



HAL
open science

Severe Asthma Standard-of-Care Background Medication Reduction With Benralizumab: ANDHI in Practice Substudy

Renaud Louis, Tim Harrison, Pascal Chanez, Francesco Menzella, George Philteos, Borja Cosio, Njira Lugogo, Gustavo de Luiz, Annie Burden, Timothy Adlington, et al.

► To cite this version:

Renaud Louis, Tim Harrison, Pascal Chanez, Francesco Menzella, George Philteos, et al.. Severe Asthma Standard-of-Care Background Medication Reduction With Benralizumab: ANDHI in Practice Substudy. *Journal of Allergy and Clinical Immunology: In Practice*, 2023, 11 (6), pp.1759-1770.e7. 10.1016/j.jaip.2023.03.009 . hal-04423655

HAL Id: hal-04423655

<https://amu.hal.science/hal-04423655v1>

Submitted on 4 Sep 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Severe Asthma Standard-of-Care Background Medication Reduction With Benralizumab: ANDHI *in Practice* Substudy

Renaud Louis, MD^{a,*}, Tim W. Harrison, MD^{b,c,*}, Pascal Chanez, MD, PhD^d, Francesco Menzella, MD^e, George Philteos, MD^f, Borja G. Cosio, MD, PhD^g, Njira L. Lugogo, MD^h, Gustavo de Luiz, MDⁱ, Annie Burden, MSc^j, Timothy Adlington, MS^j, Nanna Keeling, MPharm^k, Justin Kwiatek, PharmD^l, and Esther Garcia Gil, MD^m; on behalf of the ANDHI Study Investigators Liège, Belgium; Nottingham and Cambridge, United Kingdom; Marseille, France; Montebelluna, Italy; Saskatoon, Canada; Palma de Mallorca, Màlaga, and Barcelona, Spain; Ann Arbor, Mich; Gothenburg, Sweden; Wilmington, Del

What is already known about this topic? In the phase IIIb, placebo-controlled ANDHI double-blind study, benralizumab significantly reduced asthma exacerbations and improved symptoms, patient-reported outcomes, and lung function for patients with severe eosinophilic asthma.

What does this article add to our knowledge? Results from the ANDHI *in Practice* (IP) substudy provide insight and confidence that background medications can be reduced while maintaining asthma control with benralizumab in a clinical practice setting.

How does this study impact current management guidelines? Current Global Initiative for Asthma guidelines recommend reducing background asthma medications when symptoms have been controlled and lung function stabilized. The ANDHI IP identifies a successful approach to stepping down treatment for severe asthma in the era of biologics.

BACKGROUND: The phase IIIb, randomized, parallel-group, placebo-controlled ANDHI double-blind (DB) study extended understanding of the efficacy of benralizumab for patients with

severe eosinophilic asthma. Patients from ANDHI DB could join the 56-week ANDHI *in Practice* (IP) single-arm, open-label extension substudy.

^aDepartment of Pneumology CHU Liège, GIGAI3, University of Liège, Liège, Belgium

^bRespiratory Research Unit, Nottingham Respiratory NIHR BRC, University of Nottingham, Nottingham, UK

^cGlobal Medical Affairs, AstraZeneca, Cambridge, UK

^dDepartment of Respiratory CIC Nord INSERM/INRAE C2VN, Aix Marseille University, Marseille, France

^ePulmonology Unit, S. Valentino Hospital, Local Health Authority, Montebelluna, Italy

^fRoyal University Hospital, University of Saskatchewan, Saskatoon, Sask, Canada

^gHospital Son Espases-IdISBa and Ciberes, Palma de Mallorca, Spain

^hUniversity of Michigan, Ann Arbor, Mich

ⁱClinical Research and Respiratory Medicine Department, Vithas Xanit International Hospital, Benalmadena, Málaga, Spain

^jBiometrics, Late-stage Development, Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

^kBioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden

^lBioPharmaceuticals Medical, AstraZeneca, Wilmington, Del

^mBioPharmaceuticals Medical, AstraZeneca, Barcelona, Spain

*These authors have contributed equally to this work.

This study was funded by AstraZeneca.

Conflicts of interest: R. Louis has received unrestricted research grants from GlaxoSmithKline (GSK), AstraZeneca, Novartis, and Chiesi, and lecture or advisory board fees from GSK, AstraZeneca, Novartis, and Sanofi. P. Chanez has served as an advisory board member, consultant, or lecturer, and has received honoraria or grants from Boehringer Ingelheim, Almirall, Centocor, GSK, Merck Sharpe and Dohme (MSD), AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and Amu. F. Menzella has received research grants from AstraZeneca, Novartis, and Sanofi, and lecture fees and advisory board fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Angelini, Novartis, and Sanofi. B. G. Cosio has received honoraria for speaking at sponsored meetings from AstraZeneca, Teva,

Mundipharma, Boehringer Ingelheim, Chiesi, GSK, Sanofi, and Novartis; has received financial support to travel to meetings organized by Chiesi, Menarini, and Novartis; acts as a consultant for ALK, AstraZeneca, Mundipharma, Chiesi, and Sanofi; 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, and Menarini. N. L. Lugogo received consulting fees from AstraZeneca and Teva; participated in advisory boards for AstraZeneca, Genentech, GSK, Novartis, and Sanofi; and received grants for clinical trials from AstraZeneca, Genentech, GSK, and Sanofi. R. Louis, P. Chanez, F. Menzella, G. Philteos, B. G. Cosio, N. L. Lugogo, G. de Luiz, and T. Harrison were all ANDHI study and ANDHI IP substudy investigators and received financial support to conduct the studies. T. Harrison, N. Keeling, and J. Kwiatek are employees of AstraZeneca and hold stock options. E. Garcia Gil was an employee of AstraZeneca when the study was conducted. T. Adlington was contracted to AstraZeneca when the study was conducted and is still contracted to AstraZeneca. A. Burden was contracted to AstraZeneca when the study was conducted. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication August 17, 2022; revised February 22, 2023; accepted for publication March 5, 2023.

Available online March 21, 2023.

Corresponding author: Tim W. Harrison, MD, Respiratory Research Unit, Nottingham NIHR BRC, University of Nottingham, Nottingham City Hospital, Nottingham, NG5 1PB, UK. E-mail: Tim.Harrison@nottingham.ac.uk.

2213-2198

© 2023 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2023.03.009>

Abbreviations usedACQ-6- *Asthma Control Questionnaire-6*AE- *Adverse event*DB- *Double-blind*EOT- *End of treatment*GINA- *Global Initiative for Asthma*HD- *High dosage*ICS- *Inhaled corticosteroids*IP- *In Practice*LABA- *Long-acting β 2-agonists*LAMA- *Long-acting muscarinic antagonists*LD- *Low dosage*LTRA- *Leukotriene receptor antagonists*MD- *Medium dosage*OCS- *Oral corticosteroid*

OBJECTIVE: Assess potential for standard-of-care background medication reductions while maintaining asthma control with benralizumab.

METHODS: Following ANDHI DB completion, eligible adults were enrolled in ANDHI IP. After an 8-week run-in with benralizumab, there were 5 visits to potentially reduce background asthma medications for patients achieving and maintaining protocol-defined asthma control with benralizumab. Main outcome measures for non-oral corticosteroid (OCS)-dependent patients were the proportions with at least 1 background medication reduction (ie, lower inhaled corticosteroid dose, background medication discontinuation) and the number of adapted Global Initiative for Asthma (GINA) step reductions at end of treatment (EOT). Main outcomes for OCS-dependent patients were reductions in daily OCS dosage and proportion achieving OCS dosage of 5 mg or lower at EOT.

RESULTS: For non-OCS-dependent patients, 53.3% (n = 208 of 390) achieved at least 1 background medication reduction, increasing to 72.6% (n = 130 of 179) for patients who maintained protocol-defined asthma control at EOT. A total of 41.9% (n = 163 of 389) achieved at least 1 adapted GINA step reduction, increasing to 61.8% (n = 110 of 178) for patients with protocol-defined EOT asthma control. At ANDHI IP baseline, OCS dosages were 5 mg or lower for 40.4% (n = 40 of 99) of OCS-dependent patients. Of OCS-dependent patients, 50.5% (n = 50 of 99) eliminated OCS and 74.7% (n = 74 of 99) achieved dosages of 5 mg or lower at EOT.

CONCLUSIONS: These findings demonstrate benralizumab's ability to improve asthma control, thereby allowing background medication reduction. © 2023 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (J Allergy Clin Immunol Pract 2023;■:■-■)

Key words: Benralizumab; Eosinophils; Oral corticosteroids; Open-label extension; Severe asthma; Eosinophilic asthma

INTRODUCTION

Of approximately 339 million people with asthma worldwide, up to 10% have severe asthma.¹⁻⁵ Asthma is classified as severe when maximal, high-intensity treatment is needed for symptom control or when asthma remains uncontrolled despite optimal treatment.^{6,7} Severe asthma is a heterogeneous disease that

encompasses multiple phenotypes.^{8,9} Characterized by eosinophilic inflammation of the airways, the eosinophilic phenotype is the most common and is associated with greater risks of severe exacerbations, acute respiratory events, impaired lung function, and poor asthma control.¹⁰⁻¹⁴

Patients with uncontrolled severe asthma experience increased disease burden, including recurrent asthma exacerbations, that can lead to increased hospitalizations and death.¹⁵⁻¹⁷ Despite effective treatments for asthma such as inhaled corticosteroids (ICS), long-acting β 2-agonists (LABA), leukotriene receptor antagonists (LTRA), and long-acting muscarinic antagonists (LAMA), asthma remains uncontrolled in one-half of patients, who require additional medications such as oral corticosteroids (OCS) and biologics.^{18,19} Biologics are associated with decreased asthma exacerbation rates, reduced asthma symptoms, and improved lung function, and they have the potential to reduce exposure to high ICS and OCS dosages and related adverse events (AEs).^{5-7,17,20-23}

Benralizumab, an interleukin-5 receptor alpha (IL-5R α)-directed cytolytic monoclonal antibody, induces rapid and near-complete depletion of eosinophils.²⁴ In the 24-week, phase IIIb, randomized, placebo-controlled ANDHI double-blind (DB) study, benralizumab showed early benefits in patient-reported outcomes, health-related quality of life, and lung function, as well as a 49% reduction in annualized asthma exacerbation rates compared with placebo in patients with severe eosinophilic asthma that was not adequately controlled at baseline with background medications alone.²⁵ It is unknown whether these background medications would still be needed alongside biologic therapy for asthma control.

Asthma treatment recommendations from the Global Initiative for Asthma (GINA) advise continuous reevaluation of the need for each severe asthma treatment, including gradually reducing or stopping OCS and considering reducing ICS dosage, when symptoms have been controlled and lung function has been stabilized for at least 3 months.²⁶ More evidence-based decision making is needed around the best approach for stepping down treatment in the era of biologic therapy.^{26,27} To understand the potential for background medication reduction in patients receiving benralizumab, eligible adults with severe eosinophilic asthma who had completed ANDHI DB²⁵ had the option to enroll in the ANDHI *in Practice* (IP) open-label extension substudy. The goal of ANDHI IP was to evaluate whether benralizumab enabled patients to reduce their stable standard-of-care asthma background medications used in ANDHI DB²⁵ while maintaining asthma control in a clinical practice setting.

METHODS

The methodology and results of the phase IIIb, randomized, parallel-group, placebo-controlled ANDHI DB study have been published.²⁵ Adult patients with a screening blood eosinophil count of 150 cells/ μ L or higher and diagnosed by a physician to have severe eosinophilic asthma requiring treatment with medium-dosage (MD) to high-dosage (HD) ICS plus another background medication (eg, LABA, LAMA, LTRA, or OCS) for at least 12 months prior to enrolment were included in the ANDHI DB study.²⁵ On completion of the DB period, eligible patients could enroll in the open-label, 56-week ANDHI IP substudy, which was performed at 129 centers in 13 countries worldwide.

Before the study was initiated, the clinical study protocol, informed consent form, and any other relevant documents were reviewed and approved by an independent ethics committee or an institutional review board at each participating site. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation and Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca company policy on bioethics.

