CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761-070
Drug Name:	Fasenra (benralizumab) injection: 30 mg/mL solution in a single-dose prefilled syringe, for subcutaneous use
Indication(s):	Indicated as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
Applicant:	AstraZeneca
Date(s):	Submission Date: November 16, 2016 Primary Review Due Date: July 16, 2017 PDUFA Date: September 16, 2017
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Keywords: clinical studies, missing data, eosinophilic phenotype

Table of Contents

1 EXECUTIVE SUMMARY 6

2 INTRODUCTION 9

2.1 OVERVIEW 9
2.1.1 Class and Indication 9
2.1.2 History of Drug Development 10
2.1.3 Overview of the Clinical Program 11
2.1.4 Specific Studies Reviewed 11
2.2 DATA SOURCES 12

3 STATISTICAL EVALUATION 12

3.1 DATA AND ANALYSIS QUALITY 12
3.2 EVALUATION OF EFFICACY 13
3.2.1 Asthma Exacerbation Study - SIROCCO 13
3.2.2 Asthma Exacerbation Study - CALIMA 31
3.2.3 Oral Corticosteroid Sparing Study - ZONDA 44
3.3 EVALUATION OF SAFETY 55

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS 55

4.1 GENDER, RACE, AGE, AND GEOGRAPHIC REGION 56
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS 60

5 SUMMARY AND CONCLUSIONS 63

5.1 STATISTICAL ISSUES 63
5.1.1 Interpretation of Subgroup Analysis Finding 63
5.1.2 Sensitivity Analysis to Missing Data 63
5.1.3 Sensitivity Analyses to Important Protocol Deviation 67
5.1.4 OCS Titration Error (ZONDA) 68
5.2 COLLECTIVE EVIDENCE 69
5.3 CONCLUSIONS AND RECOMMENDATIONS 70
5.4 LABELING RECOMMENDATIONS 71

6 BIBLIOGRAPHY 71

APPENDICES 72

APPENDIX A. STRATA CLOSURE PROCESS 72
APPENDIX B. THE APPLICANT'S SENSITIVITY ANALYSIS PLAN 72
APPENDIX C. SUBGROUP ANALYSIS FOREST PLOTS 73

LIST OF TABLES

Table 1. List of All Studies Included in This Statistical Review 11
Table 2. SIROCCO and CALIMA: Secondary Efficacy Endpoints Covered in the Proposed Labeling 15
Table 3. SIRROCO: Analysis Sets 20
Table 4. SIROCCO: Proportions of Subjects in EHS versus ELS within Treatment Group (FAS) 20
Table 5. SIRROCO: Patient Disposition (FAS) 21
Table 6. SIROCCO: Baseline Demographics (FAS) 22
Table 7. SIROCCO: Baseline Disease Characteristics (FAS) 23
Table 8. SIROCCO: Annualized Rate of Clinically Significant Exacerbation (FAS) 25
Table 9. SIROCCO: Change from Baseline Pre-Bronchodilator FEV1 at Week 48 (FAS) 26
Table 10. SIROCCO: Total Asthma Symptom Score at Week 48 26
Table 11. SIROCCO: Proportion of Subjects with at Least One Clinically Significant Exacerbation (FAS) 28
Table 12. SIROCCO: ACQ6 Score at Week 48 (FAS) 28
Table 13. SIROCCO: ACQ6 Responder Analysis at Week 48 (FAS) 29
Table 14. SIROCCO: AQLQ Score at Week 48 (FAS) 29
Table 15. SIROCCO: AQLQ Responder Analysis at Week 48 (FAS) 30
Table 16. SIROCCO: Annualized Rate of Exacerbation (Adjudicated) Requiring Hospitalization or ER visit (FAS) 30
Table 17. SIROCCO: Annualized Rate of Exacerbation (Adjudicated) Resulting in Hospitalization (FAS) 31
Table 18. CALIMA: Analysis Sets (FAS) 32
Table 19. CALIMA: Patient Disposition (FAS) 33
Table 20. CALIMA: Demographics (FAS) 34
Table 21. CALIMA: Baseline Disease Characteristics (FAS) 35
Table 22. CALIMA: Annualized Rate of Clinically Significant Exacerbation (FAS) 37
Table 23. CALIMA: Pre-Bronchodilator FEV1 at Week 56 (FAS, High-dose ICS) 38
Table 24. CALIMA: Total Asthma Symptom Score at Week 56 (FAS, High-dose ICS) 39
Table 25. CALIMA: Proportion of Subjects with at Least One Clinically Significant Exacerbation (FAS) 39
Table 26. CALIMA: ACQ6 Score at Week 56 (FAS, High-dose ICS) 40
Table 27. CALIMA: ACQ6 Responder Analysis at Week 48 41
Table 28. CALIMA: AQLQ Score at Week 56 (FAS, High-dose ICS) 41
Table 29. CALIMA: AQLQ Responder Analysis at Week 56 (FAS) 42
Table 30. CALIMA: Annualized Rate of Exacerbation (Adjudicated) Requiring Hospitalization or ER visit (FAS) 42
Table 31. CALIMA: Annualized Rate of Exacerbation Resulting in Hospitalization (FAS, High-dose ICS) 43
Table 32. ZONDA: Analysis Datasets 47
Table 33. ZONDA: Patients Disposition (FAS) 48
Table 34. ZONDA: Demographics (FAS) 49
Table 35. ZONDA: Baseline Disease Characteristics (FAS) 50
Table 36. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Primary Analysis 52
Table 37. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 1 52
Table 38. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 2: Proportional Odds Model 54
Table 39. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 3 55
Table 40. SIROCCO and CALIMA: Asthma Exacerbation: Interaction Test Results for Subgroup Analyses (FAS, High-ICS) 56
Table 41. SIROCCO and CALIMA: Key Secondary Efficacy Endpoints: Interaction Test Results for Age Subgroup Analyses (FAS, High-ICS) 58
Table 42. SIROCCO: Annualized Rate of Asthma Exacerbations by Baseline Exacerbation Count (FAS + EHS) 60
Table 43. CALIMA: Annualized Rate of Asthma Exacerbations by Baseline Exacerbation Count (FAS + High-ICS + EHS) 61
Table 44. SIROCCO: Change from Baseline Pre-Bronchodilator FEV1 at Week 48 by Baseline Exacerbation Count (FAS + EHS) 61

Table 45. CALIMA: Change from Baseline Pre-Bronchodilator FEV1 at Week 56 by Baseline Exacerbation Count (FAS + High-ICS + EHS) 62
Table 46. SIROCCO: Change from Baseline Total Asthma Symptom Score at Week 48 by Baseline Exacerbation Count (FAS + EHS) 62
Table 47. CALIMA: Change from Baseline Total Asthma Symptom Score at Week 56 by Baseline Exacerbation Count (FAS + High-ICS + EHS) 63
Table 48. SIROCCO: Tipping Point Analysis of Rate of Clinically Significant Exacerbations (FAS + EHS) 66
Table 49. CALIMA: Tipping Point Analysis of Rate of Clinically Significant Exacerbations (FAS + High ICS + EHS) 66
Table 50. SIROCCO: Sensitivity Analysis to Important Protocol Deviation - Annualized Rate of Asthma Related Exacerbation (FAS) 67
Table 51. CALIMA: Sensitivity Analysis to Important Protocol Deviation - Annualized Rate of Clinically Significant Exacerbation (FAS) 68
Table 52. ZONDA: Important Protocol Deviations (FAS) 69
Table 53. SIROCCO and CALIMA: Multiple Testing Procedure 69

LIST OF FIGURES

Figure 1. NAEPP 2007 Step-wise Approach to Asthma Treatment 9
Figure 2. Overview of the Clinical Development Program for Benralizumab in Patients with Asthma 11
Figure 3. SIROCCO: Study Flow Chart....14
Figure 4. SIROCCO: Multiplicity Control – Gate Keeping Procedure 17
Figure 5. SIROCCO: Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (FAS + EHS) .27
Figure 6. CALIMA: Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (FAS + EHS + High-ICS) 40
Figure 7. ZONDA: Flow Chart 45
Figure 8. ZONDA: Panel Plot Contrasting Location Changes of Primary Analysis Approach versus Sensitivity Analysis Approach (Week 28)....53
Figure 9. SIROCCO and CALIMA: Annual Asthma Exacerbation Rate Ratio by Age Groups, Q8W vs. Placebo (FAS, High-ICS)....57
Figure 10. SIROCCO and CALIMA: Change from Baseline PB-FEV1 at EOT: Mean Difference by Age Group, Q8W vs. Placebo (FAS, High-ICS)....58
Figure 11. SIROCCO and CALIMA: Change from Baseline Asthma Symptom Score at EOT: Mean Difference by Age Group, Q8W vs. Placebo (FAS, High-ICS)....59
Figure 12. SIROCCO: Sensitivity Analysis Clinically Significant Exacerbations by Multiple Imputation (FAS + EHS) 64
Figure 13. CALIMA: Sensitivity Analysis Clinically Significant Exacerbations by Multiple Imputation (FAS + High-ICS + EHS)....65
Figure 14. SIROCCO and CALIMA: Annual Asthma Exacerbation Rate Ratio by Age Groups, Q4W vs. Placebo (FAS +High-ICS)....73
Figure 15. SIROCCO and CALIMA: Change from Baseline PB-FEV1 at EOT: Mean Difference by Age Group, Q4W vs. Placebo (FAS + High-ICS)....74
Figure 16. SIROCCO and CALIMA: Change from Baseline Asthma Symptom Score at EOT: Mean Difference by Age Group, Q4W vs. Placebo (FAS + High-ICS)....74
Figure 17. SIROCCO: Forest Plot, Q8W vs. Placebo (FAS + EHS)....75
Figure 18. SIROCCO: Forest Plot, Q8W vs. Placebo (FAS)....75
Figure 19. SIROCCO: Forest Plot, Q4W vs. Placebo (FAS + EHS)....76
Figure 20. SIROCCO: Forest Plot, Q4W vs. Placebo (FAS)....76
Figure 21. CALIMA: Forest Plot, Q8W vs. Placebo (FAS + High-ICS + EHS)....77
Figure 22. CALIMA: Forest Plot, Q8W vs. Placebo (FAS + High-ICS) 77
Figure 23. CALIMA: Forest Plot, Q4W vs. Placebo (FAS + High-ICS + EHS)....78
Figure 24. CALIMA: Forest Plot, Q4W vs. Placebo (FAS + High-ICS) 78

1 EXECUTIVE SUMMARY

AstraZeneca submitted the biologics license application (BLA): BLA 761070 in support of Benralizumab 30 mg to the Food and Drug Administration (FDA) for the treatment of severe asthma, with the proposed indication and dosing regimen as follows:

> Indication
>
> *"Benralizumab is indicated as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older."*
>
> Dosing Regimen
>
> *"The recommended dose is 30 mg of Benralizumab by subcutaneous injection every 4 weeks for the first 3 doses, and then every 8 weeks thereafter, to be administered by a healthcare professional."*

The clinical development program included a total of 10 completed clinical studies. In my statistical review, I focused on three efficacy and safety studies, which were all double-blind, multicenter, randomized, parallel-group, placebo-controlled studies, in adolescents and adults with uncontrolled severe asthma.

The brief summary below gives an overview of the efficacy results demonstrated by the program. Detailed description and discussion regarding design, conduct, analysis, and results are contained in the main text of this review.

The replicate phase 3 asthma exacerbation studies SIROCCO and CLAIMA were both confirmatory studies designed to evaluate the effect of two dosing regimens of Benralizumab on asthma exacerbations in uncontrolled severe asthma patients despite high-dose ICS/LABA (CLAIMA was expanded to accept patients on medium-dose ICS/LABA (b) (4) With the primary objective being demonstrating treatment effect of Benralizumab in the eosinophilic asthma patients, the studies were enriched to power for treatment comparisons within the eosinophil high group/strata (≥300/μL, EHS), with an enrollment ratio of 2:1 versus the eosinophils low group/strata (<300/μL, ELS); the overall type-I error rate was controlled for primary and key secondary efficacy comparisons within the EHS population only; the studies were not powered or multiplicity controlled for treatment comparisons within the ELS population.

The two studies both demonstrated that Benralizumab 30 mg Q8W was an effective treatment in reducing the annualized rate of asthma exacerbations in the high-dose ICS EHS population. In SIROCCO (full analysis set, N=809), patients given Benralizumab had significant rate reductions in asthma exacerbations compared with those given placebo: 51% (rate ratio 0.49; 95% CI [0.37, 0.64]; p<0.001) for patients given Benralizumab Q8W treatment, and 45% (rate ratio 0.55; 95% CI [0.42, 0.71]; p<0.001) for patients given Benralizumab Q4W treatment. In CALIMA (full analysis set, N=728), the rate reduction was 28% (rate ratio 0.72; 95% CI [0.54,

0.95]; p=0.019) in the Q8W group, and 36% (rate ratio 0.64; 95% CI [0.49, 0.85]; p=0.002) in the Q4W group. Statistically significant treatment effects in terms of lung function (change from baseline in pre-bronchodilator FEV_1 at the end of the trials) and asthma symptom control (change from baseline in total asthma symptom score at the end of the trials) had also been demonstrated, consistently, by the two studies for the Q8W arm in the high-dose ICS EHS population.

The potential impact of missing data on the reliability of efficacy results was assessed through a series of tipping point analyses conducted for each statistically significant comparison over asthma exacerbations. In general, for each comparison, analyses treated missing data in the control arm as arising from a mechanism based on missing-at-random (MAR) assumption and varied the degree of shifting away from the MAR imputed values in the experimental treatment arm, in order to explore the space of missing-not-at-random (MNAR) assumptions. Assumptions were varied until reaching a tipping point at which the result of the comparison of interest changed from statistically significant to not significant. In all comparisons, the tipping points were clinically implausible, in that they ranged from 2-fold to 8-fold the size of the estimated treatment effects, such that these sensitivity analyses supported the primary analysis conclusions as briefed above.

In SIROCCO, there was a statistically significant interaction ($p<0.05$) between treatment and age group in terms of the primary endpoint. In fact, estimated treatment difference was only favoring investigational product in adults, but was not favoring in adolescents. Although this finding was based on a post hoc analysis in nature with small sample size resulting in a wide confidence interval for treatment difference, it was concerning from a regulatory perspective. To further assess this finding, I conducted similar analyses on the key secondary endpoints from both studies, SIROCCO and CALIMA and found no interaction between treatment and age group. In addition, the finding of a significant interaction was not replicated in CALIMA in terms of the primary endpoint. All things considered, a significant interaction found in one study, but not supported by other study or key secondary endpoints from both studies, was not convincing enough to lead me to a definite conclusion that the drug is not working in 12 to 17 age group. Therefore, I deferred the approval decision in 12 to 17 age group to clinical team's benefit-risk assessment.

The phase 3 OCS sparing study ZONDA (full analysis set, N=187) was conducted to evaluate the efficacy of Benralizumab in reducing OCS use, measured by percent reduction in final OCS dose compared with baseline, in the targeted population. The median percent reduction from baseline in the final OCS dose was 75% among patients in the Benralizumab Q8W group, as compared with the 25% reduction in the placebo group (Wilcoxon Rank Sum Test: $p<0.001$); the median percent reduction was also 75% among patients in the Benralizumab Q4W group (Wilcoxon Rank Sum Test: $p<0.001$). In conclusion, in severe eosinophilic asthma patients requiring OCS to maintain asthma control, the primary analysis of OCS reduction data demonstrated that Benralizumab had a significant OCS sparing effect.

However, several types of OCS dose titration related misconducts occurred during the conduct of ZONDA, both before or after randomization, and resulted in a high overall protocol deviation rate (25%). While the primary analysis approach was based on the ITT principle, I performed per

protocol analyses to assess the robustness of the primary analysis results against different types of protocol deviations. My sensitivity analysis results showed that the conclusion on treatment effect in OCS sparing, based on results from primary analysis, was not influenced by the protocol deviations.

Based on my statistical review of the efficacy data from the three phase 3 studies, I conclude that Benralizumab 30 mg, administered subcutaneously every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W), was effective in decreasing the rate of asthma related exacerbations in severe eosinophilic asthma patients who were uncontrolled with standard of care therapy, and was effective in decreasing the maintenance dose of oral corticosteroid (OCS) in severe eosinophilic asthma patients whose maintenance therapy included OCS. I think that the totality of evidence demonstrated by the Benralizumab clinical program supports the approval of the indication as proposed by the BLA.

APPEARS THIS WAY ON ORIGINAL

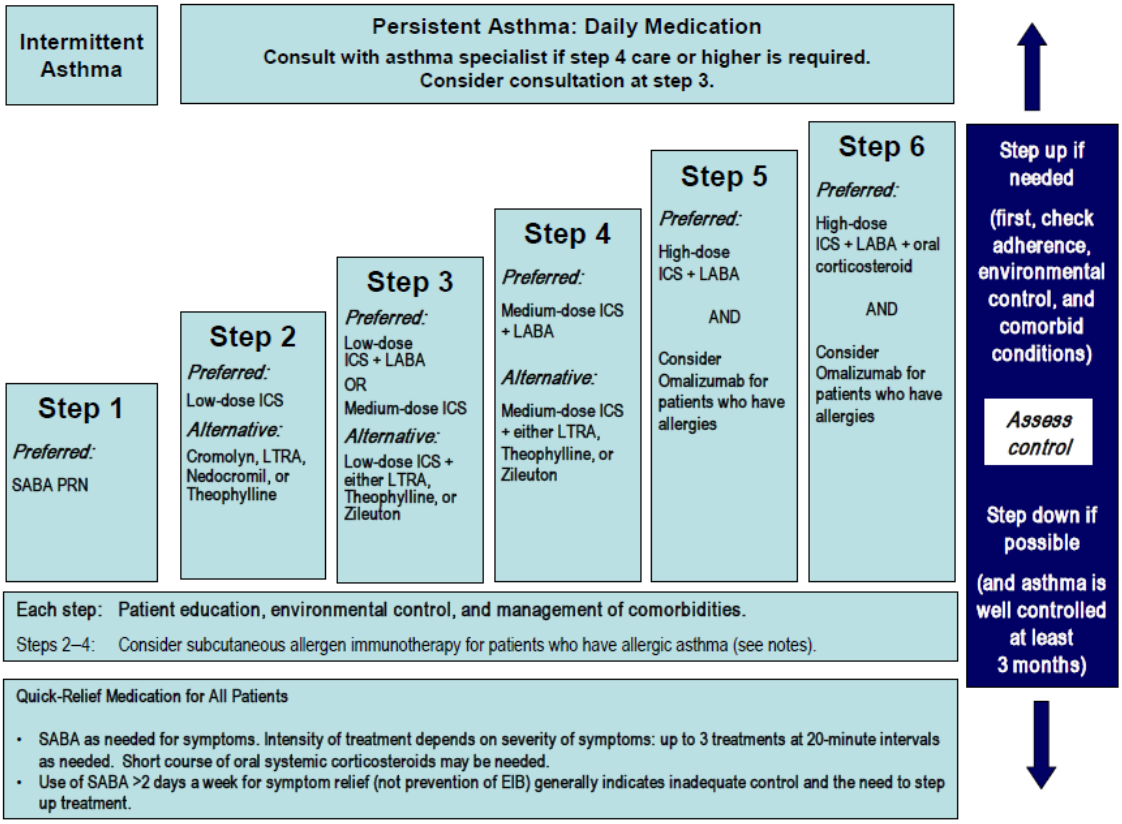
2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations. The current recommended standard of care (SOC) for asthma takes a step-wise intensification approach (NAEPP, 2007, Figure 1).

Figure 1. NAEPP 2007 Step-wise Approach to Asthma Treatment



Source: Figure 4-5 in NHLBI NAEPP EPR3, 2007.

However, there is a still a subpopulation of severe asthma patients whose symptoms are uncontrolled with high-dose inhaled corticosteroids (ICS) plus long acting beta agonist (LABA), and are at risk of severe asthma exacerbations. Severe eosinophilic asthma is one subgroup of the uncontrolled severe asthmatics defined and used by researchers and pharmaceutical companies in the pursuit of identifying a subset of severe uncontrolled asthma patients who are likely to respond to treatment with IL-5 pathway inhibitors. Severe eosinophilic asthma is characterized by increased blood eosinophil level, frequent exacerbations, airflow limitation, and absence of asthma control. Blood eosinophil count level as a biomarker is used in identifying patients: in clinical trials, a baseline blood eosinophil level of 300 cells/μL or larger has been used as a cutoff to define severe eosinophilic asthma.

Before the introduction of the biologic treatments for severe asthma, one of the limited treatment options for uncontrolled asthma is oral corticosteroid (OCS), which can lead to serious adverse events. Mepolizumab (trade name Nucala, for injection or subcutaneous use), Reslizumab (trade name Cinqair, for intravenous use) and Benralizumab are three interleukin-5 pathway inhibitors used to treat severe eosinophilic asthma. Mepolizumab (approved in 2015) and Reslizumab (approved in 2016) act by neutralizing the effects of interleukin 5 (IL-5) and blocking the activation of eosinophils by IL-5.

Benralizumab is a humanized, afucosylated, IL-5 receptor subunit alpha-directed monoclonal antibody (mAb). Compared with Mepolizumab or Reslizumab, Benralizumab not only blocks all the recruitment, activation, and mobilization of eosinophils but it also allows the depletion of eosinophils in the circulation, bone marrow, and target tissues, particularly airways and lungs in asthmatics (Tan, 2016). The current application is for Benralizumab 30 mg by subcutaneous (SC) injection *every 4 weeks for the first 3 doses, and then very 8 weeks thereafter* (Q8W) indicated as an add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients 18 years of age and older.

2.1.2 History of Drug Development

At the IND stage, the statistical team have reviewed the protocol and SAP of the Benralizumab for asthma phase 3 program and sent review comments to the applicant. Among others, the following interactions were considered important in shaping the development program, improving study designs and statistical analysis plans.

1. In the end of phase 2 meeting package, the company proposed to *enroll in the phase 3 studies only those subjects whose blood eosinophil counts are equal to or above the predefined 300 cells/μL cut-point based data generated from the phase 2b asthma study MI-CP220 and were accordingly identified as "eosinophilic"*. In the responses, the FDA disagreed with the proposal and considered the data generated could not be used to confirm the applicant selected cut-point (sent on January 23, 2013). The applicant responded by including patients with <300 cells/μL blood eosinophil count while enriching the studies for the eosinophil high group in a 2:1 ratio across the studies.

2. Statistical requested justification that sample size selection of the eosinophil low strata was sufficient enough to estimate the treatment effect in that subgroup, i.e., to reliably discriminate between the hypothesis of no treatment effect and the hypothesis of a clinically important treatment effect (sent on November 19, 2013). The sponsor provided an integrated ISE SAP to pool the two exacerbation studies to reach sufficient power in characterizing treatment effect for the eosinophil low strata.

3. Statistical comments sent to the applicant requested that the SAP should include pre-specified sensitivity analyses to possible violations of the assumptions about the missing data (sent on May 21, 2014). The applicant responded by including in the SAP

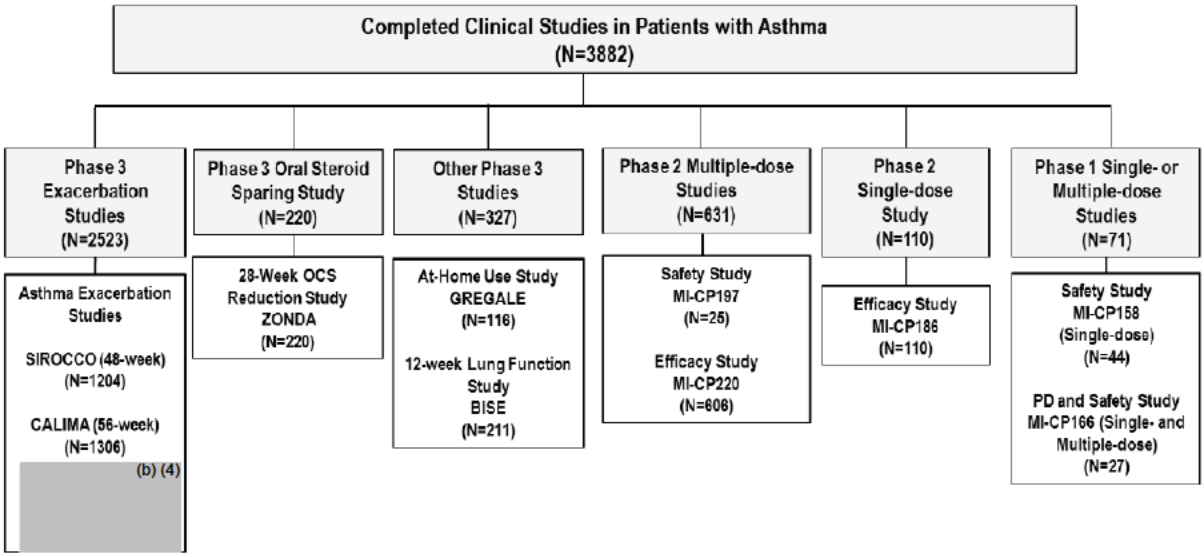
imputation based sensitivity analyses and a tipping point analysis plan to study the sensitivity of the primary analysis results to variations of assumptions on missing data.

4. Statistical comments requested clarification on if the primary analyses in SIROCCO and CALIMA will be based on the adjudicated asthma exacerbation endpoint (sent on May 21, 2014). The applicant responded by clarifying that the primary endpoint will use unadjudicated asthma exacerbation.

2.1.3 Overview of the Clinical Program

The Benralizumab for asthma clinical development program supporting application comprised 10 completed studies (Figure 2). The phase 3 program included two asthma exacerbation studies (SIROCCO and CALIMA), one OCS reduction study (ZONDA), and study to evaluate efficacy and safety in mild to moderate persistent asthma (BISE) and one at-home use study (GREGALE). (b) (4)

Figure 2. Overview of the Clinical Development Program for Benralizumab in Patients with Asthma



Source: Applicant, Module 2.5 Clinical Overview, Figure 3

2.1.4 Specific Studies Reviewed

In this review, I focused on the design, statistical analysis methods and efficacy results of studies SIROCCO, CALIMA and ZONDA. Table 1 summarizes the key design elements across the three studies.

Table 1. List of All Studies Included in This Statistical Review

Study	Design	Treatment Period*	Number of Subjects Randomized/ Completed Study	Study Population	Study Dates
D3250C0017 SIROCCO	MC, R, DB, PG, PC trial 48 weeks	Benralizumab 30 mg, Q4W Benralizumab 30 mg, Q8W Placebo	Total: 1205/1079 Q4W: 400/354 Q8W: 398/358 Placebo: 407/367	Patients **12 to 75** years of age with uncontrolled asthma and a history of exacerbations still symptomatic despite using **high-dose** ICS/LABAs with or without OCS or additional controller medications	FPE: 09/19/2013 LPLV: 04/05/2016
D3250C0018 CALIMA	MC, R, DB, PG, PC trial 56 weeks	Benralizumab 30 mg, Q4W Benralizumab 30 mg, Q8W Placebo	Total: 1306/1181 Q4W: 425/389 Q8W: 441/390 Placebo: 440/402	Patients **12 to 75** years of age with uncontrolled asthma and a history of exacerbations still symptomatic despite using **medium** or high-dose** ICS/LABAs with or without OCS or additional controller	FPE: 08/21/2013 LPLV: 03/11/2016
D3250C0020 ZONDA	MC, R, DB, PG, PC trial 28 weeks	Benralizumab 30 mg, Q4W Benralizumab 30 mg, Q8W Placebo	Total: 220/209 Q4W: 72/68 Q8W: 73/69 Placebo: 75/72	Patients **18 to 75** years of age with severe asthma who required treatment with high-dose ICS/LABAs and **chronic OCS** therapy with or without additional controller medications	FPE: 04/28/2014 LPLV: 08/08/2016

Source: Reviewer
Abbreviations: MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, SC: subcutaneous, FPE: first patient enrolled, LPLV: last patient last visit.
*Q4W: Regimen with every 4 weeks throughout the treatment period, Q8W: Regimen with every 4 weeks for the first 3 doses and then every 8 weeks thereafter.
**CALIMA was expanded to include medium-dose ICS/LABA patients (b) (4).

