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MELTEMI and COLUMBA: 5-Year Comparative Safety Analysis of Benralizumab and Mepolizumab

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Keywords:

Adverse events; Asthma; Biologic agents; Eosinophils; Injection site adverse reaction; Patient safety; Respiratory **infections**.

Abbreviations used

AE- Adverse event

EOS- Eosinophil

ER- Event rate

ICS- Inhaled corticosteroid(s)

IL- Interleukin

LABA- Long-acting β 2-agonist

OCS- Oral corticosteroid(s)

q4w- Every 4 weeks

q8w- Every 8 weeks

RTI- Respiratory tract infection

SAE- Serious adverse event

SEA- Severe eosinophilic asthma

Abstract

Background:

Benralizumab and mepolizumab are interleukin (IL)-5R α /interleukin-5-targeted monoclonal antibodies indicated as add-on treatments for patients with uncontrolled severe eosinophilic asthma (SEA).

Objective:

To evaluate and compare the safety of benralizumab and mepolizumab among patients with SEA treated in MELTEMI and COLUMBA open-label, long-term extension studies, respectively.

Methods:

MELTEMI was an extension study of benralizumab every 4 weeks (q4w) or every 8 weeks (q8w) for adults (aged 18-75 y) with SEA. MELTEMI participants transitioned from the BORA extension, preceded by participation in 1 of 3 placebo-controlled studies (SIROCCO, CALIMA, or ZONDA). COLUMBA was an extension study of mepolizumab for patients (aged \geq 12 y) with SEA who transitioned from the dose-ranging DREAM study. Safety endpoints were presented as drug exposure patient-years (MELTEMI, q4w 784.28, q8w 797.03; COLUMBA 1,201) for nonserious adverse events, serious adverse events, and infections; malignancies were counted numerically.

Results:

This analysis included 446 MELTEMI patients (benralizumab q4w 220; benralizumab q8w 226) and 347 COLUMBA patients (mepolizumab q4w). Viral upper respiratory tract infection was the most common nonserious adverse event in both studies (MELTEMI q8w 46.5%; q4w 47.3%; COLUMBA, 48.7%). Asthma-related events were the most common serious adverse events in both studies: MELTEMI 8.0% (q8w) and 8.6% (q4w) and COLUMBA 9.5%. Serious infections included pneumonia (MELTEMI q8w, 2 [0.9%]; COLUMBA, 6 [1.7%]); cellulitis (MELTEMI q8w, 1 [0.4%]; COLUMBA, 2 [0.6%]); and respiratory tract infections (COLUMBA, 2 [0.6%]). COLUMBA reported 6 malignancies and MELTEMI reported 4 malignancies in each group.

Conclusions:

This analysis demonstrated generally similar safety events between mepolizumab and benralizumab in patients with SEA.

INTRODUCTION

Asthma affects more than 260 million people worldwide.¹ About 5% of these patients have severe asthma.²⁻⁵ Estimates suggest more than half of patients with severe asthma have poorly controlled disease² and, thus, an increased risk for exacerbations.⁶

Severe eosinophilic asthma (SEA) is a phenotype of severe asthma characterized by high numbers of blood eosinophils (EOSs).⁷ Among patients with severe asthma, 80% or more have an eosinophilic phenotype.⁷ Evidence indicates a relationship between elevated blood EOS counts and exacerbation risk,⁸ which is associated with increased health care resource utilization^{9,10} and corresponding increases in health care costs.^{9,11} The cumulative health effects of asthma exacerbations, adverse effects (AEs) of oral corticosteroid (OCS) medications (to treat T-helper 2 inflammation), poor symptom control, and economic burden contribute to reduced health-related quality of life.^{12,13}

Benralizumab and mepolizumab are interleukin (IL)-5 receptor α -directed and IL-5-directed monoclonal antibodies, respectively, indicated as add-on treatments for patients with SEA.¹⁴⁻¹⁶ Benralizumab induces direct, rapid, nearly complete depletion of EOS from the peripheral blood and lungs through antibody-dependent cell-mediated cytotoxicity and is indicated for patients aged 12 years or older with SEA.^{14,17} Mepolizumab is an IL-5 antagonist that reduces the maturation, recruitment, and activation of EOS by blocking IL-5 from binding to the α -chain of the IL-5 receptor; mepolizumab is indicated for patients aged 6 years or older with SEA¹⁵ and has been shown to decrease airway EOSs by approximately 50%.¹⁸ Evidence, largely from animal studies, indicates EOS may play a role in maintaining homeostasis and defending against parasitic infections,^{19,20} although findings are mixed regarding the role of EOSs in the development of malignancies.^{21,22} There has been an ongoing debate as to whether there are differences in the safety of partial versus near-complete EOS depletion in humans who are treated to alleviate the negative effects of tissue eosinophilia and eosinophilic inflammation.^{19,23,24}

Previous phase 2 and 3 studies have demonstrated that benralizumab and mepolizumab can reduce exacerbations, reduce OCS use, improve disease control, and improve health-related quality of life in patients with SEA.²⁵⁻³³ Although these predecessor studies established the short-term safety of benralizumab and mepolizumab, additional studies are necessary for a more robust characterization of their long-term safety. MELTEMI was an open-label, long-term extension study that evaluated the safety of benralizumab. An even longer-term analysis of benralizumab safety (dubbed the MELTEMI integrated treatment period) was conducted in patients treated for up to 5 years by evaluating patients who completed 1 of 3 placebo-controlled phase 3 predecessor studies (SIROCCO, CALIMA, and ZONDA), enrolled in the BORA extension study, and subsequently transitioned into the MELTEMI study.²⁸ COLUMBA was an open-label extension study that evaluated the long-term safety of mepolizumab in patients with SEA for up to 4.5 years.³⁰ Patients who completed the predecessor DREAM study were eligible to enroll in COLUMBA.