Study design and participants

For inclusion in ANDHI IP, patients had to complete the ANDHI DB end-of-treatment (EOT) visit at the end of the 24-week DB period (visit 11/wk 24) and provide written informed consent. Exclusion criteria were reviewed in all potential participants prior to inclusion. (Exclusion criteria details can be found in the Online Repository available at www.jaci-inpractice.org).

After enrollment, patients continued their background medication regimen during an 8-week active run-in period (visits 13 and 14), followed by a 32-week period with 5 per-protocol potential background medication reduction attempts 8 weeks apart (visit 15/wk 32 to visit 23/wk 64), a 16-week maintenance period with no further reductions (visit 23/wk 64 to visit 27/wk 80), including an EOT visit (visit 27/wk 80) (Figure 1 and Video E1; available in this article's Online Repository at www.jaci-inpractice.org). All patients received benralizumab 30 mg subcutaneously once every 4 weeks for 3 doses (visits 13, 14, and 15/wk 32), and once every 8 weeks thereafter, with phone visits 4 weeks after each of the first 4 reduction visits (visit 16/wk 36, visit 18/wk 44, visit 20/wk 52, visit 22/wk 60). Some patients entered ANDHI IP on the same day as ANDHI DB EOT (visit 11/wk 24), whereas others had a gap in treatment, with open-label ANDHI IP visit 13 initiated later. Benralizumab treatment continued throughout the active run-in, reduction, and maintenance phases. Other medication(s) considered necessary for the patient's safety and well-being were given at the discretion of the investigator. Patients enrolled in ANDHI IP remained blinded to their ANDHI DB treatment.

Outcomes

Main Efficacy Analysis Set. The Main Efficacy Analysis Set included patients who received at least 1 dose of open-label benralizumab in ANDHI IP, attended the first planned reduction visit (visit 15/wk 32), and were not receiving long-term OCS for asthma at visit 15/week 32. Patients using OCS for an asthma exacerbation were included. The main outcomes for the Main Efficacy Analysis Set were the proportion of patients with at least 1 background medication reduction from baseline (visit 15/wk 32) through EOT (visit 27/wk 80) and the proportion of patients with at least 1 adapted GINA step reduction²⁶ from baseline to EOT.

The following criteria were required for background medication reduction: (1) Asthma Control Questionnaire-6 (ACQ-6) score of less than 1.5 (and no clinically meaningful deterioration in ACQ-6 score from the most recent clinic visit value [$<+0.5$] at visit 17/wk 40, visit 19/wk 48, visit 21/wk 56, and visit 23/wk 64); (2) no interim clinically meaningful exacerbation since the last visit that required an OCS burst (or an increase in the patients' maintenance OCS dosage) or a hospitalization for asthma; and (3) investigator agreement that there was no clinical or other reason not to reduce. Investigators could defer any scheduled dosage reduction if their clinical assessment was that it would not be in the patient's best interest.

For patients in the Main Efficacy Analysis Set, per-protocol background medication reductions were to be attempted at every scheduled reduction visit in eligible patients who met reduction criteria (Table I). Only single-step reductions were recommended at each visit. In general, reductions were to progress from ICS + another controller(s) (eg, HD ICS/LABA) through to either low-dosage (LD) ICS formulation and/or an as-needed reliever inhaler regimen as tolerated (Figure 2, A). All non-LABA and non-OCS controllers (eg, LTRA, LAMA, and/or xanthines) were to be discontinued before ICS or ICS/LABA were reduced.

Reduction of background medication was evaluated by adapted GINA steps²⁶:

- Step 1: no maintenance asthma controller regimen;
- Step 2: LD ICS, an LTRA, or a xanthine as monotherapy;
- Step 3: LD ICS/LABA or MD ICS as monotherapy; or LD ICS plus an LTRA or plus a xanthine;
- Step 4: MD ICS/LABA or HD ICS as monotherapy; and
- Step 5: HD ICS/LABA; or any maintenance OCS.

The GINA step assessment was qualified as "adapted" for ANDHI IP because the component of GINA step 5 that involved biologic treatment (patients currently treated with an add-on biologic) was excluded from adapted GINA categories because all patients were receiving benralizumab.²⁶

Reduction in maintenance medication was defined as discontinuation of LABA, LAMA, LTRA, or xanthines by visit 27/week 80 from visit 15/week 32, or reduction in maintenance ICS dosage from HD to MD or MD to LD, or reduction from LD maintenance to reliever ICS. (The ICS dosage classifications are presented in this article's Online Repository at www.jaci-inpractice.org.) Reduction in maintenance ICS dosage from HD to LD or from MD ICS maintenance to reliever was counted as 2 reductions. Reduction from supra-HD was also a reduction. If a patient discontinued 1 ICS medication when they had taken 2 or more concurrently (either singly or part of a combination medication) but remained in the HD ICS category, this was 1 reduction.

OCS-Dependent Analysis Set. The OCS-Dependent Analysis Set included patients who received at least 1 dose of open-label benralizumab in ANDHI IP, attended visit 15/week 32, and were receiving maintenance OCS for asthma at visit 15/week 32. These patients were analyzed as a distinct group because OCS dependence warranted prioritization of OCS elimination, which limited the time available for further medication reductions. The main outcome measures for OCS-dependent patients were the proportion of patients achieving a 50%, 75%, 90%, or 100% OCS dosage reduction from baseline to EOT and the proportion of patients achieving an OCS dosage of 5 mg or lower at EOT.

For patients in the OCS-Dependent Analysis Set, the OCS dosage was to be tapered off prior to attempting reduction of the non-OCS background controllers. In general, OCS was to be reduced by 5-mg increments every 1 to 2 weeks, at the discretion of the investigator, until a daily dose of 7.5 mg was achieved (Figure 2, B). At this point, OCS was to be reduced more slowly and in smaller decrements (eg, 1–2.5 mg every 4 wk) and could be discontinued if the investigator judged it safe to do so.

Safety

The Safety Analysis Set included all patients who received at least 1 dose of open-label benralizumab in ANDHI IP. The AEs were collected from time of consent through EOT (visit 27/wk 80).

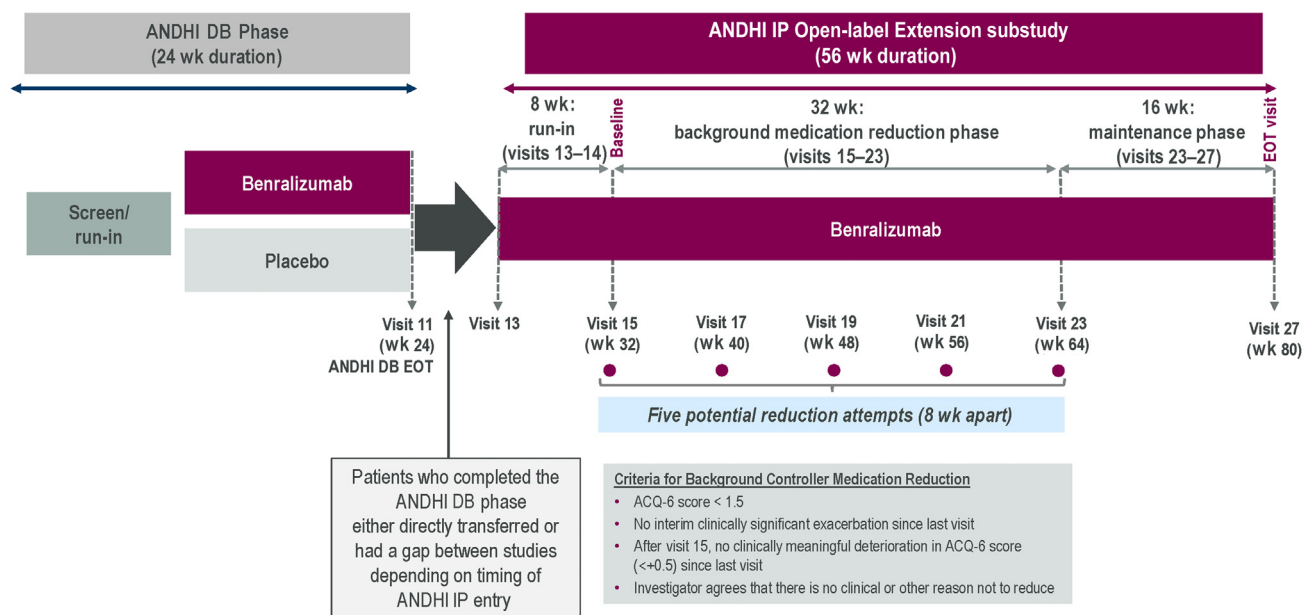


FIGURE 1. ANDHI IP study design.

TABLE 1. Recommended stepwise background asthma therapy reductions for the Main Efficacy Analysis Set (non-OCS-dependent patients) during the reduction phase

Background therapy	Recommended reduction in therapy*
ICS/LABA plus another non-OCS controller(s)†	Discontinue all the non-LABA/non-OCS controllers so that only ICS/LABA therapy remains
Daily HD ICS plus another non-LABA/non-OCS controller(s)†	Reduce the current HD ICS to an MD formulation at the first reduction visit; continue the other controllers
Daily MD ICS plus another non-LABA/non-OCS controller(s)†	Discontinue all the non-LABA/non-OCS controllers so that only daily MD ICS therapy remains
HD ICS/LABA only	Reduce ICS dosage to medium
MD ICS/LABA only	Either switch to an LD ICS/LABA or discontinue the LABA so that the patient is on daily MD or HD ICS monotherapy
HD ICS only	Reduce to MD ICS only
MD ICS only	Reduce to LD ICS
LD ICS/LABA only	Discontinue maintenance ICS/LABA and switch patient either to LD ICS or to as-needed LD ICS/formoterol (according to local practice/guidance)
LD ICS only	Either continue LD ICS or step down to as-needed SABA or as-needed LD ICS/formoterol (according to local practice/guidance) according to clinical judgment

*Per-protocol background medication reduction was to be attempted at every scheduled reduction visit in eligible patients who met the reduction algorithm criteria. Investigators were to adapt these recommendations to available local formulations and use their clinical judgment. It was to be understood that asthma reliever use was always indicated, as usual.

†Other non-LABA, non-OCS controllers include therapies such as LTRA, LAMA, or theophylline.

Unresolved AEs at visit 11/week 24 (end of the 24-wk ANDHI DB) continued to be documented for patients directly continuing benralizumab treatment with no gap between ANDHI DB and IP.

Post hoc analyses

The percentage of patients with uncontrolled asthma at EOT (ACQ-6 ≥ 1.5 or clinically significant exacerbations since visit 25/wk to be determined or during the 8 wk prior) with asthma control (ACQ-6 < 1.5) during any ANDHI IP visit before EOT was

assessed for the Main Efficacy Analysis Set and the OCS-Dependent Set.

