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Article type : Original Article: Asthma and Lower Airway Disease

Benralizumab Improves Symptoms of Patients with Severe, Eosinophilic Asthma with a Diagnosis of Nasal Polyposis

Manuscript Acceptance Date: 18-Apr-2021

Short Title: Benralizumab for Patients with Asthma and Nasal Polyposis (50/50 characters)

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ACKNOWLEDGMENTS

The authors thank the investigators, health care providers, research staff, patients, and caregivers who participated in the ANDHI trial. We also thank Nanna Keeling (AstraZeneca, Gothenburg, Sweden) for clinical operations leadership in this study. Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, incorporating author feedback, and manuscript submission, was provided by Wynne Dillon, MS (Kay Square Scientific, Newtown Square, PA, USA) and Michael A. Nissen, ELS (AstraZeneca, Gaithersburg, MD, USA). The authors thank James Kreindler (AstraZeneca, Gaithersburg, MD, USA) and Arnaud Bourdin (University of Montpellier, Montpellier, France) for support of data acquisition, statistical analysis, and interpretation of the study results for the comprehensive response analysis. This support was funded by AstraZeneca.

CONTRIBUTORS

All authors and the funder of this study participated in study design. All authors had access to and analyzed and interpreted the data, participated in the development and critical review of the manuscript, approved submission of the manuscript for publication, and are accountable for the accuracy and integrity of the work.

Manuscript title: (111/200 characters)

Abstract word count: 358/250 total(additional word count due to reviewer-requested additions to abstract)

Word count: 3865/3500 total (additional word count due to reviewer-requested additions to manuscript)

Figures/Tables: 5/6 total

Supplementary Appendix: 4tables/2figures

ABSTRACT

Background: Clinically meaningful improvement in the Sino-Nasal Outcome Test-22 (SNOT-22) was observed in patients with severe, eosinophilic asthma and nasal polyposis (NP) treated with benralizumab in the ANDHI trial. A*post-hoc* assessment of the effects of benralizumab on SNOT-22 response and asthma efficacy measures in these patients was conductedfor further characterization of the efficacy and safety of benralizumab for patients with severe asthma and NP.

Methods: Adults with severe, eosinophilic asthma who had experienced ≥2 prior-year exacerbations despite high-dosage inhaled corticosteroid plus additional controller[s] were randomised to 24 weeks of benralizumab or placebo.Patients with physician-diagnosed chronic rhinosinusitis with NP of any severity ongoing at baseline who consented to participate were includedin the current ANDHI NP substudy population.Effect on NP symptoms was assessed by the SNOT-22, with an improvement of at least 8.9 defined as clinically significant (responder). Effects on chronic asthma outcomes were assessed by means of annualised asthma exacerbation rate (AER), St. George's Respiratory Questionnaire (SGRQ) total score, forced expiratory volume in one second (FEV_1), and Asthma Control Questionnaire-6 (ACQ-6). All *p*-values were nominal.

Results: Of the ANDHI population (n=656), 23% (n=153) participated in the NP substudy (n=96 benralizumab; n=57 placebo). Patients were 50% female,with mean age of 53 years, had prior-

year AER=3.3;mean pre-bronchodilator FEV_1=55% predicted; and median BEC=510 cells/μL. For patients with high baseline SNOT-22 scores (>30), benralizumab treatment improved symptoms of NP as measured by SNOT-22 from baseline to Week 24 compared with placebo (Week 24: −10.44 [p=0.0176]).Percentage of responders to SNOT-22 was greater for benralizumab vs. placebo (71.3% vs. 45.5%; *p*=0.0036) and effect was enhanced for patients with high baseline SNOT-22 scores (>30). A 69% reduction vs. placebo in annualised AER (0.77 vs. 2.47; *p*<0.0001) andgreater clinically meaningful improvements from baseline in SGRQ total score(−16.7), FEV_1(+0.32 L), and ACQ-6(–0.88) were observed (*p*<0.0001).Benralizumab was well-tolerated. Frequency of adverse events (AEs) was similar for benralizumab (76.0%) and placebo (73.7%) groups. Most common AEs (frequency ≥5%) reported at a greater frequency inbenralizumab vs placebo included headache, sinusitis, pyrexia, and influenza.
Conclusions: These substudy data from ANDHI demonstratedthe efficacyprofile of benralizumab for patients with severe, eosinophilic asthma and NP, withimprovement in SNOT-22 and asthma outcomes.

Funding: AstraZeneca

Key words (maximum of 8): Asthma;asthma treatment;biologics;eosinophils;sinusitis

1. INTRODUCTION

Chronic rhinosinusitis (CRS) with nasal polyposis (NP) is a common disease thataffectsup to 4% of the population.[1]Itis a heterogeneous,chronic inflammatory disease with multiple endotypes.[1,2]Patients experience severe sinonasal symptoms, includingincreased nasal congestion, facial pain, nasal polyp growth, and a decrease or loss of sense of smell, as well as headache.[1–3]NP is often characterised by increased total immunoglobulin E (IgE) in NP tissue, tissue eosinophilia, and type 2 inflammatory cytokines including interleukin (IL)-4, IL-5, and IL-13,[2–8]with these increases causing debilitating, persistent symptoms.[7,9]Tissue eosinophilia is present in a majority of patients with CRSwith NP,but is less common in the East than the West.[5]

NP is often associated with severe and steroid-resistant asthma, [9–15] and it has been reported that up to 40.6% of patients with severe asthma have chronic rhinosinusitis with NP.[11]

Increasedblood eosinophil counts (BEC), airway obstruction, and inflammatory cells, as well as reduced asthma control has been reported for patients with asthma and NP compared with those without NP.[7,9,15]Therefore, the combination of asthma and NP provides significant treatment challengesand substantial disease burden, along with a significantly greater number of asthma exacerbations per year, which negatively impacts health-related quality of life (HRQoL).[9,11,16,17]For patients with severeasthma and NP, NP symptoms should be addressed to optimise asthma control.[18–20]Suboptimal control of NP reduces asthma control as well, thereby necessitating novel therapies for better patient outcomes.[9,21–24]

