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ORIGINAL RESEARCH

Benralizumab Outcomes in Patients with Severe Eosinophilic Asthma Treated in Real-Life Settings: Results of the BREEZE Study in 5 Countries From Central Eastern Europe and Baltics

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Purpose: To describe real-world clinical characteristics, treatment patterns and outcomes of severe eosinophilic asthma (SEA) patients initiated on benralizumab after treatment authorization in Central Eastern Europe and Baltic Area.

Patients and Methods: BREEZE was a retrospective, medical chart review with a pre-post design conducted in 42 clinical centers from Bulgaria, Czech Republic, Hungary, Lithuania and Romania. Eligibility included diagnosis of SEA and at least one dose of benralizumab administered in real-life settings. Descriptive statistics were used in the full analysis set and key subgroups stratified by blood eosinophils (bEOS) number, maintenance oral corticosteroids (mOCS) use and prior biologics exposure and included calculation of the annualized exacerbation rate (AER) at baseline, and weeks (W) 16 and 48.

Results: Of 381 patients included, 66% were female with overall mean age 56 ±12 years at benralizumab start. At baseline: median bEOS 580 cells/μL (74% bEOS>400), forced expiratory volume in 1 second (FEV_1) 1660 mL, mOCS use in 25% of patients (10 mg/day prednisone equivalent, 68% >5 mg/day), AER 3.05 (95% CI 2.9–3.2), and poorly controlled asthma (Asthma Control Test [ACT] <16) in 63% of patients. Median duration of exposure to benralizumab was 11.5 (95% CI 7.7–12.3) months, and discontinuation rate was 1.3% (95% CI 0.4%–3.0%). Median bEOS decreased to 0 at W16 and maintained thereafter; FEV_1 increases of +240 mL at W16 and +335 mL at W48 were reported ($p < 0.001$ for both). Overall relative reduction in AER at W16 and W48 was 92% and 93%, respectively, and 82–94% across key subgroups. mOCS dose reduction was 50%, and proportion of patients requiring >5 mg/day decreased constantly (25% at W16, 28% at W48). ACT scores increased from W16 to W56 ($p < 0.001$ for all).

Conclusion: Our findings indicate clinically meaningful benefits of benralizumab across multiple geographies and various subgroups of patients with SEA.

Keywords: real-world, biological therapy, exacerbation rate, eosinophils, maintenance oral corticosteroids, asthma control

Introduction

The prevalence of severe asthma was reported to be up to 10% among individuals with asthma.[1] Severe asthma is heterogenous and eosinophilic inflammation characterizes one phenotype, called severe eosinophilic asthma (SEA).[2,3] SEA is known to be associated with a higher risk of severe exacerbations and greater burden on healthcare resources.[4,5]

Cells of the innate immune system, eosinophils accumulate in lungs and upper respiratory pathways, have a pro-inflammatory role and an immunomodulatory function, and act as antigen presenting cells.[6–8] Interleukin-5 (IL-5) is a cytokine and modulator of the lifecycle of eosinophils, with IL-5 receptors (IL-5R) being highly expressed on their surface.[4,7] The IL-5 pathway became the focus of multiple investigations, leading to the development and approval of

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anti-IL-5/IL-5R treatments that have improved asthma symptoms and lung function, and significantly reduced the number of exacerbations.[9–15] Mepolizumab and reslizumab are anti-IL5 antibodies that bind circulating IL-5,[15] while benralizumab has a different mechanism of action: it binds the subunit alpha of the IL-5R and activates the antibody-dependent cell-mediated cytotoxicity.[4,16] Recent research indicates that immunological changes induced by benralizumab are more complex, extending to natural killer cells and may partly explain its steroid-sparing effect.[17]

The efficacy of benralizumab in treating patients with SEA has been demonstrated by several Phase III randomized clinical trials (RCTs): CALIMA and SIROCCO showed significant reductions in exacerbation rates, improvements in lung function, asthma control and quality of life, and ZONDA showed significant reductions in daily doses of maintenance oral corticosteroids (mOCS) and exacerbation rates.[10,11,18] Long-term results were further evaluated in the double-blind extension phase of these studies for up to 2 years (BORA), sustaining the benefits of initial phase III studies.[19]

To what extent the benefits reported in the RCTs translate into real-life settings is crucial for clinical decisions, and proving the effectiveness of benralizumab in patients with SEA in different geographies becomes more relevant for multiple stakeholders. To cover this knowledge gap, the BREEZE study was conducted in 5 countries from Central Eastern Europe and Baltic Area (CEE-BA), as part of the larger real-world program XALOC.[8,20] The primary objectives of the BREEZE study were to describe baseline characteristics of the patients with SEA initiated on benralizumab in routine clinical practice and treatment patterns at baseline and after benralizumab start in the study population. Other study objectives included assessment of the real-world clinical outcomes and changes in biomarkers and lung function observed during treatment with benralizumab.

Methods

Study Design and Patients

BREEZE was a single-arm, retrospective observational, multicenter, multi-country, physician-led medical chart review conducted between July 2022 and January 2023 in 42 public and private hospitals and outpatient practices with experience in SEA management and use of biological therapy from Bulgaria, Czech Republic, Hungary, Lithuania, and Romania. The study had a pre-post design, where the index date was the day of the first injection of benralizumab, the pre-index period included the last 12 months before benralizumab initiation, and the post-index period (follow-up) covered up to 56 weeks since the first injection (maximum 9 doses of benralizumab). Per the approved label, the recommended dose of benralizumab is 30 mg by subcutaneous injection every 4 weeks for the first 3 doses, and every 8 weeks after the first 3 doses.[21] All other respiratory treatments for the SEA were administered according to routine clinical practice.

Eligibility required administration of at least one injection of benralizumab following local treatment authorization in adult patients with SEA (age at least 18 years). Administration of benralizumab or other biological products in the setting of a clinical trial was the only exclusion criterion. All eligible patients identified at site level could have been included in the study, irrespective if the treatment with benralizumab was ongoing or stopped at the time of study conduct. Except Bulgaria, written informed consent was required for inclusion in the study for all patients under the investigator's care at the time of study start. In Bulgaria, non-interventional studies involving retrospective data collection and processing of the medical information performed in an anonymized manner are allowed to be conducted with informed consent waiver, and the study was granted approval with this waiver by the Ethics Committee for Clinical Trials (Етична комисия по клинични изпитвания). In the other countries, a waiver for informed consent and data collection from medical charts of the eligible patients not anymore under investigator's care at the time of study start was requested in order to reduce the bias of the final study sample toward patients with longer follow-up, better outcomes and, thus, less representative for a more general patient sample. Study approvals were obtained from Ethics Committees in all other participating countries: the University Hospital Hradec Kralove Ethics Committee in Czech Republic, the Medical Research Council (Egészségügyi Tudományos Tanács ETT TUKEB) in Hungary, Lietuvos bioetikos komitetas in Lithuania, and National BioEthics Committee for Medicines and Medical Devices (Comisia Națională de Bioetică pentru Medicamente și Dispozitive Medicale) in Romania. The study was designed and conducted in accordance with the Declaration of Helsinki, the Good Pharmacoepidemiology Practices guidelines of the International Society for Pharmacoepidemiology, as well as local regulations.

