

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761089Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review
(Addendum to OCP Review, DARRTS date 03/23/18)

BLA#	BLA - 761089
Submission Date	October 16, 2017
Submission Type	505(b)(1) Application (Priority review)
Major Amendment Date	May 14, 2018
Proposed Brand Name	AJOVY®
Generic Name	Fremanezumab (TEV 48125)
Dosage Form and Strength	Single-dose prefilled syringe for subcutaneous (SC) injection 225 mg/1.5 ml (150 mg/ml)
Proposed Indication	Migraine (Episodic/Chronic) Prophylaxis
Applicant	Teva Branded Pharmaceuticals Products R & D, Inc.
Associated IND	IND 106533
OCP Review Team	Hristina Dimova Ph.D., Gopichand Gottipati Ph.D., Kevin Krudys Ph.D., Sreedharan Sabarinath Ph.D.

BACKGROUND

The Office of Clinical Pharmacology (OCP) reviewed the information submitted in Biologic License Application (BLA) 761089 (DARRTS date 03/23/18) and recommended the approval of 225 mg once monthly and 675 mg once every 3 months (quarterly) dosing regimens for the prevention of chronic and episodic migraine (CM & EM respectively), provided there were no safety concerns with these regimens. Additionally, the OCP review team noted that some patients may benefit from a loading dose (675 mg) during the first month with the monthly dosing regimen. The primary evidence of safety and effectiveness was based on two pivotal, randomized, double-blind, placebo-controlled safety and efficacy studies, one each in EM and CM patients. The regimens studied in these pivotal trials include 225 mg once monthly regimen or 675 mg once quarterly regimen in EM patients; and 225 mg once monthly with a loading dose of 675 mg or 675 mg quarterly regimen in CM patients. Please refer to OCP review in DARRTS dated 3/23/2018 for details.

At the late-cycle meeting (LCM) with the applicant on 04/16/18, the agency noted (b) (4)

[Redacted]

[Redacted]

[Redacted]

(b) (4)

The applicant submitted a major amendment to BLA 761089 on 05/14/18, as a follow up to the LCM discussion outlined above, (b) (4)

:

(b) (4)

SUMMARY AND RECOMMENDATIONS

From a clinical pharmacology perspective, the applicant did not provide any new additional data or analyses in this major amendment. The population-PK model derived exposures and exposure-response analyses described above to support their position were reviewed previously. Please refer to the original review (DARRTS date 03/23/2018), in which the OCP review team addressed all these considerations and recommended the approval of the following dosing regimens to be administered subcutaneously using prefilled syringes for the prevention of episodic and chronic migraine:

- 225 mg monthly or
- 675 mg once every 3 months

Some patients may benefit from a loading dose of 675 mg during the first month of the monthly regimen. This was based on the observations from a pivotal study in CM patients.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Office of Clinical Pharmacology

Integrated Review

BLA Number	BLA-761089
<u>Link to EDR</u>	\\CDSESUB1\evsprod\BLA761089
Submission Date	October 16, 2017
Submission Type	505(b)(1) Application (Priority Review)
Brand Name	AJOVY®
Generic Name	Fremanezumab (TEV 48125)
Dosage Form and Strength	Single-dose prefilled syringe for subcutaneous (SC) Injection 225 mg/1.5 mL (150 mg/mL)
Route of Administration	Subcutaneous injection
Proposed Indication	Migraine (Episodic/Chronic) Prophylaxis
Applicant	Teva Branded Pharmaceuticals Products R&D, Inc.
Associated IND	IND-106533
OCP Review Team	Hristina Dimova, Ph.D., Gopichand Gottipati Ph.D., Kevin Krudys, Ph.D., Sreedharan Sabarinath, Ph.D.
OCP Final Signatory	Ramana Uppoor, Ph.D.

1. Executive Summary

In this original biologics license application (BLA), Teva Branded Pharmaceuticals Products R&D, Inc. is seeking approval for AJOVY® Fremanezumab (TEV 48125) for the prevention of chronic and episodic migraine in adults.

Fremanezumab is a fully humanized monoclonal antibody (b) (4) targeted against the calcitonin gene-related peptide (CGRP) receptor. Fremanezumab selectively binds to the CGRP ligand and blocks both α - and β -CGRP isoforms from binding to the CGRP receptor, preventing the activation of the trigeminal system. It is believed that trigeminal nociceptive tone may increase, resulting in migraine prophylaxis.

The Applicant is proposing the following dosing options for AJOVY®, to be administered subcutaneously (SC) using single-dose prefilled syringe(s) (PFS):

- 225 mg once monthly or 675 mg once every 3 months (quarterly).

(b) (4)

The Applicant is relying on two pivotal randomized, double-blind, placebo-controlled, phase 3 safety and efficacy studies, one each in patients with episodic migraine (EM) and chronic migraine (CM). The patients with CM in the pivotal trial (Study 30049) were defined as those with history of migraine (for ≥ 12 months) prior to screening and experiencing ≥ 15 headache days, with ≥ 8 migraine days with or without aura during the 28-day baseline (run-in) period. They received either monthly doses 675/225/225 mg or a quarterly dose of 675 mg administered subcutaneously.

The patients with EM in the pivotal trial (Study 30050) were defined as those with history of migraine (for ≥ 12 months) prior to screening and experiencing ≥ 6 and ≤ 14 headache days, with ≥ 4 migraine days with or without aura during the 28-day baseline (run-in) period and received either a quarterly dose of 675 mg or monthly doses of 225 mg administered subcutaneously.

The primary efficacy results from these studies showed that 225 mg once monthly and 675 mg once quarterly dosing regimens are safe and effective in reducing the baseline- and placebo-corrected monthly average number of headache days of at least moderate severity and monthly average number of migraine days during the 12-week treatment period for CM and EM respectively.

The primary focus of this review is the evaluation of the proposed dosing regimen using dose- and exposure-response relationships for efficacy and safety in chronic and episodic migraine.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in BLA 761089 and recommends approval of 225 mg once monthly and 675 mg once every 3 months (quarterly) dosing regimens for the prevention of chronic and episodic migraine in adults, provided there are no safety concerns with these regimens. Additionally, some patients may benefit from a loading dose of 675 mg during the first month with the monthly dosing regimen.

Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The evidence of effectiveness is from four placebo-controlled, randomized, double-blind, phase 2/3 efficacy and safety studies in subjects with chronic migraine (TV48125-CNS-30049 and LBR-101-021) and episodic migraine (TV48125-CNS-30050 and LBR-101-022).
General dosing instructions	The recommended dosing regimens to be administered subcutaneously using prefilled syringe(s) for the prevention of chronic and episodic migraine are: <ul style="list-style-type: none">• 225 mg once monthly or• 675 mg once every 3 months (quarterly) <div style="background-color: #cccccc; height: 20px; width: 100%; text-align: right; font-size: small;">(b) (4)</div>
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are needed.
Bridge between the “to-be-marketed” and clinical trial formulations	The to-be-marketed product is the same as the clinical trial presentation/formulation.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 The Pharmacology and Clinical Pharmacokinetics

Mechanism of Action:

Fremanezumab is a fully humanized monoclonal antibody

(b) (4)

 targeted against the calcitonin gene-related peptide (CGRP) receptor. CGRP is a 37-amino acid

neuropeptide that is a potent vasodilator and is widely distributed throughout the central and peripheral nervous systems. The CGRP is a well-validated target in the pathophysiology of migraine. Fremanezumab binds the CGRP ligand and blocks both CGRP isoforms (α - and β -CGRP) from binding to the CGRP receptor, therefore preventing the activation of the trigeminal-vascular system, resulting in the prevention/relief of migraine headache.

Absorption:

After single subcutaneous (SC) administrations of 225 mg, 675 mg, and 900 mg fremanezumab, the median time to maximum concentrations (t_{max}) was 5 to 7 days.

Distribution:

The mean steady state volume of distribution was estimated to be 6.3 L, suggesting minimal distribution to the extravascular tissues.

Metabolism and Excretion:

Fremanezumab exhibits linear pharmacokinetics, the exposures are approximately dose proportional in the range of 225 – 900 mg. Fremanezumab is degraded by enzymatic proteolysis into small peptides and amino acids. Due to its large molecular size, renal excretion of intact fremanezumab is unlikely.

Elimination:

The mean terminal elimination half-life of fremanezumab is approximately 31 days,

Specific Populations:

- No dedicated clinical studies were conducted to evaluate the effect of renal or hepatic impairment on the PK of fremanezumab. Renal or hepatic impairment is unlikely to affect the pharmacokinetics of fremanezumab.
- Fremanezumab exposures were similar in Japanese and Caucasian subjects.
- Population pharmacokinetic analyses did not reveal a clinically significant impact of age, gender, and BMI on the exposures of fremanezumab.
- AJOVY has not been studied in pediatric patients.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing regimens are 225 mg once monthly or 675 mg once every 3 months (quarterly), administered subcutaneously using PFS. Some patients may benefit from a loading dose of 675 mg during the first month of the monthly dosing regimen.

This recommendation is supported by the observed dose-efficacy and exposure-efficacy relationships for fremanezumab. The P2/3 studies indicated no apparent relationship with fremanezumab dose and efficacy in both EM and CM. The relationship with fremanezumab exposure and the primary efficacy measures (i.e., reduction in baseline- and placebo-adjusted (a) monthly average number of headache days of at least moderate severity in patients with chronic migraine and (b) monthly average number of migraine days in patients with episodic migraine) was shallow (See Sections 3.3.1 and 3.3.2)

2.2.2 Therapeutic individualization

No therapeutic individualization is necessary for extrinsic/intrinsic factors. Fremanezumab is to be administered by subcutaneous route, therefore food-drug interactions are not anticipated. In addition, its drug-drug interaction liability is considered low (See Section 3.3.4). No dedicated clinical studies were performed in subjects with renal or hepatic impairment; however, renal/hepatic impairment is not expected to significantly affect pharmacokinetics of fremanezumab.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- The recommended dosing regimens of AJOVY® are 225 mg monthly or 675 mg once every 3 months (quarterly) administered as subcutaneous injection(s) using single-use prefilled syringe(s). [REDACTED] (b) (4)
[REDACTED]
- No dose adjustment is necessary for patients based on intrinsic or extrinsic factors.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Currently, there are five FDA approved products for the prevention of migraine. These include beta-adrenergic blocking agents, e.g., propranolol (tablets and liquid) and timolol (tablets); antiepileptic drugs, e.g., divalproex sodium (tablets) and topiramate (tablets) and onabotulinumtoxin A (injectable).

Fremanezumab is a fully humanized monoclonal antibody [REDACTED] (b) (4) targeted against the calcitonin gene-related peptide (CGRP) receptor and is a second-in-class product for this indication. Currently, there are two other monoclonal antibody products that are submitted to the agency and are under review (erenumab and galcanezumab) [REDACTED] (b) (4) [REDACTED] for the same indication, targeting either CGRP ligand or CGRP receptor.

The fremanezumab clinical program consisted of 13 studies with healthy subjects and patients with CM and EM: 8 Phase 1 studies, 2 Phase 2b double-blind, placebo-controlled, safety and efficacy studies, and two Phase 3 double-blind, placebo-controlled safety and efficacy studies and 1 long-term safety study (which includes the extension arms of the pivotal phase 3 studies along with subjects enrolled additionally). The long-term safety study [REDACTED] (b) (4) [REDACTED] were ongoing at the time of the 31 May 2017 safety data cut-off date.

The key aspects of the four safety and efficacy P2/3 studies are summarized in the **Table 1** below.

Table 1 Summary of safety and efficacy studies in the clinical development program of Fremanezumab

Clinical Studies (Population, Size)	TV 48125-CNS-30049* (Chronic Migraine n=1130)	LBR-101-121^{&} (Chronic Migraine n=264)	TV 48125-CNS-30050[#] (Episodic Migraine n=875)	LBR-101-122[^] (Episodic Migraine n=297)
Primary efficacy endpoint	Monthly average number of headache days of at least moderate severity at month 3	Monthly average number of headache days of any severity at month 3	Monthly average number of migraine days at month 3	
Study Design	Randomized, Double-blind, Placebo-controlled, Safety and Efficacy Study			
Treatment(s)	675 mg once every 3 months (quarterly) 675/225/225 mg monthly	900 mg once every month 675/225/225 mg monthly	675 mg once every 3 months (quarterly) 225 mg once monthly	225 mg once monthly 675 mg once monthly
Study Extension	Additional 9 months (Study TV-48125-CNS-30051)	-	Additional 9 months (Study TV-48125-CNS-30051)	-

n: number of subjects randomized in the study;

**30049: CM: Patients with history of migraine (for ≥ 12 months) prior to screening and experienced ≥ 15 headache days, with ≥ 8 migraine days with or without aura during the 28-day baseline (run-in) period;*

[&]101-121: CM: Patients with history of headache on ≥ 15 days per month for at least 3 months and experienced ≥ 15 headache days, with ≥ 8 migraine days with aura during the 28-day baseline (run-in) period;[#]30050: EM: Patients with history of migraine (for ≥ 12 months) prior to screening and experienced ≥ 6 and ≤ 14 headache days, with ≥ 4 migraine days with or without aura during the 28-day baseline (run-in) period;

[^]101-122: EM: Patients with history of headaches on > 8 days per month for at least 3 months prior to screening, with ≥ 8 headache days (of any type) and a total of 8-14 migraine during the 28-day baseline (run-in) period. TV 48125-CNS-30049 in CM and TV 48125-CNS-30050 in EM are considered as pivotal studies

Source: Adapted based on Summary of Clinical Efficacy – Table 1 on pages 17-19

3.2 General Pharmacological and Pharmacokinetic Characteristics

The fremanezumab drug product has changed from an intravenous (IV) formulation in the early Phase 1 studies to a SC formulation in the last two Phase 1 studies (TV48125-PK-10078 and LBR-101-011) and the Phase 2/3 studies. The early Phase 1 studies (b) (4) are not considered supportive for this application due to bioanalytical assay issues (Please refer to Section 4.1 for details).

