthma such as frequent exacerbations despite being on high dose ICS/LABAs and other controllers +/- oral corticosteroids). While the data do support a greater benefit in patients with high(er) eosinophil counts, and more frequent exacerbations, the overall data suggest efficacy (albeit to a lesser degree) in all comers. The statistical team conducted several sensitivity analyses (including a tipping point analysis) to evaluate the robustness of the efficacy findings and these all support the efficacy of benralizumab. The two dosing regimens evaluated 30 mg Q4W and 30 mg Q8W are both effective. There does not appear to be any efficacy or safety advantage of the Q4W dosing regimen over the Q8W dosing regimen.

Dose and dosing Schedule

The proposed dose and dosing regimen of benralizumab 30 mg Q4W x 3 doses followed by 30 mg SC Q8W is supported by the submitted data. The dose selection for the benralizumab phase 3 studies is based on a dose response model using PK and PD data and clinical data that came from the 52-week dose-ranging study MI-CP-220 described above. The study demonstrated a dose-response trend in which the lowest dose (2 mg) did not reduce the annual exacerbation rate (AER) in patients with non-eosinophilic phenotype (RR = 109%) whereas both the 20 mg and the 100 mg dose reduced AER by 36% and 41%. The results are shown in Table 3.

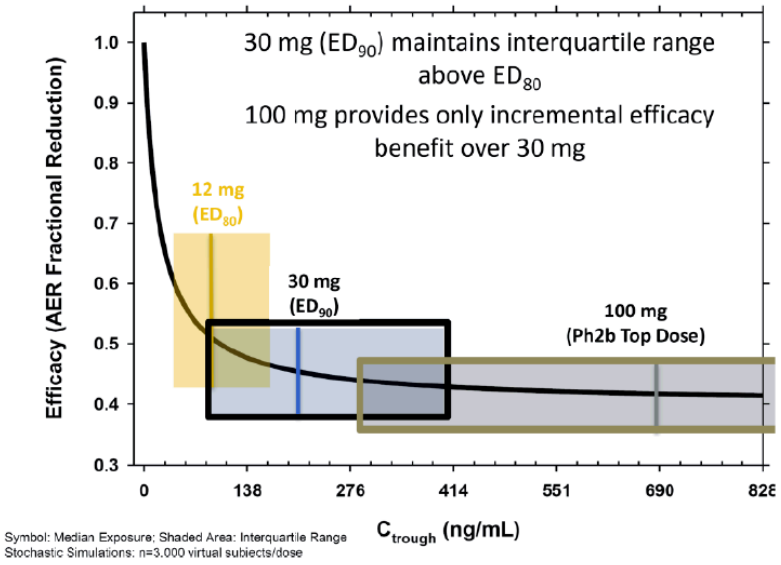
Table 3: Annual Asthma Exacerbation Rate in mITT Population

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

EOS+ = ELEN index positive and/or FeNO ≥ 50 ppb
EOS - = ELEN Index negative and FeNO < 50 ppb
FeNO= fraction of exhaled nitric oxide
Data source: CSR M-CP220, page 101, Table 11.4.1.1-1

A dose response relationship was also observed in reduction of peripheral blood eosinophil counts with a 14%, 57%, 75% and 76% reduction in mean eosinophil counts from baseline at Week 40 [i.e. the last dose of study treatment administered] in the placebo, 2 mg, 20 mg, and 100 mg treatment groups respectively. The reduction in eosinophil count was similar in 20 mg and 100 mg treatment group. An exposure-response model estimated that 30 mg SC was the estimated effective dose that gave 90% inhibition (ED_{90}) for asthma exacerbation rate following the Q4W x 3 doses + Q8W dosing regimen. The 30 mg Q8W dosing regimen was expected to maximize therapeutic efficacy (residing at the efficacy plateau of asthma exacerbation rate, pre-bronchodilator FEV_1, and ACQ responses) while reducing the impact of steady-state PK variability on the efficacy outcome (Figure 4). No dose-limiting safety issues were identified in the study. The inclusion of the more frequent regimen of 30 mg Q4W in the phase 3 studies was to ascertain if higher serum trough levels would decrease the immunogenic profile of benralizumab and potentially improve efficacy in subjects with low PK exposure.

Figure 4: A priori simulated exposure-response for the 30 mg Q8W regimen as the optimal phase 3 dose 9baseline blood eosinophil count ≥ 300/µL



Source: Summary of Clinical Efficacy Figure 22 page 168 (181)

Exacerbation effects

The primary endpoint for studies SIROCCO/study 017 and CALIMA/study 018 was the annual asthma exacerbation rate. An asthma exacerbation was defined by a worsening of asthma symptoms requiring: a) use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids; b) an emergency room/urgent care visit (defined as evaluation and treatment for < 24 hours in an emergency department (ED) or urgent care center) due to asthma that required systemic corticosteroids (as per above), or c) an inpatient hospitalization due to asthma. Statistically significant reductions in the annual asthma exacerbation rates were seen in both exacerbation studies for both dosing regimens of benralizumab compared to placebo in the eosinophil high stratum, and in the overall population (both eosinophil high and eosinophil low strata). The treatment effect in the eosinophil low stratum trended in a direction favoring benralizumab. Exacerbations requiring hospitalizations and emergency room visits were decreased in both studies but reach nominal statistical significance in only one of the studies (SIROCCO) for one comparison (benralizumab Q8W vs. placebo). Exacerbations requiring hospitalizations were numerically lower in one study (CALIMA).

