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Previous Exacerbations Predict the Risk of Future Exacerbations After Stopping Versus Continuing Mepolizumab Treatment: Secondary Analysis of the COMET Trial

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Objectives



Mepolizumab is an anti-interleukin (IL)-5 monoclonal antibody approved for use in eosinophilic diseases such as severe eosinophilic asthma, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome.¹



The COMET study (NCT02555371) demonstrated that patients with severe eosinophilic asthma who stop long-term (≥ 3 years) mepolizumab treatment experience an increased rate of exacerbations and reduced asthma control compared with patients who continue mepolizumab.²



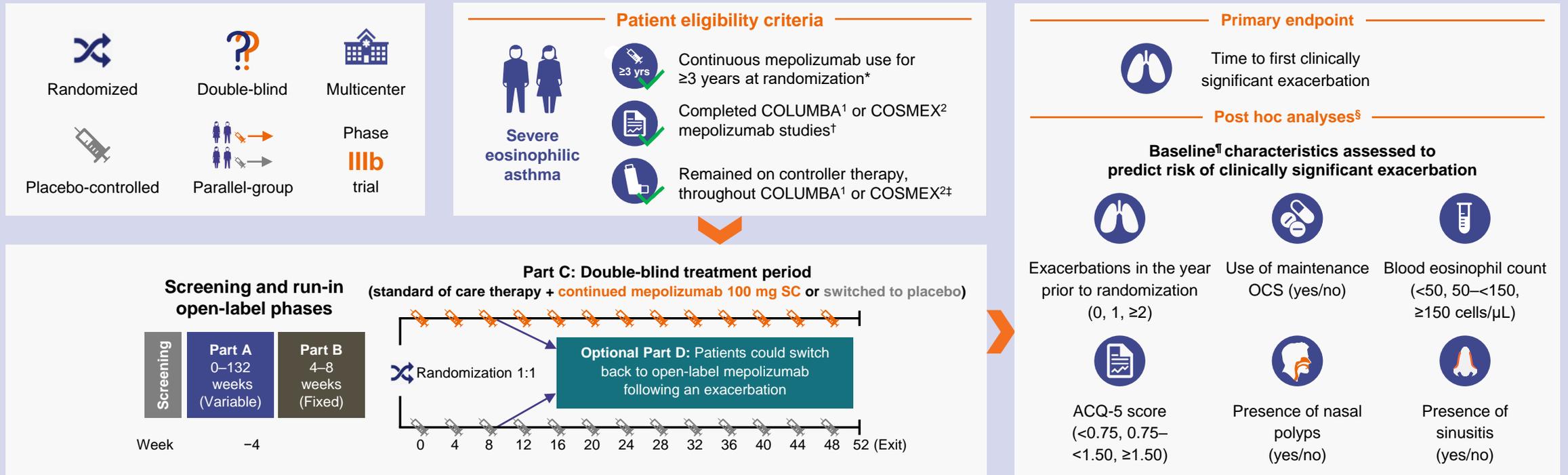
The identification of patients who are likely to exacerbate when stopping long-term mepolizumab would enable improved clinical management of a patient's disease.



Here we present further post hoc analysis of the COMET trial, undertaken to explore whether patient baseline characteristics can predict the outcome of patients stopping versus continuing long-term mepolizumab treatment in patients with severe eosinophilic asthma.