2.2 Data Sources

Data were submitted by the applicant to the CDER electronic data room in SAS transport format. Protocols, Reporting and Analysis Plans, Study Reports, correspondence, and data listings were accessed under the EDR link: \\cdsesub1\evsprod\BLA761070\761070.enx.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented or became so upon information request. I was able to reproduce the results of all key analyses.

3.2 Evaluation of Efficacy

3.2.1 Asthma Exacerbation Study - SIROCCO

3.2.1.1 Study Design and Endpoints

3.2.1.1.1 SIROCCO Study Design

SIROCCO was a randomized, double-blind, parallel group, placebo-controlled study designed to evaluated efficacy and safety of a fixed 30 mg dose of Benralizumab administered subcutaneously (SC) in two dosing regimens (every 4 weeks throughout the treatment period, versus every 4 weeks for the first 3 doses and then every 8 weeks thereafter) in patients with a history of asthma exacerbations and uncontrolled asthma receiving high-dose ICS/LABA with or without OCS and additional asthma controller. The design elements as described in the following subset sections were set to suit the purpose of the trial, to follow regulatory guidelines, and to accommodate several specifics of the trial.

3.2.1.1.1.1 Enrichment Design

From results of early phase clinical studies with Benralizumab (e.g. Phase IIb Mi-CP220), the applicant made the observation that Benralizumab *resulted in rapid and prolonged depletion of eosinophils in the peripheral blood and in the asthmatic airway with associated improvements in multiple metrics of asthma control*[1]. With the hypothesis drawn from early phase trials that the magnitude of clinical improvement was positively correlated with baseline blood eosinophil counts and was most consistently observed in patients with absolute blood eosinophil counts ≥300/μL, to address the question if baseline blood eosinophil level could predict benefit, the study included patients with both blood eosinophil counts ≥300/μL and <300/μL. To power the primary comparison of Benralizumab over placebo in patients most likely to respond to Benralizumab, the study enriched the overall population for the eosinophil high group/strata (≥300/μL, EHS) with an enrollment ratio of 2:1 versus the eosinophils low group/strata (<300/μL, ELS); the multiple testing procedure to control the overall type-I error rate covered only primary and key secondary efficacy comparisons based on EHS.

3.2.1.1.1.2 Dosing Regimens, Randomization, and Assessment Schedule in a Global Setting

Upon initial enrollment and confirmation of entry criteria, patients entered the screening/run-in period (Figure 3) of a minimum 2 weeks to allow adequate time for all of the eligibility criteria to be evaluated. Eligible patients were randomized with stratification by geographical region, age group (adult or adolescent) and baseline blood eosinophil count (≥300/μL or <300/μL).

Adult patients and adolescents in non-European (non-EU) countries were randomized to one of the three treatment arms: Benralizumab 30 mg Q4W, Benralizumab 30 mg Q8W, and placebo. To accommodate the Pediatric Committee at the European Medicines Agency's request to limit drug burden in adolescents and to study only the less frequent dose in this patient population,

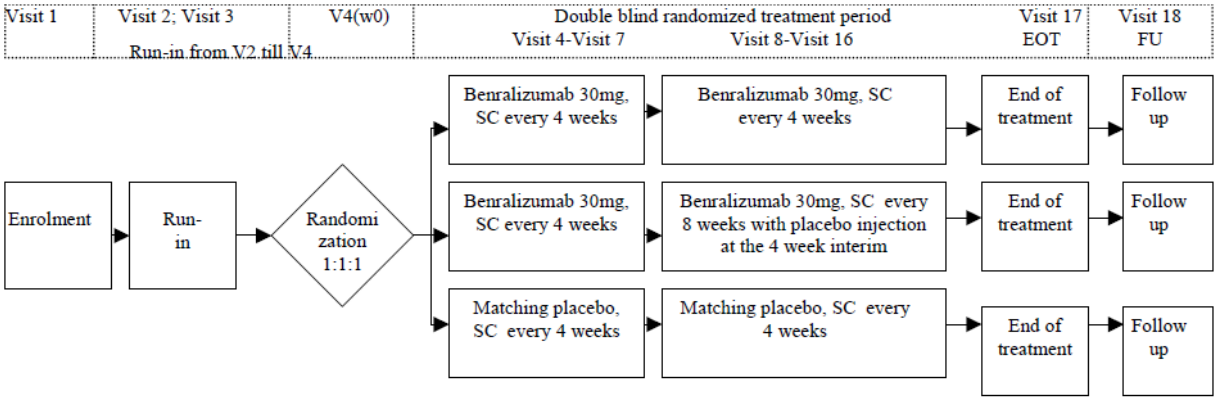
[1] SIROCCO study Protocol Section 1.2.

adolescent patients in EU countries were randomized to either the placebo or the Benralizumab 30 mg Q8W arm. See Appendix B for protocol description of the strata closure process used by the applicant at randomization.

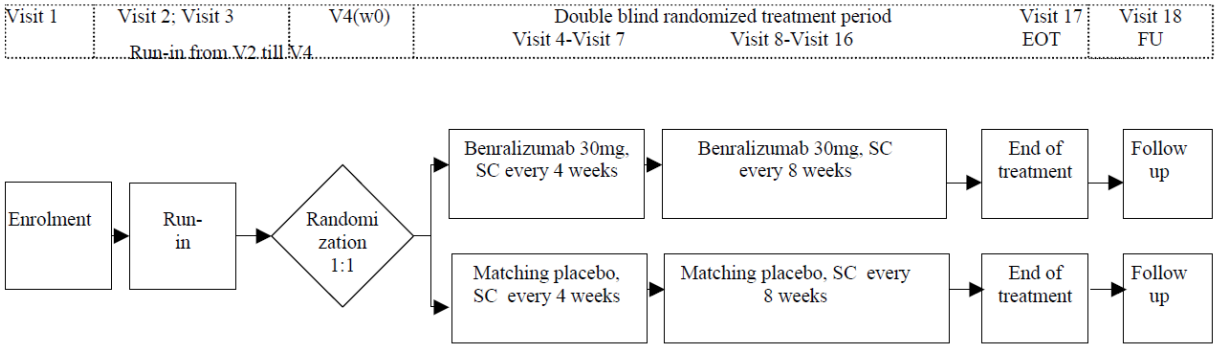
To accommodate the two dosing frequencies of Benralizumab and to keep blinding, the investigational product (IP) was administered at the study center every 4 weeks for the first 3 doses, and then every 4 or 8 weeks thereafter. After the first 3 doses, patients randomized to the 8-week regimen received placebo at visit 8 (dose 4) with active drug administered at visit 9 (dose 5) and then every second treatment visit thereafter; placebo (dummy) injections were administered at the 4-week interim treatment visits in order to maintain the blind. The double blind treatment period was 48 weeks in length with the last dose of Benralizumab or placebo administrated at week 44 and the end of treatment (EOT) visit on week 48. In the duration of the study, patients were maintained on their prescribed high-dose ICS-LABA therapy. A follow-up visit was conducted at week 56.

Figure 3. SIROCCO: Study Flow Chart

3A. For adult patients (global) and adolescent patients in non-EU countries



3B. For adolescent patients in EU countries



Source: SIROCCO CSR, Figure 1, Figure 2.

3.2.1.1.2 SIROCCO Primary and Secondary Efficacy Endpoints

The primary objective of the study was to evaluate the effect of two dosing regimens of Benralizumab on asthma exacerbations in patients on high-dose ICS/LABA with uncontrolled asthma. The primary efficacy was determined based on reduction in the rate of asthma exacerbations over 48 weeks for Benralizumab versus placebo in EHS.

The primary endpoint was annual asthma exacerbation rate, where an asthma exacerbation was defined by a worsening of asthma requiring: a) use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least 3 days; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids; b) an emergency room/urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department (ED) or urgent care center) due to asthma that required systemic corticosteroids (as per above), or c) an inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for > 24 hours).

In the SAP, the primary analysis on the annual asthma exacerbation rate was based on the **unadjudicated** annual exacerbation rate based on data reported by the investigator in the eCRF.

Secondary objectives were to assess the effect of the two dosing regimens of Benralizumab on pulmonary functions, on asthma symptoms and other asthma control metrics, on other parameters associated with asthma exacerbations, on asthma related and general health related quality of life, etc. The two key secondary efficacy endpoints were: the change in pre-bronchodilator FEV1 from baseline to Week 48 in EHS, and the total asthma symptom score change from baseline to Week 48 in EHS.

Among the rest of the secondary efficacy endpoints assessed in the study, a selected list of endpoints are also covered in this review: asthma control questionnaire (ACQ-6), and asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12)(Table 2). In addition, asthma control responder status and AQLQ (S)+12 responder status were evaluated as supportive analyses. An ACQ-6 responder was defined as a patient who had improvement on ACQ-6, ie, an ACQ-6 responder variable takes value 1 if change from baseline to end of treatment in ACQ-6 ≤-0.5 and 0 otherwise. An AQLQ(S)+12 responder was defined as a patient who had improvement on AQLQ(S)+12, ie, an AQLQ(S)+12 responder variable takes value 1 if change from baseline to end of treatment in AQLQ(S)+12 ≥0.5 and 0 otherwise.

Table 2. SIROCCO and CALIMA: Secondary Efficacy Endpoints Covered in the Proposed Labeling

Objective	Endpoint	Assessment Schedule	Coverage in this Review
To assess the effect of two dosing regimens of Benralizumab on **pulmonary function**	Change from baseline to Week 48 pre-bronchodilator FEV_1 (L)	By visit (every four weeks)	✓
To assess the effect of two dosing regimens of	(b) (4)	Bi-weekly means of daily diary	✓

Benralizumab on **asthma symptoms and** other asthma **control** metrics (as per the ePRO)	(b) (4)		
	Change from baseline to Week 48 in mean ACQ-6 score	The questionnaires were completed by the patients using the ePRO device every 2 weeks throughout the 48-week treatment period	✓
	Asthma control responder status: ACQ-6 (EOT – Baseline) ≤ -0.5	Assessment at EOT	✓
To assess the effect of two dosing regimens of Benralizumab on other parameters associated with **asthma exacerbations**	Time to first asthma exacerbation		✓
	(b) (4)		✓
To assess the effect of two dosing regimens of Benralizumab **on emergency room/urgent care visits and hospitalizations** due to asthma	Number of exacerbations resulting in ER visit or hospitalization (b) (4)		✓
	Number of exacerbations resulting in hospitalization (b) (4)		✓
To assess the effect of two dosing regimens of Benralizumab on asthma related and general health-related **quality of life**	Change from baseline to Week 48 in mean AQLQ(S)+12 score	The questionnaires were completed by the patients using the ePRO device every 4 weeks throughout the 48-week treatment period	✓
	AQLQ(S)+12 responder status: AQLQ(S)+12 (EOT – Baseline) ≥ 0.5	Assessment at EOT	✓

Source: Modified from applicant's SIROCCO SAP Section 1.1.2

3.2.1.1.3 SIROCCO Multiplicity Control

The patient population of interest was the patients with baseline blood eosinophils ≥300/μL (eosinophil high stratum, EHS). To account for multiplicity to test the primary endpoint and the two key secondary endpoints for each of the 2 dosing regimens, a gate keeping multiple testing procedure (MTP) was followed to control the overall type I error rate (Figure 4):

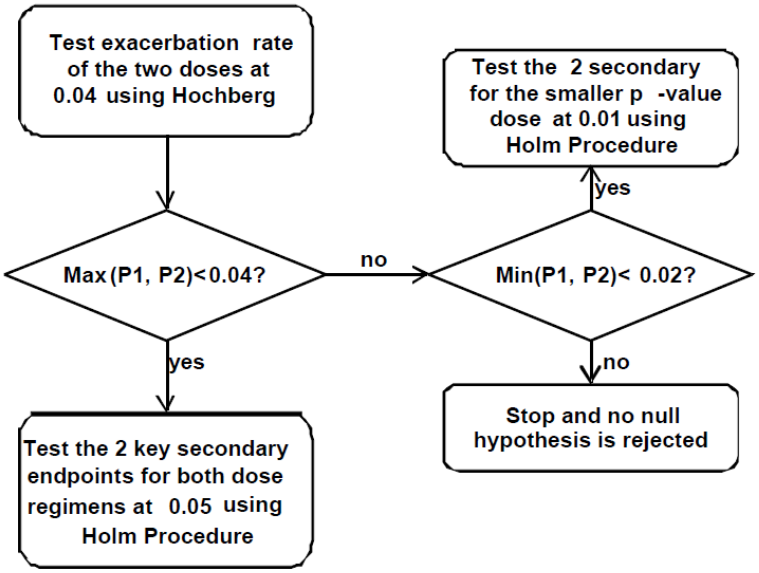
Step 1: Perform the 2 tests of annual asthma exacerbation rate (1 test for each dose regimen vs. placebo) at the family wise error rate (FWER) of 0.04 using a Hochberg procedure. If both p-values are less than 0.04, then proceed to Step 2; else if the smaller p-value is less than 0.02 then proceed to Step 2a; otherwise no null hypothesis is rejected.

Step 2: Test the 2 key secondary endpoints for both dose regimens as 1 family at the FWER of 0.05 using a Holm Procedure.

Step 2a: Test the 2 secondary endpoints for the dose with smaller-p-value at the FWER of 0.01 using a Holm Procedure. Since the correlation of the 2 test statistics for annual asthma

exacerbation rate in Step 1 is positive, due to the common placebo group, the FWER of the Hochberg Procedure is strongly controlled at 0.04. The overall FWER of the gate keeping procedure is strongly controlled at 0.05.

Figure 4. SIROCCO: Multiplicity Control – Gate Keeping Procedure



Source: SIRROCO Study SAP Edition 4, Section 4.1

3.2.1.2 Statistical Methodologies

The analyses of the primary and secondary efficacy endpoints followed the ITT principle: the analyses included all data captured during the 48-week double-blind treatment period, including data regardless of whether study treatment was prematurely discontinued, or delayed, and/or irrespective of protocol adherence, unless the patient withdrew consent to study participation.

For each efficacy endpoint, treatment effect for each of the dosing regimen of Benralizumab was compared to that of the placebo.

The applicant's blinded data review of the phase 3 asthma exacerbation studies encountered model fitting convergence issues for some of the statistical models. While study protocols indicated that country would be among the baseline covariates adjusted for in formal statistical models, prior to unblinding the study data, the applicant made decision to replace the country covariate effect with region in all analyses where this effect was included[2]. In this review, region will be used in place of the region effect.

[2] SIROCCO clinical study report (CSR) and CALIMA CSR Table 7 listed changes made to the planned analyses.

3.2.1.2.1 SIROCCO Primary Efficacy Endpoint – Primary Analysis Method

The primary analyses were based on the **unadjudicated** annual exacerbation rate based on data reported by the investigator in the eCRF. Calculation of the number of exacerbations experienced by a patient during the 48-week treatment period followed the rule specified in the protocol. In the primary analysis, the number of exacerbations observed for a patient during the 48-week double-blind treatment period was used as response variable. The SAP specified exacerbation counting rules in situations of lost to follow-up. The applicant also assessed the on-treatment annual exacerbation rate as a sensitivity analysis, using only exacerbations occurring during the on-treatment period.

In the primary analysis, annual exacerbation rate in each of the 2 Benralizumab dose regimen groups was compared to annual exacerbation rate in the placebo group using a negative binomial model. The response variable in the model was the number of asthma exacerbations experienced by a patient, over the 48-week double-blind treatment period. The model included covariates of treatment group, region, number of exacerbations in previous year, and the use of maintenance oral corticosteroids (yes/no). The logarithm of the patient's corresponding follow-up time was used as an offset variable in the model to adjust for patients having different exposure times during which the events occurred.

The model based annual exacerbation rate estimates in the individual treatment groups were estimated using the OBSMARGINS option in LSMEANS statement in SAS. The option provides predicted estimates of rates under the assumption of mean levels for baseline covariates. In the study SAP, the applicant raised the concern that in regression models such as the negative binomial that transform the linear predictor, estimation of response evaluated at the mean covariate levels may not closely approximate the overall mean population response. The study SAP proposed the marginal standardization method in calculating mean annual exacerbation rates. The marginal method uses the same fitted model, but involves using the model to predict, for each patient in the study, the mean outcome assuming assignment to each particular treatment group in turn, assuming each patient's observed values for the other baseline covariates (ie, region, OCS use, and prior exacerbations). Averaging these predictions for each treatment group provides the estimate for each arm. We agree with the applicant's proposal in that, in the negative binomial regression setting, the marginal method more closely aligns with the crude annual exacerbation rate, and as such, provides a more appropriate covariate-adjusted summary within treatment groups.

3.2.1.2.2 SIROCCO Primary Efficacy Endpoint – Subgroup Analysis Method

See section 4.1 for detail.

3.2.1.2.3 SIROCCO Primary Efficacy Endpoint – Missing Data Handling and Sensitivity Analyses

See section 5.1.2 for detail.

3.2.1.2.4 SIROCCO Secondary Efficacy Endpoint – Analysis Methods

The continuous secondary efficacy endpoints including change from baseline in pre-bronchodilator FEV1 at Week 48, change from baseline asthma symptom score at Week 48, change from baseline ACQ-6 score, AQLQ(S) + 12, etc., were analyzed for the 2 Benralizumab treatment groups and the placebo group using a mixed-effect model for repeated measures (MMRM) analysis. For each endpoint, the dependent variable was the change from baseline of the parameter at post baseline scheduled visits up to the EOT visit. The model included treatment group as the explanatory variable and region, the use of maintenance oral corticosteroids (yes/no), visit, and treatment*visit interaction as fixed effects and baseline value as a covariate. The variance-covariance matrix was assumed to be unstructured. Upon non convergence in model fitting, a compound symmetric variance-covariance matrix was to be used instead.

Responder endpoints such as proportion of patients with ≥1 asthma exacerbation were analyzed using a Cochran-Mantel-Haenszel test controlling for region, number of exacerbations in previous year, and the use of maintenance oral corticosteroids (yes/no).

Time to event endpoints such as time to first asthma exacerbation were analyzed as using a Cox proportional hazard model with the covariates of treatment, region, number of exacerbations in previous year, and the use of maintenance oral corticosteroids (yes/no).

Asthma control responder status based on ACQ-6 at Week 48 and AQLQ(S)+12 responder status based on AQLQ(S)+12 at Week 48, was analyzed using a logistic regression model with covariates of treatment, region, number of exacerbations in previous year, baseline value, and the use of maintenance OCS (yes/no), for EHS. Patients with missing or non-evaluable ACQ-6 score or AQLQ(S)+12 score at Week 48 were considered non-responders.

3.2.1.3 Analysis Datasets, Patients Disposition, Demographics and Baseline Disease Characteristics

Study SIROCCO protocol defined four analysis sets: the *all patients analysis set*, the *full analysis set*, the *safety analysis set* and the *PK analysis set*. The *all patients analysis set* comprised all patients screened for the study and was used for reporting disposition and screening failures. The *safety analysis set* included all patients who received at least 1 dose of the IP; patients were classified according to the treatment they actually received. The *full analysis set* (FAS) included all patients who were randomized and had received any IP, irrespective of their protocol adherence and whether or not they had continued participation in the study. In the design setting of SIROCCO, by its definition, the FAS was the most suitable population to support evaluation of the ITT estimand: *patients in FAS were analyzed according to their randomized treatment, irrespective of whether or not they had prematurely discontinued*. However, *patients who withdrew consent to participate in the study was included up to the date of their study termination*, and clinical data were not collected on scheduled study visits post study discontinuation. In SIROCCO, all efficacy analyses were performed using an ITT approach based on the FAS.

Of the 2681 subjects (Table 3) who were enrolled, 2232 (83.3%) entered screening/run-in, and 1205 (44.9%) were randomized to study treatments: Benralizumab 30 mg Q4W, Benralizumab 30 mg Q8W, or placebo. 810 (67%) of the randomized subjects were patients with baseline blood eosinophil count ≥300 cell/µL. Aside from one patient who was randomized to the Q4W group, all randomized patients received study drug. The safety analysis set coincided with the FAS. Patients in this study were allowed in the protocol to switch to an alternative treatment or treatments after they discontinue from randomized treatment and were encouraged to complete visits until they withdrew from the study. It was expected that the rate of treatment discontinuation would be different from the rate of study withdrawal due to this effort of post treatment discontinuation data collection. However, the overall study withdrawal rate (FAS: 10%; EHS: 10%) was only slightly lower than the corresponding treatment dropout rate (FAS: 11%; EHS: 11%).

Table 3. SIRROCO: Analysis Sets

	All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (EHS)			
	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo	Total	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo	Total
Patients Screened				2681				
	Denominator: Number of Patients Screened							
Patients Who Entered Screening/Run-in				2232 (83.3%)				
Randomized Population				1205 (44.9%)				
Denominator: Number of Randomized Population								
Randomized Population	400 (100%)	398 (100%)	407 (100%)	1205 (100%)	276 (100%)	267 (100%)	267 (100%)	810 (100%)
Safety Population	399 (99.8%)	398 (100%)	407 (100%)	1204 (99.9%)	275 (99.6%)	267 (100%)	267 (100%)	809 (99.9%)
Full Analysis Set	399 (99.8%)	398 (100%)	407 (100%)	1204 (99.9%)	275 (99.6%)	267 (100%)	267 (100%)	809 (99.9%)

Source: Reviewer

Table 4. SIROCCO: Proportions of Subjects in EHS versus ELS within Treatment Group (FAS)

Baseline Blood Eosinophil Group	Benra 30 mg q.4 weeks N=399	Benra 30 mg q.8 weeks N=398	Placebo N=407	Total N=1204
eosinophil counts >=300/µL (EHS)	275 (68.9%)	267 (67.1%)	267 (65.6%)	809 (67.2%)
eosinophil counts <300/µL (ELS)	124 (31.1%)	131 (32.9%)	140 (34.4%)	395 (32.8%)

Source: Reviewer

Table 5. SIRROCO: Patient Disposition (FAS)

	All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (FAS + EHS)			
	Benra 30 mg q.4 weeks N=399	Benra 30 mg q.8 weeks N=398	Placebo N=407	Total N=1204	Benra 30 mg q.4 weeks N=275	Benra 30 mg q.8 weeks N=267	Placebo N=267	Total N=809
Treatment Completion								
Patients Who Have Completed Treatment	349 (87.5%)	358 (89.9%)	362 (88.9%)	1069 (88.8%)	244 (88.7%)	240 (89.9%)	235 (88.0%)	719 (88.9%)
Treatment Dropout	50 (12.5%)	40 (10.1%)	45 (11.1%)	135 (11.2%)	31 (11.3%)	27 (10.1%)	32 (12.0%)	90 (11.1%)
Reason for Premature IP Discontinuation								
Withdrawal by Subject from IP	20 (5.0%)	16 (4.0%)	20 (4.9%)	56 (4.7%)	13 (4.7%)	11 (4.1%)	16 (6.0%)	40 (4.9%)
Other	9 (2.3%)	7 (1.8%)	11 (2.7%)	27 (2.2%)	6 (2.2%)	4 (1.5%)	7 (2.6%)	17 (2.1%)
Adverse Event	9 (2.3%)	8 (2.0%)	5 (1.2%)	22 (1.8%)	4 (1.5%)	6 (2.2%)	3 (1.1%)	13 (1.6%)
Protocol Deviation	5 (1.3%)	3 (0.8%)	3 (0.7%)	11 (0.9%)	4 (1.5%)	2 (0.7%)	3 (1.1%)	9 (1.1%)
Lost to Follow-up	4 (1.0%)	4 (1.0%)	2 (0.5%)	10 (0.8%)	4 (1.5%)	2 (0.7%)	1 (0.4%)	7 (0.9%)
Study-specific withdrawal criteria	3 (0.8%)	2 (0.5%)	3 (0.7%)	8 (0.7%)	0	2 (0.7%)	2 (0.7%)	4 (0.5%)
Missing*	0	0	1 (0.2%)	1 (0.1%)	0	0	0	0
Study Completion								
Patients Who Have Completed Study	354 (88.7%)	358 (89.9%)	367 (90.2%)	1079 (89.6%)	247 (89.8%)	240 (89.9%)	241 (90.3%)	728 (90.0%)
Analysis Dropout	45** (11.3%)	40 (10.1%)	40 (9.8%)	125** (10.4%)	28** (10.2%)	27 (10.1%)	26 (9.7%)	81**(10.0%)
Reason for Early Discontinuation from Study								
Withdrawal by Subject from IP	20 (5.0%)	15 (3.8%)	17 (4.2%)	52 (4.3%)	12 (4.4%)	11 (4.1%)	10 (3.7%)	33 (4.1%)
Other	9 (2.3%)	9 (2.3%)	14 (3.4%)	32 (2.7%)	5 (1.8%)	5 (1.9%)	11 (4.1%)	21 (2.6%)
Lost to Follow-up	4** (1.0%)	6 (1.5%)	3 (0.7%)	13** (1.1%)	4** (1.5%)	3 (1.1%)	1 (0.4%)	8** (1.0%)
Adverse Event	6 (1.5%)	5 (1.3%)	1 (0.2%)	12 (1.0%)	3 (1.1%)	5 (1.9%)	1 (0.4%)	9 (1.1%)
Protocol Deviation	4 (1.0%)	2 (0.5%)	2 (0.5%)	8 (0.7%)	3 (1.1%)	2 (0.7%)	1 (0.4%)	6 (0.7%)
Death	2 (0.5%)	2 (0.5%)	2 (0.5%)	6 (0.5%)	1 (0.4%)	0	1 (0.4%)	2 (0.2%)
Study-specific withdrawal criteria	0	1 (0.3%)	1 (0.2%)	2 (0.2%)	0	1 (0.4%)	1 (0.4%)	2 (0.2%)

Source: Reviewer
*Disposition reason missing in the ADAM.RSDS dataset
** Different from applicant's Table 12.1.1.1 by one subject as the subject was randomized but didn't receive study medication and was not counted in the FAS dataset. The applicant's table used *all patients analysis set*, this reviewer used FAS

As both age group (adolescents or adults) and region were stratification variables, the limitation (to lower dose or placebo) at randomization for adolescent patients in the EU countries resulted

in imbalance of number of subjects within age groups. Among the 53 adolescent FAS subjects, 11 were randomized to Benralizumab Q4W FAS compared to 19 and 23 patients being randomized to Benralizumab Q8W and placebo, respectively. Aside from this, the demographics and baseline disease characteristics were similar across the three treatment groups, for both FAS and the EHS (Table 6). There was a higher percentage of female (FAS: 66%; EHS: 65%) than male (FAS: 34%; EHS, 35%). The majority of patients were in the 18 – 65 age group (FAS: 82%; EHS: 86%). This was a global trial with European subjects comprising 53% (in FAS) of the total population. The majority of subjects were white (FAS: 73%; EHS: 71%).

