Supplementary Materials

Health outcomes after stopping long-term mepolizumab in severe eosinophilic asthma: COMET

Liu M, at al.

Contents:

Supplementary Methods

Study design

The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, all applicable patient privacy requirements, and the guiding principles of the Declaration of Helsinki. All patients provided written informed consent prior to participation in the study.

Endpoints and assessments

Overall perception of response to therapy was rated on a 7-point rating scale compared with baseline; 1: significantly improved, 2: moderately improved, 3: mildly improved, 4: no change, 5: mildly worse, 6: moderately worse, 7: significantly worse.

Unscheduled asthma-related HCRU: These healthcare contacts (including telephone calls and physician's office/home visits), unscheduled visits (including urgent care/outpatients visits, emergency room visits and hospitalisations) were recorded in the electronic Case Report Form (eCRF), while time off work/school (full or half day) due to asthma was recorded in the patient's daily electronic diary (eDiary).

Sample size and statistical analysis

In the analysis of time to first and change from baseline endpoints during Part C, a hypothetical estimand strategy was applied in the handling of the intercurrent event of treatment discontinuation or switching to Part D. Therefore, the treatment effects reported during Part C estimate outcomes if all patients had continued to take double-blind treatment throughout the 52-week period. In the analysis of the global rating of asthma severity and overall perception of response to therapy a composite estimand strategy was applied in the handling of the intercurrent event of discontinuation where patients who discontinued were included in the least favourable outcome category.

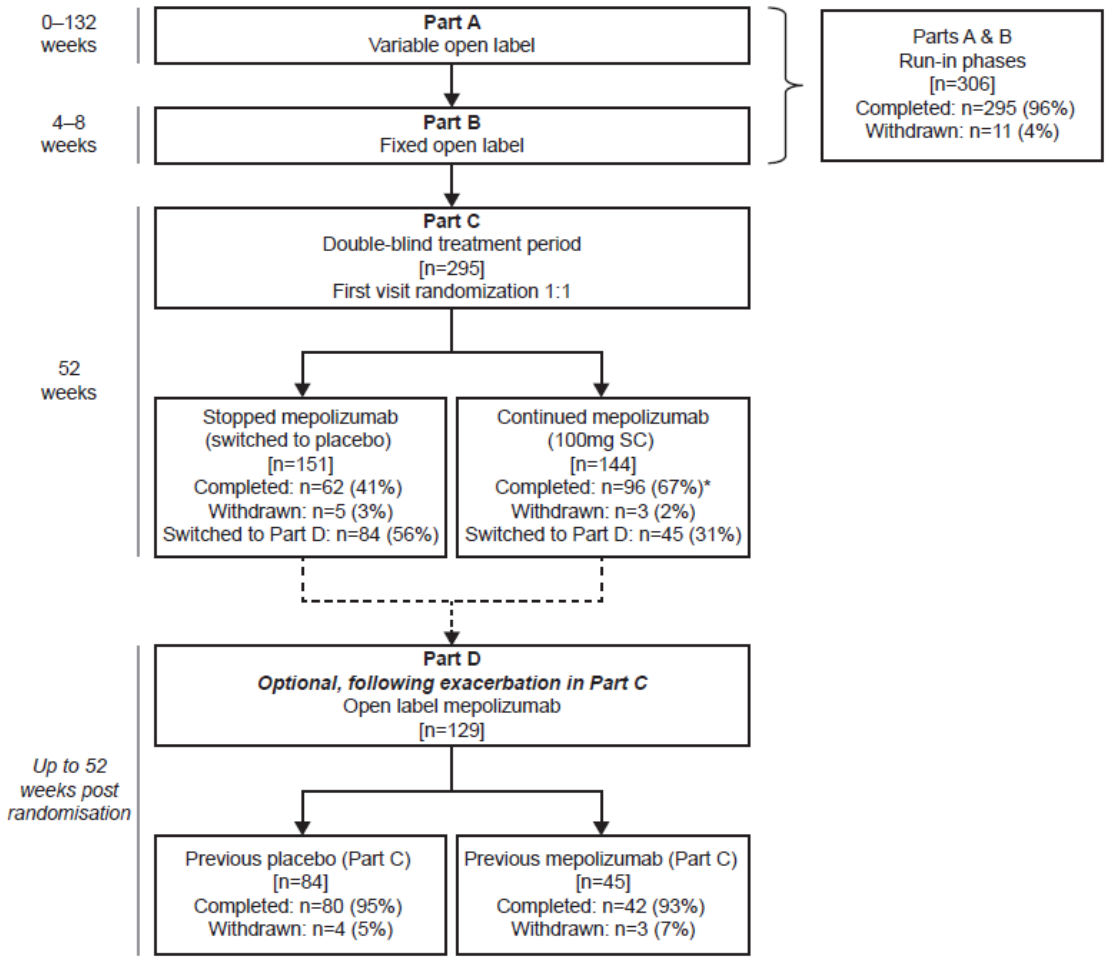
Time to event endpoints were analysed using Kaplan–Meier estimates and Cox proportional hazards models, with adjustment for covariates of region, exacerbations in the year prior to randomisation and baseline OCS use (yes versus no). Patients were considered at risk from the first dose of double-blind treatment of Part C up until their Week 52 visit, while patients who discontinued double-blind treatment prior to experiencing an event were censored following discontinuation of double-blind treatment or switching to Part D.

