ORIGINAL ARTICLE

PRP | ASPET | BRITISH PHARMACOLOGICAL SOCIETY

Population pharmacokinetic and exposure-response analysis of eptinezumab in the treatment of episodic and chronic migraine

Brian Baker[1] | Barbara Schaeffler[1] | Martin Beliveau[2] | Igor Rubets[2] | Susan Pederson[1] | MyMy Trinh[2] | Jeff Smith[1] | John Latham[1]

[1]Lundbeck Seattle BioPharmaceuticals, Bothell, WA, USA

[2]Certara Strategic Consulting, Montreal, Canada

Correspondence
Brian Baker, Lundbeck Seattle BioPharmaceuticals, 11804 North Creek Parkway South, Bothell, WA 98011, USA.
Email: brak@lundbeck.com

Abstract

Eptinezumab is a humanized mAb that targets calcitonin gene-related peptide and is under regulatory review for the prevention of episodic and chronic migraine (EM, CM). It is important to determine whether exposures achieved with intravenous (IV) administration of eptinezumab achieve desired pharmacologic effects. Population pharmacokinetics, including dose- and exposure-response analyses, were performed using patient-level data from the eptinezumab clinical trial program with IV doses ranging from 10 to 1000 mg in pharmacokinetic analyses or 10 to 300 mg in phase 2/3 clinical studies in patients with EM or CM. Exposure-response analysis explored the relationship between eptinezumab exposure metrics and efficacy parameters including monthly migraine days. The pharmacokinetic profile of eptinezumab was characterized by rapid attainment of maximum plasma concentration (ie, end of IV administration) and a terminal half-life of 27 days. Covariate analysis found that patient characteristics had no clinically significant effects on pharmacokinetic parameters and were insufficient to influence dosing. Dose- and exposure-response analyses found exposure with single doses ≥100 mg was associated with greater efficacy compared with doses ≤30 mg and a plateau of effect between 100 and 300 mg. A saturable inhibitory E_{max} model found the exposure over 12 weeks produced by single-dose eptinezumab 100 and 300 mg exceeded the exposure estimates required to achieve 90% of the maximal efficacy (EC_{90}). This pharmacokinetic analysis of eptinezumab supports dosing every 12 weeks with no adjustment for patient characteristics, including exposures associated with 100- or 300-mg doses producing optimal efficacy effects. The similar efficacy profiles support 100 mg as the lowest effective dose of eptinezumab.

KEYWORDS
calcitonin gene-related peptide, CGRP, drug dose-response relationship, eptinezumab, intravenous administration, migraine disorders, monoclonal antibody, pharmacokinetics

1 | INTRODUCTION

Migraine is a highly prevalent neurological disorder that is associated with substantial clinical and socioeconomic impact.[1] Calcitonin gene-related peptide (CGRP) is a neuropeptide, with two major forms (α and β), that is widely distributed in nociceptive pathways in the central and peripheral nervous systems and plays a key role in the signaling pathways involved in the pathophysiology of migraine.[2-4] Thus, CGRP and one of the CGRP receptors in the calcitonin family have been targets of therapeutic interventions for the prevention of migraine.[4,5]

Population pharmacokinetic (PK) analyses guide drug development and inform recommendations on individualized treatment (eg, dose adjustments) by assessing the variability in PK of a drug in individuals of a population, as well as variability based on various characteristics of individuals.[6,7] Dose-response and exposure-response analyses further the understanding of drug effects by evaluating which dose and exposure levels are associated with efficacious benefit with the least risk of adverse effects.[6] Considering that migraine is a heterogeneous disorder,[8,9] it is valuable to assess whether a migraine-targeted therapy exhibits variability across individuals to appropriately individualize treatment for optimal outcomes.

Eptinezumab (ALD403) is a humanized anti-CGRP antibody with an IgG1 backbone that binds to both the α and β forms of CGRP and is currently under development for migraine prevention. In controlled clinical studies, it has demonstrated efficacy compared to placebo in the prevention of migraine in patients with episodic migraine (EM) and chronic migraine (CM).[10-14] This report describes a population PK modeling analysis conducted for the IV administration of eptinezumab at single doses of 10-1000 mg in healthy subjects and in patients with EM and CM from eight studies in the eptinezumab clinical program.[11-13] A further goal was

to assess the dose- and exposure-response relationships of selected endpoints in patients with EM and CM who received eptinezumab.

2 | MATERIALS AND METHODS

2.1 | Study population

The eight studies with available PK and pharmacodynamic (PD) data are listed in Table 1. All eight studies were included in the population PK analysis and included a total of 2123 patients and healthy volunteers who received eptinezumab. The PK dataset included only PK information related to IV administration of eptinezumab over approximately 30 minutes to 1 hour at dose levels of 10-1000 mg in healthy subjects and in patients with EM and CM. The concentrations of free eptinezumab were measured in plasma from all eptinezumab-treated patients using validated methods. Three clinical studies (CLIN-005, CLIN-006, and CLIN-011), involving 2543 patients who received eptinezumab at doses ranging from 10 to 300 mg or placebo, provided efficacy data for the exposure-response analysis. This exposure-response analysis population is larger than the PK population because it included patients who received placebo.

2.2 | Population pharmacokinetics

2.2.1 | Model

The current population PK analysis was based on the recommendations provided in key guidance documents from the US Food and Drug

TABLE 1 Pharmacokinetic and exposure-response analyses population

| Study | Design | IV Duration | Eptinezumab dose (mg) | | | | | | | | Overall |
			0	1	3	10	30	100	300	1000	
PK population											
CLIN-001	P1, SAD, HV	1 hour	N/A	4	6	5	6	6	20	6	53
CLIN-002	P1b, SD, FEM	1 hour	N/A	N/A	N/A	N/A	N/A	N/A	N/A	81	81
CLIN-005	P2, SD, CM	1 hour	N/A	N/A	N/A	125	119	121	119	N/A	484
CLIN-006	P3, MD, FEM	1 hour	N/A	N/A	N/A	N/A	211	216	219	N/A	646
CLIN-010	P1, SD, HO/O	1 hour	N/A	N/A	N/A	N/A	N/A	16	N/A	N/A	16
CLIN-011	P3, MD CM	1 hour	N/A	N/A	N/A	N/A	N/A	354	349	N/A	703
CLIN-012	P1, SD, T1DM	1 hour	N/A	N/A	N/A	N/A	N/A	14	N/A	N/A	14
CLIN-013	P3, MD, CM	30 minutes	N/A	N/A	N/A	N/A	N/A	N/A	126	N/A	126
Overall			N/A	4	6	130	336	727	833	87	2123
Exposure-response analyses population (primary endpoint weeks 1–12)											
CLIN-005	P2, SD, CM	1 hour	122	N/A	N/A	125	119	121	119	N/A	606
CLIN-006	P3, MD FEM	1 hour	222	N/A	N/A	N/A	211	216	219	N/A	868
CLIN-011	P3, MD CM	1 hour	366	N/A	N/A	N/A	N/A	354	349	N/A	1069
Overall			710	0	0	125	330	691	687	N/A	2549

Abbreviations: CM, chronic migraine; FEM, frequent episodic migraine; HO/O, healthy overweight/obese; HV, healthy volunteers; MD, multiple dose; N/A, not applicable; P, phase; SAD, single ascending dose; SD, single dose; T1DM, type 1 diabetes mellitus.