Patients with NP experience a debilitating disease course,with mainstay medical treatment options, including intranasal corticosteroids (INCS), oral corticosteroids (OCS), nasal saline irrigations, leukotriene antagonists, and antibiotics providing only partial improvement,[15,23–27] and endoscopic sinussurgery often leading to recurrence.[28]Many patients with NP experience symptom relapse or persistent sinus disease.[15,22,24]Increased understanding of chronic respiratory inflammation in NP has led to the identification of several potential therapeutic targets.[29]Because NP is a complex inflammatory disorder, it is often resistant to medical and surgical management, leading to the recent study of biologic medications with promising yet somewhat varying results.[24,27,30–41]Beneficial treatment effects such as significantly reduced symptoms and increased HRQoL have been reported for patients with asthma and severe NP treated with biologic medications.[29,36]Owing to the studies demonstrating efficacy for biologic medications in NP, a significant paradigm shift in the management of NPhas occurred.[27]

Benralizumab is an IL-5 receptor alpha–directed cytolytic monoclonal antibody that induces direct, rapid, and nearly complete depletion of eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity.[42,43]Repeated doses of benralizumab for patients with mild to severe asthma significantly reduce airway wall and sputum eosinophil counts.[43–45]Benralizumab significantly reduced asthma exacerbations, increased lung function, and improved HRQoLfor patients with severe, eosinophilic asthma, with treatment effects sustained for up to 2 years.[46–50]In addition, pooled *post-hoc* analyses of benralizumab studies demonstrated that benralizumab provides enhanced clinical benefits for patients with increased BEC, greater exacerbation history, poor lung function, OCS use, adult asthma diagnosis, andNP.[47–54]

Although the efficacy and safety of benralizumab are well-understood for patients with severe eosinophilic asthma, limited data are available to support the potentialof benralizumab to treat patients with NP.[55–58]In case studies, patients with NP who underwent therapy with benralizumab experienced relevant clinical and functional improvements in asthmacontrol test scores and forced expiratory volume in 1 second(FEV_1) associated with depletion of blood eosinophils along with the disappearance of nasal polyps.[55–57]Additional clinical data are needed to assess further the potential for benralizumab as an effective treatment option in NP.

In the randomised, double-blind, parallel-group, placebo-controlled ANDHI trial of benralizumab compared with placebo for patients with uncontrolled, severe eosinophilic asthma, reduction in asthma exacerbations and early improvements in lung function, asthma control, and disease-specific HRQoL were observed after the first dose.[58] In the ANDHItrial overall population, a substudy of patients with physician-diagnosed NP of any severity ongoing at baseline was conducted to assess symptoms of NP with the Sino-Nasal Outcome Test-22 (SNOT-22).[58]Benralizumab improved SNOT-22 from baseline compared with placebo from the first time point assessed (Week 4) to end of treatment (Week 24; mean difference −8.91 [p=0.02040]; **Figure S1**).[58]To add to this preliminary evidence, we conducted a *posthoc* assessment of the effects of benralizumab on asthma efficacy measures and SNOT-22 response in these patients.

2. METHODS

Detailed information regarding the methodology of the ANDHI trial was previously reported.[58]

2.1 Study design and patients

ANDHI was a Phase IIIb, randomised, double-blind, parallel-group, placebo-controlled trial designed to investigate the efficacy of benralizumab in addition to standard-of-care asthma therapy conducted at 221 clinical research centers worldwide between July 2017 and September 2019 (ClinicalTrials.gov identifier: NCT03170271).[58]The study was performed in accordance

with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH)/Good Clinical Practice (GCP). Before study initiation, the clinical study protocol,informed consent form, and any other relevant documents were approved by an independent ethics committee or an institutional review board, with all patients signing informed consent.[58]

Adults aged 18–75 years of age weighing ≥40 kg with a diagnosis of severe, eosinophilic asthma who had experienced ≥2 prior-year exacerbations despite treatment with medium to high-dosage ICS plus additional controller[s](e.g., long-acting β_2 agonists [LABA], long-acting muscarinic antagonists, leukotriene antagonists, methylxanthines, or OCS), and who had been on high-dosage ICS plus an additional controller for ≥3 months before screening,along with an overall Asthma Control Questionnaire-6 (ACQ-6) score of ≥1.5, documented post-bronchodilator reversibility of ≥12% (FEV_1≥12%) using a short-acting bronchodilator or airway hyperresponsiveness or peak expiratory flow variability ≥10%, and screening BEC ≥150 cells/μL were eligible for study inclusion. [58](Complete inclusion and exclusion criteria are published with the overall study population.[58]) Eligible patients were randomised 2:1 to 24 weeks of benralizumab (30 mg every 8 weeks [first 3 doses every 4 weeks]) or placebo.[58]Patients with physician-diagnosed NP of any severity ongoing at baseline who provided additional consent to participate were included in the currentANDHI NP substudypopulation.

2.2 Study outcomes

The rhinosinusitis health status and HRQoL of the patients in the NP substudy were assessed using the SNOT-22.[58]SNOT-22 is a validated and widely used patient-reported measure of NP symptom severity, HRQoL, and effectiveness of treatment.[59–61]SNOT-22 was developed for use in chronic rhinosinusitis and assesses the symptomsand functional and emotional consequences of chronic rhinosinusitis through responses to 22 items using a 6-category scale, from 0 (no problem) to 5 (problem as bad as it can be).[59]Greaterscores indicate a poorer outcome (range 0–110). SNOT-22 was completed by patients with NP prior to other study assessments and treatment administration and assessed at baseline, Week 4 (Visit 6), Week 12 (Visit 8), and end of treatment (Week 24).Response was defined as having a minimum clinically important improvement (change from baseline of ≤–8.9) in SNOT-22 at the end of treatment.[59]

Primary and secondary asthma efficacy endpoints in the overall population have been previously reported and are described in Table S1.[59]Annualised asthma exacerbation rate (AER)was used to determine the effect of benralizumab versus placebo on the rate of asthma exacerbations over the 24-week treatment period. An asthma exacerbation was defined as a worsening of asthma leading to use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dosage) for ≥3 days; a single injectable dose of corticosteroids; an emergency room or urgent care visit owing to asthma requiring systemic corticosteroids; and/or an inpatient hospitalisation because of asthma.[59]Change from baselineto end of treatment (Week 24) in the St. George's Respiratory Questionnaire (SGRQ) total score, FEV_1, and ACQ-6were assessed in the current substudy for patients with NP. Safety and tolerability were assessed through reported adverse events (AEs), as described.[58]

2.3 Statistical Analysis

All efficacyendpoints were summarised and analysed using the NP substudy analysis set. This analysis set was defined as the subset of patients with physician-diagnosed CRS withNP included in their medical histories and ongoing at baseline who had signed the additional informed consent to participate in the substudy and who also hadreceived ≥1 dose of investigational product.