Data Collection

Data collected at baseline (index and pre-index period) included demographic, disease and treatment characteristics, and healthcare resource utilization in the last 12 months prior to benralizumab start. Medical history included key comorbidities related to asthma and chronic use of oral corticosteroids (OCS) and coronavirus disease 2019 (COVID-19). Disease characteristics included exacerbations by categories, laboratory (blood eosinophils [bEOS], fractional exhaled nitric oxide [FeNO], total immunoglobulin E [Ig E] level in peripheral blood) and spirometry parameters (forced expiratory volume in 1 second [FEV_1]) and asthma control test (ACT) scores, as available and performed in routine practice. In this study, an asthma exacerbation was defined as a worsening of asthma that led to one of the following: (1) use of systemic corticosteroids for 3 days or more or a temporary increase in a stable, background dosage of OCS; (2) an emergency department (ED) or urgent care visit (<24 hours [h]) due to asthma that required systemic corticosteroids; or (3) an inpatient admission to hospital (≥24 h) due to asthma. Healthcare resource utilization included unscheduled visits to general practitioners and specialists, ED visits, and hospitalizations. Type and duration of asthma treatments were collected (including prior biologics use).

Data collected in the post-index period included information on benralizumab (duration, discontinuation and reason for discontinuation) and concomitant respiratory treatments, asthma exacerbations, COVID-19 infection, healthcare resource utilization, same laboratory and spirometry parameters as collected at baseline, and ACT scores, if available – all parameters at each injection of benralizumab. The maximum number of benralizumab doses received by patients during the study period of interest was 9. For each patient, data collection in the post-index period was performed until the last dose of benralizumab received within the timeframe of interest for the study (up to 56 weeks [+ a window of maximum 1 week] since benralizumab initiation), according to the number of actual benralizumab administrations received in real-life practice.

All data were collected by participating study physicians from medical charts and entered into a password-protected, web-based electronic data capture system.

Statistical methods

The BREEZE study had no predefined hypothesis; therefore, no sample size was formally calculated. All analyses are descriptive. The target number of patients in each country was established based on preliminary feasibilities with sites experienced in the management of SEA patients, considering the time of benralizumab approval and/or reimbursement at study start. Data were analyzed based on observed cases only. All eligible patients who met all inclusion criteria and did not meet the exclusion criterion were included in the full analysis set (FAS). Subgroups stratified by bEOS count (threshold 300 cells/μL), baseline chronic OCS use and previous biologic therapy were explored, using the same type of analyses as for the primary dataset (FAS).

Exacerbation rates and 95% confidence intervals (95% CI) were calculated using generalized linear regression with a negative binomial distribution. The annual exacerbation rate (AER) was calculated at index, and weeks (W) 16 and 48 using the formula: (total number of exacerbations/total duration of follow-up in days) × 365.25. Timelines of interest for other measures included also W24 and W56, and results are reported based on number of cases with data available. Duration of baseline treatment, stratified by treatment type (mOCS, biologics) was calculated as time (days) between initiation of treatment and discontinuation; median duration of treatment (95% confidence intervals [CI]) was estimated using Kaplan–Meier method. Where treatment was ongoing or discontinuation has not been recorded, censoring was applied using date of data collection. An exploratory analysis to describe mean changes from baseline for blood eosinophils, FeNO level, total IgE, FEV_1, ACT scores and mOCS use was also conducted. Statistical significance of change from baseline/index date were tested using paired *t*-test or Wilcoxon signed ranks test. Adjustment for multiple comparisons included the application of Bonferroni correction, specifically for addressing changes from the index.

Statistical analysis was performed using *the R* language (https://www-r-project.org/) version RStudio 2023.03.1+446 "Cherry Blossom".

Results

Baseline Characteristics

The total number of patients included in the BREEZE study was 382. One patient met the exclusion criterion; thus, the FAS included 381 patients.

At index date, the mean age (SD) was 56.3 (12.2) years, and two-thirds of patients (71%) were <65 years. The ratio female:male was almost 2:1. At the time of asthma diagnosis, patients had a mean age (SD) of 39.4 (16.4) years. The mean (SD) duration of asthma at index date was 16.9 (13.6) years, with a median of 13 years. Most patients (88%) presented at least another asthma-related comorbidity (more frequently chronic rhinitis and allergies) and more than half (61%) had at least one OCS-related comorbidity (mainly hypertension) (Table 1). In key subgroups, the median age at asthma onset was lowest (29 years) in patients with previous biologic exposure, whereas in patients from the group with bEOS <300 cells/µL it was the highest (50 years). In patients with prior biologic exposure, a higher proportion of patients with allergies (82%) and chronic rhinitis (74%) and a higher median duration of asthma (21 years) were described (Table 1).

In the FAS, the median bEOS was 580 cells/µL (n=367), and 74% of patients had bEOS >400 cells/µL. FeNO and total IgE were available for considerably less patients (16% and 53%, respectively). Median FEV_1 at index was 1.66 L (n=353) (Table 2).

In the previous 12 months before benralizumab start, most patients (93%) reported at least one exacerbation; almost two-thirds of patients (65%) reported 3 or more exacerbations. Baseline AER was 3.05 (95% CI 2.9–3.2) (Table 2). Exacerbations requiring use of systemic corticosteroids for 3 days or more were most commonly reported in the year before benralizumab start (78% of patients).