The objective of this post hoc analysis was to evaluate the long-term safety profile of patients treated with benralizumab in the MELTEMI integrated treatment period and to determine whether it is comparable with the safety profile of patients treated with mepolizumab in COLUMBA.

METHODS

Study design

MELTEMI (NCT02808819) was a long-term, open-label extension study that evaluated the safety and tolerability of benralizumab in adults (aged 18e75 y) with uncontrolled SEA who were on medium-/high-dose inhaled corticosteroids (ICS) plus long acting β 2-agonists (LABAs).²⁸ Patients in MELTEMI received benralizumab 30 mg by subcutaneous injection every 4 weeks (q4w) or every 8 weeks (q8w). The approved dosing of benralizumab is q4w for the first 3 doses, followed by q8w thereafter.¹⁴

Patients entered MELTEMI²⁸ after 16 or more and less than 40 weeks in the BORA (NCT02258542) 56-week double-blind extension study,³⁴ which consisted of patients from 1 of 3 placebo-controlled predecessor studies: SIROCCO (NCT01928771),²⁵ CALIMA (NCT01914757),²⁷ and ZONDA (NCT02075255)³⁵ (Figure 1, A). Patients who enrolled in the BORA study continued their original 30 mg benralizumab subcutaneous dosing regimen (q4w/q8w), whereas patients who received a placebo in the predecessor studies were randomly assigned to receive benralizumab either q4w or q8w. SIROCCO and CALIMA, respectively, were 48- and 56-week phase 3 randomized, double-blind, placebo-controlled trials that evaluated the efficacy and safety of benralizumab in patients aged 12 to 75 years.^{25,27} Key eligibility criteria for SIROCCO and CALIMA included patients receiving medium- or high-dose ICS plus LABA for 1 year or longer before enrollment and had 2 or more documented asthma exacerbations in the previous year.^{25,27}

ZONDA was a 28-week phase 3 randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of benralizumab in patients aged 18 to 75 years with SEA.^{31,36} Briefly, patients eligible for ZONDA included those receiving oral glucocorticoids for 6 months or longer before enrollment, receiving oral prednisone or prednisolone at trial entry and having had 1 or more exacerbations in the previous year, and receiving medium- or high-dose ICS plus LABA for 1 year or longer before enrollment.³¹

COLUMBA (NCT01691859)³⁰ was an open-label, long-term safety extension study of mepolizumab plus standard of care for patients aged 12 years or older with uncontrolled SEA who participated in the DREAM (NCT01000506) study (Figure 1, B).²⁹ Patients were off treatment during the time between these 2 studies. When COLUMBA began, 12 to 28 months after completion of DREAM, patients received mepolizumab 100 mg q4w.³⁰ The DREAM study was a phase 2 randomized, double-blind, placebo- controlled trial to evaluate whether patients aged 12 years or older with severe, uncontrolled asthma, treated with different doses of mepolizumab, experienced a reduction in the frequency of asthma exacerbations.²⁹ Eligibility criteria for the DREAM study included high-dosage ICS plus additional controller medications for 12 months or longer and a history of 2 or more exacerbations requiring systemic corticosteroids in the previous 12 months. Patients received mepolizumab in doses of 75, 250, or 750 mg, or placebo, intravenous q4w for 52 weeks.

This comparative analysis evaluated safety endpoints using data from the previously conducted MELTEMI integrated period (ie, data from SIROCCO, CALIMA, ZONDA, BORA, and MELTEMI stand-alone period) and COLUMBA (ie, no DREAM data) studies, including nonserious AEs, serious adverse events (SAEs), infections, and malignancies. The thresholds for those safety endpoints, as reported here, consist of (1) nonserious AEs, including infections identified as nonserious AEs, that occurred in 10% or greater of patients

in 1 study arm; (2) SAEs, including infections identified as SAEs, that occurred in 2 or more patients in 1 study arm; and (3) malignancies that occurred in 1 or more patients in 1 study arm.