Administration (FDA) and European Medicines Agency (EMA).[6,7] The population PK modeling process used a nonlinear mixed-effects approach as described in Section 3b of the FDA guidance.[7] The population PK analysis was performed using Phoenix® NLME™ 8.0 (nonlinear mixed-effects modeling [NLME]) (Certara USA, Inc) with First-Order Conditional Estimation - Extended Least Squares (FOCE-ELS) and used the INTERACTION option. FOCE involves optimization of marginal log likelihood(s) using a series of iterations. The population PK model consisted of the following: (a) a description of the relationships between plasma concentration and time; (b) a variance component characterizing inter-individual variability and, if required, inter-occasion variability in model parameters; and (c) modeling of residual unexplained variability using additive, proportional, or additive and proportional models.

Figure 1 illustrates the methodology used in the population PK analyses. A two-compartment model was used as a starting point, although other models were also investigated (one- and three-compartment models). The models had the following form:

$$C_{ij} = m(D_i, t_j, \Phi_i) \cdot (1 + \varepsilon_{p,ij}) + \varepsilon_{a,ij}$$

$$\Phi_I = (\Phi_{I1}, \dots, \Phi_{Ip})$$

where C_{ij} is the concentration level at the jth collection time t_j for subject i; m represents the set of equations that define the model; D_i represents dosing history for subject i; Φ_i is the vector of p PK parameters for subject i; and $\varepsilon_{p,ij}$ and $\varepsilon_{a,ij}$ are the proportional and additive random residual error terms, respectively, associated with j^{th} concentration for subject i.

2.2.2 | Covariate analysis

Intrinsic and extrinsic covariates influencing eptinezumab clearance (CL) and volume of distribution (V_D) were explored using the stepwise forward addition procedure ($\alpha = .05$) and backward elimination process ($\alpha = .01$), with a priori statistical significance criteria for the forward and backward search directions. The potential impacts upon eptinezumab exposure by covariate effects in the final model were characterized using a forest plot to facilitate optimal understanding of covariate effects (as per FDA requirements).[15] The following intrinsic and extrinsic covariates were considered: demographics (age, body weight, sex, race, disease status [healthy subjects vs episodic or chronic migraine patients]), dose, baseline number of migraine days, immunogenicity (presence of anti-drug antibodies [ADAs] and neutralizing antibodies [NAbs]), and concomitant preventive headache/migraine medications (ie, beta-blockers, topiramate, valproate, tricyclic antidepressants).
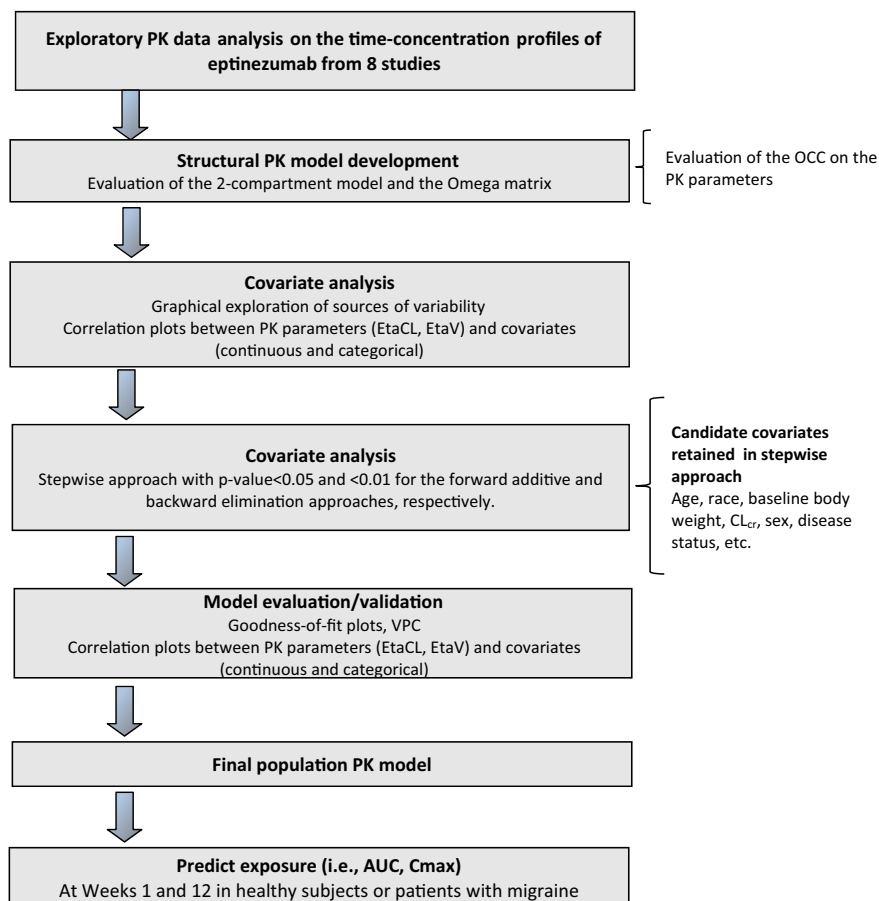

FIGURE 1 Overview of population pharmacokinetic (PK) model development of eptinezumab

2.2.3 | Model validation/qualification

Model validation/qualification was performed according to FDA and EMA guidance for industry.[6,16] The quality-of-fit was evaluated using a standard model discrimination process including statistical criteria such as maximum likelihood objective function (MOF) as well as pertinent graphical representations of goodness-of-fit (eg, fitted and observed concentrations vs time, conditional weighted residuals).[17] Diagnostic plots were derived, including (a) Observed data (DV) vs population predicted data (PRED) and individual predicted data (IPRED) with a line of unity and a locally weighted scatter plot smoothing (LOESS) line; (b) DV vs time after first administration (time) and DV vs TAD with LOESS lines for IPRED and PRED; (c) Conditional weighted residuals (CWRES) vs PRED, vs TAD and vs time; (d) Individual concentration-time profiles for all subjects comparing observed concentrations, the individual prediction line, and the population prediction line; (e) Quantile-quantile plot of CWRES (QQ plot); and (f) Individual weighted residuals (IWRES) vs IPRED, vs TAD and vs time. Based on the estimates of the final population PK model, concentration-time profiles of eptinezumab were simulated (~1000 replicates). The medians, as well as 5th and 95th percentiles, of the simulated concentrations were computed with their respective 90th percentile intervals.

2.2.4 | Dose- and exposure-response modeling

Dose-response relationships were explored prior to performing exposure-response analysis. The primary dose-response analysis was for the change in monthly migraine days (MMD) over weeks 1-12. PK parameters from the final population PK model were used to derive exposure metrics: area under the curve from time 0 to 12 weeks (AUC_{0-12wk}), maximum concentration (C_{max}), average concentration (C_{avg}), and trough concentration (C_{trough}). The exposure-response relationship of plasma eptinezumab was evaluated using these single-dose exposure parameters and the change in frequency of MMD (weeks 1-12) from studies CLIN-005, CLIN-006, and CLIN-011.[11-13] A saturable inhibitory maximum-effect (E_{max}) model was used to assess relationships between the exposure metrics of eptinezumab and the reduction in MMD. An example for AUC_{0-12wk} is as follows:

$E0 + I_{max} \times AUC/(AUC_{50} + AUC)$ where $E0$ is the predicted effect when AUC = 0 (ie, placebo effect), I_{max} is the maximum inhibitory effect, and AUC_{50} is the AUC achieving the half-maximal change in effect and AUC is the area under the concentration-time curve for eptinezumab.