Statistical analysis

Summary statistics and analyses were reported for the Main Efficacy Analysis Set and the OCS-Dependent Analysis Set and repeated for patients with controlled versus uncontrolled asthma at EOT (visit 27/wk 80) in the Main Efficacy Analysis Set. An EOT controlled asthma was defined as an ACQ-6 score less than 1.5 at EOT, as established by Juniper and colleagues,²⁸ and no clinically

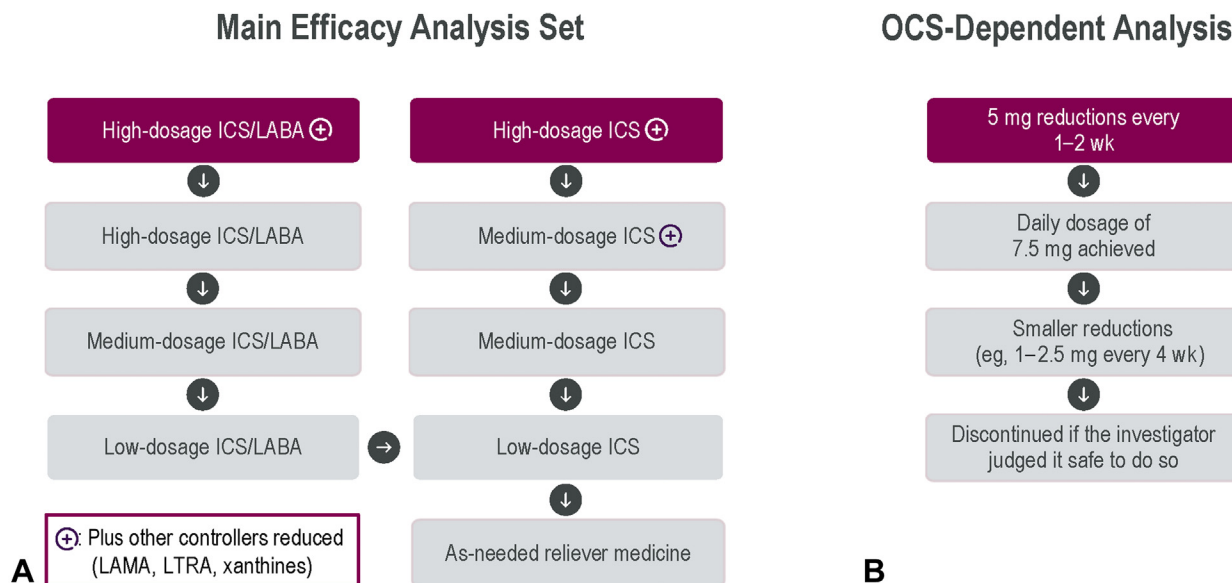


FIGURE 2. Reduction of background for (A) the Main Efficacy Analysis Set and (B) the OCS-Dependent Analysis Set.

TABLE II. Baseline patient demographics and characteristics at ANDHI DB phase baseline: Main Efficacy Analysis and OCS-Dependent Analysis Sets

Demographics/ characteristics	Main Efficacy Analysis Set (n = 390)	OCS-Dependent Analysis Set (n = 99)
Sex, female, n (%*)	232 (59.5)	58 (58.6)
Age (y), mean (SD)†	53.1 (12.43)	55.2 (11.40)
Age ≥ 18 y at asthma onset, n (%*)	269 (69.2)	84 (84.8)
Race, n (%*)		
Asian	11 (3.3)	4 (5.1)
Black	38 (11.3)	2 (2.6)
Native Hawaiian/other Pacific Islander	1 (0.3)	0
White	282 (83.7)	71 (91.0)
Other	5 (1.5)	1 (1.3)
Missing	53	21
Body mass index (kg/m ²), mean (SD)†	30.32 (7.9)	29.01 (7.0)
Blood eosinophil count at screening (cells/μL), median (range)‡	440 (60–5,020)	430 (150–1,810)
≥300, n (%*)	277 (71.4)	73 (73.7)
≥150 to <300, n (%*)	111 (28.6)	26 (26.3)
Phadiatop positive§ at baseline, n (%*)‡	214 (58.2)	41 (43.6)
Total immunoglobulin E (IU/mL), median (range)†	138.0 (1.5–7,820.2)	149.2 (1.5–9,063.8)

*Percentages calculated based upon patients with available data. Demographic/characteristic data are from ANDHI DB period baseline.

†At ANDHI DB phase baseline (visit 4).

‡At ANDHI DB phase visit 1/visit 2.

§Qualitative assessment for the presence of allergen-specific immunoglobulin E.

significant exacerbations during the 8 weeks before EOT. EOT uncontrolled asthma was defined as not meeting controlled asthma criteria at EOT. Patients who withdrew or were lost to follow-up and patients with missing ACQ-6 scores at EOT who had otherwise completed the study were considered uncontrolled. No formal hypothesis testing was conducted; all analyses were considered descriptive, and all reported *P* values are nominal. (Statistical analysis methodology details are in the Online Repository available at www.jaci-inpractice.org.)

RESULTS

Of the 616 patients who had completed the ANDHI DB study,²⁵ 504 consented to enter ANDHI IP between November 19, 2018, and October 21, 2020. A total of 503 enrolled patients (99.8%) received open-label benralizumab (1 patient [0.2%] provided informed consent for ANDHI IP but did not receive open-label benralizumab; no other study end points were recorded for this patient). Of patients receiving benralizumab, 490 (97.2%) entered the background medication reduction period (visits 15–23/wk 32–64) (For patient disposition details, see the Online Repository and [Figures E1, E2, and E3](#); available in this article's Online Repository at www.jaci-inpractice.org.)

Patients

The Main Efficacy Analysis Set included 390 patients. The OCS-Dependent Analysis Set included 99 patients. Patient characteristics in each were generally representative of a severe asthma population ([Table II](#)).

All patients except 1 were taking maintenance ICS-containing background medication at ANDHI IP baseline ([Table III](#)). In the Main Efficacy Analysis Set, 387 patients (99.2%) were taking LABA, with 359 patients (92.1%) on ICS/LABA as a fixed dose combination device. A total of 378 patients (96.9%) were on either HD or MD ICS/LABA. The proportion of patients taking

TABLE III. Asthma maintenance medications at ANDHI IP baseline (visit 15/wk 32): Main Efficacy Analysis and OCS-Dependent Analysis Sets

Medication	Statistic or category	Main Efficacy Analysis Set (n = 390)	OCS-Dependent Analysis Set (n = 99)
Maintenance ICS, n (%) [*]	Yes	389 (99.7)	99 (100.0)
	HD-ICS [†]	243 (62.3)	69 (69.7)
	SHD-ICS	9 (2.3)	4 (4.0)
	MD-ICS [†]	135 (34.6)	26 (26.3)
	LD-ICS [†]	11 (2.8)	4 (4.0)
	Other ICS [‡]	3 (0.8)	3 (3.0)
	Other ICS [‡] only	1 (0.3)	0
OCS, n (%) [§]	Yes	NA	99 (100.0)
	≤5 mg	NA	40 (40.4)
	>5 mg	NA	59 (59.6)
	Mean dosage (mg), (SD; range)	NA	9.3 (5.2; 1.0–20.0)
LABA, n (%) [*]	Yes	387 (99.2)	97 (98.0)
Maintenance ICS/LABA, n (%) [*]	Yes	359 (92.1)	83 (83.8)
	HD-ICS [†] /LABA	212 (54.4)	49 (49.5)
	SHD-ICS/LABA	7 (1.8)	4 (4.0)
	MD-ICS [†] /LABA	139 (35.6)	30 (30.3)
	LD-ICS [†] /LABA	8 (2.1)	4 (4.0)
	Other ICS/LABA [‡] only	1 (0.3)	0
LAMA, n (%)	Yes	160 (41.0)	51 (51.5)
LTRA, n (%)	Yes	205 (52.6)	42 (42.4)
Xanthines, n (%)	Yes	14 (3.6)	9 (9.1)

SHD, Supra-high dosage.

*ICS and LABA taken as part of combination therapy were included in both individual- and combination-therapy categories.

[†]Low, medium, and high ICS dosages were classified using fluticasone propionate equivalent units.

[‡]As-needed reliever regimen consistent with local practice.

[§]OCS dosages were converted to their prednisolone equivalent.

^{||}Patients receiving maintenance OCS medication for asthma at ANDHI IP baseline (visit 15/wk 32) were excluded from the Main Efficacy Analysis Set.

LAMA, LTRA, and xanthines was 41.0% (n = 160 of 390), 52.6% (n = 205 of 390), and 3.6% (n = 14 of 390), respectively. The mean (SD) OCS dosage was 9.3 mg (5.21 mg), with 59 patients (59.6%) having an OCS dosage greater than 5 mg at baseline and 40 (40.4%) with a dosage of 5 mg or lower at baseline.

Controlled asthma status

In the Main Efficacy Analysis Set, 45.9% of patients (n = 179 of 390) had controlled asthma at ANDHI IP EOT and 47.5% (n = 47 of 99) in the OCS-Dependent Set had controlled asthma at EOT (Figure E4; available in this article's Online Repository at www.jaci-inpractice.org). *Post hoc* analysis showed that, among those in the Main Efficacy Analysis Set with uncontrolled asthma at EOT, 61.1% (n = 129 of 211) had either well- or partially controlled asthma at any prior ANDHI IP visit; in the OCS-Dependent Set, 73.1% of patients (n = 38 of 52) with uncontrolled asthma at EOT had controlled asthma at a prior visit.

Background medication reductions

Main Efficacy Analysis Set. Approximately one-half of patients (53.3%; n = 208 of 390) in the Main Efficacy Analysis Set achieved at least 1 background medication reduction by EOT (visit 27/wk 80). This increased to 72.6% (n = 130 of 179) in patients with controlled asthma at EOT.

Overall, 59.0% of patients (n = 230 of 390) met the criteria for reducing their background medication at 1 or more reduction

visits. A greater proportion of patients (76.0%; n = 136 of 179) with controlled asthma at EOT met the criteria for medication reduction than patients with uncontrolled asthma at EOT (41.7%; n = 88 of 211). Overall, 41.0% of patients (n = 160 of 390) did not reduce background medication at any reduction period visit. For 23.1% of patients (n = 90 of 390), this was because they had not met the asthma control criteria, but for 17.9% (n = 70 of 390) this was because the investigator recommended not to reduce controller medication despite the patient meeting asthma control criteria.

The investigator did not recommend a reduction in asthma medication at 51.8% of visits when the other 2 reduction criteria had been met. The most reported reasons for not reducing background medications included physician considering maximum stable reduction was reached (11.8%) and for prophylactic reasons (9.2%) (Table E1; available in this article's Online Repository at www.jaci-inpractice.org).

The percentage of patients in the Main Efficacy Analysis Set on HD ICS reduced from 62.6% at baseline to 36.4% at EOT. In the subset of patients with controlled asthma at EOT, the reductions were more pronounced; 63.1% required HD ICS at baseline and 25.1% at EOT (Figure 3). By EOT, 23.9% of patients (n = 58 of 243) reduced from HD to MD ICS; 16.5% (n = 40 of 243) reduced from HD to LD; and 30.4% (n = 41 of 135) reduced from MD to LD.

Overall, 39.4% of patients (n = 63 of 160) taking LAMA medications, 33.7% (n = 69 of 205) of patients taking LTRA medications, and 11.9% (n = 46 of 387) of patients taking

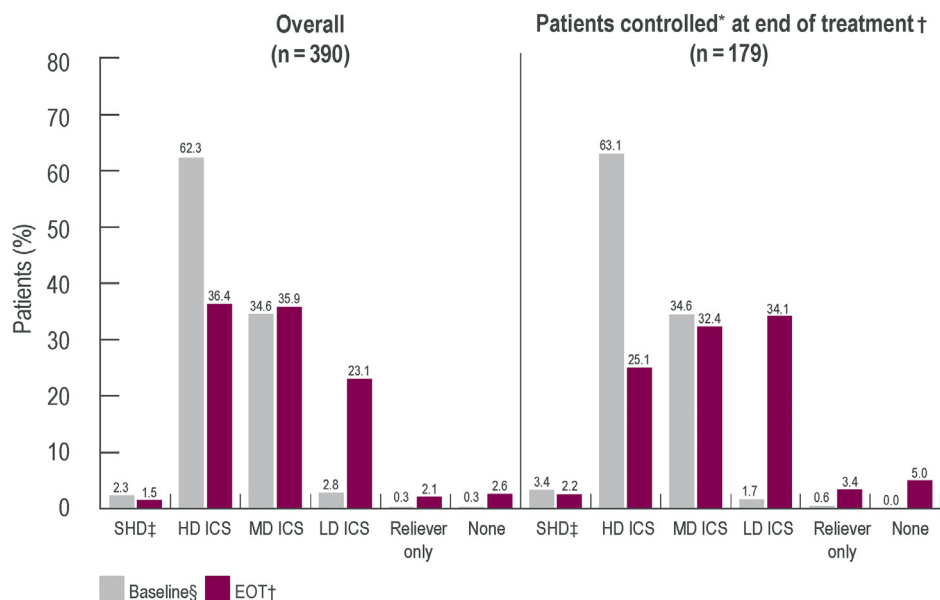


FIGURE 3. Distribution of patients by ICS dosage categories at baseline§ and EOT†: Main Efficacy Analysis Set. *SHD*, supra-high dosage. *Controlled defined as ACQ-6 score <1.5 and no clinically significant exacerbations since visit 25/week 72 (or during last 8 wk prior to visit 27/wk 80). †Start date prior to visit 27/week 80 and ongoing or with a stop date at or the day before visit 27/week 80. ‡SHD defined for this study as fluticasone furoate >200 µg; beclomethasone dipropionate >800 µg for combination fixed-dosage medications including the QVAR Redihaler; budesonide >1,600 µg; ciclesonide >640 µg; mometasone furoate >800 µg; fluticasone propionate >2,000 µg. The SHD group is a subset of the HD group. §Start date prior to visit 15/week 32 and ongoing past visit 15/week 32 or start date prior to visit 15/week 32 with a stop date on or the day before visit 15/week 32.

