IHC-PO-171 A Pharmacokinetic Bioequivalence Study of Fremanezumab Administered Subcutaneously Using an Autoinjector and a Prefilled Syringe

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BACKGROUND and OBJECTIVES

- Fremanezumab (Ajovy®) is approved for the preventive treatment of migraine in adults in the US and Europe.[1]
- Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody that selectively targets the calcitonin-gene-related peptide (CGRP) and prevents it from binding to the CGRP receptor.[2]
- Fremanezumab is currently administered as a quarterly (675 mg) or monthly (225 mg) subcutaneous (SC) injection using a prefilled syringe (PFS).
- To increase the ease of administration, an autoinjector (AI) was developed.
- The primary objective of the study reported here was to evaluate the bioequivalence of single fremanezumab dose administered SC using an AI in reference to a PFS in healthy volunteers.
- Secondary objectives of the study were to evaluate the safety and tolerability of fremanezumab administered using an AI or PFS and to evaluate the immunogenicity of fremanezumab.

METHODS

- Healthy male and female volunteers (age 18 – 55 years) received a single SC injection of 225 mg to the abdomen via AI or PFS in a parallel group design.
- Study duration was 24 weeks with 11 study site visits including a screening visit, an inpatient period lasting 6 days, and 9 outpatient visits.
- Blood samples for pharmacokinetics (PK) and anti-drug antibodies (ADA) were collected pre-dose and post-dose.
- Sample size was calculated to provide a minimum of 90% power for showing bioequivalence for the following primary PK parameters: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.
- Safety and tolerability assessments included vital signs, physical examinations, adverse event (AE) reporting, laboratory evaluations and immunogenicity.
- The bioequivalence of fremanezumab administered using an AI referenced to a PFS would be shown if the 90% confidence intervals (CIs) for the geometric least square mean ratios (GMRs) between the groups were fully contained within 0.8 to 1.25 for the primary PK parameters.

References

1. Ajovy Package Insert. https://www.ajovy.com/.
2. Melo-Carrillo A, et al. *Journal of Neuroscience* 2017; 37:7149-7163.

Disclosures

All authors are employees of Teva Pharmaceutical Industries Ltd., the manufacturer of fremanezumab and the sponsor of the research described in this report.

RESULTS

Subject Disposition and Demography

- Of the 358 subjects screened, 218 were randomized to receive fremanezumab 225 mg via AI or PFS SC injection and were evaluated for safety and tolerability. The PK population included n = 216 (AI; n = 106 and PFS; n = 110).
- Overall subject demographics were well balanced between the AI and PFS treatment groups: 50% were male, 91% white, mean age = 38 years, mean BMI = 26 kg/m^2 and mean weight = 73 kg.

Pharmacokinetics

- Mean concentration-time profiles for the AI and PFS treatment groups were very similar and overlaid each other (**Fig. 1**).
- As shown in **Table 1,** the exposure following administration of 225 mg fremanezumab using an AI, was very similar to that of fremanezumab 225 mg administered using a PFS. Additionally the half-life and t_{max} were not impacted by the presentation of study drug administration and were similar between treatments with a mean of 29 days and median of 5 days, respectively.
- Correspondingly, the point estimates for the GMR of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 1.03, 1.04, and 1.05, respectively, and the 90% CIs for the GMRs for all primary PK parameters were entirely contained within bioequivalence margins of 0.8 to 1.25 establishing bioequivalence between AI and PFS. (**Table 2**).

