# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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**SUPPLEMENTARY MATERIALS**

Manuscript: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis

**CONTENT**

## 1. EGPA mepolizumab study team

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## 3. Countries where the study was conducted

Belgium (n=3 participants), Canada (n=6 participants), France (n=13 participants), Germany (n=19 participants), Italy (n=13 participants), Japan (n=6 participants), Spain (n=4 participants), UK (n=13 participants), USA (n=59 participants).

## 4. Inclusion and exclusion criteria

**Inclusion criteria**

a. **Informed consent**: Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form. Participants must be able to read, comprehend, and write at a level sufficient to complete study-related materials.
b. **Age and gender:** Male or female participants ≥18 years.
c. **EGPA diagnosis:** participants who have been diagnosed with EGPA for at least 6 months based on the history or presence of: asthma plus eosinophilia (>1.0x$10^9$/L and/or >10% of leucocytes) plus at least two of the following additional features of EGPA:
    - A biopsy showing histopathological evidence of eosinophilic vasculitis, or
        - Perivascular eosinophilic infiltration, or eosinophil–rich granulomatous
        - Inflammation
    - Neuropathy, mono or poly (motor deficit or nerve conduction abnormality)
    - Pulmonary infiltrates, non–fixed
    - Sino–nasal abnormality

- Cardiomyopathy (established by echocardiography or MRI)
- Glomerulonephritis (hematuria, red cell casts, proteinuria)
- Alveolar hemorrhage (by bronchoalveolar lavage)
- Palpable purpura
- Positive test for ANCA (MPO or PR3).

d. **History of relapsing OR refractory disease defined as:**

- **Relapsing disease**: Participant must have a past history of at least one confirmed EGPA relapse (i.e., requiring increase in oral corticosteroid [OCS] dose, initiation/increased dose of immunosuppressive therapy or hospitalisation) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥7.5 mg/day.
- **Japan-only definition of relapsing disease:** participant must have a past history of at least one confirmed EGPA relapse (i.e., requiring increase in OCS dose, initiation of intravenous (IV) prednisolone (or equivalent), initiation/increased dose of immunosuppressive therapy, initiation/increased dose of IV immunoglobulin (IVIG) or hospitalization) within the past 2 years which occurred at least 12 weeks prior to screening (Visit 1) while receiving a dose of prednisolone (or equivalent) of ≥7.5 mg/day.
- **Refractory disease**:

  **Either**: failure to attain remission (Birmingham Vasculitis Activity Score [BVAS; scale 0–63]=0 and OCS dose ≤7.5 mg/day prednisolone or equivalent) within the prior 6 months following induction treatment with a standard regimen, administered for at least 3 months.

  Note:

  a. Participants who have received a cyclophosphamide induction regimen may be included a minimum of 2 weeks after the last dose of daily oral cyclophosphamide, or 3 weeks after the last dose of pulsed IV cyclophosphamide prior to baseline (Visit 2), if their total white blood count is ≥4x$10^9$/L (tested at the local laboratory, if necessary) prior to randomization.

  b. Participants who have received an azathioprine, methotrexate, or mycophenolate mofetil induction regimen may be included if on a stable dose for at least 4 weeks prior to baseline (Visit 2).

  c. Participants who have received an induction regimen comprising glucocorticoids alone may be included only if they have failed to attain remission after 3 months of treatment

**AND** the glucocorticoid dose is ≥15 mg/day prednisolone or equivalent for the 4 weeks prior to baseline (Visit 2).

**Or:** Within 6 months prior to screening (Visit 1), recurrence of symptoms of EGPA (not necessarily meeting the protocol definition of relapse) while tapering OCS, occurring at any dose level ≥7.5 mg/day prednisolone or equivalent.

e. **Therapy with glucocorticoids**: participant must be on a stable dose of oral prednisolone or prednisone of ≥7.5 mg/day (but not >50 mg/day) for at least 4 weeks prior to baseline (Visit 2).

f. **Immunosuppressive therapy**: if receiving immunosuppressive therapy (excluding cyclophosphamide) the dosage must be stable for the 4 weeks prior to baseline (Visit 2) and during the study (dose reductions for safety reasons will be permitted).

g. **ECG measurements**: QTc(F)<450 msec *or* QTc(F)<480 msec for participants with bundle branch block.

- The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), Fridericia's formula (QTcF), or another method, machine or manual overread.
- For participant eligibility and withdrawal decisions, QTcF will be used.
- For purposes of data analysis, QTcF will be used as primary though data using both correction formulas will be collected and analyzed. The QTc should be based on single or averaged QTc values of triplicate electrocardiograms (ECGs) obtained over a brief recording period.

h. **Female participants:** to be eligible for entry into the study, females of childbearing potential must commit to consistent and correct use of an acceptable method of birth control beginning with consent, for the duration of the trial and for 4 months after the last study drug administration.

i. **French participants:** in France, a participant will be eligible for inclusion in this study only if either affiliated to, or a beneficiary of, a social security category.

**Exclusion criteria**

a. Diagnosed with granulomatosis with polyangiitis (Wegener's) or microscopic polyangiitis.

b. **Organ–threatening EGPA:** organ-threatening EGPA as per EULAR criteria, i.e., organ failure due to active vasculitis, creatinine >5.8 g/dL (>513 µmol/L) within 3 months prior to screening (Visit 1).

c. **Life–threatening EGPA:** imminently life-threatening EGPA disease defined as any of the following within 3 months prior to screening (Visit 1).

- Intensive care required.