Methods

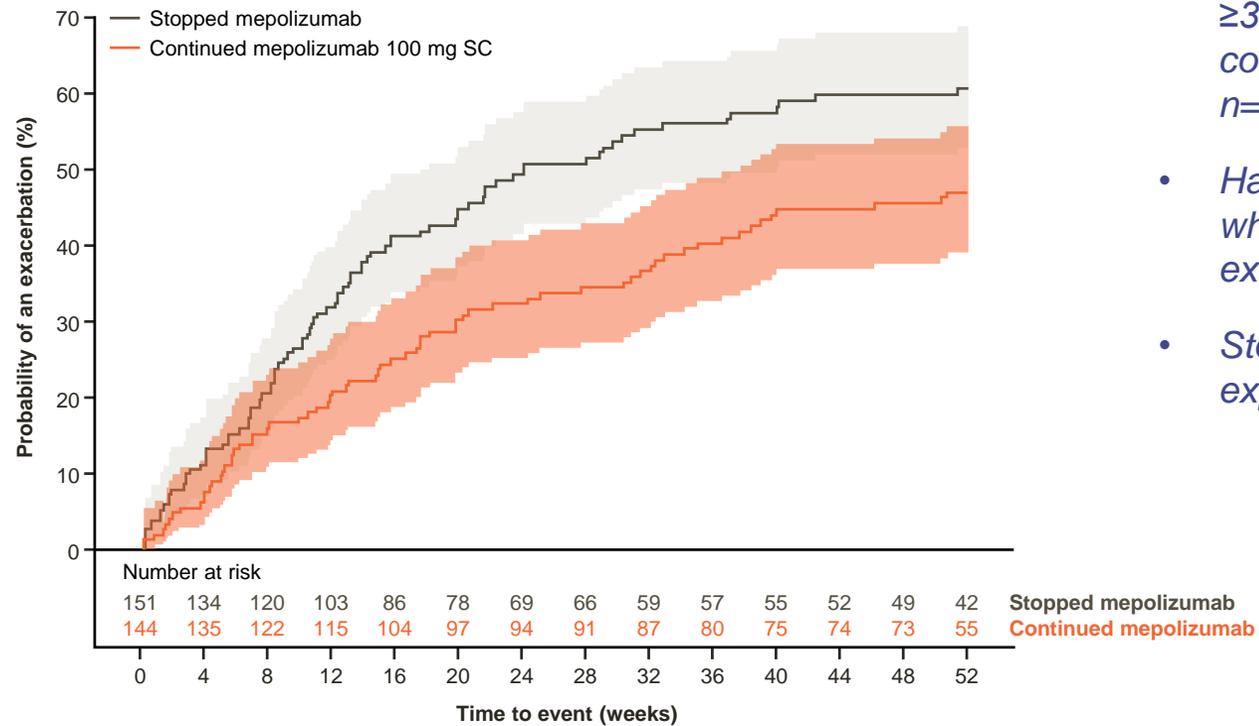
COMET (GSK ID: 201810) Study design



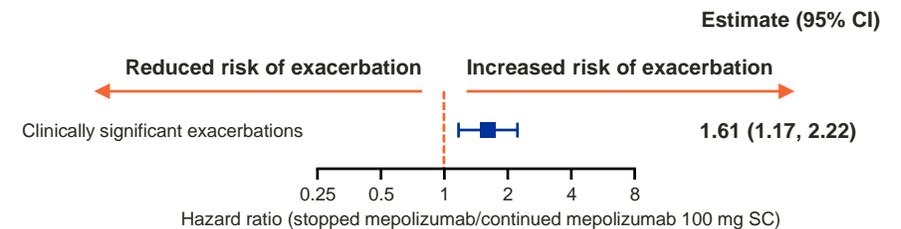
*With no treatment gaps >12 weeks between any two mepolizumab doses (84 days, equivalent to >2 consecutive missed doses); [†]patients with a clinically significant health deterioration at completion of the studies were excluded; [‡]patients with <80% adherence to controller medications during studies were excluded; [§]subgroup analyses were performed using a Cox proportional hazard model adjusted for treatment group, region, baseline OCS use, and exacerbations in the year prior to randomization. Rosenkranz bootstrap model selection was performed to correct hazard ratios (HR) for selection bias³; [¶]at COMET randomization.

