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Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis

Michael E Wechsler¹, Parameswaran Nair¹, Benjamin Terrier¹, Bastian Walz¹, Arnaud Bourdin¹, David R W Jayne¹, David J Jackson¹, Florence Roufosse¹, Lena Börjesson Sjö¹, Ying Fan¹, Maria Jison¹, Christopher McCrae¹, Sofia Necander¹, Anat Shavit¹, Claire Walton¹, Peter A Merkel¹; MANDARA Study Group

¹ From the Department of Medicine, National Jewish Health, Denver (M.E.W.); McMaster University and St. Joseph's Healthcare, Hamilton, ON, Canada (P.N.); the Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hospital Cochin, and Université Paris Cité, Paris (B.T.), and the Department of Respiratory Diseases, University of Montpellier, Centre Hospitalier Universitaire Montpellier, INSERM, Centre National de la Recherche Scientifique, Montpellier (A.B.) - all in France; the Department of Internal Medicine, Rheumatology, and Immunology, Medius Kliniken, University of Tübingen, Kirchheim-Teck, Germany (B.W.); the Department of Medicine, University of Cambridge (D.R.W.J.), and BioPharmaceuticals Medical (A.S.) and Late-Stage Respiratory and Immunology, BioPharmaceuticals Research and Development (C.W.), AstraZeneca, Cambridge, and Guy's Severe Asthma Centre, School of Immunology and Microbial Sciences, King's College London, London (D.J.J.) - all in the United Kingdom; the Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels (F.R.); Late-Stage Respiratory and Immunology, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden (L.B.S., S.N.); Late-Stage Respiratory and Immunology, BioPharmaceuticals Research and Development (Y.F., M.J.), and Translational Science and Experimental Medicine, Early Respiratory and Immunology, BioPharmaceuticals Research and Development (C.M.), AstraZeneca, Gaithersburg, MD; and the Division of Rheumatology, Department of Medicine, and the Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia (P.A.M.).

Collaborators

- **MANDARA Study Group:**

Florence Roufosse, Els Van de Perre, Ken Chapman, Jason Lee, Parameswaran Nair, Brandie Walker, Arnaud Bourdin, Pascal Chanez, Matthieu Groh, Mohamed Hamidou, Gregory Pignet, Maxime Samson, Camille Taille, Benjamin Terrier, Stephanie Finzel, Christof Iking-Konert, Joachim Kirschner, Peter Lamprecht, Bastian Walz, Nancy Agmon-Levin, Neville Berkman, Ori Elkayam, Gershon Fink, Yael Raviv, Ori Wand, Fabio Almerigogna, Andrea Antonelli, Luisa Brussino, Cristiano Caruso, Lorenzo Dagna, Jan Schroeder, Giuseppe Spadaro, Hiroaki Dobashi, Shunsuke Furuta, Tomoaki Higuchi, Tomonori Ishii, Yosuke Kamide, Anoop Chauhan, David Jackson, David Jayne, Shamsa Naveed, Naomi Amudala, Osman Dokmeci, Sanober Kable, Njira Lugogo, Galina Marder, Peter Merkel, Daniel Petroni, Ulrich Specks, Robert Spiera, Michael Wechsler, Caroline

Carpentier, Chynna Huang, Nader Khalidi, Melanie Kjarsgaard, Manali Mukherjee, Christian Pagnoux, Katherine Radford, Roma Sehmi, Loubna Alavoine, Clément Boissin, Jérémy Charriot, Anne Sophie Gamez, Julien Rohmer, Colas Tcherakian, Mathilde Volpato, Konstantinos Furlakis, Sebastian Jendrek, Sebastian Klapa, Anke Reichelt de Tenorio, Susanne Schinke, Nils Venhoff, Iliana Baglivo, Stefania Colantuono, Aikaterini Detoraki, Remo Poto, Alexandra Nanzer, Rachel Esparza, Vamsi Guntur, Lindsay Lally, Juno Pak, Elaina Shoemaker, Allen Stevens, Ella Aavenova, Ilona Ahonen, Vijay Alagappan, Eileen Babcock, Aleksandra Bąk, Erik Bark, Peter Barker, Anna Reveman Bärthel, Elena Benetti, Ebony Benjamin, Todd Bower, Yunhui Cao, Heather Chadwick, Ron A Chen, Gina D'Angelo, Chandrakant Dave, Cezary Dmochowski, Elizabeth A Duncan, Ekaterina Elegudin, Rama Empati, Yuli Fooks, Sara Frigert, Katarzyna Golasa, Pawel Gunerka, Calvin N Ho, Eduard Hofsetz, Reena Kainth, Marta Kaluska, Rohit Katial, Kawaljit Kaur, Kaci Kolberg, Michal Kramarz, Julia Kugler, Yulia Kurdyukova, Kamila Kwiecińska, Aleksandra Lech, My-Linh Le Thien, Domenico V Libri, Magdalena Lim, Emmanuelle Maho, Natalya Makulova, Ubaldo J Martin, Henrike Meyer, Katarzyna Moryc, Sebastian Niedzielec, Brad Nohe, Latifat Obajinmi, Hana Oloed, Davide Ornati, Cameron Overbeeke, Ioannis Psallidas, Berit Pürschel, Yasa Reddy, Eva Rodriguez-Suarez, Liron Romash, Vivian H Shih, Weronika Słomińska, Viola Smith, Anna Sokolnicka, V A Rasal, Elle Vandenbroucke, Sabine Werner, Nicholas White, Rebecca White, Tomasz Zawadzki, Sarah Cohen, Yifan Zhu, Alessia Longo, Veronica Tonu, Yashar Sadian

Abstract

Background:

Eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis characterized by eosinophilic inflammation. Benralizumab, a monoclonal antibody against the interleukin-5 α receptor expressed on eosinophils, may be an option for treating EGPA.