A placebo-anchored approach was used because this method was shown to be more statistically powerful than a simple placebo-corrected analysis for use in dose-response analyses.[18]

Key secondary efficacy endpoints were also assessed in the exposure-response analysis. These endpoints included ≥75% migraine responder rates (weeks 1-4), ≥75% migraine responder rate (weeks 1-12), and ≥50% migraine responder rates (weeks 1-12). A logistic regression analysis was performed to explore associations between

eptinezumab exposures (ie, AUC_{0-12wk}, C_{avg}, C_{trough}, C_{max}) and these categorical endpoints.

# 3 | RESULTS

3.1 | Patients/subjects

A total of 2123 patients and subjects from eight clinical studies who received eptinezumab were included in the population PK analysis. The number of patients/subjects receiving each dose of eptinezumab included in the PK and exposure-response populations from each study is summarized in Table 1. Patients/subjects were primarily female (83.8%), white (88.5%), and ADA-negative (83.8%) at baseline, with a median age of 39.0 years (18-71 years) and a body weight of 74.2 kg (39.2-190 kg). Renal function was normal in 55.3% of patients/subjects, with mild or moderate decreases in estimated glomerular filtration rate (eGFR) in 41.9% and 2.7% of patients/subjects, respectively. The average MMD during the screening period of studies CLIN-005, CLIN-006, and CLIN-011[11-13] was approximately 14 days (CLIN-005, 16.5 MMD; CLIN-006, 8.7 MMD; CLIN-011, 16.1 MMD).

3.2 | Population pharmacokinetics

The concentration-time profile of eptinezumab following IV dosing was adequately characterized by a two-compartment model with linear elimination. Population and individual predicted concentrations of eptinezumab from the final model suggest reasonable agreement with the observed data with high and low concentration values evenly distributed around the line of identity. Additionally, conditional weighted residuals values (ie, CWRES vs predicted concentration or time) are homogeneously distributed around 0 with only a small proportion of points exceeding ±4. Goodness-of-fit plots derived with the final population PK model of eptinezumab are presented in Figure 2. The visual predictive check (VPC) of eptinezumab concentrations is presented in Figure 3. Observed median and upper/lower 90th percentiles of observed eptinezumab concentrations were contained within the model-predicted ranges (shaded areas). These results confirm the adequacy of the final population PK model in predicting eptinezumab concentrations.

A stepwise covariate analysis was performed to identify sources of variability in PK parameters of eptinezumab. Consistent with the pharmacokinetics that are typical for monoclonal antibodies (mAbs),[19] CL and the central volume of distribution (Vc) of eptinezumab were 0.00620 L h^{-1} (0.15 L day^{-1}) and 3.64 L, respectively. The C_{max} for eptinezumab was 37.3 µg mL^{-1} following a single IV administration of 100 mg and 114 µg mL^{-1} after a single dose of 300 mg. The median time to C_{max} (T_{max}) was 30 minutes for a 30-minute IV administration and 60 minutes for a 60-minute IV administration (ie, immediately after the completion of the IV delivery). The elimination

FIGURE 2 Goodness-of-fit for final model of eptinezumab
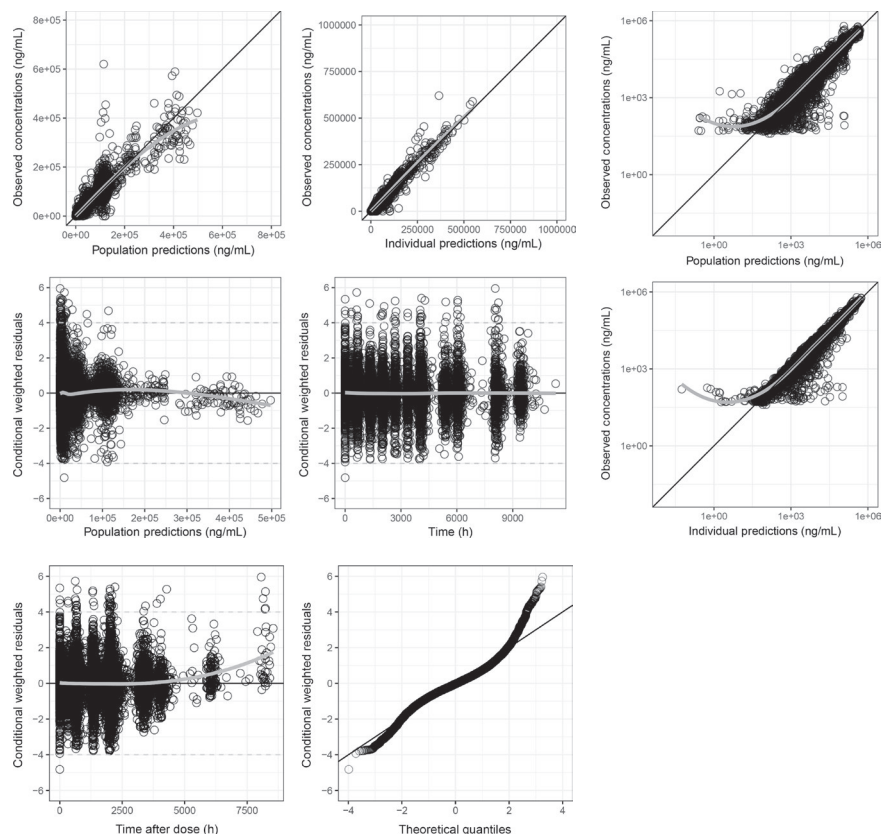
half-lives of eptinezumab associated with the α and β phases were 0.93 and 27 days, respectively. All parameters were estimated with the population PK model since relative standard error (RSE) values were less than 20%. Between-subject variability was 29% for CL and 31% for Vc. In addition, the residual variability of the model (ie, the sum of all variability not explained by the model) was 37.5 ng mL^{-1} (RSE = 5.7%).

Body weight, creatinine clearance (CL$_{cr}$, capped at a physiological value of 150 mL min^{-1}), disease state (healthy, EM, CM), and baseline migraine days were the most important covariates describing the variability of eptinezumab CL; the covariates of age, sex, race, dose, immunogenicity (presence of ADAs and NAbs), and concomitant preventive headache/migraine dropped out during covariate selection for eptinezumab CL. Body weight, disease state (healthy, EM, CM), and sex were the covariates describing the variability of Vc for eptinezumab; the covariates of age, body weight, race, dose, baseline migraine days, immunogenicity (presence of ADAs and NAbs), and concomitant preventive headache/migraine dropped out during covariate selection for eptinezumab Vc. The effect of covariates in the final model is illustrated in Figure 4. Body weight was the covariate with the greatest influence on AUC$_{0-\tau}$, and the final PK model included an allometric function of body weight on clearance. Overall, the presence of ADAs or NAbs were not important covariates describing the variability of eptinezumab PK parameters and were not retained as a covariate in the eptinezumab PK model during the covariate analysis. The 95% confidence intervals for the median ratios were generally contained within 0.8-1.20 (Figure 4). As such, the effect of most covariates was within 20% of healthy, with

the exception of disease state, as well as the minimum and maximum values of body weights of the population used in the population PK analyses (ie, 39 and 190 kg, respectively).