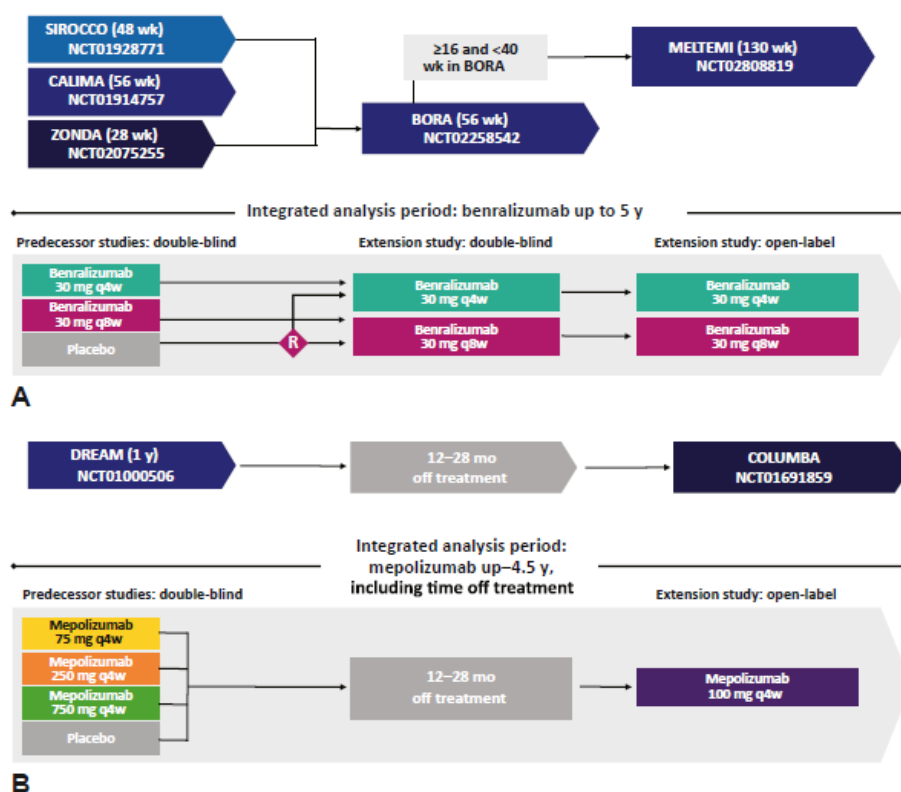


FIGURE 1. Clinical study flow diagrams for (A) MELTEMI and (B) COLUMBA. q4w, Every 4 weeks; q8w, every 8 weeks (first 3 doses q4w); R, 1:1 randomization. (A) Study design adapted from Korn et al, 2021.²⁸

Statistical analysis

Previous analyses of results from the MELTEMI study²⁸ were performed with MedDRA version 23.0 preferred terms, which was the most recent version at that time, and event rates (ERs) that were calculated with the number of patients in the numerator. To match the preferred terms and ERs reported in the COLUMBA analyses, we reanalyzed the MELTEMI data for this analysis, using MedDRA version 20.0 and ERs calculated with the number of nonserious AEs or SAEs in the numerator. Numerical safety data from COLUMBA were obtained from the [ClinicalTrials.gov](https://clinicaltrials.gov) data NCT01691859 repository and were downloaded on July 21, 2023.³⁷ COLUMBA exposure-adjusted ER data were obtained from the trial publication.³⁰ MELTEMI data were presented as both overall values and year-by-year for the full MELTEMI integrated treatment period, whereas COLUMBA data were only available, and are presented, as overall values. Statistical comparisons were not performed because this was a post hoc analysis from 2 different clinical studies.

Baseline characteristics were included to summarize the patient groups. “Baseline” for MELTEMI was defined as data from the baseline visit of the predecessor phase 3 studies (SIROCCO, CALIMA, or ZONDA). According to the [ClinicalTrials.gov](https://clinicaltrials.gov) entry, COLUMBA baseline data were defined as values from the COLUMBA visit 2 predose assessment; if there were missing values from visit 2, then values from visit 1 (screening) were used instead.³⁷

TABLE 1. Overall patient population baseline demographic and clinical characteristics

Parameter	MELTEMI*		COLUMBA
	Benra q8w, N = 226	Benra q4w, N = 220	Mepo q4w, N = 347
Exposure (y)	797.03†	784.28†	1,201†
Age (y), mean (SD)‡	51.2 (11.64)	51.8 (12.00)	52.2 (10.73)
Female, n (%)‡	144 (63.7)	140 (63.6)	224 (65)
Race, n (%)‡			
White	209 (92.5)	204 (92.7)	318 (92)
Black or African American	10 (4.4)	8 (3.6)	—
Asian	3 (1.3)	4 (1.8)	18 (5)
Other	4 (1.8)	4 (1.8)	11 (3)
BMI (kg/m ²), mean (SD)	29.3 (6.37)	29.4 (6.28)	28.6 (6.10)
Comorbid nasal polyps	41 (18.1)	37 (16.8)	24 (7)
bEOS (cells/μL), median (range)	430 (0–2,415)	410 (51–4,494)	270 (0–1,600)
Prebronchodilator FEV ₁ (% predicted), mean (SD)	56.8 (14.76)	56.1 (14.69)	60.1 (18.89)
Prebronchodilator FEV ₁ (mL), mean (SD)	1,700 (570)	1,700 (600)	1,811 (696.2)
FEV ₁ /FVC ratio, mean (SD)	0.60 (0.126)	0.59 (0.124)	0.62 (0.121)
Age of asthma onset (y), median (range)	35.8 (0–71.1)	37.6 (0–73.3)	33 (0–66)
Duration of asthma (y), mean (SD)	18.3 (14.98)	17.6 (13.26)	21.4 (14.22)
Exacerbations in past 12 mo, mean (SD)	2.8 (1.88)	2.7 (1.84)	2.7 (4.74)
>1, n (%)	210 (92.92)	199 (90.45)	280 (81)§
ACQ-5 score, mean (SD)	2.9 (0.97)	2.8 (1.00)	2.21 (1.169)
ACQ-6 score, mean (SD)	2.7 (0.92)	2.7 (0.97)	—
OCS use, n (%)	75 (33.2)	78 (35.5)	90 (26)
Concurrent therapy, n (%)			
ICS	226 (100)	220 (100)	347 (100)
LABA	226 (100)	220 (100)	339 (98)
LAMA	32 (14.2)	21 (9.5)	51 (15)
LTRA	82 (36.3)	68 (30.9)	63 (18)
Xanthine	30 (13.3)	24 (10.9)	75 (22)