Table 6. SIROCCO: Baseline Demographics (FAS)

		All Subjects				Baseline blood eosinophil ≥300/µL			
		Benra 30 mg q.4 weeks N=399	Benra 30 mg q.8 weeks N=398	Placebo N=407	Total N=1204	Benra 30 mg q.4 weeks N=275	Benra 30 mg q.8 weeks 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 (13%)	40 (10%)	53 (13%)	143 (12%)	26 (9%)	29 (11%)	32 (12%)	87 (11%)
Age	Mean (SD)	50.1 (13.4)	47.6 (14.5)	48.7 (14.9)	48.8 (14.3)	49.2 (13.1)	47.6 (14.6)	48.6 (14.7)	48.5 (14.2)
	Median (Min, Max)	52.0 (12, 75)	50.0 (12, 74)	52.0 (12, 75)	51.0 (12, 75)	51.0 (12, 74)	50.0 (12, 74)	51.0 (12, 75)	51.0 (12, 75)
Sex	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	Eastern Europe	120 (30%)	130 (33%)	137 (34%)	387 (32%)	82 (30%)	85 (32%)	83 (31%)	250 (31%)
	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	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%)

		All Subjects				Baseline blood eosinophil ≥300/µL			
		Benra 30 mg q.4 weeks N=399	Benra 30 mg q.8 weeks N=398	Placebo N=407	Total N=1204	Benra 30 mg q.4 weeks N=275	Benra 30 mg q.8 weeks N=267	Placebo N=267	Total N=809
	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: Reviewer
Abbreviations: SD = Standard Deviation; Min = Minimum, Max = Maximum

Table 7. SIROCCO: Baseline Disease Characteristics (FAS)

		All Subjects				Baseline blood eosinophil ≥300/µL			
		Benra 30 mg q.4 weeks N=399	Benra 30 mg q.8 weeks N=398	Placebo N=407	Total N=1204	Benra 30 mg q.4 weeks N=275	Benra 30 mg q.8 weeks N=267	Placebo N=267	Total N=809
Eosinophil Count									
Local Baseline Eosinophil Count (Cells/µL)	N	395	392	403	1190	274	263	264	801
	Mean (SD)	490 (413.6)	476 (403.7)	456 (365.9)	474 (394.6)	636 (417.7)	623 (406.5)	621 (351.3)	627 (392.8)
	Median (Min, Max)	385 (0, 3440)	360 (0, 3100)	370 (0, 2690)	378 (0, 3440)	500 (300, 3440)	499 (300, 3100)	500 (300, 2690)	500 (300, 3440)
Central Baseline Eosinophil Count (Cells/µL)	N	398	396	404	1198	275	267	265	807
	Mean (SD)	451 (409.8)	430 (406.8)	442 (392.2)	441 (402.7)	576 (432.1)	551 (432.7)	567 (360.9)	565 (409.9)
	Median (Min, Max)	340 (0, 3170)	310 (0, 2870)	360 (0, 3580)	330 (0, 3580)	450 (20, 3170)	440 (10, 2870)	460 (20, 2220)	450 (10, 3170)
Lung Function Characteristics									
Pre-BD FEV_1 (L)	N	393	397	400	1190	273	266	262	801
	Mean (SD)	1.655 (0.553)	1.680 (0.582)	1.660 (0.584)	1.665 (0.573)	1.673 (0.577)	1.660 (0.574)	1.654 (0.580)	1.662 (0.576)
	Median (Min, Max)	1.580 (0.54, 3.72)	1.690 (0.45, 3.54)	1.595 (0.46, 3.48)	1.625 (0.45, 3.72)	1.580 (0.54, 3.72)	1.690 (0.48, 3.54)	1.630 (0.46, 3.48)	1.630 (0.46, 3.72)
Pre-BD FEV_1 % Predicted	N	393	397	400	1190	273	266	262	801
	Mean (SD)	57.4 (14.1)	56.1 (14.6)	56.6 (15.0)	56.7 (14.6)	56.5 (14.4)	55.5 (14.6)	56.4 (14.6)	56.1 (14.5)

		All Subjects				Baseline blood eosinophil ≥300/μL			
		Benra 30 mg q.4 weeks N=399	**Benra 30 mg q.8 weeks N=398**	**Placebo N=407**	**Total N=1204**	**Benra 30 mg q.4 weeks N=275**	**Benra 30 mg q.8 weeks N=267**	**Placebo N=267**	**Total N=809**
	Median (Min, Max)	58.2 (16.8, 90.5)	57.3 (16.8, 88.0)	58.2 (13.9, 94.8)	57.9 (13.9, 94.8)	55.6 (16.8, 87.2)	56.5 (16.8, 85.5)	58.0 (17.7, 93.3)	56.8 (16.8, 93.3)
Pre-BD FEV_1/FVC Ratio	N	393	397	400	1190	273	266	262	801
	Mean (SD)	62 (12)	61 (13)	61 (13)	61 (13)	62 (12)	60 (13)	61 (13)	61 (13)
	Median (Min, Max)	62 (30, 92)	61 (26, 100)	62 (1, 98)	61 (1, 100)	61 (30, 92)	60 (26, 98)	62 (1, 98)	61 (1, 98)
FEV_1 Reversibility (%)	N	375	375	381	1131	262	253	251	766
	Mean (SD)	24.3 (22.1)	27.2 (24.5)	25.5 (23.1)	25.7 (23.3)	25.4 (23.5)	27.4 (25.0)	25.5 (22.8)	26.1 (23.8)
	Median (Min, Max)	17.8 (-6.7, 136.3)	21.6 (-12.1, 156.8)	20.4 (-26.4, 154.2)	19.3 (-26.4, 156.8)	18.3 (-6.7, 136.3)	21.3 (-10.2, 156.8)	20.4 (-26.4, 154.2)	19.3 (-26.4, 156.8)
Asthma History									
Number of Years since Asthma Diagnosis	N	399	398	407	1204	275	267	267	809
	Mean (SD)	18.75 (14.12)	18.32 (14.49)	19.37 (15.41)	18.82 (14.68)	18.52 (14.16)	18.17 (13.81)	18.19 (14.47)	18.29 (14.13)
	Median (Min, Max)	15.25 (1.1, 70.4)	14.38 (1.1, 66.9)	14.17 (1.1, 72.4)	14.76 (1.1, 72.4)	14.85 (1.1, 62.6)	14.55 (1.1, 66.9)	13.43 (1.1, 65.2)	14.36 (1.1, 66.9)
Exacerbation History									
Number of Exacerbations in Previous 12 Months	2	253 (63.4%)	252 (63.3%)	244 (60.0%)	749 (62.2%)	173 (62.9%)	164 (61.4%)	149 (55.8%)	486 (60.1%)
	3	64 (16.0%)	79 (19.8%)	76 (18.7%)	219 (18.2%)	44 (16.0%)	53 (19.9%)	53 (19.9%)	150 (18.5%)
	4 or more	82 (20.6%)	67 (16.8%)	87 (21.4%)	236 (19.6%)	58 (21.1%)	50 (18.7%)	65 (24.3%)	173 (21.4%)
Nicotine Use at Study Entry, N (%)									
Smoking Status	Current	0	1 (<1%)	5 (1.2%)	6 (<1%)	0	1 (<1%)	1 (<1%)	2 (<1%)
	Former	86 (21.6%)	70 (17.6%)	74 (18.2%)	230 (19.1%)	61 (22.2%)	46 (17.2%)	47 (17.6%)	154 (19.0%)
	Never	313 (78.4%)	327 (82.2%)	328 (80.6%)	968 (80.4%)	214 (77.8%)	220 (82.4%)	219 (82.0%)	653 (80.7%)

Source: Reviewer
Abbreviations: Pre-BD = Pre-bronchodilator, FEV_1 = Forced Expiratory Volume in 1 second.

3.2.1.4 Results and Conclusions

3.2.1.4.1 Clinically Significant Exacerbations

In the eosinophil high strata (EHS), compared with placebo, Benralizumab 30 mg Q8W reduced the number of asthma related exacerbations per patient per year by 51% (rate ratio 0.49; 95% CI [0.37, 0.64]; p<0.001), and Benralizumab 30 mg Q4W by 45% (rate ratio 0.55; 95% CI [0.42, 0.71]; p<0.001). Treatment effect in the eosinophil low strata (ELS) trended in the right direction but was lower in effect size and was not powered for significance tests. Effect sizes in the overall FAS population were similar to those of the EHS FAS the latter dominated the FAS population (67.2%).

Table 8. SIROCCO: Annualized Rate of Clinically Significant Exacerbation (FAS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rate Difference	Rate Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS	Benra 30 mg q.4 weeks	399	0.87	0.74, 1.02	-0.59	-0.83, -0.35	0.77	0.66, 0.90	0.60	0.48, 0.73	<.001*
	Benra 30 mg q.8 weeks	398	0.87	0.73, 1.02	-0.59	-0.84, -0.35	0.77	0.65, 0.90	0.59	0.48, 0.73	<.001*
	Placebo	407	1.46	1.27, 1.68			1.29	1.13, 1.48			
FAS + EHS	Benra 30 mg q.4 weeks	275	0.83	0.68, 1.02	-0.69	-1.00, -0.38	0.73	0.60, 0.89	0.55	0.42, 0.71	<.001
	Benra 30 mg q.8 weeks	267	0.74	0.59, 0.92	-0.78	-1.08, -0.47	0.65	0.53, 0.80	0.49	0.37, 0.64	<.001
	Placebo	267	1.52	1.27, 1.81			1.33	1.12, 1.58			
FAS + ELS	Benra 30 mg q.4 weeks	124	0.94	0.73, 1.23	-0.40	-0.79, -0.00	0.85	0.65, 1.11	0.70	0.50, 1.00	0.047*
	Benra 30 mg q.8 weeks	131	1.11	0.86, 1.43	-0.23	-0.65, 0.18	1.00	0.78, 1.28	0.83	0.59, 1.16	0.268
	Placebo	140	1.34	1.06, 1.69			1.21	0.96, 1.52			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.2 Pre-bronchodilator FEV_1 at Week 48

In the eosinophil high strata (EHS), the difference in least-squares mean change from baseline was 0.16 L between Benralizumab Q8W and placebo (95% CI [0.07, 0.25]; p=0.001), and was 0.11 L between Benralizumab Q4W and placebo (95% CI [0.02, 0.20]; p=0.022). A little smaller treatment effect was also found in the FAS. However, the comparisons on FAS were not multiplicity protected so these results could only be used as supportive descriptive information. In the ELS, observed treatment effect over placebo was not consistent between the two Benralizumab dosing regimens.

Table 9. SIROCCO: Change from Baseline Pre-Bronchodilator FEV1 at Week 48 (FAS)

Analysis Population	Treatment Group	Number of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS	Benra 30 mg q.4 weeks	391	0.27	0.22, 0.32	0.07	(-0.00 , 0.14)	0.060
	Benra 30 mg q.8 weeks	393	0.35	0.30, 0.40	0.15	(0.08 , 0.22)	0.000*
	Placebo	399	0.21	0.16, 0.26			
FAS + EHS	Benra 30 mg q.4 weeks	271	0.35	0.28, 0.41	0.11	(0.02 , 0.20)	0.022
	Benra 30 mg q.8 weeks	264	0.40	0.33, 0.46	0.16	(0.07 , 0.25)	0.001
	Placebo	261	0.24	0.18, 0.30			
FAS + ELS	Benra 30 mg q.4 weeks	120	0.12	0.04, 0.20	-0.03	(-0.13 , 0.08)	0.644
	Benra 30 mg q.8 weeks	129	0.25	0.17, 0.32	0.10	(-0.00 , 0.21)	0.057
	Placebo	138	0.15	0.07, 0.22			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.3 Total Asthma Symptom Score at Week 48

In the eosinophil high strata (EHS), the mean change in total asthma symptom score from baseline to week 48 was greater in patients treated with the Q8W regimen compared with placebo (treatment difference -0.25; 95% CI [-0.45, -0.06]; p=0.012). The Treat effect was not statistically significant for the comparison between Q4W dosing regimen and placebo.

Table 10. SIROCCO: Total Asthma Symptom Score at Week 48

Analysis Population	Treatment Group	Number of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS	Benra 30 mg q.4 weeks	396	-1.07	-1.19, -0.96	-0.12	(-0.28 , 0.04)	0.157
	Benra 30 mg q.8 weeks	390	-1.22	-1.33, -1.10	-0.26	(-0.42 , -0.10)	0.002*
	Placebo	406	-0.96	-1.07, -0.84			
FAS + EHS	Benra 30 mg q.4 weeks	273	-1.12	-1.26, -0.98	-0.08	(-0.27 , 0.12)	0.442
	Benra 30 mg q.8 weeks	263	-1.30	-1.44, -1.16	-0.25	(-0.45 , -0.06)	0.012
	Placebo	267	-1.04	-1.18, -0.90			

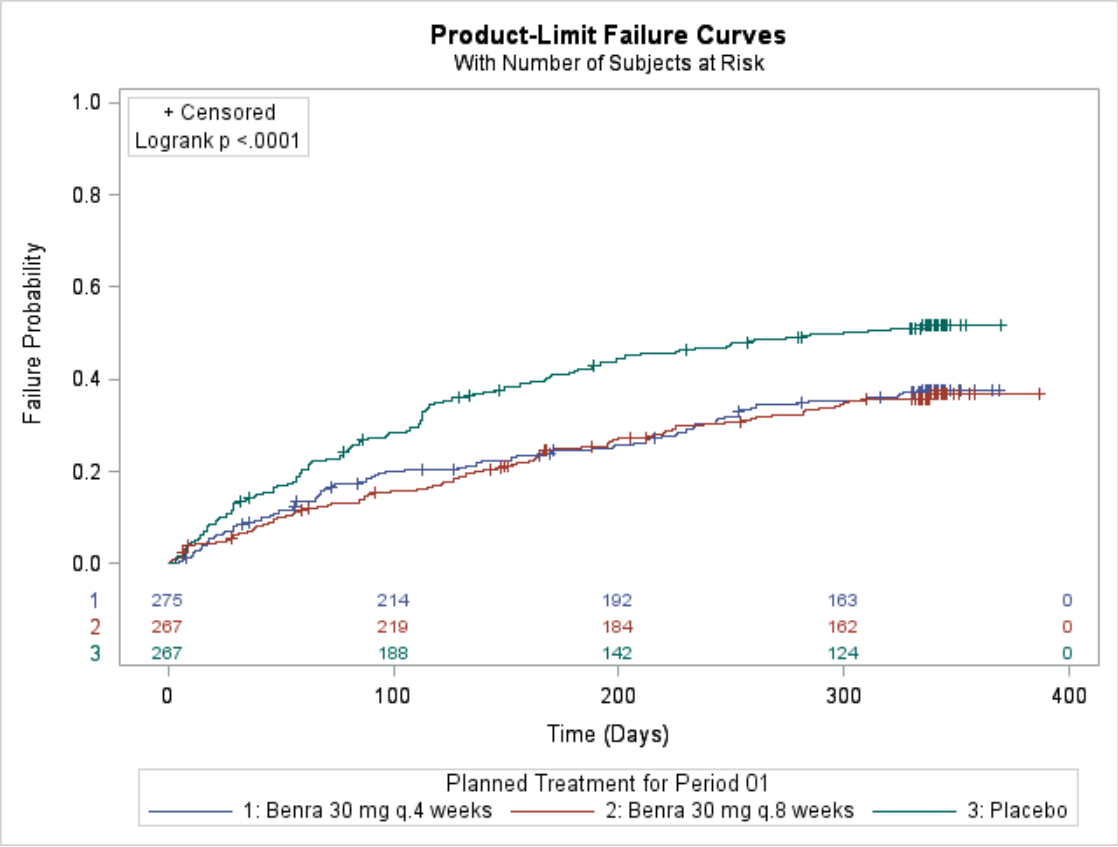
Analysis Population	Treatment Group	Number of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS + ELS	Benra 30 mg q.4 weeks	123	-0.97	-1.18, -0.76	-0.20	(-0.48 , 0.08)	0.169
	Benra 30 mg q.8 weeks	127	-1.06	-1.27, -0.86	-0.29	(-0.57 , -0.01)	0.043*
	Placebo	139	-0.77	-0.97, -0.58			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.4 Time to First Asthma Exacerbation

While the primary endpoint have assessed the annualized rate of exacerbation during the 48 weeks of trial, the Kaplan-Meier curves (Figure 5) showed the time to the first asthma exacerbation among the 809 EHS patients in FAS.

Figure 5. SIROCCO: Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (FAS + EHS)



Source: Reviewer

3.2.1.4.5 Proportion of Subjects with at Least One Asthma Exacerbation

In the EHS population, 35% of the patients in Q8W group had at least one asthma exacerbation, 51% of the patients in placebo had at least one asthma exacerbation.

Table 11. SIROCCO: Proportion of Subjects with at Least One Clinically Significant Exacerbation (FAS)

Analysis Population	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
FAS	38%	39%	52%
FAS + EHS	36%	35%	51%
FAS + ELS	43%	47%	55%

Source: Reviewer

3.2.1.4.6 ACQ6 Score at Week 48

In the high-dose ICS population EHS population, Benralizumab Q8W improved ACQ-6 score compared with placebo (LS Mean Difference: -0.29, 95% CI: [-0.48, -0.10], nominal p-value: 0.003). However, the comparison on ACQ6 score was not multiplicity protected so this result could only be used as supportive descriptive information. Treatment effect of similar size was also found in the comparison of Q8W vs. placebo (LS Mean Difference: -0.28) in the FAS.

Table 12. SIROCCO: ACQ6 Score at Week 48 (FAS)

Analysis Population	Treatment Group	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS	Benra 30 mg q.4 weeks	-1.18	-1.29, -1.07	-0.12	-0.27 , 0.04	0.136
	Benra 30 mg q.8 weeks	-1.35	-1.46, -1.24	-0.28	-0.44 , -0.13	0.000
	Placebo	-1.06	-1.17, -0.96			
FAS + EHS	Benra 30 mg q.4 weeks	-1.32	-1.45, -1.19	-0.15	-0.34 , 0.04	0.111
	Benra 30 mg q.8 weeks	-1.46	-1.59, -1.32	-0.29	-0.48 , -0.10	0.003
	Placebo	-1.17	-1.30, -1.03			
FAS + ELS	Benra 30 mg q.4 weeks	-0.89	-1.09, -0.70	-0.00	-0.27 , 0.27	0.990
	Benra 30 mg q.8 weeks	-1.11	-1.30, -0.92	-0.22	-0.48 , 0.05	0.107
	Placebo	-0.89	-1.07, -0.71			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

In the EHS, 161 (60.3%) patients in Q8W group had a greater or equal to 0.5 improvements from baseline in terms of ACQ6, as compared with 133 (49.8%) patients in placebo, corresponding to an odds ratio of 1.55.

Table 13. SIROCCO: ACQ6 Responder Analysis at Week 48 (FAS)

Analysis Population	Treatment Group	N Total	Number of Responder (%)	Odds Ratio	Odds Ratio 95% CI	p-value
FAS+EHS	Benra 30 mg q.4 weeks	275	157 (57.1%)	1.35	0.96,1.90	0.086
	Benra 30 mg q.8 weeks	267	161 (60.3%)	1.55	1.09,2.19	0.014*
	Placebo	267	133 (49.8%)			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.7 AQLQ Score at Week 48

In EHS population, Benralizumab Q8W improved AQLQ score compared with placebo (LS Mean Difference: 0.30, 95% CI: [0.10, 0.50], nominal p-value: 0.004). However, the comparison on AQLQ score was not multiplicity protected so this result could only be used as supportive descriptive information. Treatment effect of similar but smaller size was also found in the comparison of Q8W vs. placebo (LS Mean Difference: 0.18) in the FAS.

Table 14. SIROCCO: AQLQ Score at Week 48 (FAS)

Analysis Population	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS	Benra 30 mg q.4 weeks	380	1.28	1.16, 1.39	0.13	(-0.03 , 0.30)	0.113
	Benra 30 mg q.8 weeks	377	1.42	1.31, 1.54	0.28	(0.11 , 0.44)	0.001*
	Placebo	389	1.14	1.03, 1.26			
FAS + EHS	Benra 30 mg q.4 weeks	261	1.44	1.30, 1.58	0.18	(-0.02 , 0.37)	0.081
	Benra 30 mg q.8 weeks	252	1.56	1.42, 1.70	0.30	(0.10 , 0.50)	0.004
	Placebo	254	1.26	1.12, 1.40			
FAS + ELS	Benra 30 mg q.4 weeks	119	0.94	0.74, 1.14	0.01	(-0.27 , 0.29)	0.951
	Benra 30 mg q.8 weeks	125	1.13	0.93, 1.33	0.20	(-0.07 , 0.48)	0.152
	Placebo	135	0.93	0.74, 1.12			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

In the EHS, 153 (57.3%) patients in Q8W group had a greater or equal to 0.5 improvements from baseline in terms of AQLQ(S)+12, as compared with 131 (49.1%) patients in placebo, corresponding to an odds ratio of 1.42.

Table 15. SIROCCO: AQLQ Responder Analysis at Week 48 (FAS)

Analysis Population	Treatment Group	N Total	Number of Responder (%)	Odds Ratio	Odds Ratio 95% CI	p-value
FAS+EHS	Benra 30 mg q.4 weeks	275	152 (55.3%)	1.30	0.92,1.85	0.139
	Benra 30 mg q.8 weeks	267	153 (57.3%)	1.42	0.99,2.02	0.055
	Placebo	267	131 (49.1%)			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.8 Exacerbations requiring hospitalization/emergency room visit

In the EHS population, Benralizumab Q8W reduced asthma exacerbations requiring hospitalization or emergency room visit compared with placebo (Rate Ratio: 0.37, 95% CI: [0.20, 0.67], nominal p-value: <0.001). Effect of smaller size could be found in the same comparison for the FAS population. However, these comparisons were not multiplicity protected so these results could only be used as supportive descriptive information.

Table 16. SIROCCO: Annualized Rate of Exacerbation (Adjudicated) Requiring Hospitalization or ER visit (FAS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rate Difference	Rate Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS	Benra 30 mg q.4 weeks	399	0.19	0.12, 0.30	-0.08	-0.18, 0.03	0.11	0.08, 0.15	0.71	0.46, 1.10	0.126
	Benra 30 mg q.8 weeks	398	0.14	0.09, 0.23	-0.12	-0.23, -0.02	0.08	0.06, 0.12	0.54	0.34, 0.86	0.009*
	Placebo	407	0.27	0.17, 0.42			0.15	0.11, 0.21			
FAS + EHS	Benra 30 mg q.4 weeks	275	0.15	0.10, 0.24	-0.10	-0.21, 0.01	0.11	0.07, 0.16	0.61	0.37, 1.01	0.053
	Benra 30 mg q.8 weeks	267	0.09	0.05, 0.16	-0.16	-0.26, -0.06	0.06	0.04, 0.11	0.37	0.20, 0.67	<.001
	Placebo	267	0.25	0.17, 0.38			0.18	0.13, 0.25			
FAS + ELS	Benra 30 mg q.4 weeks	124	0.35	0.10, 1.29	-0.02	-0.32, 0.28	0.10	0.06, 0.20	0.94	0.42, 2.12	0.887
	Benra 30 mg q.8 weeks	131	0.34	0.09, 1.22	-0.03	-0.33, 0.26	0.10	0.05, 0.19	0.91	0.40, 2.06	0.820
	Placebo	140	0.37	0.10, 1.41			0.11	0.06, 0.20			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.1.4.9 Exacerbations Requiring Hospitalization

The study was not powered to detect treatment difference on the annual rate of exacerbations resulting in hospitalization.

Table 17. SIROCCO: Annualized Rate of Exacerbation (Adjudicated) Resulting in Hospitalization (FAS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rate Difference	Rate Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS	Benra 30 mg q.4 weeks	399	0.12	0.07, 0.23	-0.04	0.12	0.06	0.04, 0.10	0.75	0.43, 1.31	0.311
	Benra 30 mg q.8 weeks	398	0.11	0.06, 0.20	-0.06	0.11	0.05	0.03, 0.09	0.66	0.37, 1.17	0.154
	Placebo	407	0.16	0.09, 0.31		0.16	0.08	0.06, 0.12			
FAS + EHS	Benra 30 mg q.4 weeks	275	0.09	0.04, 0.18	-0.05	-0.14, 0.03	0.05	0.03, 0.10	0.62	0.31, 1.27	0.192
	Benra 30 mg q.8 weeks	267	0.07	0.03, 0.14	-0.07	-0.16, 0.01	0.04	0.02, 0.08	0.48	0.22, 1.03	0.060
	Placebo	267	0.14	0.07, 0.27			0.09	0.05, 0.14			
FAS + ELS	Benra 30 mg q.4 weeks	124	0.19	0.07, 0.52	0.00	-0.17, 0.17	0.07	0.04, 0.15	1.01	0.40, 2.57	0.978
	Benra 30 mg q.8 weeks	131	0.21	0.07, 0.61	0.02	-0.16, 0.20	0.08	0.04, 0.16	1.13	0.45, 2.81	0.798
	Placebo	140	0.18	0.06, 0.52			0.07	0.04, 0.14			

Source: Reviewer

3.2.2 Asthma Exacerbation Study - CALIMA

3.2.2.1 Study Design and Endpoints

Study design of CALIMA was generally similar to that of SIROCCO but with two main differences: CALIMA was a 56 weeks trial and SIROCCO was of 48 weeks duration; while the originally targeted study population was patients on high-dose ICS/LABA with uncontrolled eosinophilic asthma, as in SIROCCO, CALIMA was expanded[3] to include medium-dose ICS/LABA patients (b) (4).

CALIMA had the same endpoints selection as that of SIROCCO. The population of interest was patients on high-dose ICS/LABA with uncontrolled eosinophilic asthma, and all the primary and secondary efficacy endpoints were tested based on this patient group.

[3] CALIMA Study Protocol Amendment 1, dated May 13, 2014.

As in SIROCCO, the multiple testing procedure included the primary endpoint, and the two key secondary efficacy endpoints on the high-dose ICS patients in the EHS. While in SIROCCO all enrolled patients had high-dose ICS, there was also a subset of medium-dose ICS patients in the EHS in CALIMA. For each of reference in CALIMA, this review will use ***high ICS EHS*** notation to refer to the analysis subset of interest from now on.

3.2.2.2 Statistical Methodologies

Statistical analyses took the same methodologies as those employed in SIROCCO.

Aside from the changes to planned analyses described in section 3.1.2.2 of this review under SIROCCO, study CALIMA clinical study report (CSR) Table 7 listed one additional change specific to study CALMA.

3.2.2.3 Analysis Sets, Patients Disposition, Demographic and Baseline Disease Characteristics

Of the 1306 subjects who were enrolled into the study, 875 (67%) were patients with baseline blood eosinophil count ≥300 cells/μL. All randomized patients received study drug. The Randomized population coincided with the FAS; the safety analysis set also coincided with the FAS (Table 18). Patients in this study were allowed in the protocol to switch to an alternative treatment or treatments after they discontinued from randomized treatment and were encouraged to complete scheduled visits until they withdrew from the study. It was expected that the rates of treatment discontinuation would be different from the rates of study withdrawal due to this data retrieval effort. However, the overall study withdrawal rates (FAS: 10%; EHS: 9%) were only slightly lower than the corresponding treatment dropout rates (FAS: 11%; EHS: 10%).