Differences in least-squares (LS) mean change from baseline in SNOT-22 was assessedfor patientswith a high baseline SNOT-22 total score (>30). Annualised AER was defined as the total number of exacerbations × 365.25/total duration of follow-up within the treatment group in days. Annualised AER over the 24-week period and effects on asthma efficacy measures (SGRQ total score, FEV_1, and ACQ-6 at Week 24) were assessed *posthoc* for the NP substudy analysis set. For SNOT-22, SGRQ, FEV_1, and ACQ-6, analysis was via a mixed model for repeated measures (MMRM), with treatment, visit, and treatment × visit as explanatory variables and adjusted for baseline measure, region, number of exacerbations in the previous year and maintenance OCS use at baseline (for FEV_1 adjusted also for age and sex). AERs were compared via a negative binomial model with treatment as the explanatory variable and adjusted for region, number of exacerbations in the previous year, and maintenance OCS use at baseline.The

logarithm of treatment time was included as the offset variable in the model. Results were presented as a rate ratio (RR) with associated 95% confidence interval(CI). Because the ANDHI trial was not designed nor powered to assess efficacy within pre-defined subgroups, all substudy analyses were exploratory, and allNP substudy *p*-values are nominal.

A SNOT-22 responder analysis was included as a secondary analysis of the NP substudy and was conducted via a logistic regression model (with treatment as the explanatory variable and using the same covariates per MMRM), with results reported as an odds ratio (OR) with an associated 95% CIand nominal *p*-value. Patients with a missing SNOT-22 total score at the end-of-treatment visit and not completing the study were considered non-responders. For patients completing the study but missing a SNOT-22 total score at the end-of-treatment visit, the last evaluable post-baseline total score was used to define the responder status.

Comprehensive response to benralizumab was assessed based on SNOT-22 and several asthma outcomes from the ANDHI study. Comprehensive response was defined as achieving a clinically meaningful improvement at end of treatment (Week 24) in SNOT-22 of –8.9 units[59] along with 4 additional criteria: (1) 0 exacerbations; (2) change from baseline in SGRQ total score of ≤–4 units; (3) change from baseline in FEV_1 of ≥0.2 L; and (4) change from baseline in ACQ-6 total score of ≤–0.5.

Safety analyses were based on the actual treatment regimen received and included all patients with NP who receivedat least 1 dose of investigational product. All safety variables were summarised descriptively.

3. RESULTS

Results from the ANDHI trial's overall population have been published.[58]

3.1 Patients

In the overall study population for ANDHI, 656 randomised patients received investigational product (n=427 benralizumab; n=229 placebo).[58]A total of 228 (34.8%) reported having a

medical history of NP at study entry, of which 153 patients (23.3% of the overall study population) had evidence of physician-diagnosed ongoing NP at baseline and provided additionalinformed consent to participate in the NPsubstudy analysis (n=96 benralizumab; n=57 placebo) (**Figure S2**).

Of 153 patients included in the NP substudy analysis set, 143(93.5%) completed the double-blind ANDHI trial, with a similar percentage of patients for each treatment group completing (n=92 [95.8%] benralizumab andn=51 [89.5%] placebo) (*see***Figure S2**). Ten patients were withdrawn from the study:four due to AEs (n=2 [2.1%] benralizumab; n=2 [3.5%] placebo), four due to patient decision (n=2 [2.1%] benralizumab; n=2 [3.5%] placebo), onebecause of protocol-specified withdrawal criteria (n=1 [1.8%] placebo), and one due to other reason (n=1 [1.8%] placebo).

The NP substudy population was 50% female and had a mean age of 53 years. Patients had a prior-year AER=3.3;mean pre-bronchodilator FEV_1=55% predicted; Phadiatop positive=50%; and median total IgE=143 IU/L.Median BEC was 510cells/uL, with most patients with a BEC ≥300 cells/μL at baseline (82.3% and 87.7% for benralizumab and placebo, respectively; **Table 1**).A total of 71.9% of patients in each group had a past nasal polypectomy, and approximately 40% of patients in each group reported a history of sinus surgery. Demographics and baseline clinical characteristics were generally balanced between treatment groups, although imbalance was observed for patients with ≥3 prior exacerbations (51.0% and 59.6% for benralizumab and placebo, respectively) andlung function (mean pre-bronchodilator FEV_1: 1.70 for benralizumab and 1.92 for placebo). There were more male patients in the placebo group;55.2% of patients in the benralizumab group were female compared with 42.1% female patients in the placebo group. At baseline, mean total SNOT-22 score was 50.2 (51.5 and 48.2 for benralizumab and placebo, respectively).[58]

Approximately half (53.6%) of patients reported NP medication use at baseline (56.3% of benralizumab patients and 49.1% of placebo patients). 9.8% reported receiving omalizumab as a prior medication (benralizumab 8.3%; placebo12.3%). Over half of the patients (57.5%) reported concomitant NP medication use during the study (benralizumab 60.4%;placebo 52.6%). Most

frequently reported concomitant NP medications included INCS (53.6%), oral corticosteroids (5.9%), leukotriene antagonists (1.3%), and other nasal preparations (7.2%). (Details regarding concomitant NP medications for the benralizumab and placebo groups are provided in **Table S2**.)