ACQ-5, 5-Item Asthma Control Questionnaire; ACQ-6, 6-item Asthma Control Questionnaire; Benra, benralizumab; bEOS, blood eosinophils; BMI, body mass index; exp, drug exposure in patient-years; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; Mepo, mepolizumab.

*Defined as the baseline visit of the predecessor study.

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

‡Age, sex, and race data for COLUMBA were from [ClinicalTrials.gov](https://clinicaltrials.gov), downloaded July 21, 2023. All other COLUMBA baseline clinical characteristics are from Khatri et al. 2019.³⁰

§Participants from the DREAM clinical trial had a 12- to 28-month break from treatment before starting COLUMBA.³⁰

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

Safety endpoints were collected using different processes between the 2 studies. In MELTEMI, patients reported AEs at each visit and they were recorded by staff. In COLUMBA, patients recorded AEs on a worksheet, and study staff documented these at each visit.³⁰

Nonserious AE and SAE infections and malignancy data were calculated based on the percentage of patients within each respective group. Infections were listed under nonserious AEs or SAEs based on how they were reported. MELTEMI patients with 1 or more safety event per category were tabulated and reported once in each nonserious AE and SAE category. For this analysis, patients with multiple safety events in the same category and period were tabulated only once.

Nonserious AE and SAE ERs, including infections for MELTEMI and exposure-adjusted ERs for COLUMBA, were included in this analysis (available in this article's Online Repository at www.jaci-inpractice.org). The ERs were used to identify safety trends in the patient population. The results of the ER analyses were presented on a scale of 1,000 patient-years.

TABLE II. Most common nonserious AEs (in $\geq 10\%$ of patients) and nonserious cardiac AEs (≥ 1 patient)

Preferred term,* n (%)	MELTEMI†		COLUMBA‡
	Benra q8w N = 226	Benra q4w N = 220	Mopo q4w N = 347
Exposure (y)	797.03§	784.28§	1,201§
Viral upper RTI	105 (46.5)	104 (47.3)	169 (48.7)
Bronchitis	41 (18.1)	31 (14.1)	73 (21.0)
Asthma	35 (15.5)	39 (17.7)	69 (19.9)
Headache	30 (13.3)	46 (20.9)	99 (28.5)
Hypertension	30 (13.3)	23 (10.5)	32 (9.2)
Sinusitis	24 (10.6)	27 (12.3)	57 (16.4)
Upper RTI	18 (8.0)	27 (12.3)	81 (23.3)
Back pain	16 (7.1)	16 (7.3)	63 (18.2)
Arthralgia	15 (6.6)	14 (6.4)	58 (16.7)
Influenza	11 (4.9)	11 (5.0)	43 (12.4)
Pain in extremity	8 (3.5)	6 (2.7)	40 (11.5)
Injection site reaction	5 (2.2)	10 (4.5)	42 (12.1)
RTI	6 (2.7)	4 (1.8)	38 (11.0)
Cardiac disorders, n (%)			
Tachycardia	3 (1.3)	5 (2.3)	—
Sinus tachycardia	3 (1.3)	2 (0.9)	—
Angina pectoris	2 (0.9)	3 (1.4)	—
Atrial fibrillation	2 (0.9)	—	1 (0.3)
Supraventricular tachycardia	—	2 (0.9)	—
Palpitations	1 (0.4)	2 (0.9)	—
Acute myocardial infarction	—	—	1 (0.3)
Angina unstable	—	—	1 (0.3)
Arrhythmia	1 (0.4)	—	—
Atrial flutter	1 (0.4)	—	1 (0.3)
Atrial tachycardia	—	—	1 (0.3)
Cardiac failure, acute	—	—	1 (0.3)
Cardiac failure, chronic	1 (0.4)	1 (0.5)	—
Cardiac failure, congestive	—	1 (0.5)	—
Coronary artery occlusion	1 (0.4)	—	—
Extrasystoles	—	1 (0.5)	—
Left ventricular failure	—	1 (0.5)	—
Left ventricular hypertrophy	1 (0.4)	—	—
Myocardial fibrosis	1 (0.4)	—	—
Myocardial infarction	—	—	1 (0.3)
Myocardial ischemia	1 (0.4)	—	—
Nodal arrhythmia	—	1 (0.5)	—
Supraventricular extrasystoles	—	1 (0.5)	—
Tachyarrhythmia	1 (0.4)	—	—

*MedDRA version 20.0.

†For this analysis, patients with multiple safety events in the same category and period were tabulated only once.