Table 18. CALIMA: Analysis Sets (FAS)

Patients Screened				2508				
	Denominator: Number of Patients Screened							
Patients Who Entered Run-in / OCS Optimization				2183 (87.0%)				
Randomized Population				1306 (52.1%)				
Denominator: Number of Randomized Population								
	All Subjects (FAS)				**EHS + High ICS**			
	Benra 30 mg q.4 weeks	**Benra 30 mg q.8 weeks**	**Placebo**	**Total**	**Benra 30 mg q.4 weeks**	**Benra 30 mg q.8 weeks**	**Placebo**	**Total**
Randomized Population	425 (100%)	441 (100%)	440 (100%)	1306 (100%)	241 (100%)	239 (100%)	248 (100%)	728 (100%)

Safety Population	425 (100%)	441 (100%)	440 (100%)	1306 (100%)	241 (100%)	239 (100%)	248 (100%)	728 (100%)
Full Analysis Set	425 (100%)	441 (100%)	440 (100%)	1306 (100%)	241 (100%)	239 (100%)	248 (100%)	728 (100%)

Source: Reviewer

To support interpretation of the primary analysis results based on the high ICS EHS subset, patient disposition by reasons of treatment dropout or study dropout are summarized for both the high ICS EHS subset and the medium ICS EHS subset.

Table 19. CALIMA: Patient Disposition (FAS)

	FAS				**EHS + High-ICS**			
	Benra 30 mg q.4 weeks N=425	**Benra 30 mg q.8 weeks N=441**	**Placebo N=440**	**Total N=1306**	**Benra 30 mg q.4 weeks N=241**	**Benra 30 mg q.8 weeks N=239**	**Placebo N=248**	**Total N=728**
Treatment Completion								
Treatment: Completion	384 (90.4%)	382 (86.6%)	391 (88.9%)	1157 (88.6%)	225 (93.4%)	214 (89.5%)	224 (90.3%)	663 (91.1%)
Treatment: Dropout	41 (10%)	59 (13%)	49 (11%)	149 (11%)	16 (6.6%)	25 (10.5%)	24 (9.7%)	65 (8.9%)
Reason for Premature IP Discontinuation								
Withdrawal by Subject from IP	16 (3.8%)	28 (6.3%)	19 (4.3%)	63 (4.8%)	5 (2.1%)	8 (3.3%)	10 (4.0%)	23 (3.2%)
Other	10 (2.4%)	12 (2.7%)	10 (2.3%)	32 (2.5%)	3 (1.2%)	6 (2.5%)	5 (2.0%)	14 (1.9%)
Adverse Event	8 (1.9%)	9 (2.0%)	5 (1.1%)	22 (1.7%)	5 (2.1%)	5 (2.1%)	1 (0.4%)	11 (1.5%)
Study-specific withdrawal criteria	5 (1.2%)	5 (1.1%)	9 (2.0%)	19 (1.5%)	1 (0.4%)	4 (1.7%)	5 (2.0%)	10 (1.4%)
Lost to Follow-up	1 (0.2%)	4 (0.9%)	4 (0.9%)	9 (0.7%)	1 (0.4%)	2 (0.8%)	2 (0.8%)	5 (0.7%)
Protocol Deviation	1 (0.2%)	1 (0.2%)	2 (0.5%)	4 (0.3%)	1 (0.4%)	0	1 (0.4%)	2 (0.3%)
Study Completion								
Patients Who Have Completed Study	389 (91.5%)	390 (88.4%)	402 (91.4%)	1181 (90.4%)	225 (93.4%)	217 (90.8%)	230 (92.7%)	672 (92.3%)
Analysis Dropout	36 (8.5%)	51 (11.6%)	38 (8.6%)	125 (9.6%)	16 (6.6%)	22 (9.2%)	18 (7.3%)	56 (7.7%)
Reason for Early Discontinuation from Study								
Withdrawal by Subject from IP	15 (3.5%)	27 (6.1%)	19 (4.3%)	61 (4.7%)	5 (2.1%)	10 (4.2%)	12 (4.8%)	27 (3.7%)
Lost to Follow-up	5 (1.2%)	8 (1.8%)	6 (1.4%)	19 (1.5%)	4 (1.7%)	2 (0.8%)	4 (1.6%)	10 (1.4%)
Other	5 (1.2%)	9 (2.0%)	4 (0.9%)	18 (1.4%)	2 (0.8%)	6 (2.5%)	0	8 (1.1%)
Adverse Event	4 (0.9%)	3 (0.7%)	4 (0.9%)	11 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	4 (0.5%)
Protocol Deviation	3 (0.7%)	1 (0.2%)	2 (0.5%)	6 (0.5%)	2 (0.8%)	0	1 (0.4%)	3 (0.4%)

	FAS				EHS + High-ICS			
	Benra 30 mg q.4 weeks N=425	Benra 30 mg q.8 weeks N=441	Placebo N=440	Total N=1306	Benra 30 mg q.4 weeks N=241	Benra 30 mg q.8 weeks N=239	Placebo N=248	Total N=728
Death	2 (0.5%)	2 (0.5%)	1 (0.2%)	5 (0.4%)	1 (0.4%)	2 (0.8%)	0	3 (0.4%)
Screen Failure	2 (0.5%)	0	2 (0.5%)	4 (0.3%)	0	0	0	0
Study-specific withdrawal criteria	0	1 (0.2%)	0	1 (0.1%)	0	1 (0.4%)	0	1 (0.1%)

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Similar with study SIROCCO, among the 55 adolescent FAS subjects, 11 were randomized to Benralizumab Q4W FAS compared to 21 and 23 patients being randomized to Benralizumab Q8W and placebo, respectively. Aside from this, among the 1306 subjects included in the FAS population, demographics and baseline disease characteristics were similar across the three treatment groups, for both FAS and the EHS (Table 20). There was a higher percentage of female (FAS: 62%; EHS: 61%) than male (FAS: 38%; EHS, 39%). The majority of patients were in the 18 – 65 age group (FAS: 79%; EHS: 83%). This was a global trial with European subjects comprising 58% (in FAS) of the total population. The majority of subjects were white (FAS: 84%; EHS: 83%).

Table 20. CALIMA: Demographics (FAS)

		All Subjects				EHS + High ICS			
		Benra 30 mg q.4 weeks N=425	Benra 30 mg q.8 weeks N=441	Placebo N=440	Total N=1306	Benra 30 mg q.4 weeks N=241	Benra 30 mg q.8 weeks N=239	Placebo N=248	Total N=728
Age Group	>=12 - <18	11 (3%)	21 (5%)	23 (5%)	55 (4%)	3 (1.2%)	6 (2.5%)	7 (2.8%)	16 (2.2%)
	>=18 - <50	174 (41%)	179 (41%)	181 (41%)	534 (41%)	101 (41.9%)	100 (41.8%)	114 (46.0%)	315 (43.3%)
	>=50 - <65	185 (44%)	186 (42%)	169 (38%)	540 (41%)	108 (44.8%)	106 (44.4%)	96 (38.7%)	310 (42.6%)
	>=65 - 75	55 (13%)	55 (12%)	67 (15%)	177 (14%)	29 (12.0%)	27 (11.3%)	31 (12.5%)	87 (12.0%)
Age (Years)	Mean (SD)	50.0 (13.6)	49.0 (14.3)	48.8 (15.1)	49.2 (14.3)	50.1 (13.1)	49.6 (13.0)	48.5 (14.1)	49.4 (13.4)
	Median (Min, Max)	52.0 (13, 75)	51.0 (12, 74)	51.0 (12, 75)	51.0 (12, 75)	52.0 (15, 75)	51.0 (12, 74)	50.0 (12, 75)	51.0 (12, 75)
Sex	F	270 (64%)	273 (62%)	264 (60%)	807 (62%)	159 (66.0%)	138 (57.7%)	145 (58.5%)	442 (60.7%)
	M	155 (36%)	168 (38%)	176 (40%)	499 (38%)	82 (34.0%)	101 (42.3%)	103 (41.5%)	286 (39.3%)

		All Subjects				EHS + High ICS			
		Benra 30 mg q.4 weeks N=425	Benra 30 mg q.8 weeks N=441	Placebo N=440	Total N=1306	Benra 30 mg q.4 weeks N=241	Benra 30 mg q.8 weeks N=239	Placebo N=248	Total N=728
Region	Eastern Europe	149 (35%)	156 (35%)	158 (36%)	463 (35%)	86 (35.7%)	84 (35.1%)	89 (35.9%)	259 (35.6%)
	Rest of the World	99 (23%)	103 (23%)	98 (22%)	300 (23%)	54 (22.4%)	56 (23.4%)	57 (23.0%)	167 (22.9%)
	North America	75 (18%)	74 (17%)	81 (18%)	230 (18%)	45 (18.7%)	40 (16.7%)	43 (17.3%)	128 (17.6%)
	Europe	54 (13%)	58 (13%)	57 (13%)	169 (13%)	33 (13.7%)	35 (14.6%)	34 (13.7%)	102 (14.0%)
	Asia	48 (11%)	50 (11%)	46 (10%)	144 (11%)	23 (9.5%)	24 (10.0%)	25 (10.1%)	72 (9.9%)
Race	White	360 (85%)	369 (84%)	372 (85%)	1101 (84%)	209 (86.7%)	203 (84.9%)	213 (85.9%)	625 (85.9%)
	Asian	55 (13%)	55 (12%)	53 (12%)	163 (12%)	27 (11.2%)	28 (11.7%)	27 (10.9%)	82 (11.3%)
	Other	0	2 (<1%)	1 (<1%)	3 (<1%)	0	0	0	0
	Black or African American	10 (2%)	15 (3%)	14 (3%)	39 (3%)	5 (2.1%)	8 (3.3%)	8 (3.2%)	21 (2.9%)

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 21. CALIMA: Baseline Disease Characteristics (FAS)

		All Subjects				EHS + High-ICS			
		Benra 30 mg q.4 weeks N=425	Benra 30 mg q.8 weeks N=441	Placebo N=440	Total N=1306	Benra 30 mg q.4 weeks N=241	Benra 30 mg q.8 weeks N=239	Placebo N=248	Total N=728
Eosinophil Count									
Local Baseline Eosinophil Count (Cells/μL)	N	418	435	433	1286	237	236	247	720
	Mean (SD)	462 (348.3)	465 (360.0)	485 (444.7)	471 (387.0)	614 (352.9)	621 (336.7)	640 (485.8)	625 (398.5)
	Median (Min, Max)	372 (20, 2420)	400 (0, 2600)	370 (0, 4494)	380 (0, 4494)	500 (200, 2420)	500 (300, 2600)	504 (300, 4494)	500 (200, 4494)
Central Baseline Eosinophil Count (Cells/μL)	N	425	441	440	1306	241	239	248	728
	Mean (SD)	446 (362.4)	436 (376.4)	462 (428.5)	448 (390.3)	572 (387.7)	577 (386.8)	583 (460.2)	577 (413.0)
	Median (Min, Max)	350 (0, 2800)	350 (0, 2370)	370 (10, 4150)	355 (0, 4150)	470 (0, 2800)	480 (10, 2370)	470 (10, 4150)	470 (0, 4150)
Lung Function Characteristics									
Pre-BD FEV_1 (L)	N	420	440	434	1294	239	239	245	723

		All Subjects				EHS + High-ICS			
		Benra 30 mg q.4 weeks N=425	**Benra 30 mg q.8 weeks N=441**	**Placebo N=440**	**Total N=1306**	**Benra 30 mg q.4 weeks N=241**	**Benra 30 mg q.8 weeks N=239**	**Placebo N=248**	**Total N=728**
	Mean (SD)	1.757 (0.602)	1.759 (0.641)	1.771 (0.645)	1.762 (0.630)	1.750 (0.570)	1.758 (0.622)	1.815 (0.648)	1.775 (0.614)
	Median (Min, Max)	1.700 (0.28, 3.50)	1.690 (0.47, 4.35)	1.700 (0.31, 3.88)	1.700 (0.28, 4.35)	1.670 (0.52, 3.45)	1.690 (0.56, 3.79)	1.720 (0.60, 3.80)	1.690 (0.52, 3.80)
Pre-BD FEV_1 % Predicted	N	420	440	434	1294	239	239	245	723
	Mean (SD)	58.9 (14.8)	57.9 (14.9)	58.0 (14.9)	58.3 (14.9)	59.1 (13.7)	57.0 (14.2)	58.2 (13.9)	58.1 (13.9)
	Median (Min, Max)	61.0 (15.4, 128.6)	58.5 (18.3, 124.4)	59.3 (12.5, 110.0)	59.7 (12.5, 128.6)	61.1 (15.7, 88.3)	58.2 (23.2, 89.0)	58.7 (23.2, 93.7)	59.3 (15.7, 93.7)
Pre-BD FEV_1/FVC Ratio	N	420	440	434	1294	239	239	245	723
	Mean (SD)	61 (12)	60 (13)	61 (13)	61 (13)	61 (12)	60 (13)	60 (12)	60 (12)
	Median (Min, Max)	61 (20, 98)	60 (26, 93)	61 (27, 93)	61 (20, 98)	62 (25, 88)	59 (28, 93)	60 (27, 93)	60 (25, 93)
FEV_1 Reversibility (%)	N	410	433	427	1270	235	236	243	714
	Mean (SD)	28.2 (46.1)	24.6 (22.9)	27.3 (44.7)	26.7 (39.2)	26.2 (25.4)	24.9 (22.3)	25.6 (22.5)	25.5 (23.4)
	Median (Min, Max)	19.8 (-24.3, 808.5)	19.6 (-12.8, 170.5)	19.8 (-18.0, 813.8)	19.7 (-24.3, 813.8)	19.9 (-24.3, 124.4)	20.0 (-12.8, 170.5)	19.8 (-9.4, 133.4)	19.8 (-24.3, 170.5)
Asthma History									
Number of Years since Asthma Diagnosis	N	425	441	440	1306	241	239	248	728
	Mean (SD)	19.56 (14.73)	20.12 (14.89)	20.38 (14.92)	20.03 (14.84)	18.53 (13.25)	19.52 (14.17)	20.58 (15.04)	19.56 (14.19)
	Median (Min, Max)	15.84 (1.2, 69.2)	16.81 (1.1, 64.6)	16.22 (1.2, 69.9)	16.11 (1.1, 69.9)	15.64 (1.3, 66.2)	16.06 (1.2, 58.2)	17.02 (1.3, 69.9)	16.06 (1.2, 69.9)
Exacerbation History									
Number of Exacerbations in Previous 12 Months	1*	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0	0	1 (<1%)
	2	280 (65.9%)	287 (65.1%)	288 (65.5%)	855 (65.5%)	148 (61.4%)	144 (60.3%)	151 (60.9%)	443 (60.9%)
	3	89 (20.9%)	93 (21.1%)	93 (21.1%)	275 (21.1%)	54 (22.4%)	59 (24.7%)	56 (22.6%)	169 (23.2%)
	4 or more	55 (12.9%)	60 (13.6%)	59 (13.4%)	174 (13.3%)	38 (15.8%)	36 (15.1%)	41 (16.5%)	115 (15.8%)
Nicotine Use at Study Entry, N (%)									
Smoking Status	Current	0	3 (<1%)	2 (<1%)	5 (<1%)	0	1 (<1%)	1 (<1%)	2 (<1%)

		All Subjects				EHS + High-ICS			
		Benra 30 mg q.4 weeks N=425	Benra 30 mg q.8 weeks N=441	Placebo N=440	Total N=1306	Benra 30 mg q.4 weeks N=241	Benra 30 mg q.8 weeks N=239	Placebo N=248	Total N=728
	Former	100 (23.5%)	90 (20.4%)	89 (20.2%)	279 (21.4%)	66 (27.4%)	53 (22.2%)	44 (17.7%)	163 (22.4%)
	Never	325 (76.5%)	348 (78.9%)	349 (79.3%)	1022 (78.3%)	175 (72.6%)	185 (77.4%)	203 (81.9%)	563 (77.3%)

Source: Reviewer
*: Review of exacerbation history found one exacerbation in two patients did not meet the protocol criteria.

3.2.2.4 Results and Conclusions

3.2.2.4.1 Clinically Significant Exacerbations

Based on the primary analysis set, high-dose ICS patients within the eosinophil high strata (the subset on which the multiplicity protection over the primary and key secondary efficacy testing was planned), Benralizumab 30 mg Q8W reduced the number of clinically significant exacerbations per patient per year by 28% (rate ratio 0.72; 95% CI [0.54, 0.95]; p=0.019) compared with placebo, and Benralizumab 30 mg Q4W by 36% (rate ratio 0.64; 95% CI [0.49, 0.85]; p=0.002). Although tests for treatment effect in the subset of high-dose ICS patients within the eosinophil low strata (ELS) or the overall FAS population were not multiplicity protected, the observed rate ratio were similar to those of the high-dose ICS within EHS.

Table 22. CALIMA: Annualized Rate of Clinically Significant Exacerbation (FAS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rates Difference	Rates Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	357	0.73	0.61, 0.86	-0.40	-0.60, -0.20	0.66	0.56, 0.77	0.64	0.52, 0.80	<.001
	Benra 30 mg q.8 weeks	364	0.76	0.64, 0.91	-0.37	-0.57, -0.16	0.69	0.58, 0.81	0.68	0.54, 0.84	<.001
	Placebo	370	1.13	0.97, 1.31			1.02	0.88, 1.18			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	241	0.65	0.52, 0.81	-0.36	-0.59, -0.13	0.60	0.48, 0.74	0.64	0.49, 0.85	0.002
	Benra 30 mg q.8 weeks	239	0.73	0.58, 0.90	-0.29	-0.53, -0.05	0.66	0.54, 0.82	0.72	0.54, 0.95	0.019
	Placebo	248	1.01	0.84, 1.22			0.93	0.77, 1.12			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	116	0.89	0.66, 1.19	-0.49	-0.89, -0.09	0.78	0.59, 1.02	0.64	0.45, 0.92	0.015
	Benra 30 mg q.8 weeks	125	0.83	0.62, 1.11	-0.55	-0.94, -0.16	0.73	0.55, 0.95	0.60	0.42, 0.86	0.005
	Placebo	122	1.38	1.07, 1.78			1.21	0.96, 1.52			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.2.4.2 Pre-bronchodilator FEV_1 at Week 56

In the eosinophil high strata (EHS), Benralizumab improved lung function: the difference in least-squares mean change from baseline was 0.12 L between Benralizumab Q8W and placebo (95% CI [0.03, 0.20]; p=0.010), and was 0.13 L between Benralizumab Q4W and placebo (95% CI [0.04, 0.21]; p=0.005). Treatment effects of smaller size were found in the FAS. However, these comparisons were not multiplicity protected so the results could only be used as supportive descriptive information.

Table 23. CALIMA: Pre-Bronchodilator FEV1 at Week 56 (FAS, High-dose ICS)

Analysis Population	Treatment Group	Number of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	352	0.30	0.25, 0.35	0.11	(0.04 , 0.18)	0.003*
	Benra 30 mg q.8 weeks	359	0.27	0.22, 0.32	0.07	(0.00 , 0.14)	0.046*
	Placebo	360	0.20	0.15, 0.25			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	238	0.34	0.28, 0.40	0.13	(0.04 , 0.21)	0.005
	Benra 30 mg q.8 weeks	238	0.33	0.27, 0.39	0.12	(0.03 , 0.20)	0.010
	Placebo	244	0.21	0.15, 0.28			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	114	0.22	0.14, 0.30	0.06	(-0.05 , 0.18)	0.268
	Benra 30 mg q.8 weeks	121	0.14	0.06, 0.22	-0.02	(-0.13 , 0.10)	0.786
	Placebo	116	0.16	0.08, 0.23			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

3.2.2.4.3 Total Asthma Symptom Score at Week 56

In the high-dose ICS population EHS population, compared with placebo, Benralizumab Q8W statistically significantly improved total asthma symptom score at Week 56 by -0.23 (95% CI: [-0.43, -0.04], nominal p-value: 0.019). However, the same comparison of Q4W versus placebo was significant. Findings in the FAS were not significant.

Table 24. CALIMA: Total Asthma Symptom Score at Week 56 (FAS, High-dose ICS)

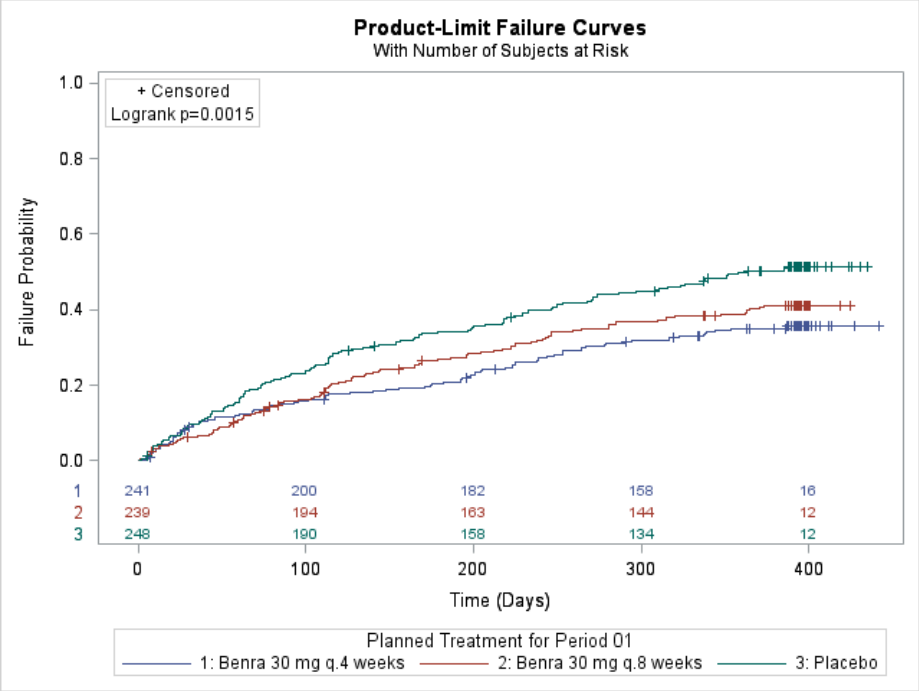
Analysis Population	Treatment Group	Number of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	356	-1.22	-1.34, -1.11	-0.13	(-0.29 , 0.03)	0.114
	Benra 30 mg q.8 weeks	361	-1.24	-1.36, -1.12	-0.15	(-0.31 , 0.01)	0.069
	Placebo	369	-1.09	-1.20, -0.98			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	241	-1.28	-1.42, -1.14	-0.12	(-0.32 , 0.07)	0.224
	Benra 30 mg q.8 weeks	237	-1.40	-1.54, -1.26	-0.23	(-0.43 , -0.04)	0.019
	Placebo	247	-1.16	-1.30, -1.02			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	115	-1.11	-1.31, -0.90	-0.16	(-0.44 , 0.13)	0.287
	Benra 30 mg q.8 weeks	124	-0.95	-1.15, -0.75	0.01	(-0.28 , 0.29)	0.966
	Placebo	122	-0.95	-1.15, -0.75			

Source: Reviewer

3.2.2.4.4 Time to First Exacerbation

While the primary endpoint have assessed the annualized rate of exacerbation during the 56 weeks of trial, the Kaplan-Meier curves (**Error! Reference source not found.**) showed the time to the first asthma exacerbation among the 768 EHS patients in FAS.

Figure 6. CALIMA: Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (FAS + EHS + High-ICS)



Source: Reviewer

3.2.2.4.5 Proportion of Subjects with at Least One Asthma Exacerbation

In the high-dose ICS EHS population, 40% of the patients in Q8W group had at least one asthma exacerbation, 51% of the patients in placebo had at least one asthma exacerbation.

Table 25. CALIMA: Proportion of Subjects with at Least One Clinically Significant Exacerbation (FAS)

Analysis Population	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
FAS	37%	37%	50%
FAS + EHS	36%	36%	49%
FAS + EHS + High-ICS	35%	40%	51%

Source: Reviewer

3.2.2.4.6 ACQ6 Score at Week 56

In the high-dose ICS population EHS population, Benralizumab Q8W improved ACQ-6 score compared with placebo (LS Mean Difference: -0.25, 95% CI: [-0.44, -0.07], nominal p-value: 0.008). However, the comparison on ACQ6 score was not multiplicity protected so this result could only be used as supportive descriptive information. Treatment effect of similar size was

also found in the comparison of Q4W vs. placebo (LS Mean Difference: -0.19) in the same population.

Table 26. CALIMA: ACQ6 Score at Week 56 (FAS, High-dose ICS)

Analysis Population	Treatment Group	No. of patients in analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	357	-1.30	-1.41, -1.19	-0.21	(-0.37 , -0.06)	0.008*
	Benra 30 mg q.8 weeks	364	-1.29	-1.40, -1.18	-0.20	(-0.35 , -0.04)	0.014*
	Placebo	369	-1.09	-1.20, -0.98			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	241	-1.38	-1.51, -1.25	-0.19	(-0.38 , -0.01)	0.043*
	Benra 30 mg q.8 weeks	239	-1.44	-1.58, -1.30	-0.25	(-0.44 , -0.07)	0.008*
	Placebo	247	-1.19	-1.32, -1.05			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	116	-1.14	-1.33, -0.94	-0.24	(-0.51 , 0.03)	0.078
	Benra 30 mg q.8 weeks	125	-1.00	-1.19, -0.81	-0.10	(-0.37 , 0.16)	0.449
	Placebo	122	-0.89	-1.08, -0.71			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

In the High-dose ICS EHS population, 151 (60.3%) patients in Q8W group had a greater or equal to 0.5 improvements from baseline in terms of ACQ6, as compared with 147 (59.3%) patients in placebo, corresponding to an odds ratio of 1.16.

Table 27. CALIMA: ACQ6 Responder Analysis at Week 48

	Treatment Group	N Total	Number of Responder (%)	Odds Ratio	Odds Ratio 95% CI	p-value
FAS+ EHS+ High-ICS	Benra 30 mg q.4 weeks	241	153 (63.5%)	1.24	0.85,1.81	0.257
	Benra 30 mg q.8 weeks	239	151 (63.2%)	1.16	0.80,1.68	0.444
	Placebo	248	147 (59.3%)			

Source: Reviewer

3.2.2.4.7 AQLQ Score at Week 56

In the high-dose ICS population EHS population, Benralizumab Q8W improved AQLQ score compared with placebo (LS Mean Difference: 24, 95% CI: [0.04, 0.45], nominal p-value: 0.019). However, the comparison on AQLQ score was not multiplicity protected so this result could only be used as supportive descriptive information. Treatment effect of smaller size was also found in the comparison of Q8W vs. placebo (LS Mean Difference: 0.18) in the FAS.

Table 28. CALIMA: AQLQ Score at Week 56 (FAS, High-dose ICS)

Analysis Population	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
FAS+ High-ICS	Benra 30 mg q.4 weeks	345	1.37	1.25, 1.48	0.16	(-0.00 , 0.33)	0.054
	Benra 30 mg q.8 weeks	353	1.39	1.27, 1.50	0.18	(0.02 , 0.35)	0.030*
	Placebo	359	1.20	1.09, 1.32			
FAS+ High-ICS +EHS	Benra 30 mg q.4 weeks	233	1.47	1.33, 1.62	0.16	(-0.04 , 0.37)	0.119
	Benra 30 mg q.8 weeks	230	1.56	1.41, 1.70	0.24	(0.04 , 0.45)	0.019*
	Placebo	240	1.31	1.17, 1.46			
FAS+ High-ICS +ELS	Benra 30 mg q.4 weeks	112	1.14	0.94, 1.33	0.17	(-0.11 , 0.44)	0.235
	Benra 30 mg q.8 weeks	123	1.06	0.87, 1.25	0.09	(-0.18 , 0.36)	0.509
	Placebo	119	0.97	0.78, 1.16			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

In the High-dose ICS EHS population, 144 (60.3%) patients in Q8W group had a greater or equal to 0.5 improvements from baseline in terms of AQLQ(S)+12, as compared with 146 (58.9%) patients in placebo, corresponding to an odds ratio of 1.03.

