Original Article

Integrated Safety and Efficacy Among Patients Receiving Benralizumab for Up to 5 Years

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What is already known about this topic? The efficacy and safety of benralizumab were demonstrated through phase 3 pivotal trials lasting 28 to 56 weeks. Previous long-term results with benralizumab are limited to 2 years of follow-up.

What does this article add to our knowledge? Results from this integrated analysis expand on previous studies by demonstrating the long-term safety and efficacy of benralizumab among patients treated for up to 5 years.

How does this study impact current management guidelines? Current guidelines do not consider the long-term impact of eliminating exacerbations in patients. Given the deleterious effects of exacerbations on disease progression, guidelines should consider zero exacerbations as an indication and a goal for biologics.

BACKGROUND: Benralizumab is an IL-5Rα–directed monoclonal antibody indicated for patients with severe, uncontrolled eosinophilic asthma.

OBJECTIVE: To evaluate the long-term safety and tolerability of benralizumab among adults treated for up to 5 years.

METHODS: This analysis included adults treated with placebo or subcutaneous benralizumab 30 mg every 4 or 8 weeks in the 48-week SIROCCO, 56-week CALIMA, and 28-week ZONDA pivotal trials, who were subsequently enrolled in the 56-week double-blind BORA extension and continued assigned regimens or initiated benralizumab (if previously on placebo) for 16 to 40 weeks, before entering the open-label MELTEMI extension. Safety was measured by adverse and serious adverse event rates. Exacerbations were evaluated in patients with blood eosinophils greater than or equal to 300 cells/μL receiving high-dose inhaled corticosteroids at baseline.

RESULTS: Overall, 446 received treatment and 384 (86.1%) completed the study; 157 (35.2%) received benralizumab for 4 or more years. Adverse and serious adverse event rates (28.5-32.4 and 6.3-8.4 per 100 patient-years, respectively) were low, stable over time, and did not increase with exposure; few (n = 8) discontinued because of adverse events. Serious infections and hypersensitivity event rates were consistent with those in previous studies. Among patients with blood eosinophils greater than or equal to 300 cells/μL–high-dosage inhaled corticosteroids receiving benralizumab every 8 weeks, at least 75% had zero exacerbations annually during the integrated analysis period.

CONCLUSIONS: In patients with severe, uncontrolled eosinophilic asthma, long-term benralizumab was safe and well tolerated for up to 5 years. There were no new safety signals, and exacerbations were eliminated in similar percentages of patients as in predecessor studies. © 2021 The Authors. Published by

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Abbreviations used
ADA- Antidrug antibody
AE- Adverse event
bEOS- Blood eosinophil
HDICS- High-dosage inhaled corticosteroid
nAb- Neutralizing antibody
OCS- Oral corticosteroid
PBO- Placebo
PBO/Q4W- Placebo to Q4W
PBO/Q8W- Placebo to Q8W
Q4W- Every 4 weeks
Q8W- Every 8 weeks
SAE- Serious adverse event

Key words: *Asthma; Exacerbation; Benralizumab; Integrated analysis; Eosinophils*

INTRODUCTION

Asthma is the most common respiratory disease in the world. With an estimated 339 million people affected worldwide, it is the 16th leading cause of life years lived with disability despite available treatments.[1-5] Because of suboptimal disease management, many with asthma have poor disease control, which is associated with increased risk of exacerbations and hospitalization, reduced health-related quality of life, and increased economic burden.[6-8] Approximately 5% to 10% of patients have severe asthma, more than half of whom also have poor disease control.[4,9,10] Estimates suggest that approximately 50% of patients with severe asthma show a T_H2-high phenotype, which is associated with biomarkers including higher blood and sputum eosinophil counts, fractional exhaled nitric oxide values, and IgE levels among others.[11-14]

Uncontrolled asthma is frequently treated with oral corticosteroids (OCSs), which are also used to treat exacerbations despite being associated with acute and long-term adverse health effects.[15-17] Patients who use 1 course of OCSs per year for an exacerbation are still considered controlled, meaning OCS use can be considerable for both controlled and uncontrolled asthma, resulting in additional morbidity for a substantial number of patients.[1] In fact, recent estimates indicate that 20% to 60% of patients with severe or uncontrolled asthma have received long-term OCS treatment.[4,10,11] Recommendations from the Global Initiative for Asthma suggest that maintenance OCSs should be avoided when possible and instead, biologics and other therapies should be the preferred add-on treatments.[1] Biologics such as benralizumab are often used as add-on medications for several years of treatment, and consequently, it is important to understand their long-term safety and efficacy for patients with asthma.[18]

Benralizumab is an afucosylated monoclonal antibody directed against the interleukin-5 receptor α, which results in rapid, nearly complete depletion of eosinophils through enhanced antibody-dependent, cell-mediated cytotoxicity.[19-21] Subcutaneous benralizumab 30 mg every 8 weeks (Q8W) is indicated as an add-on treatment for patients with severe eosinophilic asthma.[22] The efficacy and safety of benralizumab were demonstrated in 3 previous randomized, double-blind, placebo-controlled, phase 3 trials: SIROCCO (ClinicalTrials.gov identifier: NCT01928771), CALIMA (NCT01914757), and ZONDA (NCT02075255).[23-25] Previously, long-term results for benralizumab were limited to 2 years of follow-up in the BORA (NCT02258542) extension, which demonstrated a safety profile consistent with previous pivotal studies, further supporting benralizumab use in patients with severe, uncontrolled asthma.[18] We report results from the MELTEMI integrated analysis, which included patients treated with benralizumab for up to 5 years, and from the initial predecessor studies, through the double-blind BORA extension and completion of the MELTEMI extension (Figure 1).

METHODS

Study design and intervention

MELTEMI (NCT02808819) was a phase 3, open-label, safety extension in adults (aged 18-75 years) with severe, uncontrolled asthma who completed 1 of 3 phase 3, randomized, double-blind, placebo-controlled predecessor studies (SIROCCO, CALIMA, ZONDA), enrolled in the BORA extension, and finally, transitioned to the MELTEMI open-label extension (Figure 1). Eligibility criteria, study designs, and results for SIROCCO, CALIMA, ZONDA, and BORA have previously been described in detail.[18,23-27] Briefly, in predecessors, eligible patients with severe, uncontrolled asthma receiving treatment with medium- or high-dosage inhaled corticosteroids (HDICSs) plus long-acting β_2-agonists (inhaled corticosteroids/long-acting β-agonists) were randomized to placebo or benralizumab 30 mg every 4 weeks (Q4W) or Q8W. SIROCCO and CALIMA were 48- and 56-week trials, respectively, that evaluated the efficacy (annual asthma exacerbation rate) and safety of benralizumab in patients aged 12 to 75 years.[23,24] ZONDA was a 28-week trial that evaluated the efficacy (OCS dose reductions and annual asthma exacerbation rate) and safety of benralizumab in patients aged 18 to 75 years.[25]

Patients who completed treatment in predecessor studies were eligible to enroll in the 56-week double-blind BORA extension.[18,26,27] After enrollment, patients who received placebo in predecessor studies were randomized (1:1) to benralizumab Q4W or Q8W, while others patients continued their previous benralizumab regimen.[18,26] Patients assigned to the Q8W regimen in BORA received the first 3 doses 4 weeks apart; thereafter, placebo injections were administered at 4-week intervals to mask regimens. Patients were required to complete 16 to 40 weeks of treatment in BORA before transitioning to MELTEMI, to ensure those who switched from placebo had completed monthly study visits and assessments for the first 3 active doses and also that patients transitioned from BORA before the final dose at 48 weeks. Patients who met eligibility criteria could exit BORA, enroll in the MELTEMI open-label extension, and continue their same regimen.[26]

Exclusion criteria in MELTEMI included (1) any parasitic helminth infection diagnosed during a predecessor study and not successfully treated with standard of care; (2) any clinically significant change in physical examination, electrocardiogram, or hematologic or biochemical serum or urine parameters during predecessor studies that could have put the patient at risk or influenced the study results; (3) any ongoing/unresolved serious adverse events (SAEs; patients could transfer after the SAE resolved); (4) current malignancy or malignancy developed during predecessors, with some exceptions; (5) receipt of live attenuated vaccines during the treatment period