3.2 Nasal Polyposis Efficacy Assessments

Benralizumab treatment improved symptoms of NP as measured by SNOT-22 from baseline to Week 24 compared with placebofor patients with high baseline SNOT-22 scores (>30).The LS mean change from baseline was significantly greater for benralizumab compared with placebo from the first timepoint assessed, with the greatest difference observed at end of treatment(mean difference in change from baseline at Week 4: −9.07 [p=0.0076]; Week 12: −11.63 [p=0.0034]; Week 24: −10.44 [p=0.0176]) (**Figure 1**).

The percentage of patients with clinically meaningful improvements from baseline in SNOT-22(at least 8.9)[59]at Week 24 (SNOT-22 responders) was greater for benralizumab compared with placebo (71.3% vs. 45.5% [OR:2.99; 95% CI: 1.43, 6.24; p=0.0036]) (**Figure 2A**). The magnitude of the effect was further enhanced for patients with high baseline SNOT-22 scores, with a greater percentage of patients with clinically meaningful improvements from baseline in SNOT-22(at least 8.9)[59]for benralizumab compared with placebo (79.7% vs. 48.8% [OR: 4.11; 95% CI: 1.80, 9.39]; p=0.0008) (**Figure 2B**).

Benralizumab SNOT-22 responders were slightly younger in age, were more likely to be female, had agreater prior exacerbation rate, were less likely to report past polypectomy**,**were more likely to have allergies,and had greater SNOT-22 mean baseline score compared with benralizumab patients who did not meet response criteria (**Table S3**).

3.3 Asthma Efficacy Assessments

Benralizumab significantly reduced AER over the 24-week period by 69% in the NP substudy population (p<0.0001)compared with placebo (**Figure 3A**). The percentage of patients with no asthma exacerbations in the NP substudy population was greater with benralizumab (77.1%; n=74) compared with placebo (36.8%; n=21). A clinically meaningful improvement from

baseline in SGRQ total score at Week 24 was observed for patients in the NP substudy treated with benralizumab as compared with placebo (−16.7; $p<0.0001$), and those improvements were evident from Week 4 (first timepoint assessed) onward, with the greatest decrease observed at Week 24 (–28.54 for benralizumab vs. –11.8 for placebo) (**Figure 3B**).Benralizumab provided clinically meaningful improvement inFEV_1 at Week 24 versus placebo(+0.32L [$p<0.0001$]), with improvements observed from the first time point assessed (Week 2: +0.11 L) through end of treatment(**Figure 3C**). A clinically meaningful change from baseline in ACQ-6 score at Week 24 was observed for patients in the NP substudy treated with benralizumab compared with placebo (–0.88; $p<0.0001$]); improvements were achieved from the first timepoint measured, with the greatest decrease observed at Week 24 (–1.69 for benralizumab vs. –0.81for placebo) (**Figure 3D**).

At end of treatment (Week 24), the percentage of patients achieving a clinically meaningful improvement in SNOT-22, exacerbations, SGRQ total score, FEV_1, and ACQ-6 total score (comprehensive response) was greaterin the benralizumab group (42.7%) compared with the placebo group (5.3%). Percentages of comprehensive responders based on achieving a clinically meaningful improvement in SNOT-22 along with fewer than 4 additional criteria increased for patients who met 3, 2, or 1 additional criteria (up to 53.1% vs. 12.3%, 60.4% vs. 24.6%, and 64.6% vs. 29.8% for benralizumab and placebo, respectively) (**Table S4**).

3.4 Safety

In the NP substudy population, 96 patients received benralizumab and 57 received placebo. AEsduring the treatment period were reported by similar percentages ofpatients who received benralizumab (76.0%) and placebo (73.7%) (**Table 2**).Most AEs reported were mild or moderate. Most common AEs (frequency ≥5% in the benralizumab group) reported at a higher frequency in benralizumab vs. placebo included headache, sinusitis, pyrexia, and influenza. Fewer serious AEs were reported for patients in the benralizumab group compared with the placebo group (5.2% vs. 12.3%, respectively).The incidence of AEs leading to discontinuation was low in both treatment groups (n=2 [2.1%] for benralizumab; 2 [3.5%] for placebo). No patients had an AE with an outcome of death.The incidence of injection-related reactions was

low in both treatment groups (1% and 0% of patients in the benralizumab and placebo groups, respectively).

4. DISCUSSION

The results from thecurrent NP substudy from the Phase IIIb ANDHI trial[58]extend the efficacy and safety profile of benralizumab for patients with severe asthma and NP of any severity, including improvements in symptoms and impairments related to NP as well as improvements in lung function and asthma disease-specific HRQoL.The current findings suggest that benralizumab has abeneficial treatment effectand improves HRQoL for patients with severe, eosinophilic asthma and NP as demonstrated by the clinically meaningful improvement inSNOT-22 total score from baseline to end of treatment compared with placebofor patients with a high baseline SNOT-22 total score (>30).The responder analysis demonstrated the likelihood of achieving a clinically meaningful improvement in SNOT-22 total score was greater for benralizumab-treated patients compared with placebo at end of treatment, with the magnitude of the treatment effect greater for patients with high baseline SNOT-22 scores (>30).Along with significant improvements in NP symptoms,benralizumab significantly reduced the risk of asthma exacerbation and enhancedimprovements in FEV_1, ACQ-6, and SGRQ total score;43% of patients with asthma and NP treated with benralizumab were comprehensive responders, achieving clinically meaningful improvement in SNOT-22 and multiple asthma outcomes (exacerbations, HRQoL, lung function, and asthma control).

