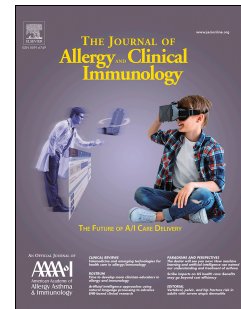


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Benralizumab for Adolescent Patients with Severe, Eosinophilic Asthma: Safety and Efficacy after Three Years of Treatment

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Conflicts of Interest

William W. Busse reports personal fees from 3M, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Circassia, Genentech, GlaxoSmithKline (GSK), ICON, Novartis, Roche, Sanofi, and Teva. Eugene R. Bleecker has performed clinical trials through his former employer, the Wake Forest School of Medicine, and his current employer, the University of Arizona, and has served as a paid

consultant for AstraZeneca, GSK, Novartis, Regeneron, and Sanofi Genzyme. J. Mark FitzGerald is an advisory board member for AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Sanofi Regeneron, and Teva, and has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Cephalon/Teva, and Novartis. Gary T. Ferguson reports grants and personal fees from Novartis, AstraZeneca, Pearl Therapeutics, and Sunovion, as well as grants from Forest and personal fees from GSK. Peter Barker, Laura Brooks, Richard F. Olsson, and Ubaldo J. Martin are employees of AstraZeneca. Mitchell Goldman was an AstraZeneca employee at the time the analyses were conducted.

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ABSTRACT

Background: Adults and adolescents with severe asthma who completed the 48-week SIROCCO and 56-week CALIMA Phase III benralizumab trials entered the safety extension study BORA (NCT02258542). The continued safety and efficacy of benralizumab in the first year of BORA (Year 2 of treatment) have been reported.

Objective: We report outcomes for adolescents during Years 2 and 3 of treatment in BORA.

Methods: Patients on benralizumab 30 mg every 4 weeks (Q4W) or every 8 weeks (Q8W) in SIROCCO/CALIMA continued their regimens in BORA (Q4W/Q4W and Q8W/Q8W, respectively), while placebo patients were re-randomized 1:1 to benralizumab (placebo/Q4W and placebo/Q8W, respectively) for 108 weeks. The primary outcome was safety; secondary outcomes included reduction of annual asthma exacerbation rate and change from baseline in prebronchodilator forced expiratory volume in 1 second (FEV₁).

Results: Adolescents (N=86) were treated with benralizumab Q8W (n=61) or Q4W (n=25); 69 completed treatment (Q8W: n=51; Q4W: n=18). For Q4W and Q8W regimens, respectively, rates of treatment-emergent adverse event (TEAEs) were 68% (17/25) and 74% (45/61), TEAEs leading to discontinuation were 4% (1/25) and 0% and, serious AEs were 8% (2/25) and 7% (4/61), and no deaths occurred. In efficacy analyses, 69% (42/61) Q8W patients were exacerbation-free (placebo/Q8W: 62% [18/29], Q8W/Q8W: 75% [24/32]). Mean $\pm$ SD change in FEV₁ at Week 108 vs. BORA baseline was 0.327 ± 0.452 L (placebo/Q8W) and 0.323 ± 0.558 L (Q8W/Q8W).

Conclusion: Safety and efficacy profiles in this 2-year extension study (up to 3 years of benralizumab treatment in adolescents), were consistent with previous findings.

CAPSULE SUMMARY

Treatment of asthma in adolescents with benralizumab 30 mg administered every 4 or 8 weeks is safe and effective for at least 3 years.

KEY MESSAGES

- Benralizumab 30 mg every 4 weeks or every 8 weeks for 3 years was safe and effective in treating asthma in 86 adolescent patients in the long-term BORA clinical trial.
- Most patients were free of asthma exacerbations and demonstrated improvements in asthma symptoms, while 6 (7.0%) experienced serious adverse events, 1 of which resulted in study discontinuation.

KEY WORDS

Asthma, benralizumab, biologics, eosinophils, immunomodulators, interleukin-5 receptor, open-label extension

ABBREVIATIONS

ACQ-6: Asthma Control Questionnaire, 6-question version

AE: Adverse event

AQLQ (S)+12: Standardized Asthma Quality of Life Questionnaire for 12 years and older

BEC: Blood eosinophil count

EU: European Union

FEV₁: Forced expiratory volume in 1 second

ICS: Inhaled corticosteroids

LABA: Long-acting β_2 -agonists

OCS: Oral corticosteroids

Q4W: Every 4 weeks

Q8W: Every 8 weeks

SC: Subcutaneous

TEAE: Treatment-emergent adverse event

INTRODUCTION

Asthma affects approximately 339 million people globally.¹ Patients with severe asthma are typically treated with high-dosage inhaled corticosteroids (ICS) combined with long-acting β_2 -agonists (LABA). Yet, asthma remains uncontrolled in many patients using these treatments, leading to recurrent exacerbations and hospitalizations.² In eosinophilic asthma, sputum and blood eosinophil counts are elevated and are associated with increased exacerbation rate and decreased lung function.^{3,4}

Interleukin 5 (IL-5) is a key cytokine in eosinophil maturation, activation, proliferation, and survival, and is under investigation as a target to decrease eosinophils in patients with eosinophilic asthma.⁵ Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity.^{6,7}