Change from baseline in eDiary endpoints were analysed using mixed model repeated measures, with adjustment for the aforementioned covariates along with baseline value, visit, and terms for the interaction of visit with baseline value and of visit with treatment group. On-treatment data was censored following discontinuation of double-blind treatment or switching to Part D.

The global rating of asthma severity and overall perception of response to therapy were analysed using a proportional odds model (multinomial [ordered] logistic generalised linear model) with adjustment for the aforementioned covariates and clinician or patient global rating of asthma severity at baseline (rating of asthma severity endpoint only). Patients were categorised according to their response.

Supplementary Figures

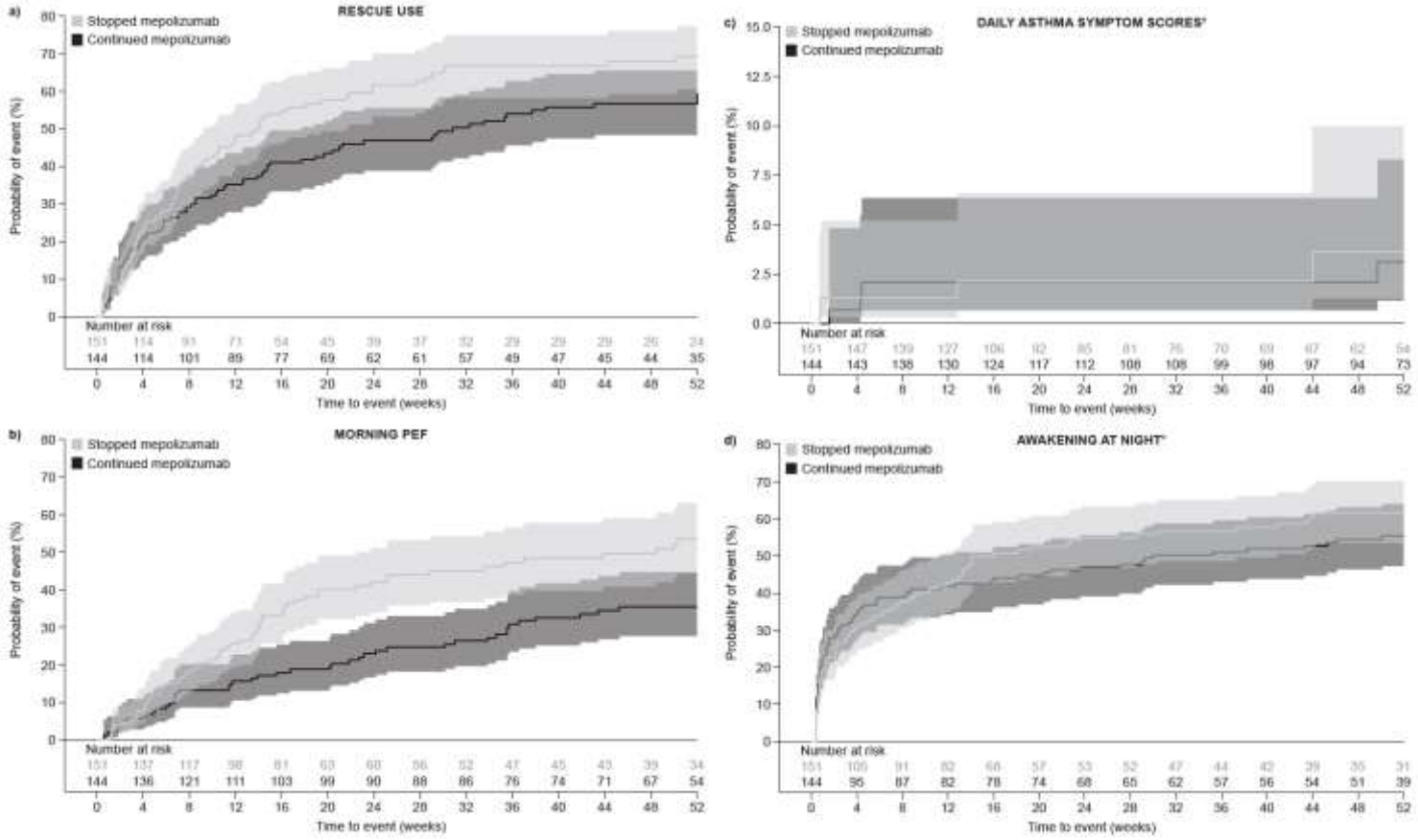
Supplementary Figure 1. Study design and patient switching across individual parts of the COMET study