A summary of fremanezumab pharmacokinetic parameters from the studies in healthy subjects TV48125-PK-10078 is provided in **Table 2** below.

Table 2 Summary of Fremanezumab Pharmacokinetic Parameters after Single-Dose SC Administration of Fremanezumab to Healthy Subjects

Parameter (Units)	Fremanezumab Dose		
	225 mg (n = 16)	675 mg (n =16)	900 mg (n = 16)
C _{max} (µg/ml)	29.7 (13.7)	104.8 (28.8)	141.1 (32.0)
^T _{max} (day)	7	5	7
AUC _{0-28d} (h*mg/ml)	15.7 (14.3)	52.0 (26.5)	74.7 (31.2)
AUC _{0-84d} (h*mg/ml)	33.1 (14.7)	108.2 (27.4)	155.7 (24.6)
AUC _{0-inf} (h*mg/ml)	42.5 (17.5)	132.8 (31.7)	197.6 (26.0)
#T _{1/2} (day)	34.9 (11.5)	32.2 (21.5)	36.2 (17.1)

Adapted from Clinical Study Report Study TV48125-PK-10078 (Table 9 and page 71)

Note: All the reported values are geometric mean (%CV)

except: ^Median for T_{max} and #Mean for T_{1/2}

In addition, a comparison of fremanezumab PK in healthy subjects and subjects with migraine based on the phase 1 studies TV48125-PK-10078, LBR-101-011 and the population PK (popPK) analyses of the Phase 2/3 studies showed no apparent difference in PK parameters between the healthy subjects and subjects with migraine (**Table 3**).

Table 3 Summary of Clinical Pharmacology of Fremanezumab

Pharmacology	
Mechanism of Action	Fremanezumab is a fully humanized monoclonal antibody (b) (4) which binds the CGRP ligand. CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilation effect that has been associated with migraine pathophysiology.
General Information	
Healthy volunteers vs. patients	There was no apparent difference in PK parameters between the healthy subjects and subjects with migraine.
Dose proportionality	Approximately dose proportional over a dose range of 225 mg through 900 mg.
Accumulation	Median accumulation ratios were 2.3 and 1.2 with once-monthly and once-quarterly regimens, respectively for both C _{max} and AUC. Steady state exposure is expected to be achieved by approximately 168 days (about 5-6 months).
Immunogenicity	A total of 1888 patients have been tested for anti-drug antibody (ADA) as of 08 November 2017. Among those, 30 patients (1.6%) were identified to have treatment-emergent anti-fremanezumab antibody responses. Seventeen patients developed neutralizing antibodies against fremanezumab. Please refer to the review from Office of Biotechnology Products for additional details on immunogenicity assessments.
Absorption	
T _{max}	Median T _{max} 5 to 7 days
Distribution	
Volume of Distribution	6.3 L
Elimination	
Mean Terminal Elimination Half-life	Approximately 31 days
Metabolism / Excretion	Fremanezumab is degraded by enzymatic proteolysis into small peptides and amino acids.
Primary excretion pathways	Due to its large molecular size, renal excretion of intact fremanezumab is unlikely.

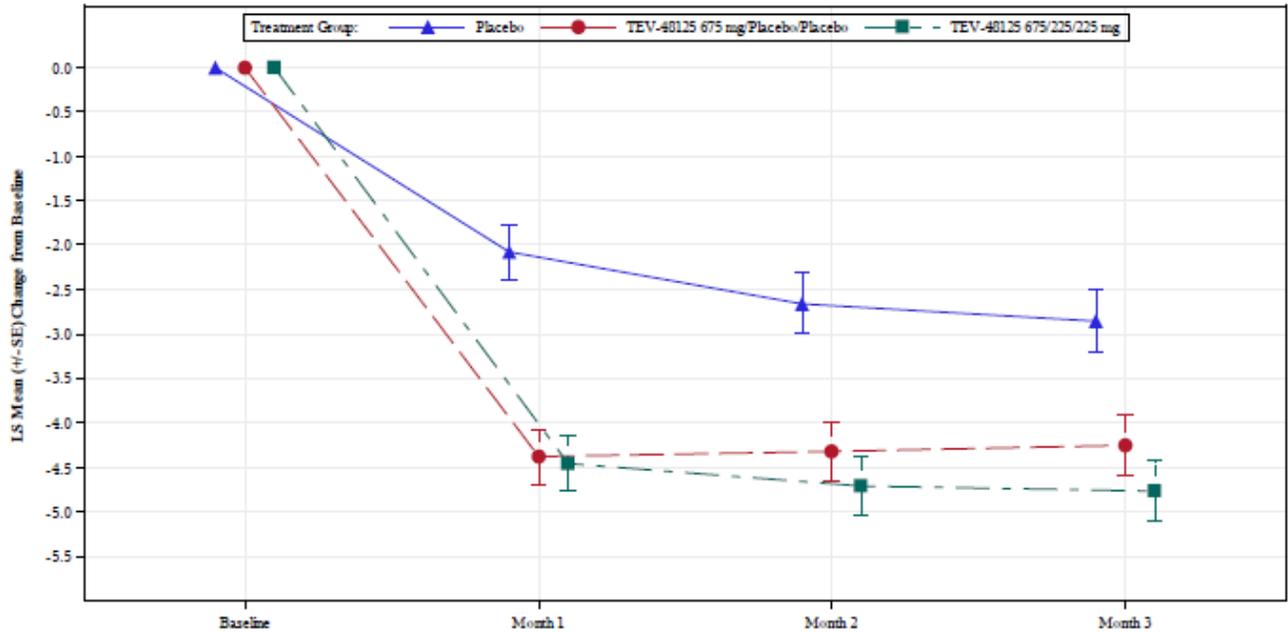
3.3 Clinical Pharmacology Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of fremanezumab in the prevention of chronic and episodic migraine is based on four placebo-controlled, randomized, double-blind, efficacy and safety studies (See **Table 1**). The mean baseline- and placebo-corrected reduction in the monthly average number of headache days of at least moderate severity favored fremanezumab in patients with chronic migraine in studies TV48125-CNS-30049 and LBR-101-021. Similarly, the mean baseline- and placebo-corrected reduction in the monthly average number of migraine days favored fremanezumab in patients with episodic migraine in studies TV48125-CNS-30050 and LBR-101-022. The shallow exposure-response relationship for efficacy in both chronic and episodic migraine indications were consistent with the observed (lack of) dose-response.