Results from the overall study population¹

Kaplan–Meier cumulative incidence curve for time to first clinically significant* exacerbation in COMET



- 295 patients exposed to continuous mepolizumab treatment for ≥ 3 years were randomized 1:1 to stop (switch to placebo, $n=151$) or continue mepolizumab treatment (100 mg SC every 4 weeks, $n=144$) for 52 weeks.
- Hazard ratios have been expressed as placebo/mepolizumab; where a hazard ratio >1 favors mepolizumab (increased risk of exacerbation with placebo).
- Stopping versus continuing mepolizumab increased the risk of experiencing an exacerbation in the next 52 weeks by 61%



Estimated from Cox proportional hazards model with covariates of treatment group, region, exacerbations in the year prior to randomization and baseline maintenance OCS therapy (OCS vs no OCS).

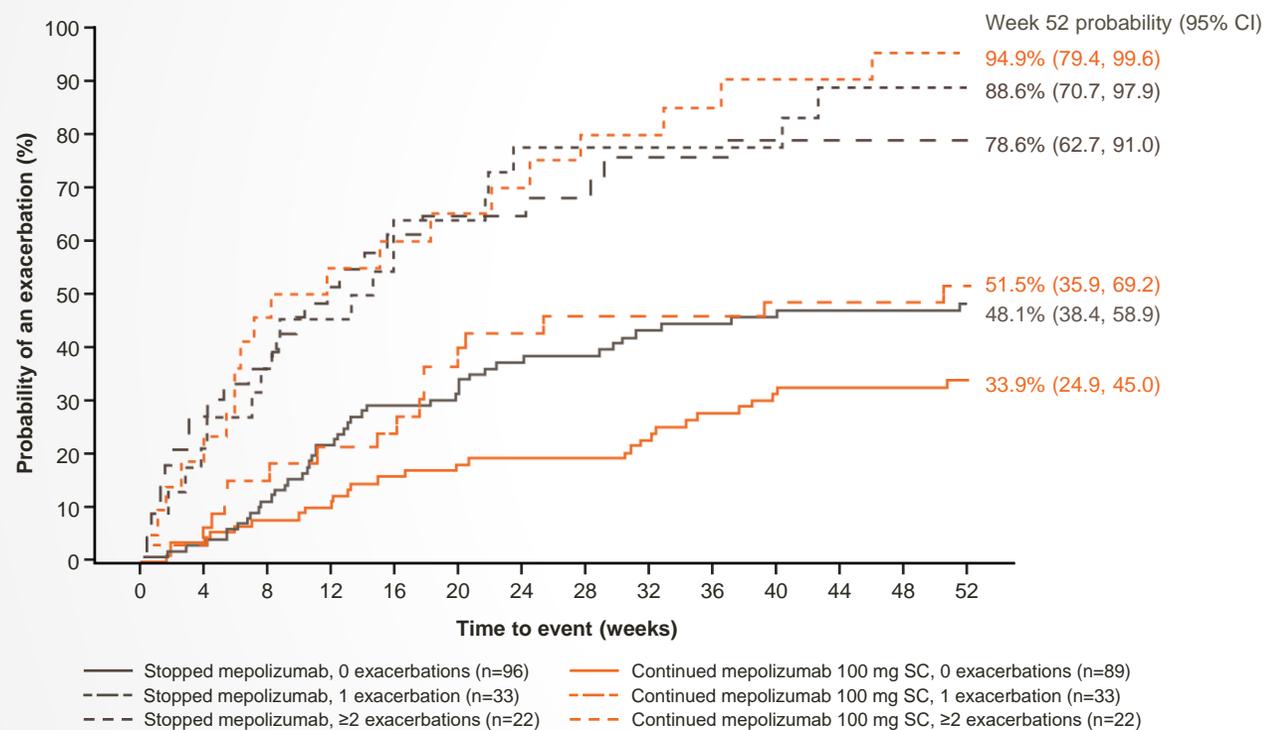
*A clinically significant exacerbation was verified using data to confirm that the exacerbation was associated with changes in peak flow, rescue medication use, nocturnal awakening due to asthma symptoms requiring rescue medication use or symptoms.