Patients received either mepolizumab (100 mg subcutaneous) or placebo every 4 weeks during Part C of the study, patients received open label mepolizumab every 4 weeks in all other study parts. *Two patients discontinued double-blind treatment during Part C (continued mepolizumab arm) but remained in the study off treatment and completed all remaining scheduled visits in Part C.

n, number of patients; SC, subcutaneous.

Supplementary Figure 2. Cumulative incidence in individual components of asthma worsening

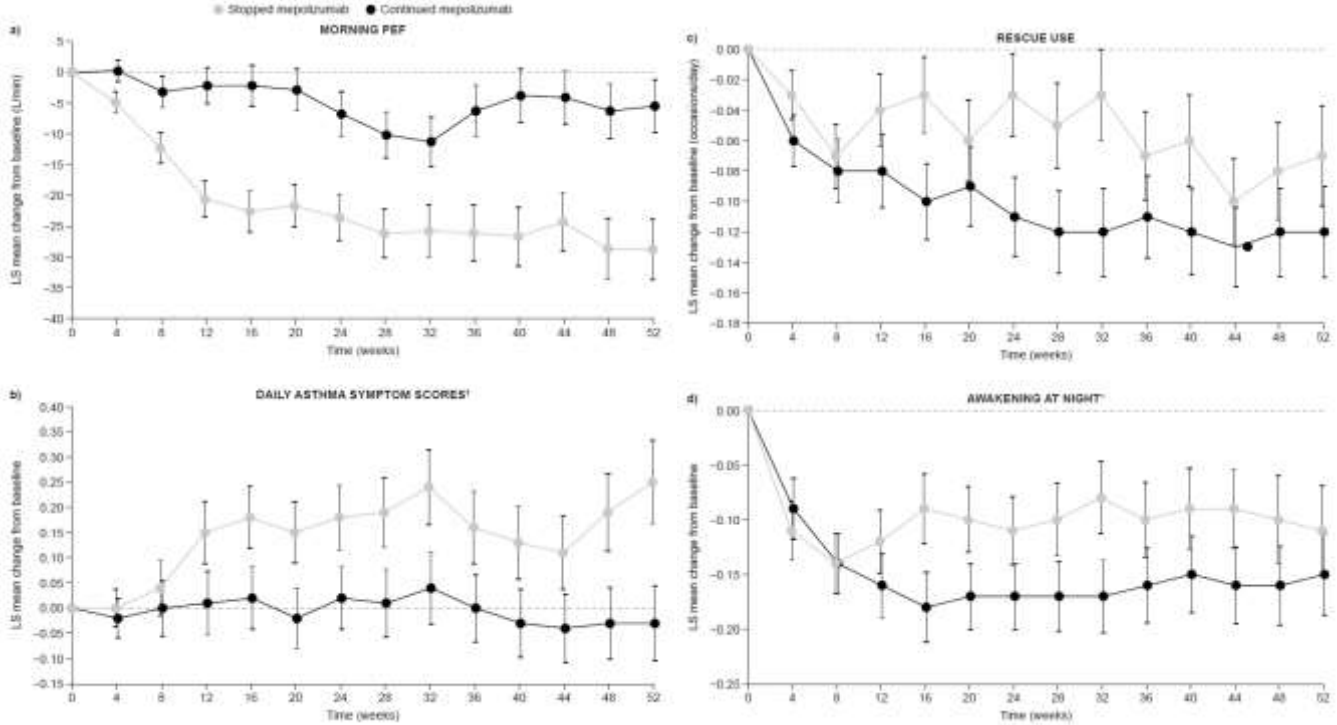


[†]Asthma symptom score evaluated using a 6-point scale of 0 (no symptoms) to 5 (symptoms so severe unable to perform normal daily activities). [*]Due to asthma symptoms requiring rescue medication use. Kaplan–Meier estimates of the probability of a worsening in each individual component with the 95%