Extreme body weights of 39 and 190 kg, as well as patients with EM or CM are therefore expected to show eptinezumab exposure levels that are statistically lower/higher compared to the typical healthy adult. However, there has not been a safety issue identified with higher eptinezumab exposure. Therefore, higher AUC is not expected to be associated with a safety issue. Moreover, a steep dose-response curve was observed (Figure 5A). There was a plateau of effect for exposures associated with doses >100 mg, whereas the second quartile of AUC$_{0-12wk}$ (corresponding to ~30-mg doses of eptinezumab) showed similar probability of response. Thus, assuming a clinical dose of 100 mg, a reduction of 50% in AUC is not expected to have a large impact on the efficacy of eptinezumab. Finally, there was negligible difference in eptinezumab exposure ratios for patients with chronic migraine vs patients with episodic migraine, as well as negligible differences in the dose-response curves when split by disease state (Figure 5B). PK parameters derived from the population PK model of eptinezumab after single and multiple doses are presented in Tables 2 and 3, respectively.

3.3 | Dose- and exposure-response analyses

The eptinezumab dose-response relationship for change in the frequency of MMD (primary endpoint) over weeks 1-12 is illustrated in Figure 6. As seen in the figure, the treatment benefit is
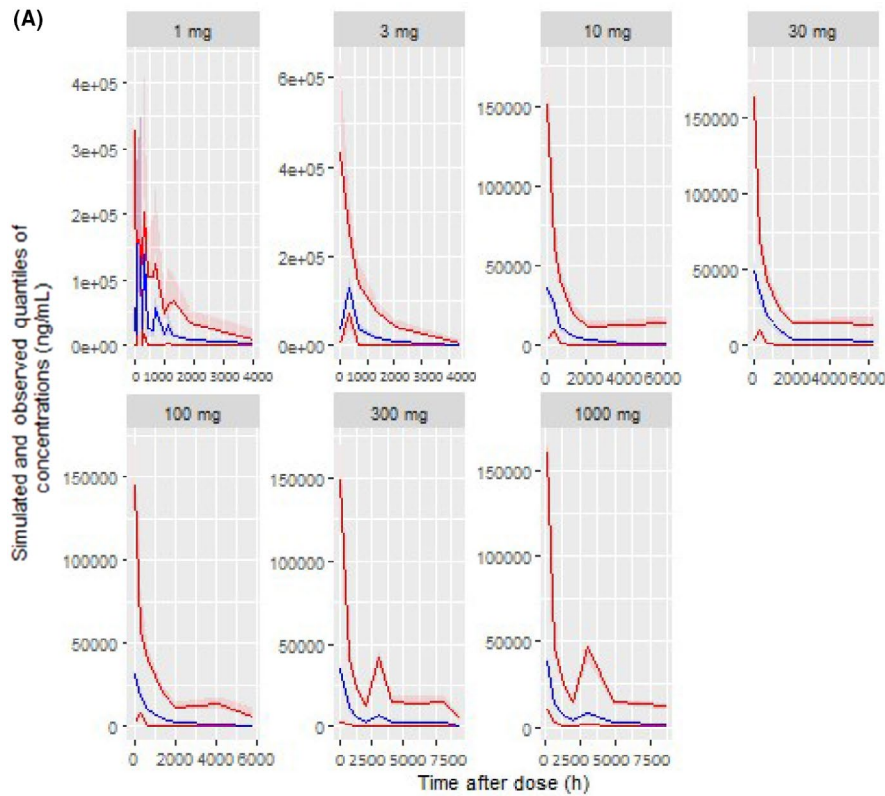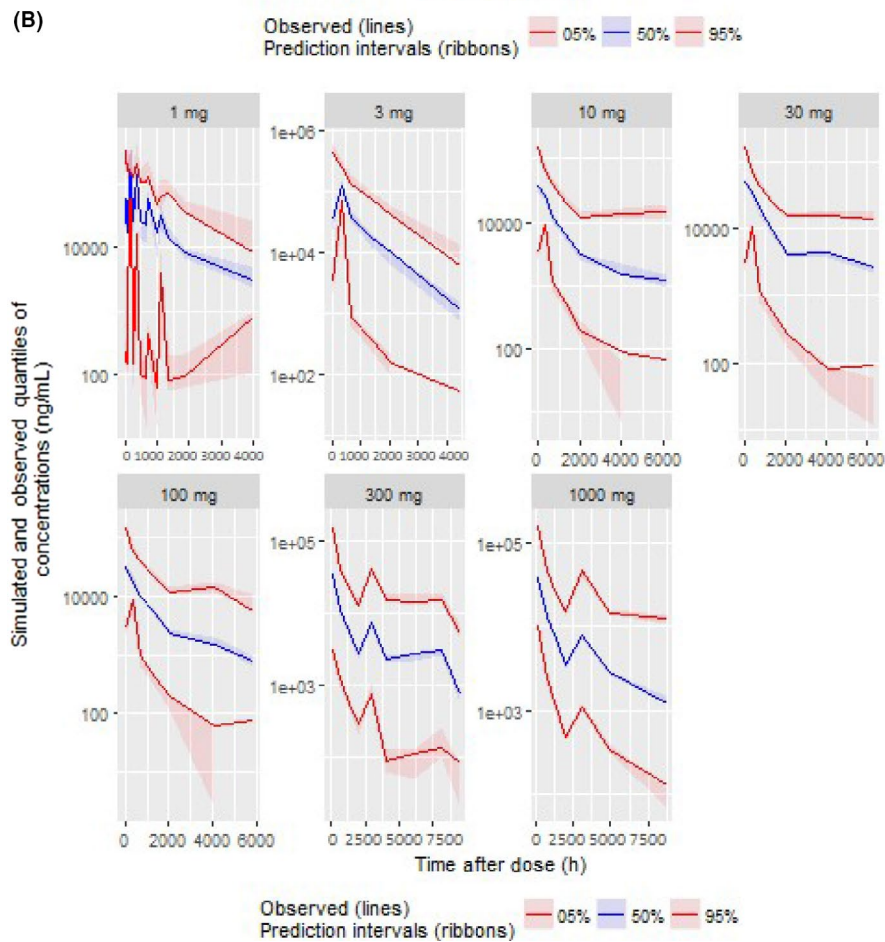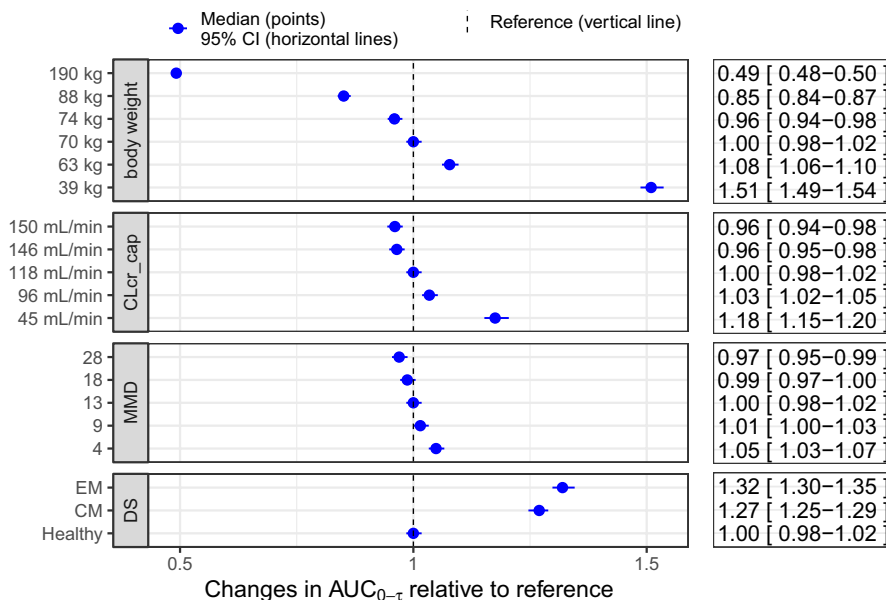
FIGURE 3 Visual predictive check by study: (A) linear plots and (B) semi-log plots