- Severe alveolar hemorrhage or hemoptysis requiring transfusion or ventilation or hemoglobin <8 g/dL (<80 g/L) or drop in hemoglobin >2 g/dL (>20 g/L) over a 48-hour period due to alveolar hemorrhage.
- Rapidly progressive glomerulonephritis with creatinine >2.5 mg/dL (>221 µmol/L) or rise in creatinine >2 mg/dL (>177 µmol/L) over a 48-hour period.
- Severe gastrointestinal involvement, for example, gangrene, bleeding requiring surgery.
- Severe central nervous system involvement.
- Severe cardiac involvement, for example, life-threatening arrhythmia, cardiac failure: ejection fraction <20%, New York Heart Association Class III/IV, acute myocardial infarction.

d. **Malignancy**: a current malignancy or previous history of cancer in remission for <12 months prior to screening (participants that had localized carcinoma (i.e., basal or squamous cell) of the skin which was resected for cure will not be excluded).

e. **Liver disease**: unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices or persistent jaundice), cirrhosis, and known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

f. **Cardiovascular**: participants who have severe or clinically significant cardiovascular disease uncontrolled with standard treatment including but not limited to:
   - Known ejection fraction of <30%, OR
   - Severe heart failure that meets New York Heart Association Class IV, OR
   - Hospitalized in the 12 months prior to Visit 1 for severe heart failure meeting New York Heart Association Class III, OR
   - Angina diagnosed less than 3 months prior to or at Visit 1 (screening).

g. **Other concurrent medical conditions**: participants who have known, pre-existing, clinically significant endocrine, autoimmune, metabolic, neurological, renal, gastrointestinal, hepatic, hematological, respiratory or any other system abnormalities that are not associated with EGPA and are uncontrolled with standard treatment.

h. **Infectious disease:** chronic or ongoing active infectious disease requiring systemic treatment.

i. **Parasitic infection**: participants with a parasitic infection within 6 months prior to screening (Visit 1).

j. **Hepatitis status:** diagnosis of chronic hepatitis B, as evidenced by positive Hepatitis B surface antigen (HBsAg) at screening (Visit 1). **Japan only**: participants positive for HBsAg, antibodies to HBsAg, i.e., Hepatitis B surface antibody (HBsAb), or Hepatitis B core antigen, i.e., Hepatitis B

core antibody (HBcAb), at screening (Visit 1). Note: participants with antibodies to HBsAg, i.e., HBsAb positive, only (i.e., negative for HBsAg and HBcAb) with a history of hepatitis B vaccination can be included.

k. **HIV:** participants with known infection with HIV.

l. **Hypersensitivity**: participants with a known allergy or intolerance to a monoclonal antibody or biologic therapy.

m. **Previous mepolizumab:** participants who have previously received mepolizumab within a 1 year period prior to screening (Visit 1).

n. **Prohibited medications**: participants receiving any of the following:

- **OCS:** participant requires an oral glucocorticoid dose of >50 mg/day prednisolone/prednisone in the 4-week period prior to baseline (Visit 2).
- **IV or subcutaneous (SC) glucocorticoids** in the 4-week period prior to baseline (Visit 2).
- **Omalizumab** within 130 days prior to screening (Visit 1).
- **Cyclophosphamide:** oral cyclophosphamide within 2 weeks prior to baseline (Visit 2) and IV cyclophosphamide within 3 weeks prior to baseline (Visit 2), if their total white blood cell count is $4x10^9$/L (measured using the local laboratory if necessary).
- **Rituximab** within 12 months prior to screening (Visit 1); in addition, the participant must have shown recovery of peripheral B-cell count to within the normal range.
- **IV or SC immunoglobulin** within 6 months prior to screening (Visit 1).
- **Interferon-α** within 6 months prior to screening (Visit 1).
- **Anti–tumor necrosis factor therapy** within 12 weeks prior to screening (Visit 1).
- **Anti-CD52 (alemtuzumab)** within 6 months prior to screening (Visit 1).

o. **Other laboratory parameter exclusions**:

- Creatinine >2.5 mg/dL (221 µmol/L)
- White blood cell count < 4 $x10^9$/L
- Platelet count <120,000/$mm^3$
- Hemoglobin <8 g/dL (<80 g/L)

p. **Pregnancy**: participants who are pregnant or breastfeeding. Participants should not be enrolled if they plan to become pregnant during the time of study participation.

q. **Alcohol/substance abuse**: a history (or suspected history) of alcohol misuse or substance abuse within 2 years prior to screening (Visit 1).

r. **Other investigational product:** participants who have received treatment with an investigational drug within the past 30 days or 5 terminal phase half-lives of the drug whichever is longer, prior to screening (Visit 1) (this also includes investigational formulations of marketed products).

s. **Other clinical study:** participant is currently participating in any other interventional clinical study.

t. **Adherence**: participants who have known evidence of lack of adherence to prescribed medications and/or ability to follow physician's recommendations.

**French participants:** the French participant has participated in any study using an investigational drug during the previous 30 days or 5 half-lives (whichever is longer).

## 5. Liver chemistry stopping criteria

1. Alanine transaminase (ALT) ≥3x upper limit of normal (ULN) and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and International Normalized Ratio [INR] >1.5, if INR measured)
2. ALT ≥8xULN
3. ALT ≥5xULN but <8 xULN that persists for ≥2 weeks
4. ALT ≥3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia)
5. ALT ≥5xULN but <8 xULN and patient is unable to be monitored for ≥2 weeks

## 6. Relapsing and refractory disease definitions post-randomization

**Relapsing disease** was defined as a history of relapse requiring an increase in glucocorticoid dose, initiation or increase in other immunosuppressive therapy, or hospitalization in the previous 2 years while receiving ≥7.5 mg prednisolone (or equivalent).

**Refractory disease** was defined as 1) failure to achieve remission following a standard induction regimen administered for at least three months or 2) recurrence of symptoms of EGPA whilst tapering glucocorticoids to a dose of ≥7.5 mg prednisolone (or equivalent) within the previous 6 months.

## 7. Other endpoints

Other pre-specified endpoints included frequency of all and major relapses of EGPA (major relapse defined as organ- or life-threatening event or BVAS ≥6 or an asthma or sino-nasal relapse requiring hospitalization) within the study period, time to first major relapse, percentage reduction in average daily prednisolone/prednisone dose during Weeks 48 to 52, mean change from baseline in BVAS, Vascular Damage Index (VDI), lung function (forced expiratory volume in 1 second [$FEV_1$] and forced vital capacity [FVC]), Asthma Control Questionnaire (ACQ)-6 score, Sino-nasal Outcome Test (SNOT)-

22 score, and biomarkers of inflammation (C-reactive protein and Erythrocyte sedimentation rate). Absolute eosinophil count was also assessed and expressed as a ratio to baseline.

