Clinical Pharmacology in Drug Development
2021, 10(9) 1018–1027

DOI: 10.1002/cpdd.902

A Pharmacokinetic Bioequivalence Study of Fremanezumab Administered Subcutaneously Using an Autoinjector and a Prefilled Syringe

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Abstract

Fremanezumab (AJOVY; Teva Pharmaceutical Industries Ltd, Netanya, Israel), approved for the preventive treatment of migraine, is available as a subcutaneous injection either once a month or once every 3 months using an autoinjector or a prefilled syringe. The present study evaluated the pharmacokinetic (PK) bioequivalence of a single subcutaneous injection of fremanezumab 225 mg administered using an autoinjector compared to a prefilled syringe in healthy volunteers. Blood samples for PK and antidrug antibodies were collected before and after dosing. Safety and tolerability assessments included physical examinations, adverse event reporting, laboratory evaluations, and immunogenicity. Following single-dose administration, the mean concentration-time profiles for the 2 treatment groups (autoinjector, n = 106; and prefilled syringe, n = 110) were similar. The point estimates for the back-transformed ratio (autoinjector/prefilled syringe) of geometric least squares means of maximum plasma concentration, area under the plasma concentration–time curve from time 0 to the time of the last measurable drug concentration, and area under the plasma concentration–time curve from time 0 extrapolated to infinity were 1.03, 1.04, and 1.05, respectively, with the 90% confidence intervals entirely contained within bioequivalence margins of 0.8 to 1.25. For both groups, median time to maximum observed concentration was 5 days and mean terminal elimination half-life was approximately 29 days. Treatment-related adverse events were reported by 39 (36%) subjects in the autoinjector group and 26 (24%) in the prefilled syringe group, and the majority were nonserious injection site reactions. The incidence of treatment-emergent antidrug antibody response was low and evenly distributed between the autoinjector (n = 3; 3%) and prefilled syringe (n = 4; 4%) groups. These results indicate that the fremanezumab autoinjector presentation provides an easy-to-use bioequivalent PK profile with a similar safety and tolerability profile to that of the prefilled syringe.

Keywords

autoinjector, bioequivalence, calcitonin-gene–related peptide, CGRP, fremanezumab, prefilled syringe

Fremanezumab (AJOVY, Teva Pharmaceutical Industries Ltd, Netanya, Israel) is approved for the preventive treatment of migraine in adults in the United States, Europe, and other countries. Fremanezumab is a

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Submitted for publication 22 October 2020; accepted 9 December 2020.

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fully humanized IgG2Δa/kappa monoclonal antibody that selectively targets the calcitonin-gene–related peptide (CGRP) and prevents it from binding to the CGRP receptor.[1] CGRP is a 37–amino acid neuropeptide with 2 isoforms (α and β) that is thought to be implicated in the pathophysiology of migraine and other headache disorders. In the periphery, CGRP may contribute to pathophysiological events in migraine, including vasodilation, inflammation and protein extravasation.[2] The phase 3 studies of fremanezumab demonstrated rapid and sustained efficacy and safety as a preventive treatment for migraine when administered as a subcutaneous injection either monthly or every 3 months using a prefilled syringe.[3–5] To further expand treatment options for patients, an autoinjector was developed and is approved for use in the United States and European Union countries. The autoinjector includes a drug-filled syringe consisting of a syringe barrel with integrated needle (gauge 27, thin walled), plunger stopper, and rigid needle shield. The syringe components in the autoinjector are identical to those in the prefilled syringe.

Several studies have shown that an autoinjector as a drug delivery device can increase patient treatment adherence, improve ease of use, and increase quality of life.[6–9] A study comparing patient preference for the autoinjector and prefilled syringe for galcanezumab found that over 90% of patients with migraine rated having a positive experience with an autoinjector and felt that an autoinjector was easy to use.[10]

The objectives of this study were to evaluate the bioequivalence of a single fremanezumab dose administered using an autoinjector compared to a prefilled syringe in healthy volunteers, and to compare safety, tolerability, and immunogenicity of fremanezumab using either administration method.

Methods

Study Approvals

This study was conducted in full accordance with the International Council for Harmonisation Good Clinical Practice Consolidated Guideline (E6) and any applicable national and local laws and regulations. Before the study was initiated, the protocol was submitted to the Institutional Review Board, IntegReview IRB (Austin, Texas) according to national or local regulations. Written informed consent was obtained from each subject before any study procedures or assessments were done. The primary investigator of the study was Dr Maria Gutierrez, and there was 1 site for the study (Teva Internal Clinics US, Miramar, Florida).

