# CLINICAL REVIEW

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| **Application Type** | BLA |
| **Application Number(s)** | 761070 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | November 16, 2016 |
| **Received Date(s)** | November 16, 2016 |
| **PDUFA Goal Date** | November 16, 2017 |
| **Division/Office** | DPARP/ODE II |
| **Reviewer Name(s)** | Sofia Chaudhry, MD |
| **Review Completion Date** | July 19, 2017 |
| **Established Name** | Benralizumab |
| **ProposedTrade Name** | Fasenra |
| **Applicant** | AstraZeneca |
| **Formulation(s)** | Subcutaneous |
| **Dosing Regimen** | 30 mg SC every 4 weeks x 3 followed by every 8 weeks |
| **Applicant Proposed Indication(s)/Population(s)** | Add-on maintenance treatment for patients with severe asthma 18 years of age and older and an eosinophilic phenotype |
| **Recommendation on Regulatory Action** | Approval |
| **Recommended Indication(s)/Population(s)** (if applicable) | Add-on maintenance treatment for patients 12 years of age and older with severe asthma and an eosinophilic phenotype |

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## Glossary

| | |
|---|---|
| AC | advisory committee |
| ACQ | asthma control questionnaire |
| AE | adverse event |
| AER | annual exacerbation rate |
| AESI | adverse events of special interest |
| AQLQ | asthma quality of life questionnaire |
| [redacted] | (b) (4) |
| AZ | AstraZeneca |
| BLA | biologics license application |
| BRF | Benefit Risk Framework |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| CRT | clinical review template |
| CSR | clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Event |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| EOP2 | end of phase 2 |
| EOT | end of treatment |
| ER | emergency room |
| FDA | Food and Drug Administration |
| $FEV_1$ | forced expiratory volume in 1 second |
| GCP | good clinical practice |
| HCP | healthcare provider |
| ICH | International Conference on Harmonization |
| ICS | inhaled corticosteroid |
| IgG | immunoglobulin gamma |
| IL | interleukin |
| IL-5 | interleukin 5 |
| IL-5R | interleukin 5 receptor |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |

| | |
|---|---|
| ITT | intent to treat |
| LABA | long-acting beta agonist |
| LAMA | long-acting anti-muscarinic |
| LTRA | leukotriene receptor antagonist |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NDA | new drug application |
| NK | natural killer |
| NME | new molecular entity |
| OCS | oral corticosteroid |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamic |
| PFS | prefilled syringe |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PT | preferred term |
| REMS | risk evaluation and mitigation strategy |
| SABA | short-acting beta agonist |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | subcutaneous |
| SOC | system organ class |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1κ) targeting the interleukin-5 receptor alpha subunit. It is a new molecular entity not approved for use in any country. The dosing regimen proposed for approval consists of a loading dose of 30 mg subcutaneously (SC) every 4 weeks followed by 30 mg SC every 8 weeks.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical perspective is Approval for benralizumab 30 mg SC Q8 following a loading dose of 30 mg SC Q4 x 3 doses for use in patients 12 years of age and older with severe asthma and an eosinophilic phenotype.

To support this application, the applicant has completed two pivotal efficacy and safety trials which demonstrate a statistically significant and clinically relevant improvement in asthma exacerbations in patients with severe asthma. In addition, a third pivotal trial demonstrates a decrease in the dose of oral corticosteroids (OCS) required to control a patient's underlying asthma.

While a treatment benefit provided to the adolescent subgroup remains inconclusive based on the data from this clinical development program, this review recommends approval in this age group. This differs from the applicant's proposed indication for use in adults 18 years of age and older. While the point estimates in both exacerbation trials favor placebo, the data are associated with wide confidence intervals which cross 1, indicating uncertainty in the results. Given the rarity of this population, a sufficiently powered study to demonstrate a treatment benefit in the adolescent population would be impractical to conduct. In addition, as there are no age-related differences in the PK and PD and no safety concerns to offset the potential efficacy of benralizumab in adolescent patients with this rare asthma phenotype, this review recommends approval in the adolescent age group.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Summary and 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.

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 FEV1 compared with placebo. An increased treatment benefit is consistently seen in patients with higher baseline peripheral blood eosinophil counts supporting the restriction of use to patients with an eosinophilic phenotype. 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. In addition, as there are no age-related differences in the PK and PD and no safety concerns to offset the potential efficacy of benralizumab in adolescent patients, this review recommends approval in the adolescent age group.

The program included an assessment of safety concerns related to immunomodulatory therapy and biologics including infections, malignancy, hypersensitivity events, and immunogenicity. No safety concerns that offset the efficacy benefits provided by benralizumab have been identified for the overall or adolescent population. While benralizumab was associated with reasonably high level of anti-drug antibody (ADA) in its clinical development program with a drop in PK and increase in eosinophil counts, no decrease in the efficacy response is seen in ADA positive subjects and no additional safety concerns have been identified.

This review recommends approval of benralizumab in patients 12 years of age and older with severe asthma and an eosinophilic phenotype. Efficacy was demonstrated in the severe asthma population with subgroup analyses demonstrating increased treatment benefit in patients with a higher baseline peripheral blood eosinophil count. No safety concerns that would preclude approval were identified in the overall population or the adolescent population. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

| 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 managed as outpatient with the use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death.<br>• 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 remains, the estimated prevalence is thought to be 3% or less. | **Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma population with severe disease continues to experience significant morbidity and the potential for mortality from this condition.** |
| **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. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Benefit** | • The applicant has demonstrated in two studies that benralizumab provides statistically significant and clinically meaningful improvements in asthma exacerbations requiring oral corticosteroids and/or ER visit/hospitalization beyond the benefit provided by high dose ICS/LABA therapy in patients with severe asthma. In addition, the data demonstrate an increased benefit in patients with higher eosinophil counts.<br>• A third pivotal phase 3 study demonstrates an ability to reduce oral corticosteroid dosing in patients who require oral corticosteroids to maintain asthma control.<br>• The program also demonstrates numeric improvements in lung function.<br>• An improvement in lung function is also seen in a smaller trial with a shorter treatment duration in milder asthmatics. Additional studies would be needed to support broadening the indication beyond severe asthma and the risk benefit of a monoclonal antibody for a milder population would need to be considered given the availability of other safe and efficacious treatment options. | Benralizumab provides for a clinically relevant treatment benefit in patients with severe asthma with an increase in treatment benefit seen in patients with higher baseline blood eosinophil counts. Approval in adolescents is recommended despite point estimates favoring placebo, given similar impact on PK and PD in adolescents and the lack of a safety concern that offsets the potential for efficacy in a younger patient with this rare and severe phenotype. |
| **Risk** | • The safety program for Benralizumab demonstrates risks that are common to monoclonal antibodies including hypersensitivity reactions and anti-drug antibody formation. | The program does not demonstrate any safety findings that offset the efficacy findings. |
| **Risk Management** | • No REMS is proposed. | The risks of hypersensitivity reactions and anti-drug antibody formation with benralizumab can be managed through labeling and routine pharmacovigilance. |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. It is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction.

The diagnosis and management of this common condition are outlined in the NAEPP[1] and GINA[2] guidelines which include a treatment approach of escalating daily maintenance therapy in accordance with a patient's symptoms. While the majority of patients are successfully managed with this step-wise treatment approach, a subset of patients remain uncontrolled despite maximal medical management and are considered to have severe asthma.

The International ERS/ATS Severe Asthma guidelines[3] define severe asthma as:

- Patients with a confirmed asthma diagnosis which requires treatments with high dose inhaled corticosteroids (ICS) plus long acting beta agonist (LABA) or leukotriene modifier/theophylline therapy to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy.

Additionally, the guidelines outline that patients who do not meet the aforementioned criteria, but whose asthma worsens when corticosteroids are tapered, also meet the definition of severe asthma. In these guidelines, "uncontrolled asthma" is defined as meeting any of the four following criteria:

- Poor symptom control: ACQ consistently > 1.5 or ACT < 20 (or "not well controlled" by NAEPP or GINA guidelines) over 3 months of evaluation
- Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids (>3 days each) in the previous year
- Serious exacerbations: at least one hospitalization, ICU stay or mechanical ventilation in the previous year

[1] National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI).National Asthma Education and Prevention Program. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. August 2007. NIH publication no. 07-4051.
[2] Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, 2013. Website accessed April 28,2015: http://www.ginasthma.org/.
[3] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.

- Airflow limitation: FEV1 <80% predicated (in the presence of a reduced FEV1/FVC)

Beyond categorizing asthma by severity, there is an active body of research working to identify additional asthma phenotypes and endotypes using various biomarkers. One approach by the Severe Asthma Research Program (SARP) employed statistical modeling to identify asthma clusters. While 5 subgroups were identified, overlap between the groups was seen with respect to identifying biomarkers[4] exemplifying the heterogeneity seen within asthma and difficulties with further sub-classification of the disease. While alternative approaches have been outlined in the academic literature, to date, there are no guidelines outlining the identification or management of specific severe asthma subgroups. The ERS/ATS severe asthma guidelines opine "Detailed efforts in this regard require organization and integration of these defining characteristics into clinically recognizable phenotypes. Ultimately, these phenotypes should evolve into asthma 'endotypes', which combine clinical characteristics with identifiable mechanistic pathways. Their identification to date remains speculative at best. In general, temporal stability of phenotypes will be required to provide evidence of their clinical usefulness. The ultimate clinical usefulness of these severe asthma phenotypes will be determined by their therapeutic consequences.[5]"

Despite the current uncertainty on how best to identify patients with particular asthma phenotypes, two monoclonal antibodies targeting the interleukin-5 pathway demonstrated efficacy in clinical development programs enriched for patients with severe asthma and parameters believed to be predicative of an eosinophilic phenotype. Mepolizumab was approved in 2015 and reslizumab in 2016 for the treatment of patients with severe asthma and an eosinophilic phenotype. These two treatment options are discussed further in Section 2.2 of this review.

## 2.2. Analysis of Current Treatment Options

If approved, benralizumab will represent the third biologic targeting the interleukin-5 pathway indicated for add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype. Corresponding to the uncertainty in the clinical community on how best to clinically define an eosinophilic phenotype, all three programs have enriched for this subgroup in different ways. Mepolizumab evaluated patients with a recent peripheral blood eosinophil count of ≥ 150 cells/µl or 12-month historical value of ≥ 300 cells/µl while reslizumab utilized a cutoff of 400 cells/µl just prior to enrollment. As discussed throughout this review, benralizumab enriched for patients with counts ≥ 300 cells/µl just prior to enrollment but also

[4] Moore et al "Identification of Asthma Phenotypes Using Cluster Analysis in the Severe Asthma Research Program" Am. J. of Respiratory and Cri Car Med; Vol 181.4 (2010):315-323.
[5] Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-373.

included patients with values < 300 cells/µl in its pivotal phase 3 trials. To identify patients with severe asthma, the mepolizumab and benralizumab programs identified patients using criteria consistent with the ETS/ARS criteria.

**Table 1: Summary of Treatments Relevant to Proposed Indication**

| Product Name | Indication | Dose | Efficacy Information and population studied |
|---|---|---|---|
| Mepolizumab<br><br>*Approved 2015* | Add-on maintenance treatment in patients ≥ 12 years of age with severe asthma with an eosinophilic phenotype | 100 mg SC every 4 weeks | *Exacerbations*<br>1 phase 2b exacerbation trial demonstrated a reduction in exacerbations. The population was enriched with patients meeting criteria believed to identify an eosinophilic phenotype. These criteria included peripheral blood eosinophil counts, airway eosinophil counts and loss of control with OCS dose reduction and FENO.<br><br>1 pivotal exacerbation trial demonstrated a reduction in exacerbations in severe asthma patients on background standard of care with peripheral blood eosinophil count ≥ 150 cells/µl[1] or historical count ≥ 300 cells/µl[2] with a history of 2 exacerbations in the prior 12 months.<br><br>*Oral Corticosteroid Reduction*<br>1 trial demonstrated an ability to reduce oral corticosteroids dosage in severe asthma patients with peripheral blood eosinophil count ≥ 150 cells/µl[1] or historical count ≥ 300 cells/µl<br><br>*Lung Function*<br>No consistent improvement in lung function was seen in this development program.<br><br>*Adolescents*<br>28 adolescents were evaluated in the program with a trend toward exacerbation reduction in mepolizumab treated patients. |
| Reslizumab<br><br>*Approved 2016* | Add-on maintenance therapy in patients ≥ 18 years old with severe asthma with an eosinophilic phenotype | 3 mg/kg IV every 4 weeks | *Exacerbations*<br>2 pivotal trials demonstrated a reduction in exacerbations and improvements in lung function in severe asthma patients with a peripheral blood eosinophil count ≥ 400 cells/µl[3] and a history of at least one asthma exacerbation in the prior 12 months.<br><br>*Lung function*<br>The two exacerbation trials and a third lung function trial in severe asthma patients with a peripheral blood eosinophil count ≥ 400 cells/µl demonstrated an improvement in lung function. |

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| | | | *All eosinophil counts*<br>1 trial evaluated lung function in asthma patients unselected for blood eosinophil levels. No association between a treatment effect and blood eosinophil levels was seen.<br><br>*Adolescents*<br>39 adolescents were evaluated in the program with point estimates favoring placebo in two exacerbation studies. Reslizumab is approved for use in patients 18 years of age and older given an unfavorable risk benefit assessment in the adolescent population. |
| [1] within 6 weeks of dosing<br>[2] within 12 calendar months of enrollment<br>[3] within 3-4 weeks of dosing<br>[4] within 3-4 weeks of dosing | | | |

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Benralizumab is a new molecular entity (NME) that is not currently marketed in the U.S. or any other country in the world. In addition to the severe asthma indication, the applicant is evaluating benralizumab as a potential treatment for chronic obstructive pulmonary disease with two phase 3 trials currently ongoing.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 summarizes the pre-submission regulatory activity pertaining to the sponsor's clinical development program

**Table 2: Summary of Presubmission Regulatory Activity**

| Date | Meeting Type | Comments |
|---|---|---|
| February 13, 2013 | EOP2 | • Dose selection for the phase 3 program was discussed including the observed efficacy data and PD modeling data from a phase 2 dose ranging trial. The sponsor proposed a 30 mg dose based on the observed data and potential for PK variability and increased immunogenicity with lower doses. The 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. The FDA recommended further dose exploration or the evaluation of more than one dose in phase 3.<br>• The FDA recommended evaluation of patients with a range of peripheral blood eosinophil counts as the link between this biomarker and the 'eosinophilic asthma' had not been established. The sponsor proposed to stratify enrollment of eosinophil high and low patients 2:1, with the primary efficacy analysis conducted in an eosinophil high population. The FDA found the proposal to be reasonable but noted that data across the population would be considered.<br>• The FDA recommended evaluation of patients across the spectrum of asthma severity to assist in the justification of restricting use of benralizumab in severe asthma<br>• Specifics parameters of the exacerbation trial designs—including treatment duration, exacerbation definition, and immunogenicity assessments—were discussed and found to be reasonable. |
| September 8, 2014 | Type C | • The sponsor notified the FDA (b) (4) the CALIMA was proposed and found to be reasonable. |
| May 22, 2014 | Type C | • (b) (4) |
| September 8, 2014 | Type C | • The sponsor's proposal to rely on data from SIROCCO and CALIMA to support registration in a severe asthma population was discussed. The FDA noted that while it recommends the evaluation of the full spectrum of asthma, targeting more severe patients may be acceptable if the program provides sufficient information to inform the selection of appropriate patients for treatment and the overall risk-benefit is commensurate with the targeted patient population.<br>• The sponsor's proposal to evaluate the prefilled syringe(PFS) in the phase 3 trials in addition to data from an at-home-use trial was reasonable to assess device performance. |

| | | |
|---|---|---|
| March 31, 2016 | Type C *Written responses* | • The format and content of a proposed BLA for benralizumab was discussed. |
| September 20, 2016 | Pre-BLA | • FDA agreed that the filing of a BLA application was reasonable based on the data provided. It also agreed that is was reasonable to include data from the AZ sponsored studies only.<br>• The strategy to pool data from SIROCCO and CALIMA was discussed and found to be reasonable.<br>• 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 labeling.<br>• FDA noted that including of data evaluating the history exacerbations and baseline eosinophil levels as independent predictors of treatment benefit into the product label would be a review issue.<br>• FDA agreed with the planned descriptive analyses for the AESI but also recommended additional integrated analyses to compare treatment groups. The agency recommended including an evaluation herpes zoster infection in its safety analysis as well. |

### 3.3. Foreign Regulatory Actions and Marketing History

Benralizumab is not marketed in any foreign county.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

The pivotal efficacy and safety trials in the benralizumab clinical development program were large multicenter trials with each site enrolling a small number of subjects which limits the potential for any individual study center to impact the efficacy and safety findings. Two clinical sites were chosen for inspection (Site # 7802 and Site 7805). Final OSI reports for these sites found that the data from these sites are valid and accurate.

## 4.2. Product Quality

Benralizumab is a humanized, afucosylated, IgG1kappa monoclonal antibody. It is supplied as a sterile, preservative free, solution for subcutaneous injection in a single-use prefilled syringe (PFS).

*Reviewer's Comment: Readers are referred to the product quality review for additional details which is pending at the time of this review.*

## 4.3. Clinical Microbiology

The microbiology review remains pending at the time of this review.

## 4.4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology and toxicology review of this application recommends Approval. Long-term animal studies have not been performed to evaluate the carcinogenic potential of benralizumab. A reproductive toxicity study did not demonstrate evidence of toxicity in cynomolgus monkeys treated with benralizumab for 9 months. Additional details of the nonclinical program can be found in the nonclinical review by Dr. Tim Robison.

## 4.5. Clinical Pharmacology

### 4.5.1. Mechanism of Action

Benralizumab is a humanized afucosylated, monoclonal antibody (IgG1 κ) that binds with high affinity and specificity to the alpha subunit of the interleukin 5 receptor (IL-5Rα). The IL-5R is primarily found on eosinophils and basophils and the Fc portion of benralizumab binds the FcγRIII on natural killer (NK) cells with high affinity. Benralizumab is believed to mediate apoptosis of the eosinophil/basophil through antibody-dependent cell-mediated cytotoxicity pathway by bringing the NK cell and eosinophil/basophil in close proximity. Benralizumab also prevents the eosinophil growth factor, IL-5, from binding its target receptor on eosinophils and basophils.

Per review by the OBP and non-clinical reviewer, the cytolytic properties of benralizumab are supported by the in-vitro and pharmacology studies and the rapid drop in peripheral blood eosinophil count further supports this proposed mechanism of action. Readers are referred to the product quality, non-clinical, the clinical pharmacology reviews and Section 4.5.2 of this review and for additional details.

### 4.5.2. **Pharmacodynamics**

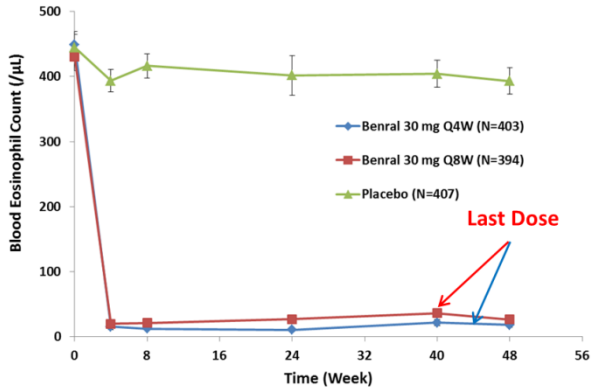
A 12-week phase 2 study evaluating 25, 100 or 200 mg of SC benralizumab or placebo every 4 weeks for 3 doses in asthma patients demonstrated complete or near complete reductions in peripheral blood eosinophil counts in all dose groups. Post-dose drops from 400 to 0, 200 to 0, and 120 to 5 cells/µL 24 hours seen for the 25, 100 and 200 mg dose groups respectively with reductions maintained through the dosing period. No change in the median peripheral blood eosinophil count was seen in the placebo dose group.

A 52-week, phase 2b study MI-CP220 evaluated three SC doses of benralizumab in asthmatic subjects and included both PD and efficacy assessments (exacerbation rate, FEV1 and ACQ). Subjects received 2, 20, or 100 mg of benralizumab of placebo every 4 weeks for the first 3 doses followed by every 8 weeks thereafter. The PD data from this trial demonstrate reduction in mean peripheral blood eosinophil mean counts from baseline at Week 40 of 14, 57, 75, and 76% for the placebo, 2mg, 20 mg, and 100 mg treatment groups respectively. Readers are referred to Section 6.1 of this review for detailed discussion of the study design, observed efficacy data, and exposure response modeling used to support dose selection for further evaluation in phase 3.

Of note, both of the aforementioned phase 2 studies used (b) (4) formulation of benralizumab which differs from the to-be-marketed formulation, a liquid formulation in a PFS.

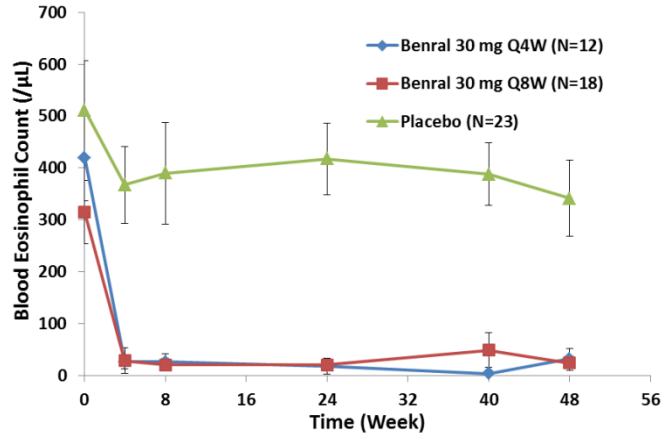
Similar reductions in peripheral blood eosinophil counts are seen in the phase 3 program. In the phase 3 exacerbation trials, both benralizumab dosing regimens demonstrate drops in peripheral blood eosinophil counts with reductions maintained for a minimum of 8 week post-dosing. Importantly, the adolescent populations from the phase 3 exacerbation trials demonstrate similar reductions in the eosinophil counts. Data from SIROCCO are show in Figure 1 for the overall population and Figure 2 for the adolescent population. Similar findings are seen in the CALIMA trial (data not shown).

**Figure 1: SIROCCO: Peripheral Blood Eosinophil Count-Time Profiles**




**Source: Clinical Pharmacology Review**

**Figure 2: SIROCCO: Peripheral Blood Eosinophil Counts in Adolescents**




**Source: Clinical Pharmacology Review**

Readers are referred to the clinical pharmacology review for additional details.

### 4.5.3. Pharmacokinetics

Pharmacokinetic data (PK) from the phase 1 and 2 clinical studies and SIROCCO, CALIMA, BISE and ZONDA were pooled and analyzed using a population PK approach. The applicant reports that subcutaneous administration of benralizumab was associated with an absorption half-life of 3.59 days, absolute bioavailability of 59% and a terminal ½ life of approximately 15 days in asthma patients.

Population PK analysis estimates that the systemic clearance of benralizumab was 18% lower in the adolescent population than in the adult population. The body weight effect on clearance

follows the same trend in both populations. Therefore, the systemic exposure in the adolescent population is expected to be approximately 20% higher than the adult population. Readers are referred to the clinical pharmacology review for additional details

## 4.6. Devices and Companion Diagnostic Issues

(b) (4) the current proposal follows the dosing administration in the pivotal trials: subcutaneous administration of benralizumab using a prefilled syringe (PFS) administered by a healthcare provider (HCP). Device-related AEs were specified as AESI and an at home study (GREGALE) evaluated all devices for reliability and performance. Readers are referred to Section 8.5.1 for discussion of device performance in these studies. There is no companion diagnostic for this application.

## 4.7. Consumer Study Reviews

Consumer studies are not applicable to this application. Benralizumab is proposed as a prescription product for administration to the patient by a healthcare professional.

# 5 Sources of Clinical Data and Review Strategy

## 5.1. Table of Clinical Studies

**Table 3: Summary of Clinical Development Program**

| Trial ID *Study Dates (month/year)* | Trial Design | Treatment Arms | Study Endpoints | Treatment Duration (weeks) | N Randomized | Study Population | Number of Centers and countries |
|---|---|---|---|---|---|---|---|
| ***Controlled Studies to Support Efficacy and Safety*** | | | | | | | |
| SIROCCO D3250C00017 *9/13-4/16* | R, DB, PC, MC | 30 mg SC Q4x3 → Q8<br>30 mg SC Q4<br>Placebo SC | AER, FEV1, ACQ and AQLQ | 48 | Total: 1205<br>>18 yo: 1152<br>12-17 yo: 53 | ≥ 12 years old with severe asthma<br><br>Enrollment stratified 2:1 for pts with eos count ≥ & < 300 cells/µL | 286 centers in 17 countries Australia, Brazil, Bulgaria, Czech Republic, France, Italy, Mexico, Peru, Poland, Russian Federation, South Africa, South Korea, Spain, Turkey, United Kingdom, United States of America, Vietnam |
| CALIMA D3250C00018<br><br>*8/13-3/16* | R, DB, PC, MC | 30 mg SC Q4x3 → Q8<br>30 mg SC Q4<br>Placebo SC | AER, FEV1, ACQ and AQLQ | 56 | Total 1306<br>>18 yo: 1251<br>12-17 yo: 55 | ≥ 12 years old with severe asthma<br><br>Enrollment stratified 2:1 for pts with eos count ≥ & < 300 cells/µL | 242 centers in 11 countries Argentina, Canada, Chile, Germany, Japan, Philippines, Poland, Romania, Sweden, Ukraine, United States |

| **Trial ID** *Study Dates (month/year)* | **Trial Design** | **Treatment Arms** | **Study Endpoints** | **Treatment Duration (weeks)** | **N Randomized** | **Study Population** | **Number of Centers and countries** |
|---|---|---|---|---|---|---|---|
| ZONDA D3250C00020 *8/13-3/16* | R, DB, PC, MC | 30 mg SC Q4x3 → Q8<br>30 mg Q4 SC<br>Placebo SC | OCS reduction, FEV1, ACQ and AQLQ | 28 | 220 | ≥ 18 years old age with severe asthma requiring oral corticosteroids<br><br>-required to have baseline eosinophil count ≥ 150 cells/≤µL | 64 centers in 12 countries (Argentina, Bulgaria, Canada, Chile, France, Germany, Poland, South Korea, Spain, Turkey, Ukraine, and United States |
| ***Studies to Support Safety*** | | | | | | | |
| BORA *(ongoing)* | R, DB | 30 mg SC Q8<br>30 mg SC Q4 | Safety | Adults: 56<br>12 – 17: 108 | 2133[1]<br>>18<br>12 – 17: | Patients who complete SIROCCO, CALIMA, or ZONDA are eligible for enrollment | |
| MELTEMI *(ongoing)* | OL | 30 mg SC Q8<br>30 mg SC Q4 | Safety | Until marketed | Total: 345[2]<br>>18<br>12 – 17: | Patients who have completed SIROCCO, CALIMA, ZONDA and 16 weeks in BORA are eligible for enrollment | |
| ***Other studies pertinent to the review of efficacy or safety*** | | | | | | | |
| MI-CP220 *12/10-8/13* | R, DB, PC, MC phase 2b dose ranging | 2 mg SC Q4x3 → Q8[3]<br>20 mg SC Q4x3 → Q8[3]<br>100 mg SC Q4x3 → Q8[3]<br>Placebo | AER | 52 | 609 | ≥ 18 years of age with moderate to severe asthma | 95 centers in 10 countries US, Russia, Brazil, Bulgaria, Poland, Argentina, Peru, Mexico, Canada, Columbia |
| BISE D3250C00032 *2/15-10/15* | R, DB, PC, MC | 30 mg Q4<br>Placebo | FEV1 | 12 | 211 | Mild to moderate asthma | 52 centers in 6 countries US, Canada, Poland, Germany, Hungary, Slovakia |
| GREGALE | OL, MC, | 30 mg Q4 | Device | 20 | | Adults with severe | 24 centers in 2 countries |

| **Trial ID** *Study Dates (month/year)* | **Trial Design** | **Treatment Arms** | **Study Endpoints** | **Treatment Duration (weeks)** | **N Randomized** | **Study Population** | **Number of Centers and countries** |
|---|---|---|---|---|---|---|---|
| D3250C00029<br><br>*4/15-3/16* | functionality, reliability, performance of PFS in at home setting | | assessment | | | asthma | US, Canada |

[1] The applicant reports that approximately 1200 patients are expected to remain in BORA through end of treatment and follow-up visit. See Section 8.2.1 of this review for the additional safety data provided in the 120 day safety update.
[2] The applicant reports that approximately 900 patients are expected to rollover from BORA into MELTEMI. See Section 8.2.1 of this review for the additional safety data provided in the 120-day safety update.
[3] the formulation of benralizumab used in this study differs from the final to-be-marketed formulation
*R = randomized, DB = double-blind, PC = placebo-controlled, MC = multicenter, PFS = pre-filled syringe, AER = annual exacerbation rate, $FEV_1$ = forced expiration volume in 1 second, ACQ = asthma control questionnaire, AQLQ = asthma quality of life questionnaire, yo = years old; pt = patients; eos = eosinophil*

### 5.2. Review Strategy

The clinical development program for benralizumab included one 52 week dose-ranging exacerbation trial (MI-CP220), 2 phase 3 exacerbation trials (SIROCCO and CALIMA), 1 steroid reduction trial (ZONDA) and a shorter 12-week lung function trial in a milder asthmatic population (BISE). A different formulation of benralizumab was used in the phase 2 study MI-CP220; however the results are adequate to inform dose selection for the phase 3 program and are presented and discussed in Section 6.1. To inform final posology for benralizumab, the phase 3 studies evaluated two dosing regimens, 30 mg every 4 weeks and 30 mg every 4 weeks followed by every 8 weeks for the remainder of the treatment period. This review abbreviates these dosing regimens as 30 Q4 and 30 Q8. The results used to support the final dose and dosing regimen for marketing are summarized in Section 7.1.4.