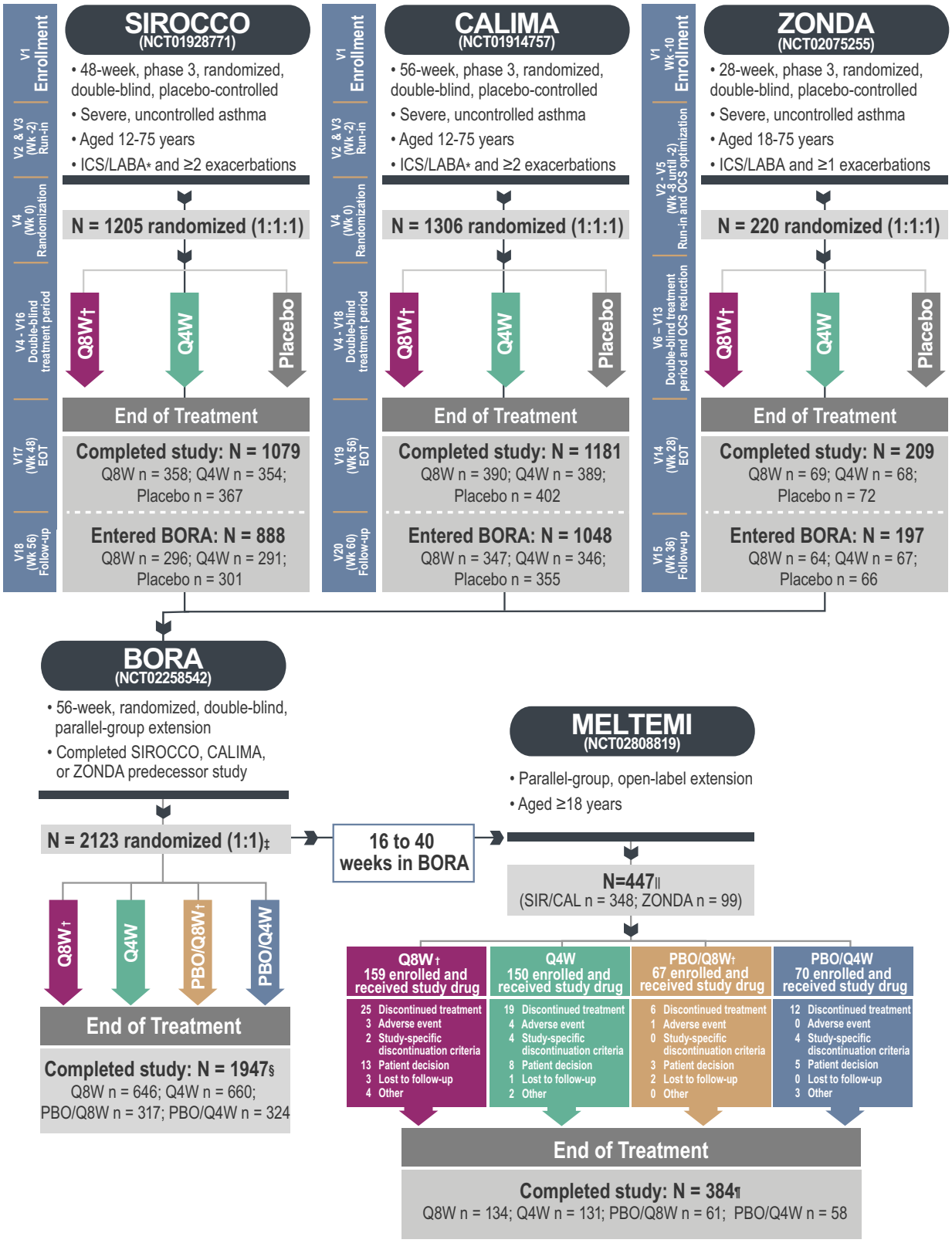

FIGURE 1. MELTEMI integrated analysis period. *ICS*, Inhaled corticosteroid; *LABA*, long-acting β_2-agonist. *Eligible patients were receiving medium- to high-dosage ICS/LABA at baseline. †Placebo injection at each 4-week interim. ‡Ten patients were excluded from randomization in BORA due to a breach of Good Clinical Practice. §Includes patients who enrolled in MELTEMI. ‖One patient enrolled in MELTEMI but did not receive treatment with the study drug. ¶Includes patients who discontinued treatment but attended all study visits.

and for certain amounts of time before and after treatment initiation; and (6) major protocol deviations in any of the predecessor studies, at the sponsor's discretion. Patients in MELTEMI were allowed to remain on treatment with benralizumab until 130 weeks for patients from countries in which benralizumab was not submitted for marketing approval; *or* for patients from countries in which benralizumab was submitted for marketing approval, until benralizumab was either commercially available or withdrawn from the approval process in their local market.

Outcomes

The MELTEMI primary end point was safety and tolerability, assessed by rates of adverse events (AEs) and SAEs during the on-treatment period. To account for differences in time on treatment with benralizumab (eg, placebo vs benralizumab treatment in predecessors or those completing MELTEMI early due to commercially available benralizumab) and differences in discontinuation rates between treatment groups, AEs were summarized by event rates, defined as the number of patients with AEs divided by the total on-treatment duration within the given treatment group and time interval, multiplied by 100. Secondary outcomes included a subset of primary and secondary end points from predecessor studies: annual asthma exacerbations, defined as a worsening of asthma requiring OCSs (or an increase in OCS dosage), in-patient hospitalization, and/or an emergency department visit, measured by the total number of exacerbations multiplied by 365.25 and divided by the total duration of on-treatment follow-up within the given treatment group and time interval (in days); absolute blood eosinophil (bEOS) counts over time; and immunogenicity, defined by antidrug antibodies (ADAs) or neutralizing antibodies (nAbs). The 6-item Asthma Control Questionnaire[28] scores, forced expiratory volume in 1 second measurements, and OCS data were not routinely collected in MELTEM, however, changes to concomitant medications were captured. These results were measured in previous studies within the integrated period, and thus, some of these results are presented below. Patients were required to remain on the same stable dose of background medication throughout the MELTEMI integrated analysis period, excluding OCS doses in ZONDA. Changes in background medications were only allowed if the changes were judged to be necessary by the site investigator.

Statistical analysis

MELTEMI was an open-label-extension: no hypothesis tests were planned, and sample size calculations and power analyses were unnecessary. The primary end point included all patients who enrolled and received at least 1 dose in MELTEMI (full analysis set). Annual exacerbation rates and bEOSs (cells/μL) were reported for the subgroup of patients with bEOSs greater than or equal to 300 cells/μL receiving HDICSs (bEOSs ≥300 cells/μL−HDICSs) at predecessor baseline, the subpopulation for primary efficacy end points in SIROCCO, CALIMA, and BORA, and a ZONDA stratification criteria (150-299 or ≥300 cells/μL).[23-26] Data were summarized with descriptive statistics. Unless otherwise indicated, "baseline" was defined as the baseline visit in predecessor studies (SIROCCO, CALIMA, or ZONDA). Results from the MELTEMI integrated analysis period are presented for patients who initiated benralizumab in predecessor studies and continued the same dose in BORA and MELTEMI (benralizumab Q4W or Q8W) and for patients treated with placebo in predecessor studies who were randomized to benralizumab Q4W or Q8W in BORA and continued the same regimen in MELTEMI (placebo to Q4W [PBO/Q4W] or placebo to Q8W [PBO/Q8W]). Results for the MELTEMI standalone period (enrollment through final visit) are presented as benralizumab Q4W and Q8W only.

Ethics

Ethics and compliance details for studies in the integrated analysis have been reported previously.[18,23-27] Before patient enrollment, independent ethics committees or institutional review boards approved the clinical study protocol. As previously reported, all patients provided written informed consent at enrollment.[18,23-27] This study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and consistent with International Council for Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics.