Study Design

The study was an open-label, single-dose, randomized parallel group bioequivalence phase 1 study to compare the pharmacokinetics (PK) of fremanezumab administered subcutaneously using 2 presentations—an autoinjector and a prefilled syringe—in healthy volunteers. A parallel-group design was chosen due to the long half-life of fremanezumab (approximately 30 days). Study duration was 24 weeks, approximately 6 half-lives, with 11 study site visits, including 1 visit during a 28-day screening period (days −28 to −2), an inpatient period lasting 7 days (−1 to day 6), and 9 outpatient visits (weeks 2 to 21).

Baseline measures collected on day −1 consisted of assessments of medical history, concomitant medications, vital signs, physical examination, drug tests, clinical laboratory tests, pregnancy test, 12-lead electrocardiogram (ECG), and adverse event reporting. Treatment on day 1 to eligible subjects involved the approved monthly clinical dose of one 225 mg subcutaneous injection of fremanezumab to the abdomen by qualified investigational center personnel using either an autoinjector or a prefilled syringe; each configuration was prefilled with a 1.5-mL minimum deliverable volume containing 150 mg/mL fremanezumab. Safety assessments were performed throughout the 7-day inpatient visit and at the 9 outpatient visits, including vital signs, physical examinations, 12-lead ECG, clinical laboratory tests, pregnancy test, immunogenicity tests, adverse events, and concomitant medications. During the inpatient visit in week 1, blood samples (4 mL) for fremanezumab PK analyses were collected at baseline (just before drug administration), day 1 (4, 8, and 12 hours after administration), day 2 (24 and 36 hours after dosing), day 3 (48 and 60 hours after dosing), day 4 (72 and 84 hours after dosing), day 5 (96 and 108 hours after dosing), and day 6 (120 hours after dosing). Blood collections for PK analyses during the 9 outpatient visits occurred on days 8 ± 1, 12 ± 1, 15 ± 1, 29 ± 2, 43 ± 2, 57 ± 2, 85 ± 2, 113 ± 2, and 141 ± 3. If there were any observations of any severe hypersensitivity reactions, blood samples for immunogenicity assessments were to be collected during the inpatient stay and outpatient visits.

Participants

Recruited subjects were healthy male and female volunteers aged 18 to 55 years and having a body mass index ranging from 18.5 to 29.9 kg/m^2. Subjects who met inclusion and exclusion criteria and were in good physical and mental health as determined during the screening period were randomized into either the autoinjector or prefilled treatment group using a randomization schedule. Weight has been shown to be a significant covariate affecting fremanezumab exposure[11]; thus, randomization allocation to the autoinjector and prefilled syringe treatment groups was stratified by 3 body

weight categories (low, 50 to <70 kg; medium, 70 to <90 kg; and high, 90 to ≤120 kg).

Blood Collection and Bioanalytical Methods

The plasma samples for PK measures were prepared by collecting blood in K2 ethylenediaminetetraacetic acid anticoagulant tubes and centrifuged, then stored at approximately −70°C. The samples were analyzed using a validated enzyme-linked immunosorbent assay method with a concentration range from 250 to 3500 ng/mL. A microplate is coated with anti-idiotype antibody to fremanezumab and blocked with the blocking solution. Each plate contains duplicates of the calibration standards, controls, and up to 31 diluted test samples. The captured fremanezumab is detected by the addition of horseradish peroxidase (HRP) conjugated anti-human IgG2-Fc specific antibody. The bound HRP activity is quantified by the color conversion of the 3,3′,5,5′ tetramethylbenzidine substrate in the presence of hydrogen peroxide. The absorbance is measured at 450 nm with 570 nm subtracted. The standard curve is generated by Watson LIMS software (Thermo Fisher Scientific, Waltham, Massachusetts) for each plate using a 5-PL (Marquardt) model with 1/Y weighting factor. The plasma fremanezumab concentrations in duplicate are interpolated from the standard curve, adjusted by dilution factor if applicable, and averaged for each sample. With regard to the assay performance, the accuracy of the calibration standards ranged from 90% to 113%, and interassay precision (coefficient of variation [%CV]) was ≤9%; the accuracy of the quality control samples ranged from 101% to 108% and interassay variability (%CV) was ≤16%. The results of the calibration standards and quality control samples indicated that the method performed reliably during the sample analysis. Additionally, incurred sample reanalysis was performed successfully, demonstrating the reproducibility of the method.