The efficacy results from the SIROCCO, CALIMA, ZONDA and BISE are presented individually in Section 6.2, 6.3, 6.4 and 6.5 respectively. A summary discussion of the results used to support the recommendation for approval is presented in Section 7. Safety of benralizumab is discussed in Section 8. The efficacy data in this review presents data from the Full Analysis Set (FAS) while the safety data relies on data in the Safety Analysis Set (SAS). The FAS includes all patients randomized to treatment irrespective of protocol adherence and continued study participation and patients are analyzed according to their randomized investigational product. The SAS includes all patients who received at least one dose of investigational product and patients are classified according to the treatment they actually received.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. MI-CP220

#### 6.1.1. Study Design

**Overview and Objective**

MI-CP220 was a phase 2b dose-ranging trial conducted to inform the dose selection of benralizumab in the phase 3 efficacy and safety studies. Three SC doses (2, 20, and 100 mg) were evaluated in this 52-week exacerbation trial. The formulation of benralizumab evaluated in this trial differs from the final to-be-marketed formulation (b) (4)

*Primary Objective:*

- to evaluate the effect of multiple-dose SC administration of benralizumab on the annual asthma exacerbation rate (AER) in adult subjects with uncontrolled asthma suspected to

be eosinophilic in nature

*Secondary Objectives:*

- To evaluate the safety and tolerability of benralizumab.
- To determine the optimal dose of benralizumab to be used in phase 3 studies.
- To describe the immunogenicity and pharmacokinetics (PK) of benralizumab.
- To assess the effect of benralizumab on other assessments of clinical activity (i.e., asthma control and pulmonary function).
- To assess the effect of benralizumab on health-related quality of life.

**Trial Design**

MI-CP220 was a phase 2b, randomized, double-blind, placebo-controlled, dose-ranging study evaluating multiple subcutaneous (SC) doses of benralizumab (2, 20, and 100 mg) in adult subjects with uncontrolled asthma on medium or high-dose ICS plus a LABA with a history of ≥ 2 exacerbations in the prior year. Eligible subjects were stratified as having a high likelihood of eosinophilic phenotype (eos+) or not (eos-) based on a FeNO ≥ 50 ppb and a positive ELEN index. The ELEN index is an applicant-derived mathematical algorithm which was designed to predict when a patient would have an elevated sputum eosinophil count ≥ 2%. Treatment was administered every 4 weeks for the first 3 doses followed by every 8 weeks thereafter for the remaining doses. Eos+ subjects were randomized 1:1:1:1 to 2, 20 or 100 mg SC benralizumab and Eos- subjects 1:1 to 100 mg SC benralizumab or placebo.

**Study Endpoints**

*Primary efficacy endpoint:*

- Annual exacerbation rate (AER) during the study (Week 1 [day1] to Week 52) for EOS+ subjects

**Statistical Analysis Plan**

The primary endpoint analysis was conducted on the modified intent to treat population (mITT) which included all randomized subjects who received any dose of investigation product. The primary comparisons were conducted on the eos+ patients and included 100 mg vs placebo, 20 mg vs placebo, and 2 mg vs placebo. The analyses conducted for the eos- subjects were planned as exploratory assessments.

**Protocol Amendments**

Three protocol amendments were made for this trial. None of the amendments impact the interpretation of the efficacy or safety findings.

**Data Quality and Integrity: Sponsor's Assurance**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures.

### 6.1.2. Study Results

**Compliance with Good Clinical Practices**

A statement of compliance with Good Clinical Practice is located in the CSR.

**Financial Disclosure**

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 13.2 of this review for additional details.

**Patient Disposition**

A total of 609 subjects were randomized in the trial and included 324 eos+ and 285 eos- negative subjects. Of these subjects, 606 received at least one dose of investigational product with three subjects (1 in the eos- placebo group and 2 in the eos-100 mg benralizumab group) discontinuing the trial prior to receiving investigational product. Trial completion was balanced across treatment arms (86-90%). Withdrawal of consent and lost to follow-up were listed as the most common reasons for trial discontinuation.

**Protocol Violations/Deviations**

Protocol deviations occurred in 19% of randomized subjects (117 of 609) with the number of deviations generally balanced between placebo and active treated subjects. Of the protocol deviations, inclusion/exclusion criteria violations were the most common deviations and occurred in 74 subjects.

*Reviewer's Comment: While the overall rate of deviations is high, the nature of the most common deviation (violation of inclusion/exclusion criteria) do not prevent the trial from informing dose selection for the further evaluation and confirmation in phase 3.*

**Demographic Characteristics**

Trial participants were primarily Caucasian (66-76%), female (60-72%), age of 45 to 50, with a mean BMI of 28-29. About half of the subjects (47%) were on high dose ICS and the other half on medium dose ICS (52%) prior to enrollment. Baseline eosinophil counts ranged from 27% with counts < 200 cells/mcl, 48% with counts < 300 cells/mcl and 35% with counts > 400 cells/mcl. Just over half of subjects had reversible disease (55%)[6].

[6] Defined by improvement in baseline FEV1 ≥ 12% following SABA administration

**Efficacy Results – Primary Endpoint**

**The trial demonstrated a reduction in the AER for the 20 mg and 100 mg dose group in eos+ subjects compared to placebo with a numerically higher response seen in the 100 mg dose group and the lowest response seen in the 2 mg dose group (Table 4,**

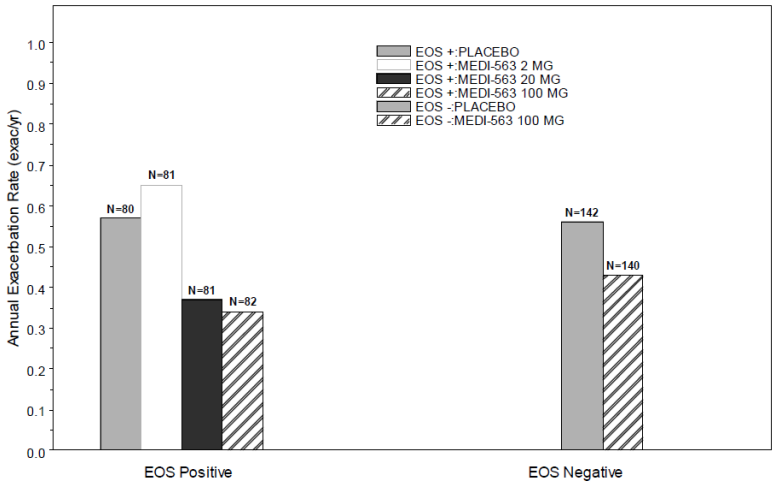
Figure 3).

**Table 4: MI-CP220 Annual Exacerbation Rate by Eosinophil Phenotype (mITT)**

| | | Eos+ | | | Eos - | |
|---|---|---|---|---|---|---|
| | **Placebo N = 80** | **2 mg N = 81** | **20 mg N = 81** | **100 mg N = 82** | **Placebo N = 142** | **100 mg N = 140** |
| **Exacerbation Rate** | 0.57 | 0.65 | 0.37 | 0.34 | 0.56 | 0.43 |
| **80% CI** | 0.46, 0.70 | 0.53, 0.78 | 0.29, 0.48 | 0.26, 0.45 | 0.48, 0.65 | 0.36, 0.52 |
| **p-value** | | 0.781 | 0.173 | 0.096 | | 0.284 |

Source: Modified from CSR MI-CP220 Table 11.4.1.1-1

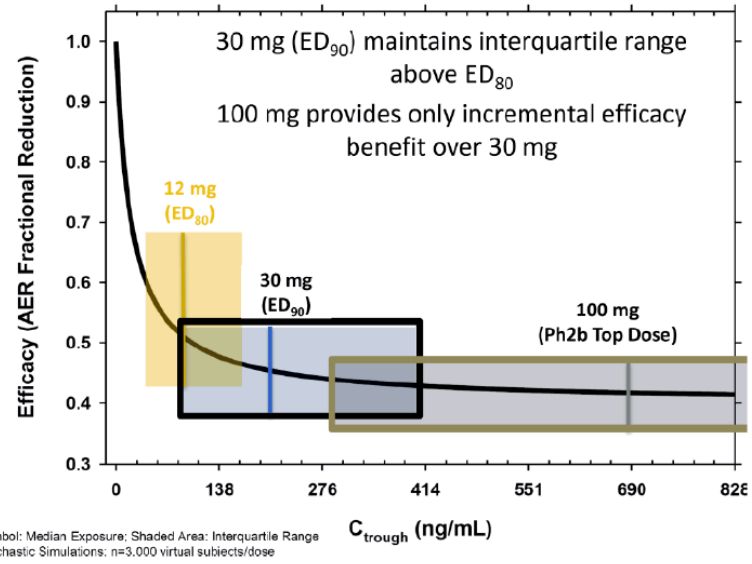
**Figure 3: Annual Exacerbation Rate by Eosinophil Phenotype,( mITT)**




Source: MI-CP220 CSR Figure 11.4.1.1-1

An exposure response model on the annual exacerbation rate was explored using the benralizumab trough concentrations at steady state and observed exacerbation rates from this study. The model estimated that the 30 mg SC route to the $ED_{90}$ dose for the Q4 x 3 followed by Q8 dosing regimen was expected to maximize efficacy while reducing the impact of steady state PK variability.

**Figure 4: MI-CP220 simulated exposure-response model**




Source: Summary of Clinical Pharmacology Figure 34

*Reviewer's Comment: The data from the MI-CP220 trial and the sponsor's exposure response model were discussed at an EOP2 meeting. The sponsor indicated that it had chosen to evaluate a 30 mg dose in its phase 3 program as it was expected to maximize efficacy while reducing the impact of lower dosing on steady-state PK variability and ADA formation. The Division noted that dose selection based on the PD modeling was risky but at the applicant's discretion. It further noted that the rate of ADA formation appeared high in the trial and stated that acceptability of choosing a high-dose to suppress formation would be dependent on the risk-benefit assessment seen in the phase 3 program. The Agency recommended evaluation of multiple doses in the phase 3 program. In response the applicant evaluated two dosing regimens, 30 mg Q4 and 30 mg Q8 following a Q4x3 loading dose in its phase 3 program. The data supporting final dose selection of benralizumab are summarized in Section 7.1.4.*

*The intended patient population for benralizumab and the population evaluated in MI-CP220 were also discussed during the EOP2 interaction. Specifically the lack of clinical criteria to identify an eosinophilic asthma population was highlighted. Following the EOP2 discussion, the applicant evaluated both a peripheral blood eosinophil low and high population in its phase 3 program, but noted that the primary analysis would be restricted to patients in the eosinophil high category. The Division found this approach to be reasonable at the time but noted that results in both populations would be considered during the BLA review.*

## 6.2. SIROCCO

### 6.2.1. Study Design

**Overview and Objective**

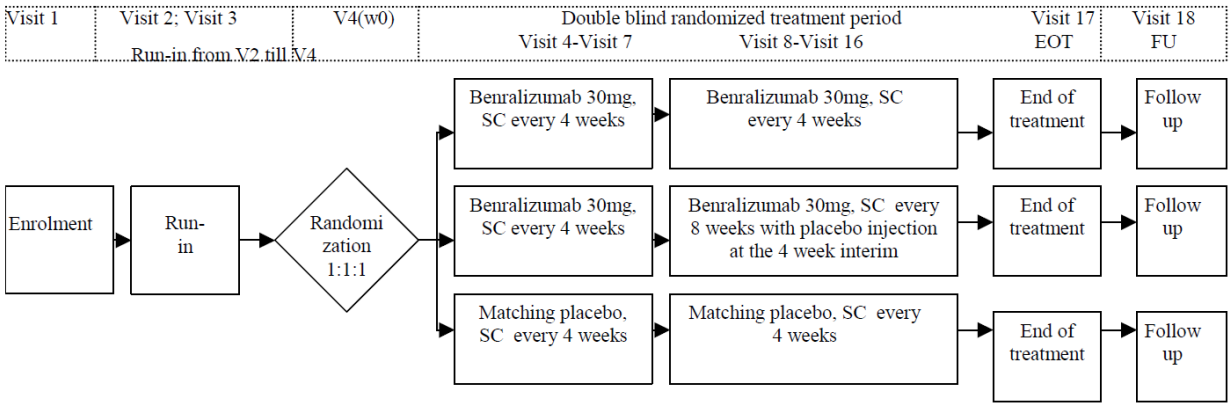
*Primary*:

- To evaluate the effect of two dosing regimens of benralizumab on asthma exacerbations in adult patients with uncontrolled asthma.

**Trial Design**

SIROCCO was multicenter, randomized, double-blind, parallel-group, placebo-controlled, phase 3 exacerbation trial. Two dosing regimens were evaluated (30 mg Q4 x3 followed by Q8 dosing and 30 mg Q4) against placebo. Doses were administered using a PFS and administered by a healthcare provider. Patients with uncontrolled asthma receiving high-dose ICS/LABA with or without additional asthma controller(s) and a history of 2 asthma exacerbations requiring OCS in the prior 12 months were enrolled and randomized 1:1:1 to the treatment arms. Patients were stratified by country/region and peripheral blood eosinophil count. The study recruited patients with blood eosinophil counts both ≥ 300/µl and < 300/µl at a ratio of 2:1. For the remainder of this review, patients with an eosinophil count ≥ 300/µL are referred to as the eosinophil high population and those with a count < 300 as the eosinophil low population. All patients remained on their background asthma therapy without change for the duration of the trial. The study included a run-in period (minimum of 2 weeks to assess study eligibility) followed by a 48-week treatment period with the last dose of benralizumab administered at Week 44 and the end of treatment visit occurring at Week 48. The trial included a formalized ECG sub-study with an ECG obtained at baseline and $C_{max}$ (6 days after the second dose).

**Figure 5: SIROCCO Study flow chart**




**Source: SIROCCO protocol Figure 1**

**Study Endpoints**

*Primary Endpoint*:

- Annual exacerbation rate[7]

*Key Secondary Endpoints:*

- Pre-dose/pre-bronchodilator FEV1 and post-bronchodilator FEV1 at the study center
- Asthma symptom score (total, daytime, and night-time)

*Select Secondary Endpoints*

- Rescue medication use
- Home lung function (morning and evening PEF)
- Nights with awakening due to asthma
- ACQ-6
- Time to first asthma exacerbation and proportion of patients with ≥ 1 asthma exacerbation
- AQLQ(S)+12
- EQ-5D-5L
- Annual rate of asthma exacerbations that are associated with an emergency room visit or hospitalization
- PK parameters
- Anti-drug Antibodies

*Safety Endpoints*

- AE/SAE
- Laboratory variables (see section 8.3.3 of this review for additional details)
- ECG (see section 8.4.8 of this review for additional details)
- Physical Examinations

*Reviewer's comment: The annual exacerbation rate and FEV1 are appropriate primary and key secondary efficacy assessments and the applicant's definition for an asthma exacerbation is consistent with that outlined in ATS/ERS summary statement on defining asthma control and exacerbations in clinical trials.[8] The ACQ6 and AQLQ(S)+12 assessments measured in this*

[7] Asthma exacerbation defined by worsening of asthma requiring use of systemic corticosteroids (or increase in dose) for at least 3 days (single depo-injectable dose is considered equivalent to 3 days), an ER visit due to asthma that required systemic corticosteroids, or an in-patient hospitalization. A worsening of asthma is defined as new or increased signs/symptoms of asthma that are concerning to patient or related to the e-diary. The e-diary was designed to alert the patient and study center for a: ↓ in am PEF ≥ 30% on at least 2 of 3 consecutive days, and/or ↑ > 50% in rescue medication on at least 2 of 3 consecutive days, and/or nocturnal awakening due to asthma requiring rescue medication use on 2 of 3 consecutive days, and/or ↑ in total asthma symptom score of at least 2 units above run-in average or highest possible score on at least 2 of 3 successive days.

[8] Reddel, Helen K., et al. "An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice." American journal of respiratory and critical care medicine 180.1 (2009): 59-99.

*program are patient reported outcome measures with established minimal clinically important differences (MCIDs) are assessment tools well-known in clinical practice. The AQLQ(S) +12 is a modification of the AQLQ assessment has been developed and validated for evaluation of adolescents and adults in clinical trials.[9] Use of this specific instrument in benralizumab clinical development program is reasonable.*

**Statistical Analysis Plan**

The primary analysis population for the primary and two key secondary endpoints includes patients with a baseline peripheral blood eosinophils count ≥ 300 cells/µl. Readers are referred to the statistical review for detailed discussion of the statistical analysis plan for this trial.

**Protocol Amendments**

A total of 9 protocol amendments were made to SIROCCO, two of which were made across all study sites while the remaining 7 were local amendments made to sites outside the United States.

- Protocol amendment 1: May 15, 2014
    - The number of study sites was increased from 200 to 400 to ensure enrollment of required number of patients
    - The inclusion criteria were expanded to enroll adolescent patients 12 to 17 years of age with adolescents enrolled in the European Union and randomized to placebo or 30 mg Q4 x 3 followed by Q8 treatment arms only.
    - The eligible screening period was decreased from 5 to 2 weeks
    - The definition for emergency room/urgent care visit was altered to include patients with an evaluation and treatment for < 24 hours, while hospitalization was defined as admission to an inpatient facility and/or evaluation and treatment in healthcare facility for > 24 hours
    - The statistical analysis plan was altered to stratify patients by country only (region removed), removed age and sex from the statistical model, and stated that an intention to treat approach would be used (readers referred to the statistical analysis plan for additional details)
    - Amendments included the correction of typographical mistakes and other editorial changes that do not fundamentally alter the study design or conduct
- Protocol amendment 2: April 23, 2015
    - The Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PCIG) assessments were added
    - The procedures for patients enrolling in the extension study were clarified
    - The time points for ADA and neutralizing antibody collection clarified

[9] Juniper, Elizabeth F., et al. "Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older." Health and quality of life outcomes 3.1 (2005): 58.

*Reviewer's Comment: The protocol amendments do not impact the interpretation of the efficacy and safety data from the trial.*

**Data Quality and Integrity: Sponsor's Assurance**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures. The sponsor also attests that it performs a GCP audit program which includes use of Global Quality Assurance group which operates independently of the study monitors.

### 6.2.2. Trial Results

**Compliance with Good Clinical Practices**

The complete study report contains a statement that it was performed in compliance with Good Clinical Practice.

**Financial Disclosure**

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 13.2 of this review for additional details.

**Patient Disposition**

A total of 2,681 patients were enrolled in the trial with 2,232 entering the screening/run-in period. Of these, 1,205 patients were randomized. All randomized patients received at least one dose of study drug with the exception of one patient in the Q4 dosing arm who didn't take any study medication. A total of 399 patients were randomized to benralizumab 30 mg Q4, 398 to 30 mg Q8 and 407 to placebo with 88%, 90% and 89% completing treatment respectively. No imbalance in the reason for discontinuation is noted across the treatment groups or study populations. Readers are referred to the statistical review for additional details and summary tables of the disposition data.

**Protocol Violations/Deviations**

A total of 91 patients had protocol deviations. Of these, 5 patients in the 30 mg Q8 group received incorrect study treatment during the study. This was caused by the sites incorrectly registering visit numbers after missed visits and administering the incorrect medication kits which by protocol should have included a placebo dose every other visit. As patients received 2 consecutive doses of benralizumab, four of these patients were reassigned to Q4W for safety and PK assessments. All other deviations were related to violations of the inclusion/exclusion

criteria and were balanced across treatment groups (6-9% across all treatment arms in both eosinophil high and overall populations). Readers are referred to statistical review for additional details.

*Reviewer's Comment: A sensitivity analysis run by the statistical reviewer showed that the protocol deviations resulting in incorrect treatment assignment do not impact the efficacy trends from the trial.*

**Table of Demographic Characteristics**

Overall, patient demographics are balanced across treatment arms. Trial participants were primarily Caucasian (73%), female (66%), with a mean BMI of 29 and average age of 49. A total of 53 adolescent patients age 12 to 17 were enrolled in the trial, with 11 (3%), 19 (5%) and 23 (6%) randomized to the Q4, Q8 and placebo arms respectively. Only 17% of the trial was enrolled in North America; however, as discussed in Section 7.1.3 and Section 8.6 of this review, no regional differences in efficacy or safety for the US population were observed.

**Table 5: SIROCCO: Demographics (FAS)**

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30mg Q4 N=399 | 30 Q 8 N=398 | Placebo N=407 | Total N=1204 | 30 Q4 N=275 | 30 Q8 N=267 | Placebo N=267 | Total N=809 |
| **Age Group** | | | | | | | | |
| >=12 - <18 | 11 (3) | 19 (5) | 23 (6) | 53 (4) | 8 (3) | 10 (4) | 12 (4) | 30 (4) |
| >=18 - <50 | 158 (40) | 178 (45) | 162 (40) | 498 (41) | 117 (43) | 123(46) | 114 (43) | 354(44) |
| >=50 - <65 | 180 (45) | 161 (40) | 169 (42) | 510 (42) | 124 (45) | 105(39) | 109 (41) | 338(42) |
| >=65 – 75 | 50 | 40 | 53 | 143 | 26 | 29 | 32 | 87 |
| **Age** | | | | | | | | |
| Mean | 50 | 48 | 49 | 49 | 49 | 48 | 49 | 49 |
| **Sex, n (%)** | | | | | | | | |
| F | 275 (69) | 252 (63) | 269 (66) | 796 (66) | 173 (63) | 174(65) | 180 (67) | 527(65) |
| M | 124 (31) | 146 (37) | 138 (34) | 408 (34) | 102 (37) | 93 (35) | 87 (33) | 282(35) |
| **Region, n (%)** | | | | | | | | |
| Eastern Europe | 120 (30) | 130 (33) | 137 (34) | 387 (32) | 82 (30) | 85 (32) | 83 (31) | 250 (31) |

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30mg Q4 N=399 | 30 Q 8 N=398 | Placebo N=407 | Total N=1204 | 30 Q4 N=275 | 30 Q8 N=267 | Placebo N=267 | Total N=809 |
| Europe | 86 (22) | 82 (21) | 84 (21) | 252 (21) | 56 (20) | 55 (21) | 53 (20) | 164 (20) |
| Rest of the World | 79 (20) | 74 (19) | 72 (18) | 225 (19) | 58 (21) | 48 (18) | 51 (19) | 157 (19) |
| North America | 68 (17) | 67 (17) | 68 (17) | 203 (17) | 47 (17) | 47 (18) | 48 (18) | 142 (18) |
| Asia | 46 (12) | 45 (11) | 46 (11) | 137 (11) | 32 (12) | 32 (12) | 32 (12) | 96 (12) |
| **Race, n (%)** | | | | | | | | |
| White | 285 (71) | 287 (72) | 302 (74) | 874 (73) | 191 (69) | 192(72) | 191 (72) | 574(71) |
| Asian | 54 (14) | 50 (13) | 50 (12) | 154 (13) | 39 (14) | 35 (13) | 36 (13) | 110(14) |
| Other | 32 (8) | 36 (9) | 25 (6) | 93 (8) | 24 (9) | 25 (9) | 22 (8) | 71 (9) |
| Black or African American | 15 (4) | 15 (4) | 16 (4) | 46 (4) | 11 (4) | 10 (4) | 10 (4) | 31 (4) |
| American Indian or Alaska native | 13 (3) | 10 (3) | 12 (3) | 35 (3) | 10 (4) | 5 (2) | 6 (2) | 21 (3) |
| Native Hawaiian or Pacific Islander | 0 | 0 | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) | 2 (<1) |

Source: Modified from Statistical Review Table 9

**Table 6: SIROCCO: Baseline Patient Characteristics (FAS)**

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 Q4 N=399 | 30 Q 8 N=398 | Placebo N=407 | Total N=1204 | 30 Q4 N=275 | 30 Q8 N=267 | Placebo N=267 | Total N=809 |
| **Median Baseline Eosinophil Count, cells/µL** | | | | | | | | |
| Local lab | 385 | 360 | 370 | 378 | 500 | 499 | 500 | 500 |
| **Lung Function** | | | | | | | | |
| Mean Pre-BD $FEV_1$ % Pred. | 57 | 56 | 57 | 57 | 57 | 56 | 56 | 56 |
| Mean Pre-BD $FEV_1$/FVC Ratio | 62 | 61 | 61 | 61 | 62 | 60 | 61 | 61 |

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 Q4 N=399 | 30 Q 8 N=398 | Placebo N=407 | Total N=1204 | 30 Q4 N=275 | 30 Q8 N=267 | Placebo N=267 | Total N=809 |
| Mean % reversibility | 24 | 27 | 26 | 26 | 25 | 27 | 26 | 26 |
| **Duration of Asthma (years)** | | | | | | | | |
| Median | 15 | 14 | 14 | 15 | 15 | 15 | 13 | 14 |
| **Number of Exacerbations in Previous 12 Months, n (%)** | | | | | | | | |
| 2 | 253 (63) | 252 (63) | 244 (60) | 749 (62) | 173 (63) | 164 (61) | 149 (56) | 486 (60) |
| 3 | 64 (16) | 79 (20) | 76 (19) | 219 (18) | 44 (16) | 53 (20) | 53 (20) | 150 (19) |
| 4 or more | 82 (21) | 67 (17) | 87 (21) | 236 (20) | 58 (21) | 50 (19) | 65 (24) | 173 (21) |
| **Smoking Status n,(%)** | | | | | | | | |
| Current | 0 | 1 (<1) | 5 (1) | 6 (<1) | 0 | 1 (<1) | 1 (<1) | 2 (<1) |
| Former | 86 (22) | 70 (18) | 74 (18) | 230 (19) | 61 (22) | 46 (17) | 47 (18) | 154 (19) |
| Never | 313 (78) | 327 (82) | 328 (81) | 968 (80) | 214 (78) | 220 (82) | 219 (82) | 653 (81) |

Source: Modified from Statistical Review Table 10

*Reviewer's Comment: The enrolled patient population is representative of a severe asthmatic population likely to use the product in clinical practice.*

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Overall compliance was high (98%) and similar across treatment groups (97.5% - 98.4%). Per the protocol, all patients were to remain on his/her baseline asthma medication throughout the study. A total of 95 patients (8%) took a disallowed concomitant medication, the most common of which was regularly scheduled SABA.

