

Outcomes following continuation or stopping long-term mepolizumab treatment in patients with severe eosinophilic asthma: the randomized COMET trial

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Disclosures

- This study was funded by GlaxoSmithKline (GSK ID 201810/NCT02555371)
- The presenting author, Wendy Moore, is presenting on behalf of her co-authors and has not been paid for this presentation
- Wendy Moore has received funding for clinical research and personal fees for participation in advisory boards from GSK, AstraZeneca and Sanofi Regeneron
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Background



Mepolizumab is a targeted anti-IL-5 mAb that has been approved for the treatment of severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis¹



The efficacy and safety of long-term treatment with mepolizumab in patients with severe eosinophilic asthma have been demonstrated **for up to 4.5 years** in previous double-blinded²⁻⁵ and open-label studies⁶⁻⁸



There are no data on the impact of stopping treatment after longer than 1 year of mepolizumab treatment




The COMET study assessed outcomes in patients with severe eosinophilic asthma who had been treated with **mepolizumab 100 mg SC for ≥3 years** and then either **stopped or continued** long-term treatment


1. GSK. NUCALA prescribing information. 2019. Available from https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF [last accessed March 2020]. 2. Pavord ID, et al. *Lancet* 2012; 380: 651–9; 3. Bel EH, et al. *N Engl J Med* 2014; 371: 1189–97; 4. Ortega HG, et al. *N Engl J Med* 2014; 371: 1198–207; 5. Chupp GL, et al. *Lancet Respir Med* 2017; 5: 390–400; 6. Lugogo N, et al. *Clin Ther* 2016; 38: 2058–70 e1; 7. Khatri S, et al. *J Allergy Clin Immunol* 2019; 143: 1742–51 e7; 8. Khurana S, et al. *Clin Ther* 2019; 41: 2041–56 e5
IL, interleukin-5; mAb, monoclonal antibody; SC, subcutaneous

COMET inclusion and exclusion criteria


+ Inclusion criteria:


 Received continuous mepolizumab treatment for **≥3 years***


 Completed the previous open-label mepolizumab studies, COLUMBA¹ or COSMEX²


 Remained on asthma controller therapy, throughout COLUMBA¹ or COSMEX²

- Exclusion criteria:

 A clinically significant health deterioration at completion of COLUMBA¹ or COSMEX²