ACT score could be retrieved from medical charts of 76% patients, with a median score of 11. For the majority of these patients, poorly controlled asthma was reported at baseline (84% of patients had ACT score <16) (Table 2).

mOCS use at baseline was reported for one-quarter of patients (n=96), with a median dose of 10 mg/day prednisone-equivalent, and two-thirds of these patients (68%) had a total dose >5 mg/day prednisone-equivalent. The median duration of mOCS at baseline was 45 (95% CI 51-NR) months. Overall, less than 10% of patients received prior biological therapy (n=34, among which 27 [79%] received omalizumab and 7 [21%] mepolizumab, respectively), with a median duration of 30 (95% CI 28–57) months. Almost all patients (99%) received a fixed dose combination of inhaled corticosteroid/long acting $beta_2$-agonist (ICS/LABA) before starting benralizumab. Most patients received a number of two (41%) or three (28%) combined other respiratory treatments. Although a high heterogeneity of treatment combinations was reported, mostly used treatments at baseline were ICS/LABA + long-acting muscarinic antagonists (LAMA) (18%), ICS/LABA + leukotriene receptor antagonists (LTRA) (16%) and ICS/LABA (13%). Across key subgroups, ICS/LABA use was similar as in FAS, but for the other concomitant respiratory treatments, more variations were described (Table 2).

Treatment Patterns During Benralizumab Treatment

Benralizumab Use

First administrations of benralizumab in real-life settings upon reimbursement in participating countries for patients enrolled in this study were made in May 2018 (Lithuania). To note, in the BREEZE cohort, part of the benralizumab injections overlapped with COVID-19 pandemic in Europe, as 53% of patients started this biologic therapy in 2020 and 2021, and delays in administering the benralizumab injection were reported.

The median (IQR) duration of exposure to benralizumab was 11.5 (7.7, 12.3) months, and the median (IQR) number of actual benralizumab injections administered per patient at the time of inclusion in the study 8 (5–8). At the time of enrolment, 146 (38%) of patients have performed 8 injections, whereas 12 (3%) patients were no longer in treatment with benralizumab.

Overall, the treatment was discontinued by 5 patients due to lack of clinical efficacy (n=1, discontinuation occurred at W8), patient preference/convenience (n=2, 1 discontinuation at W16, and 1 at W32, respectively), and moving abroad (n=2, 1 discontinuation at W32, and 1 at W40, respectively). The rate of discontinuation in the first year of treatment in this cohort was 1.31% (95% CI 0.427–3.036).

mOCS Use

At index date, mOCS was still ongoing for 65 (17%) patients, with a median dose of 7.5 mg/day prednisone-equivalent, and more than half of patients used a total daily dose >5 mg/day. During benralizumab treatment, 13 (20%) patients using

Table 1 Patient Baseline Characteristics in the FAS and Key Subgroups: Socio-Demographics, Anthropometrics, Smoking and Medical History

Characteristics	FAS (N=381)	bEOS Subgroups		mOCS Subgroups		Previous Biologic Therapy	
		bEOS<300, n=35	bEOS≥300, n=332	mOCS at Baseline, n=96	No mOCS at Baseline, n=285	Biologic-Experienced, n=34	Biologic-Naïve, n=347
Age at index date, years							
Mean (SD)	56.3 (12.2)	59.9 (11.8)	55.6 (12.3)	55.9 (13.1)	56.4 (12.0)	51.7 (13.0)	56.7 (12.1)
Median (IQR)	57 (48–66)	63 (55–67)	56 (47–66)	58 (47.5–66)	57 (48–66)	54 (44–62)	58 (49–66)
Age at asthma onset, years							
Mean (SD)	39.4 (16.4)	43.2 (18.5)	38.9 (16.2)	40.7 (16.4)	39 (16.4)	30.6 (16.6)	40.3 (16.1)
Median (IQR)	40 (29–53)	50 (32–58.5)	40 (28–50)	41 (29.75–53.5)	40 (28–51)	29 (20.75–40)	41 (30–53)
Female patients, n (%)	252 (66.1)	28 (80.0)	214 (64.5)	64 (66.7)	188 (66.0)	23 (67.7)	229 (66.0%)
Time since asthma diagnosis at index date, years							
Mean (SD)	16.9 (13.6)	16.7 (14.8)	16.8 (13.5)	15.2 (13.5)	17.4 (13.6)	21.2 (12.9)	16.4 (13.6)
Median (IQR)	13 (6–25)	13 (4.5–25)	12.5 (6–24.25)	11 (5–23)	14 (6–26)	21 (11.25–26.5)	12 (6–24)
BMI, kg/m^2							
Number of patients	372	35	327	95	277	34	338
Mean (SD)	28.3 (6.0)	30.8 (6.1)	28.0 (6.0)	27.5 (5.5)	28.6 (6.2)	28.5 (8.3)	28.3 (5.8)
Patients with BMI>25 kg/m^2, n (%)	243 (65.3)	28 (80.0)	208 (63.6)	58 (61.1)	185 (66.8)	21 (61.8)	222 (65.7)
Smoking history, n (%)							
Current smoker	17 (4.5)	2 (5.7)	14 (4.2)	2 (2.1)	15 (5.3)	-	17 (4.9)
Former smoker	72 (18.9)	5 (14.3)	64 (19.3)	24 (25.0)	48 (16.8)	7 (20.6)	65 (18.7)
Never smoker	292 (76.6)	28 (80.0)	254 (76.5)	70 (72.9)	222 (77.9)	27 (79.4)	265 (76.4)
Asthma-related comorbidities, n (%)							
At least one comorbidity	334 (87.7)	33 (94.23)	291 (87.7)	88 (91.7)	246 (86.3)	33 (97.1)	301 (86.7)
Chronic rhinitis	219 (57.5)	17 (48.6)	195 (58.7)	51 (53.1)	168 (59.0)	25 (73.5)	194 (55.9)
Allergies	186 (48.8)	19 (54.3)	160 (48.2)	50 (52.1)	136 (47.7)	28 (82.4)	158 (45.5)
Nasal polyposis	131 (34.4)	9 (25.7)	118 (35.5)	32 (33.3)	99 (34.7)	17 (50.0)	114 (32.9)
Respiratory infections	121 (31.8)	16 (45.7)	104 (31.3)	33 (34.4)	88 (30.9)	10 (29.4)	111 (32.0)
Bronchiectasis	69 (18.1)	15 (42.9)	52 (15.7)	22 (22.9)	47 (16.5)	8 (23.5)	61 (17.6)

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Table 1 (Continued).