Methods:

We conducted a multicenter, double-blind, phase 3, randomized, active-controlled noninferiority trial to evaluate the efficacy and safety of benralizumab as compared with mepolizumab. Adults with relapsing or refractory EGPA who were receiving standard care were randomly assigned in a 1:1 ratio to receive benralizumab (30 mg) or mepolizumab (300 mg) subcutaneously every 4 weeks for 52 weeks. The primary end point was remission at weeks 36 and 48 (prespecified noninferiority margin, -25 percentage points). Secondary end points included the accrued duration of remission, time to first relapse, oral glucocorticoid use, eosinophil count, and safety.

Results:

A total of 140 patients underwent randomization (70 assigned to each group). The adjusted percentage of patients with remission at weeks 36 and 48 was 59% in the benralizumab group and 56% in the mepolizumab group (difference, 3 percentage points; 95% confidence interval [CI], -13 to 18; $P = 0.73$ for superiority), showing noninferiority but not superiority of benralizumab to mepolizumab. The accrued duration of remission and the time to first relapse were similar in the two groups. Complete withdrawal of oral glucocorticoids during weeks 48 through 52 was achieved in 41% of the patients who received benralizumab and 26% of those who received mepolizumab. The mean (\pm SD) blood eosinophil count at baseline was 306.0 ± 225.0 per microliter in the benralizumab group and 384.9 ± 563.6 per microliter in the mepolizumab group, decreasing to 32.4 ± 40.8 and 71.8 ± 54.4 per microliter, respectively, at week 52. Adverse events were reported in 90% of the patients in the benralizumab group and 96% of those in the mepolizumab group; serious adverse events were reported in 6% and 13%, respectively.

Conclusions:

Benralizumab was noninferior to mepolizumab for the induction of remission in patients with relapsing or refractory EGPA. (Funded by AstraZeneca; MANDARA ClinicalTrials.gov number, [NCT04157348](https://clinicaltrials.gov/ct2/show/study/NCT04157348)).

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare inflammatory disorder characterized by asthma, necrotizing vasculitis, extravascular granulomas, and blood and tissue eosinophilia.¹⁻³ Oral glucocorticoids and immunosuppressive drugs have long been the cornerstone of treatment for EGPA, despite burdensome side effects.⁴ Although not formally approved for EGPA, treatment with either cyclophosphamide or rituximab has been recommended to induce remission in severe cases, and azathioprine, methotrexate, and mycophenolate mofetil help to maintain remission.^{4,5} However, although prolonged treatment with oral glucocorticoids reduces the risk of relapse, it is associated with progressive toxic effects.^{6,7} Relapse is also common during oral glucocorticoid tapering, and patients are often unable to fully discontinue treatment.⁸⁻¹⁰

The targeting of eosinophilic inflammation is a well-recognized strategy for the treatment of EGPA.^{4,5, 11} A previous clinical trial showed that treatment of EGPA with mepolizumab, a monoclonal antibody that inhibits eosinophil activation and differentiation by binding interleukin-5,¹² resulted in a longer duration of remission, a higher percentage of patients entering remission, a lower percentage of patients having relapse, and less use of oral glucocorticoids than placebo.¹¹ On the basis of these findings, mepolizumab was the first targeted therapy approved for EGPA.¹³

Benralizumab is a humanized, afucosylated monoclonal antibody with high affinity and specificity for the human interleukin-5 receptor α subunit (interleukin-5R α) expressed on eosinophils¹⁴ and is approved for the treatment of severe eosinophilic asthma.¹⁵ In addition to inhibiting interleukin-5 signaling, benralizumab leads to eosinophil apoptosis through antibody-dependent, cell-mediated cytotoxicity.¹⁴ In severe eosinophilic asthma, benralizumab leads to rapid, near-complete depletion of eosinophils in blood and tissue, similar to the blood eosinophil depletion seen with oral prednisone.¹⁶ The ability of benralizumab to deplete eosinophils in blood and tissue suggests that it may also be a treatment option for EGPA.¹⁷

Evidence from retrospective studies^{18,19} and pilot studies²⁰ suggests that benralizumab, at the dose approved for severe eosinophilic asthma (30 mg every 8 weeks), is associated with abatement of EGPA, including sparing of oral glucocorticoids.

This report describes the results of a phase 3 trial that evaluated the efficacy and safety of benralizumab (every 4 weeks) as compared with mepolizumab over 52 weeks in patients with relapsing or refractory EGPA who were receiving standard therapy.