Table 29. CALIMA: AQLQ Responder Analysis at Week 56 (FAS)

	Treatment Group	N Total	Number of Responder (%)	Odds Ratio	Odds Ratio 95% CI	p-value
FAS+ EHS+ High-ICS	Benra 30 mg q.4 weeks	241	148 (61.4%)	1.16	0.79,1.69	0.458
	Benra 30 mg q.8 weeks	239	144 (60.3%)	1.03	0.70,1.51	0.881
	Placebo	248	146 (58.9%)			

Source: Reviewer

3.2.2.4.8 Exacerbations requiring hospitalization/emergency room visit

The study was not powered to detect treatment difference on the annual rate of exacerbations requiring hospitalization/emergency room visit.

Table 30. CALIMA: Annualized Rate of Exacerbation (Adjudicated) Requiring Hospitalization or ER visit (FAS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rates Difference	Rates Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	357	0.10	0.07, 0.15	-0.03	-0.08, 0.03	0.05	0.03, 0.07	0.79	0.48, 1.30	0.356
	Benra 30 mg q.8 weeks	364	0.13	0.09, 0.18	-0.00	-0.07, 0.06	0.06	0.04, 0.09	0.97	0.60, 1.58	0.903
	Placebo	370	0.13	0.09, 0.18			0.06	0.05, 0.09			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	241	0.09	0.06, 0.15	-0.01	-0.07, 0.06	0.04	0.02, 0.06	0.93	0.48, 1.82	0.837
	Benra 30 mg q.8 weeks	239	0.12	0.08, 0.19	0.02	-0.05, 0.09	0.05	0.03, 0.08	1.23	0.64, 2.35	0.538
	Placebo	248	0.10	0.06, 0.15			0.04	0.02, 0.07			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	116	0.13	0.08, 0.21	-0.08	-0.18, 0.03	0.07	0.04, 0.13	0.62	0.32, 1.18	0.145
	Benra 30 mg q.8 weeks	125	0.14	0.08, 0.24	-0.06	-0.18, 0.05	0.08	0.04, 0.14	0.69	0.35, 1.33	0.267
	Placebo	122	0.21	0.14, 0.31			0.10	0.06, 0.18			

Source: Reviewer

3.2.2.4.9 Exacerbations Resulting in Hospitalization

The study was not powered to detect treatment difference on the annual rate of exacerbations resulting in hospitalization.

Table 31. CALIMA: Annualized Rate of Exacerbation Resulting in Hospitalization (FAS, High-dose ICS)

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rates Difference	Rates Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
FAS + High-ICS	Benra 30 mg q.4 weeks	357	0.07	0.04, 0.11	-0.00	-0.05, 0.04	0.04	0.02, 0.07	0.97	0.50, 1.89	0.938
	Benra 30 mg q.8 weeks	364	0.07	0.04, 0.11	-0.00	-0.05, 0.04	0.04	0.02, 0.07	0.95	0.49, 1.82	0.875
	Placebo	370	0.07	0.04, 0.11			0.04	0.03, 0.07			
FAS + High-ICS+ EHS	Benra 30 mg q.4 weeks	241	0.05	0.03, 0.10	0.00	-0.04, 0.05	0.03	0.01, 0.05	1.02	0.42, 2.49	0.970
	Benra 30 mg q.8 weeks	239	0.07	0.04, 0.13	0.02	-0.03, 0.08	0.04	0.02, 0.07	1.48	0.65, 3.37	0.356

Analysis Population	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rates Difference	Rates Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
	Placebo	248	0.05	0.03, 0.09			0.03	0.01, 0.05			
FAS + High-ICS+ ELS	Benra 30 mg q.4 weeks	116	0.10	0.05, 0.21	-0.01	-0.12, 0.09	0.07	0.03, 0.15	0.89	0.33, 2.39	0.811
	Benra 30 mg q.8 weeks	125	0.05	0.02, 0.12	-0.06	-0.15, 0.03	0.04	0.01, 0.09	0.45	0.15, 1.38	0.164
	Placebo	122	0.11	0.06, 0.22			0.08	0.04, 0.17			

Source: Reviewer

3.2.3 Oral Corticosteroid Sparing Study - ZONDA

3.2.3.1 Study Design and Endpoints

3.2.3.1.1 ZONDA Study Design

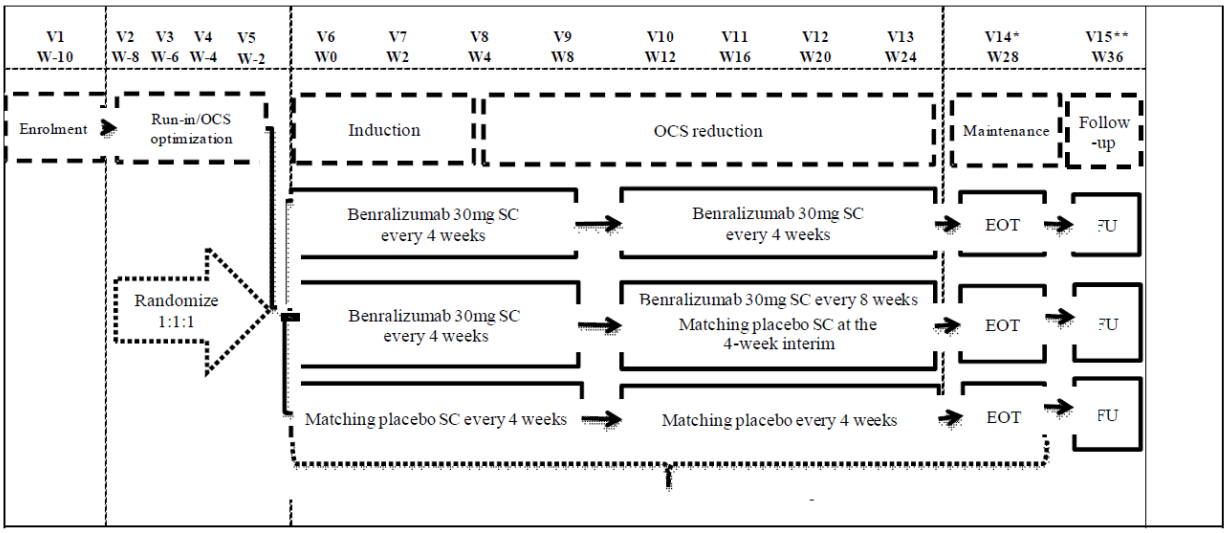
For severe asthmatic patients whose symptoms remain uncontrolled despite the use of high-dose ICS/LABA, one of the limited treatment options is to take regular treatment with OCS, which can lead to serious adverse effects and decreased quality of life. ZONDA was designed primarily to compare the effect of the two dosing regimens of Benralizumab 30 mg on percentage reduction of OCS dose in eosinophilic patients with uncontrolled asthma receiving high-dose ICS/LABA and OCS with or without additional asthma controller(s). Based on literature and the sponsor's own Benralizumab phase 2b study findings (MI-CP220), the study patient population selection criteria were set to be asthma patients with blood eosinophils ≥150 cells/μL. All patients were required to be treated with OCS for at least 6 months prior to enrollment and be on the stable maintenance dose of prednisone or prednisolone for at least 2 weeks prior to randomization. The study allowed other stable asthma therapies on top of OCS and ICS/LABA that were within expert guidance and that were not restricted per protocol.

ZONDA was a randomized, double-blind, parallel group, placebo-controlled, efficacy and safety study. The study was planned to recruit approximately 210 patients with eosinophils ≥150 cells/μL, including approximately 60 patients in the lower eosinophil stratum (≥150 to <300 cells/μL) and approximately 150 patients in the higher eosinophil stratum (≥300 cells/μL).

The study consisted of three periods: an 8-week run-in or OCS dose optimization period, a 28-week treatment period, and an 8-week follow-up period (Figure 7). At enrolment, all patients must have been on either oral prednisone or prednisolone as their OCS; patients who were on any other OCS would have been switched over to an equivalent dose of either oral prednisone or prednisolone at Visit 1.After enrolment and initial confirmation of entry criteria, the patient's OCS dose was titrated to the minimum effective dose without losing asthma control (optimized OCS dose). Patients who met eligibility criteria would have been randomized (1:1:1) to the

treatment arms, stratifying by blood eosinophil level and region, with the last dose of the IP administered at Week 24 and end-of-treatment (EOT) visit at Week 28. The treatment period consisted of 3 phases: a 4-week induction phase, during which patients would remain on the optimized OCS dose; a 20-week OCS reduction phase, during which OCS dose reduction would have been initiated at Week 4 with following dose reduction at 4-week intervals; and a 4-week maintenance phase, during which the dose of OCS reached at Week 24 or completed elimination of OCS would have been maintained. A follow-up visit would have been conducted at Week 36 (Visit 5) unless the patient decided to continue into a separate extension study, which is out of the scope of this review.

Figure 7. ZONDA: Flow Chart



Source: Study ZONDA Protocol Edition 3.0, Figure 1.

3.2.3.1.2 ZONDA Primary Endpoint: Primary Variable Derivation

The primary endpoint was percent reduction from baseline in the final OCS dose while maintaining asthma control (Week 24 – Week 28). During the OCS reduction period, patients' OCS dose reduction followed the OCS dose titration schedule specified in study protocol section 4.2.2. The percent reduction from baseline was defined as: {(Baseline dose – final dose) / baseline dose} * 100%.

For treatment/asthma control interruptions such as early withdrawal, asthma exacerbation or deterioration during the OCS reduction period, or asthma deterioration during the maintenance period, study SAP section 3.1 outlined additional percent reduction derivation rules to handle such situations. In general, under the above interruptions, a patient's final OCS dose was defined as 1 does level higher than the dose at which the interruption occurred.

Upon the identification of the OCS dose titration protocol deviation during a blinded data review, the applicant's study team amended the SAP to include a sensitivity assessment for percent reduction derivation to assess the potential impact of this violation: instances were identified for patients who recorded an exacerbation following randomization, but for whom, contrary to the process outlined in the protocol, the site appeared to continue down-titration of the OCS dose following the exacerbation. Under the sensitivity assessment approach: *for patients with no exacerbations recorded following Visit 6, the primary endpoint was derived as outlined above. For those patients who did record an exacerbation on or after Visit 6, the final OCS dose used in the percent reduction from baseline calculation was the OCS dose 1 step higher than the dose at which their first exacerbation started.*

While the study SAP outlined both data handling methods for situations of treatment/asthma control interruption and a sensitivity assessment approach, we still consider these methods could not recover the robustness in assessment of OCS sparing expected for supporting regulatory approval.

3.2.3.1.3 ZONDA Selected Secondary Outcomes

The trial also defined and assessed multiple secondary endpoints that can be grouped into the following categories: a) proportions of patients who had an OCS percent reduction of a certain size, b) other asthma control metrics including asthma exacerbations and lung function, c) blood eosinophils, etc.

3.2.3.1.4 ZONDA Patient Reported Outcomes

The study also assessed patient reported outcomes including: asthma symptom score, asthma control questionnaire (ACQ-6), and asthma quality of life questionnaire for 12 years and older (AQLQ(S)+12), etc.

3.2.3.1.5 ZONDA Multiplicity Control

A Hochberg procedure was used to control the overall type I error rate at the 0.05 level for the tests related with the two Benralizumab dose regimens for the primary endpoint, percent OCS reduction. No adjustments were made to p-values for tests on secondary efficacy variables. As such, any p-value reported for the secondary variables are considered nominal.

3.2.3.2 Statistical Methodologies

3.2.3.2.1 ZONDA Primary Endpoint Analysis Methods

The primary analysis for the OCS percent reduction endpoint used the Wilcoxon rank-sum test approach. The primary analyses were performed in the FAS population. For each of the two Benralizumab dose regimen groups, the median difference in the OCS percent reduction between Benralizumab dose regimen and placebo was derived using asymptotic Hodges-Lehmann estimation, together with associated 95% CI and p-value. The same analyses were also performed for the EHS without multiplicity control.

Two sensitivity analyses were planned by the applicant for the primary endpoint. The first sensitivity analysis was conducted to determine the robustness of the above described primary OCS percent reduction definition in handling exacerbations on or after the Visit 6. The second sensitivity analysis was performed for OCS percent reduction using a proportional odds model with adjustment for covariates including region and baseline optimized OCS dose. An ordinal form of data was first derived based on OCS percent reduction values using the following categories: 90 – 100% reduction, 75 – <90% reduction, 50 – <75% reduction, >0 – <50% reduction, and no change or any increase.

The proportional odds model has multiple advantages over the non-parametric approach adopted by the primary analysis: the ordinal form allows easy handling of missing data, in this study, missing data was assigned with to be under the no change or any increase category; the model based approach allows for adjustment of covariates. However, there is also concern with using proportional odds model without justifying the underlying proportional odds assumption.

For ZONDA, this review will only focus on the assessment of the primary efficacy endpoint and readers are referred to the applicant's CSR for further coverage of secondary efficacy results.

3.2.3.3 Analysis Sets, Patients Disposition, Demographic and Baseline Disease Characteristics

Study ZONDA protocol defined four analysis sets: ***all patients analysis set***, ***full analysis set (FAS)***, ***safety analysis set*** and the ***PK analysis set***. The ***all patients analysis set*** comprised all patients screened for the study and was used for reporting disposition and screening failures[4]. The ***safety analysis set*** included all patients who received at least 1 dose of IP; patients were classified according to the treatment they actually received. The ***full analysis set*** included all patients who were randomized and received any IP, irrespective of their protocol adherence and whether or not they continued participation in the study. By its definition, the FAS was the appropriate population to support the estimation of the de facto or ITT estimand: patients in FAS were analyzed according to their randomized treatment, irrespective of whether or not they had prematurely discontinued; patients who withdrew consent to participate in the study was included up to the date of their study termination. In ZONDA, all efficacy analyses were performed using an ITT approach based on the FAS.

Of the 369 subjects who were enrolled into the study, 271 (73%) entered the run-in phase and 220 (60%) underwent randomization. All randomized patients received study drug, so the

[4] All patients analysis set was used in ZONDA CSR Figure 2.

randomized population and the FAS coincided; the safety analysis set also coincided with the FAS (Table 32).

Table 32. ZONDA: Analysis Datasets

	All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (EHS)			
	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo	Total	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo	Total
Patients Screened				369				
	Denominator: Number of Patients Screened							
Patients Who Entered Run-in / OCS Optimization				271 (73.4%)				
Randomized Population				220 (59.6%)				
Denominator: Number of Randomized Population								
Randomized Population	72 (100%)	73 (100%)	75 (100%)	220 (100%)	62 (100%)	61 (100%)	64 (100%)	187 (100%)
Safety Population	72 (100%)	73 (100%)	75 (100%)	220 (100%)	62 (100%)	61 (100%)	64 (100%)	187 (100%)
Full Analysis Set	72 (100%)	73 (100%)	75 (100%)	220 (100%)	62 (100%)	61 (100%)	64 (100%)	187 (100%)

Source: Reviewer.

Of note, in the total 220 patients that were randomized, the number of patients in the eosinophil low stratum (≥150 to <300 cells/µL, ELS) was 33, while the study design originally targeted 60 ELS patients. The applicant's explanation for the smaller ELS patient number was that the recruitment in this group was slower than expected.

Table 33. ZONDA: Patients Disposition (FAS)

	All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (EHS)			
	Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Treatment Completion								
Patients Who Have Completed Treatment	68 (94%)	67 (92%)	72 (96%)	207 (94%)	58 (94%)	58 (95%)	61 (95%)	177 (95%)
Treatment Dropout	4 (6%)	6 (8%)	3 (4%)	13 (6%)	4 (6%)	3 (5%)	3 (5%)	10 (5%)
Reason for Premature IP Discontinuation								
Adverse Event	0	3 (4.1%)	2 (2.7%)	5 (2.3%)	0	2 (3.3%)	2 (3.1%)	4 (2.1%)
Withdrawal by Subject from IP	4 (5.6%)	1 (1.4%)	0	5 (2.3%)	4 (6.5%)	0	0	4 (2.1%)

	All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (EHS)			
	Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Study-specific withdrawal criteria	0	1 (1.4%)	1 (1.3%)	2 (0.9%)	0	0	1 (1.6%)	1 (0.5%)
Other	0	1 (1.4%)	0	1 (0.5%)	0	1 (1.6%)	0	1 (0.5%)
Study Completion								
Patients Who Have Completed Study	68 (94%)	69 (95%)	72 (96%)	209 (95%)	58 (94%)	60 (98%)	61 (95%)	179 (96%)
Analysis Dropout	4 (6%)	4 (5%)	3 (4%)	11 (5%)	4 (6%)	1 (2%)	3 (5%)	8 (4%)
Reason for Early Discontinuation from Study								
Withdrawal by Subject from IP	4 (5.6%)	1 (1.4%)	0	5 (2.3%)	4 (6.5%)	0	0	4 (2.1%)
Death	0	2 (2.7%)	0	2 (0.9%)	0	1 (1.6%)	0	1 (0.5%)
Study-specific withdrawal criteria	0	1 (1.4%)	1 (1.3%)	2 (0.9%)	0	0	1 (1.6%)	1 (0.5%)
Adverse Event	0	0	1 (1.3%)	1 (0.5%)	0	0	1 (1.6%)	1 (0.5%)
Lost to Follow-up	0	0	1 (1.3%)	1 (0.5%)	0	0	1 (1.6%)	1 (0.5%)

Source: Reviewer

Among the 220 subjects included in the FAS population, demographics (Table 34) and baseline disease characteristics (Table 35) were similar across the three treatment groups, for both the FAS and the EHS. There was a higher percentage of female (FAS: 61%; EHS: 59%) than male (FAS: 39%; EHS, 41%). The majority of patients were in the 18–65 age group (FAS: 87%; EHS: 88%). This was a global trial with European subjects comprising 68% (in FAS) of the total population. The majority of subjects were white (FAS: 93%; EHS: 94%).

Table 34. ZONDA: Demographics (FAS)

		All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (FAS + EHS)			
		Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Age	>=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%)
Age (Years)	Mean (SD)	50.2 (12.0)	52.9 (10.1)	49.9 (11.7)	51.0 (11.3)	49.6 (12.3)	52.6 (10.3)	48.9 (11.0)	50.3 (11.3)
	Median (Min, Max)	50.5 (20, 75)	53.0 (27, 75)	50.0 (21, 74)	52.0 (20, 75)	50.0 (20, 75)	53.0 (27, 75)	49.0 (21, 70)	51.0 (20, 75)

		All Subjects (FAS)				Baseline blood eosinophil ≥300/µL (FAS + EHS)			
		Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Sex	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	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%)
	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	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: Reviewer.

ZONDA targeted a more severe patient group than the asthma exacerbation studies. The patients in ZONDA had slightly higher rates of baseline exacerbations (40% with 3 or more asthma exacerbation in the previous year) than patients in SIROCCO or CALIMA had (38%, and 34%, respectively).

Table 35. ZONDA: Baseline Disease Characteristics (FAS)

		All Subjects				Baseline blood eosinophil ≥300/µL FAS + EHS			
		Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Eosinophil Count									
Local Baseline Eosinophil Count (Cells/µL)	N	71	73	74	218	61	61	63	185
	Mean (SD)	558 (345.7)	509 (320.2)	656 (589.0)	575 (439.4)	616 (338.7)	570 (316.3)	730 (608.7)	640 (446.7)
	Median (Min, Max)	462 (160, 1740)	437 (154, 2140)	535 (160, 4550)	475 (154, 4550)	510 (300, 1740)	493 (300, 2140)	580 (300, 4550)	520 (300, 4550)
Central Baseline Eosinophil Count (Cells/µL)	N	72	73	75	220	62	61	64	187
	Mean (SD)	443 (312.1)	435 (324.7)	464 (315.7)	447 (316.4)	480 (318.3)	458 (337.4)	489 (328.2)	476 (326.5)

		All Subjects				Baseline blood eosinophil ≥300/μL FAS + EHS			
		Benra 30 mg q.4 weeks N=72	**Benra 30 mg q.8 weeks N=73**	**Placebo N=75**	**Total N=220**	**Benra 30 mg q.4 weeks N=62**	**Benra 30 mg q.8 weeks N=61**	**Placebo N=64**	**Total N=187**
	Median (Min, Max)	330 (40, 1370)	380 (0, 1810)	420 (10, 1680)	380 (0, 1810)	370 (40, 1370)	440 (0, 1810)	445 (10, 1680)	430 (0, 1810)
Lung Function Characteristics									
Pre-BD FEV_1 (L)	N	72	73	75	220	62	61	64	187
	Mean (SD)	1.850 (0.741)	1.754 (0.635)	1.931 (0.662)	1.846 (0.681)	1.907 (0.722)	1.795 (0.654)	1.968 (0.675)	1.891 (0.684)
	Median (Min, Max)	1.675 (0.55, 4.14)	1.770 (0.55, 3.60)	1.840 (0.74, 3.81)	1.780 (0.55, 4.14)	1.675 (0.75, 4.14)	1.830 (0.55, 3.60)	1.860 (0.92, 3.81)	1.820 (0.55, 4.14)
Pre-BD FEV_1 % Predicted	N	72	73	75	220	62	61	64	187
	Mean (SD)	57.4 (18.0)	59.0 (17.9)	62.0 (16.5)	59.5 (17.5)	58.8 (17.7)	59.5 (18.7)	62.4 (17.0)	60.2 (17.8)
	Median (Min, Max)	56.5 (19.0, 106.5)	62.3 (22.7, 100.8)	62.5 (27.0, 99.7)	60.0 (19.0, 106.5)	57.0 (19.0, 106.5)	63.8 (22.7, 100.8)	61.8 (29.8, 99.7)	59.9 (19.0, 106.5)
Pre-BD FEV_1/FVC Ratio	N	72	73	75	220	62	61	64	187
	Mean (SD)	59 (13)	59 (12)	62 (13)	60 (13)	59 (13)	59 (12)	62 (13)	60 (13)
	Median (Min, Max)	56 (25, 92)	60 (30, 82)	62 (28, 93)	60 (25, 93)	56 (25, 86)	61 (30, 82)	62 (34, 93)	60 (25, 93)
FEV_1 Reversibility (%)	N	66	68	73	207	56	56	62	174
	Mean (SD)	24.1 (21.7)	25.1 (19.0)	23.2 (18.0)	24.1 (19.5)	23.0 (20.7)	23.9 (19.0)	22.2 (18.1)	23.0 (19.1)
	Median (Min, Max)	18.2 (-3.0, 126.0)	22.6 (-3.4, 88.0)	16.4 (-5.4, 93.4)	19.0 (-5.4, 126.0)	18.0 (-3.0, 126.0)	20.9 (-3.4, 88.0)	15.8 (-5.4, 93.4)	17.8 (-5.4, 126.0)
Asthma History									
Number of Years since Asthma Diagnosis	N	72	73	75	220	62	61	64	187
	Mean (SD)	16.66 (13.20)	17.68 (13.85)	14.86 (13.23)	16.38 (13.42)	16.30 (13.50)	17.57 (13.41)	14.52 (13.68)	16.11 (13.52)
	Median (Min, Max)	13.32 (1.2, 52.3)	16.34 (1.3, 53.0)	10.48 (1.1, 54.5)	12.18 (1.1, 54.5)	13.13 (1.2, 52.3)	16.34 (1.3, 51.9)	9.59 (1.1, 54.5)	11.98 (1.1, 54.5)
Exacerbation History									
Number of Exacerbations in Previous 12 Months	1	24 (33.3%)	21 (28.8%)	24 (32.0%)	69 (31.4%)	18 (29.0%)	19 (31.1%)	20 (31.3%)	57 (30.5%)
	2	19 (26.4%)	23 (31.5%)	22 (29.3%)	64 (29.1%)	17 (27.4%)	17 (27.9%)	19 (29.7%)	53 (28.3%)
	3 or more	29 (40.3%)	29 (39.7%)	29 (38.7%)	87 (39.5%)	27 (43.5%)	25 (41.0%)	25 (39.1%)	77 (41.2%)

		All Subjects				Baseline blood eosinophil ≥300/µL FAS + EHS			
		Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220	Benra 30 mg q.4 weeks N=62	Benra 30 mg q.8 weeks N=61	Placebo N=64	Total N=187
Nicotine Use at Study Entry, N (%)									
Smoking Status	Former	17 (23.6%)	12 (16.4%)	17 (22.7%)	46 (20.9%)	14 (22.6%)	10 (16.4%)	13 (20.3%)	37 (19.8%)
	Never	55 (76.4%)	61 (83.6%)	58 (77.3%)	174 (79.1%)	48 (77.4%)	51 (83.6%)	51 (79.7%)	150 (80.2%)

Source: Reviewer

3.2.3.4 Results and Conclusions

3.2.3.4.1 ZONDA Primary Endpoint

In the primary analysis, the median percent reduction from baseline in OCS dose were similar (75% and 75%, respectively) in the two dosing regimen groups of Benralizumab 30 mg, as compared with a 25% reduction in the placebo group ($p<0.001$ and $p<0.001$, respectively). The Hodges–Lehmann estimate of location shift for the percentage changes in the Q8W group and those of the placebo group was 37.5%.

Table 36. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Primary Analysis

	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
Descriptive Statistics			
Median Percent 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	<0.001	<0.001	

Source: Reviewer

The sensitivity analysis approach assigned OCS dose prior to asthma exacerbation in calculation of percent OCS dose reduction from baseline in the daily OCS dose. The median percent reductions was still 75% in the Q8W group, and a little smaller (70.9%) in the Q4W group, as compared with 25% in the placebo group ($p<0.001$ and $p<0.001$, respectively). The sensitivity

analysis results supported and confirmed that the above demonstrated treatment effect in OCS sparing from the primary analysis is robust and can withstand lessened evidence base accounting for protocol violations associated with asthma exacerbation. However, asthma exacerbation related protocol deviations (10% of the total population) only accounted for less than half the total protocol deviations (24.5% of the total population). We consider the overall low quality as indicated by the significant amount of protocol deviations could not be mitigated by sensitivity analysis approach.