FIGURE 4 Geometric mean ratios (90% CI) for the effect of covariates on eptinezumab exposure at steady state ($AUC_{0-\tau}$). For the continuous covariates (baseline MMD [MDBASE], body weight and CL_{or_cap}) the minimum, 25th quantile, median, 75th quantile, and maximum values of the population are presented on the y-axis. In addition, the typical body weight for an adult male (70 kg) was presented for the continuous covariate of body weight. On the right, the changes in exposure to eptinezumab are presented as median ratios and associated 95% confidence intervals. The dotted vertical line marks the $AUC_{0-\tau}$ for a typical patient (healthy female subject, weight = 70 kg; CL_{or_cap} = 118 mL min^{-1}, baseline MMD of 13 days). The effects of "test" covariates are presented relative to the aforementioned reference $AUC_{0-\tau}$. $AUC_{0-\tau}$, area under concentration-time curve during a dosing interval (12 weeks) at steady state; CL_{or_cap}, creatinine clearance capped at a physiological value of 150 mL min^{-1}; CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days
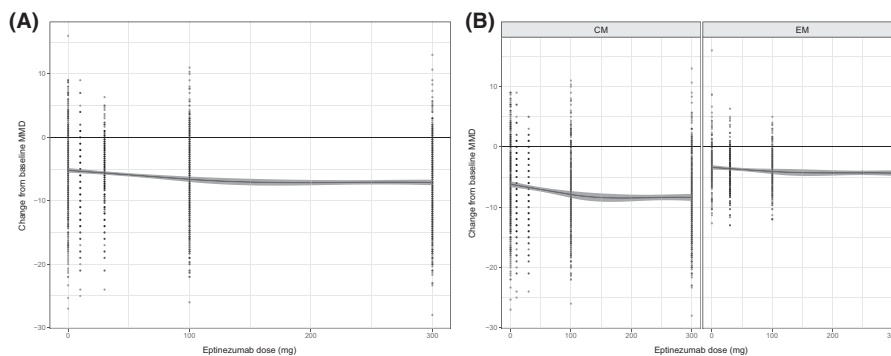
FIGURE 5 Overall dose-response relationship (A) and dose-response relationship by disease status (chronic migraine vs episodic migraine; B). The solid lines with gray shaded area are smooth (loess) regression and 95% confidence interval. CM, chronic migraine; EM, episodic migraine; MMD, monthly migraine days

most pronounced at dose levels 100 mg and higher. Overall, the dose-response curves for patients with CM (studies CLIN-005 and CLIN-011) were similar to curves for patients with EM (study CLIN-006), although the slope of the curve was somewhat steeper for patients with CM vs those with EM (Figure 3B). Doses of 100 mg or greater were generally associated with greater reductions in migraine days from baseline for both EM and CM. Figure 6 illustrates the exposure-response relationship for AUC_{0-12wk}. An AUC_{0-12wk} of 15 000 h·μg mL^{-1} or higher tended to produce a sustained decrease in migraine days compared with baseline. This exposure corresponds to the average AUC_{0-12wk} after administration of a 100-mg IV dose

of eptinezumab. Similar decreases in the number of migraine days were observed for increasing C_{max}, C_{avg}, and C_{trough} (data not shown).

Table 4 summarizes the results of the saturable inhibitory E_{max} model used to assess the relationship between eptinezumab exposure metrics and change in the frequency of MMD over weeks 1-12. Treatment with single doses of eptinezumab 100 or 300 mg provided exposures (AUC_{0-12wk}, C_{max}, C_{avg}, and C_{trough}) that exceeded the amount required to achieve 90% of the maximal efficacy (EC_{90}) estimates for patients with either EM or CM. In contrast, doses of 30 mg or lower provided exposures that were below EC_{90} estimates for patients with either EM or CM.

TABLE 2 Pharmacokinetic parameters of eptinezumab following a 30-minute to 1-hour IV administration (single dose)

PK parameter	Eptinezumab dose (mg)						
	1 (n = 4)	3 (n = 6)	10 (n = 130)	30 (n = 336)	100 (n = 727)	300 (n = 833)	1000 (n = 87)
AUC_{0-12wk}, mean (CV%), h·µg mL^{-1}	158 (57.9)	251 (24.4)	2050 (47.3)	5770 (41.1)	17 900 (29.0)	54 500 (27.7)	164 000 (24.0)
C_{max}, mean (CV%), µg mL^{-1}	0.279 (59.0)	0.460 (29.7)	4.32 (56.8)	12.4 (38.6)	37.3 (28.1)	114 (27.7)	348 (22.4)
C_{avg}, mean (CV%), µg mL^{-1}	0.0785 (57.9)	0.124 (24.4)	1.02 (47.3)	2.87 (41.2)	8.95 (29.3)	27.2 (27.8)	81.3 (24.0)
C_{trough}, mean (CV%), µg mL^{-1}	0.0232 (60.2)	0.0333 (18.8)	0.294 (50.6)	0.821 (55.4)	2.66 (46.1)	8.06 (42.4)	23.3 (34.7)

Note: A total of 5 patients/subjects received IV administrations over approximately 2 hours.
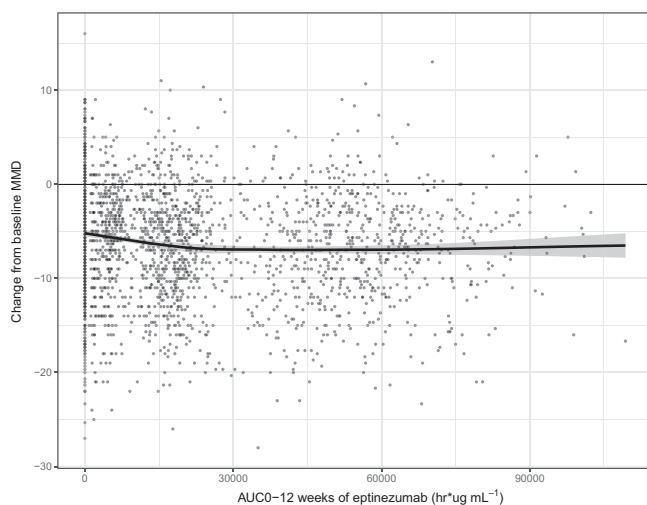
Abbreviations: AUC_{0-12wk}, area under the concentration-time curve from time zero to 12 weeks; C_{avg}, average concentration; C_{max}, maximum concentration; C_{trough}, concentration observed at the end of the dosing interval (12 weeks); CV%, coefficient of variation.

