INTRODUCTION
Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide that plays an important role in the pathophysiology of migraine. Both centrally and peripherally, CGRP is increased during migraine attacks, and inhibition of CGRP with monoclonal antibodies has resulted in effective treatment for episodic and chronic migraine. CGRP receptor antagonists and anti-CGRP antibodies have demonstrated efficacy in reducing frequency of migraine attacks (1,2). Fremanezumab (GLAXOSMITHKLINE, Collegeville, Pennsylvania, USA; TEVA PHARMACEUTICAL INDUSTRIES LTD, Netanya, Israel) is a fully humanized IgG2/kappa monomeric antibody that is being developed for the treatment of migraine. It binds both the α and β CGRP receptors and inhibits CGRP to inhibit its effects on the body. Fremanezumab provides a convenient, safe, and effective preventive therapy with a monthly or quarterly dosing schedule.

GOAL
The goal of these analyses was to characterize the population pharmacokinetics (PK) of fremanezumab in healthy subjects and in patients with episodic and chronic migraine and to explain sources of between-subject variability.

METHODS
Data Description and Study Design
The population PK analyses were performed using NONMEM. Included data following oral administration from:
- 1 Phase 1 study
- 12 0.84 mg starting doses on days 0, 28, and 675 mg starting doses on day 0
- 3 Phase 3 studies
- 2B-101-007 (167 patients with CM): 675-225-90 mg monthly or 90 mg monthly
- 2B-101-022 (188 patients with ES): 675 mg monthly or 675 mg every 3 days
- 3 Phase 3 studies
- 2B-101-030 (141 patients with CM): 675 mg by monthly doses of 225 mg for 3 or 5 days or 675 mg once quarterly
- 2B-101-039 (227 patients with CM or ES): 675 mg once monthly or 3 times 675 mg once quarterly
- 2B-101-046 (187 patients with CM or ES): 675 mg every 3 months or 675 mg per month or 675 mg once quarterly

Population Pharmacokinetic Analysis
The overall procedure for the development and refinement of the population PK model for fremanezumab are outlined in Figure 1. Figure 2 shows the process for the development of the Fremanezumab Population Pharmacokinetic Model

RESULTS
Population Pharmacokinetic Analysis
All fixed and random effect parameters were estimated with good precision and visual predictive check indicated a good fit of the model to the data (Figure 3). The typical volume of the central compartment was allometrically scaled to body weight. The calculated correlation coefficient (r^2) was approximately 0.89 for all fixed parameters. The final dose (dose 1) of 225 mg monthly to a single 225 mg dose resulted in a median accumulation ratio of 2.34 for both placebo and active dosing following the first dose (dose 12) of 225 mg to the 675 mg starting dose resulting in a median ratio of 1.18 for the 675 mg once-quarterly dosing regimen. The same response (AR: C(675 mg)-C(225 mg)) after dose (4-9) final dose compared to dose 1 resulted in a median accumulation ratio of 1.19 to 1.20 for the 675 mg once-quarterly dosing regimen.

Simulation Results
The calculated, modeled median half-life was approximately 21 days (independent of dose or dose regimen). Based on predicted exposure levels, steady state is expected to be achieved by approximately 11 days (plotted Figure 5, the C(675 mg) values in the 675 mg once-quarterly dosing regimen were consistently higher when compared to the 225 mg monthly or subcutaneous 225 mg monthly doses in the 675-225-225 mg monthly dosing regimen; as expected, the use of a starting dose of 675 mg resulted in a higher exposure in men than that observed at steady state (Figure 6). The steady state period (average dose 12 to dose 1) of 225 mg monthly to a single 225 mg dose resulted in a median accumulation ratio of 2.34 for both placebo and active dosing following the first dose (dose 12) of 225 mg to the 675 mg starting dose resulting in a median ratio of 1.18 for the 675 mg once-quarterly dosing regimen. The same response (AR: C(675 mg)-C(225 mg)) after dose 4 (final dose) compared to dose 1 resulted in a median accumulation ratio of 1.19 to 1.20 for the 675 mg once-quarterly dosing regimen. The overall procedure for the development and refinement of the population PK model for fremanezumab are outlined in Figure 1. Figure 2 shows the process for the development of the Fremanezumab Population Pharmacokinetic Model

REFERENCES

Assessment of Effects of Covariates on Fremanezumab Exposure
Based on graphical exploration of covariates (Figure 4), predicted exposures in the presence or absence of preventive medications were comparable. Fremanezumab exposures were slightly higher, but generally overlapping, in the presence of aspirin, nonsteroidal anti-inflammatory drug, or acetylsalicylic acid compared to the absence of use. In addition, exposures were also consistent across each age quartile. Exposures were somewhat higher in the Asian subcohorts compared to the other subcohorts. Covariates assessed were age, gender, race, weight, and body mass index (BMI). The overall range of exposures in male subjects was higher than in female subjects. The impact of age on fremanezumab exposure was evident with increasing body weight across the quartiles.

Association of covariates with fremanezumab exposures in healthy subjects was investigated for patients with chronic migraine or episodic migraine indicate similarity in effects between these population groups. AUC and Cmax were generally higher in female patients compared to male patients. The overall range of exposures in male subjects was higher than in female subjects. The impact of age on fremanezumab exposure was evident with increasing body weight across the quartiles.

CONCLUSIONS
A 1-compartment model with first-order absorption and elimination and weight effect on CL and V/F adequately described the fremanezumab pharmacokinetics.

Higher weight was associated with increased clearance, and weight/height reduced the volume of distribution.

Age, BMI, gender, creatinine clearance, race, and sex as well as acute and chronic medication use were also tested as covariates and not found to be statistically significant predictors of variability in PK.

There is no indication of reduced exposure to fremanezumab in patients with positive ADA status.

The model-based estimate of half-life is approximately 31 days (independent of dose or dose regimen).

Based on simulation, steady state is expected to be achieved by approximately 168 days for monthly and quarterly doses.

The use of a starting dose of 675 mg followed by 225 mg monthly resulted in achievement of plasma concentrations of 675 mg every 3 months or 675 mg once quarterly

The median accumulation ratio, based on once-monthly and once-quarterly clinically relevant dosing regimens, is approximately 2.34 and 1.20, respectively.

Figure 2. Population Pharmacokinetic Model for Fremanezumab

Figure 3. Predicted Median and 95th Percentile Concentration-time Profiles Phase 12032 Fremanezumab Population Pharmacokinetic Model Overlaid with the Phase 12032 Data and Median

Figure 4. Comparison of Simulated Median Concentration Versus Time Profiles by Dosing Regimen

Figure 5. Simulated Concentration-Time Profiles for the Doses Used in the Phase 3 Clinical Trials Administered Over 12 Months

Figure 6. Comparison of Simulated Median Concentration Versus Time Profiles by Dosing Regimen

Figure 7. Summary of Accumulation Ratios: 225 mg Monthly Dosing Regimen

Table 1. Parameter Estimates and Standard Errors for Fremanezumab Pooling Phase 12032 Final Pharmacokinetic Models Including TY112-15C-03501

Table 2. Summary of Accumulation Ratios: 225 mg Once Monthly

Table 3. Summary of Accumulation Ratios: 675 mg Once Quarterly