Anti-fremanezumab antibodies in serum were analyzed by a validated bridging enzyme-linked immunosorbent assay. The analysis was performed with a 3-tiered approach consisting of screening, drug-specific confirmatory, and titer assays. The screening assay was performed to detect antibodies that bound to fremanezumab; samples with a signal above or equal to the plate cut point were then tested to confirm the specificity of the response. A sample was designated confirmed positive if the percent signal inhibition in the presence of the competitive drug exceeded the drug-specific confirmatory cut point. Any confirmed antidrug antibody (ADA)-positive sample was titered with 2-fold serial dilutions to report the ADA titer.

Samples were incubated with a conjugate mixture consisting of biotinylated fremanezumab, digoxigenin-conjugated fremanezumab, and soluble drug (confirmatory assay only). Subsequently, the solution was transferred to a streptavidin-coated plate for another incubation to capture the immune complex. The captured ADAs were detected using an HRP-labeled anti-digoxigenin antibody. The bound HRP activity was quantitated with the substrate 3,3′,5,5′ tetramethylbenzidine. Absorbance of the enzymatic reaction product was measured at 450 nm (with background at 650 nm subtracted). The ADA method has a screening and confirmatory sensitivity of 38 and 67 ng/mL, respectively, with affinity purified rabbit anti-fremanezumab polyclonal antibodies used as a surrogate positive control. At 500 ng/mL of positive control, the assay tolerated 180 μg/mL of fremanezumab.

Pharmacokinetic and Statistical Analyses

Plasma fremanezumab concentration data were summarized using descriptive statistics by treatment and nominal time point. Concentration values that were below the limit of quantitation (0.25 μg/mL) were treated as 0, and missing values were ignored when calculating summary statistics for plasma concentrations. The plasma PK parameters for fremanezumab were estimated from the concentration-time profiles for all subjects in the PK analysis set. PK parameters used in the bioequivalence analyses were maximum observed plasma drug concentration (C_{max}), area under the plasma concentration–time curve from time 0 to the time of the last measurable drug concentration ($AUC_{0\text{-}t}$), and area under the plasma concentration–time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$). Additional PK parameters derived included the following: AUC from time 0 to 28 days ($AUC_{0\text{-}28d}$), AUC from time 0 to 84 days ($AUC_{0\text{-}84d}$), percentage of $AUC_{0\text{-}\infty}$ extrapolated (%AUC_{ext}), apparent plasma terminal elimination rate constant (λ_z), time to maximum observed concentration (t_{max}), terminal elimination half-life ($t_{\frac{1}{2}}$), apparent total body clearance, and apparent volume of distribution during the terminal phase (Vz/F). PK parameters were summarized by treatment using descriptive statistics. The data from subjects who withdrew early and missed PK sampling in a manner that affected the validity of their primary PK parameters were not included in the summary statistics or analyses.

The bioequivalence of the autoinjector and the prefilled syringe administration were assessed by comparing the following primary PK parameters: C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$. The natural log-transformed values of each parameter was analyzed using an analysis of variance model with treatment (autoinjector or prefilled syringe) as the fixed effect and cohort, weight, and sex as covariates. Geometric least square mean ratios (test/reference) and 90% confidence interval (CI) for the

ratios were derived. Bioequivalence of the autoinjector and the prefilled syringe was concluded if the 90%CI fell with the limits of the 0.80 to 1.25 for each of the parameters.

The sample size for the study was calculated based on the percent geometric %CV for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ (30.76, 35.22, and 35.39, respectively) from a previous fremanezumab phase 1 study (data on file, Teva Pharmaceutical Industries Ltd). A sample size of 92 subjects per group was estimated to provide a minimum of 90% power to show bioequivalence for all 3 primary PK parameters. Based on this estimation, together with an assumption of 15% withdrawal rate, 218 subjects were enrolled in the study.

Safety Analyses

During the study, the following safety and tolerability assessments were performed: vital sign measurements, physical examinations, recordings of adverse events, clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis), safety 12-lead ECG recordings, local tolerability evaluations (injection site reactions and pain), pregnancy tests, immunogenicity measures, and concomitant medication usage. For immunogenicity measures, serum samples were analyzed for ADA presence. A listing of ADA results with the relevant titer for positive results was provided for the safety analysis set. The impact of the presence of ADAs on PK and clinical safety parameters was evaluated if appropriate. Descriptive statistics were calculated for safety measures for all subjects who were randomized and received a study treatment dose.