Two international, randomized, placebo-controlled, Phase III trials, SIROCCO (48 weeks) and CALIMA (56 weeks), evaluated the safety and efficacy of subcutaneous (SC) benralizumab 30 mg in patients aged 12–75 years with severe asthma uncontrolled by ICS/LABA therapy. Results demonstrated that, compared with placebo, benralizumab every 4 weeks (Q4W) or every 8 weeks (Q8W) reduced exacerbations and improved lung function and asthma symptoms.^{8,9} After completing SIROCCO/CALIMA, patients could enter the BORA Phase III extension trial (Clinicaltrials.gov identifier: NCT02258542). Patients who were treated with benralizumab Q4W and Q8W in the predecessor studies continued their treatment regimens in BORA (“Q4W/Q4W” and “Q8W/Q8W,” respectively), while those who had received placebo were re-randomized to benralizumab 30 mg SC Q4W or Q8W (“placebo/Q4W” and “placebo/Q8W,” respectively). BORA was designed to evaluate adult patients for 52 weeks and adolescents for 108 weeks. Results after 1 year in BORA, which included the final adult patient results, revealed that benralizumab maintained the safety and tolerability observed in the predecessor studies.¹⁰

Adolescent patients enrolled in BORA followed the same dosing and re-randomization scheme as the overall study population, except those in the European Union who had been treated with placebo in the predecessor studies were assigned to benralizumab 30 mg Q8W (placebo/Q8W) based on regulatory requirements (see **Figure E1** in this article's Online Repository at www.jacionline.org). The primary outcome was safety, while secondary outcomes included crude annual asthma exacerbation rate (total exacerbations $\times$ 365.25 / total follow-up days),¹⁰ change from baseline in prebronchodilator forced expiratory volume in 1 second (FEV₁), Asthma Control Questionnaire, 6-question version (ACQ-6) score, and Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ [S]+12) score. Here, we report the long-term effects of benralizumab 30 mg Q4W and Q8W in adolescents that completed 2 years of treatment in BORA.¹⁰

METHODS

For detailed methods, please see this article's Online Repository at www.jacionline.org.

RESULTS AND DISCUSSION:

A total of 86 adolescents enrolled in BORA and received benralizumab Q8W (n=61) or Q4W (n=25). Baseline characteristics upon entry into BORA were generally similar across the study groups (**Table I**). Overall, 51 patients in the Q8W group and 18 patients in the Q4W groups completed treatment during the study (**Figure 1**). Among the 17 (19.8%) patients who discontinued treatment, the most common reasons were study specific discontinuation criteria (n=5 patients missed 2 consecutive or ≥ 2 overall doses of benralizumab during the study; n=1 patient required mechanical ventilation for an asthma-related event), and patient decision (n=6, specific reasons not provided). Additional discontinuations were due to loss to follow up (n=1), severe noncompliance (n=1), and for "other" reasons (n=2 patients in the Q4W/Q4W group for anomalies in laboratory testing discovered during a site audit; n=1 patient in Q8W/Q8W group who became pregnant).

The overall safety profile was consistent between patients who began treatment with benralizumab upon entering BORA vs. those who had been treated with study drug in SIROCCO/CALIMA. The

most frequent treatment-emergent adverse events (TEAEs) were pharyngitis (Q4W: 4.0% [1/25]; Q8W: 19.7% [12/61]), viral upper respiratory tract infection (Q4W: 12.0% [3/25]; Q8W: 13.1% [8/61]) and bronchitis (Q4W: 4.0% [1/25]; Q8W: 14.8% [9/61]) (**Table II**). Rates of TEAEs were generally consistent with those reported in the 1-year adolescent data and main population in BORA.⁸ No injection site reactions, treatment-related serious TEAEs, or deaths were reported, and 1 patient discontinued the study because of TEAEs (Q4W: 4.0% [1/25]). Overall, there were no appreciable differences between the Q4W and Q8W treatment groups.

In the efficacy analyses, crude annual exacerbation rates were low (≤ 0.46) across all treatment groups (**Figure 2A**). Numeric differences in exacerbation rates and proportions of exacerbation-free patients (**Figure 2B**) were observed between treatment groups, which may have been driven by the small patient numbers. The lowest crude exacerbation rate (0.2) occurred among patients who were on the Q8W regimen in the predecessor studies (Q8W/Q8W), and 75% of these patients in this group did not have an exacerbation during the study. Similar results were observed for patients with blood eosinophil count (BEC) $\geq 300/\mu\text{L}$ at baseline (**Figure 2A and 2B**).

Lung function based on mean change in prebronchodilator FEV₁ from BORA baseline to Week 108 yielded numerically greater improvements in both Q8W groups vs. the Q4W groups (**Figure 2C**), which was more pronounced in patients with baseline BEC $\geq 300/\mu\text{L}$. Notably, the placebo/Q4W group showed decreases of 41 mL (all patients) and 189 mL (baseline BEC $\geq 300/\mu\text{L}$), which may have been attributed, in part, to the high mean percent predicted normal values at BORA entry (93.7% and 91.0%, respectively) allowing for little to no room for improvement. Overall, continued improvement in FEV₁ over 2 years may be partly attributed to an expected improvement in lung function during normal physical development in adolescents.