Characteristics	FAS (N=381)	bEOS Subgroups		mOCS Subgroups		Previous Biologic Therapy	
		bEOS<300, n=35	bEOS≥300, n=332	mOCS at Baseline, n=96	No mOCS at Baseline, n=285	Biologic-Experienced, n=34	Biologic-Naïve, n=347
OCS-related comorbidities, n (%)							
At least one comorbidity	232 (60.9)	29 (82.9)	193 (58.1)	68 (70.8)	164 (57.5)	20 (58.8)	212 (61.1)
Hypertension	169 (44.4)	23 (65.7)	138 (41.6)	42 (43.8)	127 (44.6)	12 (35.3)	157 (45.2)
Obesity/metabolic syndrome	94 (24.7)	14 (40.0)	78 (23.5)	24 (25.0)	70 (24.6)	10 (29.4)	84 (24.2)
Osteoporosis/osteopenia	39 (10.2)	4 (11.4)	34 (10.2)	19 (19.8)	20 (7.0)	7 (20.6)	32 (9.2)
COVID-19, n (%)	78 (20.5)	8 (22.9)	68 (20.5)	16 (16.7)	62 (21.8)	9 (26.5)	69 (19.9)
COVID-19 leading to hospitalization, n (%)	11 (2.9)	1 (2.3)	9 (2.7)	4 (4.2)	7 (2.5)	1 (2.9)	10 (2.9)

Abbreviations: bEOS, blood eosinophils; BMI, body mass index; FAS, full analysis set; ICS, inhaled corticosteroids; IQR, interquartile range; mOCS, maintenance oral corticosteroids; SD, standard deviation.

Table 2 Patient Baseline Characteristics in the FAS and Key Subgroups: Laboratory Parameters, Asthma Control, Healthcare Resource Utilization and Treatments

Characteristics	FAS (N=381)	bEOS Subgroups		mOCS Subgroups		Previous Biologic Therapy	
		bEOS<300, n=35	bEOS≥300, n=332	mOCS at Baseline, n=96	No mOCS at Baseline, n=285	Biologic-Experienced, n=34	Biologic-Naïve, n=347
bEOS count, cells/μL							
Number of patients	367	35	332	95	272	34	333
Median (IQR)	580 (380–900)	160 (115–200)	615 (410–920)	540 (365–875)	600 (397.5–900)	493 (400–692.5)	600 (380–910)
bEOS≥400 cells/μL, n (%)	270 (73.6)	–	270 (81.3)	66 (69.5)	204 (75.0)	26 (76.5)	244 (73.3)
FeNO, ppb							
Number of patients	61	10	51	26	35	8	53
Median (IQR)	42 (20–76)	30.5 (14.75–51.1)	47 (20.5–76.5)	42.5 (23.25–98.5)	40 (17–65)	25.5 (25.5–43.75)	45 (20–77)
Total IgE, IU/L							
Number of patients	202	26	173	66	136	22	180
Median (IQR)	140.5 (51.25–522.48)	72.1 (32.08–355.62)	147.4 (61.4–543)	101.43 (36.33–541.5)	154 (62.15–474.48)	282.5 (131.5–595.6)	130.4 (44–474.48)
Index FEV_1, L							
Number of patients	273	26	244	68	205	27	246
Median (IQR)	1.66 (1.17–2.14)	1.62 (1.41–2.04)	1.68 (1.15–2.14)	1.61 (1.1–2)	1.68 (1.18–2.22)	1.6 (1.11–1.9)	1.68 (1.18–2.21)
ACT score							
Number of patients	288	20	256	79	209	30	258
Mean (SD)	11.6 (4.0)	13.1 (4.9)	11.3 (3.8)	11.9 (4.8)	11.4 (3.7)	13.6 (4.4)	11.3 (3.9)
ACT<16, n (%)	242 (84.0)	22 (73.3)	219 (85.6)	62 (78.5)	180 (86.1)	9 (63.3)	223 (86.4)
Exacerbations							
At least 1 exacerbation, n (%)	353 (92.7)	33 (94.3)	308 (92.8)	84 (87.5)	269 (94.4)	31 (91.2)	322 (92.8)
AER (95% CI)	3.05 (2.87–3.23)	2.69 (2.18–3.26)	3.11 (2.89–3.35)	3.17 (2.93–3.42)	2.7 (2.33–3.11)	3.03 (2.48–3.65)	3.05 (2.84–3.28)
Healthcare resource utilization (asthma-related), median number (IQR)							
ED visits	63 (16.5)	4 (11.4)	59 (17.8)	17 (17.7)	46 (16.1)	2 (5.9)	61 (17.6)
ICU hospitalizations	4 (1.1)	–	4 (1.2)	1 (1.0)	3 (1.1)	1 (2.9)	3 (0.9)
Non-ICU hospitalizations	115 (30.2)	8 (22.9)	103 (31.0)	26 (27.1)	89 (31.2)	13 (38.2)	102 (29.4)

(*Continued*)

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Table 2 (Continued).

Characteristics	FAS (N=381)	bEOS Subgroups		mOCS Subgroups		Previous Biologic Therapy	
		bEOS<300, n=35	bEOS≥300, n=332	mOCS at Baseline, n=96	No mOCS at Baseline, n=285	Biologic-Experienced, n=34	Biologic-Naïve, n=347
mOCS							
Patients with baseline mOCS, n (%)	96 (25.2)	16 (45.7)	79 (23.8)	96 (100)	–	14 (41.2)	82 (23.6)
Median dose prednisone equivalent, mg/day	10 (5–20)	11.25 (5–20)	10 (5–20)	10 (5–20)	–	5 (5–7.5)	10 (5–20)
Patients with >5 mg/day[a], n (%)	65 (67.7)	6 (37.5)	25 (31.7)	65 (67.7)	–	8 (57.1)	23 (28.1)
Other respiratory treatments, n (%)							
Combined ICS/LABA	377 (99.0)	35 (100)	328 (98.8)	95 (99)	282 (99)	34 (100)	343 (99)
LAMA	204 (53.5)	14 (40)	185 (55.7)	60 (62.5)	144 (50.5)	25 (75.5)	179 (51.6)
LTRA	177 (46.5)	12 (34.3)	160 (48.2)	42 (43.8)	135 (47.4)	21 (61.8)	156 (45.0)
Theophylline	53 (13.9)	6 (17.1)	43 (13.0)	22 (22.9)	31 (10.9)	7 (20.6)	46 (13.3)
Previous biologic therapy[b], n (%)	34 (8.9)	4 (11.4)	30 (9.0)	14 (14.6)	20 (7.0)	34 (100)	–

Notes: [a]Reported within the group of patients with OCS use at baseline; [b]In the last year before starting benralizumab, 31 patients had received biological therapy. In other 3 patients, biological therapy was administered before benralizumab start, but it was stopped at least 1 year before starting benralizumab. The subgroup of biologic-experienced patients includes all patients with previous exposure to benralizumab (n=34).