The marginal method was used to estimate the exacerbation rate by calculating the predicted rate for each subject with model estimated parameter values and the subject's own covariate values and then averaging these predictions for each treatment group to provide the estimate for each arm. Although this is a relatively new method, the FDA statistical review team agreed with AstraZeneca to use this approach. The FDA statistical team confirmed that this approach represents a more appropriate estimate of the annual exacerbation rates (in terms of alignment with the crude rates) compared to a model based approach. In the model based approach, the mean values of covariates in the study are calculated first and then the model- estimated

parameter values are used to calculate the annual exacerbation rates. The exacerbation results using both methods are presented in Dr. Yu (Jade) Wang's statistical review. Table 4 shows the exacerbation results for both studies using the marginal method which is the method that is reflected in the product label. Of note, estimation of treatment effect in the form of rate ratios of benralizumab arms versus the placebo, as a parameter built into the negative binomial model, will not be affected by either of the two approaches described above. Across the two studies, benralizumab had a demonstrable benefit on reducing asthma exacerbations.

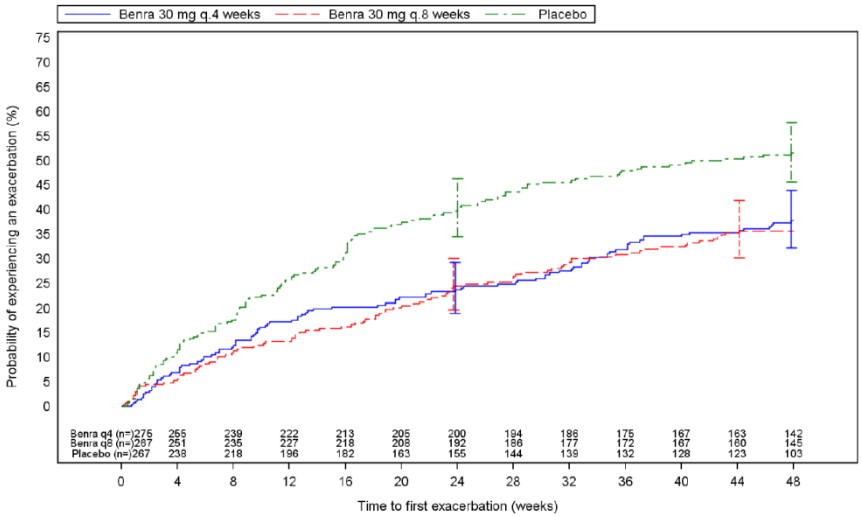
Table 4: Exacerbation Results Studies SIROCCO/017 and CALIMA/018*

Study	**Treatment (n)**	**Exacerbations**		
		Mean Rate (95% CI)	Rate diff (95% CI)	Rate ratio (95% CI) p-value
Exacerbations (all exacerbations)				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.74 (0.59,0.92)	-0.78 (-1.08,-0.47)	0.49 (0.37,0.64) p < 0.001
	Benra 30 mg Q4W (n= 275)	0.83 (0.68, 1.02)	-0.69 (-1.00,-0.38)	0.55 (0.42, 0.71) p<0.001
	Placebo (n = 267)	1.52 (1.27,1.81)	---	---
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.73 (0.58, 0.90)	-0.29 (-0.53,-0.05)	0.72 (0.54,0.95) P=0.019
	Benra 30 mg Q4W (n = 241)	0.65 (0.52,0.81)	-0.36 (-0.59,, -0.13)	0.64 (0.49,0.85) p=0.002
	Placebo (n = 248)	1.01 (0.84,1.22)	-----	----
Exacerbations requiring hospitalization/emergency room visit				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.09 (0.05,0.16)	-0.16 ((-0.26, -0.06)	0.37 (0.20,0.67) P<0.001
	Benra 30 mg Q4W (n = 275)	0.15 (0.10, 0.24)	-0.10 (-0.21,0.01)	0.61 (0.37,1.01) p =0.053
	Placebo (n 267)	0.25 (0.17,0.38)	----	----
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.12 (0.08,0.19)	0.02 (-0.05,0.09)	1.23 (0.64,2.35) p=0.538
	Benra 30 mg Q4W (n = 241)	0.09 (0.06,0.15)	-0.01 (-0.07,0.06)	0.93 (0.48,1.82) p=0.837
	Placebo (n = 248)	0.10 (0.06,0.15)	----	----
Exacerbations requiring hospitalization				
SIROCCO/017	Benra 30 mg Q4Wx3→ Q8W (n = 267)	0.07 (0.03,0.14)	-0.07 (-0.16,0.01)	0.48 (0.22,1.03) p =0.06
	Benra 30 mg Q4W (n = 275)	0.09 (0.04,0.18)	-0.05 (-0.14,0.03)	0.62 (0.31,1.27) p=0.192
	Placebo (n = 267)	0.14 (0.07,0.27)	----	----
CALIMA/018	Benra 30 mg Q4Wx3→ Q8W (n = 239)	0.07 (0.04,0.13)	0.02 (-0.03,0.08)	1.48 (0.65,3.37) p=0.356
	Benra 30 mg Q4W (n = 241)	0.05 (0.03,0.10)	0.00 (-0.04,0.05)	1.02 (0.42,2.49) p=0.970
	Placebo (n = 248)	0.05 (0.03,0.09)	----	----

*Baseline blood eosinophil counts ≥300/µL and on high-dose ICS

In both studies, treatment with benralizumab (both treatment regimens) delayed the time to first exacerbation compared to placebo. In SIROCCO the longer time to first exacerbation was indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.63, 95% CI [0.49, 0.82] for benralizumab 30 mgQ4W and 0.60 [0.46, 0.78] for benralizumab 30 mg Q8W, both nominal p <0.001).