 Treated with any mAb other than mepolizumab within 5 half-lives of screening

 Current smokers

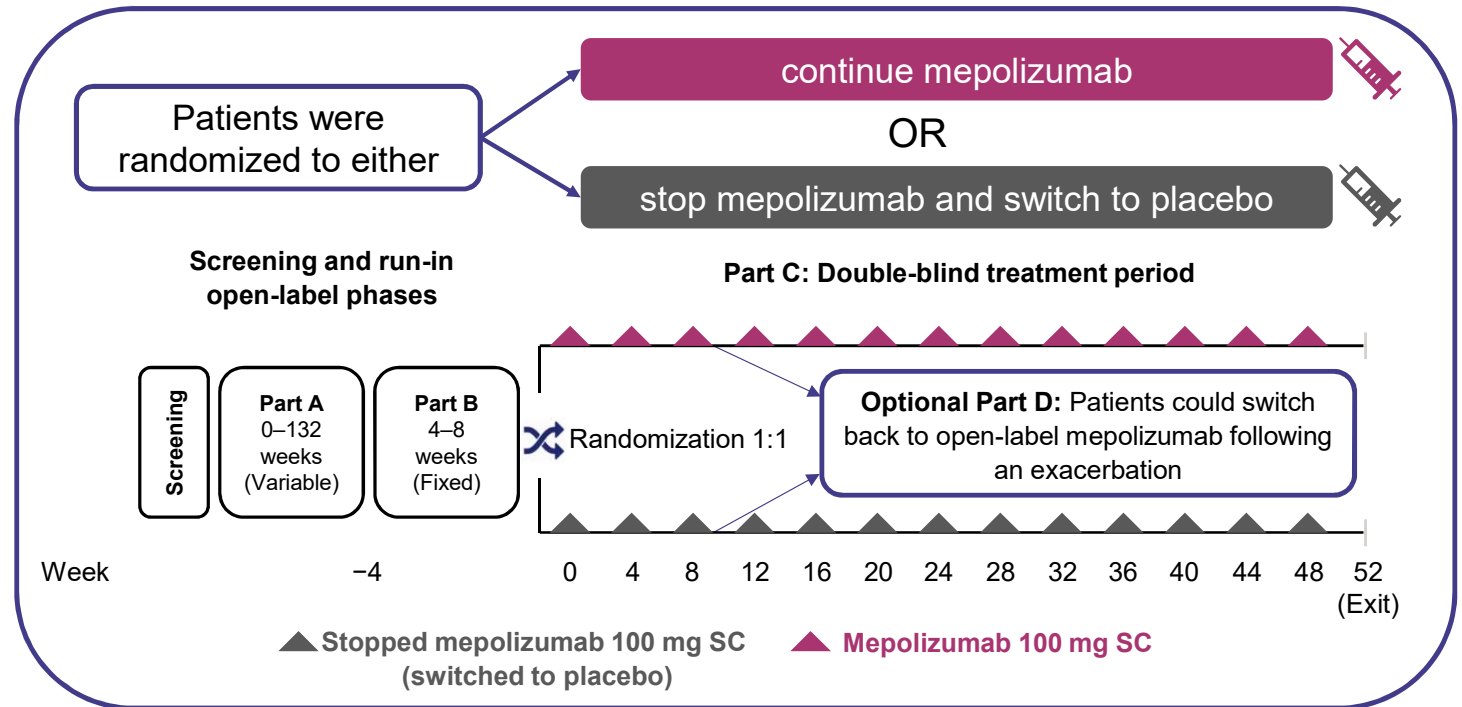
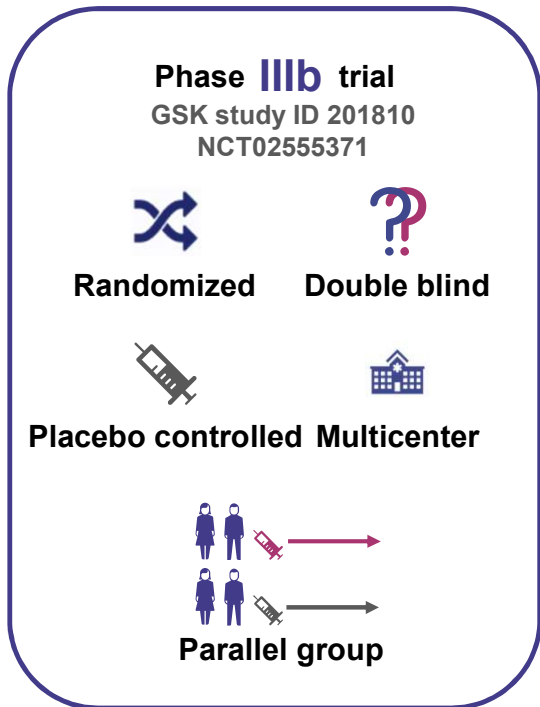
 <80% adherence to controller medications during COLUMBA¹ or COSMEX²

*With no treatment gaps >12 weeks between any two mepolizumab doses (84 days, equivalent to >2 consecutive missed doses)
COLUMBA (GSK ID MEA115666; NCT01691859); COSMEX (GSK ID 201312; NCT02135692)

1. Khatri S, et al. *J Allergy Clin Immunol* 2019; 143: 1742–51 e7

2. Khurana S, et al. *Clin Ther* 2019; 41: 2041–56 e5

COMET study design



Data are presented from the double-blind treatment period (Part C)

COMET endpoints



Primary endpoint

Time to first clinically significant exacerbation
(requiring systemic corticosteroids, ED visit or hospitalization)



Secondary endpoints










- Time to first exacerbation requiring ED visit/hospitalization
- Time to decrease in asthma control (ACQ-5 score increase from baseline ≥ 0.5 -points)
- Blood eosinophil count ratio to baseline



Other endpoints

- Time to first exacerbation requiring hospitalization
- Safety

Demographics and disease characteristics at COMET randomization were similar: both groups had previously been receiving mepolizumab for ≥ 3 years

| |  Stopped mepolizumab (N=151) |  Continued mepolizumab (N=144) | Total (N=295) |
|---|--|--|---------------------------|
|  Female n (%) | 86 (57) | 87 (60) | 173 (59) |
|  Age years, mean (SD) | 56 (11.4) | 57 (11.5) | 56 (11.5) |
|  Duration of asthma years, mean (SD) | 23 (13.8) | 25 (14.5) | 24 (14.2) |
|  Exacerbations in previous year mean (SD) | 0.6 (1.1) | 0.8 (1.5) | 0.7 (1.3) |
|  ACQ-5 score mean (SD) | 1.2 (1.04) | 1.4 (1.05) | 1.3 (1.05) |
|  Using maintenance OCS n (%), median (range) dose, mg/day* | 17 (11) 5.0 (0.0–20.0) | 21 (15) 5.0 (0.0–20.0) | 38 (13) 5.0 (0.0–20.0) |
|  Blood eosinophil count cells/ μ L, geometric mean (SD of log) | 40 (0.870) | 50 (0.881) | 50 (0.876) |