Asthma control assessed by ACQ-6 showed small mean improvement from baseline to Week 108 for adolescents in the Q8W groups (**Figure 3A**), and was maintained from the 1-year score in BORA.¹⁰ The percentages of ACQ-6 responders (defined as improvement of ≥ 0.5 units) were

31.3% (Q8W/Q8W) and 37.9% (placebo/Q8W) at Week 108 (not shown). In addition, greater mean improvements from baseline to Week 108 in AQLQ(S)+12 overall score were observed for patients who entered BORA having already received benralizumab treatment vs. those in the placebo/Q4W and placebo/Q8W groups who began benralizumab upon entering BORA (**Figure 3B**).

Overall, these results reveal that the safety and efficacy profiles in adolescents in this 2-year extension study, (Years 2 and 3 of benralizumab treatment), were consistent with previous findings for the full study population over 1 year in BORA.¹⁰ Both dosing regimens of benralizumab were well-tolerated with no unexpected safety findings. The Q4W groups generally had similar efficacy as the Q8W groups, with the exception of lung function changes, which were greater for adolescents on the Q8W regimen, and was more pronounced for patients with BEC >300/ μ L. The pattern of efficacy results for patients with BEC $\geq$ 300/ μ L were generally similar to those observed for all adolescents, although there was greater variability because of smaller number of patients per group.

In conclusion, these results support the maintenance of efficacy and safety during long-term treatment with benralizumab in adolescents. However, these results should generally be interpreted with caution, as this analysis was descriptive in nature and thus, limited by a relatively small sample size, particularly within the Q4W arms, and lack of a placebo group.

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DATA-SHARING STATEMENT

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data-sharing policy described at <https://astrazenecagroup-dt.pharmacm.com/DT/Home>.

TABLES

Table I. Demographics and clinical characteristics at BORA entry

	Dosing regimen (Predecessor study/BORA)			
	Q4W/Q4W (n=14)	Placebo/Q4W (n=11)	Q8W/Q8W (n=32)	Placebo/Q8W (n=29)
Age (yrs), mean (SD)	15.6 (1.39)	15.5 (1.63)	15.5 (1.92)	15.0 (1.70)
Range	15–18	13–18	13–18	13–18
Female, n (%)	6 (42.9)	4 (36.4)	13 (40.6)	12 (41.4)
Blood eosinophil count (cells/ μ L), mean (SD)	61.4 (187.82)	395.5 (310.04)	63.8 (298.63)	363.6 (263.03)
Range	0–710	120–1150	0–1690	40–1020
Prebronchodilator FEV ₁				
Liters, mean (SD)	2.9 (0.62)	3.1 (0.81)	2.8 (0.69)	2.9 (0.65)
Range	1.7–4.0	1.1–3.9	1.3–4.2	1.8–4.4
Percent predicted normal, mean (SD)	88.2 (19.09)	93.7 (21.07)	88.4 (18.85)	91.0 (15.08)
Range	54.6–122.6	42.7–114.0	45.7–122.1	54.6–121.5
Exacerbations in the previous 12 months, mean (SD)	1.0 (2.04)	0.1 (0.30)	0.6 (0.84)	0.6 (1.08)
Range	0–7	0–1	0–3	0–5
OCS use, n (%)	0	0	0	0
ICS total daily dosage (μ g), mean (SD)	562.9 (207.29) ^a	636.4 (233.55)	642.0 (239.41)	573.7 (211.08)
Range	250–1000	500–1000	250–1045.5	250–1136.4

FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA; long-acting β 2-agonists; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks.

^an=13 (1 patient that was treated with ICS/LABA and LTRA upon enrollment in the predecessor study was taking LTRA only at BORA entry.)

Table II. Adverse events through 108 weeks in BORA

Variable, n (%)	Dosing regimen (Predecessor study/BORA)			
	Q4W/Q4W (n=14)	Placebo/Q4W (n=11)	Q8W/Q8W (n=32)	Placebo/Q8W (n=29)
Any TEAE	10 (71.4)	7 (63.6)	24 (75.0)	21 (72.4)
Any SAE	0	2 (18.2)	0	4 (13.8)
Any AE leading to treatment discontinuation	0	1 (9.1)	0	0
Common AEs^a				
Pharyngitis	1 (7.1)	0	6 (18.8)	6 (20.7)
Viral upper respiratory tract infection	3 (21.4)	0	4 (12.5)	4 (13.8)
Bronchitis	1 (7.1)	0	4 (12.5)	5 (17.2)
Influenza-like illness	2 (14.3)	2 (18.2)	3 (9.4)	3 (10.3)
Asthma	1 (7.1)	1 (9.1)	3 (9.4)	0
Gastroenteritis viral	0	0	3 (9.4)	2 (6.9)
Tonsillitis	2 (14.3)	0	2 (6.3)	0
Upper respiratory tract infection	0	0	1 (3.1)	3 (10.3)
Viral pharyngitis	1 (7.1)	1 (9.1)	1 (3.1)	0
Sinusitis	1 (7.1)	1 (9.1)	0	0

AE, adverse event; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses Q4W); SAE, serious adverse event; TEAE, treatment-emergent adverse event.