Results

Subject Disposition and Demographic Characteristics

The safety population consisted of the 218 subjects who were randomly assigned to receive fremanezumab 225 mg via autoinjector (n = 108) or prefilled syringe subcutaneous injection (n = 110). Of the 218 subjects in the safety population, data from 2 subjects were not included in the PK population due to protocol deviations (1 subject in the autoinjector group discontinued due to pregnancy and 1 in the prefilled syringe group was lost to follow-up); thus, there were 216 subjects in the PK population (n = 106 and n = 110 for the autoinjector and prefilled syringe groups, respectively) who completed the study.

Subject demographic characteristics were well balanced between the treatment groups; demographics for both treatment groups combined included 50% male, 91% White, mean age 38 years (range, 18-55 years), mean body mass index 26 kg/m^2 (range, 19-30 kg/m^2), and mean weight 73 kg (range, 50-103 kg). Forty-five percent of subjects were in the low-weight stratum ($\geq$50 kg and $<$70 kg), 48% of subjects were in the medium-weight stratum ($\geq$70 kg and $<$90 kg), and 7% of subjects were in the high-weight stratum ($\geq$90 kg and $\leq$120 kg). More than 99% (n = 217) were of Hispanic or Latino ethnicity.

Fremanezumab Concentrations

The mean concentration-time profiles following a single subcutaneous dose of 225 mg of fremanezumab using an autoinjector or a prefilled syringe were very similar throughout the collection period (Figure 1). Mean plasma fremanezumab concentrations generally peaked between 5 and 6 days after dosing for both treatments and gradually declined thereafter in a monophasic manner. The time to attain these peak concentrations was not impacted by the use of an autoinjector vs prefilled syringe.

Pharmacokinetic Parameters

PK parameters calculated following subcutaneous administration of 225 mg of fremanezumab using an autoinjector were very similar to that of fremanezumab 225 mg administered using a prefilled syringe (Table 1).

Subgroup analyses were performed to evaluate the effects of body weight and sex on the PK parameters. As illustrated in Figure 2, some of the variability in $AUC_{0\text{-}t}$ is explained by body weights ($R^2 = 0.3733$), with lower body weights being generally associated with higher $AUC_{0\text{-}t}$. This effect was observed for men and women in both the autoinjector and prefilled syringe groups, and a similar trend was observed with C_{max} and $AUC_{0\text{-}\infty}$ (data on file, Teva Pharmaceutical Industries Ltd).

Bioequivalence for Subcutaneous Fremanezumab: Autoinjector vs Prefilled Syringe

The statistical analyses for bioequivalence were performed on the ln-transformed primary PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) using an analysis of variance model with treatment as a fixed effect, and cohort, weight, and sex as covariates. The point estimates for the back-transformed ratio of geometric means of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, resulting from the autoinjector group (test) relative to that from the prefilled syringe group (reference) were 1.03, 1.04, and 1.05, respectively. The 90%CIs of the geometric mean ratios for all parameters (C_{max}, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}t}$) were entirely contained within the bioequivalence range of 80% to 125% (Figure 3). Therefore, bioequivalence between the autoinjector and prefilled syringe was demonstrated in this study.