Re*viewer's Comment: Compliance rates are high as would be expected with a drug administered by site personnel at study visits. As benralizumab is proposed as add-on maintenance therapy in a severe asthma population, use of disallowed study medications such as regularly scheduled SABA in a small number of patients do not impact the assessment of the product's efficacy in this patient population.*

**Efficacy Results – Primary Endpoint**

Both benralizumab dosing regimens demonstrate an improvement in the annual asthma

exacerbation rate compared to placebo. This result was seen for the eosinophil high and overall population. While the results trended in the right direction for both arms in the eosinophil low population, the effect size was lower than seen in the eosinophil high population and only the Q4 treatment arm demonstrated a statistically significant reduction compared with placebo (Table 7).

**Table 7: SIROCCO: Annualized Exacerbation Rate (FAS)**

| | | Marginal Method | | Model Based Approach | | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **N** | **Mean Rate per Year 95% CI** | **Rate Difference 95% CI** | **Mean Rate per Year** | **Rates Ratio** | **Rate Ratio p-value** |
| **Overall Population** | | | | | | |
| 30 Q4 | 399 | 0.87<br>0.74, 1.02 | -0.59<br>-0.83, -0.35 | 0.77<br>0.66, 0.90 | 0.60<br>0.48, 0.73 | <.001* |
| 30 Q8 | 398 | 0.87<br>0.73, 1.02 | - 0.59<br>-0.84, -0.35 | 0.77<br>0.65, 0.90 | 0.48, 0.73 | <.001* |
| Placebo | 407 | 1.46<br>1.27, 1.68 | | 1.29<br>1.13, 1.48 | | |
| **Eosinophil High: ≥ 300 cells/µL** | | | | | | |
| 30 Q4 | 275 | 0.83<br>0.68, 1.02 | -0.69<br>-1.00, -0.38 | 0.73<br>0.60, 0.89 | 0.55<br>0.42, 0.71 | <.001 |
| 30 Q8 | 267 | 0.74<br>0.59, 0.92 | -0.78<br>-1.08, -0.47 | 0.65<br>0.53, 0.80 | 0.49<br>0.37, 0.64 | <.001 |
| Placebo | 267 | 1.52<br>1.27, 1.81 | | 1.33<br>1.12, 1.58 | | |
| **Eosinophil Low Population** | | | | | | |
| 30 Q4 | 124 | 0.94 | -0.40<br>-0.79, 0.00 | 0.85<br>0.65, 1.11 | 0.70<br>0.50, 1.00 | 0.047* |
| 30 Q8 | 131 | 1.11 | -0.23<br>-0.65, 0.18 | 1.00<br>0.78, 1.28 | 0.83<br>0.59, 1.16 | 0.268 |
| Placebo | 140 | 1.34<br>1.06, 1.69 | | 1.21<br>0.96, 1.52 | | |

Source: Modified from Statistical Review Table 11

In addition to an increased treatment benefit in patents with higher baseline eosinophil counts, a subgroup analysis of the SIROCCO primary endpoint data demonstrates an increase in the exacerbation response in patients with a more frequent history of exacerbation (≥ 3 in the prior

12 months) compared to those with fewer (2 exacerbations) in patients with high baseline blood eosinophil count.

**Table 8: SIROCCO: Exacerbation Rate by Number of Exacerbation in the Previous Year in Patient with Baseline Blood Eosinophil Count ≥ 300 cells/µL (FAS)**

| | 30 Q8<br>N = 267 | Placebo<br>N = 267 |
|---|---|---|
| **Baseline of 2 exacerbations in 12 months prior to enrollment** | | |
| N | 164 | 149 |
| Rate Difference | 0.57 | 1.04 |
| Difference from placebo | -0.47 | |
| Rate Ratio (95% CI) | 0.55 (0.37, 0.80) | |
| **Baseline of ≥ 3 exacerbations in the 12 months prior to enrollment** | | |
| N | 103 | 118 |
| Rate Difference | 0.84 | 2.15 |
| Difference | -1.28 | |
| Rate Ratio (95% CI) | 0.43 (0.29,0.63) | |

Source: Modified from Clinical Overview Table 7

Exacerbation events requiring ER visit and/or hospitalization only were also evaluated in this trial. While not specified as primary endpoints, these data are discussed in this section of the review as they are related measures. For these endpoints, the sponsor used an independent adjudication committee to determine if the events were asthma-related. This is in contrast to the primary endpoint data, which relied solely on investigator determination. The small number of events limits the analysis; however the data trend in support of the primary endpoint (Table 9). Similar results, albeit with even smaller treatment effects are seen in the hospitalization only data (data not shown) Readers are referred to the statistical review for additional details.

**Table 9: SIROCCO: Annualized Rate of Adjudicated Exacerbations Requiring Hospitalization or ER Visit (FAS)**

| | | Marginal Method | | Model Based Approach | | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **N** | **Mean rate per year 95% CI** | **Rate difference 95% CI** | **Mean rate per year 95% CI** | **Rate ratio 95% CI** | **Rate ratio p-value** |
| **Overall** | | | | | | |
| 30 Q4 | 399 | 0.19<br>0.12, 0.30 | -0.08<br>-0.18, 0.03 | 0.11<br>0.08, 0.15 | 0.71<br>0.46, 1.10 | 0.126 |

| | | Marginal Method | | Model Based Approach | | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **N** | **Mean rate per year 95% CI** | **Rate difference 95% CI** | **Mean rate per year 95% CI** | **Rate ratio 95% CI** | **Rate ratio p-value** |
| 30 Q8 | 398 | 0.14<br>0.09, 0.23 | -0.12<br>-0.23, -0.02 | 0.08<br>0.06, 0.12 | 0.54<br>0.34, 0.86 | 0.009* |
| Placebo | 407 | 0.27<br>0.17, 0.42 | | 0.15<br>0.11, 0.21 | | |
| **Eosinophil High: ≥ 300 cells/µL** | | | | | | |
| 30 Q4 | 275 | 0.15<br>0.10, 0.24 | -0.21, 0.01 | 0.11<br>0.07, 0.16 | 0.61<br>0.37, 1.01 | 0.053 |
| 30 Q8 | 267 | 0.09<br>0.05, 0.16 | -0.16<br>-0.26, -0.06 | 0.06<br>0.04, 0.11 | 0.37<br>0.20, 0.67 | <.001 |
| Placebo | 267 | 0.25<br>0.17, 0.38 | | 0.13, 0.25 | | |
| **Eosinophil Low: < 300 cells/µL** | | | | | | |
| 30 Q4 | 124 | 0.35<br>0.10, 1.29 | -0.02<br>-0.32, 0.28 | 0.10<br>0.06, 0.20 | 0.94<br>0.42, 2.12 | 0.887 |
| 3 | 131 | 0.34<br>0.09, 1.22 | -0.03<br>-0.33, 0.26 | 0.10<br>0.05, 0.19 | 0.91<br>0.40, 2.06 | 0.820 |
| Placebo | 140 | 0.37<br>0.10, 1.41 | | 0.11<br>0.06, 0.20 | | |

Source: Modified from the Statistical Review Tables 19

*Reviewer's Comment: Both dosing regimens demonstrate statistically significant and clinically meaningful improvements in the annual exacerbation rates compared to the placebo for the eosinophil high population. This review finds the treatment benefit to be compelling as the benefit is demonstrated beyond that provided by high dose ICS/LABA therapy. Similar trends are seen in the events requiring ER visit and/or hospitalization; although the analysis is limited by the small sample size.*

*The overall patient population also demonstrates a statistically significant improvement*

*compared to placebo, albeit with a smaller treatment effect. This latter finding may be driven in part by the eosinophil high population which was randomized 2:1 in this trial. While the eosinophil low patient population demonstrates numeric improvements compared to placebo, results do not consistently reach statistical significance. These trends suggest that the treatment effect increases as a patient's baseline peripheral blood eosinophil count increases. Similarly an increase in the treatment benefit is seen in patients with a more frequent exacerbation history than those with less frequent exacerbation history. It should be noted that these subgroup analysis have not been confirmed by the Agency's statistical reviewer.*

*Similar trends are seen in the events requiring ER visit and/or hospitalization; however the analysis is limited by the small sample size. While these latter analyses are not multiplicity protected, data documenting benralizumab's impact on severe asthma exacerbations (e.g., requiring ER and/or hospitalization) are clinically relevant and thus appropriate to include in product labeling.*

**Data Quality and Integrity – Reviewers' Assessment**

No data integrity concerns hindering the review of this application were identified during the review of this application.

**Efficacy Results – Secondary and other relevant endpoints**

In addition to the annual exacerbation rate, the trial evaluated the change from baseline in pre-bronchodilator FEV1 (PD-FEV1) and the total asthma symptom score as key secondary endpoints with pre-specified a plan to account for multiplicity.

*Pulmonary Function:*
Both dosing regimens demonstrate an improvement in FEV1 compared to placebo with an increase of 0.106 L (95% CI 0.016, 0.196; p= 0.022) and 0.159 L (95% CI 0.068, 0.249; p value = 0.001) for the Q4 and Q8 dose groups respectively. A review of the FEV1 data over time demonstrates that the treatment effect is maintained throughout the duration of the trial (Figure 6).

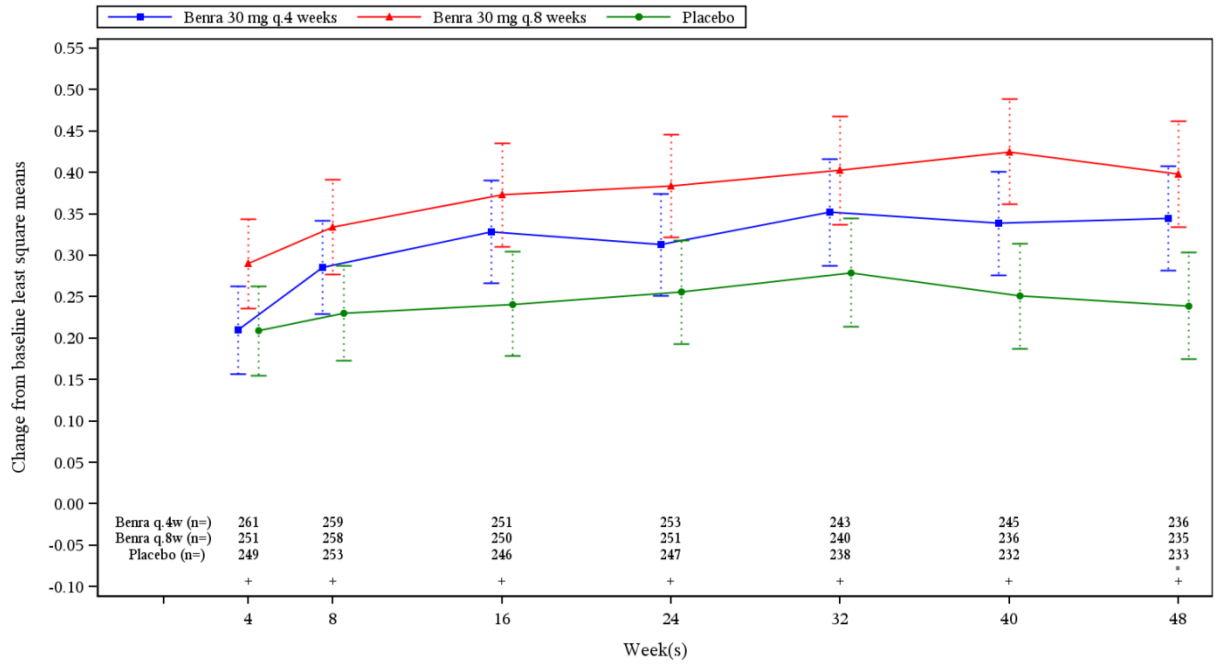
**Table 10: SIROCCO: Change from baseline Pre-BD FEV1 at Week 48 (FAS)**

| Treatment Group | Mean Change from Baseline | Mean Change 95% CI | Mean Difference | Mean Difference 95% CI | Mean Difference p-value |
|---|---|---|---|---|---|
| **Overall Population** | | | | | |
| 30 Q4 | 0.27 | 0.22, 0.32 | 0.07 | -0.00 , 0.14 | 0.060 |

| Treatment Group | Mean Change from Baseline | Mean Change 95% CI | Mean Difference | Mean Difference 95% CI | Mean Difference p-value |
|---|---|---|---|---|---|
| 30 Q8 | 0.35 | 0.30, 0.40 | 0.15 | 0.08 , 0.22 | 0.000* |
| Placebo | 0.21 | 0.16, 0.26 | | | |
| **Eosinophil High: ≥ 300 cells/µL** | | | | | |
| 30 Q4 | 0.35 | 0.28, 0.41 | 0.11 | 0.02 , 0.20 | 0.022 |
| 30 Q8 | 0.40 | 0.33, 0.46 | 0.16 | 0.07 , 0.25 | 0.001 |
| Placebo | 0.24 | 0.18, 0.30 | | | |
| **Eosinophil low < 300 cells/µL** | | | | | |
| 30 Q4 | 0.12 | 0.04, 0.20 | -0.03 | -0.13, 0.08 | 0.644 |
| 30 Q8 | 0.71 | 0.55, 0.91 | 0.61 | 0.44, 0.86 | 0.004* |
| Placebo | 1.16 | 0.92, 1.45 | | | |

Source: Statistical Review Table 12

**Figure 6: SIROCCO: Pre-bronchodilator FEV1**




Source: Figure 12.6.2.18 SIROCCO CSR

*ACQ and AQLQ*

The trial also evaluated ACQ6 and AQLQ(S)+12, although these endpoints were not included in the multiplicity plan. Both dosing regimens demonstrate numeric improvements in the mean change from baseline compared to placebo as well in the number of responders. Similar to the primary endpoint, the point estimates are numerically greater in the eosinophil high population compared to eosinophil low (data not shown). Readers are referred to the statistical review for additional details.

**Table 11: SIROCCO: ACQ6 and AQLQ(S)+12 Responder Analysis in the Eosinophil High Population (FAS)**

| Treatment Group | N Total | Number of Responder (%) | Odds Ratio | Odds Ratio 95% CI | p-value |
|---|---|---|---|---|---|
| **ACQ6** | | | | | |
| 30 Q4 | 275 | 157 (57) | 1.35 | 0.96,1.90 | 0.086 |
| 30 Q8 | 267 | 161 (60) | 1.55 | 1.09,2.19 | 0.014 |
| Placebo | 267 | 133 (50) | | | |
| **AQLQ(S)+12** | | | | | |
| 30 Q4 | 275 | 152 (55) | 1.30 | 0.92,1.85 | 0.139 |
| 30 Q8 | 267 | 153 (57) | 1.42 | 0.99,2.02 | 0.055 |
| Placebo | 267 | 131 (49) | | | |

**Source: Modified from Statistical Review Tables 16 and 18**

*Reviewer's Comment: The secondary endpoints discussed above support the findings of the primary endpoints. In particular, the improvement of 100 to 150 ml in FEV1 is seen above the benefit provided by standard-of-care therapy and represent clinically meaningful improvements in lung function. The applicant evaluated its own asthma symptom score as a key secondary endpoint in addition to ACQ and AQLQ. The ACQ and AQLQ are patient reported measures with validated minimal clinically important differences (MCIDs) and are well known in current clinical practice. As such this review recommends that the product labeling incorporate these measures to inform clinicians of the patient reported outcomes* (b) (4)

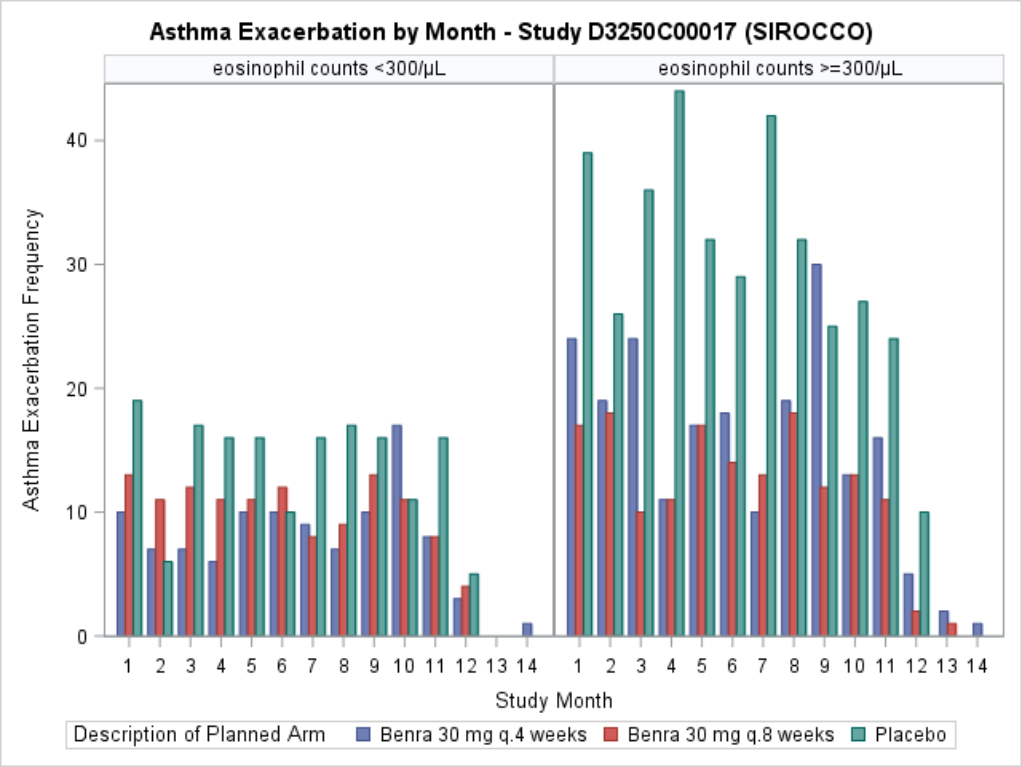
**Dose/Dose Response**

The more frequent dosing regimen does not consistently demonstrate an increased treatment benefit across the efficacy endpoints in this trial.

**Durability of Response**

A histogram plot of the exacerbation effect over time is presented below.

**Figure 7: SIROCCO: Exacerbations over time (FAS)**




Source: Statistical Reviewer

*Reviewer's Comment: No consistent improvement is seen during the Q4 loading dose period for the Q8 arm which suggests that the treatment response seen in this treatment arm is not driven by the Q4W loading dose. In addition, there does not appear to be a clustering of a response in either treatment arm over any particular time period suggesting that the exacerbation effect is maintained throughout dosing.*

**Persistence of Effect**

This trial was not designed to assess whether benralizumab's treatment benefit continues following treatment cessation.

**Additional Analyses Conducted on the Individual Trial**

Not applicable.

## 6.3. CALIMA

### 6.3.1. Study Design

The CALMA trial was similarly designed to SIROCCO with a two exceptions. First, the entry criteria were altered in a protocol amendment to allow for enrollment of patients on medium dose ICS (b) (4) This plan was discussed with the Division and found to be reasonable. Similar to SIROCCO, the primary analysis population included patients with eosinophil counts ≥ 300 cells/µl enrolled on high dose ICS. The second major difference from SIROCCO is that CALIMA included a treatment period of 56 weeks compared to 48 weeks in the SIROCCO study.

**Protocol Amendments**

- Protocol amendment 1: May 13, 2014
  - Expansion of the inclusion criteria to enroll adolescent patients 12 to 17 years of age with adolescents enrolled in the European Union randomized to placebo or the Q8 treatment arms only.
  - Expansion of the inclusion criteria to reflect the inclusion of patients on medium dose ICS (b) (4)
  - Planned statistical analysis plan outlined the intention to use an ITT approach rather than modified ITT approach
  - Additional correction of typographical mistakes and editorial changes.
- Protocol amendment 2: March 16, 2015
  - The Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PCIG) assessments were added
  - Clarification of procedures for patients who enroll in the extension study.
  - The addition of independent adjudication committees for MACE and malignancy events.

*Reviewer's Comment: The protocol amendments do not impact the interpretation of the efficacy and safety data from the trial.*

**Data Quality and Integrity: Sponsor's Assurance**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures. The sponsor also attests that performs a GCP audit program, including use of Global Quality Assurance group which operates independently of the study monitors.

### 6.3.2. CALIMA Study Results

**Compliance with Good Clinical Practices**

The complete study report contains a statement that it was performed in compliance with Good Clinical Practice.

**Financial Disclosure**

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 13.2 of this review for additional details.

**Patient Disposition**

A total of 1,306 patients were randomized to treatment with 1,157 completing treatment. Of these 875 (67%) patients had counts ≥ 300 cells/mcl with 728 of these patients on baseline high dose ICS and 127 on medium dose ICS. No imbalances in the reasons for discontinuation are noted across the treatment arms. Readers are referred to the Statistical Review for summary tables of the patient disposition data.

**Protocol Violations/Deviations**

A total of 105 patients (8%) had at least one protocol deviation during the study with a higher incidence in the benralizumab 30 mg Q8W (10.9%) compared to benralizumab 30 mg Q4W or placebo groups(6.6%). Similar to SIROCCO, CALIMA had a number of patients receiving incorrect study treatment (22 patients; 5%) in the benralizumab 30 mg Q8 group. In 13 of the 22 patients, patients were reassigned to the benralizumab 30 mg Q4 group for safety and PK purposes. Readers are referred to the discussion of the SIROCCO protocol deviations for a discussion of why this occurred.

*Reviewer's Comment: Similar to SIROCCO, a sensitivity analysis run by the statistical reviewer showed that the protocol deviations resulting in incorrect treatment assignment do not impact the efficacy trends from the trial. Reviewers are referred to the statistical review for additional details.*

**Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)**

Overall, patient demographics and baseline disease characteristics are balanced across treatment arms. Patient demographics were similar to SIROCCO. Trial participants were primarily Caucasian (84%), females (62%), with a mean BMI of 29 and average age of 49. A total of 55 adolescent patients age 12 to 17 were enrolled in the trial, with 11 (3%), 21 (5%) and 23 (5%) randomized to the Q4, Q8 and placebo arms respectively. Only 18% of the trial was enrolled in North America; however, as discussed in Section 7.1.3 and Section 8.6 of this review, no regional differences in efficacy or safety for the US population were observed.

**Table 12: CALIMA: Demographics (FAS)**

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | **30 Q4** | **30 Q8** | **Placebo** | **Total** | **30 Q4** | **30 Q8** | **Placebo** | **Total** |
| **Age Group** | | | | | | | | |
| >=12 - <18 | 11 (3) | 21 (5) | 23 (5) | 55 (4) | 9 (3) | 14 (5) | 15 (5) | 38 (4) |
| >=18 - <50 | 174 (41) | 179 (41) | 181 (41) | 534 (41) | 117 (41) | 121 (42) | 133 (45) | 371 (42) |
| >=50 - <65 | 185 (44) | 186 (42) | 169 (38) | 540 (41) | 126 (44) | 123 (42) | 112 (38) | 361 (41) |
| >=65 – 75 | 55 (13) | 55 (12) | 67 (15) | 177 (14) | 36 (13) | 32 (11) | 37 (12) | 105 (12) |
| **Sex** | | | | | | | | |
| F | 270 (64) | 273 (62) | 264 (60) | 807 (62) | 186 (65) | 170 (59) | 176 (59) | 532 (61) |
| M | 155 (36) | 168 (38) | 176 (40) | 499 (38) | 102 (35) | 120 (41) | 121 (41) | 343 (39) |
| **Region** | | | | | | | | |
| Eastern Europe | 149 (35) | 156 (35) | 158 (36) | 463 (35) | 94 (33) | 97 (33) | 99 (33) | 290 (33) |
| Rest of the World | 99 (23) | 103 (23) | 98 (22) | 300 (23) | 68 (24) | 73 (25) | 71 (24) | 212 (24) |
| North America | 75 (18) | 74 (17) | 81 (18) | 230 (18) | 53 (18) | 44 (15) | 51 (17) | 148 (17) |
| Europe | 54 (13) | 58 (13) | 57 (13) | 169 (13) | 37 (13) | 39 (13) | 39 (13) | 115 (13) |
| Asia | 48 (11) | 50 (11) | 46 (10) | 144 (11) | 36 (13) | 37 (13) | 37 (12) | 110 (13) |
| **Race** | | | | | | | | |
| White | 360 (85) | 369 (84) | 372 (85) | 1101 (84) | 241 (84) | 240 (83) | 246 (83) | 727 (83) |
| Asian | 55 (13) | 55 (12) | 53 (12) | 163 (12) | 40 (14) | 41 (14) | 41 (14) | 122 (14) |
| Other | 0 | 2 (<1) | 1 (<1) | 3 (<1) | 7 (2) | 8 (3) | 9 (3) | 24 (3) |
| Black or African American | 10 (2) | 15 (3) | 14 (3) | 39 (3) | 0 | 1 (<1) | 1 (<1) | 2 (<1) |

Source: Modified from Statistical Review Table 23

**Table 13: CALIMA: Baseline Disease Characteristics (FAS)**

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 Q4 N = 425 | 30 Q8 N = 441 | Placebo N = 440 | Total N = 1306 | 30 Q4 N = 241 | 30 Q8 N = 239 | Placebo N = 248 | Total N = 728 |
| **Median Baseline Eosinophil count, cells/µL** | | | | | | | | |
| Local lab | 372 | 400 | 370 | 380 | 500 | 500 | 504 | 500 |
| **Lung Function** | | | | | | | | |
| Mean Pre-BD % Predicted $FEV_1$ | 59 | 58 | 58 | 58 | 59 | 57 | 58 | 58 |
| Pre-BD $FEV_1$/FVC | 61 | 60 | 61 | 61 | 61 | 60 | 60 | 60 |
| Mean % reversibility | 28 | 25 | 27 | 27 | 26 | 25 | 26 | 26 |
| **Duration of Asthma (years)** | | | | | | | | |
| Median | 16 | 17 | 16 | 16 | 15 | 16 | 17 | 16 |
| **Number of Exacerbations in Previous 12 Months, n (%)** | | | | | | | | |
| 2 | 280 (66) | 287 (65) | 288 (66) | 855 (66) | 148 (61) | 144 (60) | 151 (61) | 443 (61 |
| 3 | 89 (21) | 93 (21) | 93 (21) | 275 (21) | 54 (22) | 59 (25) | 56 (23 | 169 (23) |
| 4 or more | 55 (13) | 60 (14) | 59 (13) | 174 (13) | 38 (16) | 36 (15) | 41 (17) | 115 (16) |
| **Smoking history, n (%)** | | | | | | | | |
| Current | 0 | 3 (<1) | 2 (<1) | 5 (<1) | 0 | 1 (<1) | 1 (<1) | 2 (<1) |
| Former | 100 (24) | 90 (20) | 89 (20) | 279 (21) | 66 (27) | 53 (22) | 44 (18) | 163 (22) |
| Never | 325 (77) | 348 (79) | 349 (79) | 1022 (78) | 175 (73) | 185 (77) | 203 (82) | 563 (77) |

Source: Modified from Statistical Review Table 24

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Overall treatment compliance was high (98%) and similar across treatment arms (97.3% – 97.6%). Per the protocol, all the patients were to remain on his/her baseline asthma medication through the study. A total of 81 subjects took a disallowed concomitant medication during the study. The most commonly reported disallowed medication was use of regularly scheduled SABA.