^aAt least 5% incidence in any treatment group. Patients with multiple events in the same category and study period are counted only once in that category and study period.

FIGURE LEGENDS

Figure 1. Patient disposition.

Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses Q4W)

Among the 6 patients who discontinued because of withdrawal criteria, 5 patients missed 2 consecutive doses or ≥ 2 doses overall of benralizumab during the course of the study, and 1 patient required mechanical ventilation for a severe asthma exacerbation that was considered a serious adverse event.

Figure 2. Asthma exacerbations and lung function outcomes in adolescents over 108 weeks in BORA. **(A)** Annual asthma exacerbation rates. **(B)** Percentage of exacerbation-free patients by treatment group. **(C)** Mean (SE) change from baseline to Week 108 in prebronchodilator FEV₁.

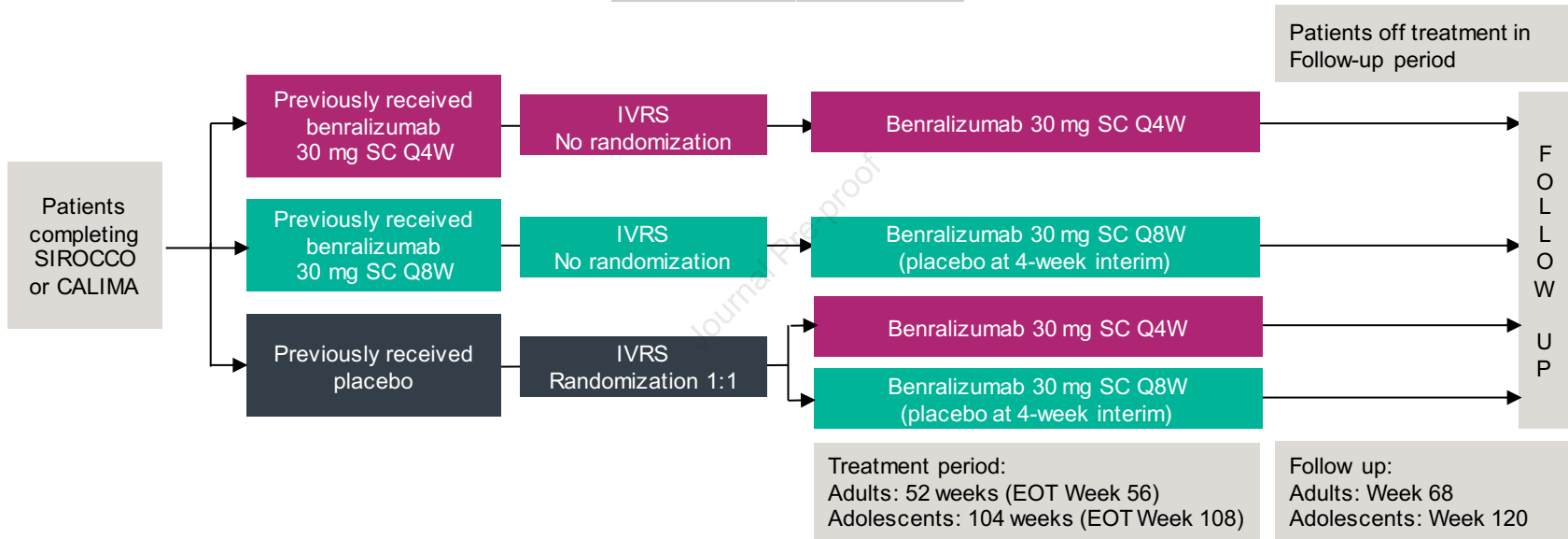
BEC, baseline eosinophil count; FEV₁, forced expiratory volume in 1 second; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses Q4W).