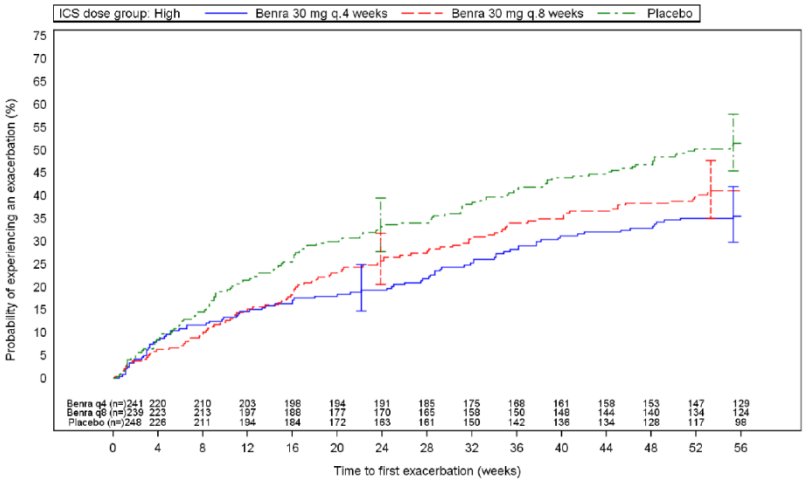
Figure 5: Time to first asthma exacerbation, Kaplan-Meier cumulative incidence curve (full analysis set, baseline blood eosinophils ≥ 300/µL (SIROCCO/study 017)



Source: D3250C0017 CSR Figure 6 page 123

In CALIMA the time to first asthma exacerbation was longer for both benralizumab 30 mg Q4W and Q8W, as indicated by a lower probability of having an asthma exacerbation compared with placebo (hazard ratio: 0.61, 95% CI [0.46,0.80], nominal p <0.001, and 0.73, 95% CI [0.55, 0.95], nominal p ≤ 0.018.

Figure 6: Figure 3: Time to first asthma exacerbation, Kaplan-Meier cumulative incidence curve (full analysis set, baseline blood eosinophils ≥ 300/µL (CALIMA/study 018)



Source: D3250C0018 CSR Figure 7 page 122

Asthma exacerbation rate was also evaluated in the oral corticosteroid reduction study ZONDA. Because the definition of an asthma exacerbation incorporates oral corticosteroid

use, the relevant exacerbation outcome in an OCS reduction study would be exacerbations requiring hospitalizations and emergency room visits. In the OCS reduction study, the number of asthma exacerbation events associated with ER visit or hospitalization over 28 weeks was lower in both benralizumab 30 mg Q4W and Q8W regimens compared with placebo (5, 1, and 14 respectively). Both benralizumab 30 mg Q4W and Q8W reduced the annual rate of asthma exacerbations associate with ER visit or hospitalization over 28 weeks compared with placebo as shown in Table 5.

Table 5: Annualized asthma exacerbation rate ratio associated with ER visits or hospitalization over 28 weeks in ZONDA

Treatment (n)	Number of events	Mean rate[1] (95% CI)	Rate diff (95% CI)	Rate ratio (95% CI)
Benra 30 mg Q 8W (n= 73)	1	0.02 (0.00,0.18)	-0.30 (-0.53,-0.07)	0.07 (0.01,0.63)
Benra 30 mg Q 4 W (=72)	5	0.14 (0.05,0.38)	-0.18 (-0.45,0.09)	0.44 (0.13,1.49)
Placebo (n=75)	14	0.32 (0.16,0.65)	--	---

Source: D3250C00020 Clinical Study Report Table 11.2.4.6 page 382
[1]Mean rate based on marginal method as in Table 4 above

Oral Corticosteroid Reduction

The primary endpoint in ZONDA/study 020 was the percent reduction from baseline of the final OCS dose during Weeks 24 to 28 while maintaining asthma control. In this study asthma control was assessed by the investigator based on a subject's FEV_1, PEF, nighttime awakenings, short-acting bronchodilator rescue use, or any other symptoms that would require an increase in OCS dose. The mean and median optimized (baseline) OCS doses were 14.7 mg and 10.0 mg and were similar across treatment groups. The majority of subjects had eosinophil levels ≥ 300/μL at baseline. Treatment with benralizumab resulted in a significant reduction in OCS use compared to treatment with placebo. The median percent reduction in daily OCS dose from baseline was 75% in patients receiving benralizumab 30 mg Q8W, or 30 mg Q4W compared to 25% in subjects receiving placebo (both p <0.001). Results are shown in Table 6.

Table 6: Percent reduction from baseline in daily OCS dose at Week 28

	Benralizumab 30 mg Q4W (n = 72)	Benralizumab Q8W (n = 73)	Placebo (n=75)
Wilcoxon rank-sum test (primary analysis)			
Baseline daily OCS dose (mg) , mean (SD)	15.78 (8.83)	14.28 (7.76)	14.15 (6.35)
Final daily OCS dose at Week 28 (mg), mean (SD)	8.25 (10.80)	6.36 (6.88)	11.25 (8.47)
Median percent reduction from baseline	75	75	25
Hodges-Lehmann estimate for difference in % reduction from baseline Benra vs. placebo (95% CI)	33.30 (16.70, 50.00) p-value <0.001	37.50 (20.80, 50.00) p-value < 0.001	--
Proportional odds model (sensitivity analysis) – probability by category N (%)			

	Benralizumab 30 mg Q4W (n = 72)	**Benralizumab Q8W (n = 73)**	**Placebo (n=75)**
90% to 100% reduction	24 (33.3)	27 (37.0)	9 (12.0)
75% to <90% reduction	14 (19.4)	10 (13.7)	6 (8.0)
50% to <75% reduction	10 (13.9)	11 (15.1)	13 (17.3)
>0% to <50% reduction	7 (9.7)	10 (13.7)	12 (16.0)
No change or increase	17 (23.6)	15 (20.5)	35 (46.7)
Odds ratio (95% CI)	4.09 (2.22, 7.57) p <0.001	4.12 (4.12 (2.22, 7.63) p < 0.001	