Methods

Trial Design

We conducted the MANDARA trial, a double-blind, 52-week, phase 3, randomized, active-controlled, noninferiority head-to-head trial with an open-label extension of at least 1 year in duration, at 50 sites across nine countries. Eligible patients were randomly assigned in a 1:1 ratio to receive benralizumab (30 mg in one injection) or mepolizumab (300 mg in three injections of 100 mg each) administered subcutaneously every 4 weeks for 52 weeks (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The more frequent doses of benralizumab for EGPA than for asthma (30 mg every 4 weeks vs. every 8 weeks) were used to account for the higher eosinophil counts in EGPA and were based on preliminary data in patients with hypereosinophilic syndrome (which has an

eosinophil burden similar to that of EGPA and shares some of its clinical and histologic features),²¹ in whom the every-4-week regimen had an acceptable side-effect profile and effectively reduced blood and tissue eosinophil levels.

Between baseline and week 4, patients were required to continue taking their stable dose of oral glucocorticoid (upward adjustments were permitted). From week 4 onward, if the patient's Birmingham Vasculitis Activity Score (BVAS) was 0 (scores range from 0 to 63, with higher scores reflecting more severe disease), the oral glucocorticoid dose was tapered downward in accordance with standard practice. If the BVAS was greater than 0, the oral glucocorticoid dose could be tapered downward at the investigator's discretion.

Trial Oversight

The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and is consistent with International Council for Harmonisation Good Clinical Practice guidelines, the applicable regulatory requirements, and the AstraZeneca policy on bioethics. A study oversight committee was assigned to support data quality and reliability by reviewing the BVAS, Vasculitis Damage Index, and relapse and remission assessments in a blinded fashion. All the patients provided written informed consent. The protocol and statistical analysis plan are available at NEJM.org.

The trial was designed and data gathered by employees of the sponsor and by academic authors. The data were analyzed by authors who are employees of the sponsor. The first author and the last eight authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by medical writers who were funded by AstraZeneca in accordance with Good Publication Practice 2022 guidelines.²⁴ The authors made the decision to submit the manuscript for publication. All the investigators had confidentiality agreements with the sponsor.

Participants and Eligibility Criteria

Adults (≥ 18 years of age) were eligible to participate if they had an EGPA diagnosis based on medical history or the presence of asthma and blood eosinophilia (eosinophil count of $>1.0 \times 10^9$ per liter, $>10\%$, or both) plus at least two additional features of EGPA and a history of relapsing or refractory disease despite therapy with oral glucocorticoids at a dose of 7.5 to 50.0 mg of prednisolone per day or equivalent (a stable dose for ≥ 4 weeks before baseline), with or without stable immunosuppressive therapy. Patients who had had organ- or life-threatening EGPA within 3 months before the first visit were excluded. Detailed eligibility criteria are provided in the Supplementary Appendix.

End Points

The primary end point was remission (defined as a BVAS of 0 and an oral glucocorticoid dose of ≤ 4 mg per day) at weeks 36 and 48. European League against Rheumatism (EULAR)-defined remission²² (BVAS of 0 and oral glucocorticoid dose of ≤ 7.5 mg per day) was examined in a supportive analysis, and an indirect, per-protocol comparison with a historic placebo group from the previous trial of mepolizumab in EGPA¹¹ was also performed.

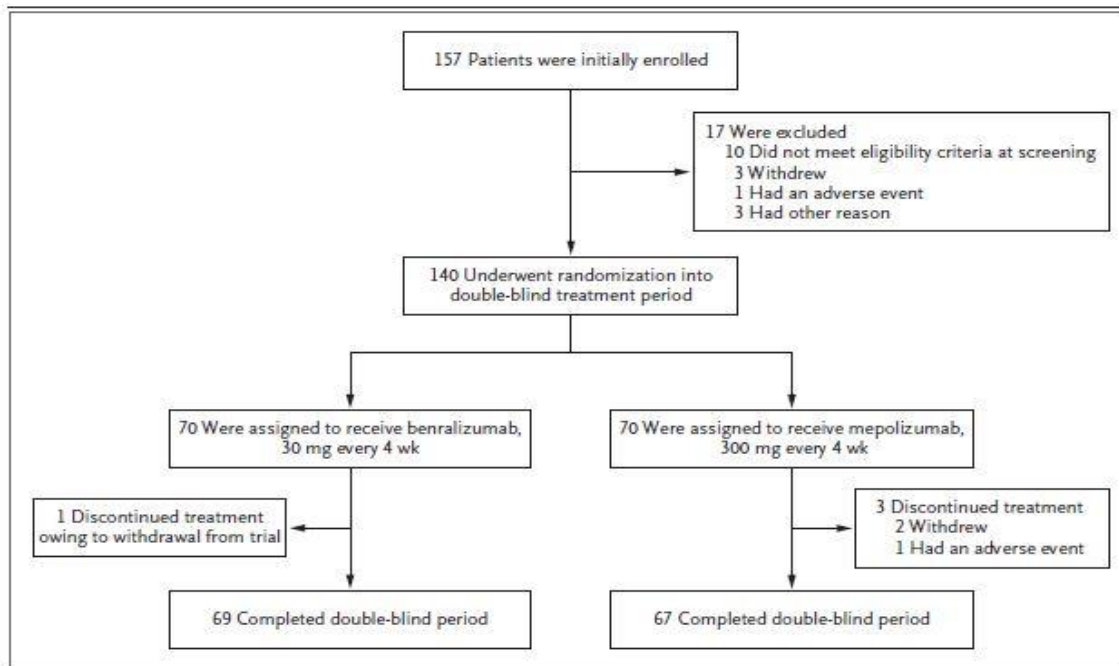


Figure 1. Enrollment, Randomization, and Follow-up.