TABLE 3 Pharmacokinetic parameters of eptinezumab following a 30-minute to 1-hour IV administration (steady state)

PK parameter	Eptinezumab dose (mg)						
	1 (n = 4)	3 (n = 6)	10 (n = 130)	30 (n = 336)	100 (n = 727)	300 (n = 833)	1000 (n = 87)
$AUC_{0-\tau}$, mean (CV%), h·µg mL^{-1}	183 (60.0)	282 (23.0)	2350 (47.5)	6640 (43.3)	20 800 (32.1)	63 100 (30.1)	187 000 (25.4)
$C_{ss,avg}$, mean (CV%), µg mL^{-1}	0.0910 (60.0)	0.140 (23.0)	1.17 (47.5)	3.29 (43.3)	10.3 (32.1)	31.1 (30.1)	93.0 (25.4)
$R_{ac}(AUC_\tau)$, mean (CV%)	1.15 (1.9)	1.13 (3.3)	1.14 (4.0)	1.14 (6.6)	1.15 (7.7)	1.15 (6.3)	1.14 (3.8)
$R_{ac}(C_{max})$, mean (CV%)	1.10 (0.68)	1.09 (2.8)	1.08 (2.4)	1.08 (2.9)	1.08 (3.7)	1.08 (3.2)	1.08 (2.1)

Note: A total of five patients/subjects received IV administrations over approximately 2 hours. Steady state was achieved after the second dose.

Abbreviations: $AUC_{0-\tau}$, area under concentration-time curve during a dosing interval (12 weeks) at steady state; $C_{ss,avg}$, average steady-state drug concentration during a dosing interval; CV%, coefficient of variation; $R_{ac}(AUC_\tau)$, accumulation ratio based on AUC_τ; $R_{ac}(C_{max})$, accumulation ratio based on C_{max}.

FIGURE 6 Exposure-response relationship over weeks 1-12. The solid line with gray shaded area is smooth (loess) regression and 95% confidence interval. AUC_{0-12wk}, area under the concentration-time curve from time zero to 12 weeks; MMD, monthly migraine days

The exposure-response analysis for secondary endpoints supports the results of the primary endpoint analysis (Figure 7). This included analyses of the relationship between eptinezumab exposure (AUC_{0-12wk}) and various categorical endpoints (ie, ≥75% migraine responder rate [weeks 1-4], ≥75% migraine responder rate [weeks 1-12], and ≥50% migraine responder rate [weeks 1-12]; Figure 7A-C). Overall, there was a statistically significant effect of eptinezumab exposure and these endpoints ($P < .05$ for all three comparisons). In particular, the third quartile of AUC_{0-12wk} (corresponding to an ~100-mg dose of eptinezumab) appeared to show a higher probability of response for all secondary endpoints, compared to the first and second quartiles of AUC_{0-12wk} (corresponding to ~10 and 30-mg doses of eptinezumab, respectively). There was a plateau of effect for exposures associated with doses >100 mg.

4 | DISCUSSION

Monoclonal antibodies targeted against the CGRP ligand or receptor represent a mechanism-based approach to therapy that specifically

TABLE 4 Inhibitory E_{max} model-derived parameters: PK/PD exposure correlation of change in frequency of mean migraine days at weeks 1-12 vs eptinezumab exposure parameters after a single dose

Eptinezumab exposure metric	Disease state	EC_{50} (CV%)	EC_{90}[a]	Mean (CV%) PK parameters following a single dose		
				30 mg	100 mg	300 mg
AUC_{0-12wk}, h·µg mL^{-1}	CM	1480 (85.6)	13 300	5770 (41.1)	17 900 (29.0)	54 500 (27.7)
	EM	1190 (225.7)	10 700			
C_{max}, µg mL^{-1}	CM	3.78 (84.0)	34.0	12.4 (38.6)	37.3 (28.1)	114 (27.7)
	EM	2.54 (228.4)	22.8			
C_{trough}, µg mL^{-1}	CM	0.109 (105.6)	0.983	0.821 (55.4)	2.66 (46.1)	8.06 (42.4)
	EM	0.183 (187.7)	1.65			
C_{avg}, ng mL^{-1}	CM	745 (85.7)	6710	2870 (41.2)	8950 (29.3)	27 200 (27.8)
	EM	585 (227.3)	5260			

Abbreviations: AUC_{0-12wk}, area under the concentration-time curve from time zero to 12 weeks; C_{avg}, average concentration; CM, chronic migraine; C_{max}, maximum concentration; C_{trough}, concentration observed at the end of the dosing interval (12 weeks); CV%, coefficient of variation; EC_{50}, concentration achieving the half-maximal change in effect; EC_{90}, concentration achieving 90% of the maximum change in effect; EM, episodic migraine; E_{max}, maximum inhibitory effect; PD, pharmacodynamic; PK, pharmacokinetic.

[a]Predicted from the EC_{50} fitted from the inhibitory E_{max} model.
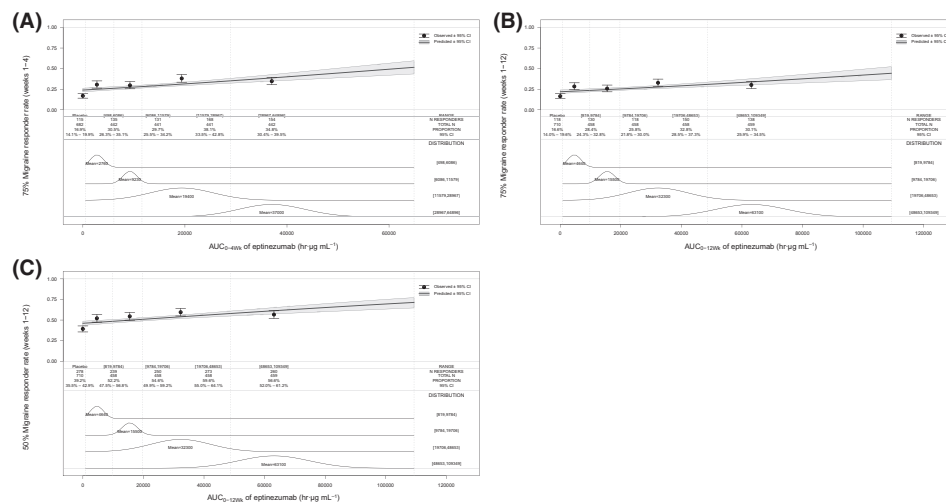
FIGURE 7 Exposure-response relationship for secondary endpoints. (A) ≥75% migraine responder rate (weeks 1-4) vs AUC_{0-4wk}; (B) ≥75% migraine responder rate (weeks 1-12) vs AUC_{0-12wk}; and (C) ≥50% migraine responder rate (weeks 1-12) vs AUC_{0-12wk}. For each quartile of eptinezumab exposure: Range, the minimum and maximum values; N responder, total number of subjects with a response; Total N, total number of subjects in each quartile of eptinezumab exposure; Proportion, N responder/Total N For each quartile of eptinezumab exposure: the minimum and maximum values are presented next to the distribution of exposure for each quartile of eptinezumab exposure. (A) Slope [95% confidence interval]: 0.428 [0.28922, 0.56589], $P < .0001$. (B) Slope [95% confidence interval]: 0.35367 [0.22059, 0.48675]; $P < .0001$. (C) Slope [95% confidence interval]: 0.36708 [0.2429, 0.4912]; $P < .0001$