Study TV48125-CNS-30049 in patients with chronic migraine, consisted of a 4-week run-in (baseline) period, followed by a 12-week double-blind treatment period during which either monthly doses 675/225/225 mg or a quarterly dose of 675 mg were administered subcutaneously. The patients enrolled in the study had a history of migraine (for ≥ 12 months) prior to screening and experienced ≥ 15 headache days, with ≥ 8 migraine days with or without aura during the 28-day baseline (run-in) period. Both dosing regimens met the pre-specified statistical criteria for the mean reduction in monthly average number of headache days of at least moderate severity at end of week 12, relative to baseline over placebo, and no dose-response was observed at the tested dose levels (**Figure 1**).

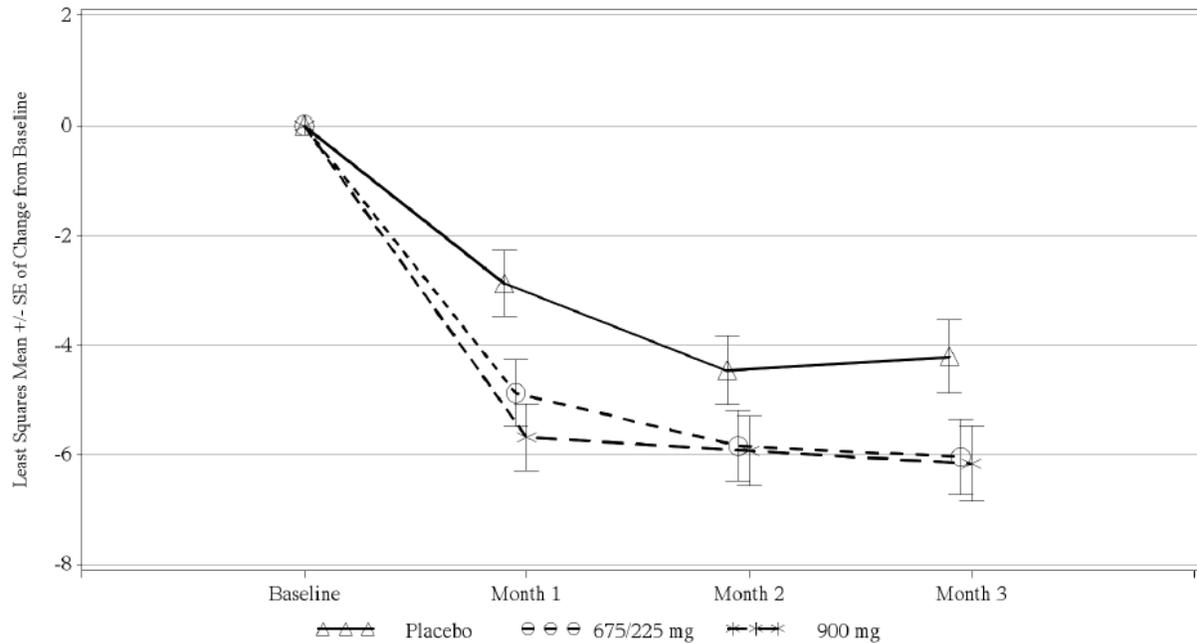
Figure 1 Least squares mean change from baseline in monthly number of headache days of at least moderate severity by month and treatment group for study TV48125-CNS-30049 in patients with chronic migraine (full analysis dataset)



Source: Clinical study report of TV48125-CNS-30049, Figure 4 on page 88

LBR-101-021 was a phase 2 study in patients with chronic migraine, identical in design to study TV48125-CNS-30049, but the dosing regimens administered during the double-blind treatment phase were either monthly doses of 675/225/225 mg or monthly doses of 900 mg, subcutaneously. The patients enrolled in the study had a history of headache on ≥ 15 days per month for at least 3 months and experienced ≥ 15 headache days per month, with ≥ 8 migraine days with aura during the 28-day baseline (run-in) period. Both dosing regimens were deemed effective in reducing the monthly average number of headache days of at least moderate severity at end of week 12, relative to baseline over placebo, and no dose-response was observed at the tested dose levels (**Figure 2**).

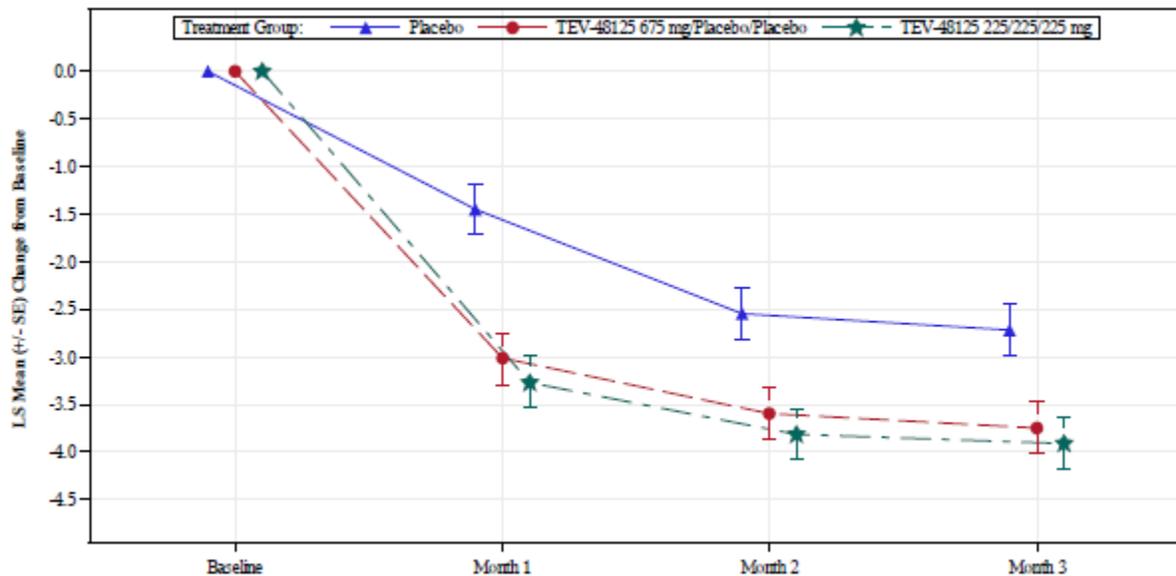
Figure 2 Least squares mean change from baseline in monthly number of headache days of at least moderate severity by month and treatment group for study LBR-101-021 in patients with chronic migraine (intent to treat dataset)



Source: Clinical study report of LBR-101-021, Figure 3 on page 71

Study TV48125-CNS-30050 in patients with episodic migraine had identical trial design as Study TV48125-CNS-30049 described above, but the dosing regimens during the double-blind treatment period were either quarterly doses of 675 mg or monthly doses of 225 mg administered subcutaneously. The patients enrolled in the study had a history of migraine (for ≥ 12 months) prior to screening and experienced ≥ 6 and ≤ 14 headache days, with ≥ 4 migraine days with or without aura during the 28-day baseline (run-in) period. Both dosing regimens met the pre-specified statistical criteria for the reduction in mean monthly average number of migraine days at end of week 12, relative to baseline over placebo, and no dose-response was observed at the tested dose levels (**Figure 3**).