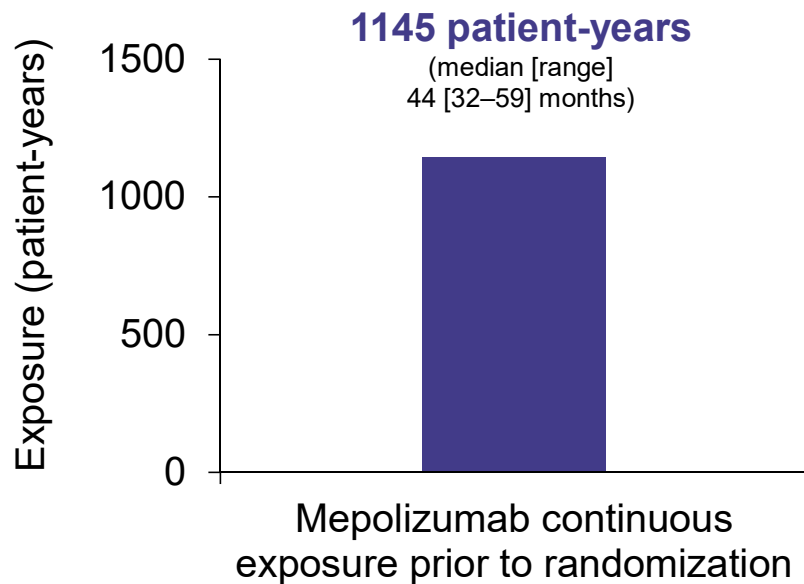
ITT population: all randomized patients who received ≥ 1 dose of double-blind study treatment
Baseline was defined as the start of double-blind treatment (randomization) in COMET

*Prednisone equivalent dose; ITT, intent-to-treat; OCS, oral corticosteroids; SD, standard deviation

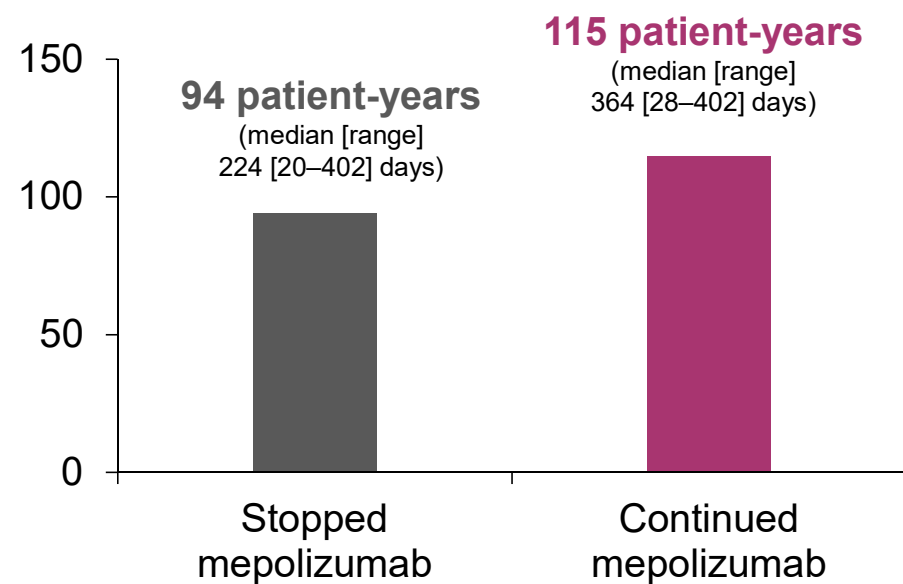
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Exposure to mepolizumab