targets the initiation and transmission of migraine.[4,20] There are currently three mAbs that inhibit CGRP biology (erenumab, fremanezumab, and galcanezumab) approved for prevention of migraine in the United States, with eptinezumab currently under regulatory review. Differences exist between these mAbs in pharmacokinetics and in binding characteristics that have the potential to influence efficacy and tolerability.[21-24] These pharmacologic differences likely explain the dosing regimens of the available agents. Some agents require a loading dose (ie, galcanezumab) and some are administered monthly (ie, galcanezumab, erenumab) rather than every 12 weeks.[25-29] Fremanezumab can be administered either monthly

or quarterly, with the quarterly dosing requiring three separate injections.[30]

Eptinezumab was designed to provide rapid and sustained efficacy due to the targeting of the soluble CGRP ligand with high selectivity and affinity paired with a IV route of administration every 12 weeks.[14] Overall, the concentration-time profile of eptinezumab was adequately characterized by a two-compartment model. Consistent with other mAbs, eptinezumab has linear elimination characteristics (CL = 0.15 L day^{-1}) and a small Vc (3.64 L).[19] The most important covariates describing the variability of eptinezumab CL were body weight, renal function, disease state (healthy, EM,

CM), and baseline MMDs, whereas the most important covariates describing the variability of V_c were body weight, disease, and sex. Although these effects are noted, the relatively small changes in CL and V_c do not suggest that dosage adjustments are necessary. These findings are in line with other mAbs that inhibit the CGRP biology (ie, galcanezumab, fremanezumab, erenumab) for which these patient characteristics do not produce clinically meaningful changes in any PK parameters.[31]

The population PK model indicates that eptinezumab doses of 100 mg produce mean C_{max} and AUC_{0-12wk} values of >37 µg mL^{-1} and >17 000 h·µg mL^{-1}, respectively, with a terminal elimination half-life of 27 days. As anticipated for the IV route of administration, eptinezumab had a short T_{max} of 30 to 60 minutes, which corresponded with the end of the IV delivery. This rapid achievement of C_{max} may provide a pharmacokinetic explanation for the rapid onset of effect observed in clinical trials.[12,13] The short T_{max} values for eptinezumab are in contrast to the longer median values for single doses of erenumab (4-11 days),[23] fremanezumab (5-11 days),[21] and galcanezumab (7-14 days),[22] which are administered subcutaneously. Delivery by the subcutaneous route of administration requires time for absorption, a process that is also associated with a loss of active drug or reduced bioavailability.[32] Due to these issues, subcutaneous administration can lead to the need to administer higher doses, more frequent administration, or a combination of both in order to achieve and maintain therapeutic exposure.

The exposure-response analysis demonstrated a trend toward increased efficacy with increased exposure. Exposure following the administration of eptinezumab 30 mg or less was insufficient to meet the EC_{90} estimates for change in the frequency of MMD. Furthermore, although the number of patients evaluated that received 30 mg was lower (n = 330) than the number receiving 100 mg (n = 691) or 300 mg (n = 687), measures of efficacy from the model (EC_{50} for AUC_{0-12wk} exposures) suggested that doses greater than 30 mg would be required to achieve a plateau for statistically reducing the number of migraine days over weeks 1-12. As eptinezumab doses increased to 100 mg, there was an increased probability of a reduction in the frequency of MMD over weeks 1-12, with a plateau of effect as the dose was further increased to 300 mg. This similar efficacy between the 100-mg and 300-mg doses supports the notion of a lowest effective dose of 100 mg.

In general, an AUC_{0-12wk} of 15 000 h·µg mL^{-1} or higher tended to produce a sustained decrease in migraine days compared to baseline. Notably, this level is below the average AUC_{0-12wk} produced by a single 100-mg dose (ie, 17 900 h·µg mL^{-1}). In the inhibitory E_{max} model, the relationship between the change in frequency of MMD over weeks 1-12 vs key metrics of exposure revealed that treatment with a single 100-mg or 300-mg dose of eptinezumab provided exposures (AUC_{0-12wk}, C_{max}, C_{trough}, or C_{avg}) that exceeded all EC_{90} estimates for the EM and CM groups. In contrast, the exposure values produced by the eptinezumab 30-mg dose or lower were below EC_{90} values for both EM and CM. The results of the exposure-response analysis for secondary endpoints reinforced the less robust response at the 30-mg dose level and the presence of a plateau effect between 100 and 300 mg. This suggests that doses of 100 and 300 mg would result in similar efficacy.

A similar exposure-response analysis conducted with the anti-CGRP mAb galcanezumab that used a lower threshold for efficacy (EC_{50}) revealed that the EC_{50} related to the rate of dissipation of migraine headache days per month was achieved only at some dose levels and only for a portion of the dosing interval.[33] In data from the FDA drug-approval package, the population PK estimated EC_{50} for galcanezumab was 43.9 µg mL^{-1}, a level that is achieved only via 240-mg monthly dosing and only for approximately half of the dosing interval (as measured by the median concentration).[33] This finding may have clinical relevance because it suggests that patients may not be achieving drug concentrations adequate to prevent migraines for significant portions of the dosing interval. Exposure-response information for erenumab provided in the FDA drug-approval package indicated that an estimated plasma concentration of 5.1 µg mL was required to achieve the EC_{50} for reduction in the probability of MMD in EM patients.[34] No patients receiving a 70-mg dose of erenumab reached EC_{50} exposure levels on the first day of dosing, and 64% achieved EC_{50} exposure levels within the first week of administration.[34] For fremanezumab, the maximal fractional reduction in MMD was described by an E_{max} function with only plasma concentration over the dosing interval, C_{avg}, provided as an exposure metric. The average concentration required to achieve the EC_{50} was estimated to be 3.6 µg mL^{-1}.[35] The less than optimal exposure-response results associated with these anti-CGRP agents may be at least partially explained by the PK profiles associated with their subcutaneous administration, which results in a longer time to T_{max} and incomplete bioavailability. This contrasts with the high binding affinity and IV administration of eptinezumab, which has 100% bioavailability and a T_{max} at the end of the IV administration, resulting in faster and robust achievement of therapeutically effective concentrations.