R*eviewer's Comment: Similar to SIROCCO, compliance rates are high and the most common disallowed study medication was use of a regularly scheduled SABA which does not impact in the interpretation of the efficacy data.*

**Efficacy Results – Primary Endpoint**

Similar to SIROCCO, both benralizumab dosing regimens demonstrate an improvement in the annual asthma exacerbation rate over the 56 weeks compared to placebo in the CALIMA trial. An increased treatment benefit is seen in patients with a higher baseline eosinophil count than those with a lower baseline eosinophil count.

**Table 14: CALIMA: Annualized Exacerbation Rate (FAS)**

| | | Marginal Method | | Model Based Approach | | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **N** | **Mean Rate per year 95% CI** | **Rate difference 95% CI** | **Mean rate per year 95% CI** | **Rates Ratio 95% CI** | **Rate Ratio p-value** |
| **Overall High dose ICS** | | | | | | |
| 30 Q4 | 357 | 0.73<br>0.61, 0.86 | -0.40<br>-0.60, -0.20 | 0.66<br>0.56, 0.77 | 0.64<br>0.52, 0.80 | <.001 |
| 30 Q8 | 364 | 0.76<br>0.64, 0.91 | -0.37<br>-0.57, -0.16 | 0.69<br>0.58, 0.81 | 0.68<br>0.54, 0.84 | <.001 |
| Placebo | 370 | 1.13<br>0.97, 1.31 | | 1.02<br>0.88, 1.18 | | |
| **Eosinophil high ≥ 300 cells/µL High Dose ICS** | | | | | | |
| 30 Q4 | 241 | 0.65<br>0.52, 0.81 | -0.36<br>-0.59, -0.13 | 0.60<br>0.48, 0.74 | 0.64<br>0.49, 0.85 | 0.002 |
| 30 Q8 | 239 | 0.73<br>0.58, 0.90 | -0.29<br>-0.53, -0.05 | 0.66<br>0.54, 0.82 | 0.72<br>0.54, 0.95 | 0.019 |
| Placebo | 248 | 1.01<br>0.84, 1.22 | | 0.93<br>0.77, 1.12 | | |
| **Eosinophil low < 300 cells/µL High Dose ICS** | | | | | | |
| 30 Q4 | 116 | 0.89 | -0.49 | 0.78 | 0.64 | 0.015 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 0.66, 1.19 | -0.89, -0.09 | 0.59, 1.02 | 0.45, 0.92 | |
| 30 Q8 | 125 | 0.83<br>0.62, 1.11 | -0.55<br>-0.94, -0.16 | 0.73<br>0.55, 0.95 | 0.60<br>0.42, 0.86 | 0.005 |
| Placebo | 122 | 1.38<br>1.07, 1.78 | | 1.21<br>0.96, 1.52 | | |

Source: Modified from Statistical Review Table 25

**Table 15: CALIMA: Exacerbation Rate by Number of Exacerbation in the Previous Year in Patients with Baseline Eosinophil Count ≥ 300 cells/≤µL on High Dose ICS (FAS)**

| | **30 Q8<br>N = 267** | **Placebo<br>N = 267** |
|---|---|---|
| **Baseline of 2 exacerbations in 12 months prior to enrollment** | | |
| N | 144 | 151 |
| Rate Difference | 0.63 | 0.62 |
| Difference from placebo | 0.01 | |
| Rate Ratio (95% CI) | 1.01 (0.70,1.46) | |
| **Baseline of ≥ 3 exacerbations in the 12 months prior to enrollment** | | |
| N | 95 | 97 |
| Rate Difference | 0.82 | 1.65 |
| Difference | -0.84 | |
| Rate Ratio (95% CI) | 0.49 (0.33, 0.74) | |

Source: Modified from Clinical Overview Table 7

In contrast to data form the SIROCCO trial, a similar number of adjudicated asthma exacerbation events resulting in ER visits or hospitalizations are seen across the treatment arms in the CALIMA trial. Similar trends are seen in the hospitalization only data (data not shown). Readers are referred to the statistical review for additional details.

**Table 16: CALIMA: Annualized Rate of Adjudicated Exacerbations Requiring ER visit or Hospitalization (FAS)**

| | | **Marginal Method** | | **Model Based Approach** | | |
|---|---|---|---|---|---|---|
| **Treatment Group** | **N** | **Mean rate per year<br>95% CI** | **Rate Difference<br>95% CI** | **Mean rate per year** | **Rates Ratio<br>95% CI** | **Rate Ratio<br>p-value** |
| **High Dose ICS, overall population** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 30 Q4 | 357 | 0.10<br>0.07, 0.15 | -0.03<br>-0.08, 0.03 | 0.05<br>0.03, 0.07 | 0.79<br>0.48, 1.30 | 0.356 |
| 30 Q8 | 364 | 0.13<br>0.09, 0.18 | -0.07, 0.06 | 0.06<br>0.04, 0.09 | 0.97<br>0.60, 1.58 | 0.903 |
| Placebo | 370 | 0.13<br>0.09, 0.18 | | 0.06<br>0.05, 0.09 | | |
| **High Dose ICS, Eosinophil Counts ≥ 300 cells/µL** | | | | | | |
| 30 Q4 | 241 | 0.09<br>0.06, 0.15 | -0.01<br>-0.07, 0.06 | 0.04<br>0.02, 0.06 | 0.93<br>0.48, 1.82 | 0.837 |
| 30 Q8 | 239 | 0.12<br>0.08, 0.19 | 0.02<br>-0.05, 0.09 | 0.05<br>0.03, 0.08 | 1.23<br>0.64, 2.35 | 0.538 |
| Placebo | 248 | 0.10<br>0.06, 0.15 | | 0.04<br>0.02, 0.07 | | |
| **High Dose ICS, Eosinophil counts < 300 cells/µL** | | | | | | |
| 30 Q4 | 116 | 0.13<br>0.08, 0.21 | -0.08<br>-0.18, 0.03 | 0.07<br>0.04, 0.13 | 0.62<br>0.32, 1.18 | 0.145 |
| 30 Q8 | 125 | 0.14<br>0.08, 0.24 | -0.06<br>-0.18, 0.05 | 0.08<br>0.04, 0.14 | 0.69<br>0.35, 1.33 | 0.267 |
| Placebo | 122 | 0.21<br>0.14, 0.31 | | 0.10<br>0.06, 0.18 | | |

Source: Modified from Statistical Review Table 33

*Reviewer's Comment: Similar to SIROCCO, CALIMA demonstrated statistically significant and clinically meaningful improvements in the AER rate for patients treated with both dosing regiments of benralizumab compared to placebo. In addition, similar trends for an increased treatment benefit as baseline blood eosinophil count increases and prior exacerbation history increases are seen. However, in CALIMA the number of exacerbations requiring ER visits and/or hospitalizations did not demonstrate a benralizumab-related improvement with similar rates seen across all treatment arms including placebo.*

*Readers are referred to the reviewer's comment from the SIROCCO Primary Endpoint Subsection for additional discussion on the clinical relevance of the efficacy data.*

**Data Quality and Integrity – Reviewers' Assessment**

No data integrity concerns hindering the review of this application were identified by this reviewer or the statistical reviewer.

**Efficacy Results – Secondary and other relevant endpoints**

CALIMA evaluated the same secondary endpoints as the SIROCCO including pulmonary function, ACQ6 and AQLQ(S)+12. Similar to the primary endpoint, both dosing regimens of benralizumab demonstrate improvements in all of these measures compared to placebo.

*Pulmonary Function*
Both dosing regimens demonstrate an improvement in $FEV_1$ compared to placebo with an increase of 0.13 L (95% CI .04, 0.21; p= 0.005) and 0.12 L (95% CI 0.03, 0.20; p value = 0.01) for the Q4 and Q8 dose groups respectively. A review of the $FEV_1$ data over time shows that the treatment effect was maintained throughout the duration of the trial similar to the SIROCCO trial (Figure 6).

*ACQ6 and AQLQ(S)+12*
The trial also evaluated ACQ6 and AQLQ(S)+12. Similar to SIROCCO, both dosing regimens demonstrate numeric improvements in the mean change from baseline compared to placebo. Numeric improvements in the responder analyses are also seen (Table 17). Readers are referred to the statistical review for additional details.

**Table 17: CALIMA: ACQ-6 and AQLQ(S)+12 Responder Analysis in Eosinophil High, High Dose ICS population (FAS)**

| Treatment Group | N Total | Number of Responder (%) | Odds Ratio | Odds Ratio 95% CI | p-value |
|---|---|---|---|---|---|
| **ACQ6** | | | | | |
| 30 Q4 | 241 | 153 (63.5%) | 1.24 | 0.85,1.81 | 0.257 |
| 30 Q8 | 239 | 151 (63.2%) | 1.16 | 0.80,1.68 | 0.444 |
| Placebo | 248 | 147 (59.3%) | | | |
| **AQLQ(S) +12** | | | | | |
| 30 Q4 | 241 | 148 (61.4%) | 1.16 | 0.79,1.69 | 0.458 |
| 30 Q8 | 239 | 144 (60.3%) | 1.03 | 0.70,1.51 | 0.881 |
| Placebo | 248 | 146 (58.9%) | | | |

Source: Modified from Statistical Review Table 30 and 32

*Reviewer's Comment: CALIMA demonstrates similar findings to the SIROCCO trial for the secondary endpoints which are supportive of the primary endpoint findings. Readers are*

*referred to Reviewer's Comment in for the Secondary endpoints subsection of the SIROCCO trial for additional discussion.*

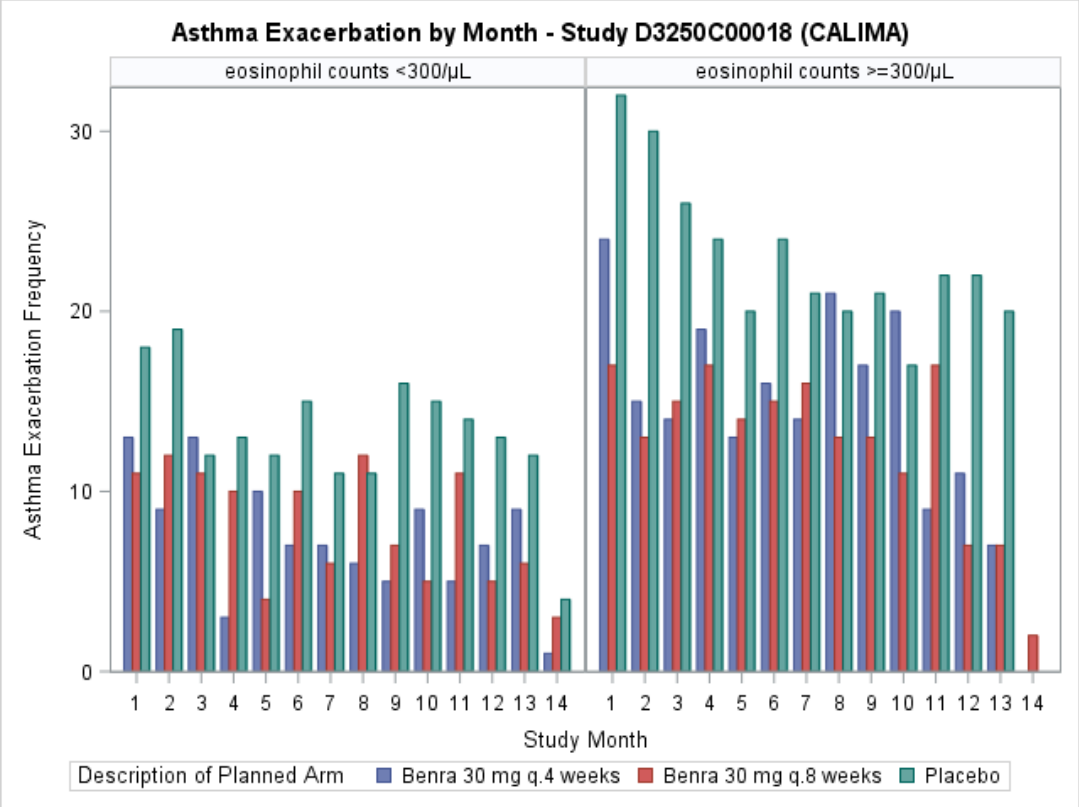
**Dose/Dose Response**

Similar to SIROCCO no consistent increase treatment effect is demonstrated by the more frequent dosing regimen for the primary or secondary endpoint data.

**Durability of Response**

A histogram plot of the exacerbation effect over time is presented below.

**Figure 8: CALIMA Histogram of Asthma Exacerbation by Month (FAS)**




Source: Statistical Reviewer

*Reviewer's Comment: The histogram of asthma exacerbation by month in the CALIMA trial demonstrates similar findings as the SIROCCO trial. See Reviewer's Comment for the durability of Response in Section 6.2.2 for additional discussion.*

**Persistence of Effect**

CALIMA was not designed to assess whether benralizumab's treatment benefit continued following treatment cessation.

**Additional Analyses Conducted on the Individual Trial**

No additional analyses were conducted on this trial.

## 6.4. ZONDA

### 6.4.1. Study Design

**Overview and Objective**

*Primary Objective*

- To compare the effect of 2 dosing regimens of benralizumab on percentage reduction of oral corticosteroid (OCS) dose in adult patients with uncontrolled asthma

**Trial Design**

ZONDA was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluating two dosing regimens (30 mg Q4 and 30 mg Q8 following Q4 x 3 loading dose) in patients with uncontrolled severe asthma. To target patients with severe asthma, the entry criteria specified that only patients receiving high-dose ICS/LABA and chronic oral corticosteroid dose (OCS) of 7.5 mg to 40 mg in the 6 months prior to study entry with or without additional controller medications were to be enrolled. In contrast to the exacerbation studies, the ZONDA entry criteria specified that patients must have a peripheral blood eosinophil count ≥ 150 cells/mcl[10]. Patients were required to have at least 1 exacerbation in the previous 12 months.

The trial included an 8 week run-in in which a patient's OCS dose was optimized by titrating to the minimum dose without loss of asthma control. Patients with a documented failure of dose reduction within 6 months prior to study entry were not required to undergo dose optimization. Failed attempts were defined as those that resulted in clinical deterioration or reduced lung function attributed to asthma including: pre-bronchodilator FEV1 < 80% of personal baseline, morning PEF < 80% of personal baseline, night time awakenings increase of > 50% of mean personal baseline, albuterol/salbutamol use > 4 puffs/day above mean personal baseline, requirement for a burst of prednisone/prednisolone to treat an asthma exacerbation[11]. For those undergoing OCS optimization, the protocol specified that the optimized steroid dose must have be reached at least 2 weeks prior to randomization.

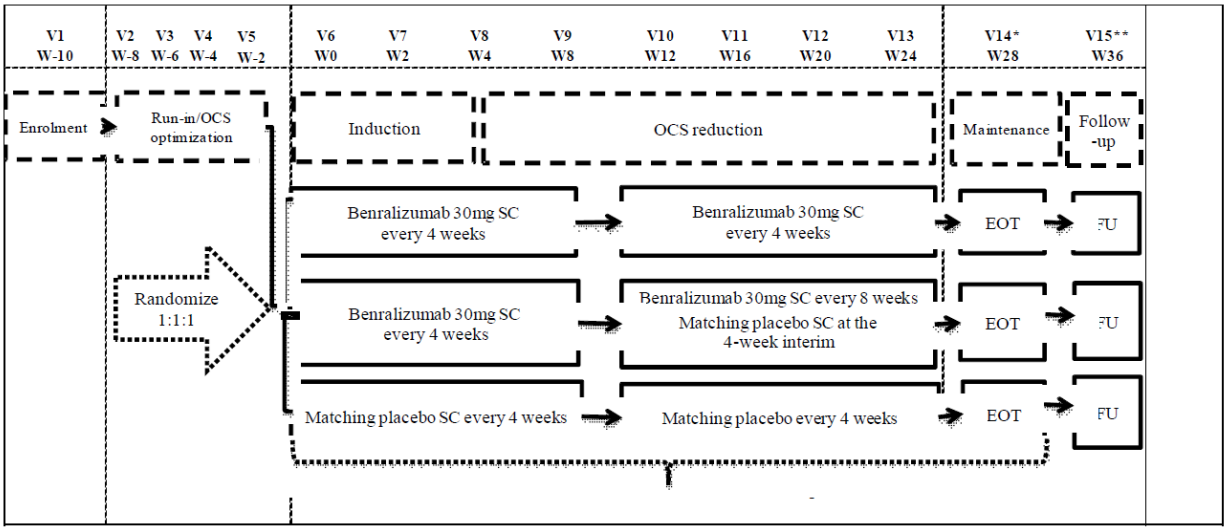
For OCS dose reduction during the optimization and dose reduction phase patients were

[10] Changed from ≥ 300 cells/mcl during protocol amendment 1
[11] A total of 48 of the 220 randomized patients were considered as historically optimized per these criteria

required to maintain asthma control prior to OCS dose titration. Asthma control was defined by: pre-BD ≥ 80% baseline, 2) morning PEF ≥ 80% measured over the prior 14 days, 3) ≤ 50% increase over prior 14 days of mean nighttime awakenings compared to baseline, SABA rescue medication use of no more than 4 inhalations/day above mean value for the prior 14 days or above 12 inhalations daily, no requirement for increase in OCS dose. A recommended dose titration schedule was provided; however, the decision for titration was made at the investigator's discretion.

Following dose optimization, patients were randomized to placebo or active treatment during the 28-week treatment period. The treatment period was divided into three phases including an induction phase (Week 0 to Week 4) during which patients remained on the optimized OCS dose, a reduction phase (Week 4 to Week 24) where a patient's OCS dose was reduced every 4 weeks and a 4-week maintenance phase (Week 24 to Week 28). During the maintenance phase the dose reached at Week 24 (or complete elimination of OCS) was maintained. Patients had a follow-up visit at Week 26 unless patients chose to enroll in the safety extension study, BORA.

**Figure 9: ZONDA Study design flow chart**




Source: ZONDA CSR Figure 1

**Study Endpoints**

*Primary*:

- Percent reduction in final OCS dose compared with baseline (Visit 6), while maintaining asthma control

*Secondary:*

- Proportion of patients with ≥50% reduction in average daily OCS dose at Visit 14 compared with the baseline dose at Visit 6 while maintaining asthma control
- Proportion of patients with average final OCS dose ≤5.0 mg daily at Visit 14 while maintaining asthma control
- Proportion of patients with ≤5.0 mg reduction on daily OCS dose at Visit 14 compared with baseline dose at Visit 6 while maintaining asthma control
- Proportion of patients with ≥1 asthma exacerbation[12] after randomization
- Time to the first asthma exacerbation after randomization
- Annual rate of asthma exacerbations that are associated with an emergency room visit or a hospitalization after randomization
- Change from baseline in pre-bronchodilator FEV1
- Change from baseline in pre-bronchodilator Inspiratory Capacity (IC), Expiratory Reserve Volume (ERV), Inspiratory Reserve Volume (IRV), Inspiratory Vital Capacity (VCIN), Expiratory Vital Capacity (VCEX), and Maximum Vital Capacity (VCMAX)
- Change from baseline in asthma symptom score (total, daytime, and night time)
- Change from baseline in rescue medication use
- Change from baseline in home lung function (morning and evening PEF)
- Change from baseline in the number of nights with awakening due to asthma requiring rescue medication
- Change from baseline in ACQ-6
- Change from baseline in AQLQ(S)+12
- PK parameters
- ADA

**Statistical Analysis Plan**

The primary endpoint was evaluated an analysis of covariance (ANCOVA) model. The change from baseline in pre-dose pre-BD FEV1 were compared between the two doses of benralizumab and placebo using a repeated measures analysis on patients with a baseline FEV1 measure and at least one post-randomization FEV1. Multiplicity was adjusted for the primary endpoint using Hochberg procedure. Readers are referred to the statistical review for additional details.

**Protocol Amendments**

- Protocol amendment 1: April 10, 2015 (made after the start of patient recruitment)
    - peripheral blood eosinophil enrollment criteria lowered from ≥ 300 cells/mcl to ≥ 150 cells/mcl.
    - Additional secondary objectives and endpoints added

[12] Same exacerbation definition in the CALIMA and SIROCCO studies; however the increase in corticosteroid dosing for the exacerbation was stipulated to be at least one level higher than the current titration step.

- Protocol amendment 2: February 10, 2016
    - The timing of database lock and un-blinding procedures were clarified to occur after the last patient had completed the end of treatment visit.

*Reviewer's Comment: The protocol amendments do not impact the interpretation of the efficacy and safety data from the trial. The lower peripheral blood eosinophil enrollment criterion allows for broader assessment of efficacy and safety parameters in patients who may receive the drug in clinical practice.*

**Data Quality and Integrity: Sponsor's Assurance**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures. The sponsor also attests that performs a GCP audit program, including use of Global Quality Assurance group which operates independently of the study monitors.

### 6.4.2. Study Results

**Compliance with Good Clinical Practices**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures. The sponsor also attests that performs a GCP audit program, including use of Global Quality Assurance group which operates independently of the study monitors.

**Financial Disclosure**

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 13.2 of this review for additional details.

**Patient Disposition**

Of the 369 patients enrolled in the study, 271 (73%) entered the run-in period/OCS optimization phase and 220 (60%) were randomized to receive treatment. Of these, 72, 73, and 75 were randomized to receive 30 mg Q4, 30 mg Q8 and placebo respectively. A total of 207 patients (94%) completed treatment with 13 (6%) patients discontinuing treatment. Similar numbers and reasons for discontinuation are seen across treatment groups. Readers are referred to the statistical review for summary tables of the disposition data.

**Protocol Violations/Deviations**

A total of 54 patients (25%) had at least one protocol deviation during the study with a higher

incidence in the placebo group (27[6%]) compared to benralizumab 30 mg Q4W (15[21%]) or Q8W groups (12 [16%]). All patients with deviations who were already randomized and dosed were allowed to continue in the study unless withdrawn for safety reasons. The most common deviations related to the OCS dose titration criteria (22%) followed by failure to meet the inclusion/exclusion criteria (5%). These deviations are summarized in Table 18.

**Table 18: ZONDA Protocol Deviations (FAS)**

| Protocol Deviation Coded Term | 30 Q4 N=72 | 30 Q8 N=73 | Placebo N=75 | Total N=220 |
|---|---|---|---|---|
| Total Number of patients with an important deviation, n (%) | 15 (21) | 12 (16) | 27 (36) | 54 (25) |
| Optimized OCS dose not reached at least 2 weeks (-3 days) prior to randomization, | 1 (1) | 1 (1) | 8 (11) | 10 (4.5) |
| Patients who experienced an asthma exacerbation after V6 and were not maintained at the protocol-specified final OCS dose level after the resolution of the exacerbation, | 3 (4) | 6 (8) | 13 (17) | 22 (10) |
| Patients who were down-titrated but did not meet the down-titration criteria, | 4 (6) | 2 (3) | 4 (5) | 10 (5) |
| Patients who were not down-titrated but met the down-titration criteria n (%) | 3 (4) | 2 (3) | 6 (8) | 11 (5) |
| Oral corticosteroid dose titration criteria which could have impacted the final OCS dose, n (%) | 4 (6) | 2 (3) | 2 (3) | 8 (4) |

Source: Modified from Statistical Review Table 4

*Reviewer's Comment: A high number of protocol deviations are seen in this trial (25%) with most deviations related to failure to adhere to protocol recommended OCS titration. While these deviations may impact the interpretation of the efficacy data, an OCS reduction trial must allow for investigator discretion with OCS titration to maintain patient safety, so deviations from the recommended titrations schemes are expected. Two of the deviations have notable imbalances between the placebo and active treatment arms: 1) optimized OCS dose not reached at least 2 weeks prior to randomization (placebo: 8 patients; 30Q4: 1; 30Q8: 1) and 2) failure to adhere to protocol-specified OCS dosing following an exacerbation (placebo: 13, 30Q4: 3, 30Q8: 6).*

*Regarding the failure to optimize prior to randomization, the reason for the imbalance is unclear since one would expect a more equal distribution following randomization. A manual review of the patients with protocol deviations by this reviewer finds that 5 of the deviations favor benralizumab, 3 would favor placebo and 2 have an unknown impact as only limited details were provided for these cases. A sensitivity analysis conducted by the statistical reviewer*

*removing these subjects from the trial shows no difference in the efficacy trends.*

*Regarding the OCS failure to adhere to protocol dose following an exacerbation, the applicant conducted a sensitivity analysis assigning the protocol recommended dose to these subjects. This analysis was confirmed by the FDA statistical reviewer and similar efficacy findings are seen in the sensitivity analysis.*

*As for the other deviations, the failure to down-titrate and the number down-titrated without meeting criteria are roughly equal. This review finds that while high, the protocol deviations in this trial are unlikely to impact the interpretability of the results.*

**Demographic Characteristics**

Overall, patient demographics are balanced across treatment arms. Trial participants were primarily Caucasian (93%), female (61%), with a mean BMI of 30 and average age of 51. Only 18% of the trial was enrolled in North America; however, as discussed in Section 7.1.3 and Section 8.6 of this review, no regional differences in efficacy or safety for the US population in this development program were observed.

**Table 19: ZONDA Demographics (FAS)**

| | Overall Population | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30mg Q4 N=72 | 30 Q 8 N=73 | Placebo N=75 | Total N=220 | 30 Q4 N=62 | 30 Q8 N=61 | Placebo N=64 | Total N=187 |
| **Age, n (%)** | | | | | | | | |
| >=18 - <50 | 33 (46) | 29 (40) | 36 (48) | 98 (45) | 30 (48) | 25 (41) | 33 (52) | 88 (47) |
| >=50 - <65 | 31 (43) | 32 (44) | 31 (41) | 94 (43) | 25 (40) | 26 (43) | 26 (41) | 77 (41) |
| >=65 – 75 | 8 (11) | 12 (16) | 8 (11) | 28 (13) | 7 (11) | 10 (16) | 5 (8) | 22 (12) |
| **Sex, n (%)** | | | | | | | | |
| F | 40 (56) | 47 (64) | 48 (64) | 135 (61) | 32 (52) | 38 (62) | 41 (64) | 111 (59) |
| M | 32 (44) | 26 (36) | 27 (36) | 85 (39) | 30 (48) | 23 (38) | 23 (36) | 76 (41) |
| **Region, n (%)** | | | | | | | | |
| Eastern Europe | 26 (36) | 27 (37) | 28 (37) | 81 (37) | 21 (34) | 20 (33) | 21 (33) | 62 (33) |
| Europe | 24 (33) | 22 (30) | 23 (31) | 69 (31) | 20 (32) | 21 (34) | 21 (33) | 62 (33) |
| North America | 13 (18) | 13 (18) | 14 (19) | 40 (18) | 12 (19) | 11 (18) | 12 (19) | 35 (19) |

| | Overall Population | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30mg Q4 N=72 | 30 Q 8 N=73 | Placebo N=75 | Total N=220 | 30 Q4 N=62 | 30 Q8 N=61 | Placebo N=64 | Total N=187 |
| Rest of the World | 6 (8) | 6 (8) | 7 (9) | 19 (9) | 6 (10) | 6 (10) | 7 (11) | 19 (10) |
| Asia | 3 (4) | 5 (7) | 3 (4) | 11 (5) | 3 (5) | 3 (5) | 3 (5) | 9 (5) |
| **Race, n (%)** | | | | | | | | |
| White | 69 (96) | 66 (90) | 70 (93) | 205 (93) | 59 (95) | 56 (92) | 60 (94) | 175 (94) |
| Asian | 3 (4) | 5 (7) | 4 (5) | 12 (5) | 3 (5) | 3 (5) | 3 (5) | 9 (5) |
| Black or African American | 0 | 1 (1) | 1 (1) | 2 (<1) | 0 | 1 (2) | 1 (2) | 2 (1) |
| Other | 0 | 1 (1) | 0 | 1 (<1) | 0 | 1 (2) | 0 | 1 (<1) |

Source: Statistical Review Table 37

**Table 20: ZONDA Baseline Disease Characteristics (FAS)**

| | All Subjects | | | | Baseline blood eosinophil ≥300/µL | | | |
|---|---|---|---|---|---|---|---|---|
| | 30 Q4 N = 72 | 30 Q8 N = 73 | Placebo N = 75 | Total N = 220 | 30 Q4 N = 62 | 30 Q8 N = 61 | Placebo N = 64 | Total N = 187 |
| **Median Baseline Eosinophil Counts, cells/µL** | | | | | | | | |
| Local lab | 462 | 437 | 535 | 475 | 510 | 493 | 580 | 520 |
| **Lung Function** | | | | | | | | |
| Pre-BD % predicted, mean | 57 | 59 | 62 | 60 | 59 | 60 | 62 | 60 |
| Pre BD $FEV_1$/FVC, mean | 59 | 59 | 62 | 60 | 59 | 59 | 62 | 60 |
| % $FEV_1$ Reversibility | 24 | 25 | 23 | 24 | 23 | 24 | 22 | 23 |
| **Number exacerbations in previous month, n (%)** | | | | | | | | |
| 1 | 24 (33) | 21 (29) | 24 (32) | 69 (31) | 18 (29) | 19 (31) | 20 (31) | 57 (31) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 2 | 19 (26) | 23 (32) | 22 (29) | 64 (29) | 17 (27) | 17 (28) | 19 (30) | 53 (28) |
| 3 or more | 29 (40) | 29 (40) | 29 (39) | 87 (40) | 27 (44) | 25 (41) | 25 (39) | 77 (41) |
| **Smoking Status, n (%)** | | | | | | | | |
| Current | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Former | 17 (24) | 12 (16) | 17 (23) | 46 (21) | 14 (23) | 10 (16) | 13 (20) | 37 (20) |
| Never | 55 (76) | 61 (84) | 58 (77) | 174 (79) | 48 (77) | 51 (84) | 51 (80) | 150 (80) |

**Source: Statistical Review Table 38**

*Reviewer's Comment: As would be expected, patients in ZONDA have even more severe disease than those enrolled in SIROCCO/CALIMA based on their need for background OCS dosing a more frequent exacerbation history despite the use of OCS.*

A majority of subjects remained on the same OCS at study entry despite the optimization phase. Importantly, this does not appear to be driven by the number of historically optimized patients which are represented in parentheses in **Table 21**.