One additional patient who had received all doses of treatment during the double-blind period had an adverse event that prevented entrance into the open-label extension phase.

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Benralizumab (N=70)	Mepolizumab (N=70)	Total (N=140)
Age — yr	52.0±13.9	52.7±14.4	52.3±14.1
Median (range)	55.0 (20–76)	55.0 (19–79)	55.0 (19–79)
Female sex — no. (%)	45 (64)	39 (56)	84 (60)
Region — no. (%)			
North America	16 (23)	16 (23)	32 (23)
Japan	4 (6)	4 (6)	8 (6)
Rest of the world	50 (71)	50 (71)	100 (71)
EGPA disease type — no. (%)			
Relapsing	45 (64)	48 (69)	93 (66)
Refractory	42 (60)	42 (60)	84 (60)
Relapsing and refractory	18 (26)	20 (29)	38 (27)
Time since diagnosis of EGPA — yr	5.39±5.38	4.93±5.92	5.16±5.64
Range	0.6–24.0	0.1–38.0	0.1–38.0
ANCA-positive status — no. (%)			
At screening†	7 (10)	7 (10)	14 (10)
At screening or historic	18 (26)	22 (31)	40 (29)
Blood eosinophil count/μL‡	306.0±225.0	384.9±563.6	345.4±429.4
Median (range)	240 (30–920)	225 (0–3830)	230 (0–3830)
EGPA disease characteristics — no. (%)			
Asthma	70 (100)	70 (100)	140 (100)
Blood eosinophilia	70 (100)	70 (100)	140 (100)
Biopsy evidence of eosinophilic vasculitis inflammation§	20 (29)	33 (47)	53 (38)

Neuropathy¶	38 (54)	45 (64)	83 (59)
Nonfixed pulmonary infiltrates	49 (70)	43 (61)	92 (66)
Sinonasal abnormality	63 (90)	66 (94)	129 (92)
Cardiomyopathy	17 (24)	13 (19)	30 (21)
Glomerulonephritis	4 (6)	2 (3)	6 (4)
Palpable purpura	7 (10)	10 (14)	17 (12)
Dose of oral glucocorticoid — mg/day**	11.09±4.58	10.95±5.88	11.02±5.25
Median (range)	10.0 (5.0–30.0)	10.0 (7.5–40.0)	10.0 (5.0–40.0)
Oral glucocorticoid dose stratum — no. (%)**			
≥12 mg/day	18 (26)	14 (20)	32 (23)
<12 mg/day	52 (74)	56 (80)	108 (77)
Nonoral glucocorticoid immunosuppressive therapy — no. (%)	26 (37)	24 (34)	50 (36)
Azathioprine	15 (21)	13 (19)	28 (20)
Methotrexate	7 (10)	5 (7)	12 (9)
Mycophenolate mofetil	4 (6)	3 (4)	7 (5)
Methotrexate sodium	1 (1)	1 (1)	2 (1)
Hydroxychloroquine	0	1 (1)	1 (1)
BVAS††	2.3±3.5	1.9±2.9	2.1±3.2

Table 1. (Continued.)

Characteristic	Benralizumab (N=70)	Mepolizumab (N=70)	Total (N=140)
BVAS >0 — no. (%)††	34 (49)	33 (47)	67 (48)
VDI score‡‡	4.0±1.8	4.0±1.8	4.0±1.8
VDI score ≥5 — no. (%)‡‡	23 (33)	21 (30)	44 (31)
Prebronchodilator FEV ₁ — liters	2.520±0.925	2.622±0.873	2.570±0.898

* Plus–minus values are means ±SD. ANCA denotes antineutrophil cytoplasmic antibodies, EGPA eosinophilic granulomatosis with polyangiitis, and FEV₁ forced expiratory volume in 1 second.

† The percentage of patients positive for ANCA was capped at approximately 10% at recruitment.

‡ The percentage of patients with a blood eosinophil count of less than 150 per microliter was capped at approximately 40% at recruitment.

§ Evidence was defined as a biopsy showing histopathological evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation.

¶ Mononeuropathy and polyneuropathy (motor deficit or nerve-conduction abnormality) are included in this category.

|| Cardiomyopathy had to be established by echocardiography or magnetic resonance imaging.

** The dose of oral glucocorticoid was calculated as the daily dose of prednisone or prednisolone, regardless of the reason for administration.

†† The Birmingham Vasculitis Activity Score (BVAS) ranges from 0 to 59, with higher scores indicating more severe disease.

‡‡ Scores on the Vasculitis Damage Index (VDI) range from 0 to 64, with higher scores indicating greater organ damage.