The presence of NP in patients with severe asthma who were treated with biologics enhances response to biologic treatment and potentially identifies a subset of better responders to biologic medications among all patients with severe asthma.[62]For patients with severe, eosinophilic asthma and NP in the current subpopulation analysis, benralizumab had an increased treatment effect on asthma efficacy endpoints relative to the overall ANDHI trial population, which included patients with and without medical history NP.[58]Patients with NP demonstrated an increased benralizumab effect on AER reduction compared with the overall ANDHI trial population (69% vs. 49%), SGRQ total score (−16.7 vs. −8.11), ACQ-6 (−0.88 vs. −0.46), andlung function (FEV_1 +0.32 L vs. +0.16 L).[58]These findings concerning an enhanced treatment

effect for patients with NP are supported by a *post-hoc* analysis of the SIROCCO and CALIMA trials, in which a medical history of NP was identified as a predictor of enhanced response with benralizumab.[52]

Case reports have shown that benralizumab induced shrinkage of nasal polyps and improved related symptoms for asthmatic patients with NP.[55–57]In one such case, benralizumab improved asthma control and resolved NP by depleting eosinophils in the peripheral blood as well as in the nasal polyp tissues of the patient.[52]The current substudy analysis of clinical study data for patients with NP further supports the preliminary clinical treatment information provided in the available case reports.In the ANDHI study, it was demonstrated that benralizumab treatment improved symptoms of NP as measured by SNOT-22 from baseline to Week 24 compared with placebo.[58]The LS mean change from baseline was significantly greater for benralizumab compared with placebo from the first time point assessed, with the greatest difference observed at end of treatment (Week 4: mean difference in change −7.47 [p=0.0105]; Week 12: mean difference in change −7.93 [p=0.0219]; Week 24: mean difference in change −8.91 [p=0.0204]).[58]In the current *post-hoc* analysis, it was observed that the magnitude of the treatment effect on the symptoms of NP was further enhanced for patients with high baseline SNOT-22 scores (>30), from the first time point assessed through the end of the treatment period.

Severe, eosinophilic asthma is one of several disorders for which eosinophils contribute largely to inflammatory infiltrates in mucosal tissue (another being CRS) especially in the presence of NP, which is commonly seen in patients with severe, eosinophilic asthma.[3,63,11]Compared with the overall patient population, the patients included in the NP substudy had greater median BEC at baseline(510 cells/μLvs. 390 cells/μL[58]), along with an increased treatment response to benralizumabbased on asthma endpoints and SNOT-22. Approximately 60% of patients had a high baseline BEC (≥450 cells/μL), which is associated with enhanced benralizumab treatment response.[49,50,52,58] In addition to eosinophils, basophilshave also been indicated to have a prognostic role in chronic rhinosinusitis with NP.[64,65]Although basophil data are not available for the current NP substudy population, treatment with benralizumab has been shown to reduce blood basophils in severe asthma by ≥75%,[66]suggesting that benralizumab effects in severe

asthma and NP may not be restricted to the depletion of eosinophils. Additional analyses are needed to understand clearly whether the enhanced effect of benralizumab on asthma outcomes for this NP population were owing to improvements in NP or driven by high BEC or reduction in basophils and to determine if improvements in NP are always associated with asthma improvements or if they are independent.

Findings from the current substudy indicate that the IL-5 receptor alpha–directed cytolytic monoclonal antibody,benralizumab,improves disease-specific HRQoL for patients with severe, eosinophilic asthma and NP of any severity, as demonstrated by the early and sustained improvement in SNOT-22. Similar improvement on SNOT-22 scores at 24 weeks was observed with inhibition of IL-4/-13 signaling (dupilumab) in a *post-hoc* analysis of data from the Liberty Asthma QUEST Phase 3 study.[67]The results from these analyses add to the available clinical data demonstrating the efficacy of biologic medications in the reduction of NP symptoms and severity for patients with NP,[24,27,30–36]as well as the reduced symptoms and increased HRQoL reported for patients with asthma and severe NP.[29,36]

Similar to the findings in previous studies,[46–48,53,58]benralizumab was well-tolerated for patients with severe, eosinophilic asthma with NP.As demonstrated in the overall ANDHI trial population,[58]AEs for patients with NP were reported by similar percentages of patients receiving benralizumab and placebo, and most AEs were mild or moderate.In addition, the most commonly reported AEs for patients receiving benralizumab were similar to those reported for the ANDHI overall trial population.[58]Most common AEs (frequency ≥5%) for benralizumab patients included headache, sinusitis, pyrexia, and influenza.Although the percentage of patients with reported sinusitis as an AE was greater in the benralizumab group, the numbers are very small, and therefore not significant. Sinusitis is an adverse drug reaction previously reported in other studies[46, 47] and included in the label for benralizumab. Fewer serious AEsin both the overall study population and the NP substudy analysis set were reported for patients in the benralizumab group compared with the placebo group.[58]

Because the aim of ANDHI was to establish the effect of benralizumab as an add-on treatment for thosepatients with uncontrolled asthma,[58] patients enrolled in the study and included in the

current NP substudy continued to receive regularlyscheduled standard-of-care treatment, which may have enhanced response.[5] In addition, patients with NP in the placebo group had a greater rate of exacerbations compared with the rate observed in the overall ANDHI trial population.[5] Therefore, patients in the placebo group may have had more severe symptoms and, as a consequence,greater comparative benefits of benralizumab treatment on asthma symptoms may have been observed in these patients with NP.

In the overall study population in ANDHI, a total of 228 patients reported a medical history of NP,[58] with a subgroup analysis based only on NP history (yes/no) demonstrating similar results as observed in patients with NP ongoing at baseline who provided written consent to be in the substudy.In the current substudy of the ANDHI clinical trialfor patients with severe asthma, NP was not part of the inclusion criteria, and the diagnosis of NP was based solely on physician-verified patient history without additional diagnostic testing. NP disease severity was not clearly defined. and objective outcome measures (e.g., polyp size, future need for surgery) were not utilised to measure the efficacy of benralizumab for NP. However,aPhase III confirmatory study of benralizumab treatment of more than 400 patients with severe bilateral NP (with or without asthma) who are symptomatic despite receiving standard-of-care therapy is currently ongoing (OSTRO; ClinicalTrials.gov identifier: NCT03401229) and will address these limitations.Patients enrolled in the OSTRO trial include a different patient population than the ANDHI trial.

