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

Wendy C. Moore1, Oliver Kornmann2, Marc Humbert3, Claude Poirier4, Elisabeth H. Bel5, Norihiro Kaneko6, Steven G. Smith7, Neil Martin8,9, Martyn J. Gilson10, Robert G. Price11, Eric S. Bradford7*, Mark C. Liu12

1Wake Forest School of Medicine, Winston-Salem, NC, USA; 2IKF Pneumologie Frankfurt, Clinical Research Centre Respiratory Diseases, Frankfurt, Germany; 3Université Paris-Saclay; Assistance Publique- Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre; and INSERM U999, Le Kremlin-Bicêtre, Paris, France; 4Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada; 5Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands; 6Kameda Medical Center, Kamogawa, Japan; 7GSK, Research Triangle Park, NC, USA; 8GSK, Brentford, Middlesex, UK; 9Institute for Lung Health, University of Leicester, Leicester, UK; 10GSK, Uxbridge, Middlesex, UK; 11GSK, Stevenage, Hertfordshire, UK; 12Johns Hopkins Asthma and Allergy Center, Baltimore, MD, USA

*Affiliation at the time of this study
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.
- Editorial support in the form of writing assistance (including the development of the initial draft, assembling tables and figures, and slide formatting) was provided by Roisin McCorkell, MSc, and Elizabeth Hutchinson, PhD, CMPP, from Fishawack Indicia Ltd, UK, and was funded by GSK.
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-blinded and open-label studies.

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.

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

IL, interleukin-5; mAb, monoclonal antibody; SC, subcutaneous
**Inclusion criteria:**

- Received continuous mepolizumab treatment for ≥3 years*
- Completed the previous open-label mepolizumab studies, COLUMBA\(^1\) or COSMEX\(^2\)
- Remained on asthma controller therapy, throughout COLUMBA\(^1\) or COSMEX\(^2\)

**Exclusion criteria:**

- A clinically significant health deterioration at completion of COLUMBA\(^1\) or COSMEX\(^2\)
- Treated with any mAb other than mepolizumab within 5 half-lives of screening
- Current smokers
- <80% adherence to controller medications during COLUMBA\(^1\) or COSMEX\(^2\)

*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)

COMET study design

Patients were randomized to either continue mepolizumab OR stop mepolizumab and switch to placebo.

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

- **Phase IIIb trial**
  - GSK study ID 201810
  - NCT02555371
- Randomized
- Double blind
- Placebo controlled
- Multicenter
- Parallel group

**Part C: Double-blind treatment period**

- **Screening and run-in open-label phases**
  - Part A: 0–132 weeks (Variable)
  - Part B: 4–8 weeks (Fixed)
- Randomization 1:1

**Weeks:**
- 0 4 8 12 16 20 24 28 32 36 40 44 48 52
- (Exit)

**Optional Part D:** Patients could switch back to open-label mepolizumab following an exacerbation

- **Mepolizumab 100 mg SC**
- **Stopped mepolizumab 100 mg SC (switched to placebo)**
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

ACQ, Asthma Control Questionnaire; ED, emergency department
Demographics and disease characteristics at COMET randomization were similar: both groups had previously been receiving mepolizumab for ≥3 years

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

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
Exposure to mepolizumab

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.

ITT population (N=295)
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

Patients with ≥1 exacerbation requiring ED visit or hospitalization

- Stopped mepolizumab: 5% (n=7/151)
- Continued mepolizumab: 7% (n=10/144)

Patients with ≥1 exacerbation requiring hospitalization

- Stopped mepolizumab: 4% (n=6/151)
- Continued mepolizumab: 1% (n=2/144)

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.

Hazard ratio 1.52
95% CI: 1.13, 2.02
P=0.005

*Kaplan–Meier cumulative incidence curve; shaded areas represent 95% CIs
Hazard ratio estimated using Cox proportional hazards models adjusted for covariates
Blood eosinophil counts increased in those who stopped mepolizumab; increases were maintained until Week 52

Blood eosinophil count rose to 270 cells/µL by Week 12 (16 weeks after the last dose)

Blood eosinophil count was maintained at 40–60 cells/µL

Week 52 ratio (stopped/continued): 6.19
95% CI: 4.89, 7.83
P<0.001

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

ITT population (N=295). Analyzed using mixed model repeated measures adjusted for covariates
The safety profile of mepolizumab was consistent with previous trials: on-treatment AEs (1)

<table>
<thead>
<tr>
<th></th>
<th>Stopped mepolizumab (N=151)</th>
<th>Continued mepolizumab (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>96 (64)</td>
<td>112 (78)</td>
</tr>
<tr>
<td>Any AE related to study treatment</td>
<td>1 (&lt;1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Any AE leading to treatment discontinuation</td>
<td>2 (1)*</td>
<td>2 (1)*</td>
</tr>
<tr>
<td><strong>Any SAE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any SAE</td>
<td>10 (7)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Any SAE related to study treatment</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any fatal SAE</td>
<td>0†</td>
<td>0</td>
</tr>
</tbody>
</table>

**Any event, number of events per 1000 patient-years of exposure**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population (N=295)</td>
<td></td>
</tr>
<tr>
<td>Stopped mepolizumab</td>
<td>3098</td>
</tr>
<tr>
<td>Continued mepolizumab</td>
<td>2740</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>AEs of special interest</th>
<th>Stopped mepolizumab (N=151)</th>
<th>Continued mepolizumab (N=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Local site reactions</td>
<td>1 (&lt;1)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>All infections*</td>
<td>66 (44)</td>
<td>84 (58)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Potential opportunistic infections†</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Neoplasms*</td>
<td>3 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Malignancies‡</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Cardiac disorders*</td>
<td>2 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Serious CVT events§</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Serious ischemic events§</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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.
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 levels\(^1\)\(^–\)\(^3\)
- 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 trials\(^1\)\(^–\)\(^7\)

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

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
- Elisabeth H. Bel has received grants for research from GSK, AstraZeneca, Teva and Novartis; and personal fees from AstraZeneca, GSK, Boehringer Ingelheim, Novartis, Sanofi/Regeneron, Teva, Sterna Biologicals, Vectura, and Chiesi
- 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