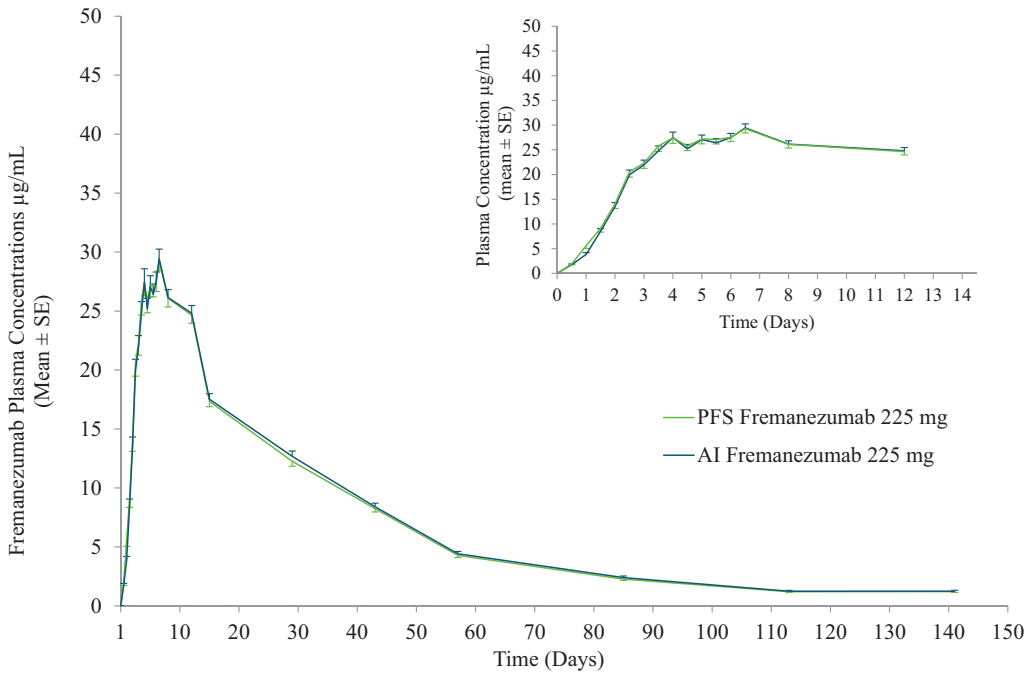

Figure 1. Time profiles of mean plasma fremanezumab concentrations by treatment on a linear scale. The mean concentration-time profiles following a single subcutaneous dose of 225 mg of fremanezumab using an autoinjector (AI) or a prefilled syringe (PFS). The *x*-axis shows the number of days relative to the day of study drug dose administration. Lower limit of quantitation: 0.25 μg/mL. Inset figure illustrates the first 14 days after dose administration.

Safety

There were no deaths, and no subjects were withdrawn from the study due to an adverse event. As shown in Table 2, the percentage of subjects reporting at least 1 adverse event was 42% (92 subjects) and was higher in the autoinjector group (54 [50%] subjects) than the prefilled syringe group (38 [35%] subjects). One subject in the prefilled syringe group reported a serious adverse event, an abscess in the soft tissue of the left elbow of severe intensity; the subject was not injected in this area, and the adverse event was not considered to be treatment related. Most reported adverse events were mild in severity (69 [32%] subjects). Sixty-five (30%) subjects reported adverse events that were considered by the investigator to have a reasonable possibility of being treatment related; 39 (36%) and 26 (24%) in the autoinjector and prefilled syringe groups, respectively. The majority of these were injection site reactions that were mild to moderate in severity. All adverse events had resolved by the time of study completion.

Fremanezumab has no known risk of liver damage. However, as previous small-molecule CGRP receptor antagonist medications in development led to drug-induced liver injury, the following adverse events were considered protocol-defined adverse events of special interest: liver enzyme elevation of special interest (aspartate aminotransferase or alanine aminotransferase $\geq$3$\times$ the upper limit of normal (ULN), total bilirubin $\geq$2$\times$ ULN, or international normalized ratio (INR) $\geq$1.5$\times$ ULN), Hy's Law events, or events of severe hypersensitivity reactions (eg, anaphylaxis). A total of 7 subjects had adverse events of special interest. Five subjects in the prefilled syringe group had elevated liver enzymes, and 2 subjects in the autoinjector group had increased INR. None of these adverse events of special interest were assessed as related to the study drug by the investigator. The investigator considered the elevated liver enzymes to have been due to patient-reported strenuous physical exertion that was job or exercise related. The elevated INR values were inconsistent with these subjects' previous INR values, and repeat testing was normal. As such, these abnormal clinical laboratory results were not considered clinically significant.

The degree and time course of the injection site reactions were comparable between treatment groups. Injection site erythema was the most common reaction, with the highest incidence, 46 subjects (21%), occurring 20 minutes after dosing on the first day of injection. All episodes of erythema resolved 2 hours after dosing on the same day.

There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory or vital signs values. Mean values for ECG parameters