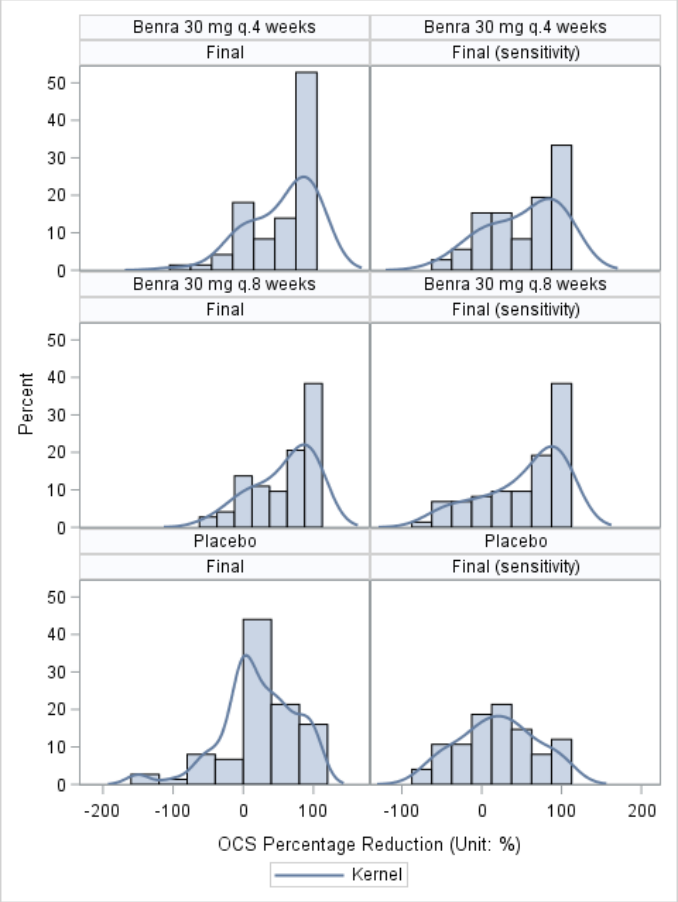
Table 37. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 1

	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
Descriptive Statistics			
Median % Reduction in Daily OCS dose from Baseline	70.9	75.0	25.0
95% CI (Distribution free)	(33.3, 75.0)	(50.0, 87.5)	(0.0, 33.3)
Wilcoxon Rank Sum Test			
Hodges-Lehmann Estimate of Location Shift for Benralizumab vs. Placebo	33.3	38.1	
95% CI (Moses CI)	(17.0, 50.0)	(16.7, 50.0)	
p value	<0.001	<0.001	

Source: Reviewer

To better understand the location shift estimates from the nonparametric analysis approach for the primary endpoint, Figure 8 is a panel plot used to illustrate the relative distributions of percent change from baseline in OCS dose under each treatment arm. The plot also contrasts the primary analysis approach with the sensitivity analysis approach: the left 3 vertical panels belong to the primary analysis approach; the right 3 vertical panels belong to the sensitivity approach. Compare the left panels with the right panels, we can see the shift to right caused by assigning patients with asthma exacerbation prior to exacerbation doses (higher dose values).

Figure 8. ZONDA: Panel Plot Contrasting Location Changes of Primary Analysis Approach versus Sensitivity Analysis Approach (Week 28)



Source: Reviewer

From the top rows on OCS percent reduction (Table 38), more patients in the Benralizumab groups had a reduction of 90% to 100% in OCS reduction (Q4W: 33%, Q8W: 37%) than in the placebo group (12%); also a reduction of 75% to 90%. In addition, 46.7% of placebo had no change or any increase as compared with 23.6% or 20.5% in Benralizumab group. The proportional odds model had an overall odds ratio for a reduction in OCS dose category in the Q8W group over placebo of 4.12 (95% CI [2.22, 7.63]; p<0.001).

Table 38. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 2: Proportional Odds Model

	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
OCS Percent Reduction: Count and Probability by Category N (%)			
90 - 100% Reduction	24 (33.3)	27 (37.0)	9 (12.0)
75% - <90% Reduction	14 (19.4)	10 (13.7)	6 (8.0)
50% - <75% Reduction	10 (13.9)	11 (15.1)	13 (17.3)
>0% - <50% Reduction	7 (9.7)	10 (13.7)	12 (16.0)
No change or any increase	17 (23.6)	15 (20.5)	35 (46.7)

	Benra 30 mg q.4 weeks	Benra 30 mg q.8 weeks	Placebo
OCS Percent Reduction: Cumulative Count and Probability N (%)			
>=90% Reduction	24 (33.3)	27 (37.0)	9 (12.0)
>=75% Reduction	38 (52.8)	37 (50.7)	15 (20.0)
>=50% Reduction	48 (66.7)	48 (65.8)	28 (37.3)
>0% Reduction	55 (76.4)	58 (79.5)	40 (53.3)
No change or any increase	17 (23.6)	15 (20.5)	35 (46.7)
Proportional Odds Model			
Odds Ratio (95% CI) p value	4.09 (2.22, 7.57) <0.001	4.12 (2.22, 7.63) <0.001	

Source: Reviewer

Table 39. ZONDA: OCS Percent Reduction from Baseline at Week 28 (FAS) – Sensitivity Analysis 3
(Removing Patients Whose Optimized OCS dose not reached at least 2 weeks (-3 days) prior to randomization)

	Benra 30 mg q.4 weeks N=71	Benra 30 mg q.8 weeks N=72	Placebo N=67
Descriptive Statistics			
Median Percent Reduction in Daily OCS Dose from Baseline 95% CI (Distribution free)	75.0 (50.0, 83.3)	75.0 (60.0, 87.5)	25.0 (0.0, 33.3)
Wilcoxon Rank Sum Test			
Hodges-Lehmann Estimate of Location Shift for Benralizumab vs. Placebo 95% CI (Moses CI) p value	33.3 (16.7, 50.0) <0.001	34.5 (17.0, 50.0) <0.001	

Source: Reviewer

3.3 Evaluation of Safety

Refer to Dr. Sofia Chaudhry's Clinical Review for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Efficacy analysis results of the two phase 3 asthma exacerbation trials, SIROCCO and CALIMA had demonstrated that for patients with severe eosinophilic asthma (baseline blood eosinophil

count ≥300/μL), who were uncontrolled by high-dose ICS plus LABA, Benralizumab 30 mg, administered subcutaneously every 8 weeks, had consistently shown reductions in asthma exacerbation requiring OCS by about 28% (CALIMA) to 51% (SIROCCO). To explore the consistency of treatment effect among subgroups within the overall targeted population, the applicant conducted a series of subgroup analyses by testing for interaction between treatment and subgroup factors. The applicant's subgroup analyses were performed for the following factors: OCS use at baseline (yes/no), gender, age group (<18, ≥18 – <65 and ≥65 years), geographic region (Asia, Eastern Europe, Europe, North America, and rest of world), BMI (≤35 kg/m2, >35 kg/m2), race group (Asian, Black or African American, Other, and White), the number of exacerbations in previous year (2, 3, ≥4 exacerbations), presence of nasal polyps (yes/no), IgE level (≤30 KU/L, >30-≤700 KU/L, >700 KU/L), atopic status (yes/no), and prior treatment with omalizumab (yes/no). For each of the subgroup factors in turn, a separate negative binomial regression model was fitted using the same model terms as used for the primary analysis with additional terms for the subgroup main effect and the treatment by subgroup interaction.

The applicant's subgroup analysis results indicated that the reductions in annual asthma exacerbation rate were similar and favored Benralizumab 30 mg Q4W and Q8W over placebo for all subgroups with the exception of adolescents (ages 12 to <18 years) in both regimens and both studies. While considering the small number of patients and events and/or a low crude placebo rate might have contributed to the inconsistent findings in the adolescent population, the applicant did not propose to include adolescents in the indicated population of this application.

For the replicate exacerbation studies: SIRROCO and CALIMA, I conducted independent subgroup analyses using the same approach on the demographic subgroup factors.

4.1 Gender, Race, Age, and Geographic Region

Interaction analyses as described above were conducted on two patient populations, the primary analysis population (EHS + High-ICS) and the all subject population (FAS), for each demographic subgroup factor.

Instead of using the applicant's approach of categorizing the population into three age groups, to follow the regulatory convention in asthma drugs, I dichotomized the population into two age groups, adolescents versus adults, for subgroup analyses. In addition, I have also conducted interaction analysis using age as a continuous variable assuming a linear trend. Interaction tests and results for studies SIRROCO and CALIMA are summarized in Table 40.

Table 40. SIROCCO and CALIMA: Asthma Exacerbation: Interaction Test Results for Subgroup Analyses (FAS, High-ICS)

Subgroup	Covariates in the Model					p-value			
	Categorical			Continuous		SIROCCO		CALIMA	
	Treatment	Region	Use of OCS	Number of exacerbations in the previous year	Subgroup, Subgroup*Treatment	EHS	FAS	EHS	FAS
Age	✓	✓	✓	✓	Age, Age*Treatment	0.0036	0.0015	0.6511	0.9480

(<18 vs. ≥18)									
Age Continuous	✓	✓	✓	✓	Age, Age*Treatment	0.0221	0.2306	0.3115	0.5493
Sex	✓	✓	✓	✓	Sex, Sex*Treatment	0.3124	0.3814	0.3946	0.3025
Region	✓		✓	✓	Region, Region*Treatment	0.0278	0.3228	0.1123	0.0939
Race	✓	✓	✓	✓	Race, Race*Treatment	0.2763	0.8046	0.0033	0.0063

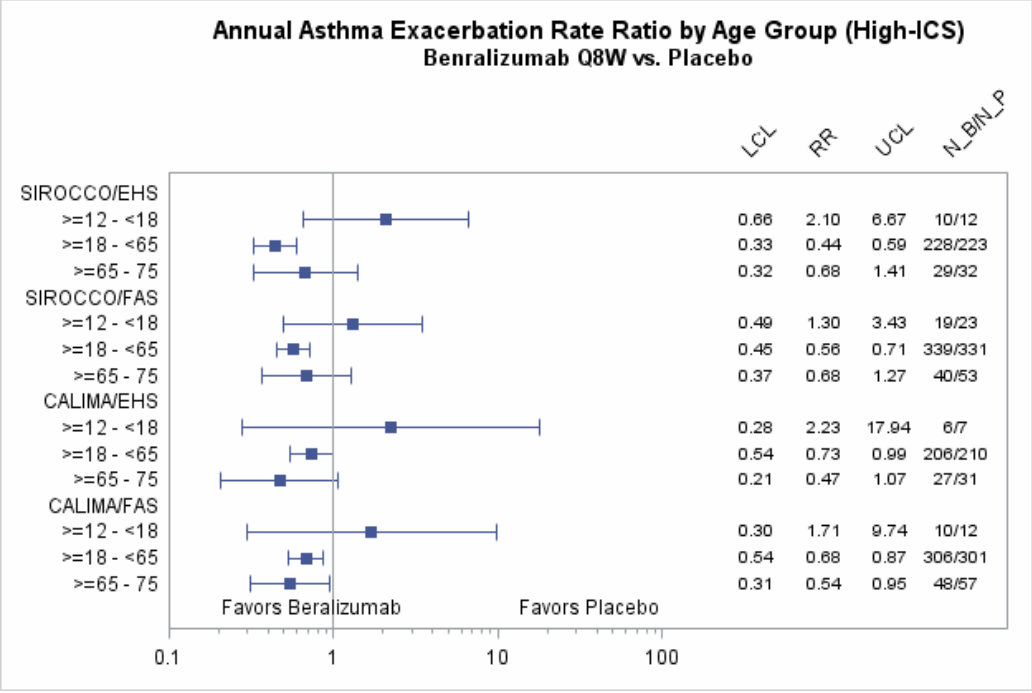
Source: Reviewer

Figure 17 to Figure 24 are the forest plots showing model based estimates of annual asthma exacerbation rate ratio over 48 weeks in SIROCCO or 56 weeks in CALIMA by subgroup for Benralizumab 30 mg versus placebo based on the EHS High-ICS population. To simplify presentation, I re-grouped geographic region into US vs. Non-US in this series of plots.

Across the 4 sets (two studies, two populations) of interaction tests, and the 8 forest plots (two dose regimens versus placebo in each set), in the adolescent subgroup, there was consistent trend in exacerbations favoring placebo (EHS + High-ICS, rate ratio versus placebo: 2.1 in SIROCCO, 2.23 in CALIMA for Benralizumab Q8W) although the 95% confidence intervals included 1 (

Figure 9). A similar trend was found in the analysis for Benralizumab Q4W (Figure 14 in Appendix).

Figure 9. SIROCCO and CALIMA: Annual Asthma Exacerbation Rate Ratio by Age Groups, Q8W vs. Placebo (FAS, High-ICS)



Source: Reviewer

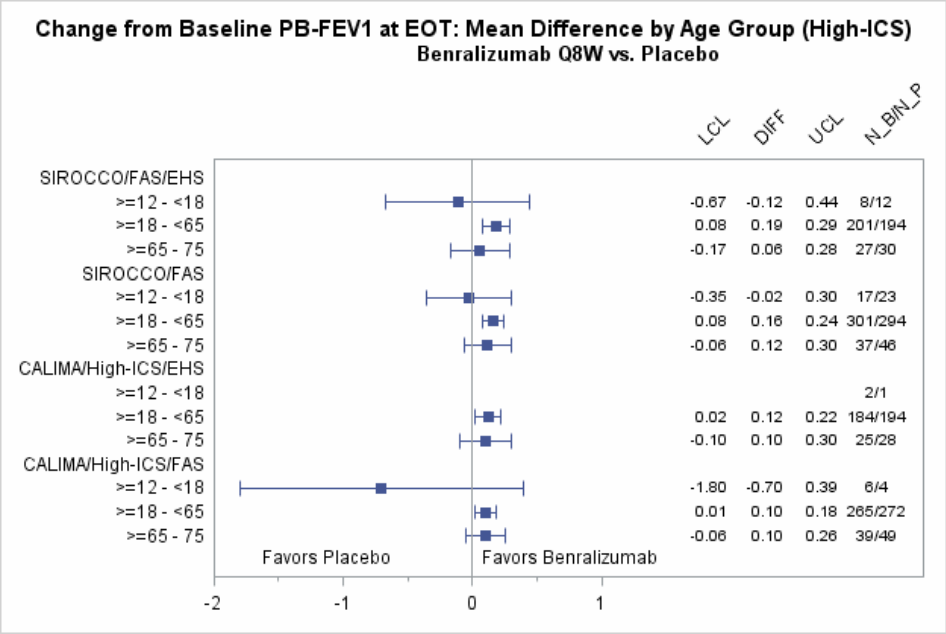
While there appears no treatment effect in terms of ARE in the adolescent group based on subgroup level point estimates of rate ratio, when considering the wide (imprecise) confidence intervals due to small sample sizes in the group and nature of the post hoc subgroup analysis, the finding from interaction tests is not definitive evidence that drug is not working in the adolescent group. In this vein, we performed additional interaction analyses on the key secondary efficacy endpoints to seek further evidence to confirm or refute findings from ARE. For each of the two studies, interaction tests were performed for the change from baseline PB-FEV1 and change from baseline Asthma Symptom Score at EOT and none of the tests showed significant interaction between treatment and age group (Table 41). Subgroup analyses are shown in Figure 10 and Figure 11, with mean differences and 95% confidence intervals, for the two key secondary efficacy endpoints at end of treatment (EOT) by age group.

Table 41. SIROCCO and CALIMA: Key Secondary Efficacy Endpoints: Interaction Test Results for Age Subgroup Analyses (FAS, High-ICS)

Subgroup	Covariates in the Model					p-value			
	Covariates					SIROCCO		CALIMA	
	Treatment	Region	Use of OCS	Age Group	Subgroup*Treatment	EHS	FAS	EHS	FAS
$PB\text{-}FEV_1$	✓	✓	✓	[12-18) [18-75)	Age Group*Treatment	0.5788	0.3414	0.6183	0.3463
	✓	✓	✓	[12-50) [50-65) [65-75)	Age Group*Treatment	0.7216	0.4656	0.7575	0.4095
Asthma Symptom Score	✓	✓	✓	[12-18) [18-75)	Age Group*Treatment	0.0980	0.1642	0.4347	0.6150
	✓	✓	✓	[12-18) [18-65) [65-75)	Age Group*Treatment	0.1014	0.1404	0.7726	0.7973

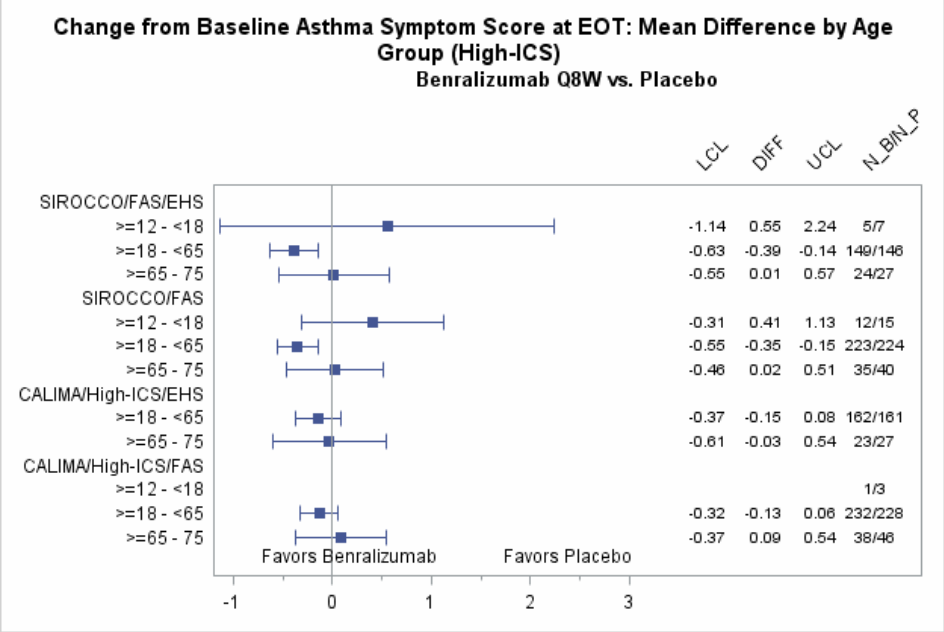
Source: Reviewer

Figure 10. SIROCCO and CALIMA: Change from Baseline PB-FEV1 at EOT: Mean Difference by Age Group, Q8W vs. Placebo (FAS, High-ICS)



Source: Reviewer

Figure 11. SIROCCO and CALIMA: Change from Baseline Asthma Symptom Score at EOT: Mean Difference by Age Group, Q8W vs. Placebo (FAS, High-ICS)



Source: Reviewer

In the interaction test of subgroup analysis for Sex, Region and Race, my examination confirmed the applicant's conclusion of consistency of treatment effects across the subgroup levels. For these factors, when a nominally significant interaction was observed within a study, it was not observed in the other study.

We have taken multiple concerns into account in interpretation of the above observed subgroup findings. As multiple interaction tests have been conducted for multiple subgroup variables, these p-values are nominal and should be interpreted in the context of the multiple comparisons. While there were some signals for potential interactions, as multiple tests were performed, consistency of observed signals across dosing regimens and trials was used to differentiate significant signs of interaction from isolated signals due to random noise. Also, small sample sizes have also been taken into consideration that the studies were not designed and powered for detecting interactions when some subgroup level had very small presence in the overall population. In this program, adolescents accounted for 4% (SIROCCO) and 2.2% (CALIMA) of the targeted EHS + High-ICS population. The unfavorably large rate ratio in the adolescent population may have resulted from the high variability in estimations based on small sample sizes.

Aside from above statistical concerns with data arisen from the Benralizumab clinical program, we also put this finding into the bigger picture of efficacy for adolescents of the anti-IL-5 pathway inhibitors drug class, as Benralizumab is the third drug in the class. A subgroup analysis conducted on the pooled adolescent population (26 subjects) in clinical program supporting approval for Mepolizumab showed that rate ratio versus placebo was less than one, favoring the Mepolizumab, while the adolescent group has the lest effect size compared with other age groups. In the Reslizumab program, one study had a rate ratio 0.95, another study had a rate ratio 3.07. While Mepolizumab was approved for patients aged 12 and older; Resilizumab was approved for adults only (patients 18 years of age or older). Across the three drugs, there is a trend that the anti-IL-5 has less or worse effect on the adolescents as compared to the effect in other age groups.

Taking the above considerations into our decision making, we think the current efficacy data does not provide substantial evidence of a clinically meaningful benefit of Benralizumab 30 mg Q8W for the treatment of severe asthma in children 12 -17 years of age. While multiplicity and small sample size may be of concern for isolated random signals, the apparently consistent findings of no evidence supporting efficacy for adolescents in this application do merit a further careful benefit-risk analysis for approval from various stakeholders' perspectives.

4.2 Other Special/Subgroup Populations

The applicant also pre-defined baseline disease characteristics related subgroups of interest in individual study SAPs to explore potential signal of inconsistent effect on ARE, with similar methodology as described above. Refer to the applicant's CSR for details.

Among other baseline factors, the applicant considered prior exacerbations (2 exacerbations, or ≥ 3 exacerbations) the most important prognostic factor. In addition to the pre-planned subgroup analyses on the primary endpoint, the applicant also conducted post-hoc analyses of these subgroups on the key secondary endpoints to explore the effect of prior exacerbations on PB FEV_1 and total asthma symptom score. (b) (4) I verified the applicant's results by conducting my own analyses and the results are included here.

Table 42. SIROCCO: Annualized Rate of Asthma Exacerbations by Baseline Exacerbation Count (FAS + EHS)

Baseline Exacerbation Count	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rate Difference	Rate Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
2	Benra 30 mg q.4 weeks	173	0.58	0.44, 0.76	-0.46	-0.76, -0.15	0.56	0.43, 0.74	0.56	0.38, 0.81	0.002*
	Benra 30 mg q.8 weeks	164	0.57	0.42, 0.76	-0.47	-0.78, -0.16	0.55	0.41, 0.73	0.55	0.37, 0.80	0.002*
	Placebo	149	1.04	0.80, 1.33			1.01	0.78, 1.30			
≥ 3	Benra 30 mg q.4 weeks	102	1.21	0.92, 1.60	-1.02	-1.66, -0.39	1.06	0.80, 1.41	0.54	0.38, 0.78)	0.001*
	Benra 30 mg q.8 weeks	103	0.95	0.69, 1.31	-1.28	-1.89, -0.68	0.84	0.62, 1.14	0.43	0.29, 0.63	<.001*
	Placebo	118	2.23	1.74, 2.86			1.96	1.55, 2.48			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 43. CALIMA: Annualized Rate of Asthma Exacerbations by Baseline Exacerbation Count (FAS + High-ICS + EHS)

Baseline Exacerbation Count	Treatment Group	N	Marginal Method				Model Based Approach				
			Mean Rate per Year	Mean Rate 95% CI	Rate Difference	Rate Difference 95% CI	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
2	Benra 30 mg q.4 weeks	148	0.46	0.35, 0.61	-0.16	-0.36, 0.05	0.44	0.34, 0.59	0.75	0.51, 1.10	0.139
	Benra 30 mg q.8 weeks	144	0.62	0.48, 0.81	0.01	-0.22, 0.23	0.60	0.46, 0.78	1.01	0.70, 1.46	0.966
	Placebo	151	0.96	0.80, 1.14			0.59	0.46, 0.77			
≥ 3	Benra 30 mg q.4 weeks	92	0.90	0.66, 1.22	-0.75	-1.25, -0.25	0.86	0.63, 1.17	0.55	0.37, 0.81	0.003*
	Benra 30 mg q.8 weeks	95	0.82	0.59, 1.13	-0.84	-1.33, -0.34	0.78	0.57, 1.07	0.49	0.33, 0.74	<.001*
	Placebo	97	1.65	1.28, 2.13			1.58	1.22, 2.04			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 44. SIROCCO: Change from Baseline Pre-Bronchodilator FEV1 at Week 48 by Baseline Exacerbation Count (FAS + EHS)

Baseline Exacerbation Count	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
2	Benra 30 mg q.4 weeks	172	0.340	0.260, 0.420	0.110	(-.004 , 0.224)	0.058
	Benra 30 mg q.8 weeks	162	0.340	0.260, 0.420	0.113	(-.002 , 0.228)	0.055
	Placebo	146	0.230	0.150, 0.310			
≥3	Benra 30 mg q.4 weeks	99	0.360	0.250, 0.470	0.108	(-.040 , 0.255)	0.151
	Benra 30 mg q.8 weeks	102	0.490	0.380, 0.590	0.235	(0.088 , 0.382)	0.002*
	Placebo	115	0.250	0.150, 0.350			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 45. CALIMA: Change from Baseline Pre-Bronchodilator FEV1 at Week 56 by Baseline Exacerbation Count (FAS + High-ICS + EHS)

Baseline Exacerbation Count	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
2	Benra 30 mg q.4 weeks	145	0.350	0.270, 0.420	0.112	(0.004 , 0.219)	0.043*
	Benra 30 mg q.8 weeks	143	0.270	0.190, 0.340	0.029	(-.079 , 0.137)	0.599
	Placebo	149	0.240	0.160, 0.310			
≥3	Benra 30 mg q.4 weeks	92	0.330	0.220, 0.430	0.151	(0.001 , 0.301)	0.048
	Benra 30 mg q.8 weeks	95	0.440	0.330, 0.550	0.265	(0.115 , 0.415)	0.001*
	Placebo	95	0.170	0.070, 0.280			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 46. SIROCCO: Change from Baseline Total Asthma Symptom Score at Week 48 by Baseline Exacerbation Count (FAS + EHS)

Baseline Exacerbation Count	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
2	Benra 30 mg q.4 weeks	171	-1.12	-1.30, -.950	-.083	(-.341 , 0.175)	0.529
	Benra 30 mg q.8 weeks	162	-1.26	-1.44, -1.08	-.223	(-.485 , 0.039)	0.095
	Placebo	149	-1.04	-1.23, -.850			

Baseline Exacerbation Count	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
≥3	Benra 30 mg q.4 weeks	102	-1.12	-1.34, -.900	-.070	(-.373 , 0.232)	0.647
	Benra 30 mg q.8 weeks	101	-1.36	-1.59, -1.14	-.317	(-.622 , -.012)	0.042*
	Placebo	118	-1.05	-1.25, -.840			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

Table 47. CALIMA: Change from Baseline Total Asthma Symptom Score at Week 56 by Baseline Exacerbation Count (FAS + High-ICS + EHS)

Baseline Exacerbation Count	Treatment Group	No. of Patients in Analysis	Mean Change from Baseline	Mean Change 95% CI	Mean Difference	Mean Difference 95% CI	Mean Difference p-value
2	Benra 30 mg q.4 weeks	148	-1.32	-1.50, -1.15	-.195	(-.440 , 0.050)	0.119
	Benra 30 mg q.8 weeks	142	-1.25	-1.43, -1.07	-.121	(-.369 , 0.126)	0.336
	Placebo	150	-1.13	-1.30, -.960			
≥3	Benra 30 mg q.4 weeks	92	-1.21	-1.44, -.980	-.003	(-.324 , 0.317)	0.983
	Benra 30 mg q.8 weeks	95	-1.62	-1.85, -1.39	-.411	(-.730 , -.093)	0.012*
	Placebo	97	-1.21	-1.43, -.990			

Source: Reviewer
Note: * indicate that the test was not multiplicity protected and the reported p-values are nominal.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

5.1.1 Interpretation of Subgroup Analysis Finding

Consistent signals of negative treatment effect have been found in the adolescent patient group through subgroup analyses on the age factor, both categorical. While we are taking consideration that there is the inherent type I error inflation with conducting multiple post hoc subgroup analyses, we are also observant in signals presented by the trial to protect vulnerable patient population, such as the adolescent, from unnecessary exposure to ineffective or even negative

treatments, although there may not yet be significant adverse events associated with the administration of Benralizumab at this time. In addition, while the interaction tests across the two exacerbation studies on age subgroup were not statistically significant at the same time, the low adolescent sample sizes and the wide confidence intervals are more likely to be the reason behind. Taking into account the above reasoning, we recommend a careful benefit-risk analysis for approval of Benralizumab in the pediatric population of adolescents.

5.1.2 Sensitivity Analysis to Missing Data

Testing of treatment effect and presentation of results with missing data is a review issue. We are interested in the evaluation of de facto estimands, e.g., comparisons between treatment groups with respect to the exacerbation rate over 48 or 56 weeks in all randomized High ICS EHS patients regardless of adherence. The primary analysis assumes that data after patients withdraw from the study are missing at random, i.e., that patients who drop out would be expected to have a similar exacerbation rate post-withdrawal to the exacerbation rate of patients on that treatment arm who remain in the study (and who have similar values of those baseline characteristics included in the model). This was a strong and unverifiable assumption.