## 8. Adjustment for multiplicity

Per protocol, adjustment for multiplicity was achieved using a closed testing procedure with the secondary endpoints nested under the primary efficacy endpoint, followed by a further hierarchical procedure within the secondary endpoints. The ordering of the secondary variables was to be as follows:

1. Time to first EGPA relapse
2. Average daily prednisolone/prednisone dose during the last 4 weeks of the study treatment period
3. The proportion of participants who achieve remission (BVAS=0 and prednisolone/prednisone dose $\leq$4 mg/day) within the first 24 weeks of the study and then remain in remission for the remainder of the study treatment period
4. Total accrued duration of remission, (defined as BVAS=0 plus prednisolone/prednisone dose $\leq$7.5 mg/day) over the 52-week study
5. The proportion of participants who are in remission (defined as BVAS=0 plus prednisolone/prednisone dose $\leq$7.5 mg/day) at both Weeks 36 and 48 of the study
6. The proportion of participants who achieve remission (defined as BVAS=0 plus prednisolone/prednisone dose $\leq$7.5 mg/day) within the first 24 weeks of the study and then remain in remission for the remainder of the study treatment period

In practice, co-primary and secondary endpoints were all statistically significant, and no adjustment was required.

## 9. Range of scores for study endpoints

- The BVAS has a range of 0–63 points. A score of 0 indicates no disease activity. The minimal clinically important difference has not been determined.[1]
- The ACQ-6 has a range of 0–6 points. Higher scores equate to less control. The minimal clinically important difference is 0.5 points.[2,3]
- The SNOT-22 has a range of 0–110 points. Higher scores relate to worse quality of life. The minimal clinically important difference is 8.9 points.[4]

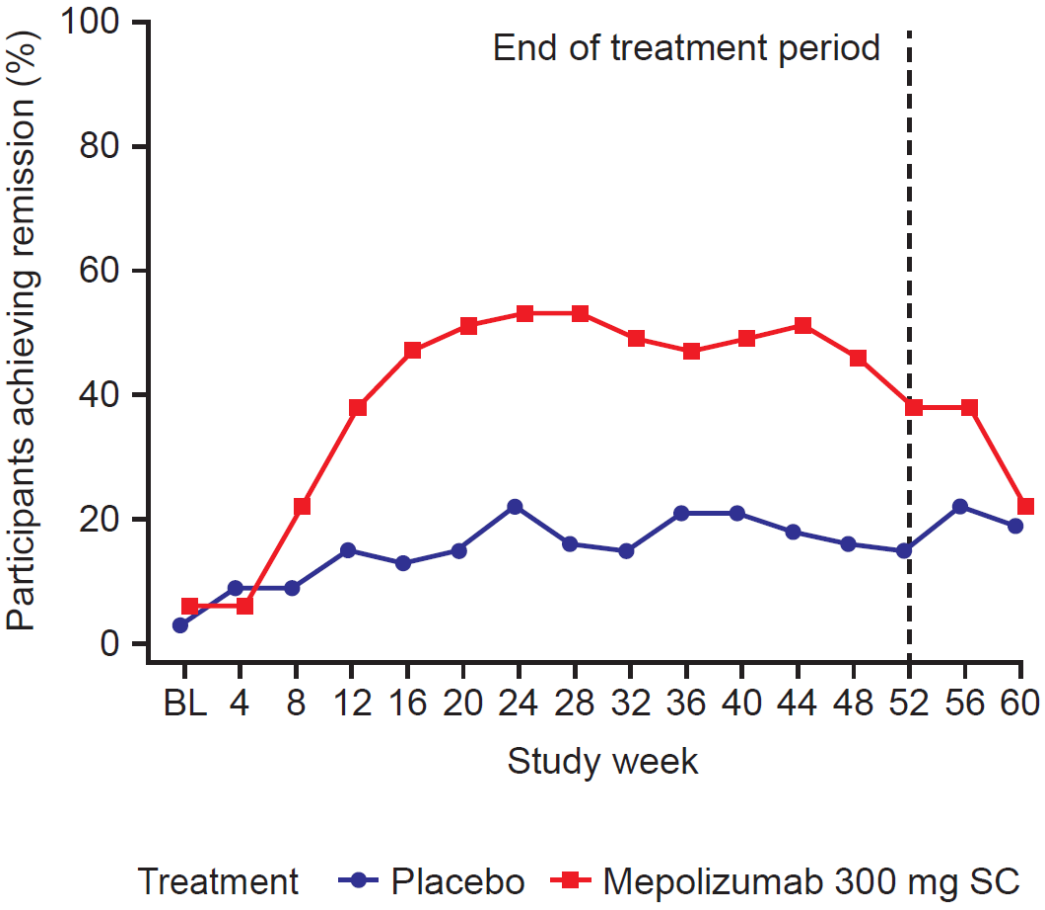
- The VDI has a range of 0–64. A score of 0 indicates no damage. The minimal clinically important difference has not been determined.[5]

## 10. Rationale for mepolizumab study dose

It was considered that the mepolizumab therapeutic dose for EGPA should be a dose that would maximize blood eosinophil reduction while maintaining an acceptable safety profile. Therefore, mepolizumab 300 mg administered SC every 4 weeks was selected based on the understanding of mepolizumab pharmacology gained through the severe asthma program. In the phase 2b/3 dose-range finding study, MEA112997 (DREAM), which investigated doses of 75, 250 and 750 mg IV every 4 weeks in patients with severe eosinophilic asthma, the doses of 250 and 750 mg IV every 4 weeks were found to provide similar blood eosinophil reduction, and this reduction was greater than that observed for the 75 mg IV every 4 weeks dose. Thus, while increasing the dose to 250 mg IV (corresponding approximately to a 300 mg SC dose based on mepolizumab absolute bioavailability) could potentially provide additional benefit over the 75 mg IV dose, increasing the dose beyond 250 mg IV would not provide additional pharmacological benefit.