Mepolizumab continuous exposure prior to randomization

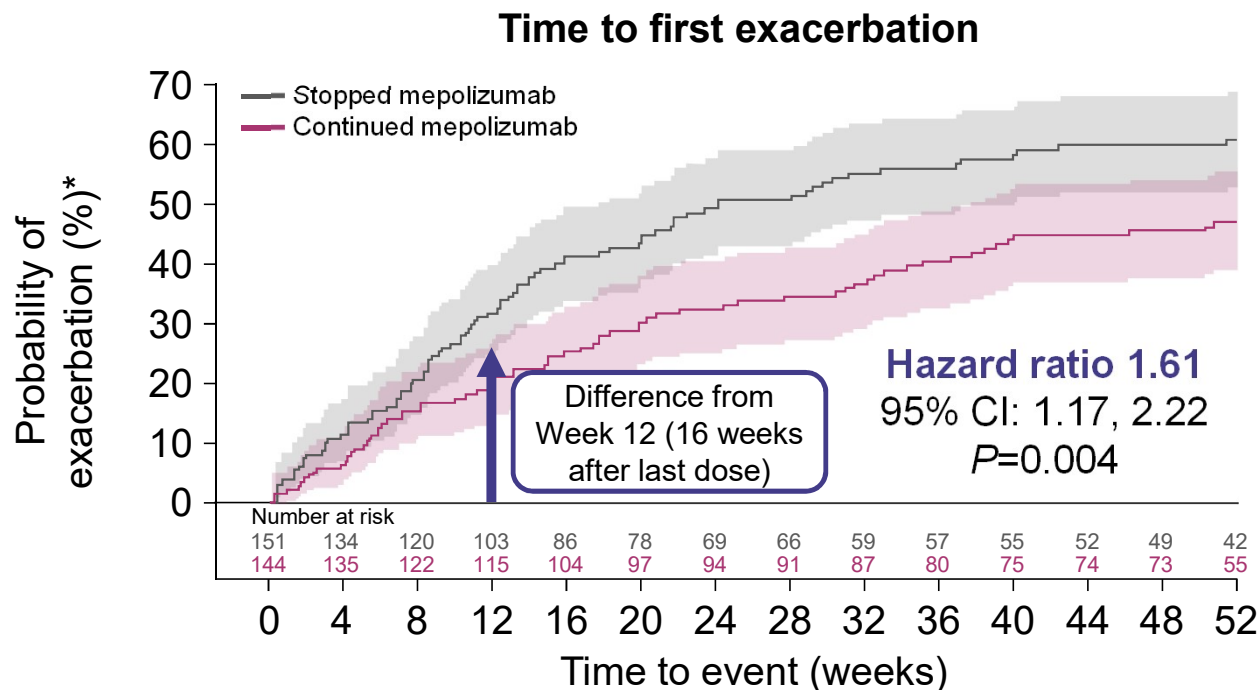
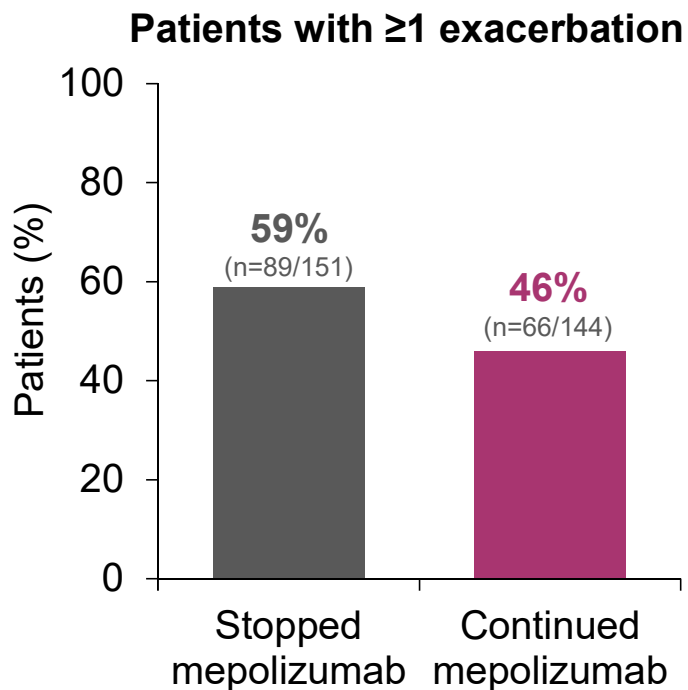