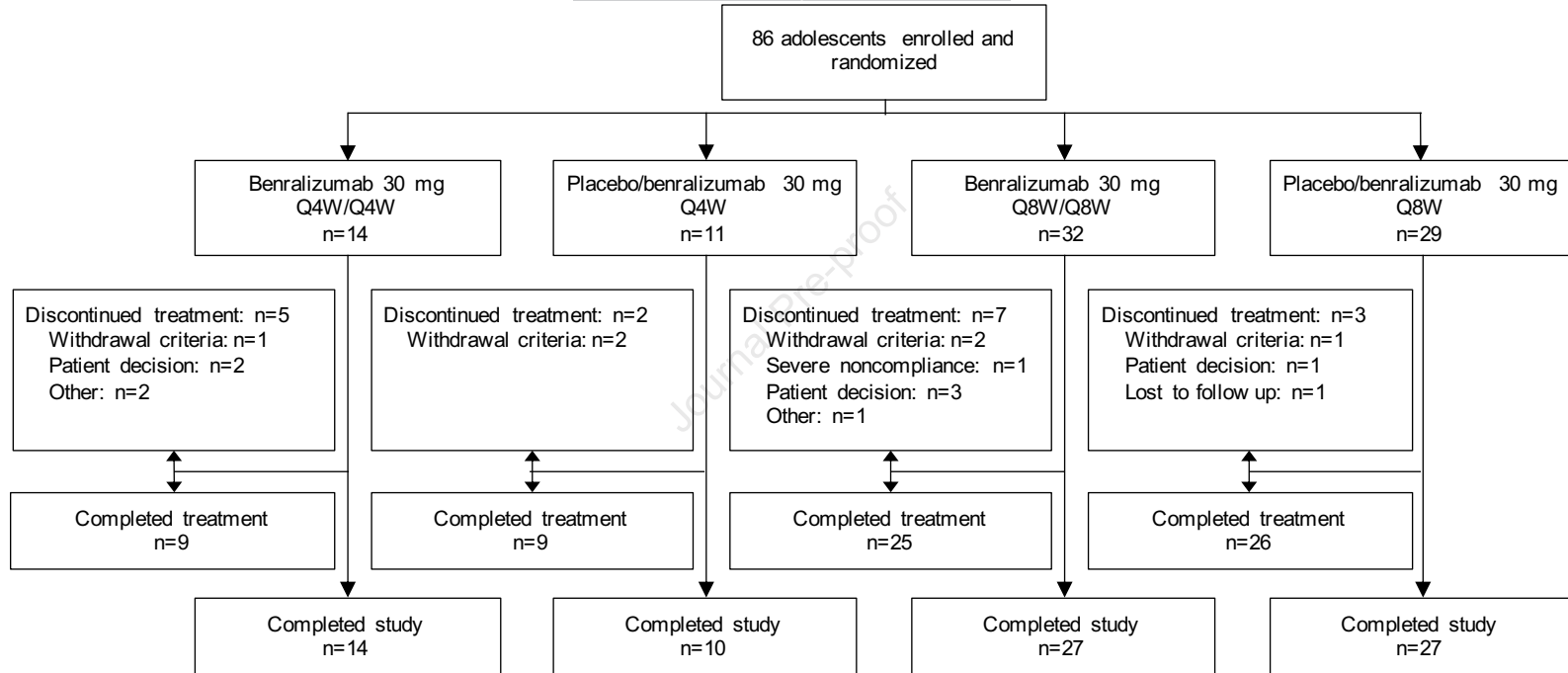
Group names based on treatment regimen in SIROCCO or CALIMA trials then BORA.