Fig 1. Mean Plasma Fremanezumab Concentrations

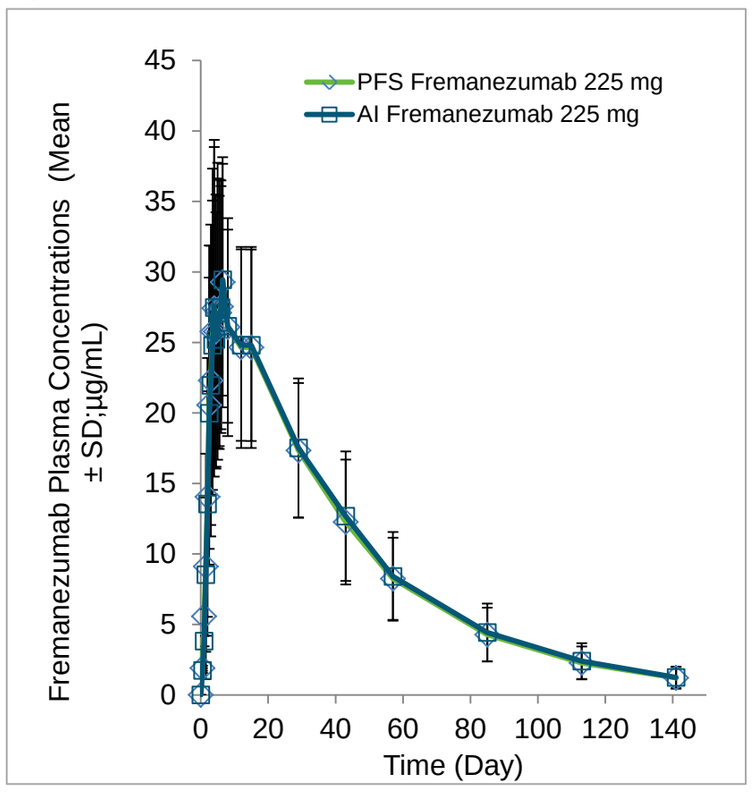

Table 1. Pharmacokinetic Parameters

Parameter	Statistic	AI Fremanezumab 225 mg (n = 106)[a]	PFS Fremanezumab 225 mg (n = 110)[a]
C_{max} (µg/mL)	Geo Mean	30.98	30.74
AUC_{0-t} (h*µg/mL)	Geo Mean	30344.6	29879.4
$AUC_{0-\infty}$ (h*µg/mL)	Geo Mean	31942.5	31096.1
T_{max} (day)	Median	5.0	5.0
$T_{1/2}$ (day)	Mean	29.48	29.40
CL/F (mL/min)	Mean	0.123	0.128

[a]AUC_{0-t}: AI = 105 and PFS = 109; $AUC_{0-\infty}$, $t_{1/2}$, CL/F: AI = 104 and PFS = 109

Table 2. Geometric least squares mean ratios (GMRs)

	AI Fremanezumab 225 mg	PFS Fremanezumab 225 mg	GMR 90% CI
Parameter	**Geometric Ls Mean (95% CI)**	**Geometric Ls Mean (95% CI)**	**(AI/PFS)**
C_{max} (µg/mL)	31.21 (29.59, 32.91)	30.39 (28.85, 32.01)	1.03 (0.96, 1.09)
AUC_{0-t} (h*µg/mL)	30645.20 (29119.59, 32250.74)	29576.13 (28134.42, 31091.71)	1.04 (0.98, 1.10)
$AUC_{0-\infty}$ (h*µg/mL)	32307.70 (30709.36, 33989.23)	30788.93 (29305.47, 32347.50)	1.05 (0.99, 1.11)

C_{max} and AUCs analyses were performed on ln-transformed parameters using a analysis of variance model with treatment as a fixed effect and cohort, weight, and gender as covariates. Ls = least square

Safety and Tolerability

- The safety profile was similar to that seen in the other fremanezumab studies. Treatment-related AEs occurred in 39 [36%] subjects in the AI group and 26 [24%] in the PFS group.
- The most frequently occurring AEs were injection site reactions which were comparable between AI and PFS groups and resolved 4 hours post-dose in 99% of subjects.
- The incidence of treatment emergent ADA response was low and evenly distributed between AI (n=3 [3%]) and PFS (n=4 [4%]) groups.

CONCLUSIONS

- The AI presentation of fremanezumab provides a bioequivalent PK profile to that of the PFS.
- Safety and tolerability were comparable between the two administration presentations and similar to the safety reported in prior studies.

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