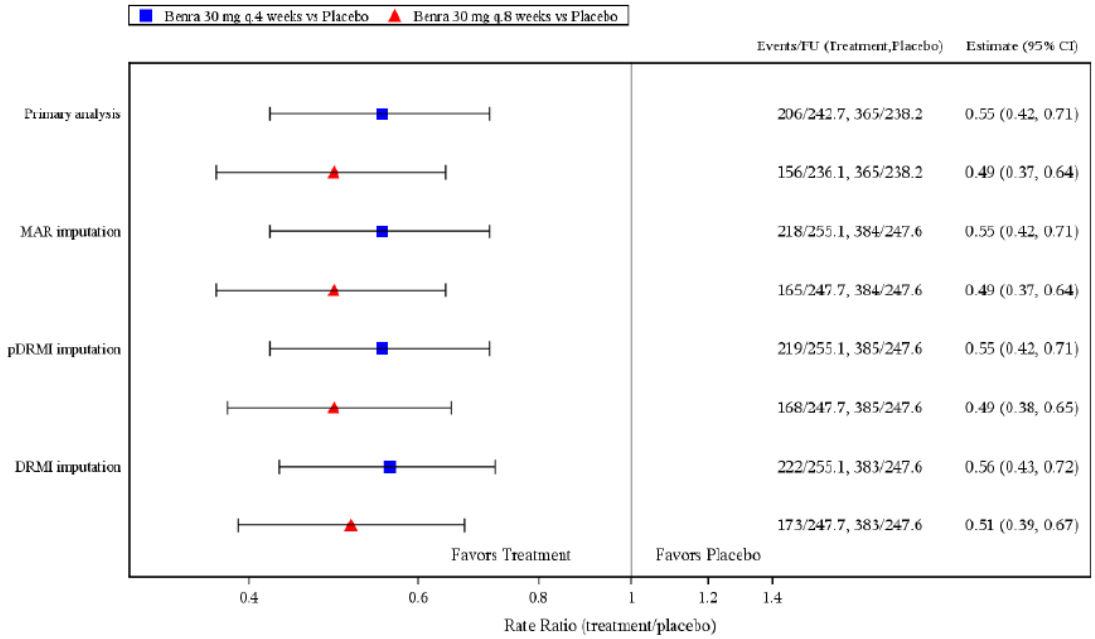
5.1.2.1 MI approaches by the Applicant

The applicant conducted multiple MI based sensitivity analyses to assess robustness to missing data with the treatment policy strategy. Results (Figure 12 and Figure 13) summarize the estimates of treatment effect under different imputation algorithm. These results are consistent with the primary analysis results.

5.1.2.2 Tipping Point Analyses by the Reviewer

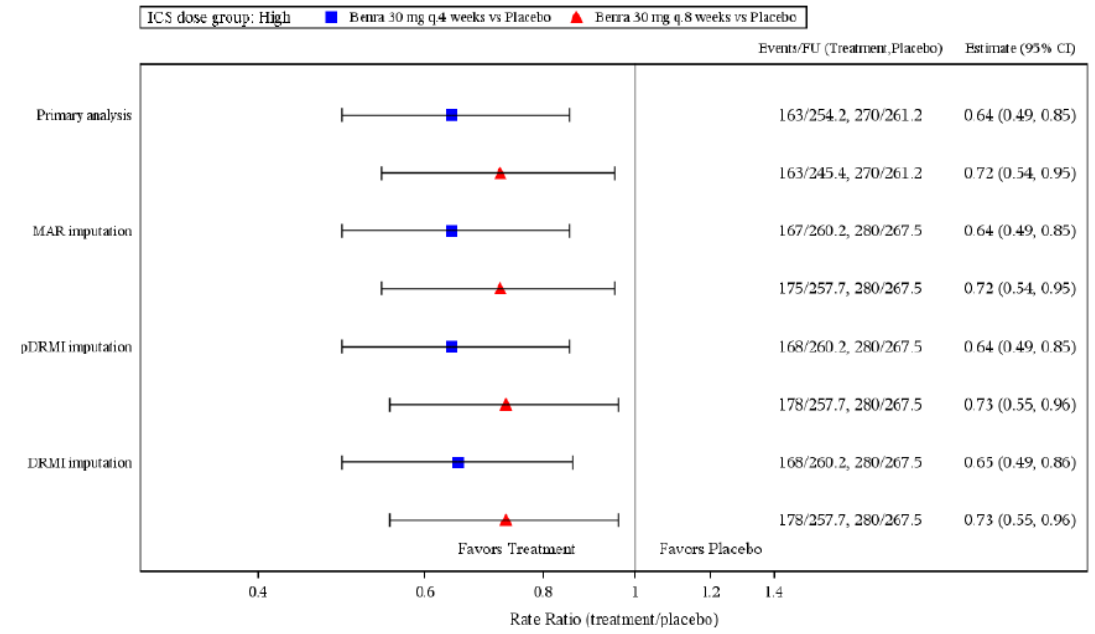
To examine the potential effect of missing data, I conducted an additional tipping point sensitivity analyses for the primary endpoint in SIROCCO and CALIMA. By varying assumptions about average values of the primary endpoint among the subsets of patients on the Benralizumab and placebo arms who withdrew from the study early. For example, in SIROCCO, the analysis varied assumptions about the rates of clinically significant exacerbations after dropout in the subsets of patients on all three arms who withdrew early. These varying assumptions included the possibility that patients with missing data from the Benralizumab arms had worse outcomes (a greater exacerbation rate post-withdrawal) than dropouts on the placebo arm. The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of those assumptions can be discussed.

Figure 12. SIROCCO: Sensitivity Analysis Clinically Significant Exacerbations by Multiple Imputation (FAS + EHS)



Source: Applicant, SIROCCO CSR Figure 17.

Figure 13. CALIMA: Sensitivity Analysis Clinically Significant Exacerbations by Multiple Imputation (FAS + High-ICS + EHS)



Source: Applicant, CALIMA CSR Figure 18.

Table 48 and Table 49 provide p-values associated with a test of whether the rate ratio differs from one for Benralizuamb 30 mg Q4W or Q8W relative to placebo in asthma exacerbation rate, respectively. These analyses incorporate both observed data and imputed data. Imputed data are

generated with varying assumptions about the rate of events for each treatment group (from 1.33 for the placebo group, 1.33 was the model based mean rate for placebo in SIROCCO, to 8.15 for Benralizumab) in patients who withdrew from the study early during the time for which they should have been observed but were not. Pink shaded regions include the cases where the assumptions regarding the post-discontinuation data are sufficient to "tip" the analysis of the risk ratio for the mean exacerbation rate (including observed and unobserved imputed data) so that the result numerically favoring the Benralizumab groups is no longer associated with a p-value less than 0.05.

In order for the hypothesis test to fail to demonstrate an advantage of Benralizumab over placebo, the mean rate of severe exacerbation would need to be at least 4 exacerbations per year larger in the Benralizumb dropouts than in the placebo dropouts for SIROCCO (both Q4W and Q8W) and Q4W in CALIMA. However, as the results in Table 49 for Q8W versus placebo indicates, the observed treatment effect could be easily tipped with a very narrow range of difference. Therefore, although these tipping point analyses largely support the findings of the key efficacy analyses of the observed data presented in the primary analyses, it should be noted that the CALIMA results was not so robust to withstand a big variation of assumptions on the missing mechanism.

Table 48. SIROCCO: Tipping Point Analysis of Rate of Clinically Significant Exacerbations (FAS + EHS)

Benralizumab Q4W vs. Placebo									
		Benralizumab Rate Post-withdrawal							
		4.65	**5.15**	**5.65**	**6.15**	**6.65**	**7.15**	**7.65**	**8.15**
Placebo Rate Post-withdrawal	**1.33**	0.014	0.023	0.039	0.057	0.079	0.114	0.150	0.205
	1.53	0.012	0.023	0.035	0.051	0.076	0.101	0.155	0.193
	1.73	0.010	0.018	0.033	0.053	0.080	0.106	0.140	0.178
	1.93	0.009	0.017	0.030	0.043	0.062	0.100	0.134	0.171
	2.13	0.009	0.017	0.027	0.041	0.072	0.090	0.123	0.161
	2.33	0.008	0.014	0.022	0.043	0.062	0.090	0.119	0.158
Benralizumab Q8W vs. Placebo									
		Benralizumab Rate Post-withdrawal							
		4.65	**5.15**	**5.65**	**6.15**	**6.65**	**7.15**	**7.65**	**8.15**
Placebo Rate Post-withdrawal	**1.33**	0.003	0.005	0.010	0.017	0.027	0.043	0.059	0.086
	1.53	0.002	0.006	0.010	0.015	0.025	0.038	0.057	0.076
	1.73	0.002	0.004	0.009	0.015	0.024	0.030	0.055	0.074

Benralizumab Q4W vs. Placebo									
		Benralizumab Rate Post-withdrawal							
		4.65	5.15	5.65	6.15	6.65	7.15	7.65	8.15
	1.93	0.002	0.004	0.007	0.014	0.024	0.035	0.050	0.066
	2.13	0.002	0.004	0.007	0.012	0.021	0.030	0.045	0.066
	2.33	0.001	0.004	0.006	0.011	0.021	0.027	0.042	0.059

Table 49. CALIMA: Tipping Point Analysis of Rate of Clinically Significant Exacerbations (FAS + High ICS + EHS)

Benralizumab Q4W vs. Placebo									
		Benralizumab Rate Post-withdrawal							
		1.16	1.66	2.16	2.66	3.16	3.66	4.16	4.66	5.16
Placebo Rate Post-withdrawal	0.93	0.004	0.006	0.009	0.014	0.020	0.028	0.042	0.057	0.074
	1.13	0.003	0.005	0.008	0.013	0.018	0.028	0.040	0.050	0.070
	1.33	0.003	0.004	0.007	0.012	0.018	0.024	0.034	0.048	0.069
	1.53	0.002	0.004	0.007	0.010	0.017	0.023	0.034	0.047	0.060
	1.73	0.002	0.004	0.006	0.009	0.015	0.022	0.029	0.045	0.059
	1.93	0.002	0.003	0.006	0.008	0.013	0.019	0.030	0.042	0.051
Benralizumab Q8W vs. Placebo									
		Benralizumab Rate Post-withdrawal							
		1.16	1.66	2.16	2.66	3.16	3.66	4.16	4.66	5.16
Placebo Rate Post-withdrawal	0.93	0.029	0.054	0.093	0.154	0.224	0.303	0.404	0.533	0.659
	1.13	0.027	0.050	0.088	0.144	0.214	0.304	0.395	0.496	0.609
	1.33	0.024	0.046	0.081	0.137	0.194	0.290	0.406	0.469	0.610
	1.53	0.023	0.043	0.077	0.124	0.191	0.276	0.371	0.456	0.585
	1.73	0.020	0.040	0.071	0.110	0.182	0.254	0.354	0.441	0.573
	1.93	0.020	0.036	0.065	0.105	0.171	0.252	0.345	0.433	0.529

Source: Reviewer

5.1.3 Sensitivity Analyses to Important Protocol Deviation

In SIROCCO, among the 5 patients with important protocol deviations, all were randomized to the Benralizumab Q8W, 4 patients had been administered two adjacent Benralizumab 30 mg doses in occasions of consecutive visits; in CALIMA, among the 22 Q8W (by randomization) patients had important protocol deviations, 13 patients received occasions of adjacent Benralizumab 30 mg doses on consecutive visits. These incidences were results of study misconduct at certain sites and had no further consequences on the efficacy measurements. This reviewer conducted sensitivity analyses by using actual treatment instead of planned treatment in the primary analyses. Results from the sensitivity analyses (Table 50 and Table 51) are very close to the primary analysis results.

Table 50. SIROCCO: Sensitivity Analysis to Important Protocol Deviation - Annualized Rate of Asthma Related Exacerbation (FAS)

	Treatment Group	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
Overall	Benra 30 mg q.4 weeks	0.78	0.67, 0.91	0.60	0.49, 0.74	<.001*
	Benra 30 mg q.8 weeks	0.76	0.64, 0.89	0.59	0.47, 0.72	<.001*
	Placebo	1.29	1.13, 1.48			
EHS	Benra 30 mg q.4 weeks	0.74	0.61, 0.91	0.56	0.43, 0.72	<.001
	Benra 30 mg q.8 weeks	0.63	0.51, 0.78	0.47	0.36, 0.62	<.001
	Placebo	1.33	1.12, 1.58			
ELS	Benra 30 mg q.4 weeks	0.85	0.65, 1.10	0.70	0.50, 0.99	0.046*
	Benra 30 mg q.8 weeks	1.00	0.78, 1.29	0.83	0.59, 1.16	0.277
	Placebo	1.21	0.96, 1.52			

Source: Reviewer

Table 51. CALIMA: Sensitivity Analysis to Important Protocol Deviation - Annualized Rate of Clinically Significant Exacerbation (FAS)

	Treatment Group	Mean Rate per Year	Mean Rate 95% CI	Rates Ratio	Rates Ratio 95% CI	Rate Ratio p-value
Overall	Benra 30 mg q.4 weeks	0.65	0.55, 0.77	0.64	0.52, 0.80	<.001*
	Benra 30 mg q.8 weeks	0.69	0.58, 0.82	0.68	0.54, 0.85	<.001*
	Placebo	1.02	0.88, 1.18			
EHS	Benra 30 mg q.4 weeks	0.60	0.49, 0.73	0.64	0.49, 0.85	0.002
	Benra 30 mg q.8 weeks	0.67	0.54, 0.83	0.72	0.54, 0.95	0.022
	Placebo	0.93	0.77, 1.12			
ELS	Benra 30 mg q.4 weeks	0.77	0.59, 1.01	0.64	0.45, 0.91	0.014*
	Benra 30 mg q.8 weeks	0.73	0.56, 0.95	0.60	0.42, 0.86	0.005*
	Placebo	1.21	0.96, 1.52			

Source: Reviewer

5.1.4 OCS Titration Error (ZONDA)

As early as the applicant conducted blinded preliminary data review, the study team identified instances of OCS titration error: for a subgroup of patients who recorded an exacerbation following randomization, contrary to the process outlined in the protocol, the sites appeared to continue down-titrating of the OCS dose following the exacerbation. In total, the titration processes of 22 (10%) patients were affected (Table 52). To address this significant issue, the study SAP included an alternative assessment approach of the percentage reduction in OCS dose: *for patients with no exacerbations recorded following Visit 6, the primary endpoint was derived as pre-planned; for those patients who did record an exacerbation on or after Visit 6, the final OCS dose used in the percent reduction from baseline calculation was the OCS dose 1 step higher than the dose at which their first exacerbation started.* I consider this approach sufficient to address the consequences of the misconduct in titration ignoring exacerbation.

However, there were also another two groups of patients (4.5% vs. 5.0%) who either had been down-titrated while not meeting the down-titration criteria or had not been down-titrated while meeting the down-titration criteria. The applicant considered these two types of violations had opposite effects on the assessment of efficacy and could cancel out the potential impact of each other; toward this end, there was no sensitivity analysis conducted to address the consequences of these two types of violations. I generally agree with the applicant's plan; however, as characterization of the OCS dose reduction was the primary objective of the trial, I consider the trial conduct as below expectation for a trial supporting regulatory approval and I doubt the overall quality of data generated by this trial.

Table 52. ZONDA: Important Protocol Deviations (FAS)

Protocol Deviation Coded Term	Benra 30 mg q.4 weeks N=72	Benra 30 mg q.8 weeks N=73	Placebo N=75	Total N=220
Number of patients with an important deviation	15 (20.8%)	12 (16.4%)	27 (36.0%)	54 (24.5%)
Optimized OCS dose not reached at least 2 weeks (-3 days) prior to randomization	1 (1.4%)	1 (1.4%)	8 (10.7%)	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 (4.2%)	6 (8.2%)	13 (17.3%)	22 (10.0%)
Patients who were down-titrated but did not meet the down-titration criteria	4 (5.6%)	2 (2.7%)	4 (5.3%)	10 (4.5%)
Patients who were not down-titrated but met the down-titration criteria	3 (4.2%)	2 (2.7%)	6 (8.0%)	11 (5.0%)
Oral corticosteroid dose titration criteria which could have impacted the final OCS dose	4 (5.6%)	2 (2.7%)	2 (2.7%)	8 (3.6%)

Source: Reviewer.

5.2 Collective Evidence

Collective evidence both across the replicate key phase 3 exacerbation studies and across the MTP hierarchies (Table 53) within each study provided substantial evidence of Benralizumab Q8W in reducing the risk of asthma exacerbations, improving lung function and asthma symptom in patients with severe eosinophilic asthma.

Table 53. SIROCCO and CALIMA: Multiple Testing Procedure

	MTP Plans: Reference Level for Statistical Significance on Unadjusted p-value for Comparisons		SIROCCO (FAS, EHS)		CALIMA (FAS, EHS, High ICS)	
			Testing Results (Benralizumab vs. placebo)	Realized Testing Procedure	Testing Results (Benralizumab vs. placebo)	Realized Testing Procedure
	Scenario 1	Scenario 2		Scenario 1		Scenario 1
Primary (Hochberg)	**α=0.04**	**α=0.04**				
	Both p<0.04	One p≥0.04 and one p<0.02	ARE Q4W: p<0.001	✓	ARE Q4W: p=0.002	✓
			ARE Q8W: p<0.001	✓	ARE Q8W: p=0.019	✓
Secondary (Holm)	**α=0.05**	**α=0.01**				
	$P_{(1)} < 0.0125$	$P_{(1)} < 0.0025$	FEV1 Q8W: p=0.001	✓	FEV1 Q8W: p=0.005	✓
	$P_{(2)} < 0.0167$	$P_{(2)} < 0.0033$	TASS Q8W: p=0.012	✓	FEV1 Q8W: p=0.010	✓
	$P_{(3)} < 0.025$	$P_{(3)} < 0.005$	FEV1 Q4W: p=0.022	✓	TASS Q8W: p=0.019	✓
	$P_{(4)} < 0.05$	$P_{(4)} < 0.01$	TASS Q4W: p=0.442	×	TASS Q4W: p=0.224	×

Source: Reviewer
Abbreviations: ARE: Asthma Related Exacerbations; TASS: Total Asthma Symptom Score

While the comparisons of treatment effect between the two dosing regimens of Benralizumab 30 mg were not included in the multiple control, we observed that the administration of the less frequent dose of the drug (Q8W) was shown to be numerically more efficacious than the more frequent dose (Q4W) in terms of improving lung function and patients quality of life as measured by total asthma symptom score.
While the studies were not planned or powered to study treatment effect in severe asthma patients with baseline blood eosinophil count below the 300 cells/μL cut-point or to test relative effectiveness of Benralizumab on the EHS versus on the ELS, we have made the observation that severe eosinophilic asthma patients selected using the blood eosinophil count above cut-point 300 cells/μL had better outcomes across multiple clinical endpoints than patients who had baseline blood eosinophil count below 300 cells/μL. In patients requiring maintenance OCS for asthma control, analysis results from ZONDA demonstrated that Benralizumab 30 mg Q8W had a significant OCS sparing effect.

5.3 Conclusions and Recommendations

The two exacerbation studies both demonstrated that Benralizumab 30 mg Q8W was an effective treatment that reduced the annualized rate of clinically significant asthma exacerbations (ARE) in the EHS. Compared with placebo, the rate reduction of ARE was 51% (rate ratio 0.49; 95% CI [0.37, 0.64]; p<0.001) in the Q8W group, and 45% (rate ratio 0.55; 95% CI [0.42, 0.71]; p<0.001 in the Q4W group in SIROCCO; 28% (rate ratio 0.72; 95% CI [0.54, 0.95]; p=0.019) in the Q8W group, and 36% (rate ratio 0.64; 95% CI [0.49, 0.85]; p=0.002) in the Q4W group in CALIMA. Statistically significant treatment effects in terms of lung function (change from baseline pre-bronchodilator FEV_1 at the end of the trials) and asthma symptom control (change from baseline total asthma symptom score at the end of the trials) were also demonstrated, consistently, by the two studies for the Q8W arm in the high-dose ICS EHS analysis set. My sensitivity analyses results supported the primary analysis conclusions.

In the OCS sparing study ZONDA, the median percentage reduction from baseline in the final OCS dose was 75% among patients in the Benralizumab Q8W group, as compared with the 25% reduction in the placebo group (Wilcoxon Rank Sum Test: $p<0.001$); the median percentage reduction was also 75% among patients in the Benralizumab Q4W group (Wilcoxon Rank Sum Test: $p<0.001$). In conclusion, in severe eosinophilic asthma patients requiring OCS to maintain asthma control, the primary analysis of OCS reduction data demonstrated that Benralizumab had a significant OCS sparing effect. Misconducts in the trial resulted in high overall protocol deviation rate (25%). My sensitivity analysis results showed that the conclusion on treatment effect in OCS sparing, based on results from primary analysis, was not influenced by the protocol deviations.

Subgroup analyses on the key secondary endpoints from both studies, SIROCCO and CALIMA, did not support the interaction found in the SIROCCO study in terms of the primary endpoint. In addition, the earlier finding of statistically significant interaction in SIROCCO was not replicated in the CALIMA in terms of the primary endpoint. The significant interaction found in one study, not supported by other study or key secondary endpoints from both studies, did not lead us to a definite conclusion that the drug is not working in 12 to 17 age group. Therefore, we deferred the approval decision in 12 to 17 age group to clinical team's benefit-risk assessment.

5.4 Labeling Recommendations

1. According to the MTP for both SIROCCO and CALIMA, the multiplicity protected endpoints included the primary endpoint and two key secondary efficacy endpoints on the comparison of the two Benralizumab dosing regimens compared with placebo. The proposed labeling included additional estimated treatment effects and addition analyses of the exacerbation endpoints. Overall Type I error is not controlled in this situation.

2. The proposed labeling used marginal treatment effect estimates (b) (4) on the primary analyses. While the marginal version estimates was proposed as supportive analysis to the primary analyses results, it is currently reported in the labeling (b) (4). We agree with the applicant in that the marginal version annual exacerbation rates more closely align with crude rates and as such is an appropriate method to report treatment exacerbation rates.

3. In section 14 of the labeling, (b) (4)

6 BIBLIOGRAPHY

NAEPP. (2007). *National Heart, Lung, and Blood Institute Nathional Asthma Education and Prevention Program Expert Panel Report 3.*

Tan, L. D. (2016). Benralizumab: a unique IL-5 inhibitor for severe asthma. *Journal of Asthma and Allergy*, 71-81.

APPENDICES

Appendix A. Strata Closure Process

1. The high-dose-ICS with eosinophil <300/mL stratum will be closed to adult patients when the total number of adult and adolescent patients in the stratum reaches 378
2. The adolescents stratum with eosinophil <300/mL stratum will be closed when the total number of adolescent patients in Study D3250C00018 and D3250C00017 altogether in the <300/mL stratum reaches 70.
3. The whole study will be closed for recruitment when the total number of adult and adolescent patients in the high-dose-ICS with eosinophil ≥300/mL stratum reaches 756.

Appendix B. The Applicant's Sensitivity Analysis Plan

Primary analysis under the Treatment Policy Estimand using the Missing at Random (MAR) assumption

The primary analysis is under the treatment policy estimand which allows for differences in outcomes over the entire study treatment period to reflect the effect of initially assigned randomized treatment as well as subsequent treatments taken. This primary analysis includes all data until patients withdraw from the study regardless of whether they discontinue from randomized treatment. The primary analysis uses the negative binomial regression model with (logarithm of) the observation period as an offset term and assumes that missing data is missing at random (MAR) and is a direct likelihood approach (DL).

Sensitivity analyses under the Treatment Policy Estimand using both MAR and MNAR assumptions

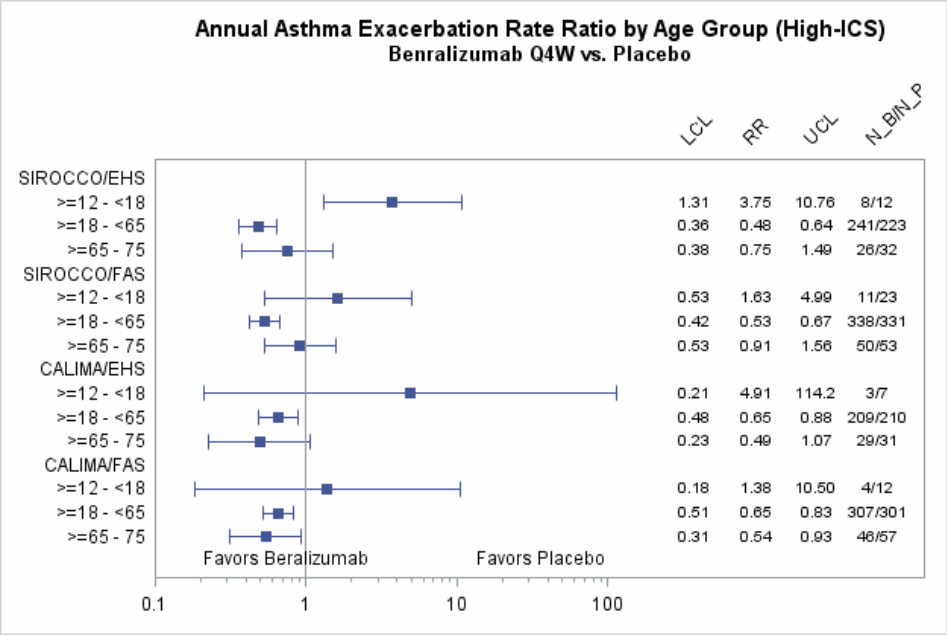
To examine the sensitivity of the results of the primary analysis to departures from the underlying assumptions, additional analyses are performed using controlled multiple imputation method introduced in [1] and further developed at AstraZeneca [2,3] which allows for different underlying assumptions to be used. As with the primary analysis the sensitivity analyses includes all data until patients withdraw from the study regardless of whether they discontinue from randomized treatment.
For this method an underlying negative binomial stochastic process for the rate of exacerbations is assumed and post study withdrawal counts are imputed conditional upon the observed number of events prior to the withdrawal. This allows various assumptions about the missing data to be analyzed by modifying the post-withdrawal model assumption.

The method involves first fitting the primary analysis, ie, negative binomial regression model to the observed data and then imputing post-withdrawal counts by sampling from the conditional negative binomial probability relating post-withdrawal counts and observed prior withdrawal counts based on various assumptions.

The following default assumptions that are used to impute the missing data who withdraw early from the study are as follows:
a) **MAR**: Missing counts in each arm are imputed assuming the expected event rate within that arm.
b) **Partial Dropout Reason-based Multiple Imputation (Partial-DRMI)**: Missing counts are imputed differently depending on the reason for dropout; counts for patients in the Benralizumab arms who dropped out for a treatment related reason are imputed based on the expected event rate in the placebo arm, whereas the remaining patients who have dropped out are imputed assuming MAR. Treatment related reasons include (1) AEs, (2) Death and (3) development of study specified reasons to stop active treatments.
c) **Dropout Reason-based Multiple Imputation (DRMI):** as for Partial-DRMI with treatment related reasons and also including severe non-compliance of protocol.