RESULTS

Patient characteristics

Overall, 447 patients enrolled in MELTEMI, including 348 (78%) from SIROCCO/CALIMA and 99 (22%) from ZONDA. The full analysis set for MELTEMI includes 446 patients who received treatment (full analysis set, N = 446); 384 (86.1%) completed treatment and 62 (13.9%) discontinued. Reasons for treatment discontinuation included patient decision (n = 29 [6.5%]), study-specific discontinuation criteria (n = 10 [2.2%]), AEs (n = 8 [1.8%]), lost to follow-up (n = 6 [1.3%]), and other reasons (n = 9 [2.0%]) (Figure 1; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In the integrated analysis, 309 received benralizumab Q4W (n = 150) or Q8W (n = 159) from predecessor studies through MELTEMI completion; 137 received placebo in predecessors and were randomized to benralizumab Q4W (PBO/Q4W, n = 70) or Q8W (PBO/Q8W, n = 67) in BORA (Table I). Percentages with bEOSs greater than or equal to 300 cells/μL−HDICSs (n = 306) were similar across those who initiated benralizumab in predecessor studies and among those who initiated benralizumab in BORA. In the standalone period (MELTEMI enrollment through final visit), 220 patients received Q4W and 226 received Q8W (Table E1).

In the integrated analysis, baseline demographic and clinical characteristics were generally similar between treatment groups overall and within the baseline bEOSs greater than or equal to 300 cells/μL−HDICSs subgroup (Table I). Demographic and clinical characteristics were also generally balanced across Q4W and Q8W in the standalone period (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Treatment durations were longer for patients who received benralizumab for the entire integrated period (mean, 3.9 ± 0.9 years and 3.7 ± 0.9 years for Q4W and Q8W, respectively) compared with those who initiated benralizumab in BORA (mean, 3.0 ± 0.9 years and 3.1 ± 0.8 years for PBO/Q4W and PBO/Q8W, respectively; Table II). Overall, 48 (10.8%) patients received benralizumab for 5 or more years and 157 (35.2%) for 4 or more years. In the standalone period, mean on-treatment durations were 26.4 ± 10.1 months and 25.4 ± 9.9 months for Q4W and Q8W, respectively (Table E1).

According to 6-item Asthma Control Questionnaire scores at BORA baseline, higher percentages of patients treated with placebo in predecessor studies had not well-controlled asthma compared with those receiving benralizumab (57.1% and 64.2% compared with 46.7% and 40.3% for Q4W and Q8W,

TABLE I. Baseline demographic and clinical characteristics among patients in the integrated analysis period (FAS)*

	Overall population (N = 446)				bEOSs ≥300 μL/HDICSs (n = 306)			
Parameter	**Benra Q8W (n = 159)**	**Benra Q4W (n = 150)**	**PBO/Q8W (n = 67)**	**PBO/Q4W (n = 70)**	**Benra Q8W (n = 110)**	**Benra Q4W (n = 105)**	**PBO/Q8W (n = 42)**	**PBO/Q4W (n = 49)**
Age (y), mean ± SD	50.8 ± 11.4	52.8 ± 11.8	52.2 ± 12.2	49.8 ± 12.2	51.2 ± 11.3	52.3 ± 12.9	52.5 ± 12.2	49.3 ± 12.2
Sex: female, n (%)	97 (61.0)	91 (60.7)	47 (70.1)	49 (70.0)	65 (59.1)	63 (60.0)	30 (71.4)	34 (69.4)
BMI (kg/m^2), mean ± SD	29.4 ± 6.6	30.0 ± 6.3	28.9 ± 5.8	28.2 ± 6.0	29.3 ± 6.6	29.3 ± 6.1	28.8 ± 6.6	28.3 ± 5.9
bEOSs (cells/μL), median (range)	480 (0-2000)	408 (51-1800)	400 (100-2415)	410 (70-4494)	590 (300-2000)	520 (300-1800)	430 (300-1190)	515 (300-4494)
Prebronchodilator FEV_1 (% predicted), mean ± SD	55.7 ± 15.5	55.7 ± 15.1	59.3 ± 12.5	57.0 ± 13.9	54.5 ± 16.3	57.0 ± 15.3	59.9 ± 12.8	58.3 ± 14.0
Reversibility (%), mean ± SD	26.2 ± 21.5	28.2 ± 26.2	29.5 ± 20.5	24.3 ± 18.9	25.9 ± 21.3	27.4 ± 26.2	29.2 ± 20.1	23.3 ± 18.8
Time since asthma diagnosis (y), median (range)	14.1 (1.3-66.9)	14.4 (1.1-60.0)	11.9 (1.3-56.9)	15.1 (1.3-54.5)	14.2 (1.3-66.9)	12.4 (1.1-50.0)	10.1 (1.3-47.9)	14.7 (1.3-54.5)
Exacerbations in past 12 mo, mean ± SD	2.9 ± 2.0	2.7 ± 2.1	2.7 ± 1.5	2.6 ± 1.1	3.1 ± 2.2	2.7 ± 1.6	2.8 ± 1.7	2.7 ± 1.2
1, n (%)	10 (6.3)	17 (11.3)	6 (9.0)	4 (5.7)	9 (8.2)	11 (10.5)	4 (9.5)	3 (6.1)
2, n (%)	87 (54.7)	87 (58.0)	34 (50.7)	35 (50.0)	49 (44.5)	58 (55.2)	18 (42.9)	24 (49.0)
≥3, n (%)	62 (39.0)	46 (30.7)	27 (40.3)	31 (44.3)	52 (47.3)	36 (34.3)	20 (47.6)	22 (44.9)
ICS, n (%)†	159 (100)	150 (100)	67 (100)	70 (100)	110 (100)	105 (100)	42 (100)	49 (100)
ICS total daily dosage (μg), median (IQR)	1000 (500-1000)	750 (500-1000)	1000 (500-1000)	1000 (500-1000)	1000 (1000-1125)	1000 (500-1000)	1000 (600-1000)	1000 (625-1000)
LABA, n (%)	159 (100)	150 (100)	67 (100)	70 (100)	110 (100)	105 (100)	42 (100)	49 (100)
ICS/LABA, n (%)†	145 (91.2)	135 (90.0)	56 (83.6)	64 (91.4)	101 (91.8)	95 (90.5)	37 (88.1)	45 (91.8)
LAMA, n (%)	27 (17.0)	17 (11.3)	5 (7.5)	4 (5.7)	24 (21.8)	14 (13.3)	5 (11.9)	2 (4.1)
LTRA, n (%)	59 (37.1)	48 (32.0)	23 (34.3)	20 (28.6)	41 (37.3)	32 (30.5)	13 (31.0)	16 (32.7)

Benra, Benralizumab; *BMI*, body mass index; *FAS*, full analysis set; *FEV_1*, forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist.

*Defined as the baseline visit of the predecessor study.

†ICSs may have been taken in a separate inhaler or as part of a fixed-dose ICS/LABA combination device.

TABLE II. Treatment characteristics, ACQ-6 score, and OCS use among patients in the integrated analysis period (FAS, on-treatment period)