Abbreviations: AER, annualized exacerbation rate; bEOS, blood eosinophils; ED, emergency department; FAS, full analysis set; ICS, inhaled corticosteroids; ICU, intensive care unit; IQR, interquartile range; LABA, long-acting beta$_2$-agonists; LAMA, long-acting muscarinic agonists; LTRA, leukotriene receptor agonists; mOCS, maintenance oral corticosteroids; SD, standard deviation.

mOCS at index date discontinued the treatment, and multiple mOCS treatment changes were described from index date until W56 (Supplemental Figure 1), with dose decreases being constantly reported (ranging from 22% to 35% of patients at each time-point). The overall mOCS dose reduction from baseline was 50%, whereas from index date it was 33% and statistically significant across timepoints of interest (p<0.001 for W16 and W24 and p=0.004 for W48) (Figure 1A).

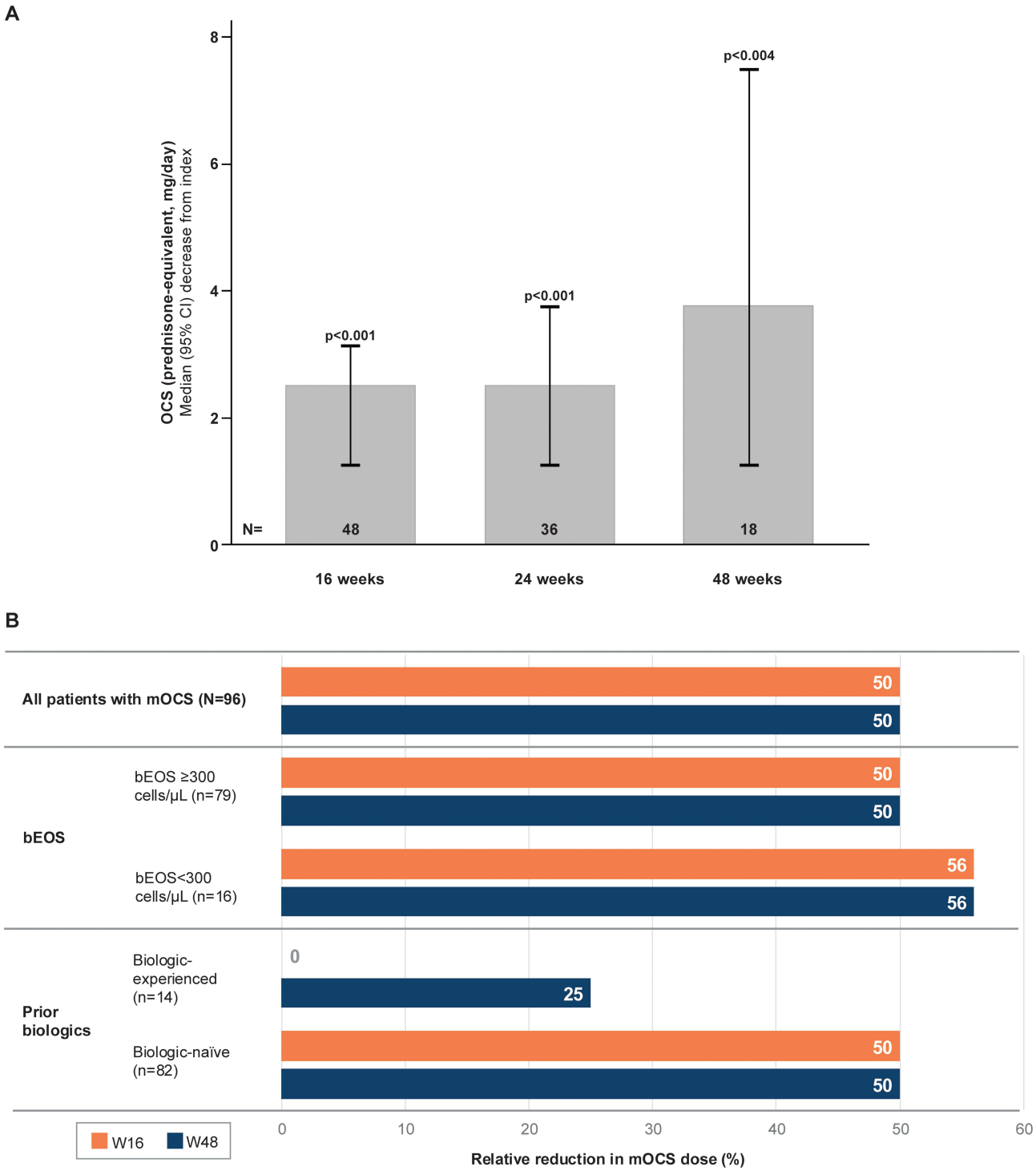

Figure 1 mOCS dose decreases during benralizumab treatment in FAS (panel (**A**) and relative dose reduction in mOCS at 16 and 48 weeks (expressed in %) in FAS and across key subgroups (panel (**B**).

Abbreviations: (b)EOS, (blood) eosinophils; CI, confidence interval; FAS, full analysis set; µL, microliter; mOCS, maintenance oral corticosteroids; W, week.

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Similar dose reductions were described in key subgroups (Figure 1B), except for patients with prior biologics, who had a lower median dose of mOCS at baseline and no decrease at W16 but 25% reduction at W48. In the group of patients with no mOCS at baseline, up to 2 patients received mOCS during benralizumab treatment.

Overall, the proportion of patients with total dose >5 mg/day of mOCS decreased constantly (54% at W4, 25% at W14, 28% at W48).

Clinical Outcomes During Treatment With Benralizumab

Exacerbations

AER reduced to 0.22 (95% CI 0.2–0.3) at W48. Overall relative reduction in AER at W16 and W48 was 92% and 93%, respectively, and 82–94% across key subgroups (Figure 2), with higher reductions in biologic-naïve patients, those with bEOS ≥300 cells/μL and irrespective of mOCS use at baseline.

At study level, 48/353 (13%) patients reporting at least 1 exacerbation at baseline presented exacerbations during benralizumab treatment (67 events overall), and out of the patients with no exacerbations reported at baseline, 3/28 (11%) presented exacerbations during benralizumab treatment (3 events). All exacerbations occurred during the period of interest for the study resolved without discontinuation of benralizumab.

For every category of exacerbation as defined in the study, a similar, marked degree of relative reduction was reported for the FAS throughout benralizumab administration (Supplemental Figure 2).