**Table 21: ZONDA: Overall OCS Total Daily Dose (mg) at Study Entry to Optimized Baseline (FAS)**

| OCS dose at study entry | N | Number of patients [a] Baseline dose (mg) 7.5 | 10 [b] | 12.5 | 15 | 17.5 | 20 | 22.5 [b] | 25 | 30 | 35 | 40 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7.5 | 31 (5) | 27 (5) | 4 | | | | | | | | | |
| 10 [b] | 82 (17) | 10 | 67 (17) | 2 | 2 | | 1 | | | | | |
| 12.5 | 6 (2) | | | 6 (2) | | | | | | | | |
| 15 | 17 (5) | | 2 | | 15 (5) | | | | | | | |
| 17.5 | 1 (0) | | | | | 1 | | | | | | |
| 20 | 58 (15) | 1 | 4 | | 10 | | 43 (15) | | | | | |
| 22.5 [b] | 2 (2) | | | | | | | 2 (2) | | | | |
| 25 | 3 (0) | | | | | | 1 | | 2 | | | |
| 30 | 12 (1) | | | | | | 1 | | 2 | 8 (1) | 1 | |
| 40 | 8 (1) | | | | | | | | | | | 8 (1) |
| Total | 220 (48) | 38 (5) | 77 (17) | 8 (2) | 27 (5) | 1 | 46 (15) | 2 (2) | 4 | 8 (1) | 1 | 8 (1) |

[a] Grey shading indicates patients who were on the same OCS total daily dose at study entry and at optimised baseline. Numbers in parenthesis represent the number of historically optimised patients.
[b] Patient E2603002 had a dose of 11.5 mg at study entry and baseline dose and was included in the 10 mg category. Patient E1001010 had a dose of 23.5 mg at study entry and baseline and was included in the 22.5 mg category (Appendix 12.2.6.1.1 and Appendix 12.2.6.1.2).
N Number of patients at study entry; OCS Oral corticosteroids.

Source: ZONDA CSR Table 17

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Compliance was generally high, ranging from 98.5 to 98.9%, as would be expected of a study in where investigational product is administered at study site visits. A total of 16 patients used disallowed concomitant medications with similar use between active treatment and placebo.

*Reviewer's Comment: Similar to the exacerbation trials, the use of disallowed study medication was use of regularly scheduled SABAs which would not impact the efficacy findings in support of benralizumab.*

**Efficacy Results – Primary Endpoint**

Both dosing regimens of benralizumab demonstrate a statistically significant decrease in the percent reduction of OCS dose from baseline to final dose at Week 28. No difference between the dosing regimens is observed. Notably, greater than 33% of patients were able to decrease his/her dose by 90 to 100% compared with only 12% of placebo patients. In contrast approximately 25% of benralizumab treated patients maintained his/her oral corticosteroid dose compared to placebo.

**Table 22: ZONDA Percent Reduction from Baseline in Daily OCS dose at Week 28 (FAS)**

| | **30 Q4 N = 72** | **30 Q8 N = 73** | **Placebo N = 75** |
|---|---|---|---|
| **Descriptive Statistics** | | | |
| Median % Reduction in Daily OCS Dose from Baseline | 75.0 | 75.0 | 25.0 |
| 95% CI (Distribution free) | (50.0, 83.3) | (60.0, 87.5) | (0.0, 33.3) |
| **Wilcoxon Rank Sum Test** | | | |
| Hodges-Lehmann Estimate of Location Shift for Benralizumab vs. Placebo | 33.3 | 37.5 | |
| 95% CI (Moses CI) | (16.7, 50.0) | (20.8, 50.0) | |
| p value | <.0001 | <.0001 | |

Source: Statistical Review Table 39

Similar to the exacerbation trials, a greater treatment effect is seen for the patients with higher eosinophil counts.

**Table 23: ZONDA Percent OCS Reduction at Week 28 by Baseline Blood Eosinophil Count (FAS)**

| | **30 Q4 N = 72** | **30 Q8 N = 73** | **Placebo N = 75** |
|---|---|---|---|

| | | | |
|---|---|---|---|
| **≥ 150 to <300 eosinophils/µL** | | | |
| N | 10 | 12 | 11 |
| mean % reduction | 40 | 47 | 50 |
| **≥ 300 eosinophils/µL** | | | |
| N | 62 | 61 | 64 |
| mean % reduction | 58 | 60 | 15 |

**Source: modified from ZONDA CSR Table 19**

*Reviewer's Comment: The efficacy data from this trial provide additional support for the efficacy of benralizumab as a treatment in severe asthmatics.*

**Data Quality and Integrity – Reviewers' Assessment**

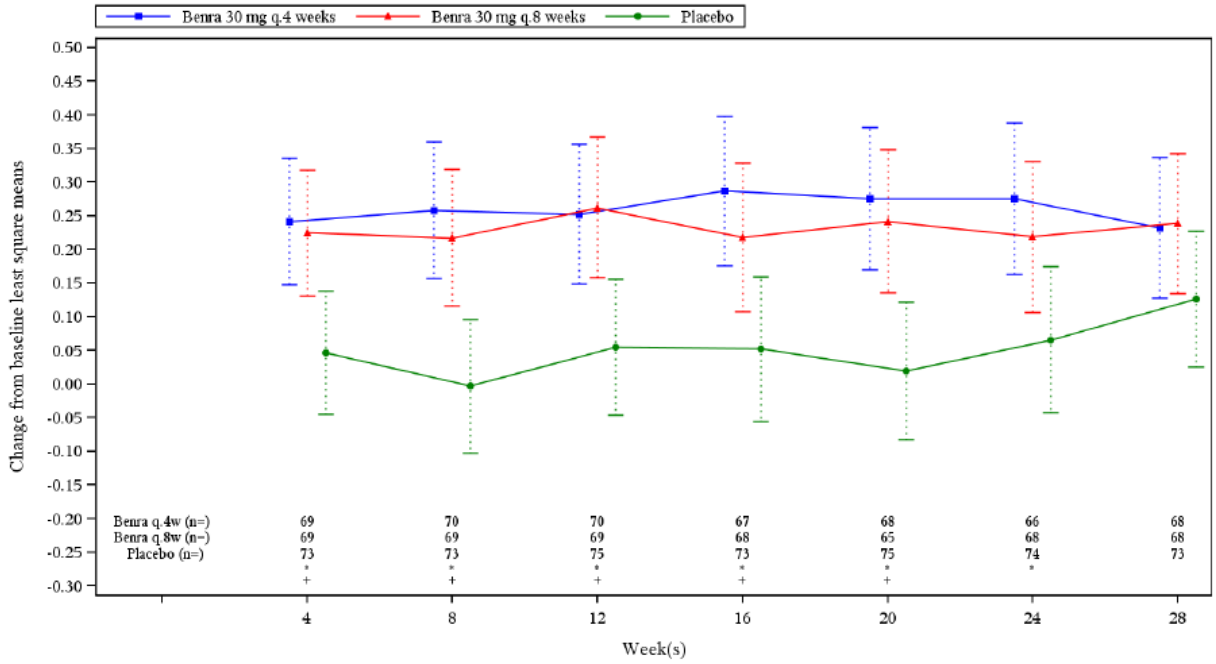
No data quality of integrity issues were identified by this reviewer for this trial.

**Efficacy Results – Secondary and other relevant endpoints**

The ZONDA trial also evaluated the annual exacerbation rate, pulmonary function, ACQ6 and AQLQ(S)+12.

In ZONDA both dosing regimens demonstrate a numeric improvement in in FEV1 at Week 28 compared with placebo; however, results were not statistically significant. The LS mean change from baseline compared to placebo was 0.105 L (95CI % -0.040, 0.251; p value 0.153) and 0.112L (95CI% -0.033, 0.258; p value 0.129) for the 30 mg Q4 and 30 mg Q8 dosing groups respectively.

**Figure 10: ZONDA: Pre-bronchodilator FEV1 Change from Baseline by Time Point (FAS)**




**Source: ZONDA CSR Figure 11.6.2.5**

For the patient reported outcomes, both dosing groups in the trial demonstrate a higher number of AQLQ and ACQ-6 responders than placebo. The trial also demonstrates a numeric reduction in the exacerbation rate (Table 24).

**Table 24: ZONDA Additional Secondary Endpoints (FAS)**

| | **30 mg Q4 N = 72** | **30 mg Q8 N = 73** | **Placebo N = 75** |
|---|---|---|---|
| **AQLQ(S)+12** | | | |
| % responder Week 28 | 60 | 60 | 52 |
| Odd ratio | 1.538 | 1.783 | -- |
| 95% CI | 0.773, 3.060 | 0.882, 3.605 | -- |
| **ACQ-6** | | | |
| % responder | 57 | 63 | 55 |
| Odd ratio | 1.165 | 1.661 | -- |
| 95% CI | 0.592, 2.295 | 0.826, 3.340 | -- |
| **Annual asthma exacerbation** | | | |
| AER[1] | | | |
| Estimate | 0.82 | 0.54 | 1.80 |
| 95% CI | 0.54, 1.24 | 0.33, 0.87 | 1.32, 2.46 |

| | 30 mg Q4 N = 72 | 30 mg Q8 N = 73 | Placebo N = 75 |
|---|---|---|---|
| **Number of exacerbations per pt, n (%)** | | | |
| 0 | 53 (74) | 56 (77) | 36 (48) |
| 1 | 11 (15) | 13 (18) | 19 (25) |
| 2 | 5 (7) | 4 (6) | 13 (17) |
| 3 | 2 (3) | 0 | 3 (4) |
| ≥ 4 | 1 (1) | 0 | 4 (5) |
| **Pts ≥ 1 exacerbation with hospitalization or ER visit[2]** | | | |
| n, (%) | 4 (6) | 1 (1) | 9 (12) |
| [1]model estimated<br>[2] investigator assessment | | | |

**Source: Modified from ZONDA CSR Table 22, 23, 11.2.11.4, 11.2.13.4**

**Dose/Dose Response**

Similar to the exacerbation trials, the from this steroid reduction trial do not support selection of the more frequent dosing regimen.

**Durability of Response**

As demonstrated by the FEV1 time curve from the trial, both dosing benralizumab dosing regiments in the trial maintained similar treatment effects on FEV1 throughout the treatment duration (Figure 10).

**Persistence of Effect**

The trial was not designed to provide information on the persistence of the treatment effect once benralizumab is discontinued.

**Additional Analyses Conducted on the Individual Trial**

Not applicable.

## 6.5. BISE

### 6.5.1. Study Design

**Overview and Objective**

*Primary Objective:*

- To evaluate the effect of benralizumab on pulmonary function in mild to moderate asthmatic patients

*Select Secondary Objectives:*

- To assess the effect of benralizumab on asthma symptoms and other asthma control metrics
- To assess the effect of benralizumab on asthma related and general health-related quality of life

**Trial Design**

BISE was a randomized, double-blind, parallel-group, placebo-controlled study evaluating 30 mg Q4 in adult patients with mild to moderate persistent asthma.[13] Patients were stratified by eosinophil count (<300 or ≥ 300 cells/mcl) and region. After enrollment patients entered a 2 to 4 week screening-run-in period and all patients were switched to either 180 or 200 mcg of budesonide dry powder inhaler (per local approved dose). Following run-in patients entered a 12 week treatment period with benralizumab or placebo administered at Week 0, 4, and 8. Follow up visits were conducted at Week 16 and 20.

**Study Endpoints**

*Primary Endpoint*:

- Change from baseline in pre-dose $FEV_1$ at Week 12

*Select Secondary Endpoints:*

- Change from baseline in mean ACQ6 at Week 12
- Change from baseline in AQLQ(12)+12 at Week 12

**Statistical Analysis Plan**

The efficacy analyses were performed on the on the Full Analysis Set (FAS) which included all patients who were randomized and received any investigational product using an Intent-to-Treat (ITT) principle.

**Protocol Amendments**

There was a single protocol amendment which clarified the tuberculosis exclusion criteria, what defined background asthma therapy and the timing of Visits 1, 2, 3.

[13] Inclusion criteria allowed for the enrollment of patients on low to medium dose ICS (100 to 500 mcg fluticasone dry powder formulation total daily dose) with or without other controller medication e.g., LTRA and/or theophylline or low dose ICS/LABA combination therapy and a morning pre-bronchodilator FEV1 > 50% to ≤ 90%.

*Reviewer's Comment: Neither of these changes alter the interpretation of the efficacy or safety data from this trial.*

**Data Quality and Integrity: Sponsor's Assurance**

The CSR outlines that quality of study data was assured though site monitoring, investigator training, and the use of data management procedures. The sponsor also attests that it undertakes a GCP audit program, including use of Global Quality Assurance group operating independently of the study monitors.

### 6.5.2. Study Results

**Compliance with Good Clinical Practices**

The CSR contains a statement that this study was performed in compliance with Good Clinical Practice.

**Financial Disclosure**

The financial disclosure information from this trial does not impact the interpretation of the efficacy or safety results. See Section 13.2 of this review for additional details.

**Patient Disposition**

A total of 211 patients were randomized to receive treatment. Of these, 106 were randomized to receive 30 mg Q4 and 105 patients to receive placebo. A total of 197 patients completed treatment with 14 (6.6 %) patients discontinuing treatment. Similar numbers and reasons for discontinuation are seen across treatment groups.

**Protocol Violations/Deviations**

A total of 10 patients had at least one protocol deviation with similar numbers seen between the benralizumab and placebo treatment groups. The majority of deviations were related to the inclusion/exclusion criteria. In addition, 3 patients in the placebo group were dosed with investigational product that had been stored outside recommended temperature range.

*Reviewer's Comment: Use of investigational product stored outside the recommended temperature range has the potential to impact efficacy of the product. However in this case, all patients received placebo making this less of a concern. Other deviations were balanced across treatment arms. Overall, the nature and number of events are unlikely to impact the analysis of the study data.*

**Table 25: BISE: Demographic Characteristics (FAS)**

| | 30 Q4 N=106 | Placebo N = 105 | Total N = 211 |
|---|---|---|---|
| **Sex** | | | |
| Male | 44 (42) | 38 (36) | 82 (39) |
| Female | 62 (59) | 67 (64) | 129 (61) |
| **Age** | | | |
| Mean years (SD) | 48 (14) | 51 (13) | 50 (14) |
| Median (years) | 51 | 52 | 52 |
| Min, max (years) | 18 - 75 | 22 - 73 | 18 – 75 |
| **Age Group, n (%)** | | | |
| ≥ 18 - < 50 | 49 (46) | 44 (42) | 93 (44) |
| ≥ 50 - < 65 | 43 (41) | 46 (44) | 89 (42) |
| ≥ 65 – 75 | 14 (13) | 15 (14) | 29 (14) |
| **Race** | | | |
| White | 98 (93) | 99 (94) | 197 (93) |
| Black or African American | 7 (7) | 4 (4) | 11 (5) |
| Asian | 1 (1) | 0 | 1(1) |
| Other | 0 | 2 (2) | 2 (1) |
| **Ethnicity** | | | |
| Hispanic or Latino | 6 (6) | 3 (3) | 9 (4) |
| Not Hispanic or Latino | 100 (94) | 102 (97) | 202 (96) |
| **BMI (kg/m²)** | | | |
| mean | 30 | 29 | 30 |
| **Region** | | | |
| United States | 29 (27) | 23 (22) | 52 (25) |
| Rest of the World[1] | 77 (73) | 82 (78) | 159 (75) |
| [1] Canada 18 (5%); Germany (57 (27%); Hungary 40 (19%); Poland 25 (12%); Slovakia 19 (9%); | | | |

Source: BISE CSR Table 10, and 11.1.2

**Table 26: BISE: Baseline Characteristics (FAS)**

| | 30 mg Q4 N = 106 | Placebo N = 105 | Total N = 211 |
|---|---|---|---|
| **Baseline eosinophil count[1]** | | | |
| Mean (SD) | 255 (203) | 268 (205) | 261 (204) |
| Median | 205 | 210 | 204 |
| **Lung Function Characteristics** | | | |
| mean % predicated pre-BD FEV1 | 70 | 72 | 71 |

| | | | |
|---|---|---|---|
| Pre-BD FEV/FVC ratio, mean | 68 | 65 | 67 |
| Reversibility, mean % | 22 | 20 | 21 |
| **Time since asthma diagnosis (years)** | | | |
| Median | 15 | 13 | 14 |
| **# exacerbation in last 12 months** | | | |
| % with 0 | 82 | 85 | 172 |
| % with 1 | 9 | 13 | 11 |
| % with 2 | 6 | 5 | 6 |
| **Asthma treatment prior to randomization n, %** | | | |
| ICS[2] | 106 (100) | 104[3] (99) | 210 (100) |
| LABA | 65 (61) | 64 (61) | 129 (61) |
| LTRA | 14 | 10 | 24 |
| **Smoking Status, n (%)** | | | |
| Never smoked | 87 (82) | 69 (66) | 156 (74) |
| Current smoker | 2 (2) | 0 | 2 (1) |
| Former smoker | 17 (16) | 36 (34) | 53 (25) |

[1] assessed via central laboratory at Visit 1
[2] all patients were on low to medium dose ICS or or low-dose ICS/LABA as per eligibility criteria
[3] 1 patient did not have any data collected for this field of the eCRF

Source: Modified from BISE CSR Tables 10, 11, 12, 11.1.6, 11.1.9, 11.1.17

*Reviewer's Comment: BISE enrolled a milder disease population than in SIROCCO, CALIMA or ZONDA. The enrolled patients have mild to moderate persistent asthma based on lung function criteria and concomitant medical treatments they were receiving.*

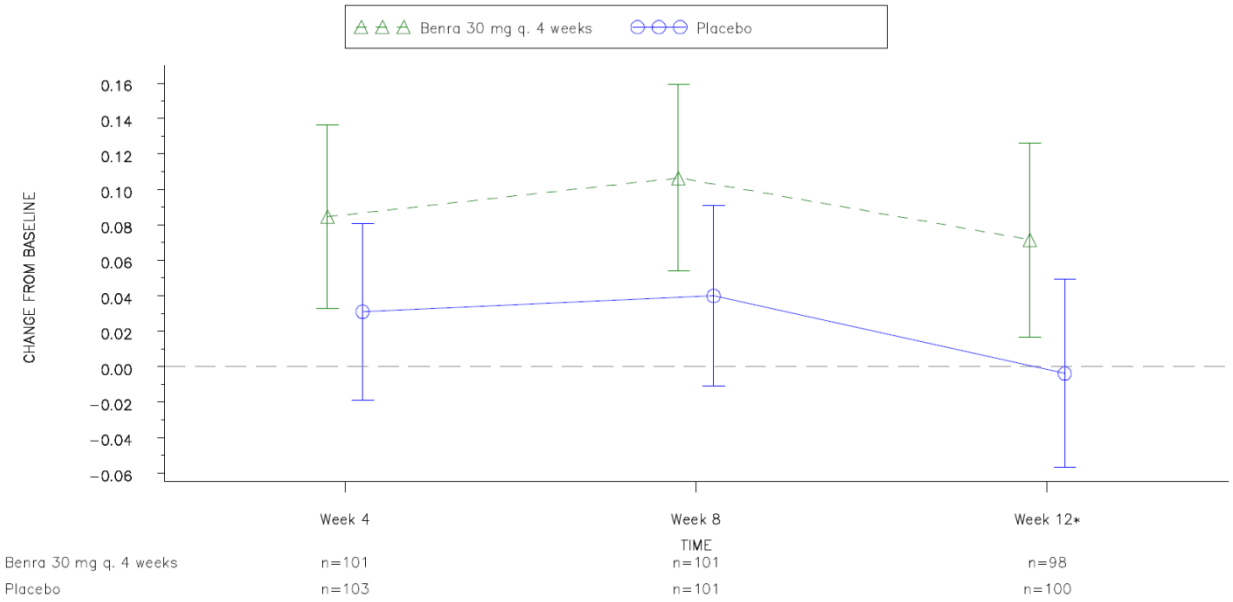
**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Mean compliance for benralizumab was 100% for each treatment group which is not unexpected for a 12 week study administering study treatment at the study center every 4 week for 3 treatment visits. There was no use of concomitant treatments that were disallowed by the protocol.

**Efficacy Results – Primary Endpoint**

The change from baseline in pre-PD FEV1 (L) at Week 12 demonstrates a difference of 0.80L (95% CI 0, 0.150, p value 0.040) between benralizumab treated subjects and placebo. Figure 11 outlines the change from baseline over the course of the study for benralizumab and placebo treated subjects.

**Figure 11:BISE: Pre-BD FEV1 Change from Baseline by Time Point (FAS)**




Source: BISE CSR Figure 3

Similar to the trends seen in the pivotal efficacy trials, the summary statistics between patients with low and high eosinophil counts reveals a larger impact in patients with benralizumab counts ≥ 300 cells/µL (Table 27)

**Table 27: BISE Change from baseline FEV1 by Eosinophil Count (FAS)**

| | ≥ 300 cells/µL | | < 300 cells/µL | |
|---|---|---|---|---|
| | **30 mg Q4 N = 28** | **Placebo N = 33** | **30 mg Q4 N = 78** | **Placebo N = 72** |
| Mean Δ from baseline at Week 12 (L) | 0.13 | -0.03 | 0.03 | -0.01 |

Source: BISE CSR Table 15

*Reviewer's Comment: The BISE trial demonstrates a statistically significant benefit in asthmatics with mild to moderate persistent disease. While an 80 ml improvement is not insubstantial in patients on maximal current therapeutic options, patients with milder asthmatic disease have multiple alternative therapeutic options to provide lung function improvements including increasing inhaled corticosteroid dosing and/or adding a controller therapy.*

**Data Quality and Integrity – Reviewers' Assessment**

No data quality or integrity concerns were identified by this reviewer.

**Efficacy– Secondary and other relevant endpoints**

ACQ and AQLQ were evaluated in the BISE study as secondary endpoints. Responder analyses (using MCID of 0.5) are summarized in Table 28. No adjustment for multiplicity was made for these secondary endpoints.

**Table 28: BISE ACQ-6 and AQLQ (FAS)**

| | 30 mg Q4<br>N = 72 | Placebo<br>N = 75 |
|---|---|---|
| **AQLQ(S)+12** | | |
| % responder Week 28 | 43 | 32 |
| Odd ratio | 1.65 | |
| 95% CI | 0.92, 2.96 | |
| **ACQ-6** | | |
| % Responder | 55 | 50 |
| Odd ratio | 1.25 | |
| 95% CI | 0.72, 2.19 | |

Source: BISE CSR Table 16, Table 18

**Dose/Dose Response**

Only a single dose was evaluated in this trial, thus dose/dose response cannot be commented upon.

**Durability of Response**

No loss of effect over time is seen in the FEV1 time curve from this trial (Figure 11).

**Persistence of Effect**

Pulmonary function was not assessed at the follow up visit, thus the impact on pulmonary function after treatment discontinuation cannot be assessed.

**Additional Analyses Conducted on the Individual Trial**

No additional analyses were conducted on the data from this trial.

# 7 Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy Across Trials

### 7.1.1. **Primary Endpoints**

Efficacy of benralizumab was demonstrated in all three pivotal trials in this development program. Both exacerbation trials demonstrate a statistically significant and clinically meaningful reduction in asthma exacerbations in patients with severe asthma on high dose ICS/LABA. In addition, the steroid reduction trial demonstrates that benralizumab treatment allows more patients to reduce the required dose of oral corticosteroids needed to maintain asthma control.

An increase in the treatment benefit is consistently seen in patients with higher baseline eosinophil counts compared to those with lower counts supporting an indication in a subset of asthma patients with an eosinophilic phenotype. In addition, this review supports restricting the indication to patients with severe disease as these were the patients enrolled in the pivotal phase 3 program. A subgroup analysis conducted by the sponsor also demonstrates an increased treatment response in patients with a more frequent exacerbation history. While the BISE trial suggests benralizumab may provide a lung function benefit in milder patients, these study results were not replicated, the trial was not long enough to evaluate the proposed dosing regimen, and patients with milder disease have multiple alternative treatment options with well-established risk benefit profiles.

With regards to the ER and/or hospitalization exacerbation data, the statistical analysis plan pre-specified an integration of these data as there were low anticipated event rates in each trial. These data are summarized in Table 29. While the pooled data numerically favors active treatment compared to placebo; this effect was primarily driven by the results from SIROCCO trial which demonstrated a treatment-related reduction while CALIMA demonstrated similar rates across the three treatment arms (see Table 9 and Table 16).

**Table 29: Annual exacerbation rate associated with adjudication ER visit and/or hospitalization for SIROCCO and CALIMA in eosinophil high population[1] integrated data (FAS)**

| | **30 Q4 N = 516** | **30 Q8 N = 506** |
|---|---|---|
| **Exacerbation requiring adjudicated ER visit or hospitalization** | | |
| Rate ratio (benralizumab/placebo) | 0.71 | 0.62 |
| 95% confidence interval | 0.47, 1.07 | 0.41, 0.95 |
| p-value | 0.106 | 0.029 |
| **Adjudicated hospitalization** | | |
| Rate ratio (benralizumab/placebo) | 0.73 | 0.80 |
| 95% confidence interval | 0.42, 1.28 | 0.46, 1.39 |
| p-value | 0.270 | 0.432 |

[1]peripheral blood eosinophil count ≥ 300 cells/mcl and high-dose ICS population

**Source: ISE Table 17**

### 7.1.2. Secondary and Other Endpoints

As discussed throughout Section 6, FEV1 and ACQ and AQLQ were evaluated in the phase 3 trials. For patients receiving the Q8 dosing regimen, improvements of 120 to 159 ml in the FEV1 are seen in severe asthma patients with peripheral blood eosinophil counts ≥ 300 cells/µL receiving high dose ICS/LABA in the exacerbation trials, and improvements of 112 ml are seen in severe asthma patients requiring OCS in the steroid reduction trial. While numeric improvements were seen in patients with lower eosinophil counts in these studies, the treatment effect was reduced. The BISE trial also demonstrates improvements in FEV1, albeit with a smaller treatment effect.