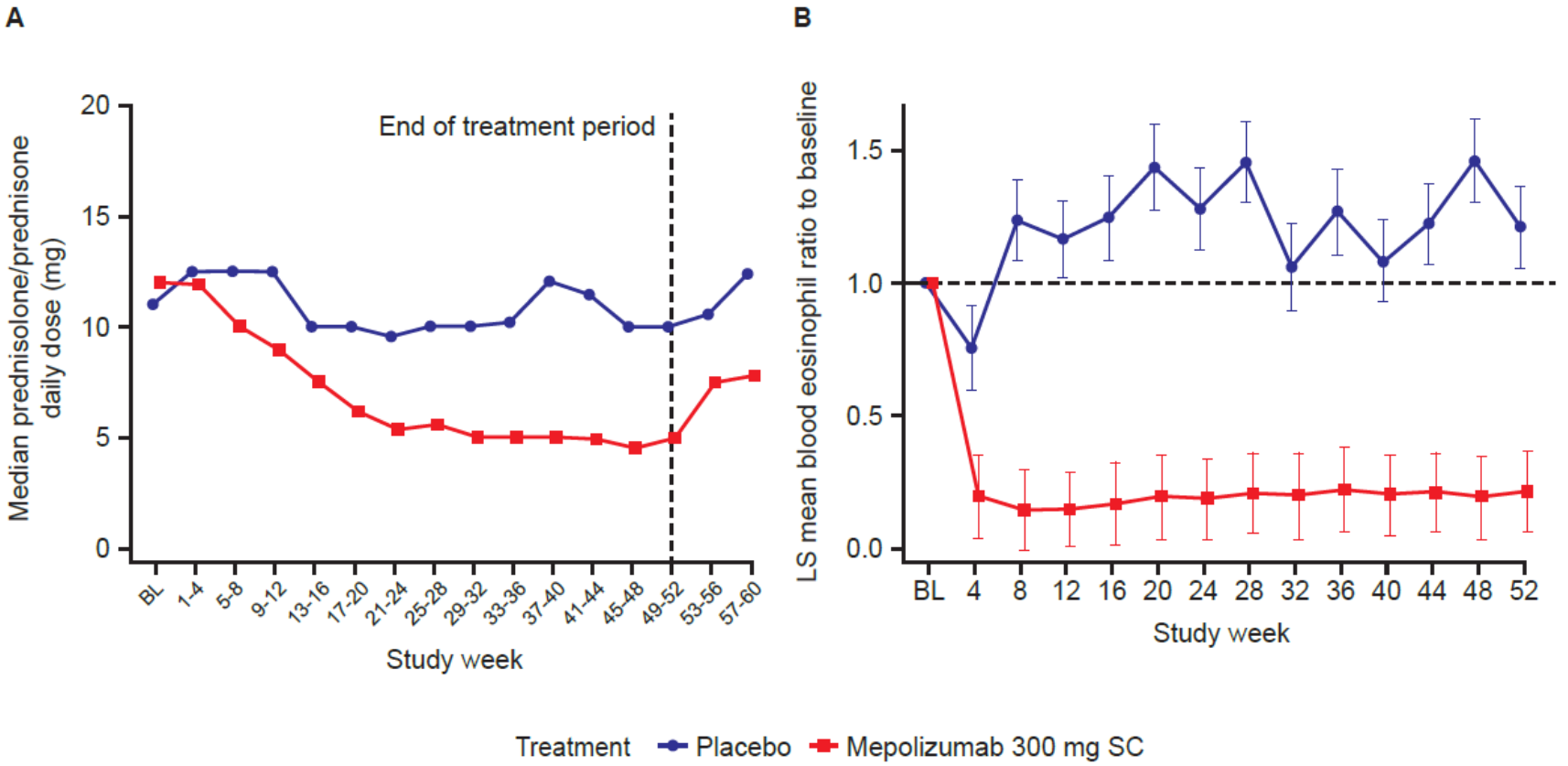
## 11. Supplementary figures and tables

**Figure S1.** Proportion of participants achieving remission (BVAS[a]=0, prednisolone/prednisone dose ≤7.5 mg/day), by visit.