Secondary end points included the total accrued duration of remission (0 weeks [never had remission], >0 to <12 weeks, 12 to <24 weeks, 24 to <36 weeks, or ≥36 weeks), remission within the first 24 weeks and maintenance of remission to week 52, the time from randomization to first relapse (with relapse defined as the presence of one of the following: active vasculitis [BVAS of >0]; active asthma symptoms, signs, or both with a corresponding worsening score on the six-item Asthma Control Questionnaire; active nasal disease, sinus disease, or both with a corresponding worsening reflected by responses to at least one of the questions on the Sino-nasal Symptoms Questionnaire and an increase in the total daily dose of oral glucocorticoid therapy to >4 mg per day of prednisolone; an increase in the dose of or the addition of immunosuppressive therapy; or hospitalization related to worsening EGPA), major relapse (defined as any organ- or life-threatening EGPA event, a BVAS of ≥6 [involving at

least two organ systems in addition to any general symptoms when present], an asthma relapse leading to hospitalization, or sinonasal relapse leading to hospitalization), the frequency of relapse during the double-blind period, the average daily oral glucocorticoid dose during weeks 48 through 52, a reduction in the dose of oral glucocorticoid by at least 50% and 100% during weeks 48 through 52, and blood eosinophil counts. Other secondary end points are described in the Supplementary Appendix. Safety and the side-effect profile were evaluated as adverse events, serious adverse events, and clinical laboratory test results.

Statistical Analysis

The primary analysis included all patients who underwent randomization and received at least one dose of treatment during the double-blind period, included in the analysis according to the intention-to-treat principle and irrespective of adherence to the protocol and continued trial participation. The primary analysis was a test of noninferiority of benralizumab to mepolizumab based on the primary end point of remission and was conducted with the use of the marginal standardization method²³ in logistic regression, with adjustment for treatment group, baseline oral glucocorticoid dose, baseline BVAS, and region (North America, Japan, or the rest of the world). From this model, the absolute difference in the percentage of patients with remission (benralizumab minus mepolizumab) was estimated, along with the associated two-sided 95% confidence interval. To show noninferiority, the lower 95% confidence limit for the absolute difference between benralizumab and mepolizumab needed to be above the prespecified margin of -25 percentage points. This noninferiority margin was necessary because of the small population of patients with this rare disease. Under the assumption that mepolizumab and benralizumab would each induce remission in 32% of patients, 140 patients would provide approximately 90% power to show noninferiority with a noninferiority margin of -25 percentage points at the 2.5% one-sided significance level. If the primary analysis showed noninferiority, a formal test for the superiority of benralizumab to mepolizumab was conducted with the use of the same model. The results were compared with the percentage of patients who had remission in the previous trial of mepolizumab in EGPA.¹¹

Secondary end points were analyzed with the use of the marginal standardization method in logistic regression (for the analysis of oral glucocorticoid dose reduction during weeks 48 through 52, remission during the first 24 weeks, and maintenance of remission to week 52), negative binomial models (for the analysis of the frequency of relapse in the double-blind period), Cox proportional-hazards model (for the analysis of time to relapse), proportional odds models (for the analysis of accrued duration of remission and average daily oral glucocorticoid dose during weeks 48 through 52), and repeated-measures analysis of covariance (for the analysis of blood eosinophil count). Because no provision for correction of multiplicity was planned for tests of secondary or other end points or for subgroup analyses, the results of these analyses are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects for secondary end points.

Results

Demographic and Clinical Characteristics

The double-blind period of the trial started on October 29, 2019, and ended on August 10, 2023; the open-label extension period is ongoing. Overall, 140 patients underwent randomization; 70 were assigned to the benralizumab group and 70 to the mepolizumab group. A total of 69 benralizumab-treated patients (99%) and 67 mepolizumab-treated patients (96%) completed the 52-week double-blind period (Fig. 1). Standard therapy during the treatment period is described in Table S1. The demographic and clinical characteristics of the patients at baseline were balanced between the treatment groups; 60% were women, and the mean (• }SD) age was 52.3 • }14.1 years (Table 1 and Table S2).

Remission

The adjusted percentage of patients with remission at weeks 36 and 48 was 59% in the benralizumab group and 56% in the mepolizumab group (difference, 3 percentage points; 95% confidence interval [CI], -13 to 18; P = 0.73 for superiority), showing noninferiority but not superiority of benralizumab to mepolizumab, since the lower bound of 95% confidence interval exceeded -25 percentage points and the P value for superiority was greater than 0.05 (Table 2 and Figs. S2 and S3).

The adjusted percentage of patients with EULAR-defined remission at weeks 36 and 48 was 79% in the benralizumab group and 74% in the mepolizumab group (difference, 5 percentage points; 95% CI, -7 to 18). Prespecified analyses based on demographic and key clinical characteristics examined the percentages of patients with remission in subgroups of both treatment groups (Fig. S4). Comparisons with the percentages of patients with remission in historic placebo and historic mepolizumab groups from the previous placebo-controlled trial of mepolizumab are shown in Table S3.11

The total accrued duration of remission with benralizumab and mepolizumab is shown in Tables 2 and S4 (odds ratio, 1.36; 95% CI, 0.75 to 2.48). A total of 42% of the patients in the benralizumab group and 36% of those in the mepolizumab group had remission within the first 24 weeks of treatment and remained in remission through week 52 (difference, 6 percentage points; 95% CI, -9 to 20).