Treatment exposure during Part C



More patients from the group that stopped mepolizumab (ie, switched to placebo; 56%, n=84/151) than from the group that continued mepolizumab (31%, n=45/144) during the double-blind treatment period (Part C) switched to open-label mepolizumab treatment (ie, Part D), resulting in a comparatively shorter treatment exposure during Part C

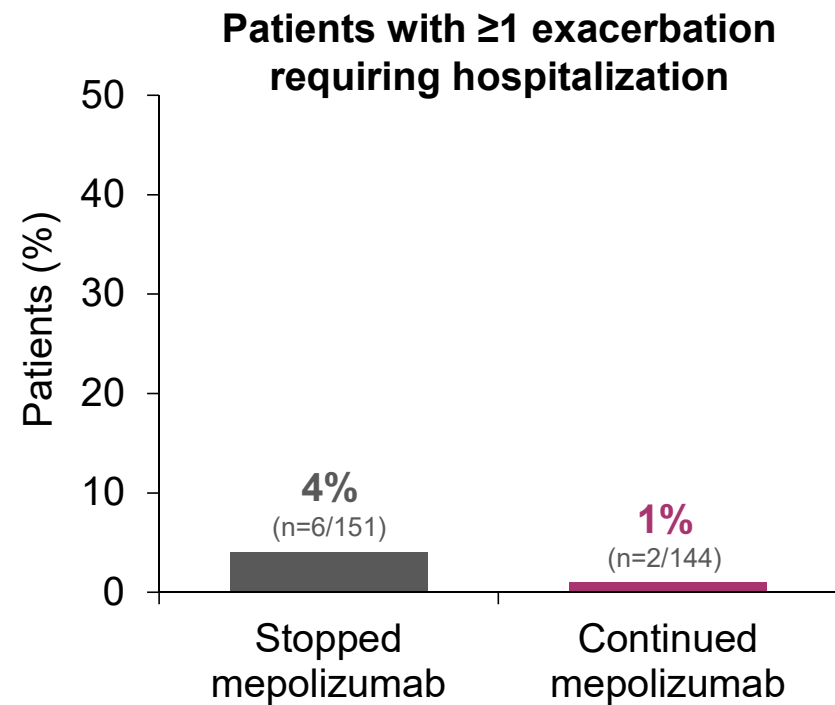
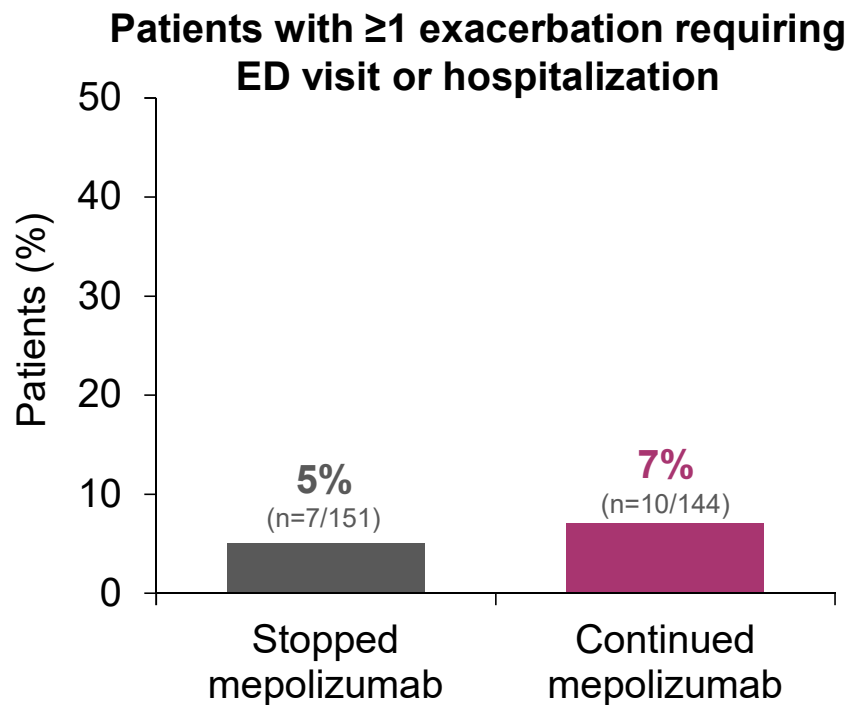
Time to first clinically significant exacerbation was significantly shorter for those who stopped versus continued long-term mepolizumab



There was a 61% increase in the risk of experiencing their first clinically significant exacerbation for those who stopped versus continued mepolizumab