Source: D3250C00020 Clinical Study Report Table 18 page 97 -98

Lung Function effects

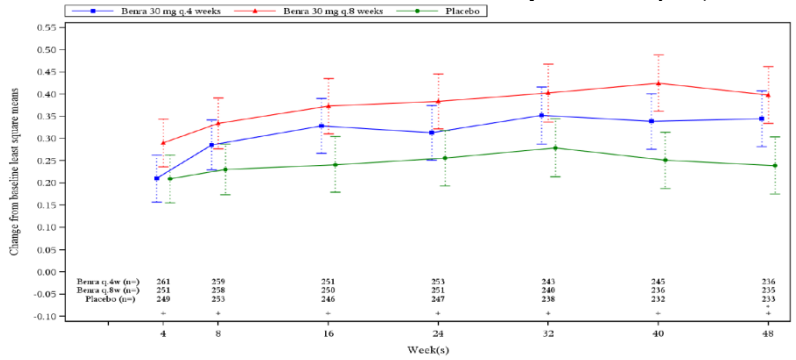
Change from baseline in mean pre-bronchodilator FEV_1 at end of treatment was assessed in both exacerbation trials and the OCS reduction trial as a secondary endpoint and as a primary endpoint in a 12-week lung function study in mild to moderate asthmatics (BISE). An improvement in lung function was seen with benralizumab treatment in the two treatment regimens in the exacerbation and OCS reduction studies. Only one dosing regimen (30 mg Q4W) was evaluated in the 12-week lung function study. The lung function results are shown in Table 7. Only data from the 30 mg Q8W dosing regimen in the pivotal phase 3 trials are shown. The 30 mg Q4W dosing regimen (in the pivotal phase 3 trials) had similar results.

Table 7: Change from baseline in mean pre-bronchodilator FEV_1 (L) at end of treatment

Trial	**Difference from placebo in mean change from pre-bronchodilator baseline FEV_1 (L) (95% CI)**
SIROCCO/study 017 (Q8W vs. placebo)	0.16 (0.07,0.25)
CALIMA/study 018 (Q8W vs. placebo)	0.12 (0.03, 0.20)
ZONDA/study 020 (Q8W vs. placebo)	0.11 (-0.33,0.26)
BISE/study032 (Q4W vs. placebo)	0.08 (0.00, 0.15)

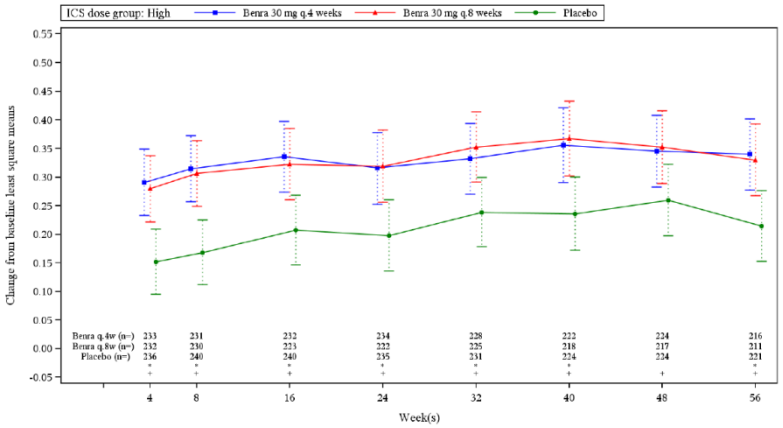
The mean change from baseline in pre-bronchodilator FEV_1 (L) for SIROCCO and CALIMA are is shown in Figures 4 and 5 below.

Figure 7: Change from baseline in pre-bronchodilator FEV_1 (L) by time point (full analysis set, baseline blood eosinophils ≥ 300/µL (SIROCCO)



Source: D3250C00017 Clinical study report Figure 8 pg 130

Figure 8: Change from baseline in pre-bronchodilator FEV1 (L) by time point (full analysis set, baseline blood eosinophils ≥ 300/µL (CALIMA)



Source: D3250C00018 Clinical study report Figure 9 pg 129

Patient reported outcome measures

Both the asthma control questionnaire (ACQ) and the Asthma Quality of Life Questionnaire (AQLQ) were used in this program. Both instruments are commonly used in asthma and have well defined measurement properties and are listed in well-recognized asthma treatment guidelines. AstraZeneca also looked at other patient reported outcome measures; i.e. the EQ-5D-5L (EuroQol 5 dimensions-5 levels) and the WPAI +CIQ (Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions) however, these instruments are less well known and are not universally used in asthma assessments. Subjects recorded asthma symptoms in a daily dairy (day and night symptoms) and AstraZeneca captured this in an asthma symptom score. As the information captured in such a dairy will already be captured in the well-known and accepted ACQ, the asthma symptom score as calculated by AstraZeneca will not be discussed further.

ACQ is a questionnaire that measures the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. The 7 items that make up the ACQ include 5 items of self-administered questions (breathlessness, nocturnal waking due to asthma, and asthma symptoms upon waking, activity limitation, and wheeze); 1 item of self-administered rescue bronchodilator use, and 1 item of FEV_1 measurement completed by clinical staff. In this program the ACQ-6 was used – i.e. the FEV_1 measurement was excluded. This is reasonable since FEV_1 was being analyzed separately as a key secondary endpoint. Questions on the ACQ are scored on a 7-point scale from 0 (totally controlled) to 6 (severely uncontrolled); thus a decrease in score indicates improvement. A change in score of 0.5 is considered to be the minimum clinically important difference (MCID). The shortened version (ACQ-6 [and sometimes ACQ-5] have been used in clinical programs and use the same minimum cut off for clinical significance. To be confident that a patient has uncontrolled asthma the optimal cut-point on the ACQ score is 1.5 (positive predictive value = 88)[6]

[6] Elizabeth F. Juniper et al. Identifying "well-controlled" and 'not well-controlled" asthma using the Asthma Control Questionnaire. *Respiratory Medicine* (2006) **100**, 616-621

The AQLQ is a disease specific health-related instrument that measures physical and emotional impact of disease. There are 32 questions in the AQLQ grouped in 4 domains – symptoms, activity limitation, emotional function, and environmental stimuli. Each of the 32 questions is scored on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment); thus an increase in score indicates improvement. The recall period for the AQLQ is 2 weeks. A change in score on 0.5 on the 7-point scale is considered the minimum clinically important difference (MCID). The AQLQ (S) +12 is the standardized version of the AQLQ for use in adolescents and adults 12 years of age and older. ACQ and AQLQ results at the end of treatment for SIROCCO, CALIMA, and ZONDA are shown in table 8 (data for the Q8W regimen only are shown). Mean baseline scores for the ACQ-6 and AQLQ were similar across treatment arms.

