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

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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 techniques.[1]
- 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. P697 [A1306] and Chapman et al. P696 [A1305]). The provision of mepolizumab in these simple, easy-to-use devices could allow administration by patients or caregivers 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 (GSK ID 204958; NCT03014674). 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, and ≥80 kg) measured at Day −1 to ensure similar weight distribution across the three treatment groups; injection site was randomized 1:1:1 to upper arm, abdomen, or thigh.
- Primary endpoints were maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC) from time zero (pre-dose) to last time of quantifiable concentration ($AUC_{[0–t]}$), and AUC from time zero to infinity ($AUC_{[0–\infty]}$).
- 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=243) was based on the number of participants needed to demonstrate a two-sided 90% confidence interval (CI) for μ(test)/μ(reference) within the guide range (0.80, 1.25) for C_{max}, $AUC_{(0–t)}$, and $AUC_{(0–\infty)}$.

Results

Participants

- Of the 246 participants randomized, 244 received the study drug (two participants were randomized in error). Participant demographics at baseline are shown in **Table 1**.

Table 1. Participant demographics

	Mepolizumab 100 mg SC			
	Liquid PFS (N=80)	Liquid AI (N=79)	Reconstituted lyophilized drug product (N=85)	Total (N=244)
Age (years)				
Mean (SD)	47.5 (14.94)	46.5 (15.00)	46.1 (15.06)	46.7 (14.95)
Range	19–76	22–80	19–75	19–80
≥65, n (%)	11 (14)	12 (15)	12 (14)	35 (14)
Female, n (%)	38 (48)	36 (46)	40 (47)	114 (47)
Weight (kg), mean (SD)	74.68 (11.80)	73.69 (10.29)	73.57 (12.81)	73.97 (11.67)
BMI (kg/m²), mean (SD)	25.07 (2.77)	24.91 (2.71)	24.79 (2.77)	24.92 (2.74)

BMI, body mass index; SD, standard deviation

PK results

- The primary PK parameters C_{max}, $AUC_{(0–t)}$, and $AUC_{(0–\infty)}$ were similar across the three mepolizumab treatment groups (**Table 2**); the 90% CIs for the treatment ratios (PFS or AI vs reconstituted lyophilized drug product) were all within the conventional bioequivalence bounds of 0.80, 1.25, demonstrating statistical PK comparability between the PFS or AI and the reconstituted lyophilized drug product (**Figure 1**).
- Secondary PK parameters were also similar across the three treatment groups (**Table 2**).

Table 2. Primary and secondary PK parameters

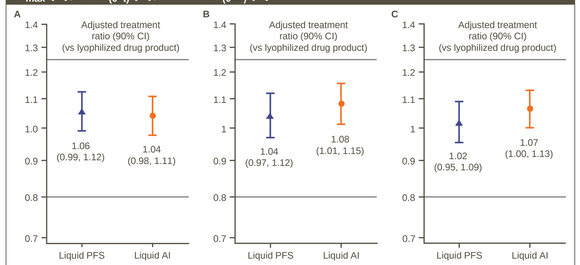
	Liquid PFS (N=80)	Liquid AI (N=79)	Reconstituted lyophilized drug product (N=85)
Primary PK parameters			
C_{max} (mcg/mL)	12.07 (11.32, 12.87)	11.98 (11.27, 12.74)	11.57 (10.92, 12.27)
$AUC_{(0–t)}$ (day*mcg/mL)	415.15 (388.36, 443.78)	434.49 (411.34, 458.94)	403.84 (377.83, 431.63)
$AUC_{(0–\infty)}$ (day*mcg/mL)	454.11 (423.03, 487.48)	478.06 (450.47, 507.34)	450.83 (425.67, 477.47)†
Secondary PK parameters			
t_{max} (days), median (range)	7.06 (1.9–14.0)	7.05 (2.9–21.0)	7.04 (0.9–14.1)
CL/F (L/day)	0.220 (0.205, 0.236)	0.209 (0.197, 0.222)	0.222 (0.209, 0.235)†
Vz/F (L)	6.94 (6.53, 7.37)	6.74 (6.41, 7.08)	7.02 (6.69, 7.37)†
$t_{1/2}$ (days)	21.83 (20.72, 23.01)	22.34 (21.21, 23.53)	21.95 (21.03, 22.92)†
t_{last} (days), median (range)	83.99 (55.9–87.9)	83.98 (81.1–87.1)	83.97 (14.0–87.0)
%AUCextrapolated	7.20 (6.19, 8.37)	7.64 (6.55, 8.90)	7.67 (6.88, 8.54)†