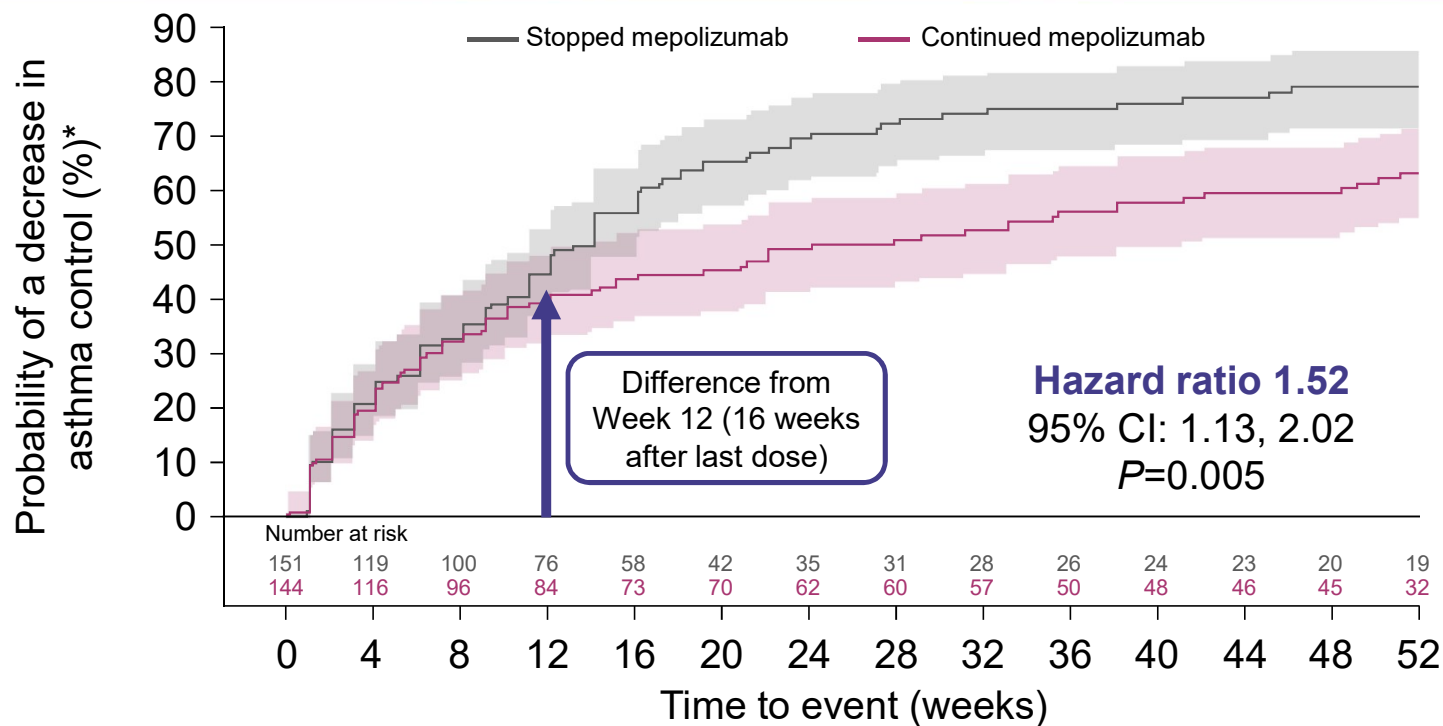
ITT population (N=295)
*Kaplan-Meier cumulative incidence curve; shaded areas represent 95% CIs
Hazard ratio estimated using Cox proportional hazards models adjusted for covariates
CI, confidence interval

Exacerbations requiring hospitalization or an ED visit and exacerbations requiring hospitalization were rare in both groups



It is possible that physicians may have switched patients to open-label mepolizumab (from either double-blind placebo or mepolizumab) before a more severe exacerbation occurred

Patients who stopped mepolizumab treatment had a significantly shorter time to a decrease in asthma control



There was a 52% increase in the risk of experiencing a decrease in asthma control (≥ 0.5 point increase in ACQ-5) for those who stopped versus continued mepolizumab