Relapse

In both groups, 30% of patients had a relapse, and the time to first relapse was similar in the two groups (hazard ratio, 0.98; 95% CI, 0.53 to 1.82) (Fig. 2). There were 34 relapses in the benralizumab group and 30 relapses in the mepolizumab group (in 21 patients in each group). The annualized relapse rates were 0.50 per year in the benralizumab group and 0.49 per year in the mepolizumab group (rate ratio, 1.03; 95% CI, 0.56 to 1.90). No major relapses occurred in the benralizumab group, and four major relapses (in 3 patients [4%]) occurred in the mepolizumab group (Table S5).

Use of Oral Glucocorticoids

The mean (+/-SD) oral glucocorticoid dose was 11.02+/-5.25 mg per day at baseline. In both the benralizumab group and the mepolizumab group, 70% of the patients received daily oral glucocorticoid doses of 4 mg or less during weeks 48 through 52 (odds ratio, 1.42; 95% CI, 0.77 to 2.62) (Figs. S5A and S5B and Table S6). The mean daily oral glucocorticoid dose over time is shown

in Fig. S5C. During the final 4 weeks of the trial, the daily dose of oral glucocorticoids was 2.98±3.76 mg in the benralizumab group and 3.43±4.12 mg in the mepolizumab group (median, 1.2 mg [range, 0.0 to 16.6] and 3.0 mg [range, 0.0 to 25.7], respectively).

During weeks 48 through 52, a total of 86% of the patients in the benralizumab group and 74% of those in the mepolizumab group had at least a 50% reduction in oral glucocorticoid dose (difference, 12 percentage points; 95% CI, -1 to 25) (Table 2 and Fig. S5A). Complete withdrawal of oral glucocorticoids during weeks 48 through 52 was achieved in 41% of the patients in the benralizumab group and 26% of those in the mepolizumab group (difference, 16 percentage points; 95% CI, 1 to 31) (Table 2 and Fig. S5A).

Table 2. Primary and Secondary Outcomes.

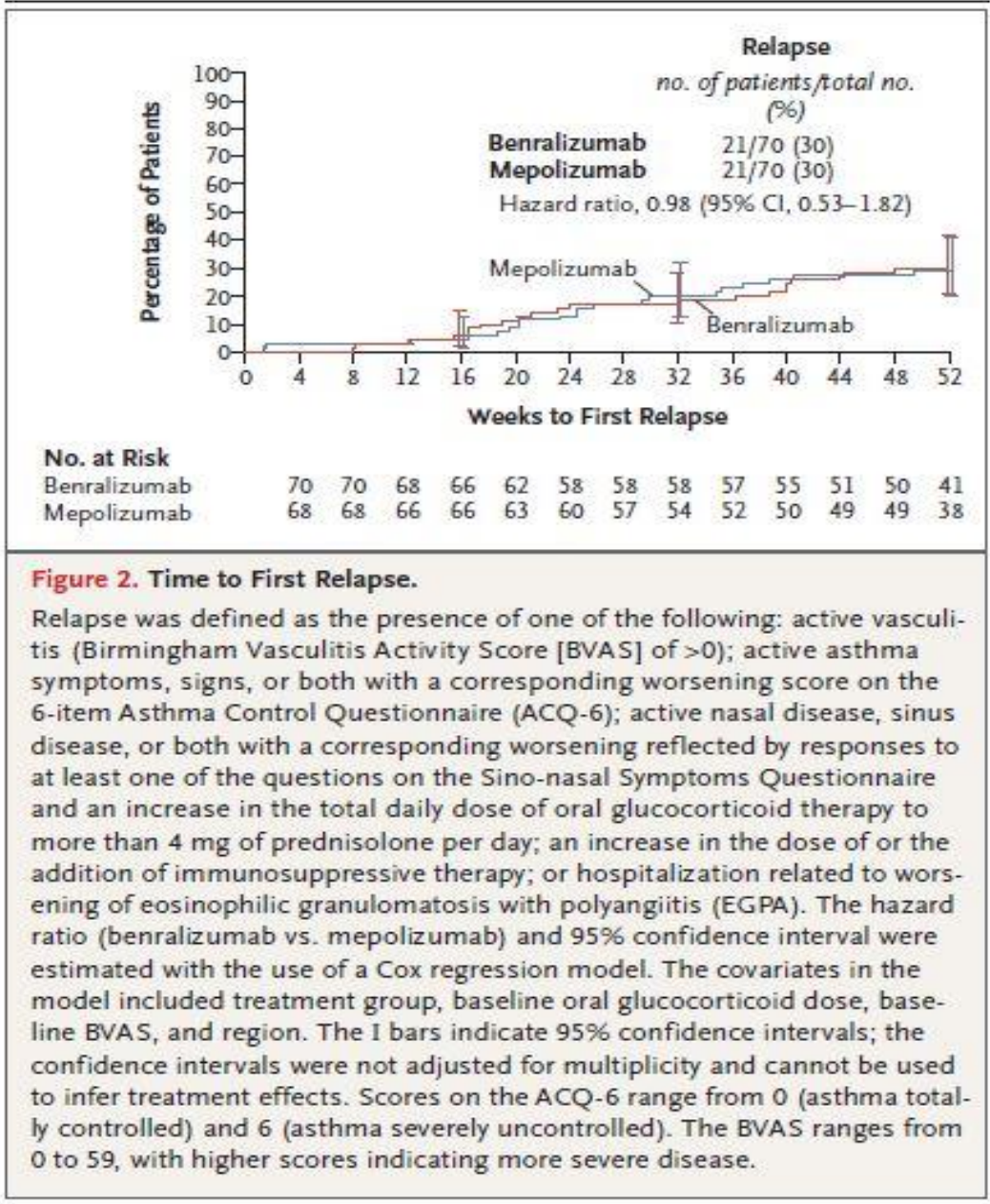
End Point	Benralizumab (N=70)	Mepolizumab (N=70)	Difference or Odds Ratio (95% CI)
Primary end point: remission at weeks 36 and 48 — adjusted % of patients	59	56	3 (-13 to 18) †‡
Secondary end points*			
Accrued duration of remission — no. (%)			1.36 (0.75 to 2.48) §
0 wk	9 (13)	15 (21)	
0 to <12 wk	12 (17)	10 (14)	
12 to <24 wk	8 (11)	8 (11)	
24 to <36 wk	21 (30)	19 (27)	
≥36 wk	20 (29)	18 (26)	
Mean daily dose of oral glucocorticoid during weeks 48 through 52 — no. (%) ¶			1.42 (0.77 to 2.62) §
0 mg	29 (41)	19 (27)	
>0 to ≤4 mg	20 (29)	30 (43)	
>4 to ≤7.5 mg	14 (20)	13 (19)	
>7.5 mg	7 (10)	8 (11)	
Reduction in oral glucocorticoid dose — adjusted % of patients ¶			
≥50% reduction	86	74	12 (-1 to 25) ‡
100% reduction	41	26	16 (1 to 31) ‡