Table 1. Pharmacometric Parameters

Parameter (Unit)	Statistic	Fremanezumab 225 mg Autoinjector (n = 106)	Fremanezumab 225 mg Prefilled Syringe (n = 110)
t_{max} (d)	n	106	110
	Median	5.00	5.00
	Min, Max	1.50, 14.00	1.00, 14.00
C_{max} (μg/mL)	n	106	110
	Mean	32.43	32.66
	SD	9.79	11.17
	%CV	30.2	34.2
	Geometric mean	30.98	30.74
$AUC_{0\text{-}28d}$ (μg • h/mL)	n	105	110
	Mean	15490.6	15432.7
	SD	4175.14	4516.40
	%CV	27.0	29.3
	Geometric mean	14938.8	14733.5
$AUC_{0\text{-}84d}$ (μg • h/mL)	n	104	109
	Mean	28502.3	28050.8
	SD	8006.02	8349.11
	%CV	28.1	29.8
	Geometric mean	27398.3	26781.7
$AUC_{0\text{-}t}$ (μg • h/mL)	n	105	109
	Mean	31837.4	31428.2
	SD	9682.08	9822.95
	%CV	30.4	31.3
	Geometric mean	30344.6	29879.4
$AUC_{0\text{-}\infty}$ (μg • h/mL)	n	104	109
	Mean	32803.4	33464.3
	SD	10184.33	10631.99
	%CV	30.4	32.4
	Geometric mean	31942.5	31096.1
$t_{\frac{1}{2}}$ (d)	n	104	109
	Mean	29.48	29.40
	SD	4.85	5.17
	%CV	16.4	17.6
CL/F (mL/min)	n	104	109
	Mean	0.12	0.13
	SD	0.04	0.05
	%CV	32.6	41.9
Vz/F (L)	n	104	109
	Mean	7.34	7.57
	SD	1.94	2.39
	%CV	26.4	31.5

$AUC_{0\text{-}28d}$, area under the plasma concentration–time curve from time 0 to 28 days; $AUC_{0\text{-}84d}$, area under the plasma concentration–time curve from time 0 to 84 days; $AUC_{0\text{-}\infty}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration–time curve from time 0 to the time of the last measurable drug concentration; C_{max}, maximum observed concentration; CL/F, apparent total body clearance; CV, coefficient of variation; Max, maximum; Min, minimum; n, number of subjects with evaluable data; N, total number of subjects; SD, standard deviation; $t_{\frac{1}{2}}$, terminal elimination half-life; t_{max}, time to maximum observed concentration; Vz/F, apparent volume of distribution during the terminal phase.

Note: $AUC_{0\text{-}t}$ for early terminated subjects was excluded from the analysis unless this subject had reached plasma concentrations that were below the limit of quantitation in the last sample collected before early termination.

showed no clinically meaningful changes from baseline, nor were there relevant differences were observed between treatment groups. A low incidence (3%) of treatment-emergent ADA response was observed. Treatment-emergent ADA-positive subjects were evenly distributed between the prefilled syringe group (4 [4%] subjects) and the autoinjector group (3 [3%] subjects). Fremanezumab exposure was affected in