CI, confidence interval; OCS, oral corticosteroids; SC, subcutaneous

1. Moore WC, et al. Am J Respir Crit Care Med 2020;201:A4211.

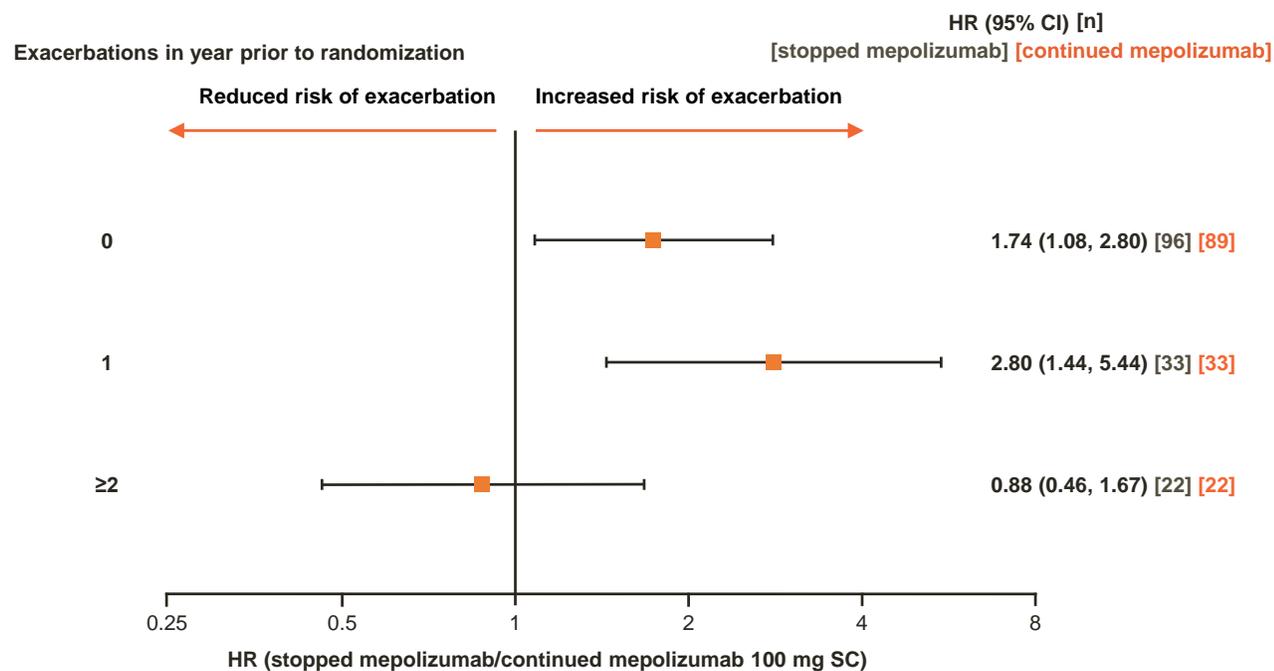
Number of prior exacerbations predictive of risk of exacerbation

Kaplan–Meier cumulative incidence curves for time to first clinically significant exacerbation in COMET grouped by exacerbations in the year prior to COMET randomization (0, 1, ≥ 2)



- *Number of exacerbations in the year prior to randomization was a strong prognostic factor for risk of exacerbation during COMET, with increasing risk of exacerbation associated with a greater number of exacerbation events in the year prior to randomization.*
 - *At Week 52, patients who experienced ≥ 2 exacerbations in the year prior to randomization had similar risk of exacerbation during COMET whether they stopped (88.6%) or continued (94.9%) mepolizumab.*
- *Patients who experienced ≤ 1 exacerbation in the year prior had longer time to first exacerbation when continuing versus stopping mepolizumab.*
- *This benefit was not seen in patients who experienced ≥ 2 exacerbations in the year prior to randomization.*