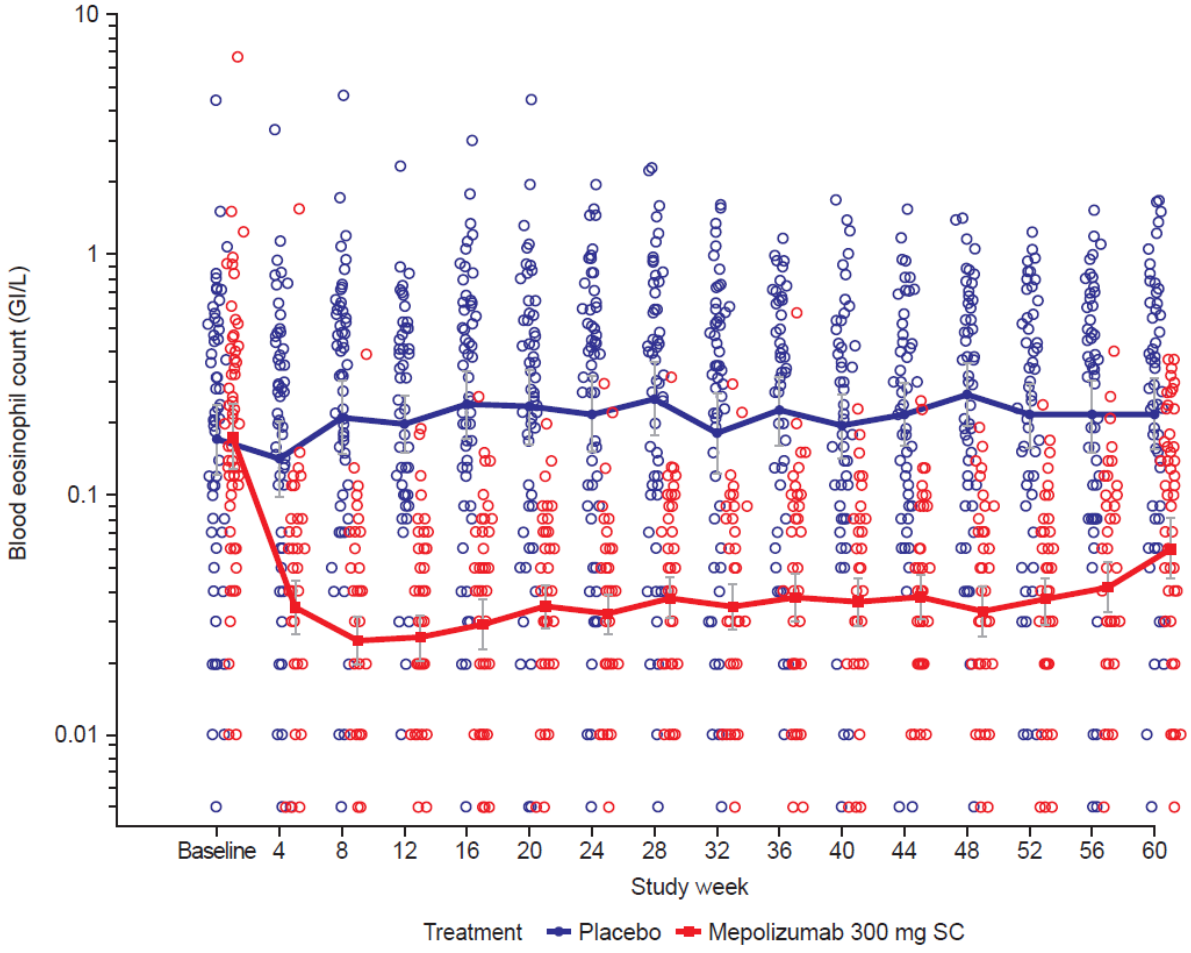

[a]BVAS scale 0–63. BVAS, Birmingham Vasculitis Activity Score; SC, subcutaneous.

**Figure S2.** (A) Median prednisolone/prednisone dose (mg/day) during each reported period; (B) LS mean ratio to baseline in blood eosinophil count[a,b] (ITT population).



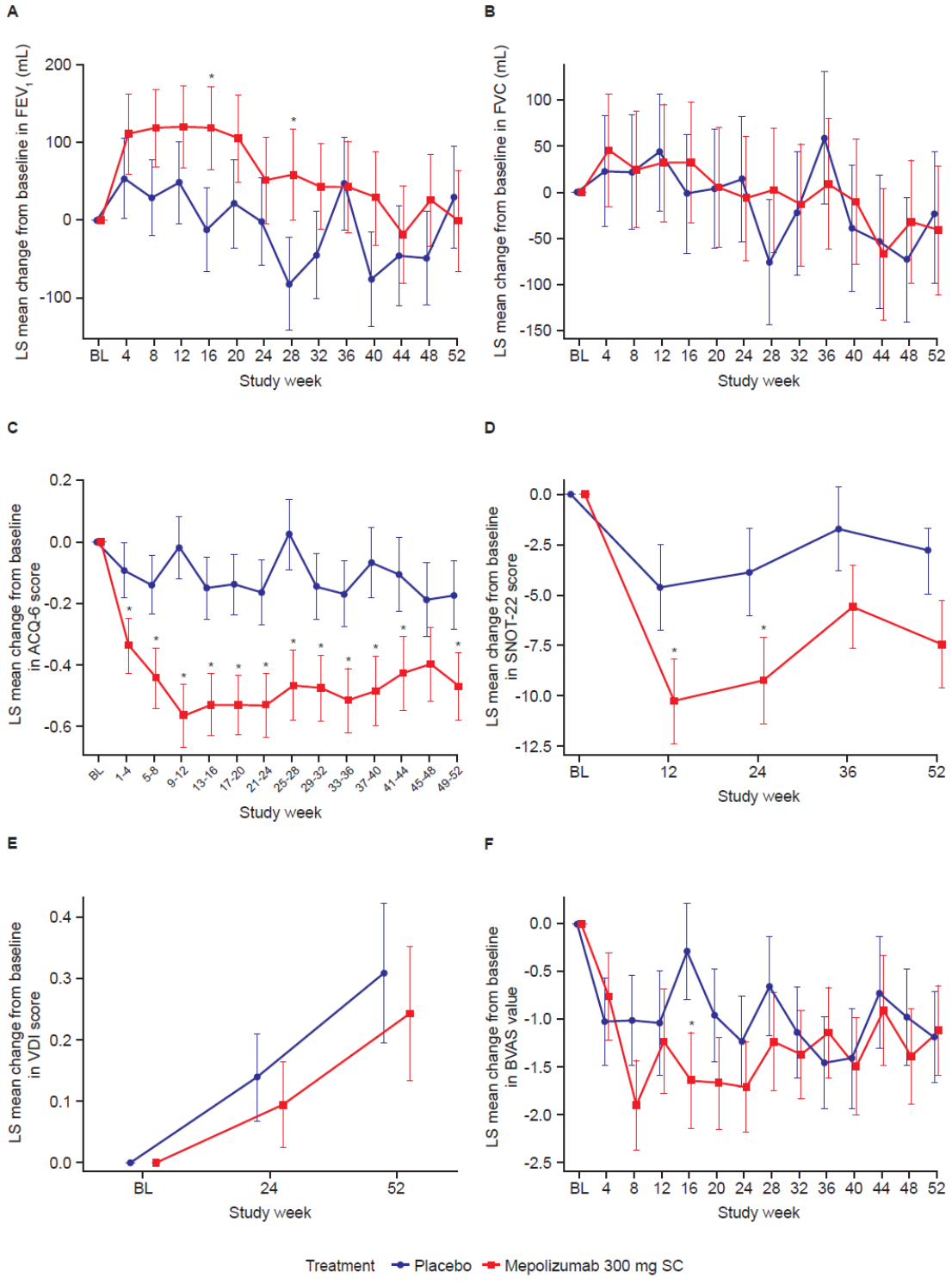

[a]Error bars represent standard error of mean; [b]analysis performed using mixed-model repeated-measures (i.e., only data from the treatment period contributed to the analysis) with terms for treatment group, baseline prednisolone/prednisone daily dose, baseline BVAS score, region, baseline value, visit, visit by baseline value, and visit by treatment group. Data were log-transformed. Where a result of 0 was recorded, a small value (i.e., minimum all non-missing results/2) was added prior to log transformation. BL, baseline; ITT, intent-to-treat; LS, least squares; SC, subcutaneous.

**Figure S3.** Absolute eosinophil count profile over the treatment and follow-up periods for mepolizumab- and placebo-treated participants.




SC, subcutaneous.

**Figure S4.** (A) Change from baseline in $FEV_1$ (mL), by visit; (B) change from baseline in FVC (mL), by visit; (C) change from baseline in ACQ-6[a] score, by visit; (D) change from baseline in SNOT-22[b] score, by visit; (E) change from baseline in VDI[c] score, by visit; (F) change from baseline in BVAS[d] value, by visit.