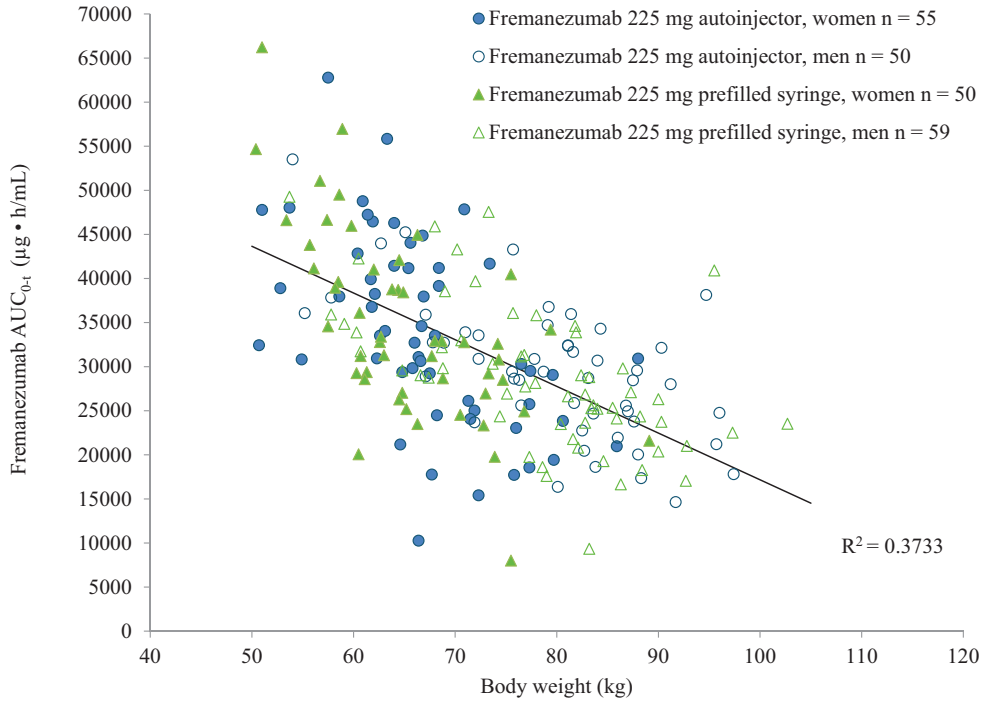

Figure 2. Scattergraph displaying the effects of body weight and sex on individual subject $AUC_{0\text{-}t}$. $AUC_{0\text{-}t}$ = area under the plasma concentration–time curve from time 0 to the time of the last measurable drug concentration ($AUC_{0\text{-}t}$). The Pearson R^2 value is defined as r*r, where r = covariance (weight, $AUC_{0\text{-}t}$)/[sqrt(variance(weight))* sqrt(variance($AUC_{0\text{-}t}$))].

Table 2. Adverse Events[a]

System Organ Class MedDRA Version 21.0 Preferred Term, n (%)	Fremanezumab 225 mg Autoinjector (n = 108)	Fremanezumab 225 mg Prefilled Syringe (n = 110)	Overall (N = 218)
Subjects with at least 1 adverse event	54 (50)	38 (35)	92 (42)
General disorders and administration site conditions	36 (33)	20 (18)	56 (26)
Injection site erythema	30 (28)	17 (15)	47 (22)
Injection site induration	8 (7)	0	8 (4)
Influenza-like illness	2 (2)	3 (3)	5 (2)
Medical device site erythema	3 (3)	0	3 (1)
Investigations	16 (15)	16 (15)	32 (15)
Alanine aminotransferase increased	11 (10)	9 (8)	20 (9)
Aspartate aminotransferase increased	1 (<1)	9 (8)	10 (5)
Hemoglobin decreased	2 (2)	1 (<1)	3 (1)
Hematocrit decreased	2 (2)	1 (<1)	3 (1)
Nervous system disorders	3 (3)	2 (2)	5 (2)
Headache	3 (3)	2 (2)	5 (2)

MedDRA, Medical Dictionary for Regulatory Activities.
[a]Adverse events occurring in at least 3 subjects by MedDRA System Organ Class and MedDRA Preferred Term.

1 ADA-positive subject. The subject had positive ADA on day 15, and the ADA titer levels increased gradually up to day 141 (final assessment). Fremanezumab concentration was quantified up to day 15 and became below the limit of quantitation at all following sample collections up to day 141. The subject was included in the PK analysis set, and ADA development was not associated with any adverse events.

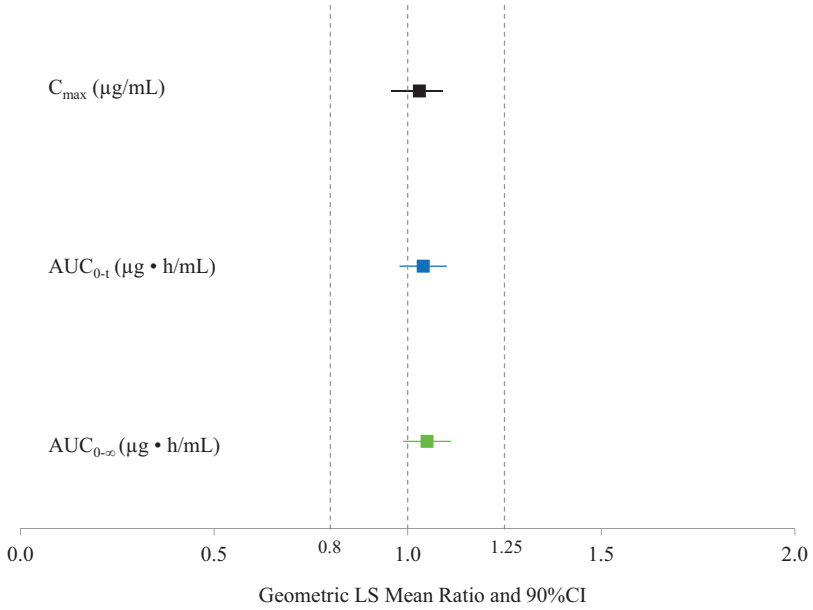

Figure 3. Forest plot of geometric least square mean ratios and 90% confidence intervals. Geometric least square mean ratios (autoinjector/prefilled syringe), the C_{max} and AUC analyses were performed on ln-transformed parameters using an analysis of variance model with treatment as a fixed effect and cohort, weight, and sex as covariates. $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; CI, confidence interval; LS, least squares.