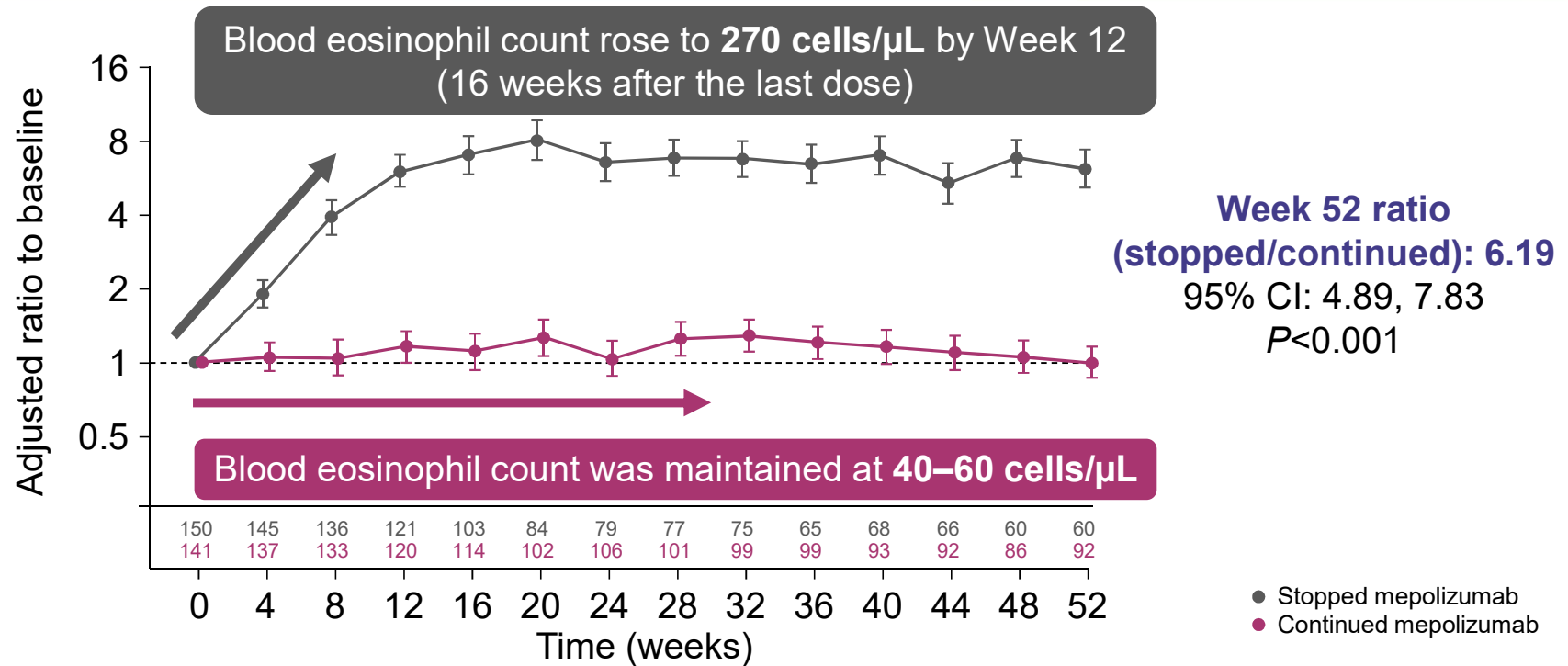
ITT population (N=295)

*Kaplan-Meier cumulative incidence curve; shaded areas represent 95% CIs

Hazard ratio estimated using Cox proportional hazards models adjusted for covariates

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Blood eosinophil counts increased in those who stopped mepolizumab; increases were maintained until Week 52





In those who stopped mepolizumab, blood eosinophil counts rose to levels seen at baseline in prior studies (230–320 cells/ μ L)^{1–3}

ITT population (N=295). Analyzed using mixed model repeated measures adjusted for covariates

1. Pavord ID, et al. *Lancet* 2012; 380: 651–9
2. Ortega HG, et al. *New Eng J Med* 2014; 371: 1198–207
3. Bel EH, et al. *New Eng J Med* 2014; 371: 1189–97


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The safety profile of mepolizumab was consistent with previous trials: on-treatment AEs (1)

| Number of patients (%) | Part C (blinded treatment) | |
|--|-----------------------------|-------------------------------|
| | Stopped mepolizumab (N=151) | Continued mepolizumab (N=144) |
|  Any AE | | |
| Any AE | 96 (64) | 112 (78) |
| Any AE related to study treatment | 1 (<1) | 5 (3) |
| Any AE leading to treatment discontinuation | 2 (1)* | 2 (1)* |
|  Any SAE | | |
| Any SAE | 10 (7) | 9 (6) |
| Any SAE related to study treatment | 0 | 0 |
| Any fatal SAE | 0† | 0 |
| Any event, number of events per 1000 patient-years of exposure | 3098 | 2740 |