In addition to improvements in lung function, the patient reported outcomes demonstrate treatment related improvements in the number of responders across the program. Overall, the secondary endpoints consistently provide supportive data demonstrating the efficacy of benralizumab.

### 7.1.3. Subpopulations

A review of the efficacy data by age, race, gender and region are discussed in this section of the review.

*Adolescents*
The exacerbation trials included an evaluation of adolescent subject's age 12 to 17 years of age. Adolescent patients in the EU were randomized to the placebo or benralizumab Q8 dosing arm only to accommodate the Pediatric Committee at the European Medicines Agency. The trials enrolled patients across the full age range with a median and mean age of 14 (Table 30).

**Table 30: Enrolled Adolescents Population by Age in SIROCCO and CALIMA (FAS)**

| | 12 years old | 13 years old | 14 years old | 15 years old | 16 years old | 17 years old |
|---|---|---|---|---|---|---|
| N (%) | 22 | 16 | 19 | 20 | 17 | 14 |

Source: Reviewer generated using ISE ADSL dataset

Baseline demographics and disease characteristics between the adolescent and overall population in SIROCCO and CALIMA are summarized in Table 31. The adolescent population has fewer females and a higher average BMI than the overall population. While the mean baseline eosinophil counts were similar to the overall population, it is notable that the adolescent patients had a higher baseline % predicated $FEV_1$ and lower mean exacerbation rate. In

addition, 37% of the enrolled adolescent patients were on medium-dose ICS.

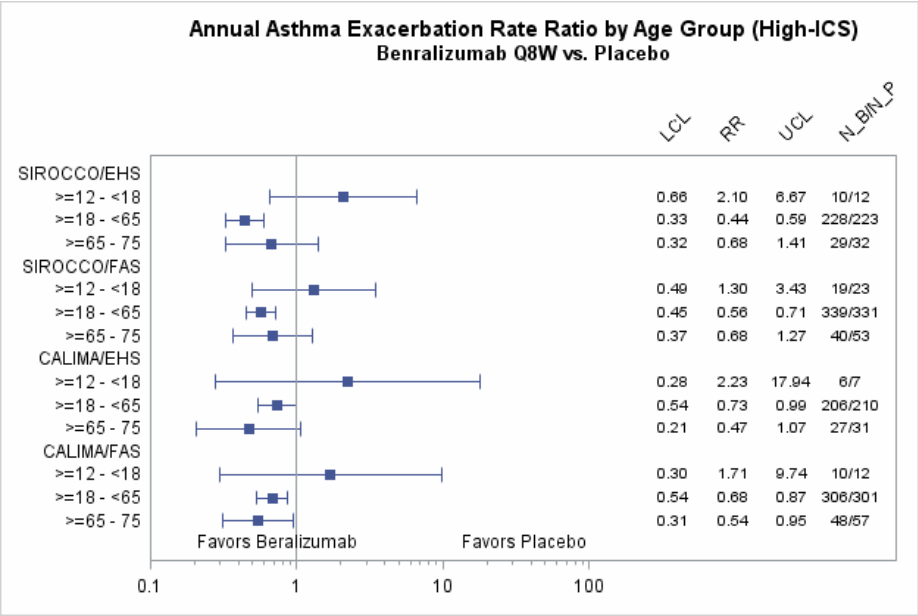
**Table 31: Adolescent and total population demographics and baseline characteristics in SIROCCO and CALIMA (FAS)**

| | Overall Population | | |
|---|---|---|---|
| | **12 to 17 years old SIROCCO + CALIMA N = 108** | **SIROCCO N = 809** | **CALIMA N = 728** |
| Female, n (%) | 45 (42) | 796 (66) | 807 (62) |
| Caucasian, n (%) | 89 (82) | 874 (73) | 1101 (84) |
| Mean BMI ($kg/m^2$) | 23 | 29 | 29 |
| Median # years since asthma diagnosis | 9 | 15 | 16 |
| % predicated FEV1 at baseline | 72 | 57 | 58 |
| % reversibility | 27 | 26 | 27 |
| Pre-BD $FEV_1$/FVC | 74 | 61 | 61 |
| Mean exacerbation history | 2.4 | 2.9 | 2.7 |
| Local mean baseline eosinophil count (cells/µL), median | | 379 | 380 |

**Source: Modified from Summary of Clinical Efficacy Table 10, Table 11 SIROCCO CSR Tables 11, 12, 13, CALIMA CSR Tables 11, 12, 13**

The point estimate for the AER in both exacerbation studies for both dose groups favors placebo in the adolescent subgroup with no trend for an increased benefit in patients with higher baseline eosinophil counts. Wide confidence intervals crossing 1 are noted indicating uncertainty in the results. Data from the Q8 dose group are presented in Figure 12. Similar findings are seen for the Q4 dose group. There is no consistent support for a treatment-related benefit demonstrated by secondary endpoints in the adolescent population enrolled in these trials either. Readers are referred to the statistical review for additional details.

**Figure 12: Annual Exacerbation Rate by Age in SIROCCO and CALIMA**

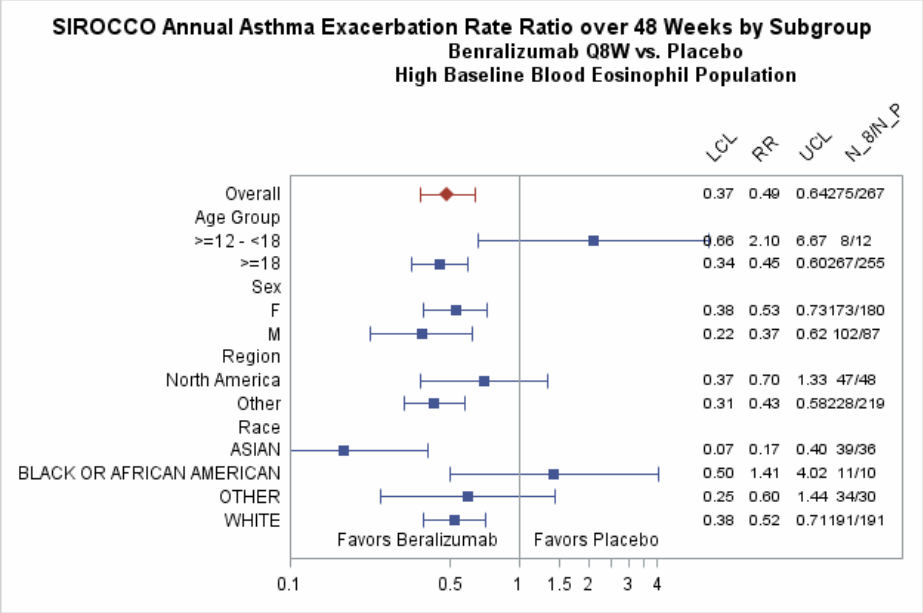



**Source: Statistical Review Figure 10**

*Additional Subgroups*

In contrast to the adolescent subgroup, patients 65 years of age and older had similar trends as the overall population. In addition, the exacerbation data were also evaluated by race, gender and region. No consistent differences from the overall population are seen. The data for Q8 dose group from SIROCCO are presented in Figure 13. Similar trends are generally seen for the Q4 dose group and in CALIMA. The exception is inconsistency in the point estimate in the Black and African American subpopulation. In some analyses, the point estimate favors treatment, while in others placebo is favored. Readers are referred to the Statistical Review for additional details.

**Figure 13: SIROCCO: Annual Exacerbation Rate Ratio by Subgroup for Q8W vs placebo in Eosinophil High Population (FAS)**




Source: Statistical Review Figure 12

*Reviewer's Comment: The point estimates consistently favors placebo in the adolescent subgroup for this clinical development program. This review recommends approval in the age group. There remains statistical uncertainty in these results as well as in the secondary endpoint data for this subgroup. While a sufficiently powered study would help to eliminate doubts regarding efficacy in this age group, given the rarity of this severe asthma phenotype, such a pediatric study would be impractical or nearly impossible to conduct. As no age-related differences in PK or PD have been identified and no safety concerns have been identified that would offset the potential for efficacy in this population, it is reasonable to extrapolate efficacy from the overall population to the adolescent subgroup and approve benralizumab in this age group.*

### 7.1.4. Dose and Dose-Response

The observed and modeling data from the phase 2, 52-week exacerbation trial provides initial support for the evaluation of a 30 mg dose group in the pivotal trials. To address the uncertainty in the dose-selection data from this trial, the applicant evaluated two dosing regimens in its phase 3 program. As discussed throughout Section 6, there is no increased treatment benefit seen for the more frequent dosing regimen.

### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

As discussed in Section 4.5.2, administration of benralizumab causes a reduction in peripheral

blood eosinophil counts within 24 hours that is maintained throughout dosing and for at least 8 weeks post-dosing. Benralizumab maintains its treatment benefit throughout dosing as demonstrated by the FEV1 by time point data in the pivotal phase 3 trials with improvement generally seen in the first 4 weeks of dosing. More precise data documenting an onset of treatment effect are not available from this program.

## 7.2. Additional Efficacy Considerations

### 7.2.1. Considerations on Benefit in the Postmarket Setting

There are no anticipated difference is how benralizumab was administered and used in the clinical trial and its expected use in the post market setting. Overall, the enrolled patient populations in the phase 3 exacerbation and steroid reduction trials closely approximate the patient population likely to receive treatment post-marketing.

### 7.2.2. Other Relevant Benefits

None.

## 7.3. Integrated Assessment of Effectiveness

The pivotal efficacy trials in this clinical development program were adequately conducted and well controlled trials that consistently demonstrate the efficacy across multiple endpoints for benralizumab 30 mg Q4 x 3 doses followed by Q8 dosing in patients with severe asthma. The enrolled patient populations in the trial are representative of a severe asthmatic population likely to use the product in clinical practice. The two exacerbation trials demonstrate statistically significant and clinically relevant treatment-related reductions in asthma exacerbations, while data from a steroid reduction trial demonstrates that more patients were able to reduce the OCS dose needed to maintain asthma control than placebo-treated patients. These primary efficacy endpoints are further supported by consistent improvements in lung function as measured by FEV1 and the number of ACQ and AQLQ responders with benralizumab treatment compared to placebo. Trends towards an increase treatment response are seen for patients with higher baseline eosinophil counts and those who exacerbate more frequently.

While the point estimates for these trials do not conclusively demonstrate efficacy in the adolescent population enrolled in this program, the wide confidence intervals crossing 1 are indicative of uncertainty in the results. Of note, the adolescents enrolled in this program appeared to have milder disease than the overall population based on prior exacerbation history and % predicated FEV1. In light of the subgroup analysis demonstrating an increased treatment benefit based on exacerbation history, this which may have impacted the efficacy

findings in the adolescent subpopulation.

# 8 Review of Safety

## 8.1. Safety Review Approach

This safety review primarily presents pooled data from the two pivotal, placebo controlled, exacerbation studies in the severe asthma population (SIROCCO and CALIMA) as the trials were of similar design, size, and duration. Additional safety data is provided from the other phase 3 trials including ZONDA, BISE and GREGALE, and the 52 week dose-selection trial MI-CP220. A pooled dataset of all on-treatment AEs and SAEs from the placebo-controlled studies was used to supplement the safety analysis. Data from these additional studies and the pooled dataset are presented where relevant. The safety analysis using data from the Safety Analysis Set (SAS) which includes all patients who received at least one dose of investigational product and are classified according to the treatment they actually receive.

Updated data from the two long-term safety extensions, BORA and MELTEMI, were provided in the 120-day safety update. While still ongoing at the time of the submission, the updated data provides just under one year of additional treatment data in approximately 1200 patients. Data from the safety update are incorporated throughout review when relevant.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

A total of 3,882 patients with asthma have been evaluated in the phase 2 and Phase 3 clinical development program for benralizumab with 2514 patients receiving at least 1 dose of benralizumab. A total of 1,387 patients enrolled in the two phase 3 exacerbation trials received benralizumab for ≥ 48 weeks (Table 32).

**Table 32: On-Treatment Exposure and Duration for Patients in the Phase 3 asthma trials**

| | Total | Benralizumab total[1] | < 12 weeks | ≥12-<24 weeks | ≥24-<48 Weeks | ≥48-<56 weeks | ≥56-<104 Weeks |
|---|---|---|---|---|---|---|---|
| **SIROCCO** | | | | | | | |
| Total N | 1204 | 797 | 14 | 27 | 91 | 563 | 102 |
| 30 Q4 | 403 | 403 | 9 | 11 | 56 | 274 | 53 |
| 30 Q8 | 394 | 394 | 5 | 16 | 35 | 289 | 49 |
| **CALIMA** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Total N | 1306 | 866 | 17 | 13 | 40 | 74 | 722 |
| 30 Q4 | 438 | 438 | 4 | 7 | 15 | 42 | 370 |
| 30 Q8 | 428 | 428 | 13 | 6 | 25 | 32 | 352 |
| **ZONDA** | | | | | | | |
| Total N | 220 | 145 | 3 | 5 | 137 | 0 | 0 |
| 30 Q4 | 72 | 72 | 1 | 3 | 68 | 0 | 0 |
| 30 Q8 | 73 | 73 | 2 | 2 | 69 | 0 | 0 |
| **Total** | **2730** | **1808** | **34** | **45** | **268** | **637** | **824** |

[1] number of patients in safety population who received at least one dose of benralizumab

Source: Modified from ISS Table 2

Data from the ongoing BORA/MELTEMI long-term extension studies were provided in the 120 day safety update using a database lock date of October 21, 2016. Similar to the presentation in the BLA application, data from patients previously enrolled in SIROCCO/CALIMA were pooled while data from patient previously enrolled in ZONDA were provided separately due to differences in the underlying patient characteristics. At the time of database lock, the safety update provided data on 637 patients in the Q4 arm for 339 days and 642 patients in the Q8 arm for 343 days from the SIRROCO/CALIMA trials. Data was also provided for 655 patients previously treated with placebo and subsequently randomized to active treatment with mean duration of treatment 337 days. Data from patients previously enrolled in ZONDA trial was provided for 67 patients in the Q4 arm, 64 patients in the Q8 arm and 66 previously on placebo with mean treatment duration of 243, 252 and 226 days respectively.

### 8.2.2. Relevant characteristics of the safety population:

Readers are referred to Section 6 for a detailed discussion of the demographics and baseline disease characteristics of the individual phase 3 trials. Table 33 provides a summary of the pooled SIROCCO/CALIMA data. In general, the safety population was predominantly female (64%), Caucasian (79%) with 15% enrolled from the United States. The demographic and baseline disease characteristics are balanced across the treatment arms.

**Table 33: Demographics Safety Population in SIROCCO/CALIMA (SAS)**

| | 30 mg Q4 N = 841 | 30 mg Q8 N = 822 | Placebo N = 847 | Total N = 2510 |
|---|---|---|---|---|
| **Age** | | | | |
| Mean, years | 50 | 48 | 49 | 49 |
| **Age group, n (%)** | | | | |
| ≥ 12 to < 18 | 24 (3) | 38 (5) | 46 (5) | 108 (4) |
| ≥ 18 to < 50 | 338 (40) | 351 (43) | 343 (41) | 1032 (41) |
| ≥ 50 to < 60 | 370 (44) | 342 (42) | 338 (40) | 1050 (42) |
| ≥ 65 | 109 (13) | 91 (11) | 120 (14) | 320 (13) |

| | | | | |
|---|---|---|---|---|
| **Sex, n %** | | | | |
| Male | 285 (34) | 308 (38) | 314 (37) | 907 (36) |
| Female | 556 (66) | 514 (63) | 533 (63) | 1603 (64) |
| **Race, n %** | | | | |
| White | 662 (79) | 639 (78) | 674 (80) | 1975 (79) |
| African American | 25 (3) | 30 (4) | 30 (4) | 85 (3) |
| Asian | 109 (13) | 105 (13) | 103 (12) | 317 (13) |
| Other | 32 (4) | 38 (5) | 26 (3) | 96 (4) |
| **Ethnicity** | | | | |
| Hispanic or Latino | 181 (22) | 180 (22) | 169 (20) | 530 (21) |
| Not Hispanic or Latino | 660 (79) | 642 (78) | 678 (80) | 1980 (79) |
| **Region** | | | | |
| United States | 125 (15) | 120 (15) | 129 (15) | 374 (15) |
| Rest of World | 716 (85) | 702 (85) | 718 (85) | 2136 (85) |
| Canada | 20 (2) | 19 (2) | 20 (2) | 59 (2) |
| South America | 159 (19) | 148 (18) | 147 (17) | 454 (18) |
| Europe | 403 (48) | 404 (49) | 422 (50) | 1229 (50) |
| Asia | 109 (13) | 108 (13) | 106 (13) | 323 (13) |
| Africa | 10 (1) | 8 (1) | 8 (1) | 26 (1) |
| Other | 15 (2) | 15 (2) | 15 (2) | 45 (2) |

Source: Reviewer generated using the ISS ADSL dataset

**Table 34: Baseline Disease Characteristics SIROCCO/CALIMA (SAS)**

| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** | **Total N = 2510** |
|---|---|---|---|---|
| Local baseline eosinophil count, median[1] | 380 | 380 | 371 | 380 |
| **Lung function** | | | | |
| Mean Pre-BD $FEV_1$ % predicated | 58 | 57 | 57 | 58 |
| Mean Pre-BD $FEV_1$/FVC | 61 | 61 | 61 | 61 |
| Mean % reversibility | 26 | 26 | 26 | 26 |
| **Duration of Asthma (years)** | | | | |
| Median | 16 | 15 | 15 | 15 |
| **Number of Exacerbations in Previous 12 Months, n (%)** | | | | |
| Mean | 2.8 | 2.7 | 2.8 | 2.8 |
| 2 | 543 (65) | 529 (64) | 532 (63) | 1604 (64) |
| 3 | 158 (19) | 167 (20) | 169 (20) | 494 (20) |
| ≥ 4 | 139 (17) | 125 (15) | 146 (17) | 410 (16) |
| **Smoking Status, n (%)** | | | | |
| Never smoked | 648 (77) | 665 (81) | 677 (80) | 1990 (79) |
| Current smoker | 0 | 4 (1) | 7 (1) | 11 (<1) |

| | 30 mg Q4 N = 841 | 30 mg Q8 N = 822 | Placebo N = 847 | Total N = 2510 |
|---|---|---|---|---|
| Former smoker | 193 (23) | 153 (19) | 163 (19) | 509 (20) |
| [1] defined as the result from Visit 1 or 3 (screening period) used to stratify the patient at randomization | | | | |

Source: modified from ISS Tables 7, 8, 9

### 8.2.3. Adequacy of the safety database:

The safety database included in this application is adequate to characterize the safety of benralizumab in the targeted patient population for use. The size and duration of the safety database exceed the ICH E-1 Guidelines and provide similar exposure as other biologic programs in severe asthma. In addition the demographics and baseline disease characteristics closely approximate the target patient population for benralizumab therapy in clinical practice. While overall enrollment in the United States is low, no regional differences are observed in the data (see Section 8.6) and a global development program is reasonable given the rarity of the study population.

## 8.3. Adequacy of Applicant's Clinical Safety Assessments

### 8.3.1. Issues Regarding Data Integrity and Submission Quality

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

### 8.3.2. Categorization of Adverse Events

In this program, an adverse event (AE) were defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. A serious adverse event was defined as an AE occurring during any study phase that fulfils one of more of the following:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity of substantial disruption of the ability to conduct normal life functions
- Is congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent of the outcomes listed above

Adverse events were collected throughout each study and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. The applicant categorized the AEs into the following groups using the following onset dates:

- On-study AE: events with an onset between the first day dosing and the scheduled follow-up visit.
- On-treatment AE: events with an onset between the first day of treatment and the scheduled end of treatment (EOT) or investigational product discontinuation (IPD) visit.
- Post-treatment AE: events with onset after the on-treatment period defined above

Previous immunomodulating therapy has been associated with an increased risk malignancy. To assess this risk with benralizumab, the applicant included an independent adjudication committee in its SIROCCO, CALIMA and ZONDA trials. In addition to malignancy, the committee was used to adjudicate major cardiac adverse events (MACE). All events with an outcome of death were reviewed by the committee. If the MACE sub-committee felt the death may be related to malignancy it was sent to the malignancy adjudication committee for further assessment.

*Reviewer's Comment: The definitions, collection, and categorization of AEs are reasonable. In addition, the coding of verbatim to preferred terms was reviewed found to be reasonable. Independent, blinded adjudication of the MACE and malignant events lends additional reassurance to the evaluation of these events.*

### 8.3.3. **Routine Clinical Tests**

The following safety laboratory tests were assessed in the SIROCCO trial:

- Serum Chemistry: Alkaline phosphatase, ALT, AST, BUN, CRP, Calcium, Chloride, CO2, Creatinine, GGT, Glucose, Phosphorus, Potassium, Sodium, Total Bilirubin, Total Cholesterol, Uric Acid
- Hematology: Hematocrit, Hemoglobin, Mean Corpuscular Volume, Platelet Count, RBC count, WBC count with differentiation[14]
- Urinalysis: Appearance, Blood, Color, Glucose, Ketones, Microscopy including WBC/high power field, RBC/HPF, pH, specific gravity

All assessments were performed at a central laboratory. Liver, renal, and CRP assessments were performed at Visits 1, 3, 6A (no CRP), 7, 11, 15 and 17 while other chemistry assessments were performed at Visits 1 and 3.

Similar laboratory assessments were performed in the CALIMA trial with the exception of CRP. The ZONDA trial also performed similar safety laboratory assessments, with liver and renal function assessed at Visits 1, 6, 10 and 14 and other chemistry parameters only at Visit 1.

All laboratory and vital sign data are summarized descriptively with mean values and change

[14] Eosinophil, basophil, monocyte counts were redacted from the central laboratory reports with the exception of Visit 1

from baseline data presented in the review. The applicant used central laboratory reference ranges to identify abnormal values and its shift tables.

*Reviewer's Comment: The assessment of routine clinical tests in the phase 3 program is adequate.*

## 8.4. Safety Results

### 8.4.1. Deaths

A total of 12 deaths were identified during the on-study period in the phase 3 exacerbation trials: 5 in the benralizumab 30 mg Q4 group, 4 in the benralizumab 30 mg Q8 group and 3 in the placebo group. Nine of the deaths occurred during the on-treatment period and 3 occurred in the post-treatment period. An additional two deaths were reported in the ZONDA trial and one death in the BISE study.

The deaths in this clinical development program are summarized in the Table 35.

**Table 35: Summary of Fatal AEs in Benralizumab Asthma Clinical Development Program**

| **Pt ID**<br>**Age & sex**<br>***Study*** | **Preferred Term**<br>***Adjudicated Outcome*** | **Time from 1st/last dose**<br>***On/post tx*** | **Key information from patient narrative** |
|---|---|---|---|
| **Benralizumab Q4** | | | |
| E6010002<br>59 yo F<br><br>*SIROCCO* | Cerebral hemorrhage<br><br>*Stroke death* | 166/1<br>*On-treatment* | Patient had history of hypertension. |
| E7826014<br>54 yo F<br><br>*SIROCCO* | Asthma<br><br>*Non CV death* | 156/22<br><br>*On-treatment* | Patient was morbidly obese with history of sleep apnea and a history of 17 prior severe asthma exacerbations, 15 of which required intubation. |
| E0202020<br>62 yo M<br><br>*CALIMA* | Completed suicide<br><br>*Non CV death* | 241/16<br><br>*On-treatment* | Patient had no history of depression, but 2 family members had died in the preceding month |
| E5721001<br>63 yo M<br><br>*CALIMA* | Road traffic accident<br><br>*Non CV death* | 25/24<br><br>*On-treatment* | No additional pertinent information. |

| **Pt ID**<br>**Age & sex**<br>***Study*** | **Preferred Term**<br>***Adjudicated Outcome*** | **Time from 1st/last dose**<br>***On/post tx*** | **Key information from patient narrative** |
|---|---|---|---|
| E7709002<br>59 yo F<br><br>*CALIMA* | Acute myocardial infarction<br><br>*Acute Myocardial infarction* | 447/80<br><br>*Post-treatment* | Patient had a history of ischemic heart disease, hypertension, and obesity. |
| E2601014<br>65 yo M<br><br>*BISE* | pancytopenia | /27<br>*Post-treatment* | This patient had a history of pancreatic resection with resultant pancreatic insufficiency, prior asbestos exposure and underlying cardiovascular disease for which he was receiving amiodarone therapy. The SAE of pancytopenia developed 27 days after last dose of benralizumab and the patient expired 157 days after his last dose. Notably, aplastic anemia has been reported in the postmarketing experience for amiodarone therapy[15]. |
| **Benralizumab Q8** | | | |
| E7830007<br>46 yo F<br>*SIROCCO* | Overdose<br><br>*Sudden cardiac death* | 1/0<br><br>*On-treatment* | This event was reported as fatal opiate overdose. The patient's medical history was significant for opiate, benzodiazepine, & cocaine use. |
| E4358001<br>51 yo F<br>*CALIMA* | Death<br><br>*Sudden cardiac death* | 81/27<br><br>*On-treatment* | The patient had no medical or surgical history beyond use of lansoprazole. |
| E7734004<br>67 yo M<br><br>*ZONDA* | Cardiac failure acute<br><br>*Undetermined death* | 23/24<br><br>*On-treatment* | The history is significant for hypertension and coronary artery disease. Patient took doses of salbutamol for dyspnea, chest pain and dizziness. He was found dead by his wife the following morning. |

[15] Amiodarone USPI . https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018972s053lbl.pdf accessed on February 17, 2017.

| **Pt ID**<br>**Age & sex**<br>***Study*** | **Preferred Term**<br>***Adjudicated Outcome*** | **Time from 1st/last dose**<br>***On/post tx*** | **Key information from patient narrative** |
|---|---|---|---|
| E7738001<br><br>*ZONDA* | Pneumonia<br><br>Non-cardiovascular death | 79/20<br><br>*On-treatment* | Patient had a history of atrial fibrillation and was hospitalized for community acquired pneumonia. During the hospital course he developed atrial fibrillation with rapid ventricular rate and continued to decline. An autopsy was performed with the cause of death was reported as pneumonia and pulmonary insufficiency. |
| E7007009<br>58 yo F<br><br>*SIROCCO* | Sudden death<br><br>*Sudden cardiac death* | 367/86<br><br>*Post-treatment* | Patient had a history of type II DM, cerebrovascular atherosclerosis, prior stroke and hypertension and was taking concomitant medical therapy for diabetes, hypertension and stroke at the time of the event. |
| **Placebo** | | | |
| E7717005<br>56 yo F<br><br>*CALIMA* | Colon neoplasm<br><br>*Undetermined death* | 92/36<br><br>*On-treatment* | Patient was found to have perforated colon due to large tumor during surgery. She declined assessment and treatment from a medical oncologist. She had no prior history of malignancy. |
| E0914008<br>42 yo male<br><br>*SIROCCO* | Pulmonary embolism<br><br>*Undetermined death* | 238/<br><br>*On-treatment* | Patient had a history of diabetes and hypertension. |
| E6231010/<br>65 yo male<br><br>*SIROCCO* | Death<br><br>*Sudden cardiac death* | 236/7<br><br>*On-treatment* | The patient had a history of myocardial infarction, stroke, and encephalopathy. Seven days after ninth dose of placebo, the patient was reported to have facial and hand swelling of unknown etiology. He was treated in the ER but refused hospitalization. An autopsy was performed but the cause of death could not be determined. |
| E7820003<br>75 yo male<br><br>*CALIMA* | Myocardial infarction | 366/29<br><br>*Post-treatment* | The patient history of cardiomyopathy, cardiac pain, hyperlipidemia, hypertension prior TIA, and complete heart block while on study requiring pacemaker insertion. |

*Reviewer's Comment: While there were several cardiovascular-related deaths in the program, no imbalance compared to placebo is seen. Similarly, no imbalance in adjudicated MACE events*

*are seen in the program which suggests against any treatment-related cardiotoxicity (see Section 8.5.4).*

*The single case of pancytopenia is confounded by the patient's underlying lying medical condition and concomitant medical therapy both of which limit the causality assessment to benralizumab. In addition to this death, a non-serious adverse event of pancytopenia was reported in the SIROCCO trial which self-resolved in 26 days. Notably, the laboratory reported sample degradation and/or platelet clumping in this case. Drug-related pancytopenia is typically thought to be an idiosyncratic drug reaction; however given the mechanism of action for benralizumab, off-target drug-related cytotoxicity should be considered. Small treatment-related imbalances in low grade leukopenia and lymphopenia are seen in the program; however no imbalances in hemoglobin or platelet parameters are seen. Readers are referred to Section 8.4.6 for a discussion of these findings.*

*While a fatality due to suicide is of concern in a drug development program, depression and suicide are not rare events in the general population. Two additional non-fatal SAEs in patients receiving active treatment are worth considering when reviewing this case. This includes one event of threatened suicide in a patient with history of borderline personality disorder and 3 prior suicide attempts and one depression event requiring hospitalization in a patient with a history of depression. The latter patient was specifically noted to have no suicidal ideation in the eCRF and case narrative. The small number of cases of this relatively common condition, and confounding factors for the fatal and non-fatal cases, limits the causality assessment.*

*Finally, regarding the case of sudden cardiac death in a patient with earlier hypersensitivity reaction, the story is concerning for the possibility of death due to anaphylaxis. While the patient received placebo therapy, hypersensitivity reactions to excipients within the drug product are possible. While the available detail for the case limits the assessment for anaphylaxis, the event was not temporally related to administration of investigational product making any possible hypersensitivity event unlikely to be related to administration of the investigational product.*

### 8.4.2. **Serious Adverse Events**

A total of 299 patients had a serious adverse event (including fatal events) with the highest number occurring in the placebo group (115 patients) followed by benralizumab 30 mg Q4 (92 patients) and benralizumab 30 mg Q8 (92 patients).