5. CONCLUSIONS

The results of this substudy from the Phase IIIbANDHI trial[58]extend the efficacy and safety profile of benralizumab for patients with NP of any severity and severe asthma with a screening BEC of ≥150 cells/μL.Benralizumab improved chronic rhinosinusitis with NP symptoms for patients with severe, eosinophilic asthma and NP.Clinically meaningful improvements in total SNOT-22 score were observed early and maintained over timefor patients with a high baseline SNOT-22 total score (>30).Greater improvement in lung function, disease-specific HRQoL, and asthma control outcomes has been observed with benralizumab for patients with NP and severe, eosinophilic asthma.Approximately half of patients with asthma and NP treated with

benralizumab were comprehensive responders, achieving clinically meaningful improvement in SNOT-22 and multiple asthma outcomes (exacerbations, HRQoL, lung function, and asthma control). This study further reinforces the relevance of NP in patients with severe, eosinophilic asthma to predicting a good treatment response to benralizumab. Additional studies of benralizumab will provide data needed to assess the effects of treatment on nasal polyp size and nasal symptoms for patients with CRSwith NP regardless of their having asthma.

DECLARATION OF INTERESTS

Giorgio Walter Canonica has previously received grant/research support from Boehringer Ingelheim, ALK, and Stallergenes, and honoraria or consultation fees from Menarini, GSK, Sanofi, Teva, Hal, AstraZeneca, and Novartis. Tim W. Harrison reports grants from the National Institute for Health Research, UK, and AstraZeneca; and personal fees and non-financial support from AstraZeneca, GSK, Vectura, Boehringer Ingelheim, Chiesi, and Synairgen. Pascal Chanez has served as an advisory board member, consultant, or lecturer, and has previously received honoraria or grants from ALK, Boehringer Ingelheim, Almirall, Centocor, GSK, MSD, AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and Amu. Francesco Menzella has received research grants from AstraZeneca, Novartis, and Sanofi; lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, and Sanofi. Renaud Louis has received unrestricted research grants from GSK, AstraZeneca, Novartis, and Chiesi, and lecture or advisory-board fees from GSK, AstraZeneca, Novartis, and Sanofi. Borja G. Cosio has received honoraria for speaking at sponsored meetings from AstraZeneca, Teva, Mundipharma, Boehringer Ingelheim, Chiesi, Esteve, GSK, Novartis and Rovi; he has received financial support to travel to meetings organized by Chiesi, Menarini, and Novartis, and he acts as a consultant for ALK, AstraZeneca, Mundipharma, Chiesi, and Sanofi, and has also received funding/grant support for research projects from a variety of governmental agencies and not-for-profit foundations, as well as from Boehringer Ingelheim, AstraZeneca, Chiesi, Menarini, and Novartis. Njira L. Lugogo received consulting fees from AstraZeneca and Teva; participated in advisory boards for AstraZeneca, Genentech, GSK, Novartis, Teva, and Sanofi; and received grants for clinical trials from AstraZeneca, Genentech, GSK, and Sanofi. Arjun Mohan has no conflicts to declare.

Giorgio Walter Canonica, Tim W. Harrison, Pascal Chanez, Francesco Menzella, Renaud Louis, Borja G. Cosio, Njira L. Lugogo, and Arjun Mohan were all ANDHI investigators and received institutional financial support to conduct the study. Annie Burden is a contract employee of AstraZeneca. Esther Garcia Gil is an employee of AstraZeneca and holds stock options.

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.

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Table 1. Demographics and Baseline Clinical Characteristics

Demographic/Characteristic	**Benralizumab (N=96)**	**Placebo (N=57)**
Sex		
Female, n (%)	53 (55.2)	24 (42.1)
Age (years)		
Mean (SD)	53.1 (12.3)	52.6 (11.1)
Race, n (%)[†]		
White	73 (91.3)	41 (91.1)
Black	3 (3.8)	2 (4.4)

Asian Other	2 (2.5) 2 (2.5)	1 (2.2) 1 (2.2)
BMI (kg/m^2) Mean (SD)	 27.38 (6.20)	 27.71 (5.54)
Exacerbations prior 12 months,rate 2, n (%) ≥3, n (%)	3.4 47 (49.0) 49 (51.0)	3.3 23 (40.4) 34 (59.6)
BEC group at screening, n (%) ≥300 cells/µL ≥150–<300 cells/µL	 79 (82.3) 17 (17.7)	 50 (87.7) 7 (12.3)
BEC at baseline (cells/µL) Median (range)	 515 (90–7970)	 500 (80–3900)
IgE values (IU/µL) Median (range)	 147.6 (4.6–6292.3)	 125.2 (9.2–7820.2)
Phadiatop Positive, n (%)	 49 (52.7)	 25 (44.6)
Pre-BD FEV_1 Mean (SD), L Percent predicted normal (SD), %	 1.7 (0.61) 53.7 (13.8)	 1.92 (0.71) 58.1 (13.8)
Post-BD FEV_1 Mean (SD), L Percent predicted normal (SD), %	 2.1 (0.76) 67.5 (17.2)	 2.3 (0.81) 71.1 (15.7)
Reversibility Mean (SD), %	 27.3 (20.5)	 24.4 (19.6)
SGRQ total score		

Mean (SD)	54.25 (15.00)	51.09 (18.05)
ACQ-6‡ Mean (SD)	2.88 (0.81)	2.96 (0.90)
SNOT-22 Mean (SD)	51.5 (20.4)	48.2 (21.2)
Allergies, n (%)	61 (63.5)	41 (71.9)
Allergic rhinitis, n (%)	14 (14.6)	7 (12.3)
Aspirin asthma trigger, n (%)	22 (22.9)	11 (19.3)
Past polypectomy, n (%)	69 (71.9)	41 (71.9)
NP medication use, n (%)	54 (56.3)	28 (49.1)
Intranasal corticosteroids	50 (52.1)	28 (49.1)
Leukotriene antagonists	2 (2.1)	0 (0)
Other nasal preparations	9 (9.4)	0 (0)

ACQ=Asthma Control Questionnaire; BD=bronchodilator; BEC=blood eosinophil counts; BMI=body mass index; FEV_1=forced expiratory volume in 1 second; IgE=Immunoglobulin E; NP=nasal polyposis; SGRQ=St. George's Respiratory Questionnaire; SNOT-22=Sino-Nasal Outcome Test-22.