	Overall population (N = 446)				bEOSs ≥300 μL/HDICSs (n = 306)			
Parameter	Benra Q8W (n = 159)	Benra Q4W (n = 150)	PBO/Q8W (n = 67)	PBO/Q4W (n = 70)	Benra Q8W (n = 110)	Benra Q4W (n = 105)	PBO/Q8W (n = 42)	PBO/Q4W (n = 49)
On-treatment duration (y), mean ± SD	3.7 ± 0.9	3.9 ± 0.9	3.1 ± 0.8	3.0 ± 0.9	3.7 ± 0.9	3.8 ± 0.9	3.1 ± 0.9	3.0 ± 0.9
Median (range)	3.5 (1.6-5.3)	3.7 (1.5-5.4)	3.1 (0.7-4.2)	3.1 (0.8-4.3)	3.5 (1.9-5.3)	3.9 (1.9-5.4)	3.1 (0.7-4.2)	3.0 (0.8-4.3)
On-treatment duration (y*), n (%)								
≥1	159 (100)	150 (100)	66 (98.5)	68 (97.1)	110 (100)	105 (100)	41 (97.6)	48 (98.0)
≥2	157 (98.7)	147 (98.0)	62 (92.5)	60 (85.7)	109 (99.1)	103 (98.1)	38 (90.5)	42 (85.7)
≥3	128 (80.5)	132 (88.0)	38 (56.7)	36 (51.4)	84 (76.4)	90 (85.7)	24 (57.1)	24 (49.0)
≥4	63 (39.6)	63 (42.0)	14 (20.9)	17 (24.3)	43 (39.1)	46 (43.8)	11 (26.2)	13 (26.5)
≥5	23 (14.5)	25 (16.7)	0	0	12 (10.9)	15 (14.3)	0	0
Total on-treatment period (patient-years)	589.8	577.5	207.2	206.8	401.8	403.6	129.3	145.4
Patients who completed MELTEMI, n (%)†	134 (84.3)	131 (87.3)	61 (91.0)	58 (82.9)	91 (82.7)	90 (85.7)	40 (95.2)	42 (85.7)
ACQ-6 score								
BORA baseline, n (%)								
Not well controlled (≥1.5)	64 (40.3)	70 (46.7)	43 (64.2)	40 (57.1)	42 (38.2)	46 (43.8)	28 (66.7)	27 (55.1)
Partly/well controlled (<1.5)	95 (59.7)	80 (53.3)	24 (35.8)	30 (42.9)	68 (61.8)	59 (56.2)	14 (33.3)	22 (44.9)
BORA last visit, n (%)								
Not well controlled (≥1.5)	56 (35.2)	61 (40.7)	28 (41.8)	25 (35.7)	34 (30.9)	43 (41.0)	20 (47.6)	16 (32.7)
Partly/well controlled (<1.5)	103 (64.8)	89 (59.3)	39 (58.2)	45 (64.3)	76 (69.1)	62 (59.0)	22 (52.4)	33 (67.3)
OCS use								
Predecessor baseline, n (%)	51 (32.1)	55 (36.7)	24 (35.8)	23 (32.9)	39 (35.5)	42 (40.0)	18 (42.9)	17 (34.7)
Total daily dosage (mg‡), median (IQR)	10 (10-20)	10 (7.5-20)	10 (8.8-15)	15 (10-20)	10 (7.5-20)	10 (7.5-20)	10 (7.5-15)	15 (10-20)
BORA baseline, n (%)	36 (22.6)	39 (26.0)	20 (29.9)	22 (31.4)	27 (24.5)	28 (26.7)	15 (35.7)	17 (34.7)
Total daily dosage (mg‡), median (IQR)	10 (5-15)	7.5 (5-10)	10 (5-13.8)	12.5 (5-20)	10 (5-15)	7.5 (5-11.3)	10 (7.5-20)	15 (7.5-20)
MELTEMI baseline, n (%)	23 (14.5)	26 (17.3)	16 (23.9)	16 (22.9)	16 (14.5)	18 (17.1)	11 (26.2)	14 (28.6)
Total daily dosage (mg‡), median (IQR)	10 (5-15)	7.5 (5-10)	8.8 (5-12.5)	7.5 (5-17.5)	7.5 (5-15)	5 (5-10)	10 (5-20)	7.5 (5-20)

ACQ-6, 6-Item Asthma Control Questionnaire; *benra*, benralizumab; *FAS*, full analysis set; *IQR*, interquartile range.

*On-treatment period was defined as the time from the first dose of benralizumab (predecessor studies or BORA) to the last on-treatment date.

†Includes patients who discontinued treatment but attended all study visits.

‡OCS doses were converted to prednisolone equivalents for this summary; only patients in the ZONDA study were allowed to reduce OCS doses.

TABLE III. AEs over time among patients in the integrated analysis period (FAS, on-treatment period)

Parameter	Benra Q8W					Benra Q4W					PBO/Q8W					PBO/Q4W				
Study phase*	Pre	E1	E2	E3	>E3	Pre	E1	E2	E3	>E3	Pre	E1	E2	E3	>E3	Pre	E1	E2	E3	>E3
Total patients	159	159	157	137	67	150	150	147	138	75	67	67	66	62	38	70	70	68	60	36
Exposure (y†)	146	159	149	95	41	135	150	143	103	47	61	67	65	50	26	63	70	64	47	26
Any AE																				
No.	115	113	96	72	29	104	108	107	87	33	53	53	42	35	12	58	61	56	41	22
Event rate‡	78.7	71.1	64.6	75.8	70.1	77.1	72.2	74.9	84.6	70.0	87.2	79.5	65.0	70.4	45.9	91.4	87.7	87.4	86.6	85.3
Any AE with outcome of death																				
No.	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Any SAE§																				
No.	13	17	19	7	1	13	15	19	12	6	5	3	6	4	2	9	7	6	5	2
Event rate‡	8.9	10.7	12.8	7.4	2.4	9.6	10.0	13.3	11.7	12.7	8.2	4.5	9.3	8.0	7.7	14.2	10.1	9.4	10.6	7.8
Any AE leading to IP discontinuation																				
No.	0	0	2	1	1	0	1	2	1	0	0	0	0	0	1	0	0	0	0	0
Event rate‡	0	0	1.4	1.1	2.4	0	0.7	1.4	1.0	0	0	0	0	0	3.8	0	0	0	0	0

benra, Benralizumab; *FAS*, full analysis set; *IP*, investigational product.

*Study phases were defined as follows: pre, predecessor study (SIROCCO, CALIMA, ZONDA); E1, extension studies year 1, which includes on-treatment period in the double-blind BORA extension as well as the open-label MELTEMI extension; E2, extension year 2; E3, extension year 3; >E3, >3 y of treatment in extension studies (BORA and MELTEMI).

†Total exposure in years across patients in the treatment group and study period.

‡Event rate per 100 patient-years (represents the number of patients with AEs divided by the total on-treatment exposure in the time period across all patients in given treatment group, multiplied by 100).

§Including events with an outcome of death.

TABLE IV. AEs, most common AEs (ER $\geq$ 5), SAEs, serious infections, hypersensitivities, and malignancies in the integrated analysis period (FAS, on-treatment period)