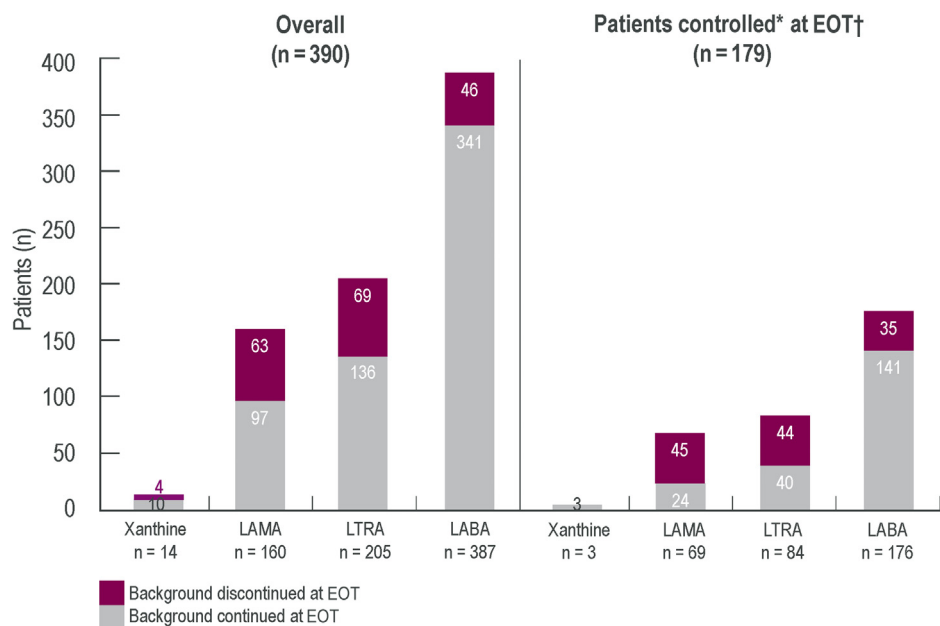


FIGURE 4. Number of patients continuing and discontinuing background medication by EOT†: Main Efficacy Analysis Set. *Controlled defined as ACQ-6 score <1.5 and no clinically significant exacerbations since visit 25/week 72 (or during last 8 wk prior to visit 27/wk 80). †Start date prior to visit 27/week 80 and ongoing or with a stop date at or the day before visit 27/week 80.

LABA medications at ANDHI IP baseline discontinued these medications by EOT (Figure 4). A higher proportion of patients with controlled asthma at EOT had discontinued at least 1 of

these medications (LAMA 65.2% [n = 45 of 69]; LTRA 52.4% [n = 44 of 84]; and LABA 19.9% [n = 35 of 176]).

Most patients (96.4%; n = 376) were categorized as adapted GINA step 4 or 5 at ANDHI IP baseline (visit 15/wk 32)

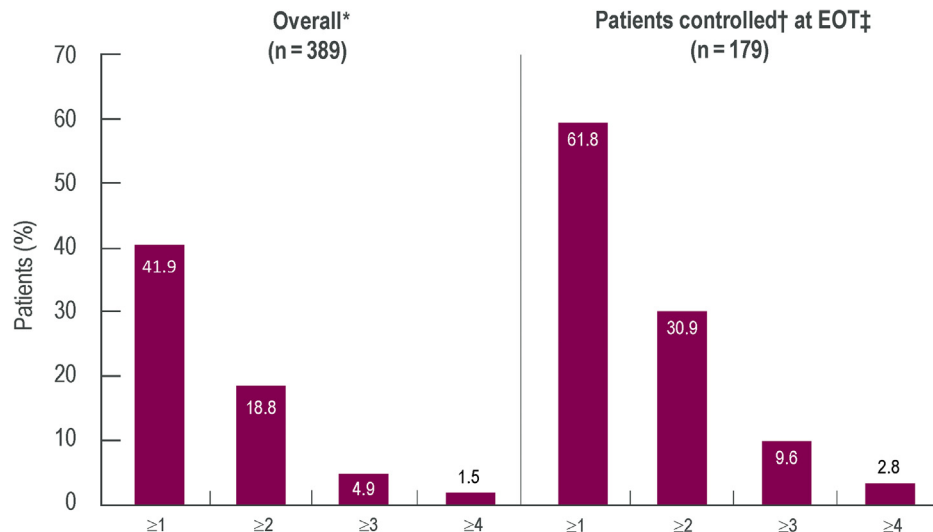


FIGURE 5. Percentage of patients achieving adapted§ GINA step reductions from baseline|| to EOT‡ Main Efficacy Analysis Set. *One patient on GINA step 1 had already achieved the minimum GINA step and therefore could not reduce further. †Controlled defined as ACQ-6 score <1.5 and no clinically significant exacerbations since visit 25/week 72 (or during last 8 wk prior to visit 27/wk 80). ‡Start date prior to visit 27/week 80 and ongoing or with a stop date at or the day before visit 27/week 80. §Adapted as calculated excluding biologic use. ||Start date prior to visit 15/week 32 and ongoing past visit 15/week 32 or start date prior to visit 15/week 32 with a stop date on or the day before visit 15/week 32.

TABLE IV. AE: Safety Analysis Set*

AE	Safety Analysis Set (n = 503) n (%)
Patients with any AE	343 (68.2)
AEs reported in > 5% of patients	
MedDRA preferred term	
Nasopharyngitis	45 (8.9)
Bronchitis	43 (8.5)
Sinusitis	35 (7.0)
Headache	29 (5.8)
Patients with ≥ 1 severe AEs	44 (8.7)
Severe adverse events reported in ≥ 1% of patients	
MedDRA preferred term	
Asthma	9 (1.8)
Patients with ≥ 1 causally related AE	45 (8.9)
Causally related AEs reported in ≥ 1% of patients	
MedDRA preferred term	
Headache	5 (1.0)
Pyrexia	5 (1.0)
Patients with any serious AE	56 (11.1)
Serious AEs reported in ≥ 1% of patients	
MedDRA preferred term	
Asthma	18 (3.6)
Influenza	5 (1.0)
Patients with any hypersensitivity†	44 (8.7)

MedDRA, Medical Dictionary for Regulatory Activities.

*AEs were coded with the use of the MedDRA, version 23.0.

†Includes the following MedDRA preferred terms: *Conjunctivitis allergica*, *Eczema*, *Rash*, *Rhinitis allergica*, and *Urticaria*.

(GINA step 1 n = 1 [0.3%]; GINA step 2 n = 0; GINA step 3 n = 13 [3.3%]; GINA step 4 n = 133 [34.1%]; and GINA step 5 n = 243 [62.3%]). In the Main Efficacy Analysis Set, 41.9% of patients (n = 163 of 389) achieved at least 1 adapted

GINA step reduction from baseline to EOT, with 18.8% of patients (n = 73) achieving 2 or more step reductions. In patients with controlled asthma at EOT, 61.8% (n = 110 of 178) achieved at least 1 adapted GINA step reduction, with 30.9% (n = 55) reducing by at least 2 adapted GINA steps (Figure 5).

OCS-Dependent Analysis Set. In OCS-dependent patients, 50.5% (n = 50 of 99) eliminated OCS by EOT, and 63.8% (n = 30 of 47) with controlled asthma eliminated OCS by EOT (Figure E5; available in this article's Online Repository at www.jaci-inpractice.org). Of patients whose OCS dosage was greater than 5 mg at the start of ANDHI IP, 61.0% (n = 36 of 59) had reduced their dosage to 5 mg or lower by EOT. Mean OCS dosage at ANDHI IP baseline was similar for controlled (9.12 mg) and uncontrolled (9.40 mg) patients at EOT. Mean OCS dosage at EOT was 2.48 mg for patients with asthma control at EOT, a 72.8% decrease from baseline versus a mean OCS dosage at EOT of 5.57 mg for patients with uncontrolled asthma, a 40.7% decrease.

Safety

A total of 503 patients received open-label benralizumab during ANDHI IP (Safety Analysis Set). Their mean (SD) exposure duration was 319.0 days (73.03 d). Overall, 68.2% of patients (n = 343 of 503) had at least 1 AE during ANDHI IP (Table IV). The AEs reported in more than 5% of patients overall in the ANDHI IP substudy (nasopharyngitis, bronchitis, sinusitis, and headache) were consistent with the most commonly reported AEs in ANDHI DB. There were 56 patients (11.1%) with any serious AE and 12 (2.4%) with AEs leading to discontinuation. Most AEs reported were assessed by the investigator as mild to moderate in intensity and unrelated to benralizumab. No deaths were reported.

DISCUSSION

In the ANDHI IP open-label extension substudy, most non-OCS-dependent patients with severe eosinophilic asthma who received benralizumab successfully reduced background medications while maintaining good asthma control, and half of the OCS-dependent patients eliminated OCS use. In today's clinical practice, standard-of-care asthma controller regimens are stepped up until control is achieved; however, evidence-based decision making regarding the best approach for stepping down treatment in the era of biologic therapy is warranted.^{26,27} Reducing asthma background medication use while maintaining asthma control is emerging as a potential treatment goal that may lessen the treatment burden, decrease AE risk, and reduce cost.^{26,29} As background asthma treatment reductions become more common, clinical evidence of effective step-down strategies is needed to inform decisions.³⁰ The ANDHI IP results provide confidence that background medications can be reduced while maintaining asthma control with benralizumab in a clinical practice setting.

Overall, 39.4% of patients ($n = 63$ of 160) discontinued LAMA medications by EOT and 33.7% ($n = 69$ of 205) discontinued LTRA medications, compared with 11.9% ($n = 46$ of 387) discontinuation for LABA medications. These discontinuations increased in patients with controlled asthma at EOT. These findings align with the ANDHI IP protocol-defined background medication reduction criteria, which stated that all non-LABA and non-OCS background medications (eg, LTRA, LAMA, and/or xanthines) should be discontinued before ICS or ICS/LABA reduction. The protocol for background medication reduction in ANDHI IP was developed to follow the reverse of the GINA step-up treatment²⁶ and to optimize safety and practicality. Medications usually added as advanced GINA steps (eg, LTRA, LAMA) were reduced or stopped first, followed by ICS dosage reductions. Discontinuing treatments such as LAMA and LTRA medications before ICS and LABA, which have established safety and efficacy at low and moderate dosages, potentially involved less risk for the patient despite the known safety risks of HD ICS.³¹ In addition, ICS/LABA medications are typically delivered in a single device, making it difficult to reduce LABA dosages without concurrent ICS reductions.