* Confidence intervals for secondary end points were not adjusted for multiplicity and cannot be used to infer treatment effects.
† P=0.73.
‡ Value is the percentage-point difference. Percentages and percentage-point differences were estimated with the use of a marginal standardization method in a logistic-regression model, with treatment group, baseline dose of oral glucocorticoid, baseline BVAS, and region as covariates.
§ Value is an odds ratio. Odds ratios were estimated with the use of a proportional odds model with covariates for treatment group, baseline dose of oral glucocorticoid, baseline BVAS, and region.
¶ The oral glucocorticoid dose was calculated as the daily dose of prednisone or prednisolone, regardless of the reason for administration. For patients who withdrew from the trial before week 52, the daily dose of oral glucocorticoid in the previous 28 days was used to derive the mean daily dose and percentage decrease in dose from baseline during weeks 48 through 52. Patients who discontinued treatment before week 48 were considered to have not had a response in the analysis of the percentage reduction in oral glucocorticoid dose.

Blood Eosinophil Counts

Reductions in blood eosinophil counts in both groups were observed as early as week 1 and were maintained at all time points. The baseline blood eosinophil counts were 306.0±225.0 per microliter in the benralizumab group and 384.9±563.6 per microliter in the mepolizumab group; at week 1 they had decreased to 46.7 ±39.8 and 119.8±136.4 per microliter, respectively, and at week 52 they had decreased to 32.4 ±40.8 and 71.8 ±54.4 per microliter, respectively. The leastsquares mean ratios of the blood eosinophil count at week 1 to the value at baseline were 0.15 in the benralizumab group and 0.39 in the mepolizumab group; the ratios at week 52 were 0.10 and 0.26, respectively (adjusted geometric mean ratio between the groups, 0.38 [95% CI, 0.29 to 0.49] at week 1 and 0.36

[95% CI, 0.27 to 0.49] at week 52) (Fig. S6). (Data for additional secondary end points are provided in Figs. S7 through S14 and Tables S7 through S14.)



Safety

Adverse events were reported in 90% of the patients who received benralizumab and 96% of those who received mepolizumab (Table 3). The most often reported adverse events were coronavirus disease 2019 (Covid-19) (in 21% of the patients in the benralizumab group and 27% of those in the mepolizumab group), headache (17% and 16%), and arthralgia (17% and 11%) (Table 3 and Table S15). No patients in the benralizumab group had adverse events leading to treatment discontinuation; two patients who received mepolizumab had a serious adverse event (prostate cancer) that was not considered related to treatment but did result in discontinuation of participation in the trial.

Serious adverse events were reported in 6% of the patients in the benralizumab group and 13% of those in the mepolizumab group (Table 3). The most often reported serious adverse events were Covid-19 (1% of the patients in each group) and prostate cancer (no patients in the benralizumab group and 3% of those in the mepolizumab group). No deaths occurred.