Error bars represent standard error of mean. *denotes statistically significant difference between mepolizumab and placebo. [a]ACQ-6 scale 0–6 points, minimal clinically important difference 0.5 points; [b]SNOT-22 scale 0–110 points, minimal clinically important difference 8.9 points; [c]VDI scale 0–64; [d]BVAS scale 0–63 points. ACQ, Asthma Control Questionnaire; BL, baseline; BVAS, Birmingham Vasculitis Activity Score; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LS, least squares; SC, subcutaneous; SNOT, Sino-nasal Outcome Test; VDI, vascular damage index.

**Table S1**. Standard of care therapy taken during the treatment period.

| | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **Participants taking glucocorticoids during the treatment period, n (%)[a]** | | |
| Prednisone | 49 (72) | 47 (69) |
| Prednisolone | 22 (32) | 22 (32) |
| Methylprednisolone sodium succinate | 4 (6) | 6 (9) |
| Methylprednisolone | 4 (6) | 4 (6) |
| Dexamethasone | 3 (4) | 1 (1) |
| Hydrocortisone sodium succinate | 2 (3) | 1 (1) |
| Hydrocortisone | 0 (0) | 1 (1) |
| Triamcinolone | 1 (1) | 0 (0) |
| Triamcinolone acetonide | 0 (0) | 1 (1) |
| **Participants taking immunosuppressive therapy at baseline, n (%)** | | |
| Azathioprine | 10 (15) | 20 (29) |
| Methotrexate | 11 (16) | 13 (19) |
| Mycophenolic acid | 6 (9) | 6 (9) |
| Cyclosporine | 3 (4) | 0 (0) |
| Hydroxyurea/hydroxycarbamide | 2 (3) | 0 (0) |
| Leflunomide | 1 (1) | 1 (1) |
| Mycophenolate mofetil | 0 (0) | 1 (1) |

[a]As patients could take more than one glucocorticoid type during the study, the total of the percentages is greater than 100%.

**Table S2**. Reasons for treatment discontinuation.

| | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **Participants who prematurely discontinued treatment, n (%)** | 9 (13) | 5 (7) |
| **Reason for discontinuation, n (%)** | | |
| Adverse event | 0 (0) | 2 (3) |
| Lack of efficacy | 3 (4) | 0 (0) |
| Protocol deviation | 0 (0) | 0 (0) |
| Participant reached protocol defined stopping criteria | 2 (3) | 1 (1) |
| Study closed/terminated | 0 (0) | 0 (0) |
| Lost to follow-up | 0 (0) | 0 (0) |
| Investigator discretion | 1 (1) | 0 (0) |
| Decision by participant or proxy | 3 (4) | 2 (3) |
| Other | 0 (0) | 0 (0) |

**Table S3.** Summary of participant demographics and EGPA diagnostic and baseline characteristics (ITT population).

| | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **EGPA history** | | |
| EGPA diagnostic disease characteristics (history or presence of) | | |
| Asthma with eosinophilia, n (%) | 68 (100) | 68 (100) |
| Biopsy evidence[a], n (%) | 31 (46) | 25 (37) |
| Neuropathy, mono or poly[b], n (%) | 24 (35) | 32 (47) |
| Pulmonary infiltrates, non-fixed, n (%) | 48 (71) | 50 (74) |
| Sino-nasal abnormality, n (%) | 64 (94) | 64 (94) |
| Cardiomyopathy[c], n (%) | 7 (10) | 13 (19) |
| Glomerulonephritis, n (%) | 0 (0) | 1 (1) |
| Alveolar hemorrhage, n (%) | 1 (1) | 3 (4) |
| Palpable purpura, n (%) | 8 (12) | 9 (13) |
| ANCA positive (MPO or PR3), n (%) | 13 (19) | 13 (19) |
| Relapsing disease, n (%) | 49 (72) | 51 (75) |
| Refractory disease, n (%) | 40 (59) | 34 (50) |
| Failed induction therapy, n (%) | 5 (7) | 1 (1) |
| Recurrence of symptoms whilst tapering, n (%) | 35 (51) | 33 (49) |
| Duration[d] of EGPA (years), mean (SD) | 5.9 (4.9) | 5.2 (4.4) |
| Relapses of EGPA in previous 2 years, n (%) | **N=67** | **N=68** |
| 0 | 3 (4) | 2 (3) |
| 1 | 19 (28) | 20 (29) |
| 2 | 12 (18) | 22 (32) |
| 3–5 | 18 (26) | 15 (22) |
| >5 | 15 (22) | 9 (13) |
| Requirement for immunosuppressive therapy since diagnosis, n (%) | 49 (72) | 56 (82) |
| **Baseline characteristics (Visit 2)** | | |
| Age, mean (SD) | 48 (14) | 49 (12) |
| Male, n (%) | 30 (44) | 26 (38) |
| Body mass index, kg/m$^2$, mean (SD) | 28.2 (5.7) | 27.5 (4.4) |
| ANCA positive (MPO or PR3)[e], n (%) | 6 (9) | 7 (10) |
| Absolute eosinophil count, cells/µL, geometric mean (standard logs) | 172 (1352) | 177 (1289) |
| BVAS[f] >0, n (%) | 48 (71) | 37 (54) |
| VDI[g], mean (SD) | 4.4 (2.8) | 4.7 (3.4) |
| Prednisolone/prednisone dose (mg/day), median (min, max) | 11.0 (7.5, 50.0) | 12.0 (7.5, 40.0) |
| Requirement for immunosuppressive therapy, n (%) | 31 (46) | 41 (60%) |

[a]A biopsy showing histopathological evidence of eosinophilic vasculitis, or perivascular eosinophilic infiltration, or eosinophil-rich granulomatous inflammation; [b]mono or poly (motor deficit or nerve conduction abnormality); [c]established by echocardiography or MRI; [d]from date of diagnosis; [e]immunoassay performed using COVANCE laboratory; [f]BVAS scale 0–63 points; [g]VDI scale 0–64.
ANCA, antineutrophil cytoplasmic antibody; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; ITT, intent-to-treat; MPO, myeloperoxidase; MRI, magnetic resonance imaging; PR3, proteinase 3; SD, standard deviation; VDI, vasculitis damage index.