Risk of exacerbation for patients who stop vs continue mepolizumab



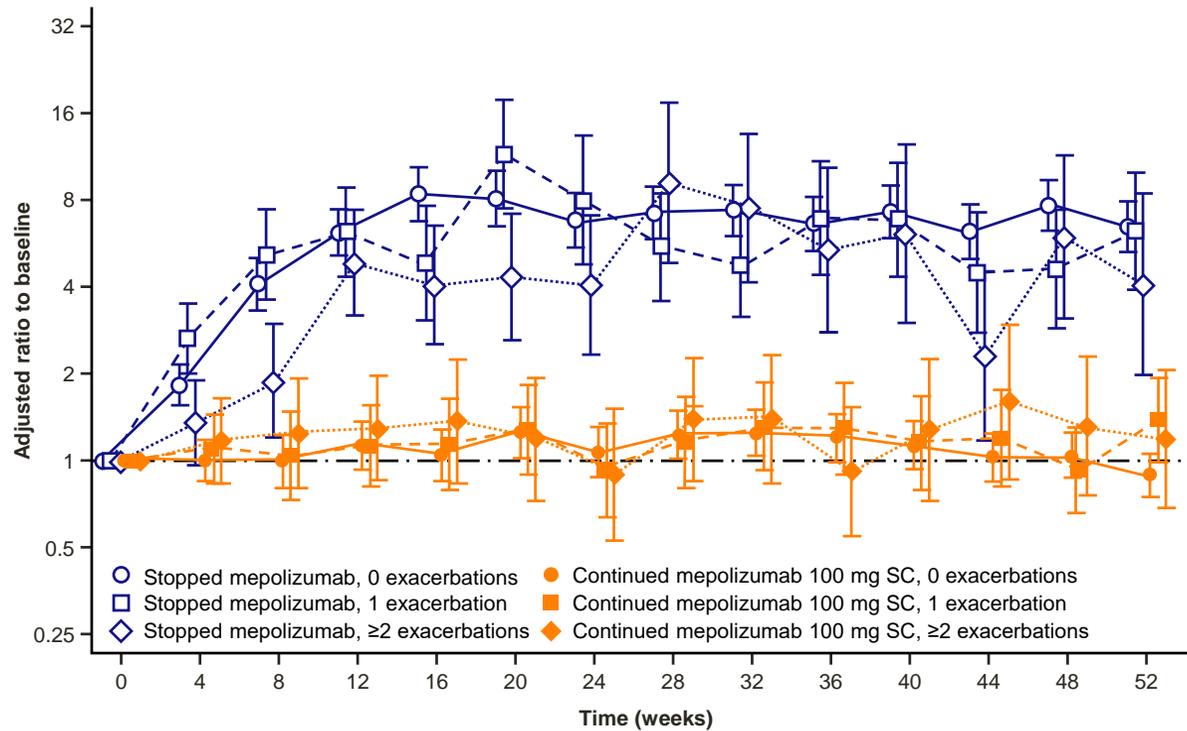
- Stopping versus continuing mepolizumab increased the risk of exacerbation in the next 52 weeks (during COMET).
 - For patients with 0 exacerbations in the year prior, stopping mepolizumab increased the risk by **74%**.
 - For patients with 1 exacerbation in the year prior, stopping mepolizumab increased the risk by **180%**.
- This increased risk from stopping mepolizumab was not seen for patients with ≥ 2 exacerbations in the year prior to randomization.

Estimated separately for each subgroup using a Cox proportional hazards model with covariates of treatment group, region and baseline maintenance OCS therapy (OCS vs no OCS).

Interaction P -values: Across all categories, $P=0.174$; ≥ 2 exacerbations vs ≤ 1 exacerbation, $P=0.017$. Results in the subgroup of ≥ 2 prior exacerbations were similar when assessed using bias adjusted HRs following Rosenkranz model selection.