‡COLUMBA data were from the ClinicalTrials.gov website, downloaded July 21, 2023.

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

||Injection site reaction data for the MELTEMI q8w group included injection site erythema, site pain, hematoma, edema, and pruritus, and for the MELTEMI q4w group, erythema, site pain, hematoma, edema, pruritus, swelling, bruising, hypesthesia, induration, and paresthesia.

RESULTS

This comparative analysis included 446 MELTEMI patients and 347 COLUMBA patients overall. Of the 446 MELTEMI patients, 220 were in the benralizumab q4w group, and 226 were in the benralizumab q8w group (Table I). Of the MELTEMI patients who were enrolled for up to 5 years, those in the q4w group had a total drug exposure of 784.28 patient-years, and those in the q8w group had a total drug exposure of 797.03 patient-years, for a combined total drug exposure of 1,581.31 patient-years.²⁸ The 347 COLUMBA patients who were enrolled for up to 4.5 years had a total drug exposure of 1,201 patient-years.³⁰

TABLE III. MELTEMI most common nonserious AEs year by year (in > 10% of patients)*†

Preferred terms,‡ n (%)	Benra q8w						Benra q4w					
	Overall	Pre	E1	E2	E3	E>3	Overall	Pre	E1	E2	E3	E>3
Total patients	226	159	226	223	199	105	220	150	220	215	198	111
Exposure (y)	797.03‡	146.09‡	225.55‡	213.14‡	144.69‡	67.55‡	784.28‡	134.96‡	219.20‡	206.97‡	150.22‡	72.93‡
Viral upper RTI	105 (46.5)	27 (17.0)	50 (22.1)	43 (19.3)	25 (12.6)	10 (9.5)	104 (47.3)	30 (20.0)	42 (19.1)	55 (25.6)	37 (18.7)	11 (9.9)
Bronchitis	41 (18.1)	13 (8.2)	20 (8.8)	7 (3.1)	8 (4.0)	2 (1.9)	31 (14.1)	8 (5.3)	13 (5.9)	10 (4.7)	6 (3.0)	6 (5.4)
Asthma	35 (15.5)	10 (6.3)	19 (8.4)	11 (4.9)	7 (3.5)	1 (1.0)	39 (17.7)	19 (12.7)	15 (6.8)	8 (3.7)	5 (2.5)	2 (1.8)
Headache	30 (13.3)	12 (7.5)	9 (4.0)	17 (7.6)	10 (5.0)	1 (1.0)	46 (20.9)	17 (11.3)	20 (9.1)	20 (9.3)	15 (7.6)	1 (0.9)
Hypertension	30 (13.3)	4 (2.5)	12 (5.3)	11 (4.9)	9 (4.5)	3 (2.9)	23 (10.5)	6 (4.0)	8 (3.6)	5 (2.3)	6 (3.0)	5 (4.5)
Sinusitis	24 (10.6)	7 (4.4)	14 (6.2)	4 (1.8)	3 (1.5)	0	27 (12.3)	6 (4.0)	14 (6.4)	7 (3.3)	4 (2.0)	4 (3.6)
Upper RTI	18 (8.0)	10 (6.3)	6 (2.7)	5 (2.2)	4 (2.0)	0	27 (12.3)	12 (8.0)	9 (4.1)	5 (2.3)	7 (3.5)	1 (0.9)
Back pain	16 (7.1)	4 (2.5)	5 (2.2)	3 (1.3)	2 (1.0)	4 (3.8)	16 (7.3)	5 (3.3)	5 (2.3)	8 (3.7)	3 (1.5)	0
Arthralgia	15 (6.6)	7 (4.4)	4 (1.8)	5 (2.2)	3 (1.5)	0	14 (6.4)	4 (2.7)	5 (2.3)	3 (1.4)	2 (1.0)	0
Influenza	11 (4.9)	3 (1.9)	1 (0.4)	5 (2.2)	3 (1.5)	0	11 (5.0)	5 (3.3)	0	3 (1.4)	3 (1.5)	0
Pain in extremity	8 (3.5)	5 (3.1)	1 (0.4)	2 (0.9)	0	0	6 (2.7)	0	1 (0.5)	4 (1.9)	2 (1.0)	0
Injection site reaction	5 (2.2)	0	2 (0.9)	4 (1.8)	1 (0.5)	0	10 (4.5)	3 (2.0)	4 (1.8)	7 (3.3)	2 (1.0)	0
RTI	6 (2.7)	2 (1.3)	0	2 (0.9)	1 (0.5)	1 (1.0)	4 (1.8)	3 (2.0)	1 (0.5)	0	0	0

E1, extension studies year 1; E2, extension year 2; E3, extension year 3; E>3 >3 y of treatment in extension studies; Pre, pre-treatment study (SIROCCO, CALIMA, ZONDA).

*Nonserious AEs were aligned with the MELTEMI patient nonserious AEs in Table 1I.

†For this analysis, patients with multiple safety events in the same category and period were tabulated only once.

‡MedDRA version 20.0.

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

||Injection site reactions for the q8w group included erythema, site pain, hematoma, edema, and pruritus; injection site reactions for the q4w group included erythema, site pain, hematoma, edema, pruritus, swelling, bruising, hypohidrosis, induration, and paresthesia.

