Two-Year Integrated Efficacy and Safety Analysis of Benralizumab in Severe Asthma

FitzGerald JM, Bleecker ER, Bourdin A, et al. *J Asthma Allergy.* 2019;12:401-413.

KEY TAKEAWAYS

- This 2-year integrated analysis of efficacy and safety included adult patients from the SIROCCO and CALIMA trials (first year of benralizumab treatment), and the BORA safety extension trial (adult patients from SIROCCO and CALIMA who continued benralizumab treatment for an additional year).
- The objective was to explore whether the efficacy benefit (annual asthma exacerbation rate and lung function, among others) and safety observed in SIROCCO and CALIMA were maintained with an additional year of treatment.
- It demonstrated that reductions in the occurrence of asthma exacerbations and improvements in lung function and asthma symptoms that were observed in the first year of benralizumab treatment were maintained during the second year of benralizumab treatment with an acceptable and stable safety profile.

PURPOSE

To evaluate whether the efficacy and safety profile of benralizumab, which was previously established after 1 year of treatment, was maintained after an additional year of treatment.

REMINDER

The BORA extension trial was designed to address the safety and efficacy of benralizumab in the year after patients entered BORA. Data from the preceding clinical trials, SIROCCO and CALIMA, were not included.

In this 2-year integrated analysis, data from the adult completion phase of BORA were integrated with results from SIROCCO and CALIMA. The maintenance of efficacy and safety was examined in the second year of treatment, with safety presented as both cumulative events throughout the 2 years of treatment and relative changes from the first to the second year of treatment.

METHODS

PARTICIPANTS

Data were evaluated for adult patients who were previously enrolled in SIROCCO or CALIMA and moved into the BORA extension trial (allowing evaluation of a full 2 years of data).*

Data from BORA could be integrated with SIROCCO and CALIMA due to their:

- Similar treatment duration
- Identical endpoints
- Consistent efficacy and safety assessment schedule
- Similar inclusion/exclusion criteria

Patients who received placebo in SIROCCO or CALIMA and were randomized into 1 of the 2 active treatment groups in BORA were not included in the integrated analysis because they did not remain on the same treatment throughout the follow-up period.

** Please refer to FitzGerald et al. 2019 for a detailed overview of patient baseline characteristics and patient disposition.*

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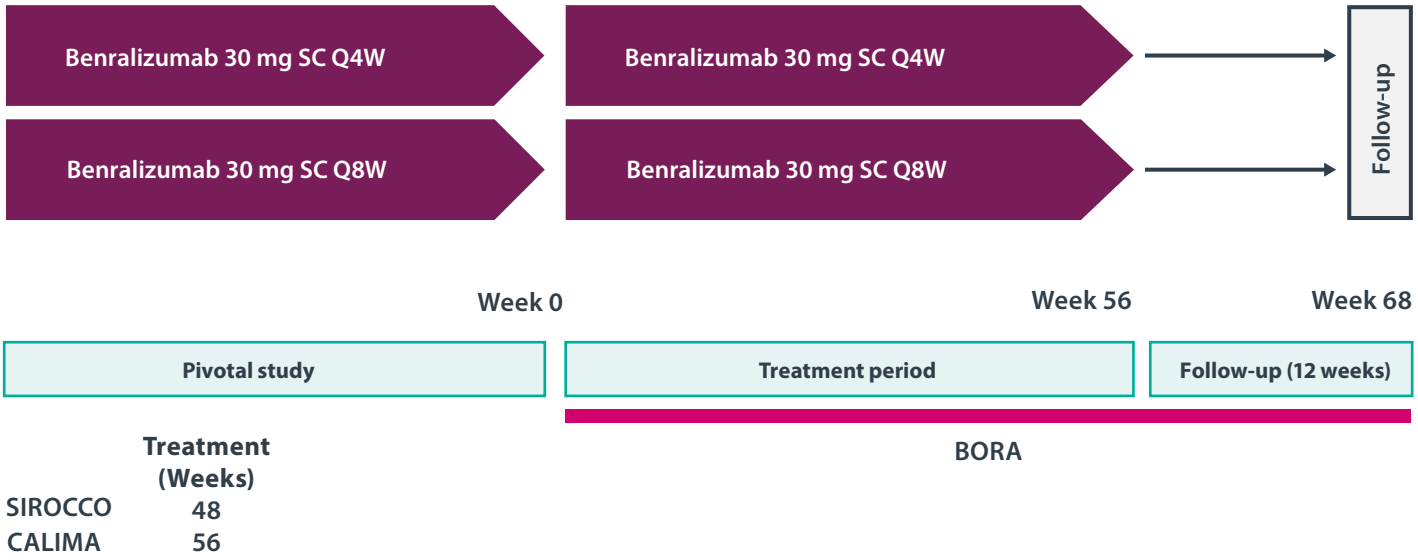
METHODS *(Continued)*