†Race data missing for 16 patients in the benralizumab group and 12 patients in the placebo group. Percentages are based on the numbers of patients with data.

‡Baseline measurement was the last non-missing assessment prior to or on the day of the first dose of study treatment.

Table 2. Adverse Events During the On-treatment Period for Patients in the Benralizumab and Placebo Groups

	Benralizumab (n=96) n (%)†	Placebo (n=57) n (%)†
Adverse Event Category		
Any AE	73 (76.0)	42 (73.7)
Any SAE	5 (5.2)	7 (12.3)
Any AE leading to discontinuation	2 (2.1)	2 (3.5)
Any AE leading to death	0	0
Adverse Events Reported by ≥5% of Patients in Benralizumab Group		
Headache	15 (15.6)	4 (7.0)
Sinusitis	9 (9.4)	2 (3.5)
Nasopharyngitis	8 (8.3)	7 (12.3)
Pyrexia	7 (7.3)	3 (5.3)
Influenza	5 (5.2)	0 (0)
Injection-Related Reaction	1 (1.0)	0 (0)

AE=adverse event; SAE=serious adverse event.

†Patients with multiple AEs in the same category/preferred term were counted only once in that category/preferred term; patients with AEs in more than one category/preferred term were counted once in each of those categories/preferred terms.

FIGURE LEGENDS

Figure 1. Improvement from Baseline in SNOT-22 for Patients Treated with Benralizumab Versus Placebo: Patientswith SNOT-22 Total Score >30 at Baseline†

SNOT-22=Sino-Nasal Outcome Test-22.

Mean SNOT-22 total scores at baseline were similar for those patients in each treatment group with a high baseline total score of >30.

†Analysis via mixed model for repeated measures, with treatment, visit, and treatment × visit as explanatory variables and adjusted for baseline SNOT-22, region, exacerbations in previous year, and OCS use at baseline.

Figure 2. Responder Analysis: Percentage of Patients with Clinically Meaningful Improvements in SNOT-22 for Benralizumab Versus Placebo

MCID=minimum clinically important difference; NP=nasal polyposis; SNOT-22=Sino-Nasal Outcome Test-22.

The likelihood of achieving SNOT-22 responder status (MCID of –8.9 units) at end of treatment was greater for the benralizumab group compared with the placebo group (p=0.0036). The likelihood of achieving MCID was even greater for benralizumab patients with a high baseline SNOT-22 total score of >30 (p=0.0008). Percentage of patients with clinically meaningful improvements in SNOT-22 of 8.9 units[53] for benralizumab compared with placebo: (A) All patients with NP; (B) Patients with a high SNOT-22 total score >30 at baseline.

†Due to missing baseline data, two benralizumab patients and two placebo patients could not be classified as either responders or non-responders.

Figure 3.Reduction in Annualised Asthma Exacerbation Rate and Improvement from Baseline in SGRQ Total Score, Lung Function, and ACQ-6 for Patients with NP Treated with Benralizumab Versus Placebo

ACQ=Asthma Control Questionnaire; AER=annual exacerbation rate; FEV_1=forced expiratory volume in 1 second; L=liter; NP=nasal polyposis; OCS=oral corticosteroids; SE=standard error about the mean; SGRQ=St. George's Respiratory Questionnaire.

Reduction in AER and LS mean improvement from baseline in SGRQ total score (SE), lung function (SE), and ACQ-6(SE) for patients with severe, eosinophilic asthma and NP of any severity treated with benralizumab versus placebo. (A) AER analysis via negative binomial

modelincludingtreatment, region, exacerbations in previous year, and maintenance oral corticosteroid use at baseline. (B) SGRQ analysis via mixed model for repeated measures including treatment, baseline SGRQ, region, exacerbations in previous year, OCS use at baseline, visit, and treatment × visit. (C) Lung function analysis via mixed model for repeated measures,includingtreatment, baseline FEV_1, region, exacerbations in previous year, OCS use at baseline, age, sex, visit, and treatment × visit. (D) ACQ-6 analysis via mixed model for repeated measures, includingtreatment, baseline ACQ-6, region, exacerbations in previous year, OCS use at baseline, visit, and treatment × visit.

[†]95% confidence interval, $p<0.0001$.