Values are geometric mean (95% CI) unless otherwise indicated; †n=84.
CL/F, apparent clearance following SC dosing; t_{last}, last time point where the concentration is above the limit of quantification; t_{max}, time to C_{max}; $t_{1/2}$, terminal phase elimination half-life; Vz/F, apparent volume of distribution following SC dosing; %AUCextrapolated, percentage of $AUC_{(0–\infty)}$ obtained by extrapolation

PK results by injection site

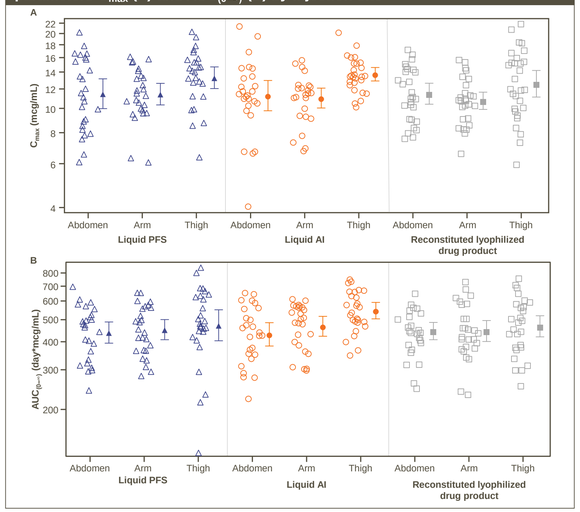
- Overall, mepolizumab geometric mean exposure observed across the three sites of injection investigated (upper arm, abdomen, or thigh) did not appear to markedly differ, irrespective of the treatment groups, though geometric mean C_{max} (all three treatment groups) and geometric mean $AUC_{(0–\infty)}$ (AI group) tended to be slightly higher following injection in the thigh (**Figure 2**).

Figure 1. Treatment ratios (90% CI)* for the plasma mepolizumab PK parameters C_{max} (A), $AUC_{(0–t)}$ (B), and $AUC_{(0–\infty)}$ (C)



*Treatment ratios are of estimated geometric means that were adjusted for injection site (upper arm, abdomen, or thigh) and baseline weight (log_e scale).
The dashed lines show the conventional bioequivalence bounds of 0.80 and 1.25.

Figure 2. Individual participant + geometric mean (95% CI) mepolizumab PK parameters C_{max} (A) and $AUC_{(0–\infty)}$ (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 treatments groups.

Safety

- The overall incidence of any on-treatment adverse events (AEs) was similar across the three treatment groups, with no on-treatment serious AEs (SAEs) or deaths reported (**Table 3**); there was a low incidence (5%) of anti-drug antibodies (none neutralizing) reported.

Table 3. Summary of AEs

n (%)	Liquid PFS (N=80)	Liquid AI (N=79)	Total liquid (N=159)	Reconstituted lyophilized drug product (N=85)	Total (N=244)
Any on-treatment AE	30 (38)	27 (34)	57 (36)	25 (29)	82 (34)
AE related to treatment	20 (25)	17 (22)	37 (23)	17 (20)	54 (22)
AE leading to treatment discontinuation/study withdrawal	0	0	0	0	0
Any on-treatment SAE	0	0	0	0	0
SAE related to treatment	0	0	0	0	0
Fatal SAEs	0	0	0	0	0
Any post-treatment SAE	0	0	0	1 (1)	1 (<1)

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 C_{max}, $AUC_{(0–t)}$, and $AUC_{(0–\infty)}$ (PFS or AI vs reconstituted lyophilized drug product) were all within the conventional bioequivalence bounds of 0.80, 1.25.
- 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

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2. Noone J, Blanchette CM. *J Med Econ.* 2018;21:201–11; 3. WHO. http://apps.who.int/medicinedocs/pdf/s2218e/s2218e.pdf [last accessed December 21, 2018].

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