Demographics and baseline characteristics

Demographics and baseline characteristics were generally similar across the MELTEMI and COLUMBA studies (Table I). Patients in the MELTEMI q4w, MELTEMI q8w, and COLUMBA groups had a mean (SD) age of 51.8 y (12.00 y), 51.2 years (11.64 y), and 52.2 years (10.73 y), respectively. Across all 3 treatment groups, approximately 64% of patients were female, and approximately 92% of patients were white. The mean (SD) time in years since patients had been diagnosed with asthma were similar between the 2 studies, MELTEMI q8w 18.3 years (14.98 y) and q4w 17.6 years (13.26 y) and COLUMBA 21.4 years (14.22 y).

TABLE IV. SAEs (in > 2 patients)

Preferred terms,* n (%)	MELTEMI†		COLUMBA‡
	Benra q8w N = 226	Benra q4w N = 220	Mevo q4w N = 347
Exposure (y)	797.03‡	784.28‡	1,201‡
Asthma	18 (8.0)	19 (8.6)	33 (9.5)
Pneumonia	2 (0.9)	—	6 (1.7)
Chronic sinusitis	2 (0.9)	—	—
Limb injury	2 (0.9)	—	—
Nasal polyps	2 (0.9)	—	—
Cellulitis	1 (0.4)	—	2 (0.6)
Cataract	1 (0.4)	2 (0.9)	—
Influenza	1 (0.4)	2 (0.9)	1 (0.3)
Noncardiac chest pain	1 (0.4)	2 (0.9)	1 (0.3)
Sciatica	1 (0.4)	—	2 (0.6)
Asthenia	—	2 (0.9)	—
Lower limb fracture	—	2 (0.9)	1 (0.3)
RTI	—	—	2 (0.6)
Bursitis	—	—	2 (0.6)
Cholelithiasis	—	—	2 (0.6)
Epilepsy	—	—	2 (0.6)
Intervertebral disc protrusion	—	—	2 (0.6)
Prostate cancer	—	—	2 (0.6)
Death¶	—	1 (0.5)	6 (1.7)

*MedDRA version 20.0.

†For this analysis, patients with multiple safety events in the same category and period were tabulated only once.

‡COLUMBA data were from ClinicalTrials.gov, downloaded July 21, 2023.

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

||In the COLUMBA trial, 1 patient had a childhood history of epilepsy.

¶The death in MELTEMI was attributed to influenza and did not occur during the on-treatment period.²⁸ COLUMBA deaths were due to sudden death; respiratory arrest; morbid obesity, chronic asthma, and sleep apnea; myocardial infarction; acute heart failure; and severe asthma exacerbation. None of these deaths, as assessed by the investigator, were considered causally related to the study drug.

Nonserious AEs

The most common nonserious AEs across MELTEMI and COLUMBA were viral upper respiratory tract infections (RTIs): benralizumab q4w 47.3% (104 of 220), benralizumab q8w 46.5% (105 of 226), and mepolizumab q4w 48.1% (169 of 347) (Table II). Similar patterns were observed in the ERs per 1,000 patient-years (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). Viral upper RTIs were most prevalent in year 1 for the MELTEMI q8w group (22.1% [50 of 226]) and year 2 for the MELTEMI q4w group (25.6% [55 of 220]; Table III); those rates decreased in year 3 and beyond for both the q8w and the q4w groups. Results were similar for ER data (Table E2; available in this article's Online Repository at www.jaci-inpractice.org). No viral upper RTI exposure-adjusted ER data were available for COLUMBA. No parasitic infections were reported in MELTEMI or COLUMBA. The next most common nonserious AEs were bronchitis, asthma, and headaches, and rates were generally similar between MELTEMI and COLUMBA, except for headaches, which were somewhat higher in COLUMBA (28.5% [99 of 347]) than in MELTEMI (q8w 13.3% [30 of 226]; q4w 20.9% [46 of 220]; Table II). The ERs for these 3 nonserious AEs generally decreased over time in both MELTEMI q8w and q4w groups (Table E2). The most frequent nonserious cardiac AE was tachycardia (q8w 1.3% [3 of 226]; q4w 2.3% [5 of 220]).

In 5 nonserious AE types, the percentage of patient-reported events was roughly twice as high in COLUMBA as in MELTEMI. The 5 nonserious AEs were upper RTI, back pain, arthralgia, pain in the extremity, and RTIs; COLUMBA (n ¼ 347) 23.3% (81), 18.2% (63), 16.7% (58), 2.7% (6), and 11% (38), respectively; MELTEMI (n ¼ 226) q8w 8.0% (18), 7.1% (16), 6.6% (15), 3.5% (8), and 2.7% (6), respectively; and MELTEMI (n ¼ 220) q4w 12.3% (27), 7.3% (16), 6.4% (14), 2.7% (6), and 1.8% (4), respectively (Table II). The MELTEMI year-by-year events show 0 events occurred after 3 years of time in the study, except for 4 reports of back pain, 1 report of RTI in the q8w group, and 1 report of upper RTI in the q4w group (Table III). It is noteworthy that substantially fewer patients continued in the MELTEMI trial after year 3 as evidenced by the n and level of treatment exposure in year > 3.