CI, confidence interval; HR, hazard ratio; OCS, oral corticosteroids; SC, subcutaneous

Change in blood eosinophils by prior exacerbation subgroups

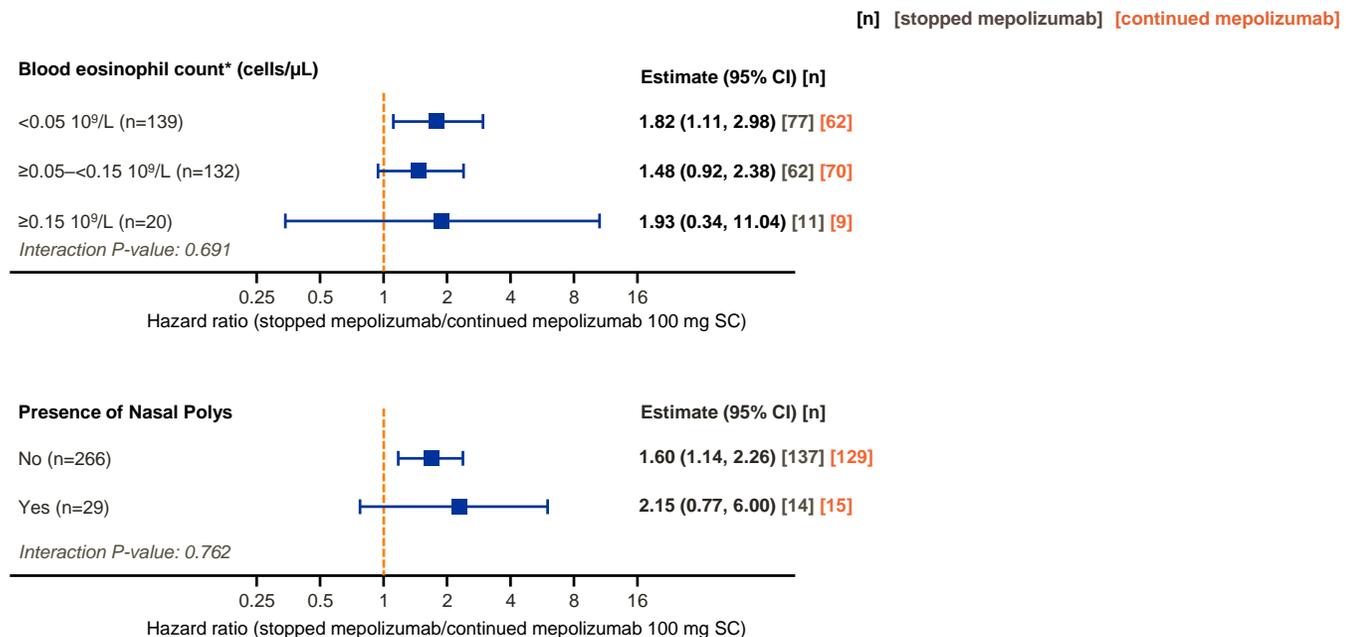
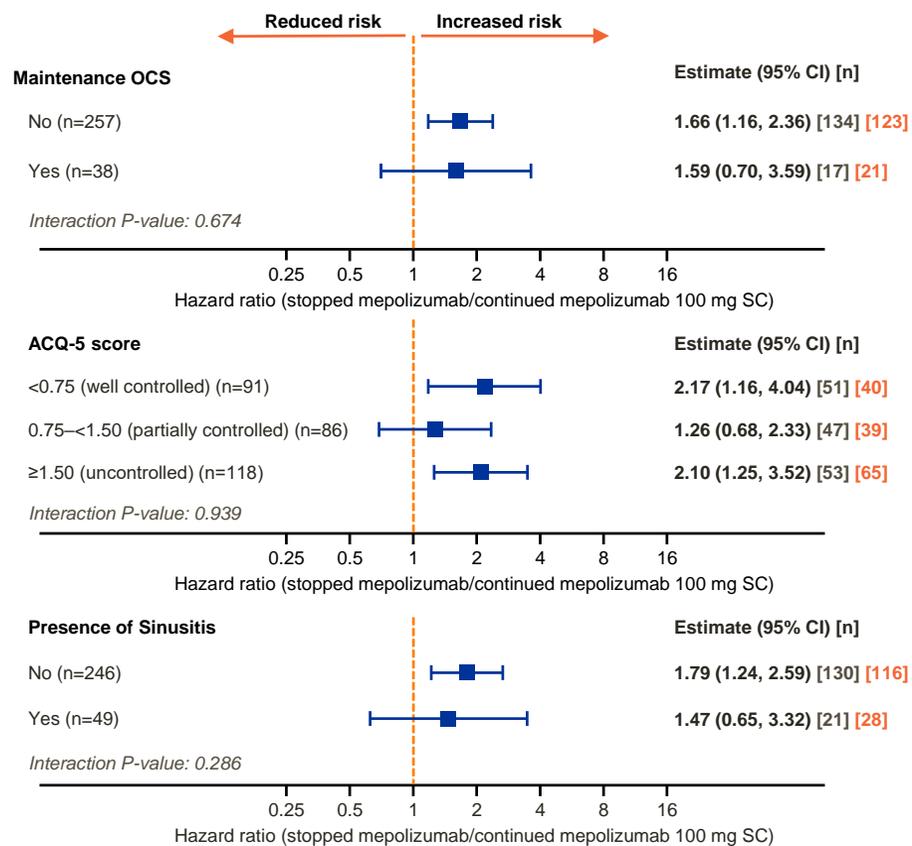