Laboratory Parameters, Lung Function and ACT Scores

During treatment with benralizumab, the median bEOS count decreased to a median of 0 (IQR 0–10) at W16 and was maintained to a median of 0 thereafter, at every subsequent visit ($p \leq 0.001$ for all) (Figure 3A). A general, consistent trend of FEV_1 improvement across visits was observed (at W48 median FEV_1 +335 mL, $p<0.001$) (Figure 3B). The improvements in median overall ACT scores were significant at each moment of evaluation, ranging from +9 points at W16 and W24, to +9.5 points at W48 ($p<0.001$ for all) (Figure 3C). Overall, the percentage of patients with asthma control (ACT>19) increased during benralizumab treatment, ranging from 50% to 68% at every timepoint of interest in patients with ACT performed at that injection visit. Around 10% of patients had a constant increase exceeding 3

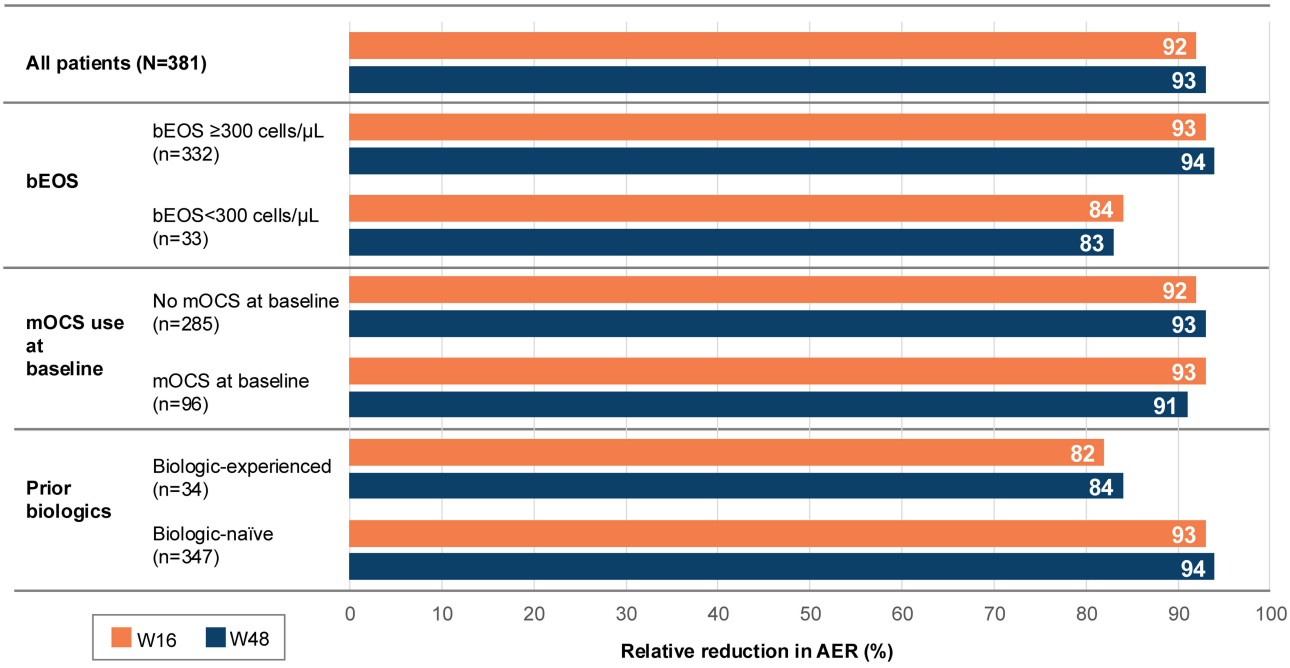

Figure 2 Relative reduction of AER at 16 and 48 weeks from baseline (expressed in %) in FAS and key subgroups.
Abbreviations: AER, annualized exacerbation rate; bEOS, blood eosinophils; FAS, full analysis set; μL, microliter; mOCS, maintenance oral corticosteroids; W, week.

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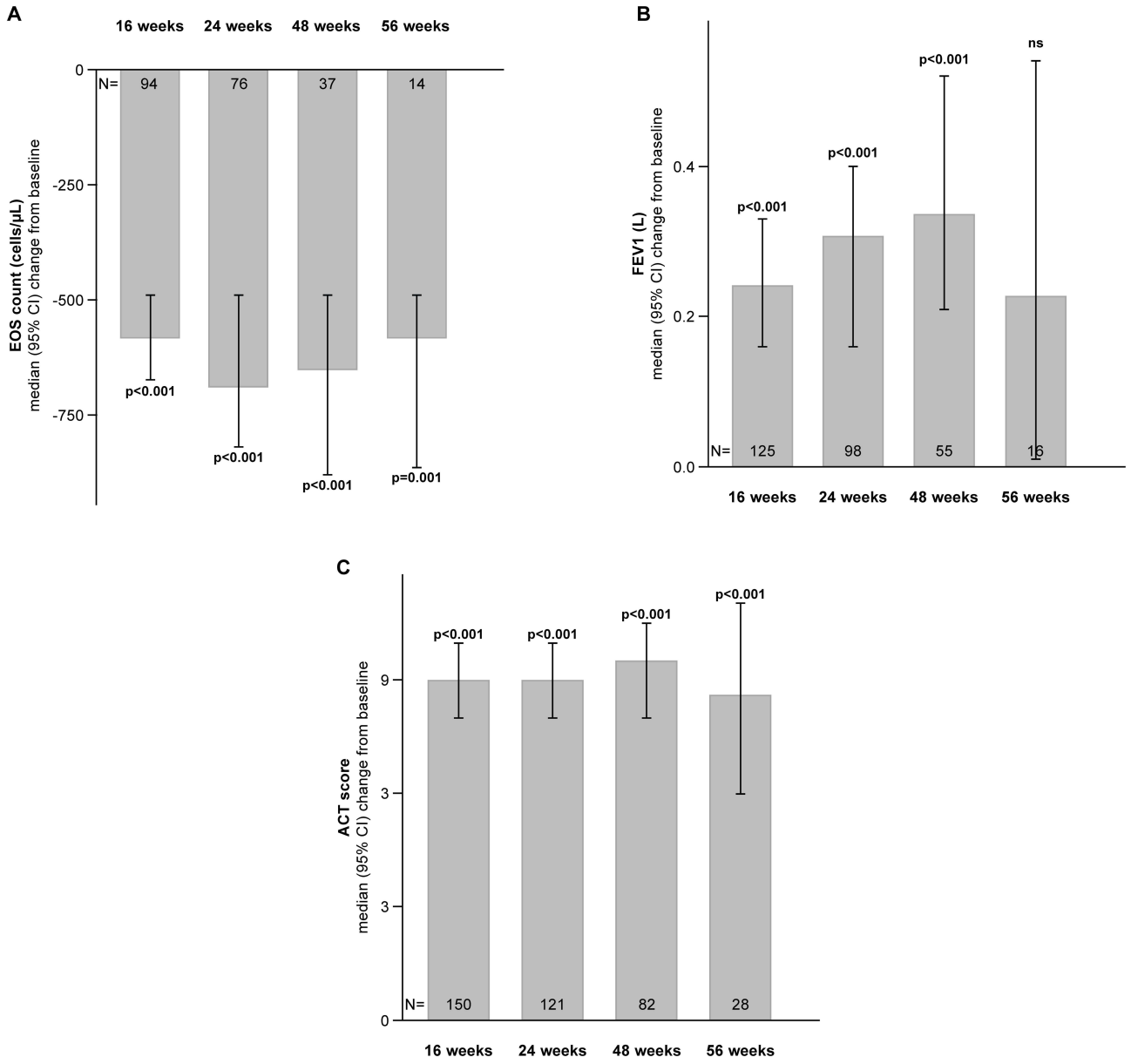

