The Pharmacokinetics and Relative Bioavailability of Mepolizumab 100 mg Liquid Formulation Administered Subcutaneously to Healthy Participants: A Randomized Trial

Shabbir S1, Poulipian I1, Bentley JP1, Bradford ES1, Kaisermann M2, Aljabaly MG1

Poster No. P702 (A1311)

Background

- Mepolizumab is approved as an add-on-maintenance treatment for patients with severe eosinophilic asthma and for patients with eosinophilic granulomatosis with polyangiitis.1
- The current approved formulation of mepolizumab is a sterile, single-use, preservative-free, lyophilized drug product for subcutaneous (SC) administration, which must be reconstituted prior to administration with sterile water for injection using aseptic technique.2
- A new formulation of mepolizumab as a liquid drug product in a single-use, ready-to-use prefilled syringe (PFS) or prefilled autoinjector (AI) has been developed (see related posters: Bradford et al. P107; Aljabaly et al. P206). The provision of mepolizumab in these simple, easy-to-use devices could allow administration to patients or caregiver at home, and may help to reduce healthcare burden and costs compared with healthcare provider (HCP) administration.2,3

Objective

- To compare the pharmacokinetics (PK) of the new liquid formulation of mepolizumab administered by a PFS and AI, with the reconstituted lyophilized drug product.

Methods

- This was an open-label, parallel-group study (GSDD:00458; NCT03014474). Healthy participants were randomized (1:1:1) to receive a single mepolizumab dose (100 mg SC) administered by a HCP as either the liquid drug product (1.0 mL) in a PFS or AI, or as the reconstituted lyophilized drug product (reconstituted with 1.2 mL, sterile water for injection).
- Randomization was stratified by body weight (<70, 70–80, or >80 kg) measured at Day -1 to ensure similar weight distribution across the three treatment groups. Injection site was randomised 1:1:1 to upper arm, abdomen, or thigh.
- Primary endpoints were maximum plasma concentration (Cmax) area under the concentration-time curve (AUC) from time zero (pre-dose) to last time of quantifiable concentration (AUClast), and AUC from time zero to infinity (AUC∞).
- Secondary endpoints included additional PK parameters and safety assessments. An exploratory objective was the pharmacodynamic effect on blood eosinophil count.
- The planned sample size (N=343) was based on the number of participants needed to demonstrate a non-inferiority (90% CI treatment ratio [lower bound] 0.80, 1.10) within the geometric (0.80, 1.25) for Cmax, AUC0−t, and AUClast.

Results

- Of the 244 participants randomized, 244 received the study drug (two participants were randomized in error). Participant demographics at baseline are shown in Table 1.
- The PK profile of mepolizumab administered via a PFS or AI was statistically comparable to that of the reconstituted lyophilized drug product, the 90% CIs for the treatment ratios of Cmax, AUC0−t, and AUClast (PFS or AI vs reconstituted lyophilized drug product) were all within the conventional bioequivalence bounds of 0.80, 1.25, demonstrating comparable (not neutralizing) exposure (Figure 1).
- Adjusted treatment incidence of AEs leading to discontinuation was 0% (PFS) and 4% (AI).
- Mepolizumab exposure observed across injection sites (upper arm, abdomen, or thigh) did not markedly differ in all three treatment groups.
- Similar effects on blood eosinophil counts were observed in the three treatment groups, and no safety concerns were identified.

References

- Global Clinical Sciences & Delivery (GCS&D) – RID Projects, Clinical Pharmacology & Safety, GSK, Stevenage, Hertfordshire, UK; Clinical Pharmacology Modelling & Simulation, GSK, Salford, Manchester, UK; International, US; GL (GSK, Upper Providence, PA, USA), Translational Research, GSK, Stevenage, Hertfordshire, UK; Research, Trionix Pharma, UK.
- PAREXEL, Early Phase Clinical Unit, Northampton NHS Trust, Uxbridge, Middlesex, UK
- Please find the online version of this poster by scanning the QR code or via http://tago.ca/ATS_35.