- The differences in blood eosinophils in those who continued mepolizumab or stopped mepolizumab (switched to placebo) was also assessed by the subgroups of exacerbations in the year prior to COMET randomization (0, 1, ≥2).
- Results appeared consistent across all prior exacerbation subgroups, with blood eosinophils in participants who stopped mepolizumab (randomized to placebo) returning to baseline pre-treatment levels from Week 12 onwards in each subgroup, whereas blood eosinophils in participants who continued mepolizumab remained unchanged.

Estimated from MMRM with covariates of baseline, region, exacerbations in the year prior to randomization, baseline maintenance OCS therapy (OCS vs no OCS), treatment and visit, plus interaction terms for visit by baseline, visit by treatment group, exacerbations in the year prior by treatment group and visit by exacerbations in the year prior by treatment group.

MMRM, Mixed Model with Repeated Measures; OCS, oral corticosteroids

Risk of exacerbation at week 52



No other baseline characteristic was predictive of a differential treatment effect in exacerbation risk at Week 52

Estimated separately for each subgroup using Cox proportional hazards models with covariates of treatment group, region, exacerbations in the year prior to randomization and baseline maintenance OCS therapy (OCS vs no OCS).

*4 patients (1 placebo, 3 mepolizumab) with missing blood eosinophil counts were excluded from this analyses.

CI, confidence interval; OCS, oral corticosteroids; SC, subcutaneous

Conclusions

- Following ≥ 3 years of mepolizumab treatment, the number of exacerbations in the year prior to COMET randomization was a strong prognostic factor to predict future exacerbation risk.
- Patients who had ≤ 1 prior exacerbation were at higher risk of exacerbation when stopping versus continuing mepolizumab, consistent with the primary findings of COMET.
- Patients with ≥ 2 prior exacerbations had a similar exacerbation risk after stopping or continuing mepolizumab; however, this subgroup was small.
- Differences in blood eosinophil count were consistent across all subgroups of exacerbations in year prior to randomization.
 - Blood eosinophils in participants who stopped mepolizumab returned to pre-treatment levels from Week 12 onwards in each prior exacerbation subgroup whereas blood eosinophils in participants who continued mepolizumab remained unchanged.
- Other baseline characteristics analyzed included the use of maintenance OCS, blood eosinophil count, ACQ-5 score, and presence of nasal polyps or sinusitis, which did not identify a differential treatment effect in exacerbation risk at Week 52.
- These data are from post hoc analyses, so should be interpreted with caution and considered as hypothesis generating.
- Further studies are required to understand the impact of discontinuing mepolizumab in patients with a high (≥ 2) number of prior exacerbations.