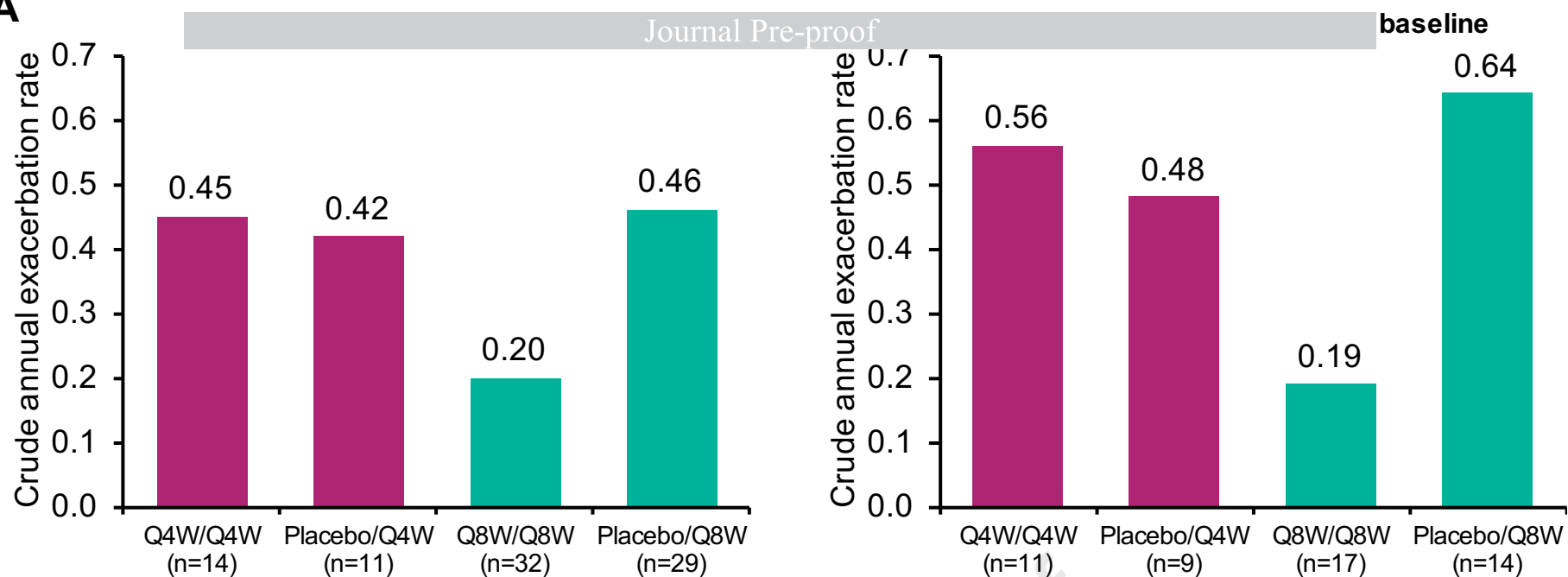
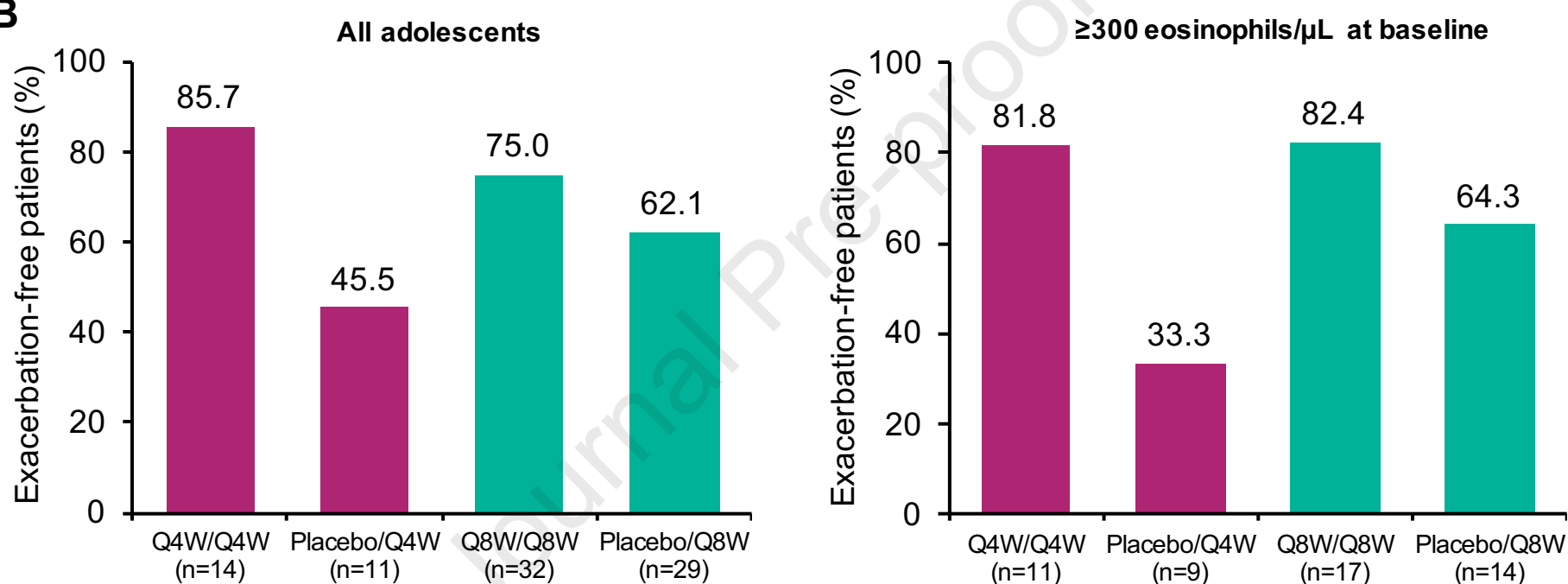
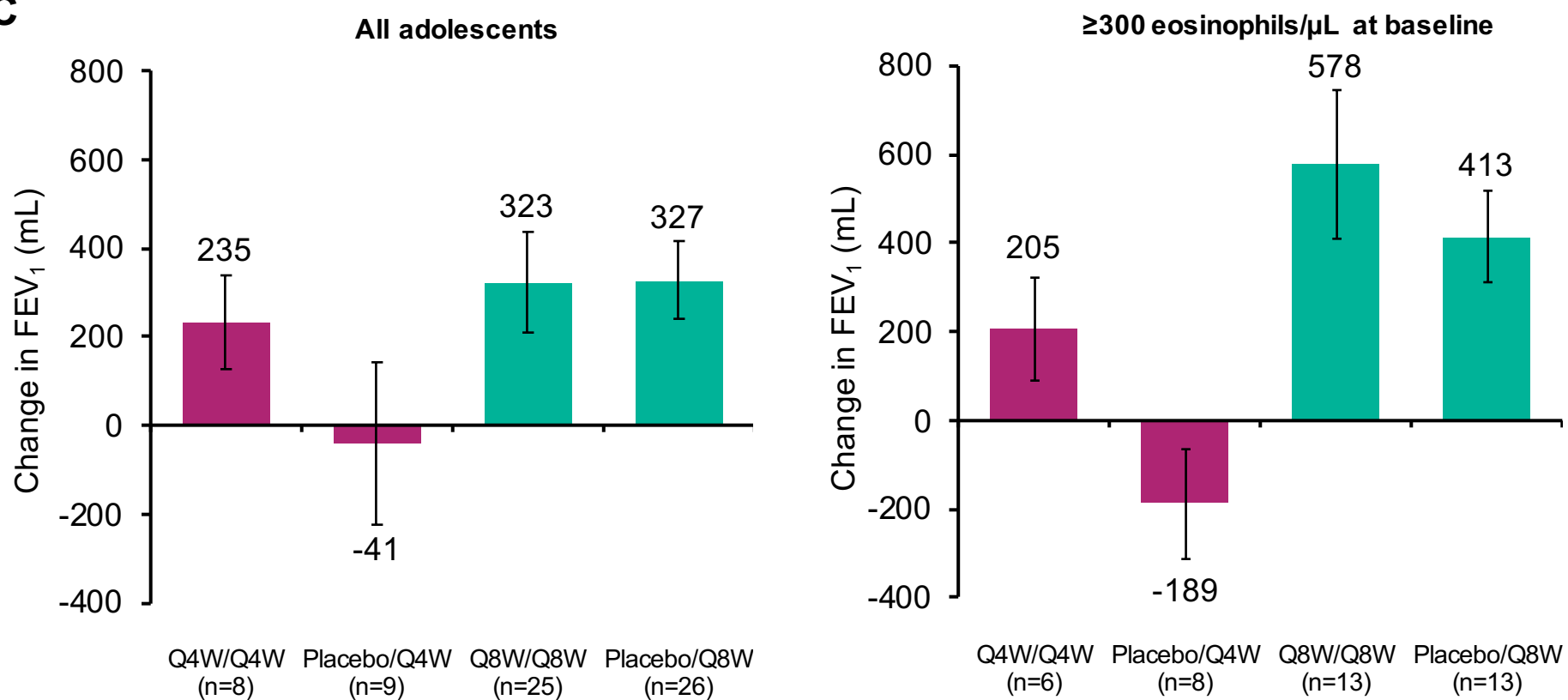
Figure 3. Mean (SE) changes from BORA baseline in health-related quality of life and productivity at Week 108 based on **(A)** ACQ-6 and **(B)** AQLQ(S)+12 scores