STUDY DESIGN

The integrated analysis assessed adult patients who continued into BORA receiving benralizumab 30 mg subcutaneously either every 4 weeks (Q4W) or every 8 weeks (Q8W), with high-dosage (or medium-dosage for CALIMA) inhaled corticosteroids (ICS) plus long-acting β2-agonists (LABA) in the pivotal studies (Figure 1).



	Treatment (Weeks)
SIROCCO	48
CALIMA	56

FIGURE 1. Benralizumab 2-Year Integrated Analysis Study Design.

Q4W, every 4 weeks; **Q8W,** every 8 weeks (first 3 doses Q4W); **SC,** subcutaneously.

STATISTICAL ANALYSIS

Patients were grouped into the All Patients Set and the Full Analysis Set.

All Patients Set

The All Patients Set included patients who received at least 1 dose of benralizumab in SIROCCO or CALIMA regardless of entry into BORA

Full Analysis Set

The Full Analysis Set included patients who received benralizumab, completed SIROCCO or CALIMA, and received at least 1 dose of benralizumab in BORA[†]

[†] *Full Analysis Set excluded patients who transitioned into MELTEMI (a subsequent, separate, open-label, 130-week safety and efficacy long-term extension trial). Including these patients in the Full Analysis Set could have confounded adverse event rates and annualized exacerbation data as they did not complete the full treatment period in BORA.*

Statistical analysis:

- Included patients who received benralizumab and high-dosage ICS/LABA
- Was performed for patients with baseline blood eosinophil counts ≥300 cells/μL and <300 cells/μL in SIROCCO/CALIMA
- Excluded a placebo comparison, since no placebo comparison is available for the long-term integrated data
- Presented data that were summarized with descriptive statistics (mean, standard deviation [SD], median, range), qualitative summaries, and 95% confidence intervals (CIs); ie, analysis of these endpoints was not multiplicity protected

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ENDPOINTS

LONG-TERM EFFICACY ENDPOINTS

ASTHMA EXACERBATIONS

- Annual asthma exacerbation rate (AER)
- AER associated with hospitalizations and emergency department visits

CHANGE FROM BASELINE IN LUNG FUNCTION

- Mean prebronchodilator forced expiratory volume in 1 second (FEV1)

ASTHMA CONTROL

- Asthma Control Questionnaire 6 (ACQ-6)
- Asthma Quality of Life Questionnaire (standardized) for 12 years and older (AQLQ(S)+12)

LONG-TERM SAFETY AND TOLERABILITY ENDPOINTS

Adverse events (AEs)

Hypersensitivity

Serious adverse events (SAEs)

Immunogenicity

DID YOU KNOW?

Lung function is assessed using spirometry to measure the volume, time, and flow of air inhaled and exhaled.

Depending on the goal of spirometry, such as supporting a diagnosis versus determining response to treatment, bronchodilators may be withheld before the test.

1. **The patient's age, height, sex, and ethnicity** should be recorded to determine predicted spirometry values that will be used for comparison.
2. **The test begins with the patient** putting on a nose clip and taking normal easy breaths into and out of a mouthpiece that is connected to a spirometer.
3. **Once the person is comfortable with the technique,** they are asked to inhale as deeply as possible, and then quickly exhale as fast, as hard, and for as long as possible.
4. **The total volume expired can be plotted on a graph** with volume in liters on the y-axis, and time in seconds on the x-axis.

The maximum amount of air that is expired during this forceful expiration is called the forced vital capacity, or FVC, and the air expired during just the first second, is called the forced expiratory volume in 1 second, or FEV1. These values are usually represented as a ratio. A reduced FEV1 to FVC ratio compared to predicted values—normally greater than 75% to 80% in adults—indicates expiratory airflow limitation.