Discussion

This randomized head-to-head trial involving patients with EGPA showed noninferiority of benralizumab to mepolizumab in the induction of remission at weeks 36 and 48. The results for secondary end points, including control of disease activity, durability of response, and duration of accrued and sustained remission, appeared to be similar in the two groups, although firm conclusions may not be drawn. The annualized rates of relapse and time to first relapse were also similar in the two groups. More than 70% of the patients in each group had at least a 50% reduction in their oral glucocorticoid dose; complete withdrawal of oral glucocorticoids during weeks 48 through 52 was achieved in 41% of the patients in the benralizumab group and 26% of those in the mepolizumab group, which suggests that treatment of EGPA with benralizumab or mepolizumab may help to reduce dependency on oral glucocorticoids and reduce related morbidity. These results suggest that targeting eosinophils as a therapeutic strategy in EGPA can lead to a high percentage of patients with remission and a low percentage having relapse despite substantial reductions in the use of oral glucocorticoids, providing further evidence of the critical role of eosinophils in the pathophysiological processes underlying EGPA. However, although anti-interleukin-5 and anti-interleukin-5R α drugs primarily target eosinophils, they also have effects on other immune cells, such as mast cells and basophils. 14

The trial population had a range of clinical manifestations similar to those seen in the previous placebo-controlled mepolizumab trial.¹¹ The percentage of patients who received mepolizumab and had remission in this trial appeared to be higher than that in the previous trial, as was the percentage of patients who received mepolizumab and were able to completely discontinue oral glucocorticoids. This difference may be due in part to differences in trial design; the current trial is an active-comparator trial, whereas the previous trial was placebo-controlled. In the years between the trials, clinical practice has evolved, and physicians have more experience in using eosinophil-targeted EGPA treatments and aiming for full sparing of oral glucocorticoids.^{4,5} Thus, in the current trial, physicians may have had more confidence in tapering oral glucocorticoids. The possibly lower percentage of patients who had relapse in the current trial may partly reflect the effect of social distancing and isolation measures during the Covid-19 pandemic, which has previously been shown to be associated with a reduced frequency of asthma exacerbations.²⁵

Both benralizumab and mepolizumab had acceptable side-effect profiles in this trial, with few serious adverse events and no new safety signals. The safety profile of benralizumab did not show any meaningful difference with that of mepolizumab and was similar to the safety profile that had previously been observed in trials involving patients with severe eosinophilic asthma, ²⁶⁻²⁸ as well as in real-world analyses of benralizumab in patients with EGPA.^{18,19} The safety profile of mepolizumab was consistent with that observed in the previous placebo-controlled mepolizumab trial.¹¹

Table 3. Adverse Events during the Double-Blind Phase.*		
Event	Benralizumab (N=70)	Mepolizumab (N=70)
	<i>no. of patients (%)</i>	
Any adverse event	63 (90)	67 (96)
Most common adverse events†		
Covid-19	15 (21)	19 (27)
Headache	12 (17)	11 (16)
Arthralgia	12 (17)	8 (11)
Nasopharyngitis	6 (9)	10 (14)
Sinusitis	5 (7)	8 (11)
Any serious adverse event	4 (6)	9 (13)
Serious adverse events		
Covid-19	1 (1)	1 (1)
Appendicitis	0	1 (1)
Bronchitis	1 (1)	0
Urinary tract infection	0	1 (1)
Wound infection	0	1 (1)
Cholangitis	0	1 (1)
Eosinophilic hepatic infiltration	0	1 (1)
Prostate cancer	0	2 (3)
Peripheral neuropathy	1 (1)	0
Syncope	1 (1)	0
Acute respiratory failure	0	1 (1)
Any adverse event leading to discontinuation of treatment	0	2 (3)
Adverse events leading to discontinuation		
Prostate cancer	0	2 (3)
Any adverse event with outcome of death	0	0

* Adverse events were classified with the use of *Medical Dictionary for Regulatory Activities*, version 26.0, preferred terms. The total duration of exposure during the double-blind period was 70.2 patient-years in the benralizumab group and 70.3 patient-years in the mepolizumab group. Covid-19 denotes coronavirus disease 2019.

† The five most common events are listed.

Strengths of the current trial include the head-to-head design; the high patient retention rate; the review of the BVAS, Vasculitis Damage Index, and status with respect to the primary end point by the study oversight committee; and the documentation of use of oral glucocorticoids throughout the trial. Limitations include the small sample size due to the rarity of the disease, which precludes conclusions based on subgroup analyses or the exploration of alternative dosing strategies. Furthermore, secondary end points were not multiplicity-corrected, which limited their interpretation. Finally, the duration of the double-blind period and the different

starting doses of oral glucocorticoids at baseline may not have allowed all patients to discontinue oral glucocorticoids. Further work is necessary to understand the role of anti-interleukin-5 and anti-interleukin-5R α drugs in the management of active organ-threatening EGPA manifestations. Future studies are also necessary to determine whether eosinophil depletion in patients with EGPA is associated with complete discontinuation of oral glucocorticoid treatment; however, the results of this trial and the previous trial suggest that complete discontinuation of oral glucocorticoids may now be an achievable treatment goal during receipt of eosinophil-targeted drugs.

This trial showed noninferiority of benralizumab to mepolizumab for the achievement of remission at weeks 36 and 48 in patients with relapsing or refractory EGPA who were receiving standard care.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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