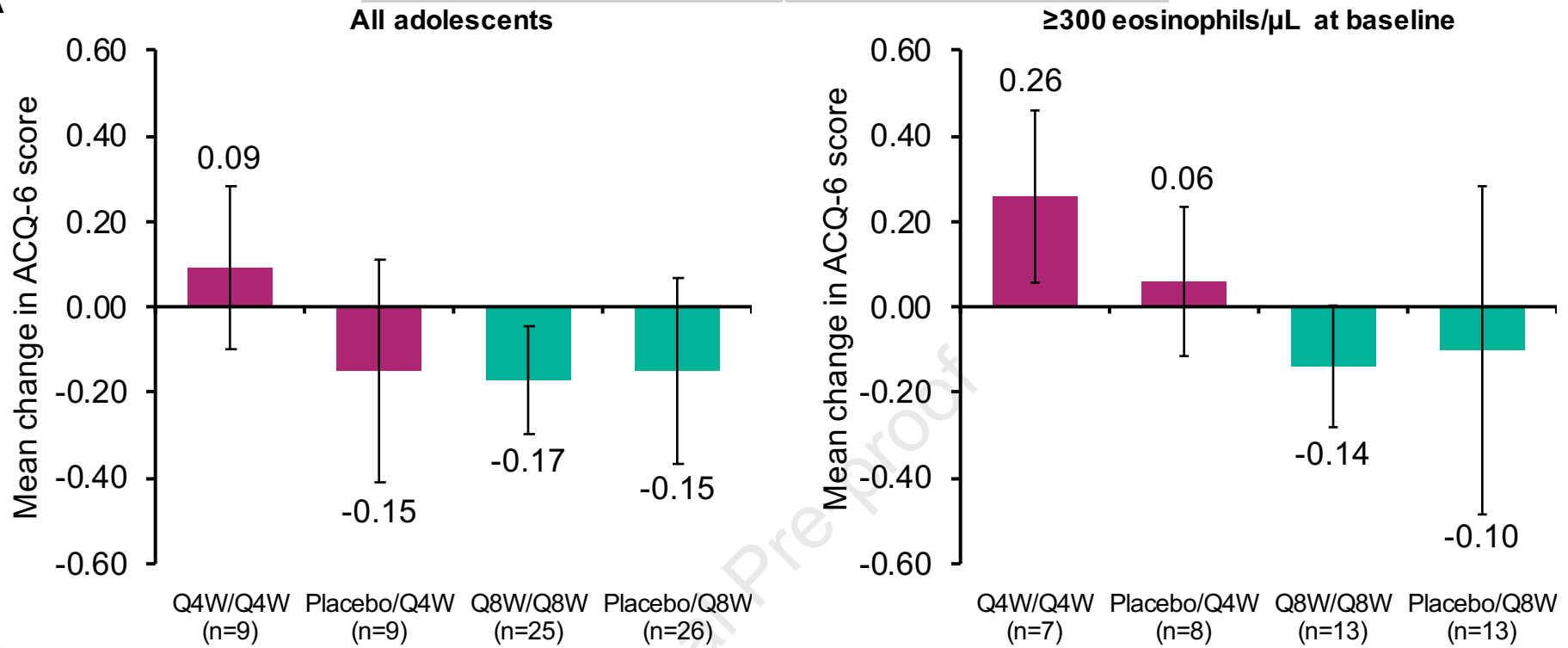
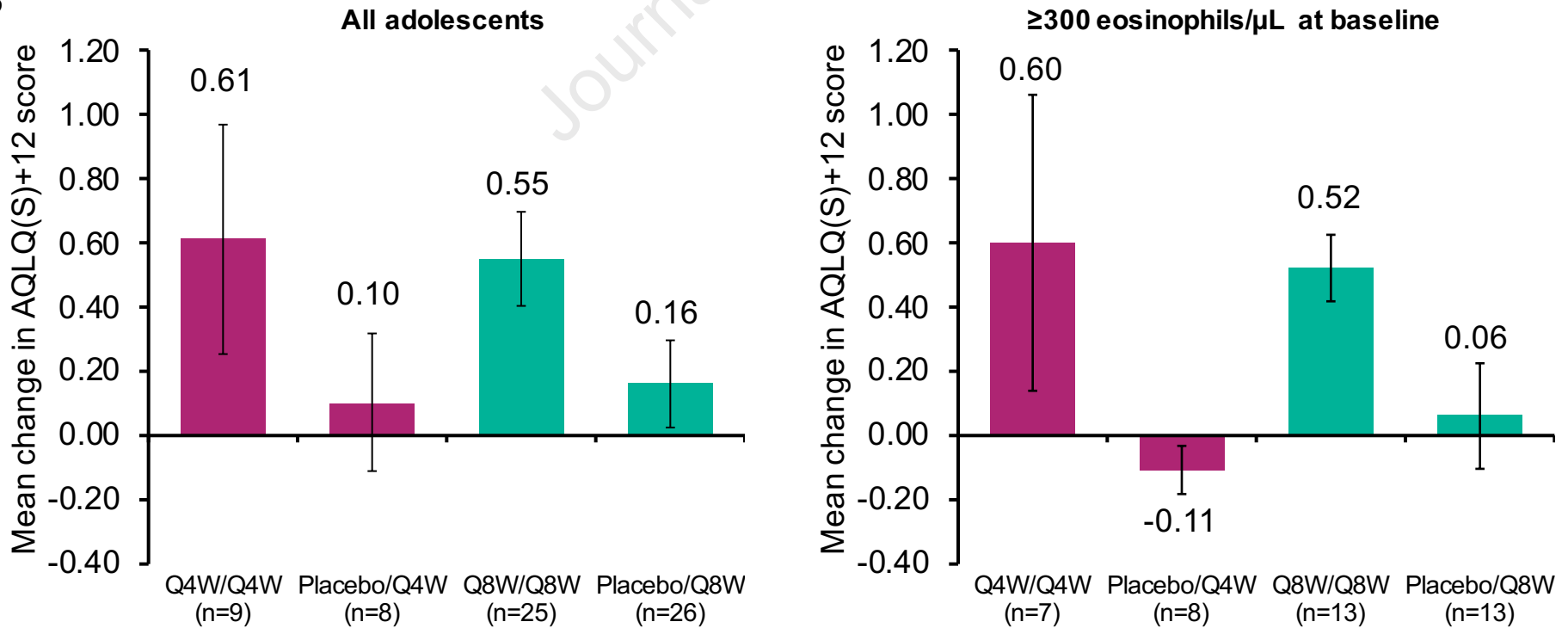
ACQ-6, Asthma Control Questionnaire-6, 6-question version; AQLQ(S)+12, Standardized Asthma Quality of Life Questionnaire for 12 Years and Older; Q4W, every 4 weeks; Q8W, every 8 weeks (first 3 doses Q4W).