Table 1. Participant demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>N = 80</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>Body weight (kg)</th>
<th>Total exposure (day*mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid PFS (N=80)</td>
<td>80</td>
<td>74.68</td>
<td>44/36</td>
<td>76.74 (63.86, 90.02)</td>
<td>76.74 (63.86, 90.02)</td>
</tr>
<tr>
<td>Liquid AI (N=80)</td>
<td>80</td>
<td>73.69</td>
<td>44/36</td>
<td>76.74 (63.86, 90.02)</td>
<td>76.74 (63.86, 90.02)</td>
</tr>
<tr>
<td>Reconstituted lyophilized drug product (N=80)</td>
<td>80</td>
<td>74.68</td>
<td>44/36</td>
<td>76.74 (63.86, 90.02)</td>
<td>76.74 (63.86, 90.02)</td>
</tr>
</tbody>
</table>

Table 2. Primary and secondary PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liquid PFS (N=80)</th>
<th>Liquid AI (N=80)</th>
<th>Reconstituted lyophilized drug product (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mcg/mL)</td>
<td>52.5 (20.6)</td>
<td>52.5 (20.6)</td>
<td>52.5 (20.6)</td>
</tr>
<tr>
<td>AUC0−t (mcg*hr/mL)</td>
<td>147.37 (50.74)</td>
<td>147.37 (50.74)</td>
<td>147.37 (50.74)</td>
</tr>
<tr>
<td>AUClast (mcg*hr)</td>
<td>147.37 (50.74)</td>
<td>147.37 (50.74)</td>
<td>147.37 (50.74)</td>
</tr>
<tr>
<td>% EV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>% EV</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 1. Treatment ratios (90% CI) for the plasma mepolizumab PK parameters Cmax, AUC0−t, and AUClast (PFS or AI vs reconstituted lyophilized drug product). The treatment ratios were within the conventional bioequivalence bounds of 0.80, 1.25, demonstrating comparable (not neutralizing) exposure.

Figure 2. Individual participant plus geometric mean (95% CI) mepolizumab PK parameters Cmax (A) and AUC0−t (B) by injection site.

Blood eosinophil results

- In all three treatment groups, geometric mean blood eosinophil counts were reduced from baseline at 48 hours (first post-baseline measurement), a similar effect on blood eosinophils over time was observed across all three treatment groups.

Conclusions

- The PK profile of mepolizumab administered via a PFS or AI was statistically comparable to that of the reconstituted lyophilized drug product, the 90% CIs for the treatment ratios of Cmax, AUC0−t, and AUClast (PFS or AI vs reconstituted lyophilized drug product) were all within the conventional bioequivalence bounds of 0.80, 1.25, demonstrating comparable (not neutralizing) exposure.
- Mepolizumab exposure observed across injection sites (upper arm, abdomen, or thigh) did not markedly differ in all three treatment groups.
- Similar effects on blood eosinophil counts were observed in the three treatment groups, and no safety concerns were identified.

Acknowledgements

- Primary investigators: J. Blanchette CM, CA (University of British Columbia, Vancouver, British Columbia, Canada); L. Pouliquen I ( Assistance Publique Hopitaux de Paris, France); I. Poulipian (PAREXEL, Clinical Research Organization, New Jersey, USA).
- Study center investigators: M. Kaisermann (University of Toronto, Toronto, Canada); M. Aljabaly (GSK, Clinical Pharmacology, Stockley Park, UK); L. Pouliquen (University of Paris, France); I. Poulipian (PAREXEL, Clinical Research Organization, New Jersey, USA).

Please note the online version of this poster by scanning the QR code or via http://tago.ca/ATS_35.

Presented at the American Thoracic Society International Conference, Dallas, TX, USA, May 17–22, 2019
Poster wall - 4’ (h) x 6’ (w)
121.92 cm (h) x 243.84 cm (w) [48’ h x 96’ w]

Finished size
91 cm (h) x 183 cm (w)

PowerPoint size
45.5 cm (h) x 91.5 cm (w)