Table 8: ACQ-6 and AQLQ (s) + results for SIROCCO, CALIMA, and ZONDA (Baseline eosinophil count ≥ 300/µL)

	Benralizumab 30 mg Q8W	**Placebo**
ACQ-6 responder analysis at ≥ 0.5 threshold at end of treatment		
	Benralizumab 30 mg Q8W	**Placebo**
SIROCCO Benra vs placebo, odds ratio (95% CI)	60%	57% 1.55 (1.09,2.19)
CALIMA Benra vs. placebo, odds ratio (95% CI)	63%	59% 1.16 (0.80,1.68)
ZONDA Benra vs. placebo, odds ratio (95% CI)	63%	54.7% 1.66(0.83, 3.34)
AQLQ (S) +12 responder analysis at ≥0.5 threshold at end of treatment		
	Benralizumab 30 mg Q 8W	**Placebo**
SIROCCO Benra vs. placebo, odds ratio (95% CI)	57%	49% 1.42 (0.99,2.02)
CALIMA Benra vs. placebo, odds ratio (95% CI)	60%	59% 1.03 (0.70,1.51)
ZONDA Benra vs. placebo, odds ratio (95% CI)	60%	52.0% 1.78 (0.88, 3.61)

Effect of Eosinophil count and exacerbation history (potential predictors of efficacy)

Reduction in exacerbation rates were observed irrespective of baseline peripheral eosinophil counts; however, patients with a baseline blood eosinophil count ≥ 300/µL showed greater response than those with counts < 300/µL. There was also a trend for a greater exacerbation response in subjects with a history of 3 or more exacerbations within the 12 months prior to randomization to benralizumab in the SIROCCO and CALIMA trials. Lung function improvement was also numerically better in subjects with higher eosinophil counts and more frequent prior exacerbation history.

AstraZeneca explored various eosinophil cut-off points to assess the interaction between treatment effect and baseline blood eosinophil count. The studies were not powered nor

designed to test these interactions and no definitive conclusions should be drawn from these exploratory analyses. That said, there was no clear threshold that determined benefit when evaluating by baseline blood eosinophil count categories and efficacy was observed across all baseline blood eosinophil categories with a greater treatment effect observed in subjects with higher baseline blood eosinophil levels than those with lower baseline blood eosinophil levels. This trend was also evident for change from baseline in pre-bronchodilator FEV_1.

Table 9: Exacerbation rate and pre-bronchodilator FEV_1 by baseline blood eosinophil counts < 300 µL and ≥300µL (Integrated SIROCCO/CALIMA)

	Rate difference	**95% CI**
Annual asthma exacerbation rate: Rate ratio		
Eosinophil count < 300/µL		
Benra 30 mg Q8W (n =256)	0.73	(0.57,0.94)
Benra 30 mg Q4W (n = 240)	0.68	(0.53,0.87)
Placebo (n = 262)		
Eosinophil count ≥300/µL		
Benra 30 mg Q8W (n =506)	0.58	(0.48,0.70)
Benra 30 mg Q4W (n = 516)	0.59	(0.49,0.72)
Placebo (n = 515)		
Pre-bronchodilator FEV_1 (L) change from baseline at Week 48: Difference in LS means		
Eosinophil count < 300/µL		
Benra 30 mg Q8W (n =250)	0.044	(-0.031,0.120)
Benra 30 mg Q4W (n = 234)	-0.001	(-0.078,0.076)
Placebo (n = 254)		
Eosinophil count ≥300/µL		
Benra 30 mg Q8W (n =502)	0.128	(0.064,0.191)
Benra 30 mg Q4W (n = 509)	0.094	(0.031,0.157)
Placebo (n = 505)		

Data source: Summary of Clinical Efficacy 2.7.3 Table 26 page 140 (181)

Subgroup population analysis

Efficacy data were analyzed based on the typical subgroups such as gender, age, ethnicity, and geographical regions. In the pediatric population (12 to 17 years) the point estimate favored placebo in both exacerbation trials. However the confidence intervals were wide for both estimates. The statistical review team commented that the current efficacy does not provide substantial evidence of a clinically meaningful benefit of benralizumab in children 12 to 17 years of age. It is important to keep in mind the small sample size and the fact that these studies were not powered for efficacy in this age range. That said, the interaction tests across the two exacerbation trials on age subgroup were not statistically significant. Furthermore, the inherent type I error inflation with conducting multiple post hoc subgroup analyses must be considered. That said, in view of the robust efficacy in the overall population and the biologic plausibility that benralizumab would be expected to have the same effect in children 12 to 17 years of age, the subgroup analysis would not on its own determine whether benralizumab should be approved in children 12 to 17 years of age or not (see Pediatric Section). The Forest plots for exacerbation and FEV_1 subgroup analysis (age) are shown below copied from Dr. Yu (Jade) Wang's statistical review.