Injection site reactions occurred in 12.1% (42 of 347) of patients in COLUMBA and in 4.5% (10 of 220) and 2.2% (5 of 226) of patients in the MELTEMI q4w and q8w groups, respectively (Table II). Injection site reaction ERs for COLUMBA was 107 per 1,000 patient-years and in MELTEMI was 53.55 and 11.29 per 1,000 patient-years in the q4w and q8w groups, respectively. The MELTEMI year-by-year event rates were highest in the q4w group in year 2 with 22 events involving 7 patients for an ER of 106.30 per 1,000 patient-years; then it dropped in year 3 with 6 events involving 2 patients for an ER of 39.94 per 1,000 patient-years (Table E2).

Serious adverse events

The majority of SAEs for both MELTEMI and COLUMBA occurred in only 1 to 2 patients. The exception is with asthma-related SAEs, which were the most common SAE in both MELTEMI q4w 8.6% (19 of 220), MELTEMI q8w 8.0% (18 of 226), and COLUMBA 9.5% (33 of 347; Table IV). The SAE ERs were comparable across all 3 groups. In MELTEMI, the ER for the q8w group was 35.1 events per 1,000 patient-years, and for the q4w group, 40.8 events per 1,000 patient-years. In COLUMBA, the exposure-adjusted ER was 39 events per 1,000 patient-years (Table E3; available in this article's Online Repository at www.jaci-inpractice.org).

TABLE V. MELTEMI SAE year by year (in ≥ 2 patients)†**

Preferred terms, n (%)	Borra q8w						Borra q4w					
	Overall	Pw	E1	E2	E3	E>3	Overall	Pw	E1	E2	E3	E>3
Total patients	226	159	226	223	199	105	220	150	220	215	198	111
Exposure (y)	797.03 [‡]	146.09 [‡]	226.55 [‡]	213.14 [‡]	144.69 [‡]	67.55 [‡]	784.28 [‡]	134.96 [‡]	219.20 [‡]	206.97 [‡]	150.22 [‡]	72.93 [‡]
Asthma	18 (8.0)	6 (3.8)	6 (2.7)	7 (3.1)	4 (2.0)	1 (1.0)	19 (8.6)	10 (6.7)	7 (3.2)	5 (2.3)	5 (2.5)	0
Pneumonia	2 (0.9)	0	2 (0.9)	0	0	0	—	—	—	—	—	—
Chronic sinusitis	2 (0.9)	0	1 (0.4)	1 (0.4)	0	0	—	—	—	—	—	—
Limb injury	2 (0.9)	0	1 (0.4)	1 (0.4)	0	0	—	—	—	—	—	—
Nasal polyps	2 (0.9)	0	1 (0.4)	0	1 (0.5)	0	—	—	—	—	—	—
Cellulitis	1 (0.4)	0	0	0	1 (0.5)	0	—	—	—	—	—	—
Cataract	1 (0.4)	0	0	1 (0.4)	0	0	2 (0.9)	1 (0.7)	0	0	1 (0.5)	0
Influenza	1 (0.4)	1 (0.6)	0	0	0	0	2 (0.9)	0	1 (0.5)	2 (0.9)	0	0
Noncardiac chest pain	1 (0.4)	0	0	1 (0.4)	0	0	2 (0.9)	0	1 (0.5)	1 (0.5)	0	0
Sciatica	1 (0.4)	0	0	1 (0.4)	0	0	—	—	—	—	—	—
Asthenia	—	—	—	—	—	—	2 (0.9)	0	0	1 (0.5)	1 (0.5)	0
Lower limb fracture	—	—	—	—	—	—	2 (0.9)	0	0	1 (0.5)	1 (0.5)	0
Death	—	—	—	—	—	—	1 (0.5)	0	1 (0.5)	0	0	0

*SAEs were aligned with the MELTEMI patient AEs in Table IV.

†For this analysis, patients with multiple safety events in the same category and period were tabulated only once.

‡MedDRA version 20.0.

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

||The death in MELTEMI was attributed to influenza and did not occur during the on-treatment period.

The MELTEMI q8w group asthma-related SAEs were consistent for years 1 and 2, followed by a decrease with only 1 event after 3 years of treatment. The MELTEMI q4w group had a gradual decline between years 1 and 2, with no additional serious asthma events reported after year 3 (Table V). The SAE asthma year-by-year MELTEMI ERs were highest during year 3 for the q8w group (41.47 per 1,000 patient-years) and highest in year 1 for the q4w group (45.6 per 1,000 patient-years; Table E4; available in this article's Online Repository at www.jaci-inpractice.org). The second most common SAE, pneumonia, was reported in 6 patients in COLUMBA; pneumonia was reported in 2 patients in the MELTEMI q8w group and in no patients in the q4w group. There were no major cardiac AEs.

Malignancies

Eight malignancies were reported in patients from MELTEMI, 4 in each treatment group, and 6 malignancies were reported in patients from COLUMBA. The 4 malignancies in the MELTEMI q8w group consisted of 1 case each of basal cell carcinoma, papillary thyroid cancer, prostate cancer, and transitional cell carcinoma: 1 case was reported for each of the first 3 years of the study, and 1 case was reported in the time after year 3. The 4 malignancies in the MELTEMI q4w group consisted of 2 cases of basal cell carcinoma and 1 case each of adenocarcinoma of the colon and transitional cell carcinoma. One case was reported in year 1, 2 cases in year 2, and 1 case after 3 years. The 6 malignancies in COLUMBA included 3 patients with basal cell carcinoma, 2 patients with prostate cancer, and 1 patient with breast cancer.