However, some people with asthma will have a normal ratio. After a baseline spirometry, many individuals will undergo bronchodilator responsiveness testing (also called a reversibility test) to determine if a bronchodilator improves airflow. A hallmark of asthma is a reduced FEV1 that is reversible after the use of a bronchodilator. Reversibility is defined as an increase of over 12% and over 200 milliliters from baseline. Patients already diagnosed with asthma may have repeated spirometry to evaluate treatment response and disease progression.

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RESULTS

EFFICACY OUTCOMES

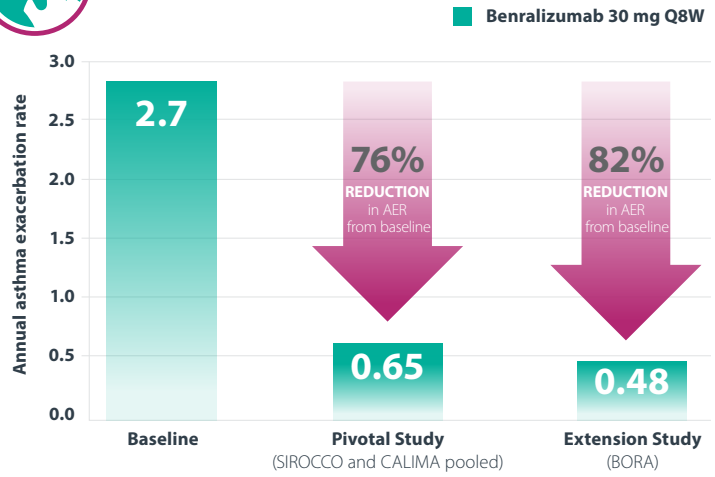
Efficacy endpoints were conducted on the Full Analysis Set.

Efficacy outcomes are presented for adult patients who had blood eosinophil counts ≥300 cells/µL at baseline in the original SIROCCO or CALIMA studies and received benralizumab Q8W and high-dosage ICS/LABA, unless otherwise indicated.

DID YOU KNOW?

Data from the SIROCCO and CALIMA studies were pooled into a larger compiled data set. Analyses run on pooled data may reveal relationships that would not be detected in the individual study. Pooling analysis of SIROCCO and CALIMA was conducted to better understand the relationship between the clinical efficacy of benralizumab and baseline blood eosinophil counts and exacerbation history.

ASTHMA EXACERBATIONS



In patients who continued on benralizumab Q8W from SIROCCO and CALIMA into BORA, **AER in year 1 was maintained in year 2,** demonstrated by a reduction in AER from baseline:

- **76% reduction** in year 1
- **82% reduction** in year 2

Approximately 88% of the patients did not experience exacerbations that led to hospitalization or emergency department visits.

FIGURE 2. Annual Asthma Exacerbation Rate for Adult Patients in the Pivotal Study (SIROCCO and CALIMA pooled) and the Extension Study (BORA).[a]

[a] Full Analysis Set, on-treatment period, blood eosinophil counts ≥300 cells/µL (blood eosinophil counts at baseline of preceding pivotal studies). n = 318 for patients receiving benralizumab 30 mg Q8W. Baseline value represents exacerbation rate over the year before the pivotal study entry.

Q8W, every 8 weeks (first 3 doses Q4W).

REMINDER

The BORA trial previously demonstrated that 74% of patients who continued on Q8W dosing from SIROCCO or CALIMA into BORA had 0 exacerbations.

LUNG FUNCTION

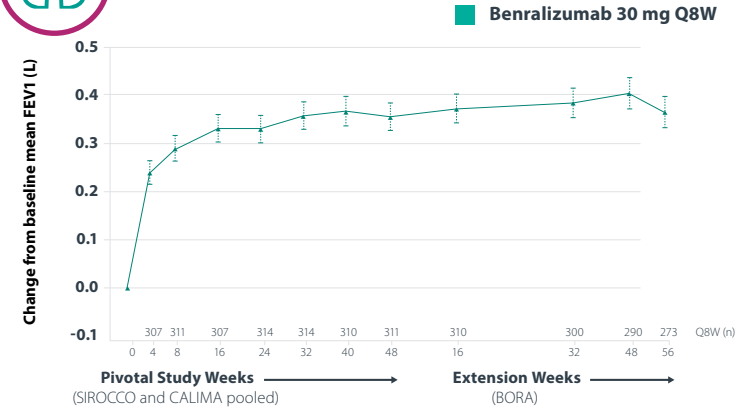


FIGURE 3. Change from Pivotal Study (SIROCCO and CALIMA pooled) Baseline in Lung Function (Mean Prebronchodilator FEV1) With Benralizumab During the 2-Year Integrated Analysis.[a]

[a] Full Analysis Set, on-treatment period, blood eosinophil counts ≥300 cells/µL.