confidence intervals reflected by shaded intervals. Patients meeting the eDiary criterion for at least 2 consecutive days were considered as experiencing a worsening.

PEF, peak expiratory flow.

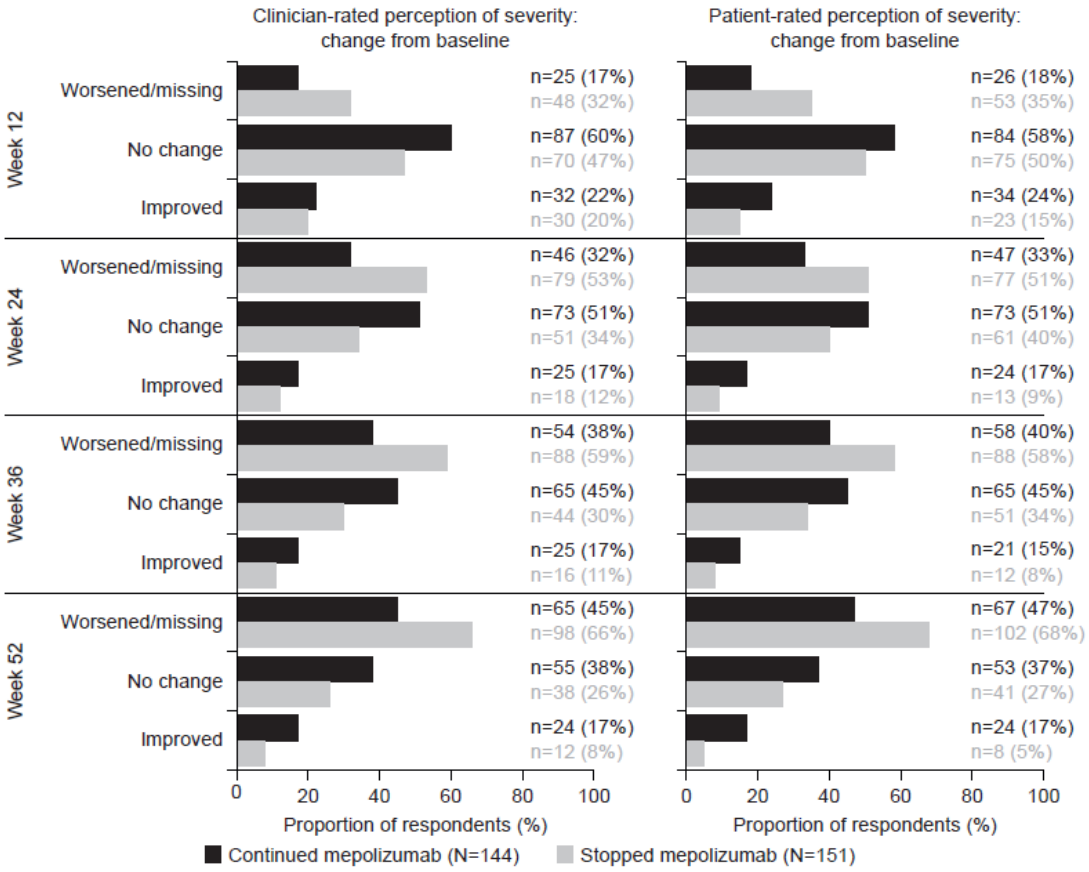
Supplementary Figure 3. LS mean change from baseline in individual components of asthma worsening



†Asthma symptom score evaluated using a 6-point scale of 0 (no symptoms) to 5 (symptoms so severe unable to perform normal daily activities). *Due to asthma symptoms requiring rescue medication use. Least squares mean change from baseline estimated using a mixed model repeated measures analysis with terms for treatment group and adjustment for baseline covariates. Error bars represent standard error.

LS, least squares; PEF, peak expiratory flow.