DISCUSSION

MELTEMI and COLUMBA have demonstrated the longterm safety and tolerability of benralizumab and mepolizumab in patients with SEA.²⁵⁻³⁰ This side-by-side analysis of METLEMI and COLUMBA reinforces the safety of targeting EOS as a treatment strategy for patients with SEA. Furthermore, the findings demonstrate that the safety profile of partial EOS reduction with mepolizumab is comparable with that of near-complete EOS depletion with benralizumab.

Overall, this comparative analysis shows similar rates of nonserious AEs and SAEs occurred during both extension studies. There were no parasitic infections reported in either study. The higher percentage of headaches, bronchitis, asthma, upper RTIs, back pain, arthralgia, pain in extremities, and RTIs in COLUMBA could be due to differences in reporting criteria and data collection methods. The increase in injection site reactions that occurred in the MELTEMI q4w group is most likely due to patients receiving benralizumab at twice the rate of the patients in the q8w rate; nevertheless, the percentages of patients experiencing an injection site reaction in MELTEMI were less than in COLUMBA.

Asthma-related events were the leading type of SAE for both studies across all 3 treatment groups. This result was not unexpected, given the challenge to control SEA in this patient population. It is also the basis for treating these patients with benralizumab and mepolizumab.^{8,38} Results from the 4 predecessor studies, SIROCCO, CALIMA, ZONDA, and DREAM, have demonstrated that treating patients with SEA with benralizumab or mepolizumab does lead to reductions in asthma exacerbations.^{25-27, 29, 31} Indeed, more than half of the patients in MELTEMI achieved 0 exacerbations, and more than a third of the patients in COLUMBA achieved 0 exacerbations.^{28,30} Finally, malignancies and deaths were reported in both studies; the numbers of malignancies were low and similar across both studies; and the deaths either occurred outside the on-treatment period²⁸ or were determined not to be causally related to the study drug.^{20,30}

Strengths

This comparison of safety metrics between the COLUMBA and the MELTEMI studies was possible because the MELTEMI study results were reanalyzed using MedDRA version 20.0 and an updated definition for safety ERs (overall as well as year-by-year event rates), both of which match the results reported from the COLUMBA study. Furthermore, both studies have similar patient populations that were followed for similar amount of time on treatments, with the approved dosing for patients with SEA, plus an additional arm that evaluated more frequent dosing with benralizumab (q4w) in MELTEMI. Another strength was access to COLUMBA data through ClinicalTrials.gov and direct access to MELTEMI data. The ability to obtain COLUMBA data from ClinicalTrials.gov enabled us to perform a more direct comparison of RTIs. Another strength of this study was the inclusion of safety data for the benralizumab q4w arm, which were included to lend insights on other eosinophilic diseases, where higher exposure than the approved SEA dose may be an effective treatment.³⁹

Limitations

The different years and lengths of time in which patients received these treatments (eg, the off-treatment period between the DREAM study and initiation of treatment in COLUMBA) could have contributed to differences in the results. COLUMBA was the first study, which may have made safety reporting more vigilant. Patients who participated in the mepolizumab OCS reduction study (SIRIUS, NCT01691508)⁴⁰ were not included in COLUMBA, whereas MELTEMI enrolled patients from ZONDA, an OCS reduction study with benralizumab. Conversely, the population in the MELTEMI integrated study period consisted of patients from 1 of 3 randomized placebo-controlled trials, who then participated in the BORA double-blind extension and the MELTEMI open-label extension study, which may also influence safety reporting. Results from the COLUMBA analysis did not include data from patients' time on-treatment in the DREAM predecessor study. Comparing 2 different studies with separate patient populations and slightly different study designs offers an indirect comparison of safety events, which resulted in the numeric comparisons we provided. However, indirect comparisons have inherent limitations owing to differences in the methods and patient populations when capturing and reporting safety data.⁴¹ The use of 2 different data sources for the COLUMBA study^{30,37} also could have introduced inconsistencies in the data. A recall bias is also possible given that patients used worksheets to track AEs in COLUMBA, whereas patients in MELTEMI recalled their AEs during their visits. The different data sources and potential recall bias could explain some of the differences in the nonserious AE results. Finally, the lack of a head-to-head randomized control trial data limited our ability to test these assumptions fully.⁴¹

In conclusion, this comparative analysis of safety in MELTEMI and COLUMBA demonstrated that benralizumab and mepolizumab have generally similar safety and tolerability, despite differing mechanisms of action. This side-by-side comparison reinforces the safety of targeting EOS in patients with SEA. The rates of nonserious AEs, SAEs, and malignancies in patients treated with benralizumab generally remained stable or decreased over subsequent years. Data to date suggest that near-complete depletion of EOS does not present an increased safety risk compared with partial EOS reductions, which is particularly relevant considering the safety risks of alternative therapies (eg, OCS). Further studies are needed to continue evaluating the long-term safety of these biologic agents.

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