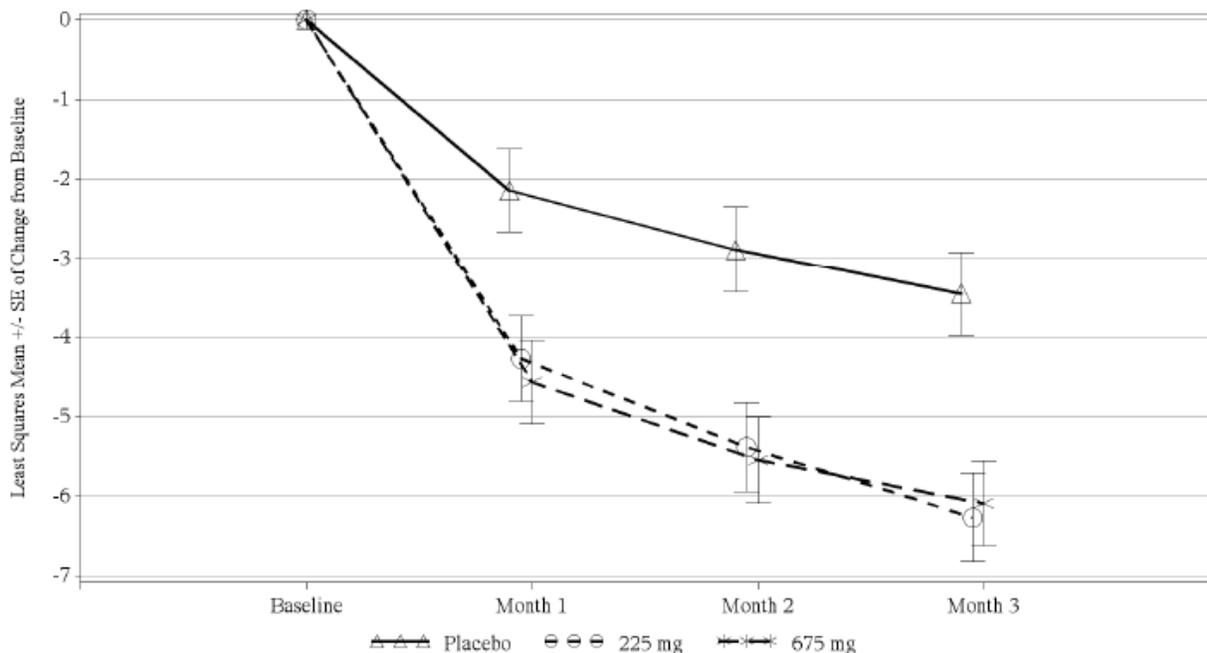
Figure 3 Least squares mean change from baseline in monthly number of migraine days by month and treatment group for study TV48125-CNS-30050 in patients with episodic migraine (full analysis dataset)



Source: Clinical study report of TV48125-CNS-30050, Figure 3 on page 71

LBR-101-022 is a phase 2 study in patients with episodic migraine, whose trial design and dosing regimens administered during the double-blind treatment phase were either 225 mg or 675 mg monthly. The patients enrolled in the study had a history of headaches on > 8 days per month for at least 3 months prior to screening, with ≥ 8 headache days (of any type) and a total of 8-14 migraine days during the 28-day baseline (run-in) period. Both dosing regimens met the pre-specified statistical criteria for the reduction in mean monthly average number of migraine days at end of week 12, relative to baseline over placebo, and no dose-response was observed at the test dose levels (**Figure 4**).

Figure 4 Least squares mean change from baseline in monthly number of migraine days by month and treatment group for study LBR-101-022 in patients with episodic migraine (full analysis dataset)



Source: Clinical study report of LBR-101-022, Figure 2 on page 62

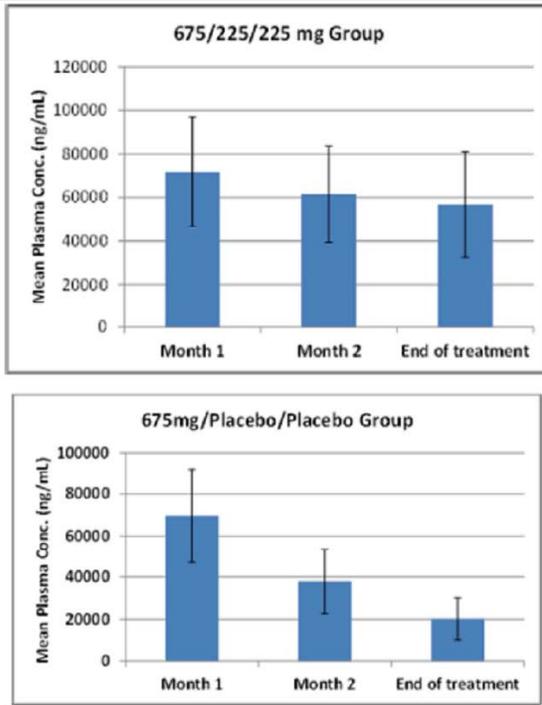
In the Phase 2 and 3 clinical studies, fremanezumab doses (225 mg and 675 mg) were administered subcutaneously into the abdomen, upper arm, and thigh; and the injection sites were generally not consistent for the same subject within visits. The mean observed trough plasma concentrations for the various dosing regimens as tested in these trials are shown in Figure 5 below.

Exposure-response (E-R) analyses using the average plasma concentrations of fremanezumab over the dosing interval (C_{av}) for each month and the mean reduction from baseline over placebo in (a) the monthly average number of headache days of at least moderate severity in chronic migraine, or (b) the monthly average migraine days in episodic migraine was conducted. The E-R analyses showed a shallow relationship between efficacy and fremanezumab concentrations (shown in Figure 6 and Figure 7 for CM and EM respectively) and were consistent with the observed (lack of) dose-response relationships. It should be noted that the E-R relationship shown in the figures is reflective of month 3 only, although the E-R analyses was conducted using all data (Please refer section 3.3.2 and 4.3.1 for more details).

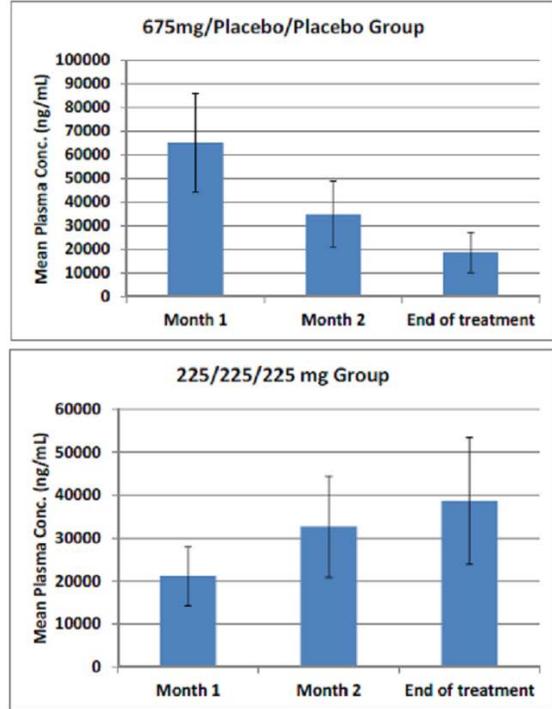
The efficacy results from the phase 2/3 trials are summarized in Table 4.