In the pooled SIROCCO/CALIMA database, asthma followed by pneumonia are the most commonly reported preferred terms with a higher incidence of both seen in the placebo group compared with active treatment. Given the potential for a pneumonia signal to be hidden by the splitting of events across preferred terms, this reviewer grouped pneumonia-related terms

and found no treatment-related increase. Additional discussion of the pneumonia and other infectious events can be found in Section 8.5.2 of this review.

The only SAE PTs occurring more commonly in an active treatment arm compared to placebo in any of the pivotal phase 3 trials are nephrolithiasis and hypertension. All of the nephrolithiasis SAEs occurred in patients receiving 30 mg Q4 of benralizumab and required hospitalization[16]. Although infrequent, treatment-emergent adverse events of nephrolithiasis also occurred more frequently in active treatment compared to placebo in the SIROCCO/CALIMA safety dataset (30 Q4: 5 events [0.6]; 30 Q8 3 events [0.4]; placebo: 1 event [0.1]). No imbalance in hematuria as captured by urinalysis assessments in the program is seen. Similar incidences of hypertension AEs are seen between placebo and active treatment and no treatment-related increase in blood pressure is seen in the program (see Section 8.4.7).

No additional consistent treatment related safety findings are seen from a review of SAE data from the larger pooling of placebo-controlled trials or review of the data from the individual trials.

**Table 36: On-Treatment Serious Adverse Events Occurring in > 2 patients In Any Group by SOC and PT in SIROCCO/CALIMA and ZONDA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4** | **30 mg Q8** | **Placebo** |
| **SIROCCO/CALIMA** | | | |
| N | 841 | 822 | 847 |
| Any SAE | 92 (10.9) | 92(11.2) | 115 (13.6) |
| Respiratory, thoracic & mediastinal disorders | 48 (5.7) | 42 (5.1) | 59 (7.0) |
| Asthma | 43 (5.1) | 42 (5.1) | 54 (6.4) |
| Infections and Infestations | 12 (1.4) | 18 (2.2) | 19 (2.2) |
| Pneumonia | 2 (0.2) | 2 (0.2) | 6 (0.7) |
| Pneumonia bacterial | 2 (0.2) | 1 (0.1) | 3 (0.4) |
| Musculoskeletal & connective tissue disorders | 9 (1.1) | 4 (0.5) | 9 (1.1) |
| Osteoarthritis | 2 (0.2 | 1 (0.1) | 3 (0.4) |
| Vascular disorders | 1 (0.1) | 3 (0.4) | 5 (0.6) |
| Hypertension | 0 | 3 (0.4) | 1 (0.1) |
| Renal and urinary disorders | | | |
| Nephrolithiasis | 3 (0.4) | 0 | 0 |
| **ZONDA, N (%)** | | | |

[16] CALIMA: Two patients were enrolled in CALIMA (E5723007 and E5744006) and one in SIROCCO (E0909013). All 3 patients required hospitalization. Two patients were specifically noted to require lithotripsy while no procedure was noted in the third narrative.

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4** | **30 mg Q8** | **Placebo** |
| N | 72 | 73 | 75 |
| Any SAE | 7 (9.7) | 7 (9.6) | 14 (18.7) |
| Infection and infestations | 2 (2.8) | 2 (2.7) | 8 (10.7) |
| Influenza | 0 | 0 | 2 (2.7) |
| Pneumonia | 0 | 2 (2.7) | 3 (4.0) |
| Respiratory, thoracic and mediastinal disorders | 2 (2.8) | 1 (1.4) | 7 (9.3) |
| Asthma | 2 (2.8) | 1 (1.4) | 4 (5.3) |
| Status asthmaticus | 0 | 0 | 3 (4.0) |

Source: Modified from Module 5.3.5.3 ISS Table 20 and ZONDA Table 44

*Reviewer's Comment: Reassuringly, a higher total number of SAEs as well as asthma and pneumonia SAEs are seen in the placebo group compared to active treatment. Regarding the infrequent hypertension SAEs, there is no corresponding treatment-related increase in blood pressure seen in the program. While a small treatment-related imbalance is also seen in the TEAEs for nephrolithiasis, the small number of cases for this common medical condition limits the causality assessment to treatment.*

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

A total of 44 patients had TEAEs leading to discontinuation of investigational product in the phase 3 exacerbation studies. More patients receiving active treatment withdrew compared to those receiving placebo. Events occurring in more than one individual are summarized in Table 37. An increased number of discontinuations due to urticaria are seen in both treatment arms compared to placebo. Hypersensitivity events, including urticaria and urticarial events leading to discontinuation are discussed in further detail in Section 8.5.1.

**Table 37: Adverse Events Occurring in ≥ 2 Patients in Any Group Leading to Drug Discontinuation from SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Any event | 18 (2.1) | 18 (2.1) | 8 (0.9) |
| Urticaria | 1 (0.1) | 2 (0.2) | 0 |
| Rash | 0 | 0 | 2 (0.2) |
| Asthma | 1 (0.1) | 2 (0.2) | 1 (0.1) |
| Arthralgia | 0 | 2 (0.2) | 0 |

Source: ISS Table 22

### 8.4.4. Significant Adverse Events

In the pivotal phase 3 trials more patients in the placebo group reported AEs severe in intensity than patients receiving active treatment. Events occurring in more than 2 patients in any treatment group and more commonly than placebo from the SIROCCO/CALIMA trials include: bronchitis, headache, influenza, back pain, arthralgia, osteoarthritis, toothache, migraine and appendicitis (Table 38). In the ZONDA trial, all AE reported as severe in intensity in more than 2 patients occurred more frequently in the placebo group.

**Table 38: On-Treatment Adverse events in Any Treatment Group with a Severe Maximum Intensity Reported in > 2 patients In Any Treatment Group in CALIMA/SIROCCO and ZONDA Trials (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4** | **30 mg Q8** | **Placebo** |
| **SIROCCO/CALIMA** | | | |
| N | 841 | 822 | 847 |
| Any event | 69 (8.2) | 78 (9.5) | 85 (10) |
| Nasopharyngitis | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| Asthma | 21 (2.5) | 24 (2.9) | 32 (3.8) |
| Bronchitis | 2 (0.2) | 1 (0.1) | 1 (0.1) |
| Headache | 3 (0.4) | 1 (0.1) | 1 (0.1) |
| Influenza | 2 (0.2) | 3 (0.4) | 2 (0.2) |
| Back pain | 0 | 2 (0.2) | 1 (0.1) |
| Arthralgia | 1 (0.1) | 2 (0.2) | 0 |
| Urticaria | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| Contusion | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| Osteoarthritis | 2 (0.2) | 2 (0.2) | 1 (0.1) |
| Pneumonia | 1 (0.1) | 2 (0.2) | 7 (0.8) |
| Toothache | 1 (0.1) | 2 (0.2) | 0 |
| Migraine | 2 (0.2) | 1 (0.1) | 0 |
| Pneumonia bacterial | 1 (0.1) | 2 (0.2) | 3 (0.4) |
| Drug Hypersensitivity | 0 | 1 (0.1) | 2 (0.2) |
| Appendicitis | 0 | 3 (0.4) | 0 |
| **ZONDA** | | | |
| N | 72 | 73 | 75 |
| Any event | 6 (8.3) | 7 (9.6) | 11 (14.7) |
| Asthma | 1 (1.4) | 0 | 3 (4.0) |
| Bronchitis | 0 | 1 (1.4) | 2 (2.7) |
| Status Asthmaticus | 0 | 0 | 3 (4.0) |

Source: Reviewer generated using ISS ADAE dataset

*Reviewer's Comment: A review of the AE by severity does not reveal any concerning safety findings related to active treatment. While several events have small benralizumab-related*

*imbalances compared to placebo, the overall incidences are low and imbalances are not consistently seen in both active treatment groups suggesting against a drug-related effect.*

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent adverse events occurring in ≥ 3 % of the population include: nasopharyngitis, asthma, upper respiratory tract infection, bronchitis, headache, sinusitis, influenza, rhinitis allergic, pharyngitis, rhinitis, hypertension, back pain, arthralgia, cough and pyrexia. Of these, events that occurred more commonly in active treatment than placebo include: nasopharyngitis, headache, rhinitis allergic, pharyngitis, arthralgia, cough, and pyrexia (Table 39).

**Table 39: Most Common Reported Adverse Events Reported in ≥ 3% of Any Treatment Group During the On-Treatment Period by PT in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 Q4 N = 841** | **30 Q8 N = 822** | **Placebo N = 847** |
| Nasopharyngitis | 137 (16.3) | 125 (15.2) | 139 (16.4) |
| Asthma | 121 (14.4) | 92 (11.2) | 146 (17.2) |
| Upper respiratory tract infection | 73 (8.7) | 68 (8.3) | 77 (9.1) |
| Bronchitis | 64 (7.6) | 63 (7.7) | 82 (9.7) |
| Headache | 63 (7.5) | 71 (8.6) | 53 (6.3) |
| Sinusitis | 38 (4.5) | 42 (5.1) | 65 (7.7) |
| Influenza | 39 (4.6) | 33 (4.0) | 47 (5.5) |
| Rhinitis allergic | 31 (3.7) | 28 (3.4) | 31 (3.7) |
| Pharyngitis | 33 (3.9) | 33 (4.0) | 21 (2.5) |
| Rhinitis | 28 (3.3) | 27 (3.3) | 32 (3.8) |
| Hypertension | 23 (2.7) | 28 (3.4) | 33 (3.9) |
| Back pain | 27 (3.2) | 19 (2.3) | 31 (3.7) |
| Arthralgia | 19 (2.3) | 32 (3.9) | 19 (2.2) |
| Cough | 25 (3.0) | 27 (3.3) | 18 (2.1) |
| Pyrexia | 32 (3.8) | 24 (2.9) | 14 (1.7) |

Source: ISS Table 15

### 8.4.6. Laboratory Findings

The clinical laboratory data in this phase 3 program includes hematology, clinical chemistry and urinalysis data in addition to flow cytometry for immunoglobulins and lymphocytes subsets in the phase 3 exacerbation trials. The review of the phase 3 trials laboratory data included a review of the changes in the mean data, changes across time in addition to shift tables and plots.

*Hematology*
In addition to an expected decrease in eosinophil/basophil levels, a numeric imbalance in lymphopenia is seen in the SIROCCO/CALIMA trial. The shifts are mild (grade 1 and grade 2) with no imbalance to a more clinically significant grade 3 or 4 lymphopenia seen (Table 40). In addition, no imbalance is seen in the lymphocyte subset data (data not shown). A review of the lymphocyte counts over time for the individuals with decreased counts reveals that the drops were typically transient with a return to normal levels while continuing treatment. In addition, while temporally-related infections are seen in some cases, the infectious events are generally mild and common events (e.g., nasopharyngitis, sinusitis), occurred in similar proportion of placebo and benralizumab treated subjects, and were not associated with any significant clinical sequelae. In addition, no benralizumab-related imbalance in infectious SAEs other than herpes zoster is seen (See section 8.5.2 for additional discussion of infectious AE data).

A small numeric imbalance is also seen in Grade 1 leukopenia with no imbalance seen in the more severe grades. Small treatment-related drops in the mean neutrophil counts are seen in both SIROCCO and CALIMA; however the mean values remained within the normal range in both studies. Review of the neutrophil shift data shows an imbalance in grade 1 neutropenia in both treatment arms compared to placebo in SIROCCO, but consistent treatment-related decreases are not seen in CALIMA. No imbalance in grade 2 neutropenia or higher is seen.

Isolated adverse events of cytopenia were reported in active treatment groups while there were no reported cases in the placebo groups. Reports of anemia are balanced across treatment arms (Table 41). None of these events were SAEs, rated as severe in intensity by the investigator, or resulted in drug discontinuation. The patient with the non-serious AE of pancytopenia had WBC, hemoglobin, and platelet counts below the lower limits of normal with the laboratory reporting sample degradation and/or platelet clumping with the sample. The event was reported as resolved 26 days after the start.

**Table 40: Summary of Select Hematology Parameters in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4** | **30 mg Q8** | **Placebo** |
| **Lymphocytes by maximum CTCAE grade in SIROCCO and CALIMA** | | | |
| N | 841 | 822 | 847 |
| Grade 1: LLN – 800/mm$^3$ | 53 (6.4) | 59 (7.3) | 33 (3.9) |
| Grade 2: < 800 – 500/mm$^3$ | 18 (2.2) | 18 (2.2) | 10 (1.2) |
| Grade 3: < 500 – 200/mm$^3$ | 3 (0.4) | 1 (0.1) | 5 (0.6) |
| Grade 4: < 200/mm$^3$ | 0 | 0 | 0 |
| **Lymphocytes by maximum CTCAE grade in ZONDA** | | | |
| N | | | |
| Grade 1: LLN – 800/mm$^3$ | 2 (2.8) | 3 (4.3) | 5 (6.7) |
| Grade 2: < 800 – 500/mm$^3$ | 3 (4.2) | 1 (1.4) | 3 (4.0) |

| | | | |
|---|---|---|---|
| Grade 3: < 500 – 200/mm$^3$ | 1 (1.4) | 0 | 0 |
| Grade 4: < 200/mm$^3$ | 0 | 0 | 0 |
| **Leukocytes by maximum CTCAE grade** | | | |
| **SIROCCO** | | | |
| Grade 1 | 38 (9.5) | 38 (9.8) | 21 (5.2) |
| Grade 2 | 1 (0.3) | 8 (2.1) | 4 (1.0) |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| **CALIMA** | | | |
| Grade 1 | 37 (8.5) | 29 (6.8) | 8 (1.8) |
| Grade 2 | 2 (0.5) | 3 (0.7) | 1 (0.2) |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| **ZONDA** | | | |
| Grade 1 | 3 (4.2) | 4 (5.8) | 1 (1.3) |
| Grade 2 | 0 | 0 | 0 |
| Grade 3 | 0 | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| **Neutrophils maximum CTCAE grade post-baseline** | | | |
| **SIROCCO** | | | |
| Grade 1 | 27 (6.8) | 28 (7.2) | 16 (4.0) |
| Grade 2 | 5 (1.3) | 9 (2.3) | 9 (2.2) |
| Grade 3 | 0 | 0 | 1 (0.2) |
| Grade 4 | 0 | 1 (0.3) | 0 |
| **CALIMA** | | | |
| Grade 1 | 28 (6.4) | 17 (4.0) | 18 (4.1) |
| Grade 2 | 6 (1.4) | 8 (1.9) | 3 (0.7) |
| Grade 3 | 1 (0.2) | 0 | 0 |
| Grade 4 | 0 | 0 | 0 |
| **ZONDA** | | | |
| Grade 1 | 1 (1.4) | 1 (1.4) | 0 |
| Grade 2 | 0 | 0 | 1 (1.3) |
| Grade 3 | 0 | 0 | 1 (1.3) |
| Grade 4 | 0 | 0 | 0 |

Source: Modified from response to IR dated 4/11/2017, SIROCCO CSR Tables 12.3.6.3.2 and CALIMA CSR Table 12.3.6.3.2, and ZONDA CSR Table 11.3.7.3.1

**Table 41: Hematology-Related Adverse Events from SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Pancytopenia | 0 | 1 (0.1) | 0 |

| | Number of patients (%) | | |
|---|---|---|---|
| | 30 mg Q4 N = 841 | 30 mg Q8 N = 822 | Placebo N = 847 |
| Leukopenia[1] | 1 (0.1) | 2 (0.2) | 0 |
| Neutropenia | 1 (0.1) | 1 (0.1) | 0 |
| Anemia[2] | 8 (1) | 6 (0.7) | 6 (0.7) |
| Thrombocytopenia | 0 | 1 (0.1) | 0 |
| [1]includes the following PTs: leukopenia and WBC decreased<br>[2] includes the following PTs: hemoglobin decreased, anemia, iron deficiency anemia, normochromic normocytic anemia, nephrogenic anemia, anemia megaloblastic | | | |

Source: Reviewer generated using ISS ADAE dataset

*Clinical Chemistry Data and Urinalysis*

No clinically significant differences between active treatment and placebo patients are seen from a review of the clinical chemistry data. Elevated transaminases are seen during the phase 3 trials; however, numbers are generally balanced between active treatment and placebo arms. No cases meeting criteria for Hy's law were reported in the program.

**Table 42: Select Chemistry Parameters in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | 30 mg Q4 | 30 mg Q8 | Placebo |
| **Alanine Aminotransferase normal to high** | | | |
| SIROCCO | 58 (16.2) | 62 (17.6) | 69 (18.8) |
| CALIMA | 75 (19.2) | 61 (16.3) | 62 (16.1) |
| ZONDA | 6 (9.8) | 13 (21) | 7 (10.1) |
| **Aspartate Aminotransferase normal to high** | | | |
| SIRROCO | 52 (13.9) | 41 (11.4) | 49 (13.3) |
| CALIMA | 56 (13.8) | 43 (10.8) | 42 (10.3) |
| **Total Bilirubin normal to high** | | | |
| SIRROCO | 19 (4.9) | 11 (2.9) | 14 (3.6) |
| CALIMA | 13 (3.1) | 14 (3.4) | 15 (3.6) |
| **Alkaline phosphatase normal to high** | | | |
| SIROCCO | 41 (11.2) | 34 (9.7) | 26 (7.3) |
| CALIMA | 33 (8.3) | 30 (7.7) | 27 (6.7) |
| **GGT normal to high** | | | |
| SIROCCO | 54 (15.8) | 42 (13.0) | 53 (15.2) |
| CALIMA | 41 (10.8) | 58 (15.7) | 36 (9.4) |

Source: SIROCCO CSR Table 12.3.6.3.1 and CALIMA CSR Table 12.3.6.3.1

*Reviewer's Comment: A numeric imbalance in mild lymphopenia, leukopenia and neutropenia is seen between placebo and active treatment. Review of the leukocyte and neutrophil shift data reveals no imbalance in shifts to grade 2 or greater in active treatment arms compared to*

*placebo and no consistent decrease is seen in hemoglobin or platelet counts. In addition, there are a few AEs of leukopenia, pancytopenia and neutropenia seen in active treatment arms with no cases in the placebo-treated patients. While small imbalances are seen in these data, this reviewer is reassured by the mild and transient nature of the drops, and lack of associated clinically significant infections or sequelae with the laboratory and cytopenia-related AE findings. Review of the other laboratory data does not reveal any concerning findings.*

### 8.4.7. Vital Signs

Pre-dose vital signs (pulse, temperature, blood pressure and respiratory rate) were obtained at baseline and every clinic visit (every 4 weeks) throughout the study duration for the phase 3 exacerbation trials. The applicant did not provide an assessment of pooled data citing a lack of clinically significant alterations in the individual SIROCOO and CALIMA trials. A review of the data from the phase 3 studies confirms that no consistent alterations in vital signs are seen. Similar incidences of vital-sign related treatment emergent adverse events are seen across treatment groups in the phase 3 exacerbation studies (Table 43).

**Table 43: Select Vital Sign Related Adverse Events from SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Hypertension[1] | 20 (2.4) | 15 (1.8) | 23 (2.7) |
| Hypotension[2] | 2 (0.3) | 2 (0.2) | 0 |
| Includes the following PTs: Hypertension, hypertensive crisis, essential hypertension, blood pressure increased | | | |
| Includes the following PTs: Hypotension and orthostatic hypotension | | | |

Source: Reviewer generated using ISS ADAE dataset

*Reviewer's Comment: Benralizumab does not appear to impact vital sign parameters based on review of the phase 3 trial data.*

### 8.4.8. Electrocardiograms (ECGs)

As part of its routine ECG assessment, the sponsor included an ECG sub-study in 201 patients in the SIROCCO trial. Assessment included ECGs performed in triplicate at baseline and after the second treatment dose. There is no imbalance in the incidence of changes exceeding reference ranges for the PR, QRS, RR internal or for heart rate < 45 or > 120. In addition, no treatment-related increase in the number of QTcF outliers is seen (Table 44).

**Table 44: QTcF Outlier by Timepoint: ECG sub-study SIROCCO (SAS)**

| | Number of patients (%) | |
|---|---|---|
| | **Total 30 mg Q4 N = 131** | **Placebo N = 70** |
| **Baseline** | | |
| >450 ms | 2 (1.5) | 4 (5.7) |
| >480 ms | 1 (0.8) | 1 (1.4) |
| >500 | 0 | 0 |
| **Week 4 Day 6** | | |
| >450 ms | 2 (1.5) | 5 (7.1) |
| >480 ms | 1 (0.8) | 0 |
| >500 ms | 0 | 0 |
| Increase from baseline > 30 ms | 0 | 0 |
| Increase from baseline > 60 ms | 0 | 0 |

Source: SIROCCO CSR Table 12.3.7.2.3

*Reviewer's Comment: A review of the ECG-related TEAEs in SIROCCO and CALIMA did not reveal any consistent treatment-related imbalances in events.*

### 8.4.9. QT

As benralizumab is a monoclonal antibody, QT prolongation is not anticipated with use and no hERG study was performed. See Section 8.4.8 for discussion of the routine ECG assessments in the clinical development program including the results of a ECG sub-study in the SIROCCO trial.

### 8.4.10. Immunogenicity

The applicant provided an immunogenicity assessment using all of the trials in its clinical development program. In this program, anti-drug-antibodies (ADA) were assessed using a 3-tier approach: 1) screen (detection), 2) confirm (specificity) and, 3) titre (semi-quantitation). Samples were deemed ADA positive if they tested positive in the confirmatory assay. All positive ADA samples were then testing in a ligand-binding neutralization assay for the ability to interfere with benralizumab's interaction with its target. To evaluate the impact of positive ADA, PK parameters, peripheral blood eosinophil counts, exacerbations rates and AEs were analyzed between ADA positive and negative patients. Immunogenicity data from each of the individual studies in the development program were reviewed. However this review primarily presents pooled data from the phase 3 exacerbation studies.

In the SIROCCO and CALIMA trials treatment-emergent ADA developed in 13-15% of patients in the benralizumab treatment groups compared with 4% in the placebo treatment group. Of the positive patients in the active treatment arms, 8-10% were persistently positive and the

majority of ADA positive patients had positive nAB assays (Table 45) and most patients seroconverted by Week 24 (see Figure 14). Decreases in PK parameters with increases in peripheral blood eosinophil counts are seen in ADA positive patients (data not shown). Readers are referred to the clinical pharmacology review for additional details.

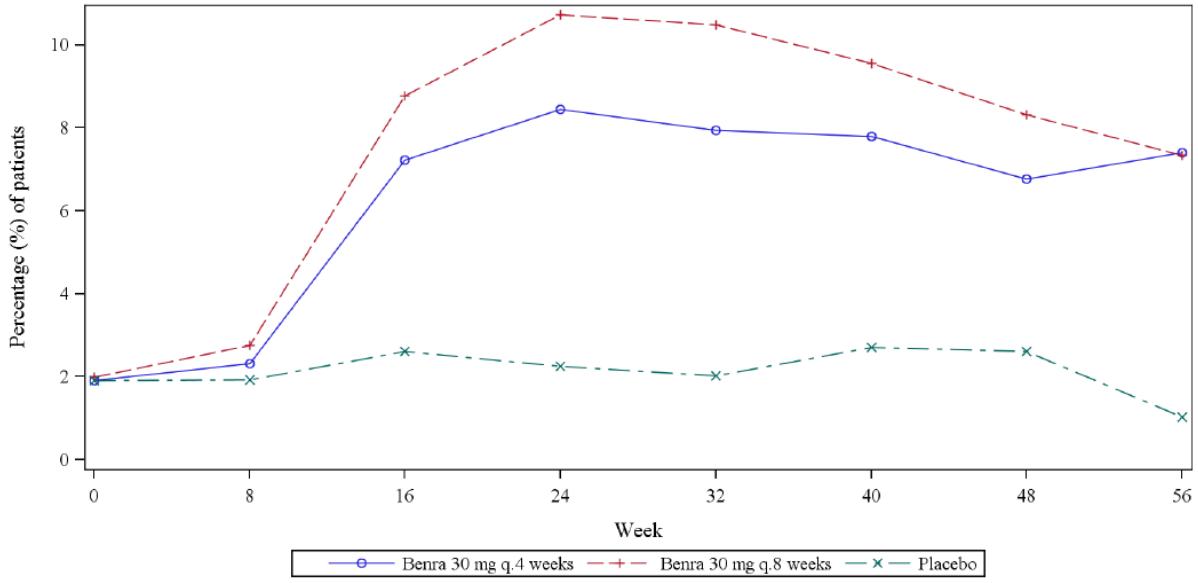
**Table 45: Summary of ADA Positive Response in SIROCCO/CALIMA (SAS)**

| | Percentage of patients | | |
|---|---|---|---|
| | **30mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Positive at any visit | 13 | 15 | 4 |
| Only post baseline positive[1] | 11 | 13 | 2 |
| Persistently positive[2] | 8 | 10 | 3 |
| % of ADA+ patients who are nAB positive at any visit[3] | 68 | 80 | 56 |

[1]number of patients with positive result/number of patients with at least one ADA result
[2] defined as positive result ≥ 2 post-baseline assessments with ≥ 16 weeks between first and last positive or positive at last post-baseline assessment
[3] number of patients with positive result/number of patients with nAB result

Source: Modified from Table 13 and 17 Integrated Summary of Immunogenicity

**Figure 14: Percentage of Patients with Positive ADA Results by Visit in SIROCCO/CALIMA (SAS)**




Source: Figure 11 Integrated Summary of Immunogenicity

A review of the crude exacerbation rate between ADA positive and negative patients is limited by the smaller number of ADA positive patients. However, no trend towards a decrease in efficacy is seen these data. In addition, similar changes in FEV1 are seen in ADA positive versus negative patients (Table 46).