5 | CONCLUSIONS

This population PK and exposure-response analysis demonstrates that eptinezumab exhibits linear pharmacokinetics, with C_{max} achieved at the end of the IV administration (T_{max}). The relatively low exposure metrics required to achieve EC_{90} and half-life of 27 days support less frequent, every 12 weeks, IV administration with 100 mg or greater. The relatively small change in clearance associated with patient-related factors (eg, body weight), the absence of dose-limiting toxicity, and the relatively flat exposure response at doses of 100-300 mg support that there is no need for dose adjustments for patient-related factors. There was increased efficacy for both the primary and secondary endpoints with increased exposure of eptinezumab followed by a plateau of effect. The 100-mg and 300-mg doses provide exposures that exceed the EC_{90} estimates

for AUC_{0-12wk}, C_{max}, C_{avg}, and C_{trough} in both EM and CM patients. These data demonstrate that eptinezumab 100 mg, administered every 12 weeks, is an appropriate dosing regimen for patients with episodic or chronic migraine.

ACKNOWLEDGEMENTS

DISCLOSURES

BB, BS, SP, and JS are full-time employees of Lundbeck Seattle BioPharmaceuticals. MB, IR, and MT have nothing to disclose. Within the past year, JS or an immediate family member held stock or stock options greater than 5% of the company or greater than $10 000 in value in Alder BioPharmaceuticals (now a part of H. Lundbeck A/S). JL and JS were full-time employees of Alder BioPharmaceuticals (now known as Lundbeck Seattle BioPharmaceuticals) at the time of study.

AUTHORS' CONTRIBUTIONS

BB and JS: research design. BS: clinical trial management. MB, IR, and MT: conduct and reporting of population pharmacokinetics and exposure-response analyses. SP and JL: management of bioanalysis activities. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content, approved the final manuscript, and take responsibility for the integrity of the data and accuracy of the data analysis.

REFERENCES

1. Deen M, Correnti E, Kamm K, et al. Blocking CGRP in migraine patients - a review of pros and cons. *J Headache Pain*. 2017;18:96.
2. Schou WS, Ashina S, Amin FM, Goadsby PJ, Ashina M. Calcitonin gene-related peptide and pain: a systematic review. *J Headache Pain*. 2017;18:34.
3. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev*. 2014;94:1099-1142.
4. Raffaelli B, Reuter U. The biology of monoclonal antibodies: focus on calcitonin gene-related peptide for prophylactic migraine therapy. *Neurotherapeutics*. 2018;15:324-335.
5. Schuster NM, Rapoport AM. Calcitonin gene-related peptide-targeted therapies for migraine and cluster headache: a review. *Clin Neuropharmacol*. 2017;40:169-174.
6. EMA. Guideline on reporting the results of population pharmacokinetic analyses. Committee for Medicinal Products for Human Use (CHMP), Doc. Ref. CHMP/EWP/185990/06. 2007. https://www.ema.europa.eu/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf. Accessed January 16, 2019.
7. FDA. Guidance for industry population pharmacokinetics. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). 1999. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM072137.pdf. Accessed January 16, 2019.
8. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2018;17:954-976.
9. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) study and American Migraine Prevalence and Prevention (AMPP) study: demographics and headache-related disability. *Headache*. 2016;56:1280-1289.
10. Dodick DW, Goadsby PJ, Silberstein SD, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *Lancet Neurol*. 2014;13:1100-1107.
11. Dodick DW, Lipton RB, Silberstein S, et al. Eptinezumab for prevention of chronic migraine: a randomized phase 2b clinical trial. *Cephalalgia*. 2019;39:1075-1085.
12. Ashina M, Saper J, Cady R, et al. 2020. Eptinezumab in episodic migraine: the randomized, double-blind, placebo-controlled PROMISE-1 study, in press.
13. Lipton RB, Goadsby PJ, Smith J, et al. 2020. PROMISE-2: efficacy and safety of eptinezumab in patients with chronic migraine, in press.
14. Baker B, Schaeffler B, Cady R, et al. Rational design of a monoclonal antibody (mAB) inhibiting calcitonin gene-related peptide (CGRP), ALD403, intended for the prevention of migraine. *Neurology*. 2017;88: P2.155.
15. Menon-Andersen D, Yu B, Madabushi R, et al. Essential pharmacokinetic information for drug dosage decisions: a concise visual presentation in the drug label. *Clin Pharmacol Ther*. 2011;90:471-474.
16. FDA. Guidance for industry. Exposure-response relationships - study design, data analysis, and regulatory applications. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf. Accessed January 15, 2019.
17. Nguyen THT, Mouksassi M-S, Holford N, et al. Model evaluation of continuous data pharmacometric models: metrics and graphics. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:87-109.
18. Liu J, Jadhav P, Wang Y, Gobburu J. Improper selection of a pre-specified primary dose-response analysis delays regulatory drug approval. *AAPS J*. 2013;15:407-414.
19. Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:576-588.
20. Tso AR, Goadsby PJ. Anti-CGRP monoclonal antibodies: the next era of migraine prevention? *Curr Treat Options Neurol*. 2017;19:27.
21. Cohen-Barak O, Weiss S, Rasamoelisolo M, et al. A phase 1 study to assess the pharmacokinetics, safety, and tolerability of fremanezumab doses (225 mg, 675 mg and 900 mg) in Japanese and Caucasian healthy subjects. *Cephalalgia*. 2018;38:1960-1971.
22. Monteith D, Collins EC, Vandermeulen C, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of the CGRP binding monoclonal antibody LY2951742 (galcanezumab) in healthy volunteers. *Front Pharmacol*. 2017;8:740.
23. de Hoon J, Van Hecken A, Vandermeulen C, et al. Phase I, randomized, double-blind, placebo-controlled, single-dose, and multiple-dose studies of erenumab in healthy subjects and patients with migraine. *Clin Pharmacol Ther*. 2018;103:815-825.
24. Vu T, Ma P, Chen JS, et al. Pharmacokinetic-pharmacodynamic relationship of erenumab (AMG 334) and capsaicin-induced

dermal blood flow in healthy and migraine subjects. *Pharm Res.* 2017;34:1784-1795.

25. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia.* 2018;38:1026-1037.

26. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med.* 2017;377:2123-2132.

27. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim B-K, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia.* 2018;38:1442-1454.

28. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. *Neurology.* 2018;91:e2211-e2221.

29. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet.* 2018;392:2280-2287.

30. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. *JAMA.* 2018;319:1999-2008.

31. Kielbasa W, Helton DL. A new era for migraine: pharmacokinetic and pharmacodynamic insights into monoclonal antibodies with a focus on galcanezumab, an anti-CGRP antibody. *Cephalalgia.* 2019;39:1284-1297.

32. Richter WF, Jacobsen B. Subcutaneous absorption of biotherapeutics: knowns and unknowns. *Drug Metab Dispos.* 2014;42:1881-1889.

33. FDA. Drug approval package: Emgality (galcanezumab-gnlm). Pharmacology review(s). https://www.accessdata.fda.gov/drugs atfda_docs/nda/2018/761063Orig1s000ClinPharmR.pdf. Accessed January 16, 2019.

34. CDER Clinical Pharmacology review 761077Orig1s000 - Erenumab. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761077Orig1s000ClinPharmR.pdf. Accessed May 17, 2019.

35. CDER Clinical Pharmacology review 761089Orig1s000 - fremanezumab. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761089Orig1s000ClinPharmR.pdf. Accessed May 20, 2019.