Figure 5 Mean observed trough plasma concentrations (ng/ml) in pivotal trials

Phase 3: TV48125-CNS-30049 (CM)

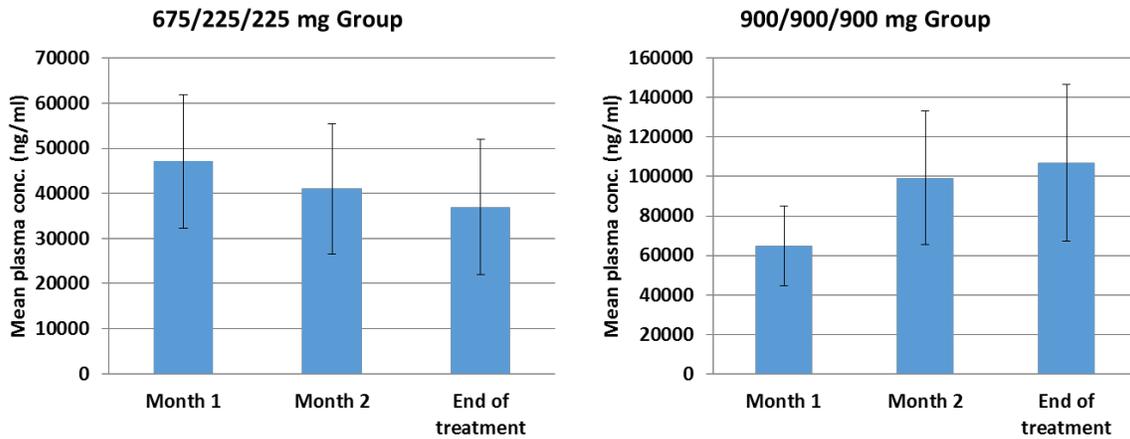


Phase 3: TV48125-CNS-30050 (EM)



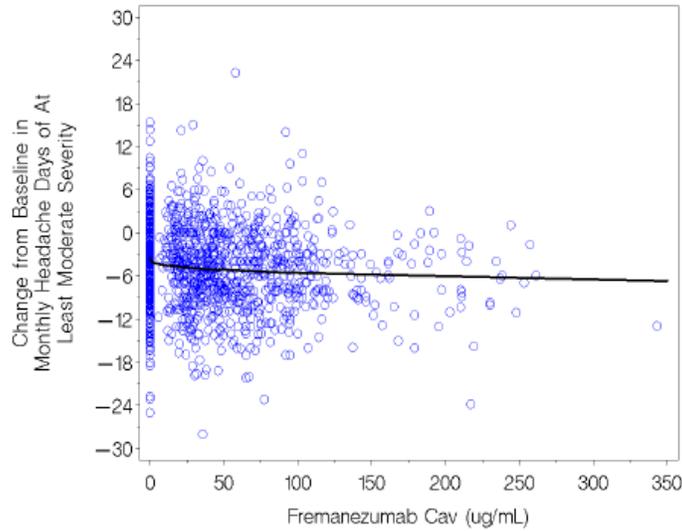
Source: Clinical study report for TV48125-CNS-30049 and TV48125-CNS-30050: Figure 18/page124 and Figure 19/page 118 respectively

Phase 2: LBR-101-021 (CM)



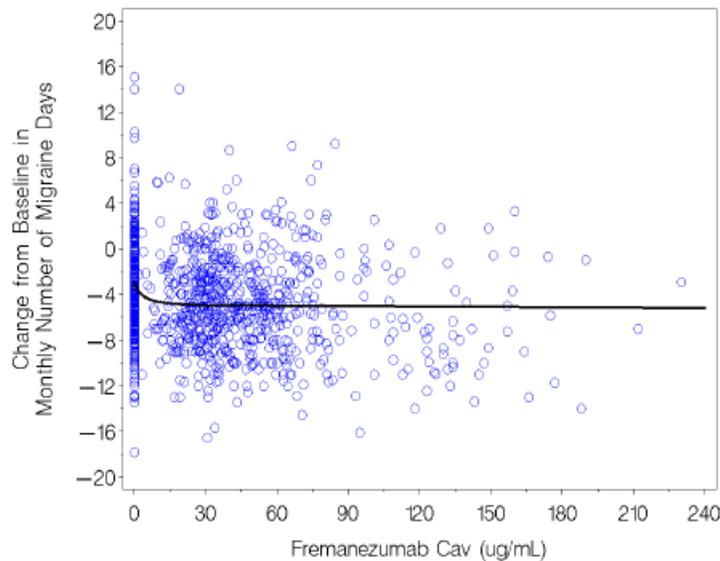
Source: Adapted from Clinical study report for LBR-101-021: Table 20 on page 93

Figure 6 Final model predicted change from baseline in monthly average number of headache days of at least moderate severity at month 3* versus fremanezumab C_{av} in chronic migraine



Source: Exposure-response analyses report (CP-17-06) Figure 32 on Page 150

Figure 7 Final model predicted change from baseline in monthly average number migraine days at month 3* versus fremanezumab C_{av} in episodic migraine



Source: Exposure-response analyses report (CP-17-06) Figure 17 on Page 134

Please note that the solid black line in both the plots reflects the final model predicted exposure-response relationship at month 3 only and is shown for representative purpose. Please see Appendix 4.3 for further details of the exposure-response analysis.

Table 4 Summary of the efficacy results from phase 2/3 studies

P3 Study TV48125-CNS-30049 (CM)			
	Placebo (N=371)	675 mg Quarterly (N=375)	675/225/225 mg Monthly (N=375)
Change from baseline monthly average # headache days of at least moderate severity at week 12	-2.5 (0.31)	-4.3 (0.31)	-4.6 (0.30)
Placebo-corrected		-1.8 (0.33)	-2.1 (0.33)
P2 Study LBR-101-021 (CM)			
	Placebo (N=89)	675/225/225 mg Monthly (N=87)	900 mg Monthly (N=85)
Change from baseline monthly average # headache days of at least moderate severity at week 12	-4.2 (0.67)	-6.0 (0.69)	-6.2 (0.69)
Placebo-corrected		-1.8 (0.87)	-2.0 (0.86)
P3 Study TV48125-CNS-30050 (EM)			
	Placebo (N=290)	675 mg Quarterly (N=288)	225 mg Monthly (N=287)
Change from baseline in # monthly migraine Days at week 12	-2.2 (0.24)	-3.4 (0.25)	-3.7 (0.25)
Placebo-corrected		-1.3 (0.27)	-1.5 (0.28)
P2 Study LBR-101-022 (EM)			
	Placebo (N=104)	225 mg Monthly (N=95)	675 mg Monthly (N=96)
Change from baseline in # monthly migraine Days at week 12	-3.5 (0.53)	-6.3 (0.55)	-6.1 (0.53)
Placebo-corrected		-2.8 (0.64)	-2.6 (0.64)

Source: Clinical study reports from respective studies: 30049: Table – 7, Page 84;

101-021: Table 11, Page 70; 30050: Table – 7, Page 78; 101-022: Table 6, Page 61.