**Table 46: Crude Exacerbation Rates by ADA Status in SIROCCO/CALIMA (SAS)**

| | 30mg Q4 N = 841 | 30 mg Q8 N = 822 | Placebo N = 847 |
|---|---|---|---|
| **Crude Exacerbation Rates** | | | |
| Negative ADA | 0.81 | 0.71 | 1.23 |
| Positive ADA | 0.58 | 0.71 | 1.40 |
| Persistently positive ADA[1] | 0.55 | 0.62 | 1.27 |
| Persistently positive ADA patients with positive nAB | 0.47 | 0.62 | 1.44 |
| **Mean Δ from baseline in pre-bronchodilator FEV1 at end of treatment (mL)** | | | |
| Negative ADA | 281 | 310 | 208 |
| Positive ADA | 356 | 289 | 106 |
| Persistently positive ADA[1] | 396 | 315 | 137 |
| Persistently positive ADA patients with positive nAB | 379 | 315 | 139 |
| [1] defined as positive result ≥ 2 post-baseline assessments with ≥ 16 weeks between first and last positive or positive at last post-baseline assessment | | | |

Source: Modified from Tables 22 and 23 Integrated Summary of Immunogenicity

While limited by the smaller number of ADA+ patients, review of the AE and SAE data between ADA+ and ADA- patients demonstrates no consistent treatment-related differences between groups. A similar proportion of ADA+ positive patients reported a hypersensitivity events (3%; 10 patients) as the general trial population (approximately 3%). Of the ADA+ patients reporting a hypersensitivity event, 4 were in the Q4 treatment group, 5 in the Q8 group and 1 in placebo.

*Reviewer's Comment: A review of the data does not reveal a consistent pattern suggestive of an ADA-related safety effect.*

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. Hypersensitivity

Monoclonal antibodies are associated with an increased risk of hypersensitivity events including anaphylaxis.

To assess for hypersensitivity events in this application, the applicant used a modified hypersensitivity SMQ. This reviewer evaluated the list of included/excluded terms and found the list to be reasonable. The modified SMQ identified 78 patients with a treatment-emergent hypersensitivity related AEs with events balanced across treatment groups (Table 47). Reported terms included, angioedema, rash and urticaria. To supplement the applicant's assessment, this reviewer ran a hypersensitivity (narrow), anaphylaxis (narrow) and a modified hypersensitivity SMQ with terms related to asthma/bronchospasm removed. Similar trends were seen.

A case of anaphylaxis attributed to benralizumab administration by the investigator and resulting in drug discontinuation was reported in the 120-day safety update from the BORA study. Twenty-five minutes following drug administration, the patient was reported to have nausea and vomiting and loss of consciousness. Epinephrine was administered and the patient recovered. The patient was reported to have a normal tryptase level but it was drawn 1 hour and 50 min after the event. A histamine level was reported to be elevated.

In addition to this case, there were two investigator-reported anaphylaxis events that occurred in the placebo-controlled clinical trials. Both events occurred in the same patient with a history of peanut allergy. In both instances the investigator attributed the event to the patient's underlying food allergy. Neither event was temporally related to benralizumab exposure and the patient subsequently received additional benralizumab doses without difficulty.

In addition, a total of 5 cases of drug hypersensitivity were reported in the phase 3 exacerbation trials. In these cases, the reporting investigator attributed all cases to other medications and all patients successfully received subsequent benralizumab doses without issue.

To supplement the applicant's anaphylaxis assessment, this reviewer reviewed the AE line listings to look for a compilation of terms consistent with anaphylaxis. No additional cases beyond the investigator reported cases were found by this reviewer; however, the analysis was limited by the lack reported detail in many events. Unfortunately the case report form did not elicit specific symptom information from investigator at the time of a potential hypersensitivity event which would have allowed by a more thorough assessment for anaphylaxis. For instance, five cases of urticaria leading to treatment withdrawal were found; however none of the cases provided sufficient detail to rule out anaphylaxis.

**Table 47: Hypersensitivity-Related AEs in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Any Hypersensitivity related | 26 (3.1) | 24 (2.9) | 8 (3.3) |

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Preferred Term | | | |
| Urticaria | 16 (1.9) | 15 (1.8) | 15 (1.8) |
| Drug Hypersensitivity | 2 (0.2) | 3 (0.4) | 2 (0.2) |
| Eye swelling | 0 | 0 | 3 (0.4) |
| Swelling face | 1 (0.1) | 1 (0.1) | 1 (0.1) |
| Angioedema | 1 (0.1) | 0 | 1 (0.1) |
| Drug eruption | 0 | 1 (0.1) | 1 (0.1) |
| Face edema | 1 (0.1) | 1 (0.1) | 0 |
| Hypersensitivity | 0 | 0 | 2 (0.2) |
| Urticaria papular | 1 (0.1) | 1 (0.1) | 0 |
| Allergic gastroenteritis | 1 (0.1) | 0 | 0 |
| Allergic granulomatous angiitis | 1 (0.1) | 0 | 0 |
| Allergic pharyngitis | 1 (0.1) | 0 | 0 |
| Allergy to vaccine | 0 | 0 | 1 (0.1) |
| Anaphylactic reaction | 0 | 1 (0.1) | 0 |
| Erythema multiforme | 0 | 0 | 1 (0.1) |
| Erythema nodosum | 0 | 0 | 1 (0.1) |
| Eyelild edema | 0 | 0 | 1 (0.1) |
| Laryngeal edema | 0 | 1 (0.1) | 0 |
| Lip swelling | 0 | 1 (0.1) | 0 |
| Edema mouth | 0 | 0 | 1 (0.1) |
| Palatal edema | 1 (0.1) | 0 | 0 |
| Reaction to preservatives | 1 (0.1) | 0 | 0 |

Source: ISS Table 25

*Reviewer's Comment: Cases of anaphylaxis are expected to occur with use of monoclonal antibodies. This reviewer concurs with the investigator's assessment that the anaphylaxis case in the 120-day safety update represents a case of anaphylaxis related to benralizumab exposure and this term should be included in the Hypersensitivity W&P for the product.*

### 8.5.2. Infections

Infections are a potential risk with use of any immunomodulating therapy and eosinophils are known to assist in the defense against helminthic parasitic infections. Thus, an analysis of serious infections, opportunistic infections, and helminthic infections are of particular interest for this application.

The incidence of SAEs and PT sin the Infections and Infestations SOC are similar between active and placebo treated patients in the SIROCCO/CALIMA trials. Of these, pneumonia or its variants

are the most commonly reported events. This is not unexpected in a severe asthma population and events occur more commonly in the placebo arm. As multiple pneumonia-related preferred terms were reported in the development program, this review tabulated these terms and found no benralizumab-related imbalance.

In the ZONDA trial, SAEs in the Infections and Infestations SOC were reported in 2% of the benralizumab treated subjects compared to 8% of placebo treated subjects. Again, pneumonia or variants thereof are the most commonly reported term.

**Table 48: On-treatment SAEs Occurring in ≥ 2 Patients in Any Group in the Infections and Infestations SOC in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Infections and infestations | 12 (1) | 18 (2) | 19 (2) |
| Pneumonia | 2 (<1) | 2 (<1) | 6 (1) |
| Pneumonia bacterial | 2 (<1) | 1 (<1) | 3 (<1) |
| Influenza | 2 (<1) | 2 (<1) | 1 (<1) |
| Appendicitis | 0 | 2 (<1) | 0 |
| Urinary Tract infection bacterial | 0 | 0 | 2 (<1) |

Source: ISS Table 24

No cases of helminthic infections were reported in the phase 3 exacerbation studies or the corticosteroid reduction trial, ZONDA. Two benralizumab treated patients in the 52-week dose ranging study MI-CP220 tested positive for strongyloides serology: a 54 year old white male in the United States and a 53 year old female from Peru. Both patients were asymptomatic and had already received investigational product prior to recognition of the positive tests. The Peruvian patient tested negative for stool parasites while the patient from the United States was not tested. Both received appropriate anti-strongyloides treatment and no treatment modification was made in either case.

In the benralizumab exacerbation trials, similar incidences of herpes zoster are seen between active (30 Q4: 4 [1], 30 Q8 6 [1]) and placebo treated patients (6 [1]). One additional case each is seen from benralizumab treated patients in the ZONDA trial (30 mg Q8) and the GREGALE trial, the latter of which did not include a placebo arm. Two SAEs of herpes zoster have been reported from the development program in benralizumab treated subjects versus no reports in placebo treated patients. One SAE was reported in the Q8 dose group in CALIMA trial and occurred in a 48 year old white female in the United States who was receiving methotrexate for rheumatoid arthritis. The second report occurred in a 50 year Russian female in the benralizumab q8 week group in the 52 week dose ranging trial, MI-CP220. The latter case was

temporally associated with the initiation of systemic corticosteroids after she was patient was hospitalized for an asthma exacerbation.

*Reviewer's Comment: While the only two herpes zoster SAEs occurred in benralizumab treated patients, both cases had confounding concomitant medication use (methotrexate and temporally related systemic steroids) which makes it difficult to determine if therapy with benralizumab was a contributing factor. Taken in the context of a lack of an imbalance in the overall number of herpes zoster AEs, this review does not recommend inclusion of these data into product labeling at this time, but recommends continued routine pharmacovigilance for herpes zoster infections.*

*The two cases with positive strongyloides serology did not demonstrate a worsening of infections with use of benralizumab. It addition, it is notable that 20% of the study population for CALIMA was enrolled from South America in endemic areas for helminthic infections. No helminthic infections were reported from this trial. Despite these considerations, the inclusion of this risk in product labeling, consistent with other IL-5 targeting therapies, is appropriate given the role eosinophils are believed to play in helminthic infection host defense.*

### 8.5.3. **Malignancy**

As outlined in Section 8.3.2, an independent adjudication committee assessed blinded data to assess the diagnosis of malignancy. All deaths in the program and SAEs under the SMQ for malignant tumors were submitted to the committee for adjudication

A total of 5 patients had 5 TEAE submitted to the malignancy sub-committee all of which were adjudicated as new malignancies. In addition, 1 patient developed prostate cancer during the treatment period in the CALIMA study but this diagnosis was not known until after database lock for study; this case is included in the summary of events from CALIMA/SIRROCO (Table 49).

The number of adjudicated malignancies in the SIROCCO/CALIMA database are limited with similar number of cases seen in active treatment arms and placebo. (benralizumab: 4/1663 0.2% and placebo: 1/847 0.1%). All of the observed events are common malignancies in the general population with no specific tumors occurring in more than one individual. There were no reported reoccurrences of prior malignancy; however, generalizability of this finding to the general population is limited as only 2% of patients were reported to have prior history of neoplasm prior to enrollment[17].

[17] Source: ISS Table 1.1.9.1 Medical History – current (Studies 17 and 18, Safety Analysis Set).

**Table 49: Adjudicated Malignancies in SIROCCO/CALIMA (SAS)**

| | Number of Patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| New malignancy during on-study period[a] | 3 (0.4) | 1 (0.1) | 1 (0.1) |
| Reoccurrence of previous cancer | 0 | 0 | 0 |
| [a] Cases include ovarian cancer (1), gall bladder cancer (1), gastric cancer (1), colon cancer (1), breast cancer (1), prostrate cancer (1) discovered following database lock | | | |

Source: ISS Table 28

When you include data from ZONDA, BISE, GREGALE and MI-CP220 an additional three malignancies were reported. These include a report of thyroid carcinoma in a patient receiving 30 mg Q4 benralizumab, cervical carcinoma in a patient treated with placebo, and malignant melanoma in a patient receiving 100 mg benralizumab in MI-CP220.

A total of 10 adjudicated malignancies have been reported in the 120-day safety update (10/1934; 0.5%). Of these, there were three reported B-cell lymphoma cases. One occurred in a patient who previously received placebo, therefore the patient had relatively shorter exposure to benralizumab and the dose remains blinded, and one case each occurred in the Q4 and Q8 treatment groups. Details for these three cases are summarized below.

- Patient E0311502: 62 year old Australian white male was diagnosed with CD5+ low grade/indolent non-Hodgkin lymphoma. The patient received benralizumab 30 mg Q8 in the preceding exacerbation study as well as in the BORA study. He had not associated B symptoms. Of note the patient had preceding lymphocytosis for 2 years prior to the diagnosis.
- Patient E1001501: 60 year old Canadian white female was diagnosed with stage II diffuse large B cell lymphoma. The patient received benralizumab 30 mg Q4 in the preceding exacerbation study as well as in the BORA study. The applicant notes that the patients was taking levothyroxine which they surmise may have been due to underlying hashimoto's disease. However, no specific thyroid disease beyond a benign thyroid nodule is specifically noted in the case narrative.
- Patient E2622007: 62 year old German white male was diagnosed with stage II large B cell lymphoma 16 days after his last dose of benralizumab. He previously received placebo in the preceding exacerbation trial and was randomized to benralizumab Q4 or Q8 he was enrolled in the BORA study and had less than 1 year of exposure (7 months) to benralizumab.

*Reviewer's Comment: The role of eosinophils in host defense against cancer was discussed during both Pulmonary Allergy Drugs Advisory Committee Meetings held for mepolizumab and*

*reslizumab on June 11, 2015 and December 9, 2015 respectively[18]. In both meetings, members of the committee opined that the literature evaluating the role of eosinophils in host tumor defense remains mixed with literature suggesting both pro- and anti-tumor effects. While a mechanism of action for an increased cancer risk remains unknown for eosinophil modulating therapies, the development, worsening or hastening of malignancy is worth considering with any immunomodulating therapy.*

*The reports of three lymphoma cases in the 120 day safety update are notable; however, no imbalance in malignant events is seen in the controlled database. When looking at the case narratives of the lymphoma cases, none of the individuals represent an unusual patient demographic and two patients had potential confounding factors. Given the limitations of the current data and the lack of an imbalance in the malignant events in the controlled database, this review does not recommend including a risk of malignancy in product labeling at this time. Of note, the applicant has ongoing trials in the COPD population which will provide additional placebo-controlled data to further assess the risk of malignancy.*

### 8.5.4. Cardiac Safety

As outlined in Section 8.3.2, an independent adjudication committee assessed all cases of death for adjudication in addition to evaluation of all investigator reported cases non-fatal MI and non-fatal stroke (hemorrhagic, ischemic, embolic).

A total of 17 patients had 18 TEAEs submitted for adjudication. Of these 11 patients were adjudicated as having MACE. No imbalance between active treatment and placebo is seen. Table 50 summarizes the adjudicated events.

**Table 50: Adjudicated MACE in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| Adjudicated MACE | 4 (0.5) | 5 (0.6) | 5 (0.6) |
| Cardiovascular death | 2 (0.2) | 3 (0.4) | 2 (0.2) |
| Myocardial infarction | 2 (0.2) | 1 (0.1) | 2 (0.2) |
| Hospitalization for unstable angina | 0 | 1 (0.1) | 0 |
| Stroke | 0 | 0 | 1 (0.1) |

Source: ISS Table 27

[18] Transcripts for the June 11, 2015 and December 9, 2015 PADAC committees. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815.htm Accessed on June 6, 2017

*Reviewer's Comment: The data do not suggest a causal link between benralizumab therapy and increased risk of MACE; however, the assessment is limited by the small number of events.*

### 8.5.5. Injection Site Reactions

A total of 61 patients reported injection site reactions (defined as pain, erythema, induration or reaction) in the exacerbation trials with no notable imbalance observed across treatment groups. There are a greater number of reports with use of the arm as the administration site.

**Table 51: Any Injection Site Reactions in SIROCCO/CALIMA (SAS)**

| | Number of patients (%) | | |
|---|---|---|---|
| | **30 mg Q4 N = 841** | **30 mg Q8 N = 822** | **Placebo N = 847** |
| **Any Injection site reaction** | | | |
| Any site | 27 (3.2) | 18 (2.2) | 16 (1.9) |
| Arm | 17 (2) | 13 (1.6) | 11 (1.3) |
| Stomach | 9 (1.1) | 5 (0.6) | 6 (0.7) |
| Thigh | 3 (0.4) | 6 (0.7) | 5 (0.6) |

Source: Modified from ISS Table 30

*Reviewer's Comment: A low number of injection site reactions are not unexpected with the injection of any product and the characteristics of the reported reactions do not appear unusual (data not shown).*

### 8.5.6. Device malfunctions

Benralizumab was administered in an accessorized pre-filled syringe in the phase 3 program by healthcare professionals. The applicant reports no incidences of TEAE related to device malfunction in the phase 3 exacerbation studies or ZONDA.

In addition to passive reporting of device failure in the exacerbation studies, the BLA application contains data from an 'at home use study' GREGALE. This study was an open-label study evaluating the functionality and reliability of the accessorized pre-filled syringe (APFS) when administered by a patient or care giver. This study included a prospective assessment of device performance. In this study, patients and investigators were queried about device performance and all devices were returned to the applicant and evaluated as functional or malfunctioning. A total of 573 devices were dispensed during the study, of which 1 used in the clinic was reported to have malfunctioned. A root cause analysis conducted by the sponsor indicates that the most likely cause was operator error during assembly of the device which led to syringe separation when used by the user. This is the only report of syringe detachment during this study or the phase 3 studies.

Two additional devices were reported as malfunctioning per the patient questionnaires. In one case the patient noted that they did not fully depress the plunger (due to a sneeze) and a second case where the patient failed to inject the dose because they failed to remove the cap. Both cases appear to be related to user error rather than a malfunctioning device.

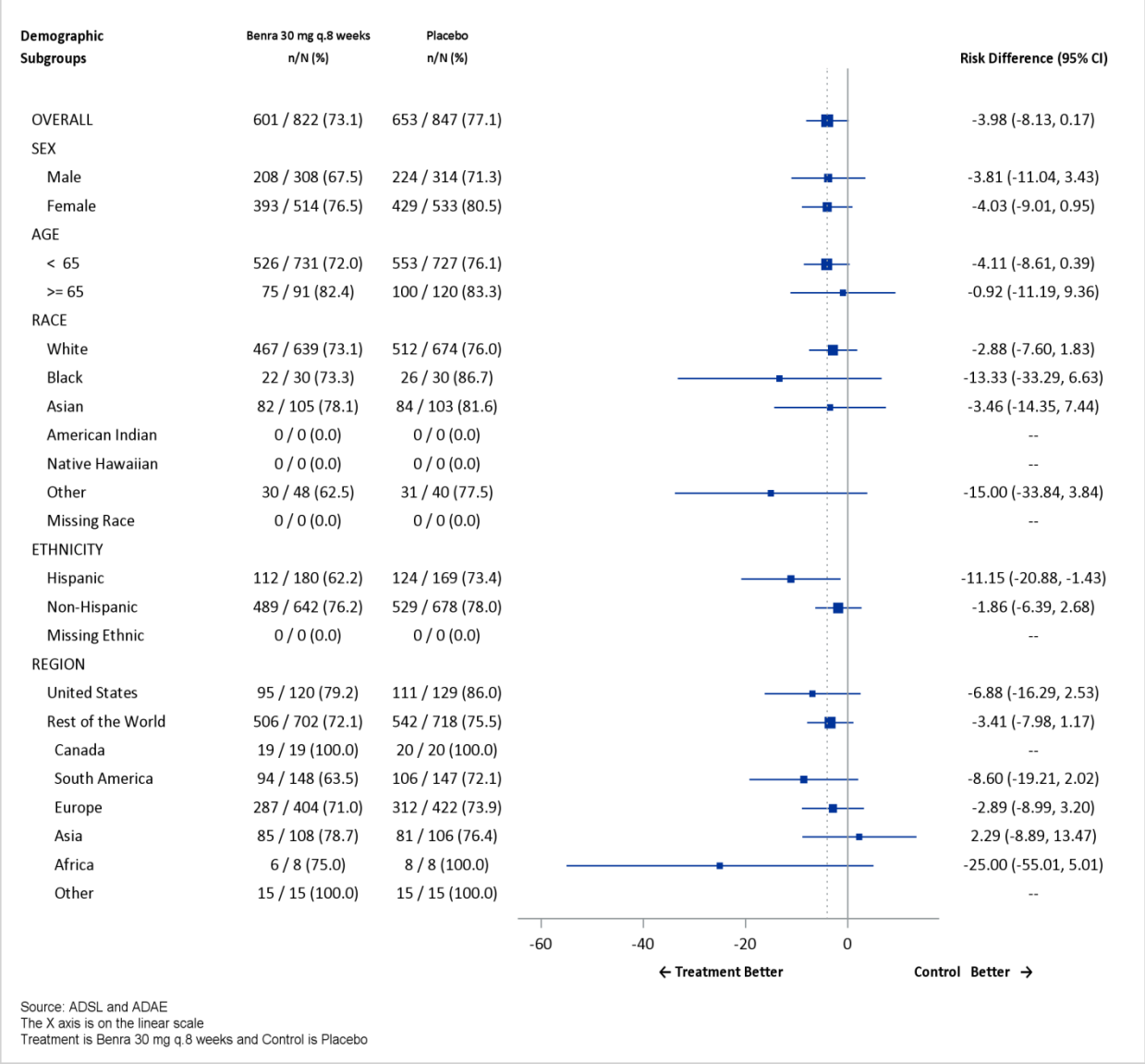
*Reviewer's Comment: Overall, the device appears to have performed satisfactorily across the phase 3 development program. Review of the device from a CMC and CDRH standpoint are pending at the time of this review. A full review of the GREGALE beyond a review of device complaints is deferred at this time* (b) (4)

## 8.6. Safety Analyses by Demographic Subgroups

Adolescents were not enrolled in the Q4W treatment group in Europe per EMA recommendations resulting in an imbalance in the number of enrolled subjects in this treatment arm. Overall, the total incidence of AEs in the adolescent population are lower than the general population and a review of the PTs does not reveal any safety concerns (data not shown).

Adverse event data using the SIRROCCO/CALIMA dataset was also evaluated by gender, race and region (Figure 15). The analysis of the subgroups is limited by the small number of events.

**Figure 15: Forest Plot of AE by Subgroup in SIROCCO/CALIMA (SAS)**




Source: Generated using OCS Demographics tool using the ISS ADAE datasets

*Reviewer's Comment: Review of the safety data by subgroup is limited by the small number of events in some groups; however the data do not reveal any concerning safety findings.*

## 8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies/clinical trials conducted for this application.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

Benralizumab is immunomodulatory and malignancy is a safety issue of concern. See Section 8.5.3 for additional details.

### 8.8.2. Human Reproduction and Pregnancy

There were a total of 14 pregnancies reported in the SIROCCO and CALIMA studies. A total of 8 patients reported a pregnancy in SIROCCO (2 each in Q4W, Q8W dose group and 4 in the placebo group). Of these 5 patients delivered a full term infant, with one patient in the Q4 dose group reported to have a spontaneous abortion at 6 weeks and one patient in the placebo group reported to have a spontaneous miscarriage at 8 weeks 6 days,. There was no pregnancy outcome data available on one patient who received benralizumab Q4 and discontinued the study. A total of 6 patients reported pregnancies in CALIMA (3 patients Q4W, 1 in Q8W, and 2 in the placebo group and 1 reported pregnancy in the female partner of patient in Q4W). A total of 3 patients and the female partner delivered full term healthy infants and there were two elective abortions (one each in the 30 Q4 and placebo group).

*Reviewer's Comment: The development program took standard measures to limit the incidence of pregnancy during the clinical trials. No assessment of the impact of benralizumab treatment can be made based on the limited data.*

### 8.8.3. Pediatrics and Assessment of Effects on Growth

Benralizumab is not expected to impact growth.

### 8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no anticipation of patient abuse or dependence on benralizumab based on its mechanism of action. In addition, the potential risk of abuse is partially mitigated by its administration by a healthcare professional in the clinic.

There were no formal studies conducted to assess the potential for withdrawal or rebound. A review of the post-treatment AEs does reveal any concerns for withdrawal or rebound effects.

## 8.9. Safety in the Postmarket Setting

### 8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

### 8.9.2. Expectations on Safety in the Postmarket Setting

No anticipated differences in how the drug was administered and used in the clinical trial versus its expected use in the postmarket setting that could lead to increased risk.

Off-label use is a possibility in other eosinophilic conditions; however it is anticipated that off-label use would be infrequent as these are rare disorders (e.g., hypereosinophilic syndrome, eosinophilic granulomatous polyangiitis, eosinophilic gastrointestinal disease [EGID]). As these rare conditions lack any approved therapies and can be associated with significant morbidity, a similar if not higher level of risk could be acceptable in these populations.

### 8.10. Additional Safety Issues From Other Disciplines

Not applicable

## 9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held for this BLA and there were no external clinical consultations requested.

## 10 Labeling Recommendations

### 10.1. Prescribing Information

Labeling negotiations remain ongoing at the time of this review. A high level of summary of labeling recommendations includes:

- The approved age range should extended to ≥ 12 years of age reflecting the population studied in the phase 3 exacerbation trials
- While not multiplicity protected, the subgroup analyses of the primary endpoint should be presented in labeling as these data provide clinically relevant information regarding the treatment effect on severe exacerbations (e.g., ER visits and/or hospitalizations) and assist in the selection of appropriate patients for treatment (subgroup analysis by baseline eosinophil count and exacerbation history).
- Responder data from the patient reported outcomes (ACQ6 and AQLQ) should be included in Section 14.
- Dose selection data from MI-CP220 should be included in Section 12 and 14.
- Summary results from the BISE trial should be included in Section 14.

### 10.2. Patient Labeling

At the time of this review, review of the patient labeling materials remains pending.

### 10.3. Nonprescription Labeling

Not applicable.

## 11 Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of this drug, no additional risk management strategies required beyond labeling are recommended. Therefore, the subsequent subsections are not applicable for this review and have been omitted

## 12 Postmarketing Requirements and Commitments

This review recommends that a (b) (4) PK/PD study be conducted in pediatric (b) (4) patients 6 to 11 years of age with a 12 month safety extension to characterize the PK/PD and safety of benralizumab.

## 13 Appendices

### 13.1. References

References are footnoted throughout the review.

### 13.2. Financial Disclosure

**Covered Clinical Study (Name and/or Number): D3250C00017 (SIROCCO); D3250C00018 (CALIMA); D3250C00020 (ZONDA); D3250C00029 (GREGALE); D3250C00032 (BISE); D3250L00001 (MI-CP220)**

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified:<br>D3250C00017 (SIROCCO): 1244 (391 principal investigators) | | |

| | | |
|---|---|---|
| D3250C00018 (CALIMA): 1065 (309 principal investigators)<br>D3250C00020 (ZONDA): 288 (ZONDA principal investigators)<br>D3250C00029 (GREGALE): 99 (26 principal investigators)<br>D3250C00032 (BISE): 142 (57 principal investigators)<br>D3250L00001 (MI-CP220):574 (104 principal investigators) | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): none reported | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: 2<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 26 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

Two investigators had disclosable financial information:

- Dr. (b) (6) reported $ 351,085 funding for an investigator initiated research product. Site (b) (6), with which he is affiliated, enrolled (b) (6) (out of 2014) and randomized (b) (6) out of 1296 subjects in CALIMA.

- Dr. (b) (6) reported a significant payment for research collaboration at a level of approximately 700-800, 000 USD. Site (b) (6), with which he is affiliated, enrolled (b) (6) subjects and randomized (b) (6) subjects out of 1296 subjects in CALIMA.

The two investigators with disclosable information and those for whom follow up information could not be obtained recruited a small sample of the total study populations. Given the small proportion of the study totals involved, it is unlikely that any misconduct could impact study results.

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

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/s/

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SOFIA S CHAUDHRY
07/19/2017

LYDIA I GILBERT MCCLAIN
07/19/2017