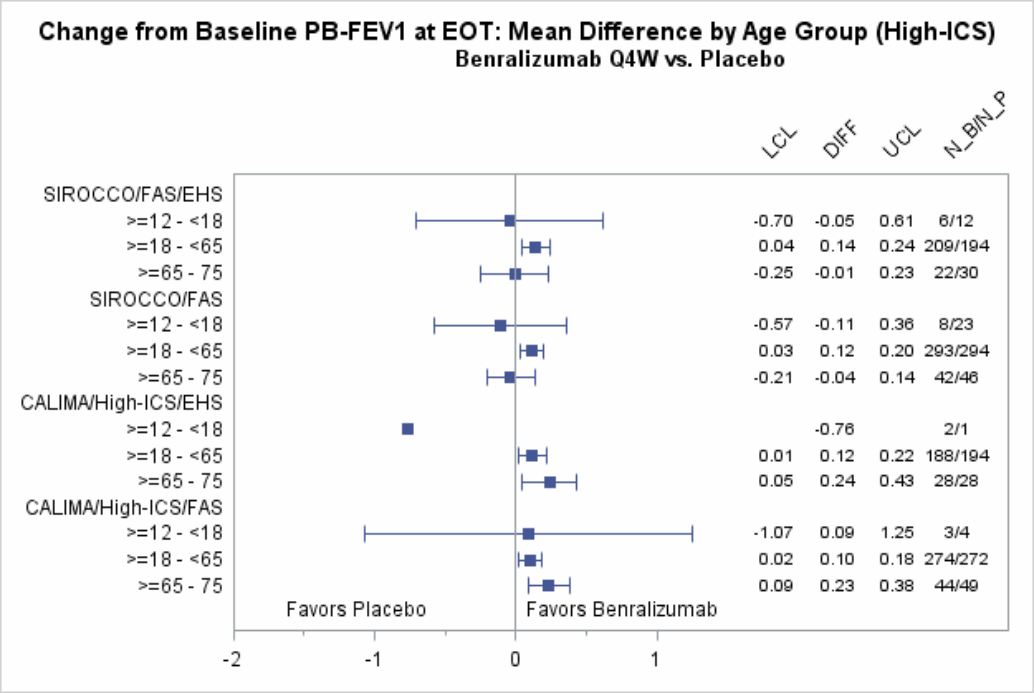
Appendix C. Subgroup Analysis Forest Plots

Figure 14. SIROCCO and CALIMA: Annual Asthma Exacerbation Rate Ratio by Age Groups, Q4W vs. Placebo (FAS +High-ICS)



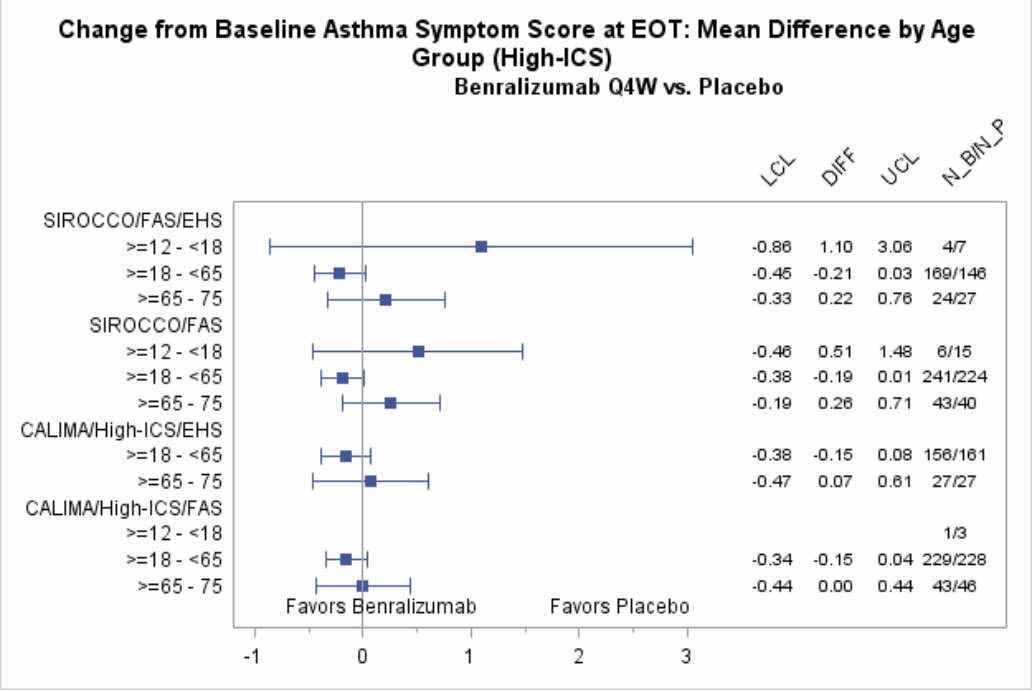
Source: Reviewer

Figure 15. SIROCCO and CALIMA: Change from Baseline PB-FEV1 at EOT: Mean Difference by Age Group, Q4W vs. Placebo (FAS + High-ICS)



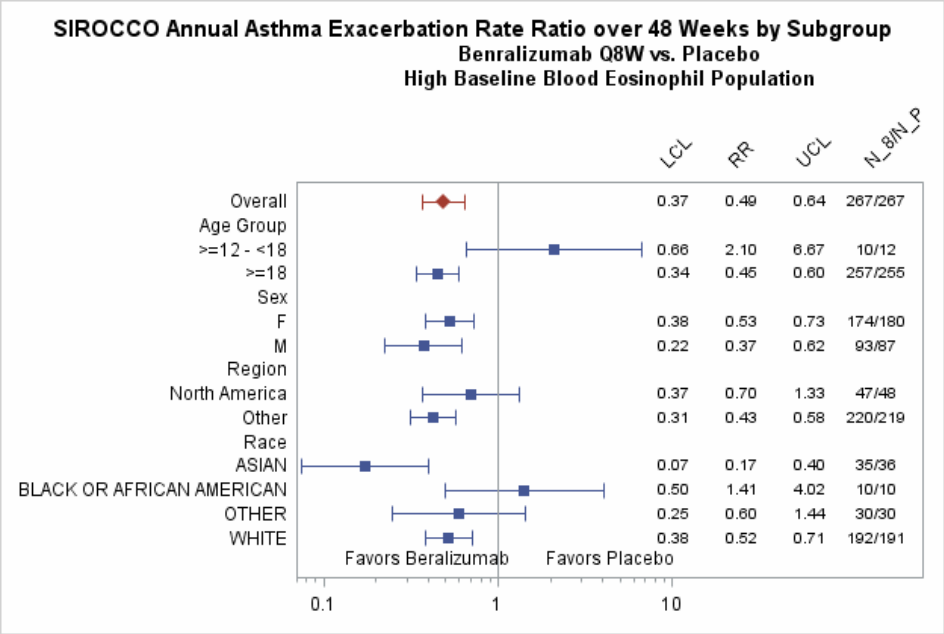
Source: Reviewer

Figure 16. SIROCCO and CALIMA: Change from Baseline Asthma Symptom Score at EOT: Mean Difference by Age Group, Q4W vs. Placebo (FAS + High-ICS)



Source: Reviewer

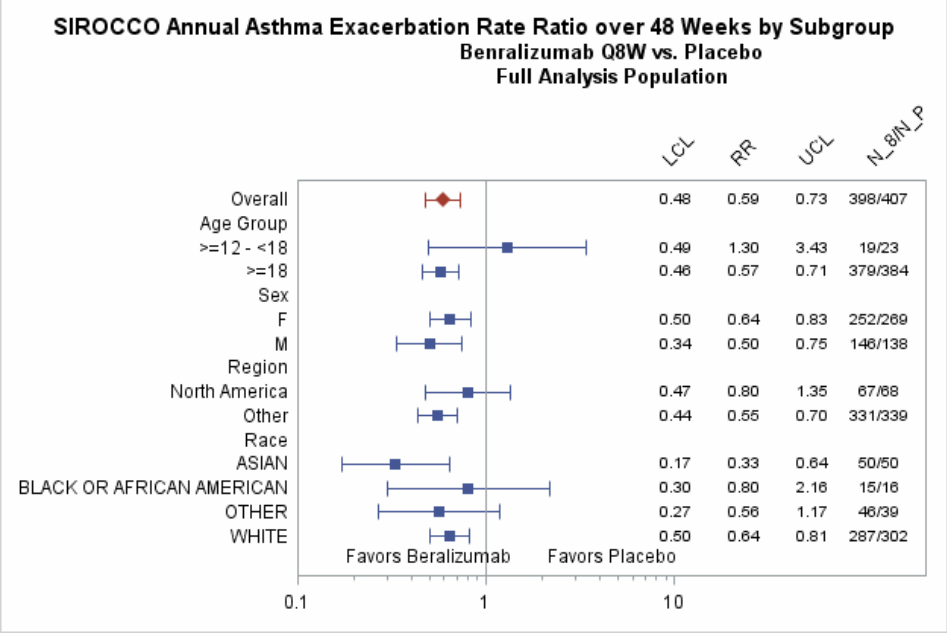
Figure 17. SIROCCO: Forest Plot, Q8W vs. Placebo (FAS + EHS)



Source: Reviewer

Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_8: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

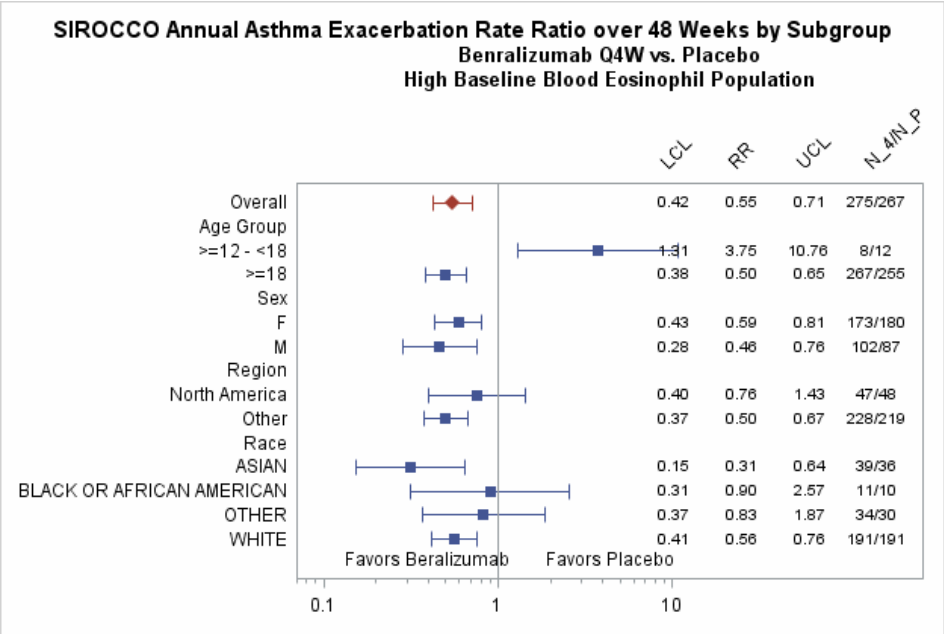
Figure 18. SIROCCO: Forest Plot, Q8W vs. Placebo (FAS)



Source: Reviewer

Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_8: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

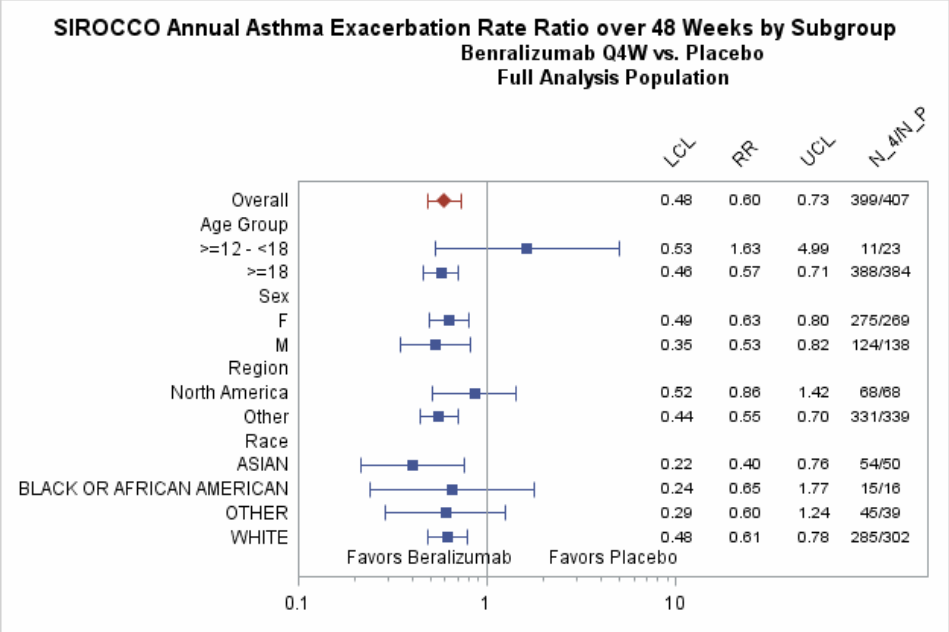
Figure 19. SIROCCO: Forest Plot, Q4W vs. Placebo (FAS + EHS)



Source: Reviewer

Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_4: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

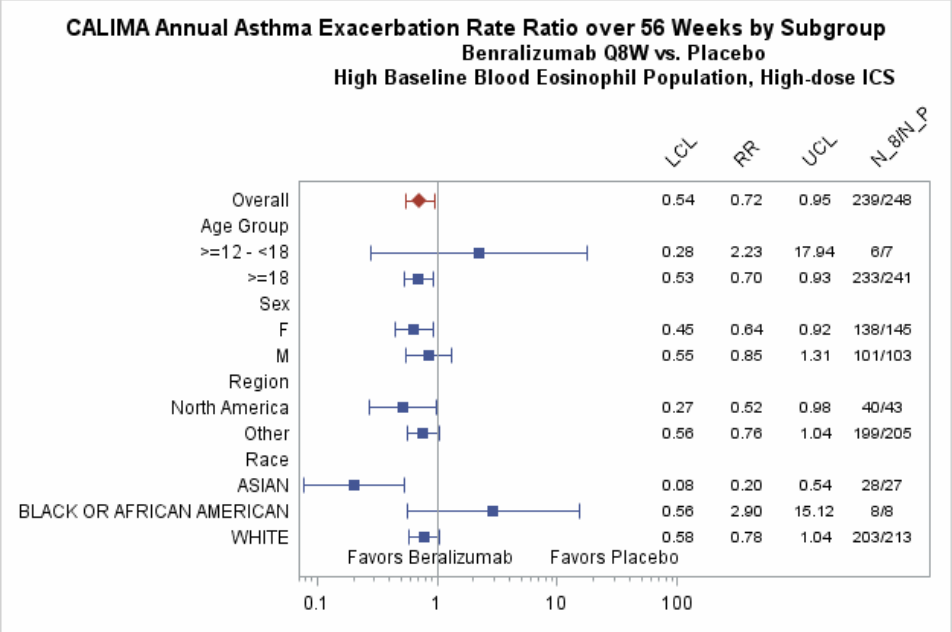
Figure 20. SIROCCO: Forest Plot, Q4W vs. Placebo (FAS)



Source: Reviewer

Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_4: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

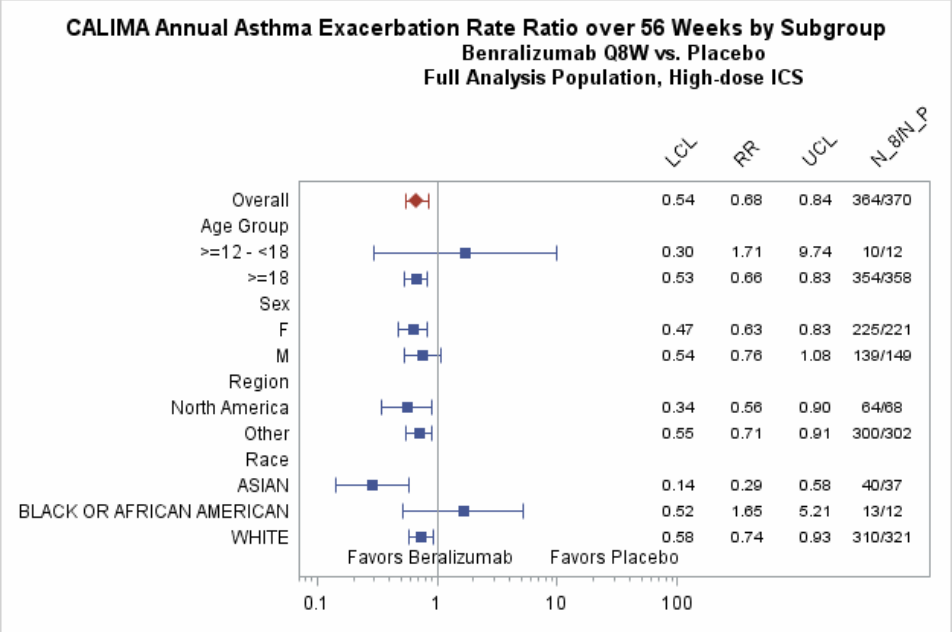
Figure 21. CALIMA: Forest Plot, Q8W vs. Placebo (FAS + High-ICS + EHS)



Source: Reviewer

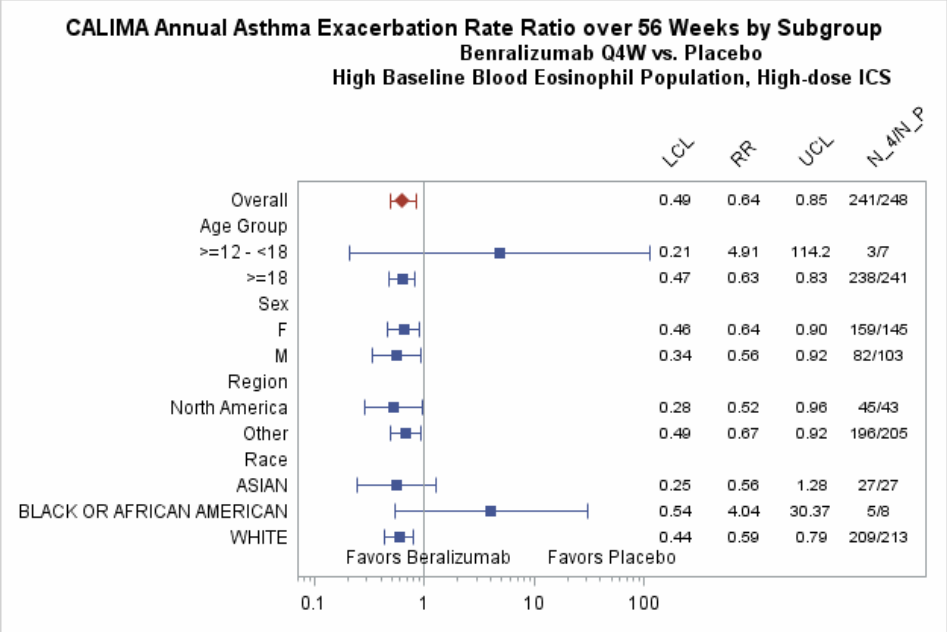
Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_8: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

Figure 22. CALIMA: Forest Plot, Q8W vs. Placebo (FAS + High-ICS)



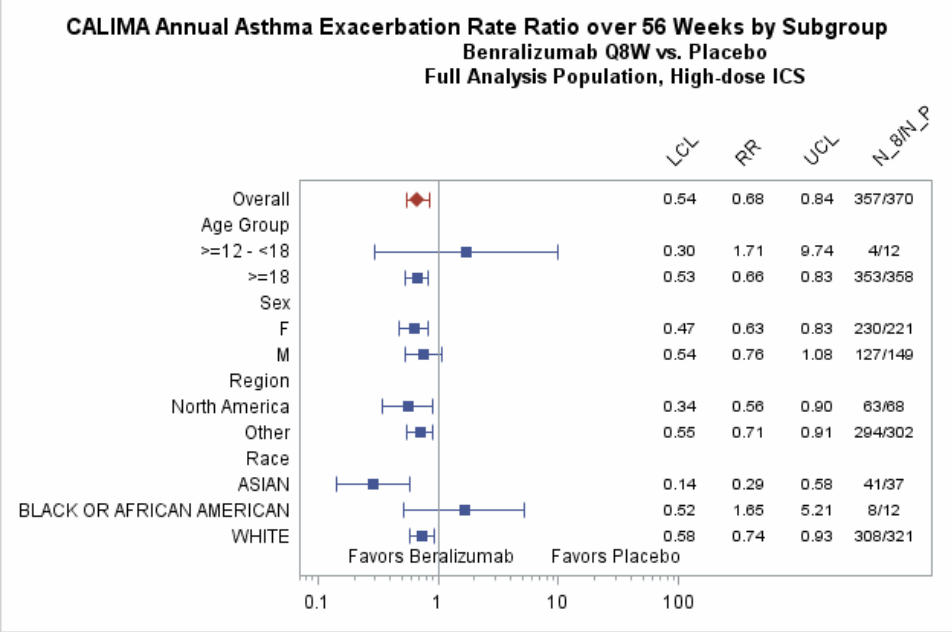
Source: Reviewer
Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_8: Number of subjects under Q8W; N_P: Number of subjects under Placebo.

Figure 23. CALIMA: Forest Plot, Q4W vs. Placebo (FAS + High-ICS + EHS)



Source: Reviewer
Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_4: Number of subjects under Q4W; N_P: Number of subjects under Placebo.

Figure 24. CALIMA: Forest Plot, Q4W vs. Placebo (FAS + High-ICS)



Source: Reviewer

Abbreviations: RR: Estimated rate ratio of Benralizumab vs. Placebo. LCL: Lower confidence limit of the 95% confidence interval for rate ratio; UCL: Upper confidence limit of the 95% confidence interval for rate ratio; N_8: Number of subjects under Q4W; N_P: Number of subjects under Placebo.

APPEARS THIS WAY ON ORIGINAL

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/s/

YU WANG
07/20/2017

YONGMAN KIM
07/20/2017
I concur.

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	BLA 761-070
Related IND #:	IND 100237
Product Name:	Generic name: Benralizumab Strength: 30 mg/mL Dosage form: Injection, solution in a single-dose prefilled syringe
Indication(s):	Add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
Applicant:	AstraZeneca
Dates:	Date received: November 16, 2016
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Yu (Jade) Wang
Concurring Reviewers:	Gregory Levin
Medical Division:	DPARP
Clinical Team:	Sofia S. Chaudhry (Reviewer), Lydia Gilbert-McClain (Division Deputy Director) Badrul A. Chowdhury (Division Director)
Project Manager:	Colette Jackson

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

To support the efficacy of benralizumab as an add-on maintenance treatment for adult patients with severe asthma with an eosinophilic phenotype, the completed phase 3 clinical development program included two replicate primary registration trials (SIROCCO and CALIMA) for asthma exacerbation; one OCS reduction study (ZONDA), and two supporting studies (BISE and GREGALE) for mild to moderate asthma and at-home use, respectively. There are also three ongoing studies: two long-term safety studies (BORA and MELTEMI) (b) (4)

My review will be focused on the two asthma exacerbation studies and the OCS reduction study.

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Number of Subjects Randomized**	Endpoint/Analysis	Preliminary Findings
D3250C0017 SIROCCO	MC, R, DB, PG, PC trial (48 wks)	Multiple SC doses: Benra 30 mg Q4W* / 276 Benra 30 mg Q8W*/ 267 Placebo/ 267	Primary: Annual exacerbation rate Key Secondary: FEV_1, and Total asthma symptom score	The applicant's primary analysis result and sensitivity analyses to missing data demonstrated that Benralizumab 30 mg at two dosing regimens significantly reduced annual exacerbation rates as compared to placebo in severe asthma patients with baseline blood eosinophil count ≥300/μL.
D3250C0018 CALIMA	MC, R, DB, PG, PC trial (56 wks)	Multiple SC doses: Benra 30 mg Q4W* / 288 Benra 30 mg Q8W*/ 290 Placebo/ 297	Primary: Annual exacerbation rate Key Secondary: FEV_1, and Total asthma symptom score	The applicant's primary analysis result and sensitivity analyses to missing data demonstrated that Benralizumab 30 mg at two dosing regimens significantly reduced annual exacerbation rates as compared to placebo in severe asthma patients with baseline blood eosinophil count ≥300/μL.
D3250C0020 ZONDA	MC, R, DB, PG, PC trial (28 wks)	Multiple SC doses: Benra 30 mg Q4W* / 72 Benra 30 mg Q8W*/ 73 Placebo/ 75	Primary: Percentage reduction in final OCS dose compared with baseline while maintaining asthma control	The applicant's non-parametric primary analysis results (Wilcoxon rank-sum test) and the corresponding sensitivity analysis (to modeling) of % reduction in OCS dose demonstrated that Benralizumab 30 mg at each of the two dosing regimens significantly reduced OCS dose while maintaining asthma control in randomized patients. There was no sensitivity analysis to missing data while the average discontinuation rate was 5.9% across the three arms.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, Benr: Benralizumab, **Q4W: Regimen with Q4W throughout the treatment period, Q8W: Regimen with Q4W for the first 3 doses and then Q8W thereafter, Number of randomized patients with baseline blood eosinophil count ≥300/μL.

2. Assessment of Protocols and Study Reports

Based on the filing review of the protocol and the study report submitted for each trial referenced in Table 1 above, the reviewer's findings upon contents of the documents are summarized in the "Response/Comments" column of Table 2.

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**Yes. A blinded, pooled analysis was conducted to potentially modify the sample size. No adjustment was needed because the analysis was based on the blinded, pooled estimates. Meeting minutes will be requested.**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Yes**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**The adequacy of missing data sensitivity analyses will be examined during the review. Additional analyses may be requested and conducted if determined important.**

3. Electronic Data Assessment

Based on the filing review of the electronic data submitted in the application, the reviewer's comments are summarized in Table 3.

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	The dataset location is clear
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Systematically organized
Are the define files sufficiently detailed?	Yes

Content Parameter	Response/Comments
List the dataset(s) that contains the primary endpoint(s)	ADEFFRE (SCIROCCO and CALIMA) ADAMCM (ZONDA)
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	✓			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	✓			There is no ISS or ISE protocol; instead, the corresponding SAPs were submitted.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	✓			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	✓			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	✓			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

NA

5.2. Information Requests/Review Issues

In each of the exacerbation studies (SIROCCO and CALIMA), both the SAP and Clinical Study Report described that there was an interim sample size re-estimation analysis based on a blinded estimate of the placebo exacerbation rate and shape parameter conducted before the last patient with eosinophil counts ≥ 300/μL was randomized. The applicant noted that the blinded sample size re-estimation analysis was "performed by AstraZeneca internal personnel or it designees." This type of analysis based on pooled blinded data does not directly affect the type I error rate, so no adjustment is needed, but it is potentially concerning from a study conduct perspective that the analysis was done by "AstraZeneca internal personnel" rather than by an independent monitoring committee. Also, there are no interim meeting minutes submitted under the current BLA. To further investigate the conduct of the interim analysis and its potential impact on interpretability of study results, we have the following information request for the applicant:

You note that your blinded sample size re-estimation analysis was "performed by AstraZeneca internal personnel or it designees." Please clarify who performed the analysis and reviewed the data, what procedures were in place to keep sponsor personnel blinded to comparative interim results, and what were the detailed results from the interim analysis. Submit minutes from any interim monitoring meetings, including meetings to discuss the interim analysis results.

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/s/

YU WANG
01/13/2017

GREGORY P LEVIN
01/13/2017