Please refer to the statistics review by Dr. Sharon Yan and Dr. Kun Jin for further details

3.3.2 Is the proposed general dosing regimen appropriate for the general population for which the indication is being sought?

The Applicant is seeking approval of (b) (4) dosing options for the prevention of both chronic and episodic migraine:

- 675 mg once every 3 months (quarterly)
- 225 mg once monthly, and

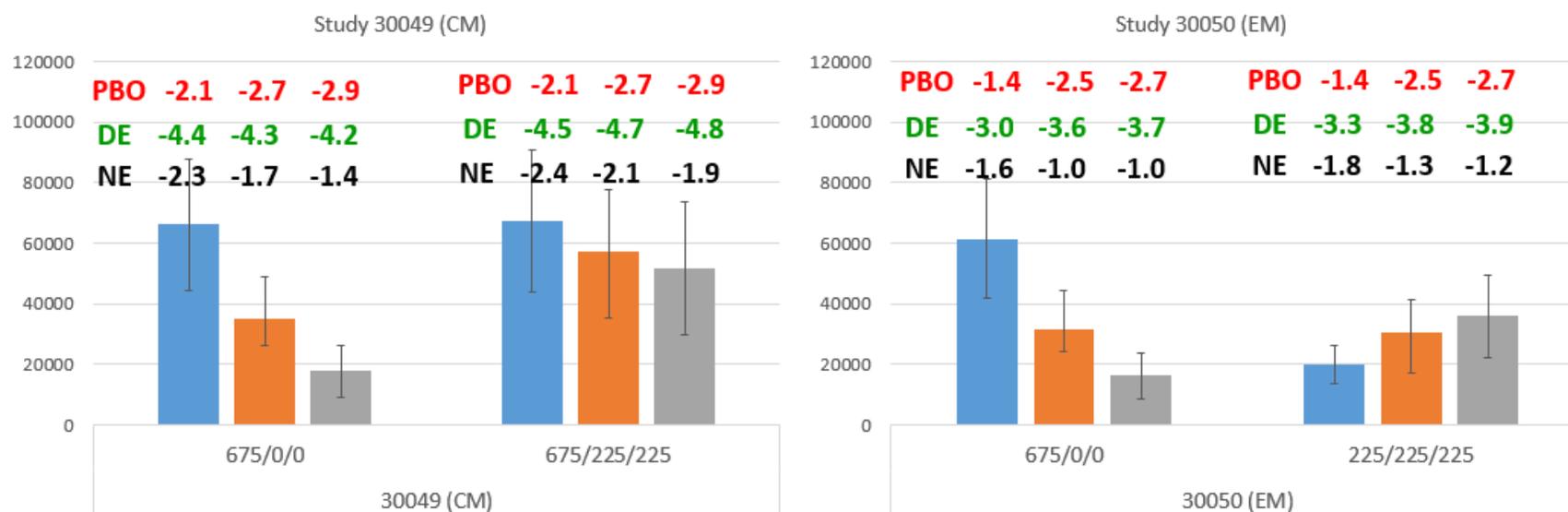
(b) (4)

The considerations for each of the dosing option are discussed in detail below:

Quarterly dosing regimen (675 mg)

The (675 mg) quarterly dosing regimen was tested in phase 2/3 trials in both CM and EM populations. Based on the efficacy results presented above, and assuming no potential safety concerns, the Office of Clinical Pharmacology review team considers this dosing regimen to be approvable. The mean change from the baseline in the primary efficacy endpoint in the placebo-and treatment arms at each monthly visit in the pivotal trials is shown in **Figure 8**. It can be noted from the figure for the quarterly dosing regimen that the time course of treatment response (in green), is either relatively consistent in chronic migraine (i.e., about 4.3 days) or improves slightly in episodic migraine (i.e., 3 to 3.7 days) at each monthly visit. These trends in the 675 mg quarterly regimen arm are indicative of the durability of the response in patients with both CM and EM during the dosing interval. Furthermore, given that the treatment response at every month was found to be statistically significant (please refer statistics review by Dr. Sharon Yan and Dr. Kun Jin for further details), and shallow exposure-response as discussed above, it is likely that the 675 mg quarterly regimen provides adequate levels of exposure to maintain efficacy throughout the dosing interval.

Figure 8: Summary of the geometric mean of observed trough plasma concentrations (ng/ml) and observed mean change from baseline in the primary efficacy endpoint results in the placebo and treatment arms.



Placebo response in red, Response in treatment arm in green and net placebo-corrected response in treatment arms in black.

The bars represent the mean observed plasma trough concentrations (ng/ml) at monthly visits –

Month 1 in blue, Month 2 in orange and Month 3 in grey.

Error bars reflect the standard deviation.

Source: Clinical study reports of study 30049: Table – 22 on page 123 & Summary 15.8.1.2 in pages 480-481;

Clinical study reports of study 30050: Table – 21 on page 117 & Summary 15.8.1.2 in pages 402-403

Monthly dosing regimen (225 mg)

This regimen was tested in study 30050 and found to be safe and effective in patients with EM, while it was not explored in patients with CM. The Office of Clinical Pharmacology review team considers this dosing regimen acceptable as effective for prevention of migraine in patients with CM in addition to EM population for the following reasons:

- The pharmacokinetics/exposures of fremanezumab are not expected to be affected by migraine type (i.e., CM vs. EM). The mean trough plasma concentrations following 225 mg once monthly dosing regimen in patients with CM at month 1 should be similar to that observed in patients with EM (geometric mean C_{av} at month 1 = 19965.3 ng/ml [%CV = 32.3%]).
- The observed exposure-response relationship is shallow (See Figures 6 & 7) in both EM and CM. **Figure 8** shows that the geometric mean [%CV] exposures (C_{av} = 17709.4 ng/ml [49.2%] and 16256.8 ng/ml [46.2%]) during month 3 following 675 mg once quarterly regimen in patients with CM & EM from study 30049 & study 30050 respectively are comparable to those expected during month 1 (C_{av} = 19965.30 ng/ml [32.3%]) following 225 mg monthly regimen. Given the favorable primary efficacy endpoint results for 675 mg once quarterly regimen and the durability of response (as discussed above) at month 3 in patients with chronic migraine, a 225 mg monthly regimen should also be effective in CM.