For ACQ-6, low numbers represent better control. For AQLQ(S)+12, high number suggest better quality of life.





A**B****C**

A**B**

ONLINE REPOSITORY

METHODS

BORA was a Phase III extension trial (Clinicaltrials.gov identifier: NCT02258542) that enrolled patients who completed the 1-year SIROCCO/CALIMA trials. The complete methods for BORA were published previously.¹⁰ Patients who enrolled in BORA and had been treated with benralizumab Q4W and Q8W in the predecessor studies were to continue the same treatment in BORA (“Q4W/Q4W” and “Q8W/Q8W,” respectively), while placebo patients were re-randomized to benralizumab 30 mg SC Q4W or Q8W (“placebo/Q4W” and “placebo/Q8W,” respectively). However, because regulatory requirements, adolescent patients (defined as those aged 12–17 years at SIROCCO/CALIMA enrollment) in the European Union who received placebo in SIROCCO/CALIMA were all assigned to benralizumab 30 mg Q8W (placebo/Q8W; see **Figure E1** below). Adolescents in BORA were treated for 108 weeks with a follow-up visit at Week 120. The primary outcome was safety, while secondary outcomes included crude annual asthma exacerbation rate (total exacerbations × 365.25 / total follow-up days), change from baseline in prebronchodilator forced expiratory volume in 1 second (FEV₁), Asthma Control Questionnaire, 6-question version (ACQ-6) score, and Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ [S]+12) score. All data were analyzed and presented descriptively.

Figure E1. Study design.¹⁰

EOT, end-of-treatment; IVRS, interactive voice response system; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Adolescent was defined as 12–17 years of age at the start of the predecessor study. All adolescent patients enrolled in the Europe received benralizumab 30 mg Q8W. All patients previously randomized to benralizumab 30 mg Q8W received placebo at Weeks 0 and 4 in the BORA study to maintain blinding.