Patients with severe asthma that remains uncontrolled with standard-of-care medication are often prescribed long-term OCS despite the significant AEs associated with long-term exposure.⁷ OCS tapering may be facilitated with treatment directed toward a pathway underlying inflammation (ie, eosinophils)²⁷ and may also be more effective than OCS for asthma control.⁷ In ANDHI IP, most patients who were OCS-dependent at the start of the substudy achieved OCS dosage reduction by EOT; one-half eliminated OCS use altogether and three-quarters were receiving 5 mg or lower by EOT. This builds on the growing body of evidence including results from the recently completed PONENTE steroid-sparing study, which demonstrated the potential of benralizumab to enable OCS-dependent patients to reduce or eliminate OCS without compromising disease control.^{27,32-36}

In a study examining ICS adherence and clinical outcomes in OCS-dependent patients with severe eosinophilic asthma completing 1 year of benralizumab or mepolizumab, ICS adherence did not impact benralizumab efficacy.³⁷ Patients treated with benralizumab had similar exacerbation rate

reductions irrespective of ICS adherence, unlike patients treated with mepolizumab, who had worse outcomes with poor ICS adherence.³⁷ Studies in patients with severe atopic asthma also support the feasibility of ICS reductions. In 2 phase III trials, those patients with severe atopic asthma who required daily ICS received either omalizumab or placebo for 16 weeks, followed by a forced ICS reduction period, in which the ICS dosage was reduced by a set amount until discontinuation or symptom worsening, and a subsequent dosage increase to optimize control.^{38,39} In both trials, ICS (beclomethasone or fluticasone) dosages were reduced by 50% in patients who received placebo.^{38,39} These outcomes cannot be compared directly with the ANDHI IP findings because of differences in dose-reduction strategies and patient populations. Withdrawing ICS or reducing dosage has been shown to be safe in patients with non-eosinophilic asthma irrespective of baseline asthma control, with an elevated blood eosinophil count having the possibility to predict the failure to stop ICS.⁴⁰ Benralizumab induces rapid and nearly complete eosinophil depletion,²⁴ which may be associated with the safe reduction of ICS observed.

Approximately 46% of patients ($n = 179$ of 390) in the Main Efficacy Analysis Set had controlled asthma at EOT, with an ACQ-6 score lower than 1.5 at EOT and no clinically significant exacerbations. These findings are consistent with ANDHI DB and other phase III studies in which background medications were kept stable and asthma control improved.^{25,41,42} The current results reinforce the asthma control benefits of benralizumab, despite background medication reduction.

Patients with EOT asthma control achieved more reductions from baseline than patients without EOT asthma control, which may be because reductions were only allowed in patients meeting asthma control criteria at specific visits. More than one-half of those who were uncontrolled at EOT were controlled at prior visits and a medication reduction may have occurred.

When interpreting the background reduction results, it is important to note that ANDHI IP was conducted in a clinical practice extension setting with no control group. Patients and physicians could opt to forego therapy reductions even though step-down criteria were met. Although 230 patients met the criteria for a therapy reduction during the reduction period and 208 had a medication reduction through the end of the trial, investigators did not recommend reduction at approximately half (51.8%) of reduction visits at which reduction criteria had been met, with the most common reasons being the physician considering maximum stable reduction reached and prophylaxis. The relative passivity of physicians to adjust background medications according to the level of asthma control has been reported.⁴³ Yet, reducing the dose of ICS may attenuate the risk of osteoporosis and decrease the risk of adrenal insufficiency.⁴⁴ Further analysis may identify reasons behind resistance to stepping down therapy and foster development of strategies to build confidence and encourage dosage reductions in clinical practice. Without a control group in this open-label study, it is not feasible to determine whether the background medication reductions would have been achieved without biologic treatment, especially in patients with asthma control. It is uncertain whether asthma control would be lost again in these patients, especially because some studies have shown that HD ICS are no more effective (ie, with no statistically or clinically significant differences in lung function or asthma symptoms) than MD ICS.⁴⁵ The ongoing open-label, parallel-group, active-controlled,

multicenter, phase IV SHAMAL study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04159519) Identifier: NCT04159519), designed to assess how extensively ICS/LABA may be tapered in adult patients with severe eosinophilic asthma who have achieved disease control with benralizumab, may support implementation of dosage reductions.⁴⁶

The safety profile of benralizumab during ANDHI IP was consistent with ANDHI DB²⁵ in the same patient group and with other benralizumab trials that demonstrated the safety and tolerability of benralizumab for up to 5 years.^{33,34,47} No clinically meaningful differences were observed in AE incidence when comparing patients by previous treatment (benralizumab or placebo) during ANDHI DB, indicating consistent safety of benralizumab over varying treatment durations. This study confirms findings from previous studies and post-marketing data that demonstrate benralizumab is well tolerated, with an overall AE profile similar to placebo in type and frequency.⁴⁷

ANDHI IP was ongoing during the global coronavirus disease 2019 (COVID-19) pandemic. Although the contingency measures and alternative processes implemented resulted in minimal impact on the substudy's overall conduct, data, and interpretation, the pandemic did limit the potential of ANDHI IP to fully assess background medication reductions. (Refer to the Online Repository available at www.jaci-inpractice.org for details.)

ANDHI IP demonstrates that standard-of-care background medications, including OCS, can be tapered and adapted GINA steps reduced for patients with severe eosinophilic asthma treated with benralizumab while maintaining symptom control in a clinical setting. These findings support benralizumab's efficacy in allowing background medication reduction. Additional studies are required to assess the extent of background medication reductions and whether severe eosinophilic asthma can be managed with benralizumab and an anti-inflammatory—containing reliever in case of worsening in clinical practice.

Acknowledgments

A. Burden was contracted to AstraZeneca at the time of the study. Her current affiliation is Ardnahor Consulting Limited, Kilcreggan, UK. T. Adlington was contracted to AstraZeneca at the time of the study. E. Garcia Gil was an employee of AstraZeneca at the time of the study. Her current affiliation is Almirall, Barcelona, Spain.

This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03170271), NCT03170271. The funder of the study participated in the study design. All authors, including those employed by the funder of the study, participated in the data collection, data analysis, data interpretation, and writing of the article. The funder reviewed the publication, without influencing the opinions of the authors, to ensure medical and scientific accuracy and the protection of intellectual property. The corresponding author had access to all data in the study and had the final responsibility for the decision to submit the manuscript for publication.

The authors wish to thank the investigators, health care providers, research staff, patients, and caregivers who participated in the ANDHI IP study. We also thank James Zangrilli, MD, (former employee of AstraZeneca when the ANDHI study was conducted) 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

THE ANDHI STUDY INVESTIGATORS (BY COUNTRY)

Austria: Wolfgang Pohl: Karl Landsteiner Institute for Experimental and Clinical Pneumology, Sigmund Freud University; Daniel Doberer: Department of Respiratory and Critical Care Medicine at Klinik Floridsdorf.

Belgium: Jean Benoit Martinot: Sleep Laboratory, CHU-UCL Namur, Site Sainte-Elisabeth, Belgium Institute of Experimental and Clinical Research; Maud Deschamphelleire: CHR Citadelle de Liège Hospital; Rudi Peché: CHU Charleroi; Ulrike Himpe: Department of Respiratory Medicine, AZ Delta Roeselare.

Canada: Kenneth Chapman: University of Toronto; Amarjit Cheema: Cheema Research, Inc.; Delbert Dorscheid: University of British Columbia Vancouver; Clare Ramsey: University of Manitoba; Jeffrey Rolf: University of British Columbia; Brandie Walker: University of Calgary; Ronald Olivenstein: McGill University; Claude Poirier: Pierre LeGardeur Hospital; Pierre Larivee: Coordonnateur d'essais Clinique.

Denmark: Anne Sofie Bjerrum: Aarhus University Hospital; Ingrid Titlestad: University of Southern Denmark; Ole Hilberg: Southern Danish University Hospital.

Finland: Maritta Kilpeläinen: University of Turku.

France: Philippe Bonniaud: University of Bourgogne-Franche-Comté; Camille Taillé: Université Paris Cité; Iuliana-Angelica Tiotiu: University Hospital of Nancy; Pierre-Olivier Girodet: Bordeaux University; François-Xavier Blanc: Nantes Université; Johana Pradelli: Universitaire de Nice; Alain Didier: Toulouse University Hospital Centre; Cecilia Nocent Ejnaini: Centre Hospitalier de la Côte Basque; Gaetan Deslee: University Hospital of Reims; Christophe Pison: CHU Grenoble Alpes; Youcef Douadi: Saint Quentin Hospital Center; Guillaume Mahay: CHU Rouen; Gilles Devouassoux: University Claude Bernard Lyon 1; Boris Melloni: University Hospital of Limoges; Pauline-Marie Roux: University Hospital of Besançon; Arnaud Bourdin: University of Montpellier; Stephanie Fry: Institut Pasteur Lille, Univ Lille.

Germany: Thomas Schaum: Diabetologie RED Institut für medizinische Forschung und Fortbildung GmbH; Christian Schulz: Universitätsklinikum Regensburg; Dirk Skowasch: Universitätsklinikum Bonn Venusberg-Campus 1; Christian Taube: University Hospital Essen; Tobias Welte: Hannover Medical School and Member of the German Center of Lung Research; Wolfgang Gleiber: Goethe University Hospital; Randolph Brehler: Universitätsklinikum Münster Klinik für Hautkrankheiten Allergologie, Berufsdermatologie und Umweltmedizin; Jens Schreiber: Otto-von-Guericke-University; Wolfgang Schuette: Krankenhaus Martha-Maria Halle-Dölau; Juliane Kronsbein: Bergmannsheil University Hospital Bochum; Reiner Bonnet: Friedrich-Schiller-University Jena; Ekkehard Beck: Ekkehard Beck IFG Institut für Gesundheitsförderung Ruedersdorf.

Italy: Donato Lacedonia: University of Foggia; Laura Pini: University of Brescia; Gianenrico Senna: University and General Hospital of Verona; Cristiano Caruso: FONDAZIONE POLI-CLINICO A. Gemelli; Alberto Papi: University of Ferrara; Nunzio Crimi: University of Catania; Francesco Blasi: Università degli Studi di Milano; Pierachille Santus: c/o ASST Fatebenefratelli Sacco; Giorgio Walter Canonica: Humanitas University; Bianca Beghé: University of Modena & Reggio Emilia; Gabriella Guarnieri: University of Padua; Girolamo Pelaia: University Magna Graecia of Catanzaro; Manlio

Milanese: ASL 2 Savonese; Silvia Peveri: UOsD Allergologia G. da Saliceto Hospital; Claudio Micheletto: Integrated University Hospital; Angelo Guido Corsico: University of Pavia; Nicola Scichilone: University of Palermo; Giuseppe Spadaro: University of Naples Federico II.

The Netherlands: Bas Langeveld: Afdeling longziekten en tuberculose; Jurgen Holters: Canisius-Wilhelmina Ziekenhuis Nijmegen; Jan Willem van den Berg: AB Zwolle Postbus; Arthur Smit: Onze Lieve Vrouwe Gasthuis; Lennart Conemans: Maastricht University Medical Center; Helena van Veen: Medisch Spectrum Twente; Gerald Staaks: Meander Medical Centre.

Norway: Sverre Lehmann: University of Bergen.

Spain: Jose Maria Echave-Sustaeta: Hospital Universitario Quirónsalud Madrid; Christian Domingo Ribas: Universitat Autònoma de Barcelona; Gustavo de Luiz Martinez: Hospital Internacional Vithas Xanit Benalmadena Málaga; Ruperto Gonzalez Perez: Hospital Universitario de Canarias; Juan Luis Garcia Rivero: University Hospital Marques de Valdecilla; Xavier Muñoz Gall: Hospital Vall d'Hebron; Jose Gregorio Soto Campos: Jerez University Hospital (Cádiz); Paloma Campo Mozo: Regional Hospital of Málaga; Carmen Vidal Pan: Universidad de Santiago de Compostela; Ana Gomez-Bastero Fernandez: Virgen Macarena University Hospital; Sergio Campos Tellez: Hospital Universitario Central de la Defensa; Carlos Martinez Rivera: Hospital Universitari Germans Trias i Pujol; Irina Diana Bobolea: Hospital Clinic Barcelona; Raquel Morillo Guerrero: Instituto de Salud Carlos III; Aythamy Henriquez Santa: Inститут Hospital Infanta Elena; Jacinto Ramos Gonzalez: University Hospital of Salamanca; Ismael Ali Garcia: Hospital Universitario Infanta Leonor; Juan Luis Rodriguez Hermosa: University Complutense of Madrid.