FEV1, forced expiratory volume in 1 second; **Q8W,** every 8 weeks.

Improvements in FEV1 that were observed at the end of treatment with benralizumab Q8W in SIROOCO and CALIMA were maintained during the BORA extended treatment period (Figure 3).

- **343 mL increase** in FEV1 from baseline at treatment end in SIROCCO and CALIMA
- **364 mL** increase in FEV1 from baseline at extension week 56 in BORA

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REMINDER

Mean change from baseline in prebronchodilator FEV1 was a key secondary endpoint in both SIROCCO and CALIMA. In the pivotal studies, both SIROCCO and CALIMA demonstrated that the prebronchodilator FEV1 increase relative to baseline for the benralizumab Q8W cohort was greater than for the placebo cohort throughout the treatment period starting at week 4 and maintained throughout the treatment periods (48 weeks and 56 weeks, respectively).

DID YOU KNOW?

Due to differences in trial-to-trial protocols, design, and patient populations, it is not appropriate to make head-to-head comparisons between benralizumab, mepolizumab, and dupilumab.

Long-term safety and efficacy of mepolizumab (Nucala) was evaluated in the 3.5 year open-label COLUMBA trial conducted in patients who had previously participated in the DREAM trial. Patients were invited to participate in COLUMBA 12 to 28 months after they completed the DREAM trial. All patients received 100 mg mepolizumab, regardless of previous treatment regimen.

Initial improvements in lung function were not maintained and decreased to baseline levels by Week 200. Mean prebronchodilator FEV1:

- Baseline: 1811 mL (SD: 696.2)
- Week 24: 1955 mL (SD: 728)
  - Mean change from baseline: 144 mL
- Week 200: 1855 mL (SD: 660)
  - Mean change from baseline: 44 mL

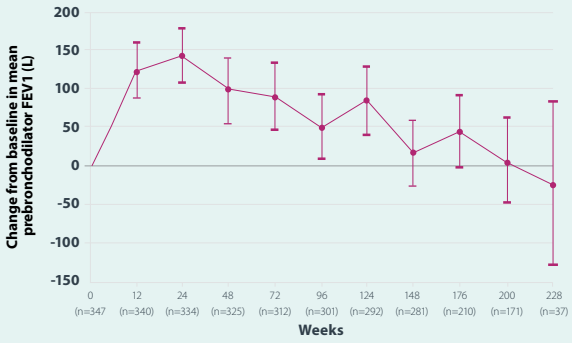

FIGURE 4. Change from Baseline in Lung Function (Mean Prebronchodilator FEV1) With Mepolizumab During the COLUMBA Study.[a]

[a] Vertical bars show 95% CIs. Minimum clinically important difference (FEV1): 100 mL.

FEV1, forced expiratory volume in 1 second.

Long-term safety and efficacy of dupilumab (Dupixent) was evaluated for up to 96 weeks in the open-label TRAVERSE extension trial. All patients received 300 mg dupilumab every 2 weeks regardless of whether they received placebo in the parent study (referred to as placebo-dupilumab) or dupilumab in the parent study (referred to as dupilumab-dupilumab).

Prebronchodilator FEV1 improvements observed during the parent studies (DRI12544 and QUEST) were sustained during TRAVERSE. Week 96 mean changes from parent study (dupilumab-dupilumab) baseline:

- DRI12544 dupilumab-dupilumab: 270 mL (SD: 460)
- QUEST dupilumab-dupilumab: 310 mL (SD: 470)

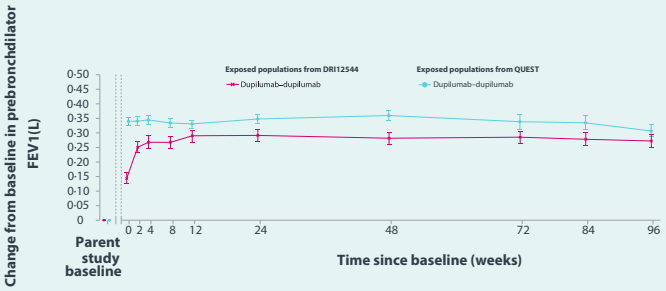

FIGURE 5. Change from Parent Study Baseline in Lung Function (Mean Prebronchodilator FEV1) in the Overall Exposed Populations from DRI12544 and QUEST.[a]

[a] Data is presented as mean (standard error). Prebronchodilator FEV1 was assessed in the overall exposed population (observed cases) using descriptive statistics. Week 0 represents the start of the open-label extension. Patients from DRI12544 had a treatment gap of between 16 and 52 weeks before enrolment in TRAVERSE.