Figure 3 Changes from baseline in bEOS, lung function and asthma control during benralizumab treatment in FAS: bEOS (panel **A**), FEV1 (panel **B**) and ACT score panel (**C**).
Abbreviations: ACT, asthma control test; (b) EOS, (blood) eosinophils; CI, confidence interval; FAS, full analysis set; FEV1, forced expiratory volume in 1 second; (µ)L, microliter.

units (minimally clinically important difference [MCID]) at every timepoint of interest (13% at W16 and 10% at W48).

Similar trends of eosinophil depletion, consistent improvements in lung function and asthma control, as reported in the FAS were described in key subgroups, with some variations due to reducing number of patients over time in lower-sized subgroups (Supplemental Figures 3–5).

Discussion

The BREEZE study, which is part of the larger real-world program XALOC conducted in several European countries, describes the baseline characteristics of a large cohort of 381 patients initiated on benralizumab in real-life settings in 5 countries from the CEE-BA region. The findings support the effectiveness of benralizumab at multiple levels: reductions in exacerbation and mOCS use and improvements in lung function and asthma control. To our knowledge, BREEZE is

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the first non-interventional study conducted in this patient population from CEE-BA countries, building the first real-world evidence in this region on the characteristics and outcomes of SEA patients initiated on this IL-5R biological therapy.

The results of the BREEZE study are in line with the published results of pooled and individual cohort studies from the XALOC program,[20] namely ANANKE (Italy, n=205),[22] BPAP (United Kingdom, n=208),[8] ORBE-II (Spain, n=204),[23] BETREAT (Portugal, n=74),[24] POWER (Canada, n=131),[25] but also other non-interventional studies like PROMISE in Belgium (n=73)[26] and ZEPHYR 2 in United States (n=429 patients in the eosinophil group)[27] (Supplemental Table 1). Data gathered from these real-world studies performed in various geographies support the therapeutic effects of benralizumab in SEA with sustained improvement over time of clinical outcomes. A recently published pragmatic trial showed that eosinophil depletion led to the attenuation of the airway hyperresponsiveness in patients with severe uncontrolled asthma.[28] Corroborated with the results of other recent real-life analyses on benralizumab use in SEA patient population indicating longer term beneficial effects (up to 3 years), the new data underscore its potential utility as disease-modifying treatment.[29]

To improve asthma-related symptoms and prevent exacerbations, mOCS treatment continues to be used in patients with SEA, despite the known side effect profile. In our cohort, 1 in 4 patients was using mOCS at baseline. Even though some discontinuations were reported within the year before benralizumab start, around 1 in 5 patients was still receiving concomitant OCS when benralizumab was initiated. This is a lower percentage of patients with regular OCS at the start of benralizumab as compared to the Italian and Spanish XALOC cohorts, although baseline reports are similar.[22,23] The difference may reside in the more granular calculations performed in the BREEZE study, with the reference point (index date) being more accurate in describing the changes made during benralizumab treatment, from the first injection. Also, a lower percentage of patients (20%) was reported as discontinuing mOCS as compared to ANANKE (43%) and ORBE-II (53%) cohorts or PROMISE (78%),[22,23,26] but the funneling approach used in the BREEZE study may be one limitation, lacking a pre-defined and unitary minimal period of benralizumab use for the entire cohort. Nevertheless, the OCS dose reductions over time were significant and the proportion of patients requiring lower doses of mOCS increased during the biological therapy use, adding thus to other real-life studies that showed meaningful changes in OCS intake during treatment with benralizumab.[18,27,30,31]

In this context, it is relevant to underline the entire spectrum of effectiveness of benralizumab over time on exacerbation rate, bEOS level, lung function, asthma control and exacerbations in this study, comparable to the other real-world cohorts.[20,22,24,26,29–31] The exacerbation rate decreased by more than 90%, from an initial AER of 3.05 to 0.24 at 16 weeks and maintained over time (0.22 at 48 weeks). All exacerbations occurred during the study resolved without discontinuation of benralizumab. Despite a lower number of patients with available blood tests during the study, a fact which might be owed to variability in local practice and restrictions due to the COVID-19 pandemic, we observed complete bEOS depletion. Despite initial concerns over risks associated with immune-suppression due to this effect, the pooled analyses from RCTs, including long-term extension MELTEMI (up to 5 years), post-marketing surveillance and/or studies, showed the good tolerability profile and no change in the risk-benefit profile.[7,32,33] In our cohort, significant improvements in lung function were described (FEV_1 increase of +240 mL after 16 weeks of treatment and +335 mL at 48 weeks, $p < 0.001$ for both). Of note, these values are in line with other XALOC studies results[22,23] and exceed the biological variability of FEV_1 for severe asthma,[34] a direction that may be worth exploring in more depth in future studies. Asthma control increased significantly over time, with a median difference in ACT score of 9 units (at 16, 24 and 48 weeks, $p<0.001$ for all), with the proportion of patients with ACT score of at least 20 increasing to almost two-thirds of patients evaluated at each visit as compared to baseline, when for the majority of patients uncontrolled asthma was reported (ACT<16 in 84% of patients). Similar trends of reductions in the exacerbation rate, depletion of eosinophils, and improvements in lung function and asthma control were observed in key subgroups, although the data were more heterogenous due to lower sample sizes. All these results support the early and durable response to benralizumab treatment in multiple patients' profiles, which ultimately translates into improved outcomes for a broader category of patients. Long-term benefits in patients receiving benralizumab up to 5 years have been shown in the extensions of RCTs,[32] which are recently complemented by real-world evidence.[29] Consequently, a growing interest in defining clinical remission in asthma and more specifically clinical remission in severe asthma with biologic therapy can be observed.[35–38]