	Predecessor studies			Extension studies*			
Parameter	Placebo (n = 137) [exp = 124]†	Benra Q8W (n = 159) [exp = 146]†	Benra Q4W (n = 150) [exp = 135]†	Benra Q8W (n = 159) [exp = 444]†	Benra Q4W (n = 150) [exp = 443]†	PBO/Q8W (n = 67) [exp = 207]†	PBO/Q4W (n = 70) [exp = 207]†
Patients with any AE, n (ER)	111 (89.4)	115 (78.7)	104 (77.1)	136 (30.7)	139 (31.4)	59 (28.5)	67 (32.4)
AEs ≥5 per 100 patient-years, n (ER)‡							
Nasopharyngitis	27 (21.7)	26 (17.8)	26 (19.3)	53 (11.9)	49 (11.1)	25 (12.1)	24 (11.6)
Asthma	33 (26.6)	15 (10.3)	27 (20)	33 (7.4)	23 (5.2)	9 (4.3)	10 (4.8)
Bronchitis	24 (19.3)	14 (9.6)	8 (5.9)	19 (4.3)	14 (3.2)	13 (6.3)	14 (6.8)
Headache	9 (7.2)	12 (8.2)	17 (12.6)	22 (5.0)	28 (6.3)	8 (3.9)	11 (5.3)
Viral upper respiratory tract infection	0	4 (2.7)	5 (3.7)	17 (3.8)	19 (4.3)	5 (2.4)	11 (5.3)
Sinusitis	14 (11.3)	7 (4.8)	6 (4.5)	11 (2.5)	15 (3.4)	9 (4.3)	8 (3.9)
Upper respiratory tract infection	8 (6.4)	11 (7.5)	12 (8.9)	7 (1.6)	16 (3.6)	3 (1.5)	2 (1.0)
Patients with any SAE, n (ER)‡	14 (11.3)	13 (8.9)	13 (9.6)	37 (8.3)	37 (8.4)	13 (6.3)	16 (7.7)
SAEs in ≥2 patients, n (ER)‡							
Asthma	8 (6.4)	6 (4.1)	10 (7.4)	12 (2.7)	9 (2.0)	2 (1.0)	4 (1.9)
Noncardiac chest pain	0	0	0	1 (0.2)	2 (0.5)	0	0
Nasal polyps	1 (0.8)	0	0	2 (0.5)	0	<2	<2
Chronic sinusitis	1 (0.8)	0	0	2 (0.5)	0	<2	<2
Limb injury	1 (0.8)	0	0	2 (0.5)	0	<2	<2
Serious infections, n (ER)‡	1 (0.8)	3 (2.0)	1 (0.7)	5 (1.1)	7 (1.6)	4 (1.9)	4 (1.9)
Serious infections in ≥2 patients, n (ER)‡							
Chronic sinusitis	<2	0	0	2 (0.5)	0	<2	<2
Any hypersensitivity AE, n (ER)‡	14 (11.3)	10 (6.9)	11 (8.2)	23 (5.2)	21 (4.8)	12 (5.8)	12 (5.8)
Any hypersensitivity AE in ≥2 patients, n (ER)‡							
Rhinitis, allergic	5 (4.0)	4 (2.7)	4 (3.0)	5 (1.1)	2 (0.5)	4 (1.9)	5 (2.4)
Urticaria	3 (2.4)	0	1 (0.7)	5 (1.1)	5 (1.1)	3 (1.5)	2 (1.0)
Eczema	3 (2.4)	2 (1.4)	2 (1.5)	1 (0.2)	6 (1.4)	2 (1.0)	2 (1.0)
Rash	2 (1.6)	1 (0.7)	1 (0.7)	2 (0.5)	4 (0.9)	2 (1.0)	2 (1.0)
Angioedema	0	0	0	1 (0.2)	0	0	2 (1.0)
Conjunctivitis, allergic	2 (1.6)	0	0	0	3 (0.7)	1 (0.5)	2 (1.0)
Drug hypersensitivity	1 (0.8)	0	0	0	2 (0.5)	1 (0.5)	0
Any malignancy AE, n (ER)‡	0	0	0	3 (0.7)	3 (0.7)	1 (0.5)	1 (0.5)
Neoplasms§	0	0	0	3 (0.7)	3 (0.7)	1 (0.5)	1 (0.5)

benra, Benralizumab; *ER*, event rate per 100 patient-years; *exp*, exposure; *FAS*, full analysis set.

*Extension studies include time on treatment in the double-blind BORA extension as well as the open-label MELTEMI extension.

†Total exposure in years across patients in treatment group and study period.

‡Event rate represents the number of patients with AEs divided by the total on-treatment exposure in the time period across all patients in given treatment group, multiplied by 100.

§Benign, malignant, and unspecified, including cysts and polyps (n = 1 adenocarcinoma of colon, n = 3 basal cell and n = 2 transitional cell carcinoma, n = 1 papillary thyroid cancer, n = 1 prostate cancer).

TABLE V. Immunogenicity in the integrated period (FAS, on-treatment period)

Immunogenicity*	Benra Q8W (n = 159) [exp = 444]†	Benra Q4W (n = 150) [exp = 443]†	PBO/Q8W (n = 67) [exp = 207]†	PBO/Q4W (n = 70) [exp = 207]†
ADA, n (%)				
Prior/MELTEMI ADA −/−	128 (80.5)	127 (84.7)	51 (76.1)	54 (77.1)
Prior/MELTEMI ADA +/−	15 (9.4)	11 (7.3)	3 (4.5)	7 (10)
Prior/MELTEMI ADA −/+	3 (1.9)	0	3 (4.5)	4 (5.7)
Prior/MELTEMI ADA +/+	12 (7.5)	10 (6.7)	10 (14.9)	5 (7.1)
Missing‡	1 (0.6)	2 (1.3)	0	0
nAb, n (%)				
Prior/MELTEMI nAb −/−	1 (0.6)	1 (0.7)	0	0
Prior/MELTEMI nAb +/−	0	1 (0.7)	1 (1.5)	1 (1.4)
Prior/MELTEMI nAb −/+	2 (1.3)	0	2 (3.0)	0
Prior/MELTEMI nAb +/+	9 (5.7)	8 (5.3)	7 (10.4)	4 (5.7)

benra, Benralizumab; *exp*, exposure; *FAS*, full analysis set.
*Immunogenicity reported as negative or at least 1 positive result (at any point) in previous studies (throughout the predecessor [SIROCCO, CALIMA, ZONDA] and BORA studies) or as negative or at least 1 positive result (at any point) in the MELTEMI study.
†Total exposure in years across patients in treatment group and study period.
‡Missing values include 3 patients with ADA values from the prior period (1 positive and 2 negative) who had missing values for MELTEMI.

respectively; Table II). At the BORA final visit, rates of not well-controlled asthma (35%-42%) were similar across treatment groups. A similar trend was observed for the bEOSs greater than or equal to 300 cells/μL—HDICSs subgroup. The percentages of patients using OCSs (ranging from 32% to 37% among treatment groups) were similar at predecessor baseline and decreased slightly at the baseline visit in BORA (ranging from 23% to 31%) in patients receiving benralizumab (Table II), which could be related to the OCS reduction component in ZONDA. Indeed, the percentages of patients using OCSs decreased further by the MELTEMI baseline visit (ranging from 15% to 24% across treatment groups). This trend was similar in the bEOSs greater than or equal to 300 cells/μL—HDICSs subgroup.

SAFETY

In the integrated analysis, AE rates by year were generally similar over time for patients who initiated benralizumab in predecessors (65-85 per 100 patient-years), and these rates were generally lower than in patients who first initiated benralizumab in BORA (46-88 per 100 patient-years; Table III). SAE rates per year were generally similar among treatment groups (2.4-14.2 per 100 patient-years) over time in the integrated period (Table III). There were no AEs leading to death during the on-treatment period. There was 1 death during the integrated period, outside the on-treatment window, in a patient who had received benralizumab Q4W. The death was due to influenza, occurred 85 days after the final dose, and was assessed by the investigator as not related to treatment. AEs leading to discontinuation were reported in 2 to 3 patients per year of the integrated period, mostly among the Q4W and Q8W treatment groups. In the standalone period, approximately 2% of patients in each group discontinued treatment because of an AE (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).[18]

Overall, across treatment groups, event rates for AEs (28.5-32.4 per 100 patient-years), SAEs (6.3-8.4 per 100 patient-years), serious infections (1.1-1.9 per 100 patient-years), hypersensitivity AEs (4.8-5.8 per 100 patient-years), and malignancy AEs (0.5-0.7 per 100 patient-years) were similar during extension studies (BORA and MELTEMI). These rates were generally the same or lower than in predecessor studies (Table IV; see Table E3). In the standalone period, percentages with AEs (88% and 77% for Q4W and Q8W, respectively) and SAEs (19% and 20%, respectively) were similar to those in previous studies (Table E3).[18] The most common AEs across treatment groups in extension studies were nasopharyngitis (11.1-12.1 per 100 patient-years), worsening asthma (4.3-7.4 per 100 patient-years), bronchitis (3.2-6.8 per 100 patient-years), headache (3.9-6.3 per 100 patient-years), viral upper respiratory tract infection (2.4-5.3 per 100 patient-years), sinusitis (2.5-4.3 per 100 patient-years), and upper respiratory tract infection (1.0-3.6 per 100 patient-years; Table IV). In the standalone period, the most common AEs were similar to those in the integrated period (Table E3).

In the integrated analysis period, ADAs were detected in the following percentages per treatment group: 4.5% to 10% in study periods before MELTEMI (SIROCCO, CALIMA, ZONDA, BORA); 1.9% to 5.7% during MELTEMI; and 6.7% to 14.9% in both the study periods before, as well as during, MELTEMI (Table V). nAbs were generally expressed in less than 2% per treatment group in either the study periods before MELTEMI (ie, SIROCCO, CALIMA, ZONDA, BORA) or during MELTEMI. nAbs were expressed in 5.3% to 10.4% per treatment group in both the study periods before, as well as during, MELTEMI. Similar rates of ADAs and nAbs were observed in the standalone period (Table E3). There was no indication that ADA status affected the incidence of AEs or SAEs, and there was no correlation between ADAs and hypersensitivity AEs.