ITT population (N=295); *Two additional participants randomized to the 'continued mepolizumab' group and 1 additional participant randomized to the 'stopped mepolizumab' group discontinued blinded treatment due to an AE and are not included in this table
 †One post-treatment fatal SAE of 'Death' leading to treatment discontinuation (stopped mepolizumab group) considered not related to treatment
 AE, adverse event; SAE, serious adverse event

The safety profile of mepolizumab was consistent with previous trials: on-treatment AEs (2)

| Number of patients (%) | Part C (blinded treatment) | |
|--|-----------------------------|-------------------------------|
| | Stopped mepolizumab (N=151) | Continued mepolizumab (N=144) |
|  AEs of special interest | | |
| Systemic reactions | 0 | 0 |
| Anaphylaxis | 0 | 0 |
| Local site reactions | 1 (<1) | 5 (3) |
| All infections* | 66 (44) | 84 (58) |
| Serious infections | 2 (1) | 2 (1) |
| Potential opportunistic infections† | 2 (1) | 2 (1) |
| Neoplasms* | 3 (2) | 5 (3) |
| Malignancies‡ | 0 | 2 (1) |
| Cardiac disorders* | 2 (1) | 1 (<1) |
| Serious CVT events§ | 1 (<1) | 0 |
| Serious ischemic events¶ | 0 | 0 |

ITT population (N=295); *Infections from infections and infestations SOC. Neoplasms from neoplasms benign, malignant and unspecified (including cysts and polyps) SOC. Cardiac disorders from cardiac disorders SOC; †identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy (Winthrop, 2015); ‡identified from neoplasms benign, malignant and unspecified (including cysts and polyps) SMQs; §serious CVT events identified from cardiac disorders SOC, vascular disorders SOC and SMQs; ¶subset of serious CVT events identified through SMQs. CVT, cardiac vascular & thromboembolic; SMQs, standard MedDRA queries; SOC, system organ class

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Conclusion

Patients with severe eosinophilic asthma who stopped long-term (≥ 3 years) mepolizumab treatment had the following, versus those who continued:



An increase in exacerbations and shorter time to first exacerbation



A reduction in asthma control



An increase in blood eosinophil counts back to pre-treatment levels¹⁻³



Differences in efficacy outcomes were seen from Week 12 (16 weeks after the last dose)



Data from COMET show a safety profile of mepolizumab consistent with previous trials¹⁻⁷

These results support **continued mepolizumab treatment having sustained clinical benefits** in patients with severe eosinophilic asthma

1. Pavord ID, et al. *Lancet* 2012; 380: 651-9; 2. Bel EH, et al. *N Engl J Med* 2014; 371: 1189-97
3. Ortega HG, et al. *N Engl J Med* 2014; 371: 1198-207; 4. Chupp GL, et al. *Lancet Respir Med* 2017; 5: 390-400
5. Lugogo N, et al. *Clin Ther* 2016; 38: 2058-70 e1; 6. Khatri S, et al. *J Allergy Clin Immunol* 2019; 143: 1742-51 e7
7. Khurana S, et al. *Clin Ther* 2019; 41: 2041-56 e5

Additional disclosures

- Oliver Kornmann has received grants and personal fees from AstraZeneca, GSK, Novartis, Boehringer Ingelheim, Sanofi Aventis, and Roche
- Marc Humbert has received personal fees from GSK, AstraZeneca, Novartis, Roche, Sanofi, and Teva
- Claude Poirier has received personal fees for clinical research from AstraZeneca, and personal fees for being an advisory committee member, participating in clinical research, and acting as a speaker from Boehringer Ingelheim, GSK, Novartis, and Sanofi
 - Prof. Poirier did not provide feedback on the development of this oral presentation
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- Norihiro Kaneko reports that he has nothing to declare
- Steven G. Smith, Neil Martin, Martyn J. Gilson, and Robert G. Price are employees of GSK and own stocks/shares
- Eric S. Bradford is a former employee of GSK
- Mark C. Liu has received grants for clinical trials from Boehringer Ingelheim, GSK, MedImmune, Mereo BioPharm, and Gossamer Bio