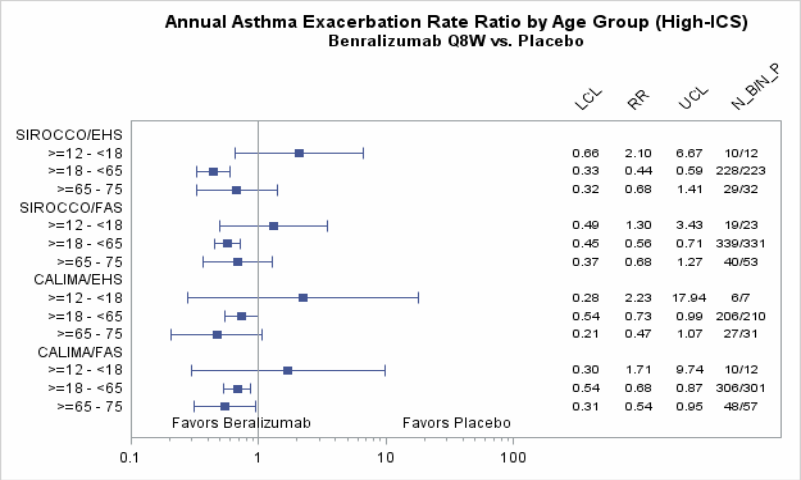


Figure 9: Annual asthma exacerbation rate ratio

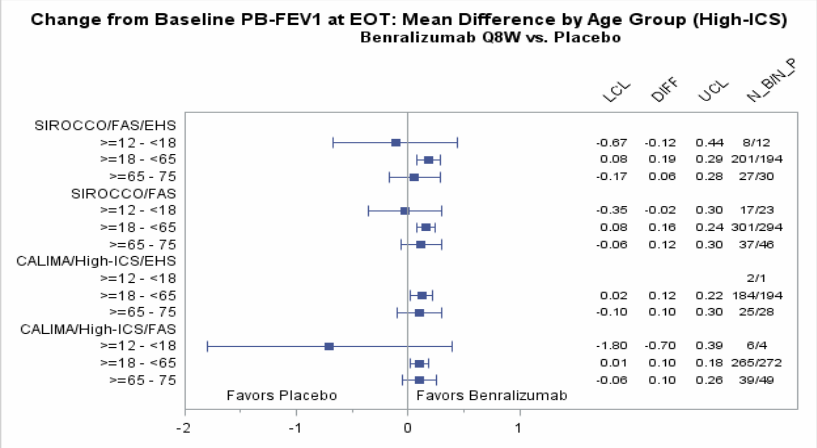


Figure 10: Change from baseline in pre-bronchodilator FEV_1 mean difference by age group

8. Safety

Safety database

The safety assessment of benralizumab for asthma is based on the studies shown in Table 1. Most of the safety data are from the placebo-controlled exacerbation trials SIROCCO and CALIMA. As a reminder these trials had slightly different duration (48 weeks for SIROCCO and 56 weeks for CALIMA). The Agency agreed to use the pooled safety data out to 48 weeks to inform the safety information for labeling. A total of 2511 subjects were randomized in the two exacerbation studies of whom 822 subjects received benralizumab 30 mg SC Q8W and 841 received benralizumab 30 mg SC Q4W. A total of 1,387 subjects received benralizumab for ≥ 48 weeks. Across the phase 2 and 3 program, a total of 3,882 subjects with asthma received at least 1 dose of benralizumab. Safety information from the long-term open extension studies BORA and MELTI was provided in the 120-day safety update (database lock date October 21, 2016) and provided safety data on an additional 1279 subjects from the two exacerbation trials (637 on benralizumab 30 mg Q4W, and 642 on Benralizumab 30 mg

Q8W). Safety data from subjects previously enrolled in ZONDA and subjects previously on placebo and rolled over to active treatment in the long-term extension were also provided in the 120-day safety update. The safety database is adequate to evaluate the safety of benralizumab.

Safety findings and Conclusion

The submitted data support the safety of benralizumab at the proposed dose of 30 mg SC Q8W for the treatment of asthma. AstraZeneca conducted a comprehensive safety analysis of the data that included the safety assessments typically done in clinical development programs such as evaluation of deaths, serious adverse events (SAEs), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, urinalysis, and ECGs. All laboratory assessments were performed at a central laboratory. Given that the product is a biologic for injection, events of special interest were allergic reactions including anaphylaxis, local injection site reactions, infections, malignancy, and immunogenicity.

Deaths, SAEs, dropouts, discontinuations
There were 15 deaths in the asthma clinical studies; 4 were reported on placebo, 5 in the benralizumab Q8W arm, and 6 in the benralizumab Q4W arm. In 7 of the cases, the causes of death were cardiovascular (including stroke and MI) and in 6 of these cases the patients had underlying cardiovascular co-morbidities and risk factors for heart disease and stroke. There was one report of sudden cardiac death in a 51 year old female with no prior medical or surgical history beyond the use of lansoprazole. There was one death due to pancytopenia but the patient had a history of pancreatic insufficiency following pancreatic resection [for chronic pancreatitis] with resultant pancreatic insufficiency, prior asbestos exposure and underlying cardiovascular disease for which he was receiving amiodarone. Amiodarone has been reported to cause aplastic anemia. The other 7 deaths were pulmonary embolism (1 case – placebo), neoplasm of the colon (1 case – placebo), pneumonia (1 case - benralizumab Q8W), opioid overdose (1 case – benralizumab Q8W); road traffic accident (1 case – benralizumab Q4); suicide (1 case – benralizumab Q4W), and asthma (1 case – benralizumab Q4). There is no pattern to the deaths and none of the deaths in the program appear to be related to benralizumab. An independent adjudication committee assessed all cases of death.

Serious adverse events (SAEs)[7] occurred with comparable frequencies between benralizumab and placebo treatment groups with a slightly higher frequency in the placebo treatment groups (11.2% in benralizumab 30 mg Q8W, 10.9% in benralizumab 30 mg Q4W, 13.6% in placebo). The majority of the SAEs were related to respiratory disorders with asthma being the most frequent disorder followed by pneumonia. The frequency of these events were similar across the treatment groups but with a trend towards a higher incidence in the placebo group. In the pooled safety database for SIROCCO/CALIMA the percentage of patients with a

[7] Defined as in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threating adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death form the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect.

serious asthma event was 6.4 in the placebo group compared to 5.1 in both benralizumab treatment arms. Pneumonia was reported in less than 1% of patients across all treatment arms.