FIGURE 1

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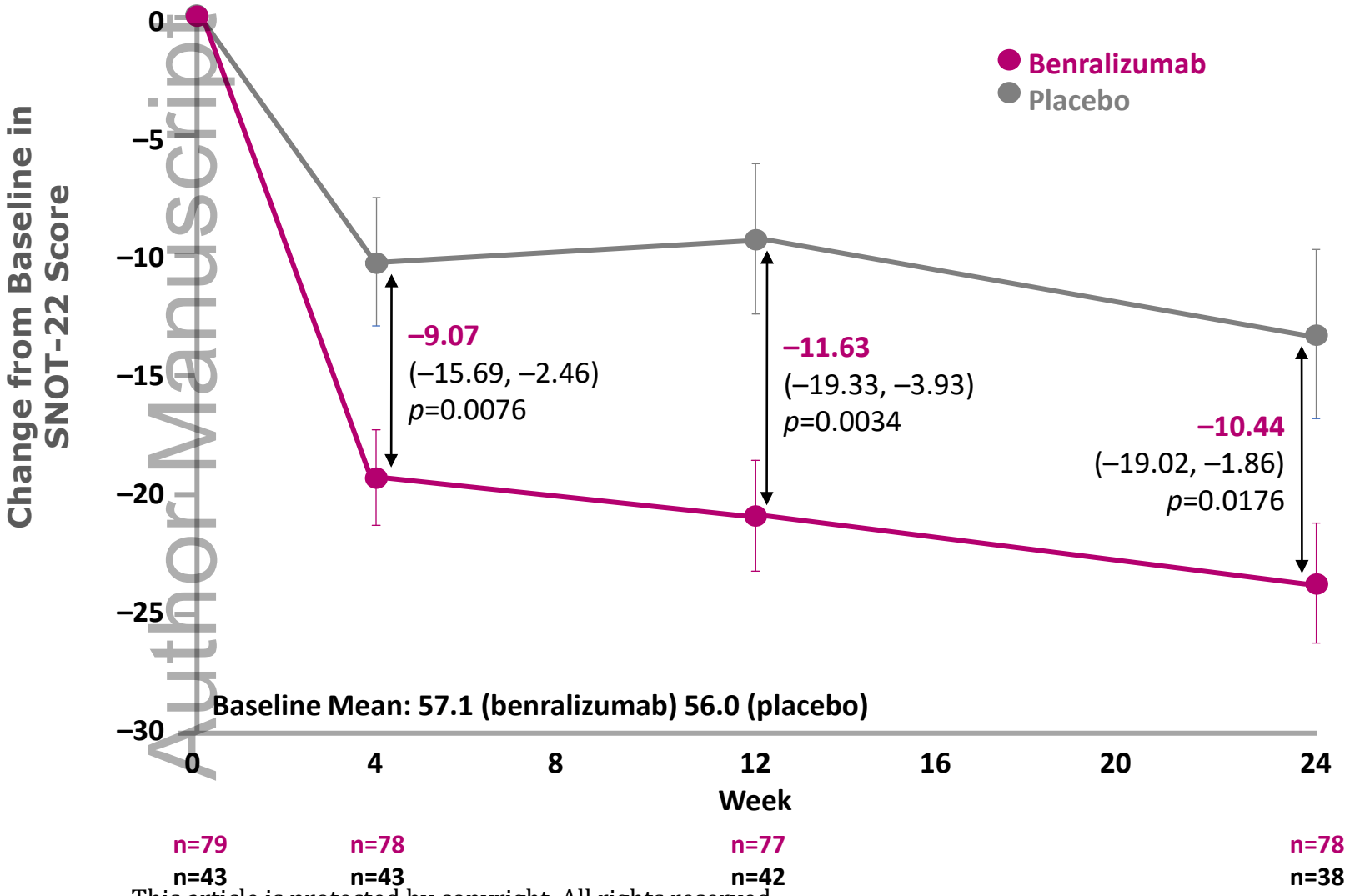

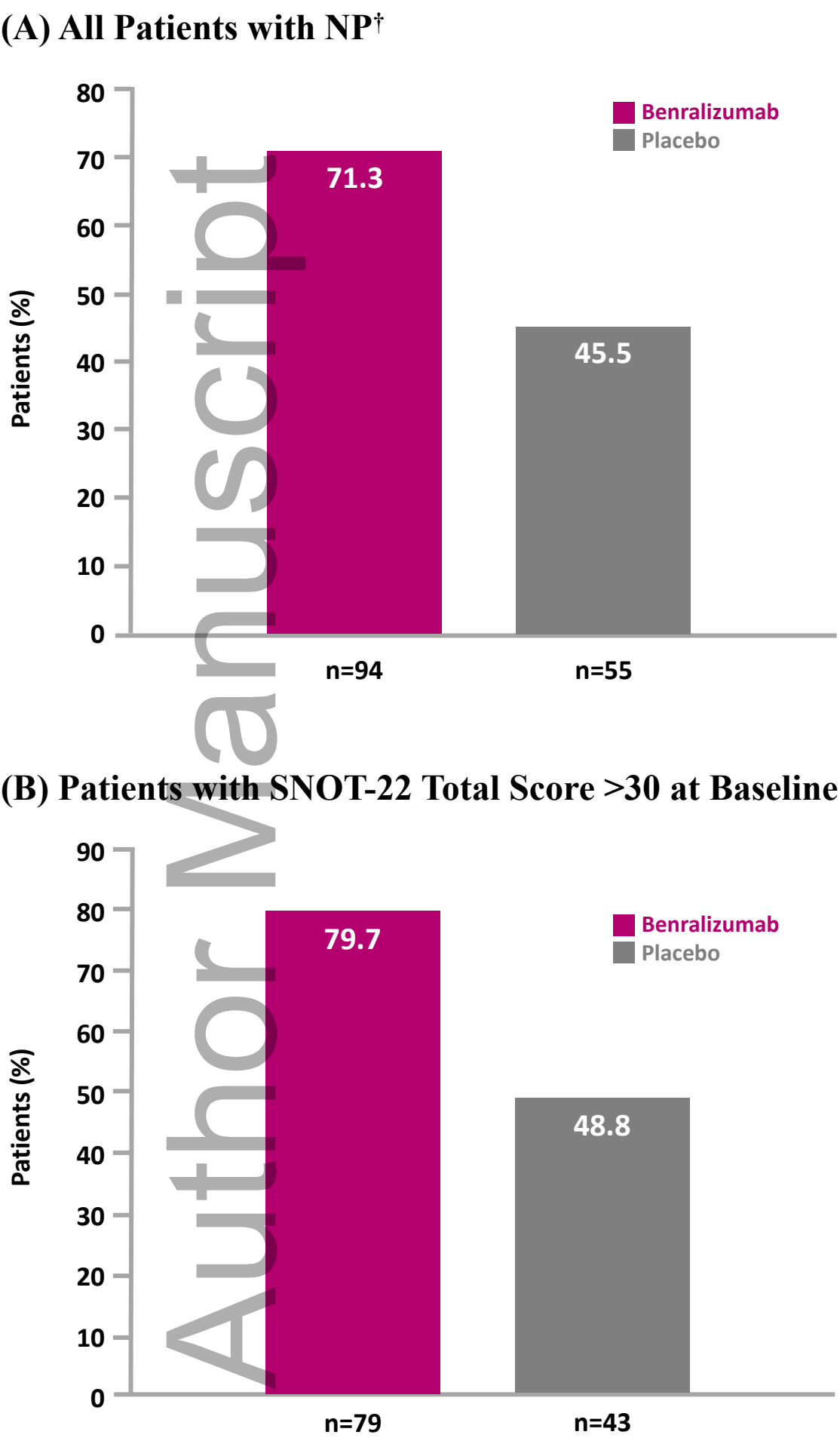

FIGURE 3

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