**Table S4.** Accrued duration of remission over 52-week treatment period according to subgroup.

| Accrued duration of remission[a] over 52-week treatment period | Placebo (N=68) | Mepolizumab (N=68) | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|---|---|
| **Region** | **North America** | | **Rest of world** | |
| n | 32 | 33 | 36 | 35 |
| 0 weeks, n (%) | 27 (84) | 18 (55) | 28 (78) | 14 (40) |
| >0–<12 weeks, n (%) | 4 (13) | 5 (15) | 4 (11) | 3 (9) |
| 12–<24 weeks, n (%) | 0 (0) | 2 (6) | 3 (8) | 7 (20) |
| 24–<36 weeks, n (%) | 0 (0) | 4 (12) | 0 (0) | 6 (17) |
| ≥36 weeks, n (%) | 1 (3) | 4 (12) | 1 (3) | 5 (14) |
| Odds ratio (95% CI), mepolizumab/placebo | 7.41 (2.12, 25.85) | | 5.38 (1.90, 15.19) | |
| **Age** | **<50 years** | | **≥50 years** | |
| n | 33 | 31 | 35 | 37 |
| 0 weeks, n (%) | 26 (79) | 12 (39) | 29 (83) | 20 (54) |
| >0–<12 weeks, n (%) | 5 (15) | 6 (19) | 3 (9) | 2 (5) |
| 12–<24 weeks, n (%) | 2 (6) | 4 (13) | 1 (3) | 5 (14) |
| 24–<36 weeks, n (%) | 0 (0) | 4 (13) | 0 (0) | 6 (16) |
| ≥36 weeks, n (%) | 0 (0) | 5 (16) | 2 (6) | 4 (11) |
| Odds ratio (95% CI), mepolizumab/placebo | 8.05 (2.50, 25.88) | | 4.77 (1.46, 15.61) | |
| **Sex** | **Female** | | **Male** | |
| n | 38 | 42 | 30 | 26 |
| 0 weeks, n (%) | 33 (87) | 19 (45) | 22 (73) | 13 (50) |
| >0–<12 weeks, n (%) | 3 (8) | 5 (12) | 5 (17) | 3 (12) |
| 12–<24 weeks, n (%) | 2 (5) | 5 (12) | 1 (3) | 4 (15) |
| 24–<36 weeks, n (%) | 0 (0) | 6 (14) | 0 (0) | 4 (15) |
| ≥36 weeks, n (%) | 0 (0) | 7 (17) | 2 (7) | 2 (8) |
| Odds ratio (95% CI), mepolizumab/placebo | 9.71 (3.02, 31.23) | | 4.32 (1.33, 14.02) | |
| **Race** | **White** | | **Other** | |
| n | 61 | 64 | 7 | 4 |
| 0 weeks, n (%) | 48 (79) | 30 (47) | 7 (100) | 2 (50) |

| | | | | |
|---|---|---|---|---|
| >0–<12 weeks, n (%) | 8 (13) | 8 (13) | 0 (0) | 0 (0) |
| 12–<24 weeks, n (%) | 3 (5) | 9 (14) | 0 (0) | 0 (0) |
| 24–<36 weeks, n (%) | 0 (0) | 10 (16) | 0 (0) | 0 (0) |
| ≥36 weeks, n (%) | 2 (3) | 7 (11) | 0 (0) | 2 (50) |
| Odds ratio (95% CI), mepolizumab/placebo | 5.23 (2.34, 11.66) | | N/A | |
| **Immunosuppressive therapy usage at baseline** | **Yes** | | **No** | |
| n | 31 | 41 | 37 | 27 |
| 0 weeks, n (%) | 24 (77) | 21 (51) | 31 (84) | 11 (41) |
| >0–<12 weeks, n (%) | 2 (6) | 3 (7) | 6 (16) | 5 (19) |
| 12–<24 weeks, n (%) | 3 (10) | 7 (17) | 0 (0) | 2 (7) |
| 24–<36 weeks, n (%) | 0 (0) | 5 (12) | 0 (0) | 5 (19) |
| ≥36 weeks, n (%) | 2 (6) | 5 (12) | 0 (0) | 4 (15) |
| Odds ratio (95% CI), mepolizumab/placebo | 3.39 (1.11, 10.38) | | 11.85 (3.50, 40.13) | |
| **Duration of EGPA** | **≤4 years** | | **>4 years** | |
| n | 32 | 34 | 36 | 34 |
| 0 weeks, n (%) | 30 (94) | 17 (50) | 25 (69) | 15 (44) |
| >0–<12 weeks, n (%) | 2 (6) | 6 (18) | 6 (17) | 2 (6) |
| 12–<24 weeks, n (%) | 0 (0) | 3 (9) | 3 (8) | 6 (18) |
| 24–<36 weeks, n (%) | 0 (0) | 4 (12) | 0 (0) | 6 (18) |
| ≥36 weeks, n (%) | 0 (0) | 4 (12) | 2 (6) | 5 (15) |
| Odds ratio (95% CI), mepolizumab/placebo | 17.08 (3.41, 85.54) | | 4.26 (1.53, 11.91) | |
| **Baseline blood eosinophil count[b]** | **≥150 cells/µL** | | **<150 cells/µL** | |
| n | 40 | 39 | 28 | 29 |
| 0 weeks, n (%) | 36 (90) | 14 (36) | 19 (68) | 18 (62) |
| >0–<12 weeks, n (%) | 3 (8) | 6 (15) | 5 (18) | 2 (7) |
| 12–<24 weeks, n (%) | 1 (3) | 6 (15) | 2 (7) | 3 (10) |
| 24–<36 weeks, n (%) | 0 | 6 (15) | 0 | 4 (14) |
| ≥36 weeks, n (%) | 0 | 7 (18) | 2 (7) | 2 (7) |
| Odds ratio (95% CI), mepolizumab/placebo | 26.10 (7.02, 97.02) | | 0.95 (0.28, 3.24) | |

| **Baseline VDI[c] score** | **<5** | | **≥5** | |
|---|---|---|---|---|
| n | 36 | 38 | 32 | 30 |
| 0 weeks, n (%) | 27 (75) | 17 (45) | 28 (88) | 15 (50) |
| >0–<12 weeks, n (%) | 5 (14) | 6 (16) | 3 (9) | 2 (7) |
| 12–<24 weeks, n (%) | 2 (6) | 6 (16) | 1 (3) | 3 (10) |
| 24–<36 weeks, n (%) | 0 (0) | 4 (11) | 0 (0) | 6 (20) |
| ≥36 weeks, n (%) | 2 (6) | 5 (13) | 0 (0) | 4 (13) |
| Odds ratio (95% CI), mepolizumab/placebo | 4.03 (1.49, 10.87) | | 24.12 (4.91, 118.50) | |

[a]BVAS (scale 0–63)=0, prednisolone/prednisone dose ≤4 mg/day; [b]the baseline absolute eosinophil count threshold was originally 200 cells/µL but was changed after unblinding to 150 cells/µL in order to be aligned with US prescribing information for mepolizumab in patients with severe eosinophilic asthma; [c]VDI scale 0–64.