Exacerbations and bEOS levels

Annual asthma exacerbations and bEOS levels over time during the integrated period are reported for the bEOSs greater than or equal to 300 cells/μL—HDICSs subgroup with a focus on the Q8W dose, which corresponds with the approved benralizumab regimen.[22] In patients treated with benralizumab Q8W, the annualized exacerbation rate was 0.5 in predecessor

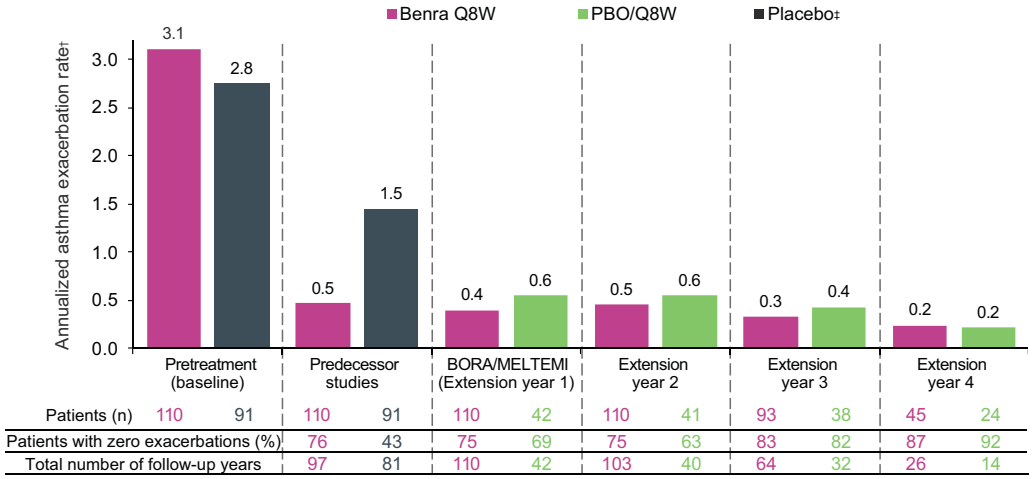

FIGURE 2. Asthma exacerbations among patients receiving benralizumab Q8W during the integrated analysis period (baseline bEOSs ≥300 cells/μL—HDICSs*). *Benra*, Benralizumab. *Per Global Initiative for Asthma (GINA) recommendations, HDICSs defined as >500 μg fluticasone propionate equivalents daily. †Annual exacerbation rate defined as 365.25 × total number of exacerbations/total duration of on-treatment follow-up within the treatment group and time interval (days). ‡Placebo (n = 91) from predecessor studies includes 49 patients in the PBO/Q4W group and 42 patients in the PBO/Q8W group during the extension studies.

studies and was less than or equal to 0.5 in subsequent years of the integrated analysis period (Figure 2). In predecessor studies, the annualized exacerbation rate was 1.5 among patients receiving placebo. In those who switched from placebo to Q8W in BORA, the annualized exacerbation rate decreased to 0.6 and was less than or equal to 0.6 in subsequent years of the integrated period. Similar trends were observed in the Q4W and PBO/Q4W treatment groups, respectively (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In the standalone period, the annualized exacerbation rate was 0.5 in both treatment groups and among all patients overall (N = 446; 1044.8 total follow-up years) (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

In the Q8W treatment group, 76% of patients had zero exacerbations in predecessor studies and thereafter, at least 75% had zero exacerbations per year for the remainder of the integrated period (Figure 2). Among patients treated with placebo, 43% had zero exacerbations in predecessor studies. In patients who switched from placebo to Q8W in BORA, 69% had zero exacerbations per year, and thereafter, greater than or equal to 63% had zero exacerbations per year for the remainder of the integrated period. Similar trends were observed in the Q4W and PBO/Q4W treatment groups, respectively (Figure E1). In the Q8W and PBO/Q8W treatment groups, 59% and 57% had zero exacerbations across the BORA and MELTEMI extensions (304.4 and 129.3 total follow-up years, respectively; see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Similarly, in the standalone period, 57% of -patients treated with benralizumab (Q4W or Q8W) had zero exacerbations (1044.8 total follow-up years; Table E4). Among patients who initiated benralizumab in predecessor studies, median bEOS levels reached 0 cell/μL by predecessor week 4 and remained at or near 0 cell/μL through the end of the integrated period (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). In patients who initiated benralizumab in BORA, median bEOS levels reached 0 cell/μL by week 12 in BORA and remained at or near 0 cell/μL through the end of the integrated period (Figure E3).

DISCUSSION

Previous phase 3 predecessor studies (SIROCCO, CALIMA, ZONDA) demonstrated the safety and efficacy of benralizumab for reducing exacerbation rates and OCS use in patients with severe, uncontrolled eosinophilic asthma.[18,23-27] In asthma management, biologic therapies such as benralizumab are often used over several years of treatment; given the mechanisms of action of benralizumab through eosinophil depletion in blood and tissues, as well as the importance of eosinophils in both pathophysiological (eg, host protection against infections) and homeostatic immune processes,[29,30] it is critical to understand the long-term safety and efficacy of benralizumab for patients with asthma.[19-21] Until now, findings were limited to 2 years of follow-up in the BORA integrated study.[18] The MELTEMI integrated analysis reported above included patients who completed a predecessor study, enrolled in BORA (16-40 weeks), and subsequently switched to and completed the MELTEMI study.

Results from this MELTEMI integrated analysis indicate that benralizumab was safe and well tolerated among patients with severe, uncontrolled eosinophilic asthma treated for up to 5 years, and these findings are consistent with those of previous reports.[18,23-26] Rates of AEs, SAEs, serious infections, and hypersensitivity AEs were generally stable over time and did not increase with higher benralizumab exposure. Furthermore, rates of patients with at least 1 AE (28.5-32.4 per 100 patient-years) or at least 1 SAE (6.3-8.4 per 100 patient-years) in these extension studies were comparable with those reported in the BORA 2-year analysis (41.5-43.1 and 7.5-9.1 per 100 patient-years, respectively).[18] Indeed, the safety results from this

integrated analysis period expand on those from the previous 2-year analysis, which excluded patients from ZONDA and patients who switched from placebo to benralizumab at BORA enrollment.[18] Taken together, these data demonstrate that long-term (up to 5 years) eosinophil depletion with benralizumab is not associated with an increased risk of serious infection or new safety signals (1581.3 total patient-years). Moreover, these safety data are in line with long-term findings for mepolizumab.[31] The prevalence of ADAs among patients in this integrated analysis was consistent with the expression of ADAs among patients in the pivotal studies and the extension studies.[18,23-26] There was also no indication of a connection between ADA status and the incidence of AEs or SAEs.

In the bEOSs greater than or equal to 300 cells/μL—HDICSs subgroup, for patients who initiated treatment with benralizumab in predecessor studies, reductions in bEOS levels and annual asthma exacerbation rates were maintained throughout the integrated analysis period (up to 5 years). Among patients treated with placebo in predecessor studies, after initiating benralizumab in BORA, median bEOS levels reached 0 cell/μL by week 12 and annualized exacerbation rates were similar across treatment groups, generally less than or equal to 0.5, after the first year in extension studies (BORA and MELTEMI). Among those who began benralizumab Q8W in predecessor studies, 75% or more patients had zero exacerbation per year for each year in the MELTEMI integrated analysis period. Similar results were observed for patients receiving benralizumab Q4W and after the first year of treatment for patients who initiated benralizumab in BORA (PBO/Q4W or PBO/Q8W). Overall, in this MELTEMI integrated analysis, exacerbation rates were low in patients treated with benralizumab, which is consistent with results from pivotal studies as well as previous analyses of the BORA study.[18,23-26] Although current treatment guidelines do not consider the effects of eliminating exacerbations,[1] achieving and maintaining zero exacerbations is likely a key criterion for progressing toward asthma remission under treatment.[32] Indeed, given that exacerbations were eliminated in almost 60% of patients with bEOSs greater than or equal to 300 cells/μL—HDICSs treated with the approved benralizumab regimen, during extension studies (BORA and MELTEMI), and at least 75% had zero exacerbations annually over the 5-year integrated analysis period, additional studies should be undertaken to characterize the subgroups of patients who remained exacerbation free while on benralizumab.