Sweden: Nikolai Stenfors: Umeå University; Alf Tunsäter: Skane University Hospital; Dan Curiac: Sahlgrenska University Hospital; Ines Vinge: Fysikalisk Medicin i Stockholm AB.

Switzerland: Christophe von Garnier: University of Lausanne; Joerg Leuppi: Cantonal Hospital Baselland and University of Basel; Peter Schmid-Grendelmeier: University Hospital of Zürich.

United Kingdom: Shuaib Nasser: Cambridge University Hospital NHS Foundation Trust; Rekha Chaudhuri: Gartnavel General Hospital; Monica Nordstrom: St. Peter's Hospital; Dinesh Saralaya: Bradford Teaching Hospitals NHS Foundation Trust; Paul Pfeffer: North Central and East London Severe Asthma Service; Adel Mansur: University Hospitals Birmingham; Philip Short: Ninewells Hospital.

United States: Sally Wenzel: University of Pittsburgh; William Brett Cherry: Riverside Medical Clinic; Heidi Zafra: Medical College of Wisconsin; Erika Gonzalez: University of Texas Health Science Center; Weily Soong: AllerVie Research-Alabama Allergy & Asthma Center; Benjamin Davis: University of Iowa Hospitals and Clinics; Neil Kao: Allergic Disease and Asthma Center; Iftikhar Hussain: Vital Prospects Clinical Research Institute; Diego Jose Maselli Caceres: UT Health at San Antonio; James Harris: South Bend Clinic; William Calhoun: University of Texas Medical Branch; Ileana Rodicio: Florida Center for Allergy and Asthma Research; David Kaufman: Ochsner LSU Asthma, Allergy, and ENT Center; Mark Moss: University of Wisconsin School of Medicine and Public Health; Eric Szejman: Virtua Medical Group; Roy St. John: Aventiv Research; Samuel DeLeon: Urban Health Plan Inc.; Kaharu Sumino: Washington University School of Medicine; Ravindra Kashyap:

University of Illinois College of Medicine; Jeffrey Leflein: Respiratory Medicine Research Institute of Michigan; Rizan Hajal; Faisal Fakhri: Clinical Site Partners, LLC; David Hill: Waterbury Pulmonary Associates; Robert Lin: Weill Cornell School of Medicine; Mikell Jarratt: Clinical Research of Gastonia; Vijay Subramaniam: TPMG Lung & Sleep Specialists; Robert Sussman: Overlook Medical Center; Nayla Mumneh: Novartis; Joan Reibman: New York University School of Medicine; Jared Darveau: Gundersen Health System; Ricardo Tan: California Allergy and Asthma Medical Group; Tonny Tanus: Kern Allergy Medical Clinic; Vinay Sikand: Pulmonary Ultimate Research Experience; Gailen Marshall; Hemalini Mehta: Clinical Research Institute; Jeremy Cole: Clinical Research LLC; Brad Goodman: Aeroallergy Research Laboratories of Savannah; Deborah Goss: Hackensack Sleep & Pulmonary Center; Jose Bardelas: Allergy and Asthma Center of North Carolina; Aaron Milstone: Williamson Medical Center; Vinay Mehta: Asthma and Immunology Associates; Lee Clore: Allergy & Asthma Specialists, P.S.C.; Mark Millard: Baylor Martha Foster Lung Care Center; Michael Palumbo: Allergy and Clinical Immunology Associates; Dileep Puppala: Houston Pulmonary Sleep and Allergy Associates/Horizon Clinical Research Group; Mila Leong: Pediatric Pulmonary & Asthma Associates of South Jersey; Bruce Prenner: Allergy Associates Medical Group Inc.; Emory Robinette: Abingdon, LLC; Hengameh Heidarian Raissy: University of New Mexico; David Fost: Allergy Consultants; Warren Pleskow: Scripps Health; Michael Marcus: Maimonides Medical Center; Jonathan Ilowite: Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; Wendy Moore: Wake Forest School of Medicine; Gary Steven: Allergy, Asthma & Sinus Center, S.C.; Luis De la Cruz: Velocity Clinical Research; Geoffrey Chupp: Yale School of Medicine; William Berger: Allergy & Asthma Network; Christopher Randolph: Yale Center for Allergy Asthma and Immunology; Fernando Holguin: University of Colorado; Shahrukh Kureishy: Metroplex Pulmonary and Sleep Center; Edward Campbell: National Clinical Resources.

DATA SHARING

Data underlying the findings described in this manuscript may be requested in accordance with AstraZeneca's data sharing policy described at <https://astrazenecagrouptrials.pharmacm.com//ST/Submission/Disclosure>

provided by Wynne Dillon, MS, and Kathryn Fogarty, PhD (Kay Square Scientific, Newtown Square, Pa). This support was funded by AstraZeneca.

REFERENCES

1. Hekking PPW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1789-858.
3. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional World Health Survey. *BMC Public Health* 2012;12:204.
4. Ryan D, Heatley H, Heaney LG, Jackson DJ, Pfeffer PE, Busby J, et al. Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol Pract* 2021;9:1612-23.

5. Kerkhof M, Tran TN, Soriano JB, Golam S, Gibson D, Hillyer EV, et al. Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population. *Thorax* 2018;73:116-24.
6. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;391:783-800.
7. Busse WW. Biological treatments for severe asthma: a major advance in asthma care. *Allergol Int* 2019;68:158-66.
8. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
9. Gaga M, Zervas E, Samitas K, Bel EH. Severe asthma in adults: an orphan disease? *Clin Chest Med* 2012;33:571-83.
10. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. *J Asthma Allergy* 2014;7:53-65.
11. Brussino L, Heffler E, Bucca C, Nicola S, Rolla G. Eosinophils target therapy for severe asthma: critical points. *Biomed Res Int* 2018;2018:7582057.
12. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J* 2014;44:97-108.
13. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
14. Newby C, Agbetile J, Hargadon B, Monteiro W, Green R, Pavord I, et al. Lung function decline and variable airway inflammatory pattern: longitudinal analysis of severe asthma. *J Allergy Clin Immunol* 2014;134:287-94.
15. Colas L, Hassoun D, Magnan A. Needs for systems approaches to better treat individuals with severe asthma: predicting phenotypes and responses to treatments. *Front Med (Lausanne)* 2020;7:98.
16. Chen S, Golam S, Myers J, Bly C, Smolen H, Xu X. Systematic literature review of the clinical, humanistic, and economic burden associated with asthma uncontrolled by GINA steps 4 or 5 treatment. *Curr Med Res Opin* 2018;34:2075-88.
17. Menzies-Gow A, Canonica GW, Winders TA, Correia de Sousa J, Upham JW, Fink-Wagner AH. A charter to improve patient care in severe asthma. *Adv Ther* 2018;35:1485-96.
18. Demoly P, Gueron B, Annunziata K, Adamek L, Walters RD. Update on asthma control in five European countries: results of a 2008 survey. *Eur Respir Rev* 2010;19:150-7.
19. González Barcala FJ, de la Fuente-Cid R, Alvarez-Gil R, Tafalla M, Nuevo J, Caamaño-Isorna F. Factors associated with asthma control in primary care patients: the CHAS study. *Arch Bronconeumol* 2010;46:358-63.
20. Braunstahl GJ, Chlumský J, Peachey G, Chen CW. Reduction in oral corticosteroid use in patients receiving omalizumab for allergic asthma in the real-world setting. *Allergy Asthma Clin Immunol* 2013;9:47.
21. Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res* 2019;20:179.
22. McGregor MC, Krings JG, Nair P, Castro M. Role of biologics in asthma. *Am J Respir Crit Care Med* 2019;199:433-45.
23. Bardin PG, Price D, Chanez P, Humbert M, Bourdin A. Managing asthma in the era of biological therapies. *Lancet Respir Med* 2017;5:376-8.
24. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthma with sputum eosinophilia. *J Allergy Clin Immunol* 2013;132:1086-96.
25. Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med* 2021;9:260-74.
26. Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. Updated 2020. Accessed April 6, 2023. https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final_-_wms.pdf
27. Menzies-Gow A, Gurnell M, Heaney LG, Corren J, Bel EH, Maspero J, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. *Lancet Respir Med* 2022;10:47-58.
28. Juniper EF, Bousquet J, Abetz L, Bateman ED, GOAL Committee. Identifying "well-controlled" and "not well-controlled" asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616-21.
29. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald JM, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
30. Cataldo D, Louis R, Michils A, Peche R, Pilette C, Schleich F, et al. Severe asthma: oral corticosteroid alternatives and the need for optimal referral pathways. *J Asthma* 2021;58:448-58.
31. Chipps B, Taylor B, Bayer V, Shaikh A, Mosnaim G, Trevor J, et al. Relative efficacy and safety of inhaled corticosteroids in patients with asthma: systematic review and network meta-analysis. *Ann Allergy Asthma Immunol* 2020;125:160-70.e3.
32. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448-58.
33. Busse WW, Bleecker ER, FitzGerald JM, Ferguson GT, Barker P, Sproule S, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019;7:46-59.
34. Korn S, Bourdin A, Chupp G, Cosio BG, Arbetter D, Shah M, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. *J Allergy Clin Immunol Pract* 2021;9:4381-92.e4.
35. Pelaia C, Crimi C, Benfante A, Caiaffa MF, Calabrese C, Carpagnano GE, et al. Therapeutic effects of benralizumab assessed in patients with severe eosinophilic asthma: real-life evaluation correlated with allergic and non-allergic phenotype expression. *J Asthma Allergy* 2021;14:163-73.
36. Bourdin A, Shaw D, Menzies-Gow A, FitzGerald JM, Bleecker ER, Busse WW, et al. Two-year integrated steroid-sparing analysis and safety of benralizumab for severe asthma. *J Asthma* 2021;58:514-22.
37. d'Ancona G, Kavanagh J, Roxas C, Green L, Fernandes M, Payne V, et al. Differential effects of unscheduled ICS withdrawal between patients receiving benralizumab and mepolizumab. *Am J Respir Crit Care Med* 2020;201:A7740.
38. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
39. Holgate ST, Chuchalin AG, Hébert J, Lötvall J, Persson GB, Chung KF, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632-8.
40. Demarche S, Schleich F, Henket M, Paulus V, Louis R, Van Hees T, et al. Step-down of inhaled corticosteroids in non-eosinophilic asthma: a prospective trial in real life. *Clin Exp Allergy* 2018;48:525-35.
41. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
42. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CAL-IMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
43. Louis R, Joos G, Michils A, Vandenhoven G. A comparison of budesonide/formoterol maintenance and reliever therapy vs. conventional best practice in asthma management. *Int J Clin Pract* 2009;63:1479-88.
44. Kachroo P, Stewart ID, Kelly RS, Stav M, Mendez K, Dahlin A, et al. Author Correction. Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma. *Nat Med* 2022;28:1723.
45. Beasley R, Harper J, Bird G, Majers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma. Time for a new therapeutic dose terminology. *Am J Respir Crit Care Med* 2019;199:1471-7.
46. Jackson DJ, Kent BD, Humbert M, Heaney LG, Korn S, Keith M, et al. Enabling reductions in maintenance ICS/LABA therapy using as needed anti-inflammatory reliever for patients with severe eosinophilic asthma controlled with benralizumab: SHAMAL phase IV clinical study. *Am J Respir Crit Care Med* 2020;201:A3020.
47. Jackson DJ, Korn S, Mathur SK, Barker P, Meka VG, Martin UJ, et al. Safety of eosinophil-depleting therapy for severe, eosinophilic asthma: focus on benralizumab. *Drug Saf* 2020;43:409-25.