CI, confidence interval; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis; VDI, vascular damage index.

**Table S5.** Summary of remission (BVAS[a]=0, prednisolone/prednisone dose ≤7.5 mg/day) endpoints (ITT population).

| Endpoint | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **Accrued duration of remission over 52-week treatment period** | | |
| 0 weeks, n (%) | 36 (53) | 15 (22) |
| >0–12 weeks, n (%) | 19 (28) | 15 (22) |
| 12–<24 weeks, n (%) | 0 (0) | 7 (10) |
| 24–<36 weeks, n (%) | 7 (10) | 9 (13) |
| ≥36 weeks, n (%) | 6 (9) | 22 (32) |
| Odds ratio (95% CI), mepolizumab/placebo | 5.31 (2.63, 10.74); p<0.001 | |
| **Remission at Weeks 36 and 48** | | |
| Number of participants, n (%) | 7 (10) | 28 (41) |
| Odds ratio (95% CI), mepolizumab/placebo | 7.19 (2.60, 19.87); p<0.001 | |
| **Remission within the first 24 weeks sustained until Week 52** | | |
| Number of participants, n (%) | 2 (3) | 16 (24) |
| Odds ratio (95% CI), mepolizumab/placebo | 11.39 (2.35, 55.24); p=0.003 | |

[a]BVAS scale 0–63 points. BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; ITT, intent-to-treat.

**Table S6**. Summary of additional efficacy outcomes (ITT population).

| Endpoint | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **Annualized relapse rate** | | |
| Relapse rate | 2.27 | 1.14 |
| Rate ratio (95% CI), mepolizumab/placebo | 0.50 (0.36, 0.70); p<0.001 | |
| **Average daily prednisolone/prednisone dose at Weeks 48–52** | | |
| 0, n (%) | 2 (3) | 12 (18) |
| >0–≤4.0 mg/day, n (%) | 3 (4) | 18 (26) |
| >4–≤7.5 mg/day, n (%) | 18 (26) | 10 (15) |
| >7.5 mg/day, n (%) | 45 (66) | 28 (41) |
| Odds ratio (95% CI), mepolizumab/placebo | 0.20 (0.09, 0.41); p<0.001 | |
| **Percentage reduction from baseline in average prednisolone/prednisone dose at Weeks 48–52** | | |
| No reduction or withdrawal from treatment[a], n (%) | 33 (49) | 14 (21) |
| <25% reduction, n (%) | 9 (13) | 8 (12) |
| 25–<50% reduction, n (%) | 11 (16) | 8 (12) |
| 50–<75% reduction, n (%) | 11 (16) | 16 (24) |
| 75–<100% reduction, n (%) | 3 (4) | 10 (15) |
| 100% reduction, n (%) | 1 (1) | 12 (18) |
| Odds ratio (95% CI), mepolizumab/placebo | 4.32 (2.28, 8.19); p<0.001 | |

[a]Includes one subject who achieved an average prednisolone/prednisone dose of zero during weeks 48–52 but withdrew from treatment.
CI, confidence interval; ITT, intent-to-treat.

**Table S7.** EGPA relapse categories.

| | Placebo (N=68) | Mepolizumab (N=68) |
|---|---|---|
| **EGPA relapses during the 52-week study period** | | |
| All relapses | | |
| Number of participants, n (%) | 56 (82) | 38 (56) |
| Number of events | 154 | 88 |
| Vasculitis[a] | | |
| Number of participants, n (%) | 15 (22) | 12 (18) |
| Number of events | 18 | 12 |
| Asthma[b] | | |
| Number of participants, n (%) | 22 (32) | 13 (19) |
| Number of events | 31 | 21 |
| Sino-nasal[c] | | |
| Number of participants, n (%) | 8 (12) | 4 (6) |
| Number of events | 9 | 4 |
| Vasculitis/Asthma | | |
| Number of participants, n (%) | 13 (19) | 8 (12) |
| Number of events | 20 | 9 |
| Vasculitis/Sino-nasal | | |
| Number of participants, n (%) | 12 (18) | 5 (7) |
| Number of events | 15 | 6 |
| Asthma/Sino-nasal | | |
| Number of participants, n (%) | 17 (25) | 12 (18) |
| Number of events | 31 | 18 |
| Vasculitis/Asthma/Sino-nasal | | |
| Number of participants, n (%) | 16 (24) | 10 (15) |
| Number of events | 30 | 18 |
| Any vasculitis[d] | | |
| Number of participants, n (%) | 44 (65) | 29 (43) |
| Number of events | 83 | 45 |
| Any asthma[d] | | |
| Number of participants, n (%) | 41 (60) | 25 (37) |
| Number of events | 112 | 66 |
| Any sino-nasal[d] | | |
| Number of participants, n (%) | 35 (51) | 24 (35) |
| Number of events | 85 | 46 |

[a]Active vasculitis (BVAS (scale 0–63) >0); [b]active asthma symptoms and/or signs with a corresponding worsening in ACQ-6 (scale 0–6 points; minimal clinically important difference 0.5 points) score; [c]active nasal and/or sinus disease with a corresponding worsening in one of the sino-nasal symptom questions; [d]relapse category with or without another relapse category defined.
ACQ, Asthma Control Questionnaire; BVAS, Birmingham Vasculitis Activity Score; EGPA, eosinophilic granulomatosis with polyangiitis.

## 12. References

1. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham Vasculitis Activity Score (version 3). Ann Rheum Dis 2009;68:1827-32.
2. Cloutier MM, Schatz M, Castro M, et al. Asthma outcomes: composite scores of asthma control. J Allergy Clin Immunol 2012;129:S24-33.
3. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-7.
4. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol 2009;34:447-54.
5. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum 1997;40:371-80.