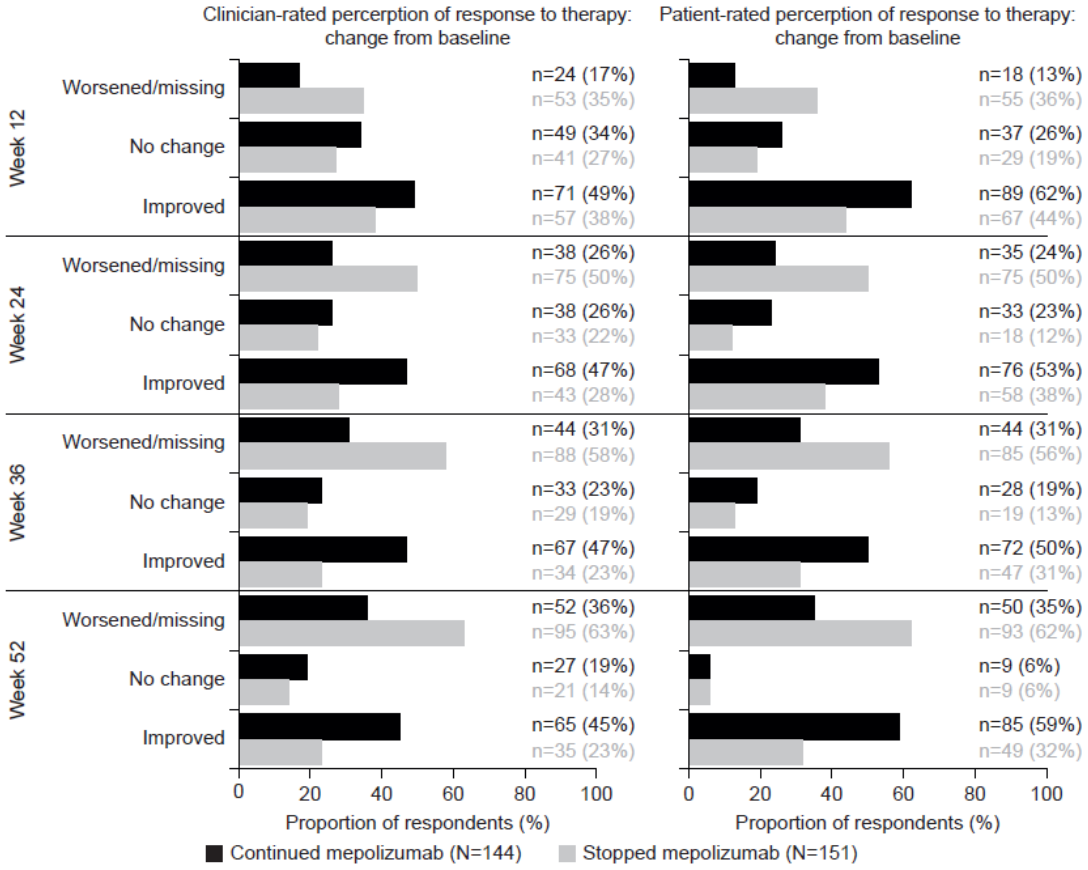
Supplementary Figure 4. Change from baseline in global rating of asthma severity



Perceived asthma severity was rated on a 4-point scale: 'mild', 'moderate', 'severe', 'very severe'. Three patients with missing clinician-rated global rating of asthma severity at baseline were not included in the analysis of clinician-rated perceptions of severity. Data was classified as missing when a rating was not given/obtained or when patients were switched back to open label mepolizumab treatment (Part D). Comparisons in asthma severity were made versus the rating at baseline. 'Worsened/missing' indicates any category shift at the given time point towards worsening, and 'Improved' indicates any category shift at the given time point towards improvement.

n, number of patients.

Supplementary Figure 5. Change from baseline in overall perception of response to therapy



The overall evaluation of perceived response to therapy was rated on a 7-point scale and compared with baseline. Responses included: 1 = significantly improved; 2 = moderately improved; 3 = mildly improved; 4 = no change; 5 = mildly worse; 6 = moderately worse; 7 = significantly worse. Data was classified as missing when a rating was not given/obtained or when patients were switched back to open label mepolizumab treatment (Part D). An improved response includes patients who responded with 'significantly improved', 'moderately improved', and 'mildly improved'; a worsened response includes patients who responded with 'mildly worse', 'moderately worse', 'significantly worse', or missing responses.

n, number of patients.