Because the MELTEMI extension was open-label, no placebo arm was included and thus, improvements in patients treated with benralizumab could not be compared against controls. Although this study was not powered to support comparisons between the 2 doses, results are presented for both the approved regimen (Q8W) and the regimen with higher exposure (Q4W). Patients who did not experience treatment benefits with their asthma may have been more likely to discontinue the study versus those who did experience benefits and similarly, patients who experienced certain SAEs in predecessor studies were not eligible to enter MELTEMI, both of which could contribute to selection bias. The results from this integrated analysis are consistent with those from the SIROCCO, CALIMA, ZONDA, and BORA studies, relative to the differences in time on treatment, which was at least 5 years for almost 11% and at least 4 years for more than 35% of patients overall in the integrated analysis period.[23,24,26]

CONCLUSIONS

This MELTEMI integrated analysis reaffirms findings from the SIROCCO, CALIMA, ZONDA, and BORA trials. These data demonstrate that among patients with severe, uncontrolled eosinophilic asthma receiving benralizumab for up to 5 years, long-term eosinophil depletion was not associated with an increased risk of serious infection or any new safety signals, and the reductions in bEOS levels and asthma exacerbations rates observed in preceding studies were maintained through long-term follow-up.[18,23,24,26] These findings further support the long-term safety and efficacy of benralizumab for achieving and maintaining asthma control in patients with severe, uncontrolled eosinophilic asthma.

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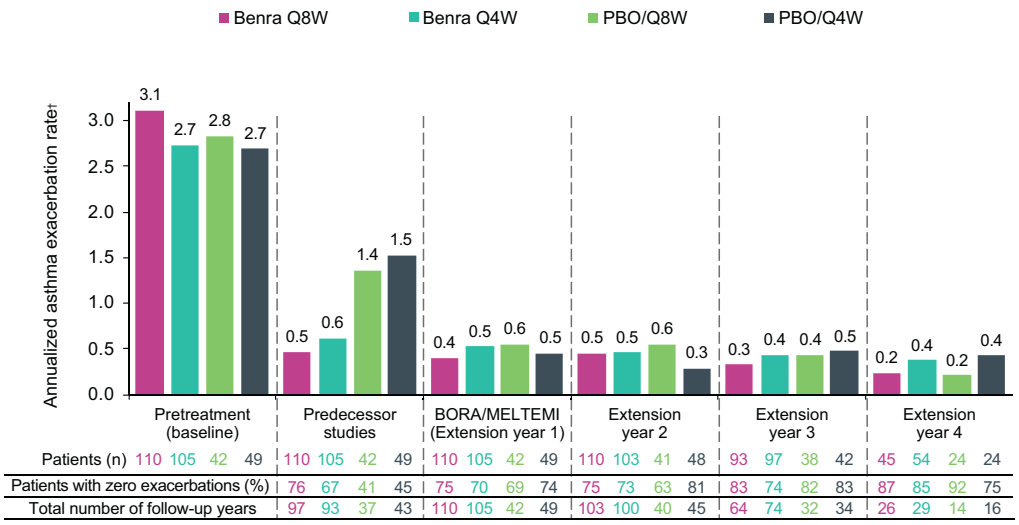

FIGURE E1. Asthma exacerbations among patients in the integrated analysis period (baseline bEOSs ≥300 cells/μL—HDICSs*). *Benra*, Benralizumab; *bEOS*, blood eosinophil; *HDICS*, high-dosage inhaled corticosteroid; *PBO*, placebo; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks. *Per Global Initiative for Asthma (GINA) recommendations, HDICSs defined as >500 μg fluticasone propionate equivalents daily. †Annual exacerbation rate was defined as 365.25 × total number of exacerbations/total duration of on-treatment follow-up within the treatment group and time interval (days).

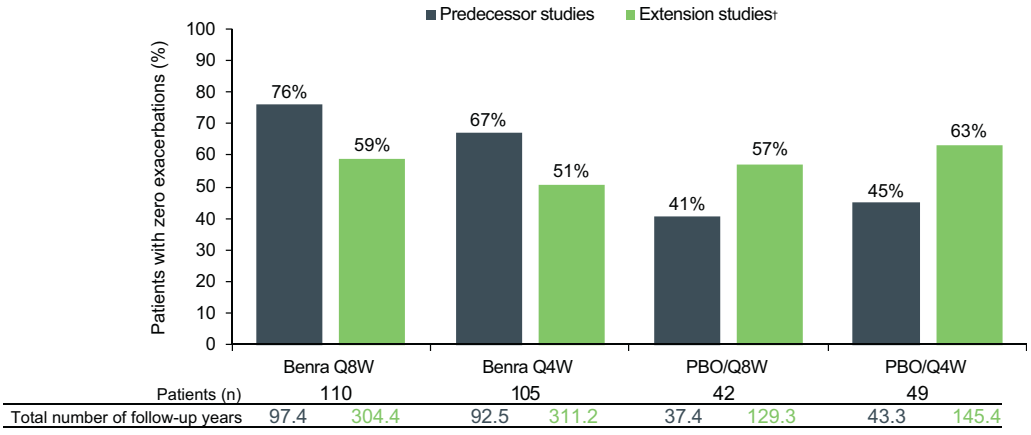

FIGURE E2. Patients with zero exacerbations in the integrated analysis period (baseline bEOSs ≥300 cells/μL—HDICSs*). *Benra*, Benralizumab; *bEOS*, blood eosinophil; *HDICS*, high-dosage inhaled corticosteroid; *PBO*, placebo; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks. *Per Global Initiative for Asthma (GINA) recommendations, HDICSs defined as >500 μg fluticasone propionate equivalents daily. †Extension studies include time on treatment in the double-blind BORA extension as well as the open-label MELTEMI extension.

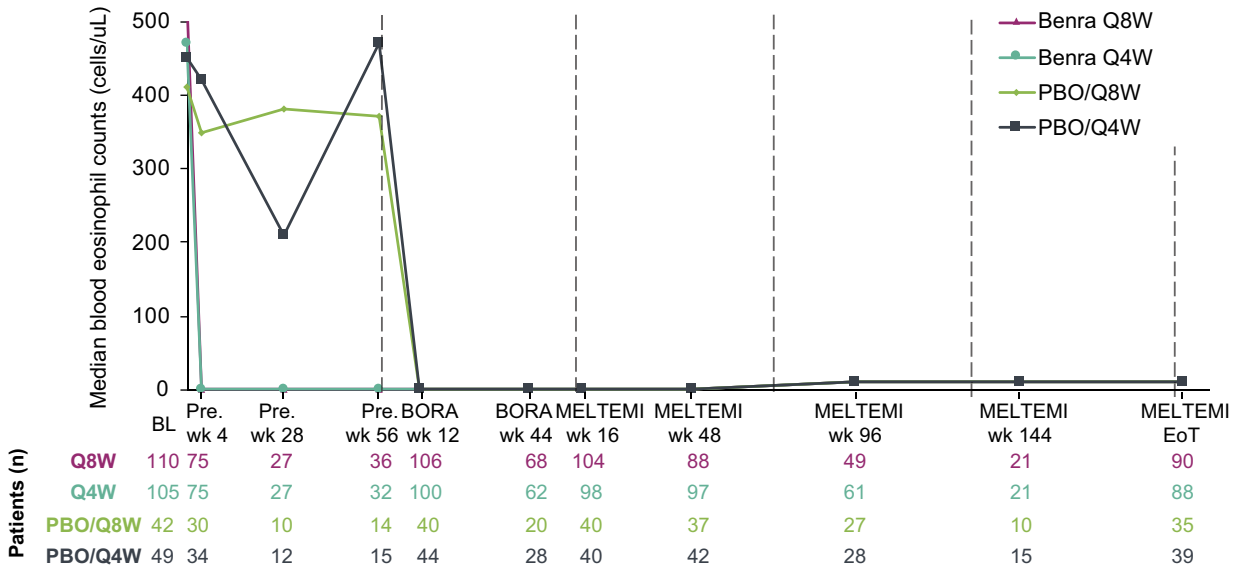

FIGURE E3. Median bEOS levels among patients in the integrated analysis period (baseline bEOSs ≥300 cells/μL—HDICSs*). *Benra*, Benralizumab; *bEOS*, blood eosinophil; *BL*, baseline; *EoT*, end of treatment; *HDICS*, high-dosage inhaled corticosteroid; *PBO*, placebo; *Pre.*, predecessor study; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks. *Per Global Initiative for Asthma (GINA) recommendations, HDICSs defined as >500 μg fluticasone propionate equivalents daily.