Although there is no unitary consensus, clinical remission is a composite measure of no exacerbations, no OCS use, no symptoms and lung function stabilization or improvement. In a post-hoc pooled analysis from RCTs data, clinical remission under benralizumab was reached by 15–23% of patients after 6 months and 15% after 12 months.[39] The results translated in real-life settings and an integrated analysis from the XALOC-1 program, including the patients from Canada, Italy, Spain and UK (n=797) showed that half of patients reached clinical remission after 12 months.[40] Other analyses showed percentages of 40% for no exacerbations and no mOCS use after more than 12 months since treatment start (ZEPHYR-4, n=2895),[41] 44% (ORBE-II, n=204)[23] at 1-year follow-up, and up to 84% for partial and clinical remission after 3 years in smaller size study (n=46).[29] These are encouraging results, which further stress the need of early identification of patients, established referral paths and treatments according to guidelines.

In the CEE-BA cohort, only a reduced percentage of patients (<10%) were biologic-experienced. Such finding is in line with the SHARP ERS study, indicating heterogeneity in the availability and use of biological therapies for severe asthma in Europe, with differences across countries.[42] Presumably, the use of biologics in severe asthma in CEE-BA increased over time. It is also important to note that this is a pooled data analysis, and national criteria for disease severity, benralizumab reimbursement conditions in terms of lung function, biomarker and exacerbation thresholds, and treatment guidelines in the countries participating in the BREEZE study are not similar. This may account for differences observed versus other cohorts, which included patients only at country level.

The rate of treatment discontinuations in the CEE-BA cohort was very low (1.31% [95% CI 0.427–3.036]), and lack of clinical efficacy was reported only in one case, the rest being situations of moving abroad or patient preference. Also, partly due to the overlap with the pandemic and local contexts related either to the availability of benralizumab treatment in the pharmacies from hospitals/outpatient clinics (described in Romania) or self-administration reports (as the case for Czech Republic), delays in performing injections were reported throughout routine visits. Delays in receiving biologic treatment doses have been reported in other analyses, but they have not been correlated with outcomes,[43] a direction that may be worth exploring in the future.

The real-world nature of this study is both an advantage and a limitation. Collecting data in a comprehensive, standardized manner across multiple sites and countries, allowed building solid real-world evidence coming from various healthcare settings in the region and provided meaningful insights into the characteristics of the SEA patients initiated on benralizumab and their clinical outcomes under this biological therapy. Due to the observational/non-interventional nature of the study and the inherent characteristics of such design, findings in the BREEZE study may be subject to selection bias, limitations in availability of biological and spirometry data, and variability in local treatment practices and guidelines, which may have impacted the generalizability of our findings. In addition, the generalizability of our results to other patient populations or comparability to other studies is restricted due to the lack of a comparison arm.

The treatment with benralizumab was initiated for many patients during the COVID-19 pandemic, which disrupted the continuity of care, impacted the healthcare systems worldwide and restricted the patient's evaluation to a minimum, especially in this high-risk patient population.[44] This has also been reported in our study, where the low number of laboratory and spirometry evaluations may hinder direct comparisons with other studies. However, reductions in exacerbations have been reported during the pandemic,[45] and our results might have been impacted to some extent by this phenomenon.

Other limitations include the lack of a pre-defined follow-up period, which limited the evaluation of outcomes in a homogenous manner and the funneling approach, which led to a constant decrease in the number of patients consistently evaluated at all time points. Lastly, the study had a secondary data collection design and no safety objective; therefore, only spontaneous reports consisting in exacerbations (n=7) were reported via local pharmacovigilance system. However, no exacerbation led to discontinuation of benralizumab. For all that and considering the lack of regional/national treatment or disease registries in participating countries, we consider that our findings are relevant for the medical community and decision-makers and provide an important knowledge base to improve asthma care and management in the region.

Conclusion

The BREEZE study describes the baseline characteristics of a large cohort of 381 patients receiving benralizumab for SEA in real-life settings in 5 countries from CEE-BA. The findings support the effectiveness of benralizumab at multiple levels: reductions in exacerbations and of the maintenance OCS use and improvements in lung function and asthma control. Same findings as in the full dataset applied to subgroups stratified by blood eosinophil count, OCS use at baseline and previous biologic therapy. Thus, clinically meaningful benefits of benralizumab shown in randomized clinical studies translate into routine clinical practice across geographies and led to improved outcomes in different profiles of patients with SEA.

Abbreviations

ACT, asthma control test; AER, annualized exacerbation rate; (b)EOS, (blood) eosinophils; BMI, body mass index; CEE-BA, Central Eastern Europe and Baltic Area; CI, confidence intervals; COVID-19, coronavirus disease 2019; ED, emergency department; FAS, full analysis set; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; h, hours; ICS, inhaled corticosteroids; ICU, intensive care unit; IgE, immunoglobulin E; IL, interleukin; IL-5R, interleukin-5 receptors; IQR, interquartile range; LABA, long-acting $beta_2$-agonists; LAMA, long-acting muscarinic agonists; LTRA, leukotriene receptor agonists; mOCS, maintenance oral corticosteroids; (μ)L, (micro)liter; RCTs, randomized clinical trials; SEA, severe eosinophilic asthma; SD, standard deviation; W, week.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Ethics Approval and Informed Consent

The study protocol (protocol code D3250R00108 from 11-Apr-2022) was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) (or Ethics Committee [EC]) in each of the participating countries. Except Bulgaria, written informed consent was required for inclusion in the study for all patients under Investigator's care at the time of study start. In all the other cases and Bulgaria, an informed consent waiver for data collection was granted. The following IRB/EC has approved the study: in Bulgaria, the Ethics Committee for Clinical Trials (Етична комисия по клинични изпитвания) with approval number ЕККИ-СТ-0699 from 20-Jul-2022; in Czech Republic, the University Hospital Hradec Kralove Ethics Committee with approval number 2022-09-003 from 22-Sep-2022; in Hungary, the Medical Research Council (Egészségügyi Tudományos Tanács ETT TUKEB) with approval number BMEU/730-3/2022/EKU from 12-Jul-2022; in Lithuania, Lietuvos bioetikos komitetas with approval number L-22-06/3 from 01-Jul-2022; and in Romania, the National BioEthics Committee for Medicines and Medical Devices (Comisia Națională de Bioetică pentru Medicamente și Dispozitive Medicale) with approval number 16SNI from 30-Jun -2022.

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Disclosure

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