Dropouts and discontinuations due to adverse events occurred more frequently in patients receiving benralizumab (2.1% in benralizumab-treated patients vs. 0.9% in placebo) in the SIROCCO/CALIMA trials. There was no pattern observed or single preferred term that accounted for the differences between groups in patients who discontinued due to adverse events.

Common adverse events[8]*:*
Common adverse events were typical of those seen in asthma development programs and were reported in 73% of patients exposed to benralizumab in the 2 exacerbation trials compared to 77% exposed to placebo. Common adverse events reported included nasopharyngitis (16% in Benralizumab Q4W, 15% in Benralizumab Q8W, vs 16% in placebo), asthma (14% in benralizumab Q4W, 11% in benralizumab Q8W, vs 17% in placebo, upper respiratory tract infection (9% in Benralizumab Q4W, 8% in benralizumab Q8W, vs 9% in placebo. Headache (8%), pyrexia (3%) and pharyngitis (4%) were reported with higher frequency (≥3%) in the benralizumab treatment arms[9] compared to placebo (6%, 2%, and 2% respectively). When looking at the safety data out to 56 weeks, arthralgias were reported more frequently in the benralizumab Q8W treatment arm (4%) compared to 2 % in the Benralizumab Q4W and placebo arms and cough was reported in 3% of the benralizumab treatment arms compared to 2% in placebo.

Laboratory findings and ECGs, vital signs
Other than the expected reduction in blood eosinophil counts, there were no clinically meaningful effects on hematologic parameters. There were no signals in the clinical chemistry, or urinalysis. ECGs were performed as part of a routine assessment and were done in a sub-study in 201 patients in the SIROCCO trial. No safety concerns were found with the ECG findings. Vital signs (pulse, temperature, blood pressure, and respiratory rate) were obtained at baseline and at every clinic visit and other than vital sign abnormalities related to adverse events discussed elsewhere, there were no clinically meaningful changes in vital signs.

Adverse events of interest

- *Hypersensitivity reactions*

Hypersensitivity reactions including urticaria, urticarial rash, and anaphylaxis have been reported with biologics. The clinical program used the accepted definition of anaphylaxis.[10] There were two events of anaphylaxis in the same patient in the controlled clinical trials however the patient had a history of peanut allergy and in both instances the investigator attributed the event to the patient's underlying food allergy. Neither event was temporally

[8] Data presented rounded to nearest whole number and represent the pooled database out to 56 weeks. The pooled database out to 48 weeks was previously agreed upon to be used in the label. When the 48 week database is used, arthralgia and cough fall off as common AEs meeting the threshold for the label.
[9] Data represents both benra Q4W and Q8W treatment arms except as otherwise noted.
[10] Sampson, HA, Munoz-Furlong A, Campbell RL et al. Second symposium on the definition and management of anaphylaxis: summary report-second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J allergy clin Immunology* **2006;** 117:391-397

related to benralizumab exposure. The patient subsequently received additional benralizumab doses without difficulty. There was one case of anaphylaxis reported in the 120-day safety update. The event occurred in a patient who developed nausea and vomiting and loss of consciousness 25 minutes following administration of benralizumab. Epinephrine was administered and the patient recovered. The patient had a normal tryptase level but this was drawn almost 2 hours after the event. The histamine level was reported to be elevated. With the grouping of hypersensitivity terms together (urticaria, urticaria popular, and rash) the incidence of hypersensitivity reactions was 3% in the benralizumab and placebo treatment group in the exacerbation trials.

- *Infections*

A signal for opportunistic infections was not observed in the benralizumab program. There were 2 cases of herpes zoster but these were confounded by concomitant immunosuppressant medication use (methotrexate, systemic steroids). Given the role of eosinophils in the defense against helminthic parasitic infections patients with known helminthic infections were excluded from the program. There were two reports of positive *strongyloides* serology in the program but in neither case was there a worsening of infection with the use of benralizumab. Pneumonia (bacterial), influenza, and appendicitis were the most commonly reported infections. The incidence of these events was < 1% and was similar across the benralizumab treatment arms and placebo.

- *Malignancy*

There was no imbalance in malignancy events in the controlled clinical trials. In the 120-day safety update there was a report of three lymphoma cases but the case narratives suggest that these patients already had other underlying risk factors for lymphoma and it is unlikely that benralizumab is implicated in these events.

- *Immunogenicity*

Immunogenicity is a potential for all therapeutic proteins and the development of anti-drug-antibodies (ADA) can result with treatment. In the exacerbation trials treatment-emergent ADA developed in 13 – 15% of patients in the benralizumab treatment groups compared with 4% in the placebo treatment group. The majority of the ADA positive patients (12%) had neutralizing antibodies. Compared to antibody negative patients, patients with positive ADA had increased clearance of benralizumab and increased blood eosinophil levels however there was no observed effect on efficacy or safety.

- *Cardiac safety*

There was no *a priori* cardiac safety concern with this product however, in addition to the adjudicating of the cases of death; the independent adjudication committee evaluated all investigator reported cases of non-fatal MI and non-fatal stroke (hemorrhagic, ischemic, and embolic). There was no imbalance between benralizumab treatment and placebo for MACE events.

9. Advisory Committee Meeting

An Advisory Committee (AC) meeting was not convened for this application. Benralizumab is the third product targeting the IL-5 pathway for the treatment of asthma. The general issues about the appropriate population, the role of eosinophils in determining treatment, the risk-balance considerations for biologics such as this anti-IL 5 for asthma have all been discussed before at AC meetings. Benralizumab did not present any new safety concerns that would warrant discussion at an AC meeting.