ONLINE REPOSITORY

Severe asthma standard-of-care background medication reduction with benralizumab: ANDHI *in Practice* substudy

ANDHI *IN PRACTICE* EXCLUSION CRITERIA

Patients could not enter the substudy if any of the following exclusion criteria were fulfilled:

- Patients who had participated in the ANDHI double-blind (DB) study but failed to complete the ANDHI DB end-of-treatment (EOT) visit 11. Patients who had completed the ANDHI DB follow-up visit 12 were not excluded from participation in ANDHI *in Practice* (IP).
- Patients who were unable to commit to the monthly visits as required by the protocol or unable to commit to undergoing protocol-guided reductions in asthma therapy, as directed by the investigator.
- Patients who experienced a severe or serious treatment-related adverse event (AE) during the ANDHI DB study, and those for whom the investigator judged that it was not in patients' best interests to extend possible treatment with benralizumab.
- Patients with approved or off-label use of systemic immunosuppressive medications within 3 months prior to the first visit of ANDHI IP (visit 13). These included but were not limited to small molecules such as methotrexate, cyclosporine, azathioprine, and immunosuppressive/immunomodulating biologics such as tumor necrosis factor blockers. Regular use of systemic oral corticosteroids (OCS) was also excluded except for the indication of asthma.
- Patients who received live attenuated vaccines 30 days prior to the first visit of ANDHI IP (visit 13); other types of vaccines were allowed.
- Patients who had planned surgical procedures during the study.
- Patients with positive urine pregnancy test at visit 13, or patients who were actively breastfeeding or lactating.

STATISTICAL ANALYSIS METHODOLOGY

- All analyses based on Global Initiative for Asthma (GINA) step reduction considered patients starting at adapted GINA step ≥ 2 only. The baseline adapted GINA step was determined based on maintenance asthma medications at visit 15/week 32. The final step was determined based on asthma medications at visit 27/week 80 (EOT).
- For patients who withdrew or were lost to follow-up prior to EOT (visit 27/wk 80), a last observation carried forward approach was used, and asthma controller medications and reductions were assessed based on patients' last site visits. Visit 15/week 32 was used if there was no suitable prior visit, and the number of reductions was calculated as 0.
- Proportions of patients achieving 1 or more asthma controller medication reductions, X or more GINA step reductions (in which X ranged from 1 to 4), and Y GINA step reductions (in which Y ranged from 0 to 4 and 0 included no change and any increase in adapted GINA step) were estimated with nominal 95% CI derived using the exact Clopper-Pearson method.
- The statistical analyses were performed by IQVIA using SAS version 9.4 or higher.

PATIENT DISPOSITION

Of the 504 enrolled patients, 1 (0.2%) did not receive open-label benralizumab. This patient provided informed consent for the substudy, but no other events were recorded. Of patients receiving benralizumab, 490 (97.2%) entered the background medication reduction period (visits 15–23/wk 32–64). Of these patients, 390 were included in the Main Efficacy Analysis Set, 99 were included in the OCS-Dependent Analysis Set, and 1 is not in either set because the patient did not attend visit 15. A total of 459 patients (91.1%) entered the maintenance period of the substudy, and 447 of these patients (88.7%) completed this period. A total of 12 patients (2.4%) did not complete the maintenance period, with the main reason being patient decision (6 patients [1.2%]). A total of 450 patients (89.3%) completed open-label benralizumab treatment during the substudy, and 447 (88.7%) completed the substudy. Fifty-two (10.3%) discontinued benralizumab treatment during the substudy, with the main reason for discontinuation being patient decision (22 patients [4.4%]). All patients who discontinued benralizumab treatment also discontinued the substudy. Three patients who had completed benralizumab treatment withdrew before end of treatment (for reasons of “other”—coronavirus disease 2019 [COVID-19] movement restriction [2 patients] and patient withdrawal [1 patient]).

The Main Efficacy Analysis Set (n = 390) and the OCS-Dependent Analysis Set (n = 99) were distinct patient groups.

IMPACT OF THE COVID-19 PANDEMIC ON ANDHI *IN PRACTICE*

The ANDHI IP substudy was ongoing as the COVID-19 pandemic was occurring globally. Although the contingency measures and alternative processes implemented during the substudy resulted in minimal impact on the overall conduct, data, and interpretation of results, the pandemic period did limit the potential of the substudy to fully assess reductions in background medication. Missed or reduced on-site visits, decisions not to reduce medication despite patients meeting the reduction criteria, and a general cautious approach by investigators for recommending reductions, especially during the pandemic period, were all influencing factors for how many opportunities patients had to reduce their asthma controller medication. Despite these indirect effects related to the COVID-19 pandemic, 93% of scheduled visits took place, and 3% had a reason for not reducing related to COVID-19.

Enrollment of patients for the substudy was completed before the pandemic started and, therefore, was not impacted. One of the 504 enrolled patients (0.2%) had a COVID-19-related adverse event (AE) recorded during the substudy. Of the 504 patients enrolled, 3 (0.6%) did not complete the substudy maintenance phase (defined as post visit 23/wk 64 up to and including scheduled EOT [visit 27/week 80] or investigational product discontinuation visit for those patients who prematurely discontinued study treatment [or last patient contact post visit 13 if EOT or investigational product discontinuation visit was missing], inclusive), 2 patients (0.4%) discontinued benralizumab treatment during the substudy, and 3 patients (0.6%) were withdrawn from the substudy, all owing to logistical restrictions associated with the COVID-19 pandemic. Other COVID-19-related discontinuation reasons represent logistical restrictions.

The impact of any COVID-19–related study disruption or patient illness during ANDHI IP on the efficacy analyses was considered minor. Although 40% of patients had COVID-19–related study disruptions, the majority of scheduled visits were completed on-site. Results of sensitivity analyses performed to assess the impact of the COVID-19 pandemic were supportive of the main efficacy results.

The number of scheduled reduction visits in which the reason for not recommending a reduction in background asthma medication was specifically COVID-19–related was low (27 visits [3.0%]), even though indirect effects related to COVID-19, including reduced number of on-site visits and general cautious approach followed by investigators in recommending reductions, could have occurred.

One COVID-19–related AE (COVID-19 infection) was reported. The event was mild in intensity, resolved after 15 days without treatment, and did not lead to withdrawal of the patient from the substudy.

MAINTENANCE ICS DOSAGE CATEGORIES BY COMPOUND^{E1}

Maintenance ICS dosage categories for adults and adolescents (≥ 12 years of age) used in ANDHI IP, by total daily dosage:

Single-dosage beclomethasone dipropionate medications (pressurized metered-dose inhaler [pMDI], standard [non-fine] particle; hydrofluoroalkane propellant [HFA], non-chlorofluorocarbon propellant [CFC]), excluding the QVAR Redihaler: low (200–500 μg), medium (>500–1000 μg), high (>1,000 μg), and supra-high (not applicable [NA])

Combination fixed-dosage beclomethasone dipropionate medications (pMDI, extra-fine particle; HFA, non-CFC), including the QVAR Redihaler: low (100–200 μg), medium (>200–400 μg), high (>400 μg), and supra-high (>800 μg)

Budesonide (dry powder inhaler [DPI]): low (200–400 μg), medium (>400–800 μg), high (>800 μg), and supra-high (>1,600 μg as metered; 1,280 μg as delivered)

Ciclesonide (pMDI, extra-fine particle; HFA, non-CFC): low (80–160 μg), medium (>160–320 μg), high (>320 μg), and supra-high (>640 μg)

Fluticasone furoate (DPI): low (NA), medium (100 μg), high (200 μg), and supra-high (>200 μg)

Fluticasone propionate (DPI): low (100–250 μg), medium (>250–500 μg), high (>500 μg), and supra-high (>2,000 μg)

Fluticasone propionate (pMDI, standard [non-fine] particle; HFA, non-CFC): low (100–250 μg), medium (>250–500 μg), high (>500 μg), and supra-high (>2,000 μg)

Mometasone furoate (DPI): low (NA), medium (200–400 μg), high (>400 μg), and supra-high (>800 μg)

Mometasone furoate (pMDI, standard [non-fine] particle; HFA, non-CFC): low (NA), medium (200–400 μg), high (>400 μg), and supra-high (>800 μg)

REFERENCES

- E1. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Updated 2020. Accessed April 6, 2023. https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final_-_wms.pdf

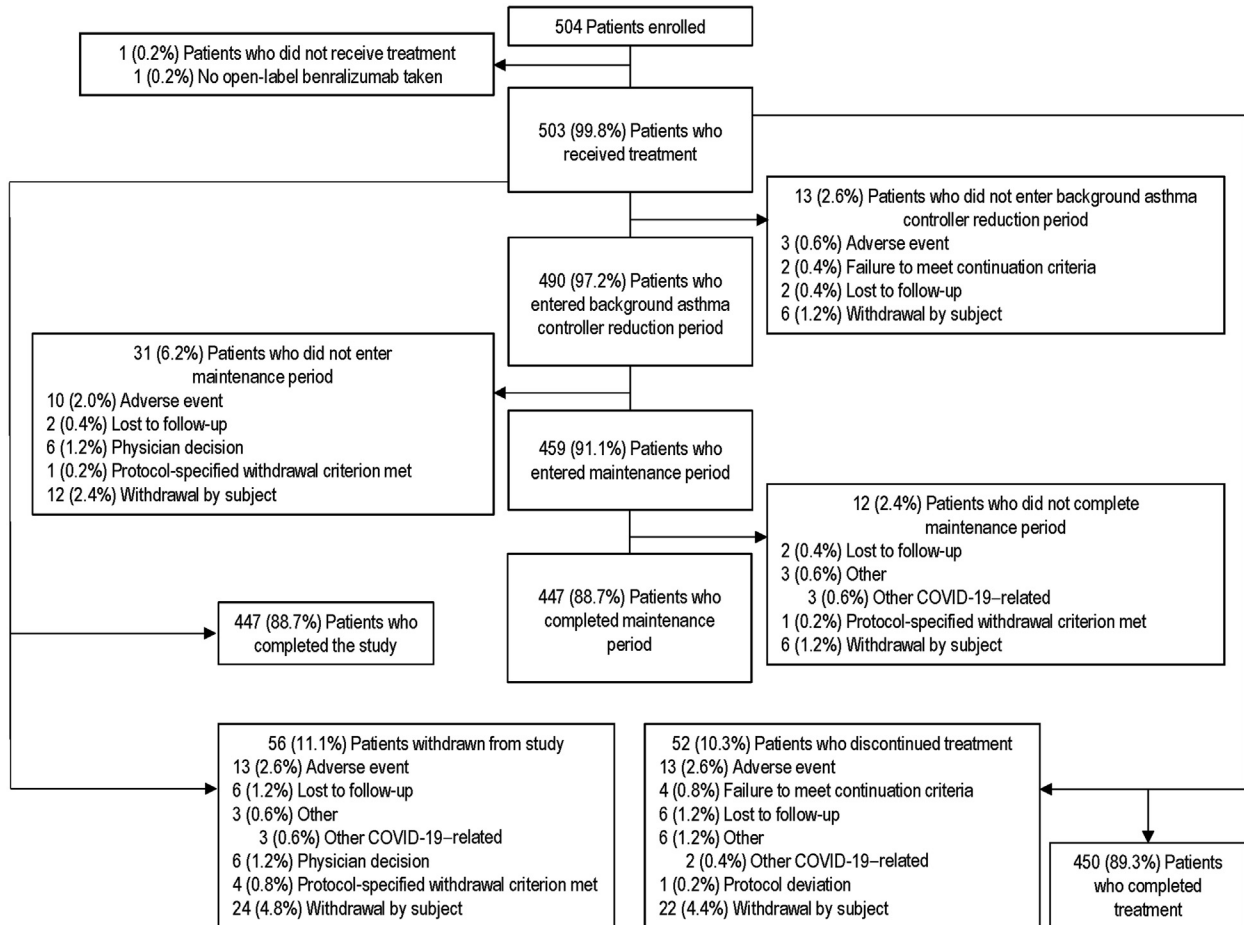


FIGURE E1. Patient disposition: overall.