TABLE E1. Treatment characteristics and study dispositions for patients in the MELTEMI standalone period (FAS, on-treatment period)

Parameter	Benra Q8W (n = 226)	Benra Q4W (n = 220)	Total (N = 446)
On-treatment duration (mo*), mean ± SD	25.4 ± 9.9	26.4 ± 10.1	25.9 ± 10
Median (range)	25.8 (0-42.3)	26.9 (0-42.3)	26.7 (0-42.3)
Total on-treatment period (patient-years)	477.6	483.1	960.8
Patients who completed MELTEMI, n (%)†	195 (86.3)	189 (85.9)	384 (86.1)
Patients who discontinued treatment, n (%)	31 (13.7)	31 (14.1)	62 (13.9)
AEs	4 (1.8)	4 (1.8)	8 (1.8)
Development of study-specific discontinuation criteria	2 (0.9)	8 (3.6)	10 (2.2)
Patient decision	16 (7.1)	13 (5.9)	29 (6.5)
Patient lost to follow-up	5 (2.2)	1 (0.5)	6 (1.3)
Other	4 (1.8)	5 (2.3)	9 (2)
Patients who discontinued treatment but completed study follow-up	0	0	0

AE, Adverse event; *benra*, benralizumab; *FAS*, full analysis set; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks.
*On-treatment period was defined as the time from the first dose of benralizumab in the MELTEMI study to the last on-treatment date.
†Includes patients who discontinued treatment but attended all study visits.

TABLE E2. Baseline demographic and clinical characteristics for patients in the MELTEMI standalone period (FAS, on-treatment period)*

Parameter	Benra Q8W (n = 226)	Benra Q4W (n = 220)	Total (N = 446)
Age (y), mean ± SD	53 ± 11.6	53.5 ± 12	53.2 ± 11.8
Women, n (%)	144 (63.7)	140 (63.6)	284 (63.7)
bEOSs (cells/μL), median (range)	0 (0-2060)	0 (0-680)	0 (0-2060)
Time since asthma diagnosis (y), median (range)	15.5 (2.3-68.6)	15.7 (1.8-61.7)	15.6 (1.8-68.6)
Exacerbations in past 12 mo, mean ± SD	0.5 ± 0.99	0.5 ± 1	0.5 ± 0.99
1, n (%)	38 (16.8)	38 (17.3)	76 (17.0)
2, n (%)	16 (7.1)	20 (9.1)	36 (8.1)
≥3, n (%)	11 (4.8)	9 (4.2)	20 (4.3)
ICS, n (%)†	226 (100)	218 (99.1)	444 (99.6)
ICS total daily dosage (μg), mean (range)	908.9 (100-3500)	844 (250-3650)	877 (100-3650)
LABA, n (%)	223 (98.7)	217 (98.6)	440 (98.7)
ICS/LABA, n (%)†	200 (88.5)	196 (89.1)	396 (88.8)
LAMA, n (%)	23 (10.2)	23 (10.5)	46 (10.3)
LTRA, n (%)	74 (32.7)	64 (29.1)	138 (30.9)

Benra, Benralizumab; *bEOS*, blood eosinophil; *FAS*, full analysis set; *ICS*, inhaled corticosteroid; *LABA*, long-acting β_2-agonist; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks.
*Defined as the baseline visit in the MELTEMI study.
†ICSs may have been taken in a separate inhaler or as part of a fixed-dose ICS/LABA combination device.

TABLE E3. AEs, hypersensitivities, and malignancies among patients in the MELTEMI standalone period (FAS, on-treatment period)

Parameter	Benra Q8W (n = 226)	Benra Q4W (n = 220)	Total (N = 446)
Patients with any AE, n (%)	173 (76.5)	193 (87.7)	366 (82.1)
AEs in ≥5% of patients, n (%)			
Nasopharyngitis	62 (27.4)	63 (28.6)	125 (28)
Headache	21 (9.3)	32 (14.5)	53 (11.9)
Asthma	30 (13.3)	22 (10)	52 (11.7)
Viral upper respiratory tract infection	19 (8.4)	28 (12.7)	47 (10.5)
Bronchitis	22 (9.7)	22 (10)	44 (9.9)
Hypertension	23 (10.2)	14 (6.4)	37 (8.3)
Sinusitis	11 (4.9)	17 (7.7)	28 (6.3)
Acute sinusitis	8 (3.5)	13 (5.9)	21 (4.7)
Bronchitis bacterial	9 (4.0)	12 (5.5)	21 (4.7)
Upper respiratory tract infection	7 (3.1)	14 (6.4)	21 (4.7)
Osteoarthritis	4 (1.8)	11 (5.0)	15 (3.4)
Rhinitis	3 (1.3)	11 (5.0)	14 (3.1)
Any AE leading to IP discontinuation, n (%)	5 (2.2)	4 (1.8)	9 (2)
Any SAE, n (%)*	45 (19.9)	42 (19.1)	87 (19.5)
SAEs in ≥1% of patients, n (%)			
Asthma	12 (5.3)	8 (3.6)	20 (4.5)
Any serious infection, n (%)	6 (2.7)	10 (4.5)	16 (3.6)
Any hypersensitivity AE, n (%)	23 (10.2)	22 (10)	45 (10.1)
Hypersensitivity AEs in ≥1% of patients, n (%)			
Rhinitis, allergic	8 (3.5)	4 (1.8)	12 (2.7)
Urticaria	5 (2.2)	4 (1.8)	9 (2)
Eczema	0	6 (2.7)	6 (1.3)
Rash	2 (0.9)	4 (1.8)	6 (1.3)
Conjunctivitis allergic	0	4 (1.8)	4 (0.9)
Malignancy event by SEAC, n (%)†,‡	3 (1.3)	3 (1.4)	6 (1.3)
Any ADA results available, n (%)	225	218	434
ADA positive at any visit	28 (12.4)	19 (8.7)	47 (10.6)
nAb positive, n (%)	24 (10.7)	13 (6.0)	37 (8.4)

ADA, Antidrug antibody; *AE*, adverse event; *benra*, benralizumab; *FAS*, full analysis set; *IP*, investigational product; *nAb*, neutralizing antibody; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks; *SAE*, serious adverse event; *SEAC*, safety endpoint adjudication committee.
*Including events with an outcome of death.
†Neoplasms including benign, malignant, and unspecified, including cysts and polyps.
‡Predefined malignancy events of interest were submitted to the safety endpoint adjudication committee for independent external adjudication to see whether they met charter definition of a malignancy event of interest. Only those with an event according to established criteria are tabulated.

TABLE E4. Asthma exacerbations among patients in the MELTEMI standalone analysis period (FAS, on-treatment period)

Parameter	Benra Q8W (n = 226)	Benra Q4W (n = 220)	Total (N = 446)
Total number of follow-up years	524.3	520.5	1044.8
Annualized asthma exacerbation rate*	0.5	0.5	0.5
Patients with zero exacerbations, n (%)	129 (57.1)	124 (56.4)	253 (56.7)

Benra, Benralizumab; *FAS*, full analysis set; *Q4W*, every 4 weeks; *Q8W*, every 8 weeks.
*Annual exacerbation rate defined as 365.25 × total number of exacerbations/total duration of on-treatment follow-up within the treatment group and time interval (days).