10. Pediatrics

The agreed upon pediatric study plan (PSP) for benralizumab consisted of the inclusion of 12 – 17 year old patients in the adult development program, deferral of studies in children (b) (4) to 11 years of age, and a plan to request a waiver for children (b) (4) years of age.[11] AstraZeneca included 108 adolescents 12 to 17 years of age in the 2 exacerbation trials. These patients were required to have a history of 2 or more exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator $FEV_1 < 90\%$) despite regular treatment with medium or high dose ICS and LABA with or without OCS or other controller medications. Although the point estimate for efficacy in subgroup analysis favored placebo, the similar PK and PD between adolescents and adults, the fact that the studies were not powered for efficacy in the 12 to 17 year olds, and the knowledge that the disease characteristics are similar in adults and pediatric patients can allow for extrapolation of efficacy from the adults to the pediatric population.[12] The overall safety profile of benralizumab is favorable and there were no safety concerns in patients 12 to 17 years of age. Taken together, these observations support extending the indication to patients 12 years of age and older.

The application was presented at the Pediatric Review Committee (PeRC) meeting on August 2nd, 2017. The committee agreed that the PREA requirements for the 12 to 17 year olds had been fulfilled and agreed with the Division's recommendation to extend the indication to adolescents 12 to 17 years of age. The applicant will be asked to conduct PK and safety studies in children 6[13] to 11 years of age to support the PREA requirements in that age group. These studies will be conducted as post-marketing required (PMR) studies under PREA. The PREA requirement for studies in children less than 6 years of age is waived because studies would be impossible or highly impracticable (because the number of patients in this age group would be very small).

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[11] IND 100,237 Advice 9/30/2013

[12] "Under PREA (section 505B*a) (2) (B) of the FD&C act), if the course of disease and the effects of the drug are sufficiently similar in adults and pediatric patients, effectiveness in the pediatric population may be extrapolated from adult data." *Guidance for Industry and Review Staff – Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*

[13] Although AstraZeneca's initial iPSP was a planned request for waiver in children (b) (4) to match the PREA requirement for the currently approved anti-IL product mepolizumab.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

Application integrity Policy (AIP)
Review of the application did not raise concerns of any wrongful acts that would lead to questions about the reliability of the data.

Exclusivity and patent issues
There are no exclusivity and patent issues of concern with this application

Office of Scientific Investigations (OSI) audits
The Division of Clinical Compliance evaluation in the Office of Scientific Investigations (OSI) conducted an inspection as part of a routine audit. Two clinical sites from the 2 large exacerbation trials were selected for inspection. There were no irregularities identified during the OSI audit that would impact data integrity

Financial disclosure
AstraZeneca submitted acceptable financial disclosure statements. Two investigators had disclosable financial interest in AstraZeneca. These investigators recruited a small sample of the total study populations and were not large enough to alter the outcome of any study. In addition, the multi-center nature of the study makes it unlikely that the financial interest could have influenced or biased the results of these studies in any way.

Other Good Clinical Practice (GCP) issues:
All studies were conducted in accordance with acceptable good clinical practice standards and adhered to regulatory requirements for clinical trials conduct

12. Labeling

The product label was reviewed by the Division, OSE/DMEP, DRISK, and OPDP. Various changes to different sections of the label were done to reflect the data accurately, remove extraneous information, and to streamline the label to communicate the findings of the clinical program and the risk benefit accurately to healthcare providers. At this time the labeling negotiations are still ongoing but most of the labeling issues have been resolved and the label is close to being final.

- Proprietary name
  The proposed proprietary name FASENRA was reviewed and has been approved by DMEPA.

- Physician labeling
  Major labeling issues addressed during labeling negotiations include:

Indication and usage: AstraZeneca's original proposal was for patients 18 years of age and older. The program included 108 pediatric patients 12 to 17 years of age. They were required to have the same entry criteria as the adult population. The point estimate for exacerbation benefit did not favor the 12 to 17 year old age group in subgroup analysis but the confidence intervals were very wide. The studies were not powered for efficacy in the 12 to 17 year olds and the PK and PD effects of benralizumab were comparable to that in the adult population. Therefore the Division supported AstraZeneca's subsequent justification to modify the indication to extend the age range to include adolescents 12 years of age and older

Dosage and administration: AstraZeneca proposed a dosing regimen of q8W dosing. The dosing schedule proposed is for 30 mg SC every 4 weeks for the first 3 doses followed by 30 mg every 8 weeks. This is the dosing strategy that was studied in the phase 3 program and it is acceptable.

Efficacy information: Exacerbation effects, lung function effects, and patient reported outcomes based on the ACQ and the AQLQ will be described in the label. Section 14 of the label was substantially revised from what AstraZeneca proposed initially with the removal of (b) (4) discussion in section. Also the dose-ranging study MI-CP-220 and the dedicated 12-week lung function study were added to section 14.

Safety: The most notable change was the addition of the term "anaphylaxis" to the other terms in the hypersensitivity warning. Although no cases of anaphylaxis related to benralizumab was seen in the controlled trials, the case seen in the 120-day safety update is convincing and as a monoclonal antibody benralizumab is expected to cause anaphylaxis in some patients.

- Patient labeling and Medication Guide

The product will not have a medication guide. Benralizumab will have patient counselling information and the patient information was reviewed by the patient labeling team. AstraZeneca has incorporated the recommendations

- Carton and immediate container labels

These were reviewed by the various disciplines and found to be acceptable.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

The proposed regulatory action for this BLA is approval for patients 12 years of age and older.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

REMS will not be required for this application. The information necessary to use Benralizumab safely and effectively can be adequately provided through the prescribing information and patient labeling

- Recommendation for other Postmarketing Requirements and Commitments

AstraZeneca will conduct post-marketing required studies to support the PREA requirements for pediatric patients 6 to 11 years of age. AstraZeneca will also commit to perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions as a post-marketing commitment (PMC).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LYDIA I GILBERT MCCLAIN
10/19/2017

BADRUL A CHOWDHURY
10/19/2017
I concur