FEV1, forced expiratory volume in 1 second.

ASTHMA CONTROL AND QUALITY OF LIFE

Improvements in ACQ-6 and AQLQ(S)+12 scores that were observed at the end of treatment with benralizumab Q8W in SIROCCO and CALIMA were maintained during the BORA extended treatment period.

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SAFETY OUTCOMES

Integrated safety analyses were conducted on both the Full Analysis Set and All Patients Set.

- For patients in the Full Analysis Set, there were no new or unexpected occurrence of AEs (Table 1).
- For patients in the All Patients Set, AE rates were numerically greater during the pivotal study period than during the extension period.

ADVERSE EVENTS

The most common AEs (≥10%) reported for SIROCCO/CALIMA patients in the Full Analysis Set who received benralizumab and entered BORA were viral upper respiratory tract infection, upper respiratory tract infection, and bronchitis. AE rates are listed in Table 1.

SERIOUS ADVERSE EVENTS

Worsening asthma was the most common SAE, with an event rate of 2.85 (Q8W) per 100-patient years (100-PYs).

TABLE 1. Adverse Events for SIROCCO/CALIMA Pivotal Study Patients During the 2-Year Integrated Analysis Period (Full Analysis Set, On-Treatment Period, All Patients Regardless of Blood Eosinophil Count)

	BENRALIZUMAB 30 MG Q8W (N = 512) (EXP = 1051.11)[a]	
	n (%)	EVENT RATE (PER 100-PYS)
Any AE	436 (85)	41.48
Any AE leading to treatment discontinuation	8 (2)	0.76
Any SAE	79 (15)	7.52
SAEs associated with infections	17 (3)	1.62
Deaths[b]	2 (<1)	0.19
Injection-site reactions	20 (4)	1.90
Hypersensitivity AEs	19 (4)	1.81

[a] Total on-treatment period (years) across all patients in the specific group.

[b] Patients who entered BORA. Ten deaths were reported for patients who received benralizumab in SIROCCO/CALIMA, regardless of whether they entered BORA.

AE, adverse event; **Q8W,** every 8 weeks (first 3 doses Q4W); **SAE,** serious adverse event.

The safety profile for patients at year 2 was consistent with that at year 1 of the analysis for all patients, regardless of blood eosinophil counts.

AE rates for the Q8W cohort were numerically smaller for the extended period compared with the pivotal study period.

SAE rates were similar across study periods for the All Patients Set.

Hypersensitivity was comparable across treatment groups.

Anti-drug antibodies (ADAs) were expressed by 17% of patients who received benralizumab Q8W with 13% having neutralizing antibodies.

Serious infection rates were similar for the Q8W cohort in the extended period and in the pivotal study period for patients who continued into BORA. No cases of helminth infections were reported.

Two-Year Integrated Efficacy and Safety Analysis of Benralizumab in Severe Asthma *(Continued)*

STUDY LIMITATIONS

- There was no placebo control arm during the second year of analysis as the primary endpoint was safety as part of a long-term extension study
- There was potential for selection bias in the trial because:
  - Patients who enrolled in BORA completed their respective treatments in the SIROCCO or CALIMA pivotal studies, and patients who did not experience a benefit or experienced an AE would not have been included
  - A restricted number of patients were followed for the full 1-year extension due to rollover of patients into the MELTEMI trial

CONCLUSIONS

- The benralizumab 2-year integrated analysis results indicate that the efficacy established in the first year of treatment with benralizumab were maintained during the second year
- The safety profile for patients at year 2 was consistent with that at year 1 of the analysis for all patients, regardless of blood eosinophil counts
- The 2-year integrated analysis of efficacy and safety results from the SIROCCO, CALIMA, and BORA phase III trials further support the use of benralizumab for the treatment of patients with severe, uncontrolled asthma with an eosinophiic phenotype

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