Discussion

This study evaluated the bioequivalence and safety of fremanezumab administered using an autoinjector compared to administration using a prefilled syringe. Following single-dose subcutaneous administration of 225 mg of fremanezumab, plasma concentration–time profiles and exposure parameters were equivalent when comparing the autoinjector group to those for the prefilled syringe group. As seen in previous studies of fremanezumab,[12] lower body weights were generally associated with higher peak and overall exposures, and this effect occurred in both the autoinjector and prefilled syringe groups. Consistent with the fremanezumab population PK model[11] and published findings with other monoclonal antibodies,[13] higher body weight was associated with increased central clearance and distribution volume. However, no dose adjustments are recommended for fremanezumab, as it has previously been shown that different fremanezumab exposures due to weight have no impact on efficacy.[14]

The PK profile was bioequivalent between the autoinjector and prefilled syringe administration, as the 90%CIs of the geometric means of the exposure PK parameters, C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}, were fully contained within the bioequivalence limits of 80% to 125%. The geometric mean values of AUC_{0-28} were very similar between the autoinjector and the prefilled syringe groups, which is the dosing interval for the 225 mg monthly approved dose for migraine. The $t_{\frac{1}{2}}$, t_{max}, apparent total body clearance, and V_z/F were also not impacted by use of an autoinjector compared to a prefilled syringe. The median t_{max} was 5 days and mean $t_{\frac{1}{2}}$ was 29 days for both the autoinjector and prefilled syringe groups; and both parameters are consistent with previously reported values following a subcutaneous administration of fremanezumab at 225 mg.[11,12] There was a very low apparent clearance for both the autoinjector and prefilled syringe treatment regimens (approximately 0.12 mL/min) compared to the human glomerular filtration rate (125 mL/min). These values are similar to those reported for other fremanezumab studies and are generally consistent with previously reported values for therapeutic monoclonal antibodies.[15,16] Likewise, the observed mean Vz/F values for the autoinjector and prefilled syringe were also consistent with previously reported volumes of distribution for IgG antibodies, indicating a volume of distribution greater than plasma volume but less than the volume of extracellular fluid.[15]

Overall, fremanezumab when administered as a single 225-mg injection to the abdomen using an autoinjector or a prefilled syringe was well tolerated. The safety profile was similar to the safety results observed in other fremanezumab studies. Most treatment-related adverse events were mild to moderate injection site reactions and were comparable between treatments. Erythema was the most common reaction at the site of injection; the highest incidence was reported at 20 minutes after

injection, with resolution occurring within 2 hours after injection. A low incidence of treatment-emergent ADA response was observed across treatment groups and was not associated with any adverse events.

Fremanezumab is approved as a migraine preventive treatment with 2 dosing options available: 225 mg once monthly or 675 mg every 3 months. The findings from this bioequivalence study demonstrated bioequivalence between the autoinjector and prefilled syringe for the 225-mg dose. As the quarterly 675-mg dose is administered using 3 subcutaneous injections of 225 mg, this study supports bioequivalence for the 675-mg dose as well. Both the fremanezumab flexible dosing schedule and the new autoinjector were designed to improve treatment options for patients with migraine. A simulated human factor study of the fremanezumab autoinjector found that patients, caregivers, and health care professionals were able to successfully complete the administration using the autoinjector according to the instructions for use and that 87% to 98% of patients found the autoinjector easy to use and were confident in their ability to use it.[17] Thus, these results, together with the results of this bioequivalence study, which found no differences in the PK profile between the autoinjector and prefilled syringe administration procedures, support the use of both the autoinjector and the prefilled syringe as device choices that can be offered to patients for their migraine treatment.

Conflicts of Interest

All authors are employees of Global Research and Development Teva Pharmaceutical Industries, Ltd.

Funding

The studies described in this report were sponsored by Global Research and Development Teva Pharmaceutical Industries Ltd (Netanya, Israel).

Author Contributions

I.C., O.C.-B., M.S., M.G., O.S., and L.R.-G. designed the research protocols. M.G., as primary investigator, performed the research, and Y.K. monitored the pharmacovigilance data. M.R., S.L., H.S., H.H., I.C., O.C.-B., P.S.L., and M.G. analyzed the data. M.R., S.L., and H.S. contributed new reagents and analytical tools. I.C., O.C.-B., and P.S.L. wrote the article. All authors reviewed and edited the article and approved the final content for submission.

Data Sharing Statement

Qualified researchers may request access to patient-level data and related study documents, including the study protocol and the statistical analysis plan. Patient-level data will be deidentified, and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please email USMedInfo@tevapharm.com to make your request.

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