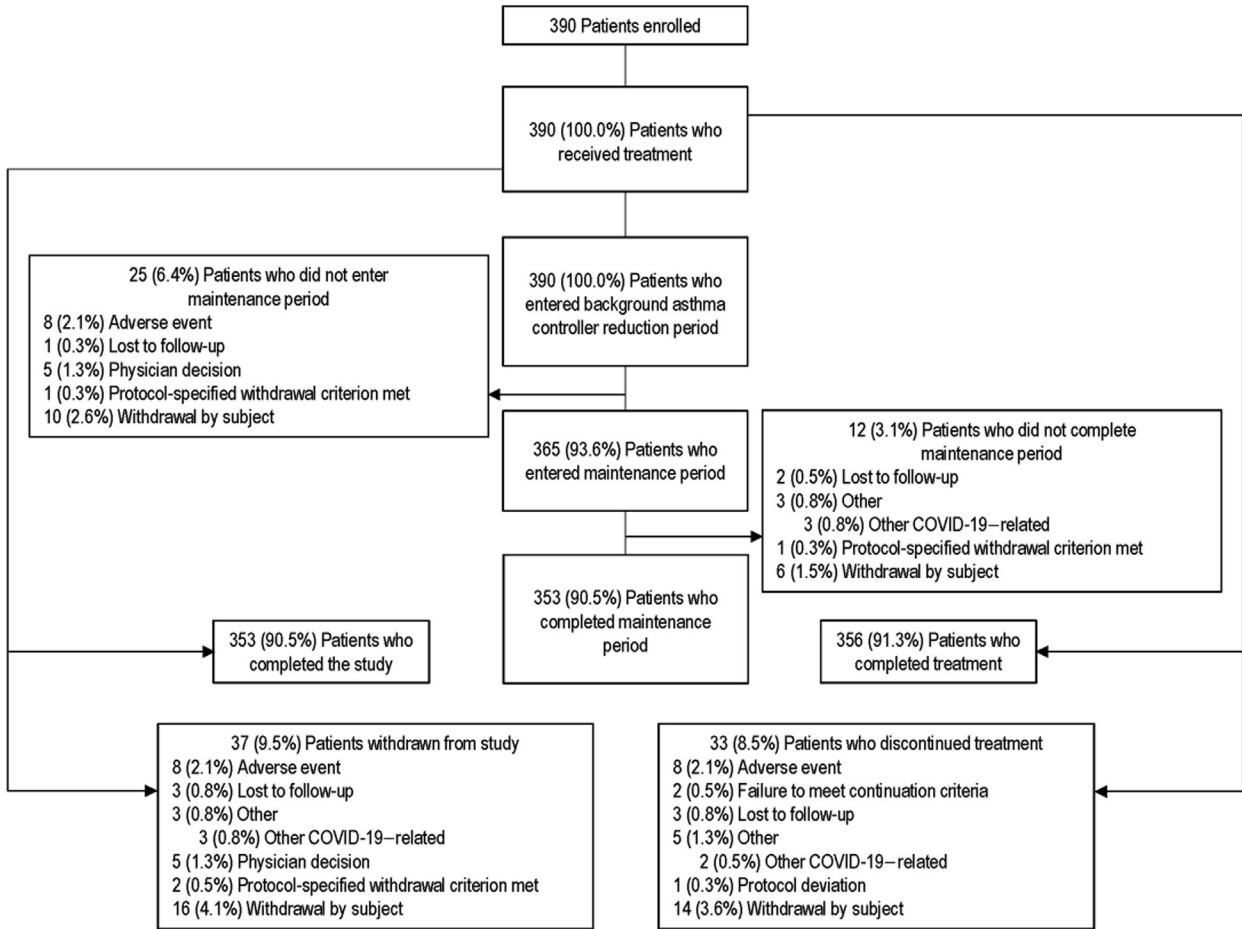


FIGURE E2. Patient disposition: Main Efficacy Analysis Set.

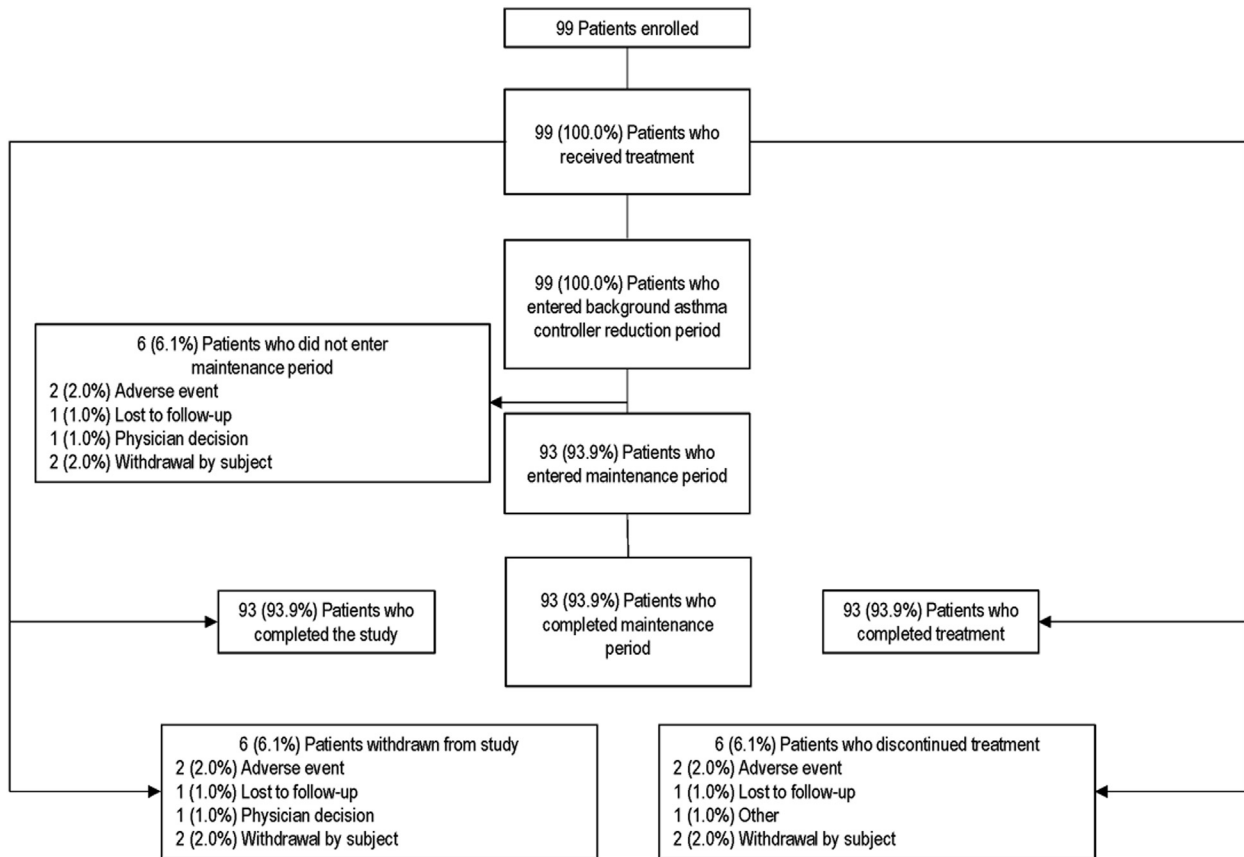


FIGURE E3. Patient disposition: OCS-Dependent Analysis Set. *OCS*, Oral corticosteroid.

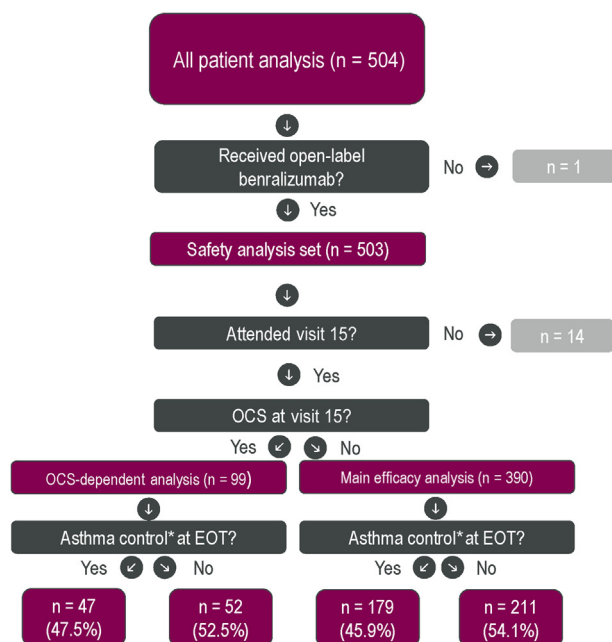


FIGURE E4. Asthma control in the Main Efficacy Analysis Set and the OCS-Dependent Analysis Set. *EOT*, End of treatment; *OCS*, oral corticosteroids. *Controlled defined as Asthma Control Questionnaire-6 score < 1.5 and no clinically significant exacerbations since visit 25/week 72 (or during last 8 wk prior to visit 27/wk 80).

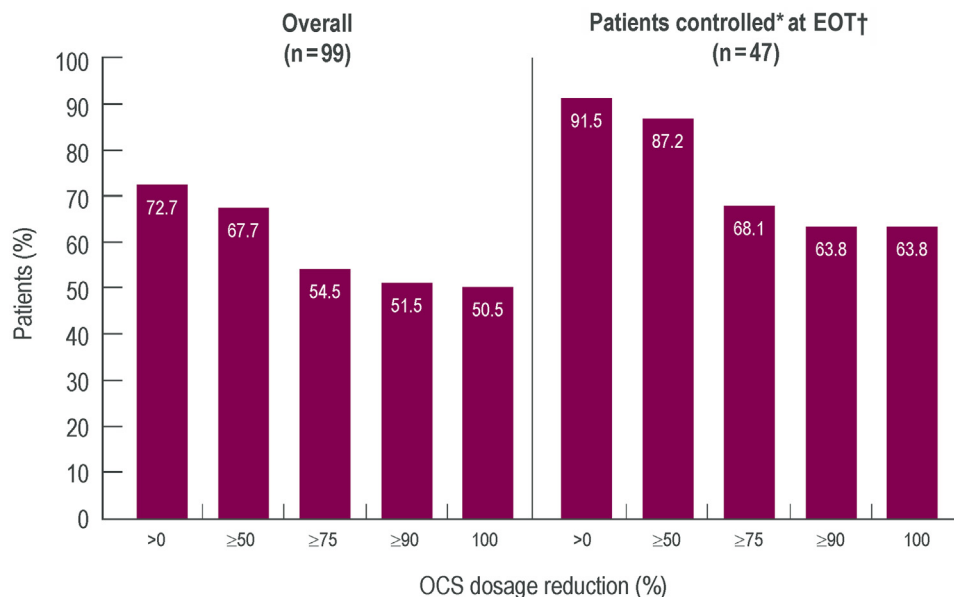


FIGURE E5. Reductions in OCS dosage from baseline‡ to EOT† in OCS-dependent patients OCS, Oral corticosteroid. *Controlled defined as Asthma Control Questionnaire-6 score < 1.5 and no clinically significant exacerbations since visit 25/week 72 (or during last 8 wk prior to visit 27/wk 80). †Start date prior to visit 27/week 80 and ongoing or with a stop date at or the day before visit 27/week 80. ‡Start date prior to visit 15/week 32 and ongoing past visit 15/week 32 or start date prior to visit 15/week 32 with a stop date on or the day before visit 15/week 32.

TABLE E1. Reasons for investigator not recommending background medications reduction when reduction criteria were met

Main Efficacy Analysis Set (n = 390)	Visits, n (%)
Background medication reduction criteria were met	906
Investigator recommended background medication reduction	433 (47.8)
Investigator did not recommend background medication reduction (any reason except COVID-19)	442 (48.8)
Investigator did not recommend background medication reduction because of COVID-19	27 (3.0)
Investigator decision missing	4 (0.4)
Reason description when investigator did not recommend reduction	
Physician decision to put reduction on hold until next visit	17 (1.9)
Physician decision for prophylactic reasons	83 (9.2)
Patient decision	51 (5.6)
Deterioration after last reduction attempt	10 (1.1)
Physician considers maximum stable reduction reached	107 (11.8)
Respiratory signs/symptoms/condition	46 (5.1)
Exercise-related	7 (0.8)
Impaired/deteriorated lung function	57 (6.3)
COVID-19—related: physician decision for prophylactic reasons	19 (2.1)
COVID-19—related: patient decision	7 (0.8)
COVID-19—related: other	1 (0.1)
Comorbidity	12 (1.3)
Other	52 (5.7)