(b) (4)

In conclusion, we recommend the approval of 225 mg once monthly and 675 mg once quarterly dosing regimens in patients with chronic and episodic migraine. (b) (4)

We believe these regimens will provide clinicians and patients better ability to optimize treatment with fremanezumab.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustment is not necessary based on intrinsic factors such as race, age, gender, bodyweight, BMI, renal or hepatic impairment. Population pharmacokinetic analysis did not reveal a clinically relevant impact of age, gender, body weight, or BMI on exposures of fremanezumab. While dedicated renal/hepatic impairment studies were not conducted, renal/hepatic impairment are not expected to affect the pharmacokinetics of fremanezumab. Results from a study in healthy Japanese and Caucasian subjects at doses of 225 mg, 675 mg and 900 mg showed that fremanezumab plasma concentration-time profiles were similar for Japanese and Caucasian subjects at all dose levels.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Since fremanezumab is administered by subcutaneous injection, food-drug interactions are not anticipated.

Fremanezumab is a monoclonal antibody and is not a cytokine modulator, therefore it is unlikely to influence drug metabolizing enzymes/transporters. Fremanezumab is an IgG2 isotype which is directed against a non-immunologic and soluble (not cell-bound) target, thus the risk of cytokine release is considered low. In addition, fremanezumab was tested for

stimulation of pro-inflammatory cytokine release in human whole blood obtained from 8 healthy donors with low basal cytokine levels (Study 111320). Fremanezumab did not elicit significant cytokine release (TNF- α , IL-6, INF- γ , or IL-1 β) in any donor, including at concentrations up to 100 $\mu\text{g}/\text{mL}$.

Therefore, no drug-drug interaction studies were conducted in vitro or in vivo.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support approval of the to-be-marketed formulation?

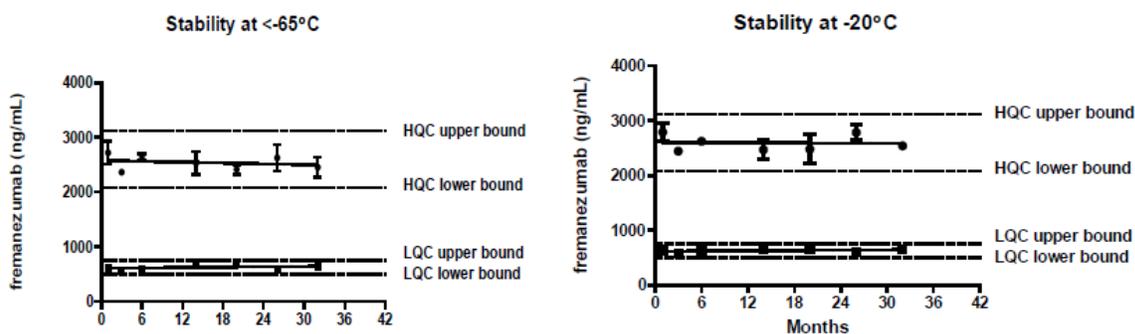
The to-be-marketed product (PFS) is same as the clinical trial formulation tested in pivotal studies. The Applicant will market the PFS (b) (4)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Fremanezumab plasma concentrations were determined using two ELISA assays. Early Phase 1 studies utilized a chemiluminescence ELISA performed by (b) (4) (method validation (b) (4)). Inconsistent assay results were observed in these early Phase 1 studies. Therefore, an optimized and validated bioanalytical method by Teva (SOP-015503-AVR-01) was developed. The analysis of PK samples from the Phase 1 bridging study in healthy Japanese and Caucasian subjects (TV48125-PK-10078), for which samples were analyzed using the Teva method (SOP-015503), demonstrated higher fremanezumab exposures relative to the results of the original PK sample analysis from the Phase 1 LBR-101-011 study in healthy volunteers, for which samples were analyzed with the (b) (4) method. An investigation was performed by retesting a subset of LBR-101-011 study samples using the (b) (4) method. The results showed that only 14% of the retested samples were within 30% of the original results; therefore, the criteria for method reproducibility were not met. Thus, a decision was made to reanalyze all samples from LBR-101-011 using the validated Teva method (SOP-015503).

For Study LBR-101-011, samples for the fremanezumab concentration determination were stored frozen below -65°C for 41 months before re-testing with the Teva bioanalytical method SOP-015503. Sample stability up to 32 months was demonstrated using quality control samples prepared from normal human plasma samples spiked at low and high levels of fremanezumab and stored at $<-65^{\circ}\text{C}$ and -20°C prior to testing (see Figure below).



LQC=low quality control (nominal concentration is 625 ng/mL); HQC=high quality control (nominal concentration is 2600 ng/mL); N=3 per QC level, measured fremanezumab concentration shown with standard deviation; bound= nominal concentration \pm 20% .

Current stability data indicate that samples are stable at 32 months. Stability evaluation to cover the 41-month period of storage required for this study is still ongoing; results will be available in July of 2018. (b) (4)

The ELISA method for the analysis of fremanezumab in human plasma SOP-015503-AVR-01 was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance (See DARS Consult Response in DARRTS dated 3/19/2018 for additional details).

This method (SOP-015503-AVR-01) was implemented in the sample analyses of the Phase 1 study TV48125-PK-10078, the Phase 2 studies and the Phase 3 studies.

The early Phase 1 studies are not considered supportive due to the assay issue described above and were not reviewed.

4.2 Pharmacometrics Assessment: Population PK Analyses

4.2.1 Applicant's Population PK analysis:

Population PK (PopPK) analyses were conducted by the sponsor to characterize the PK of fremanezumab in healthy subjects and subjects with episodic and chronic migraine (EM & CM respectively). Their key objectives were to (1) evaluate the effects of intrinsic and extrinsic factors on PK of fremanezumab that can potentially explain the inter-individual differences in PK and aid in appropriate dose adjustment, if necessary; and (2) derive the exposure metrics that can be used for subsequent exposure-response analyses of the efficacy and safety endpoints.

Data from 6 clinical studies, which included one phase 1 study (TV48125-PK-10078), two phase 2b studies (LBR-101-021 and LBR-101-022) and three phase 3 studies (TV48125-CNS-30049, TV48125-CNS-30050 and TV48125-CNS-30051) were used in the fremanezumab population PK analyses. A brief description of these studies is given in **Table 5**.

Table 5 Summary of the characteristics of the studies used for PopPK analyses

Study ID	Subjects	Doses	Description of data
TV48125-PK-10078	Phase 1: Healthy Japanese subjects (N = 32)	225, 675, 900 mg (SC)	<u>Rich PK</u> : Predose, 4, 8, 12 h (on day 1); 24, 36 h (on day 2), 48, 60 h (on day 3); 72, 84 h (on day 4); 96, 108 h (on day 5); 120 h (day 6);
	Healthy Caucasian subjects (N = 32)	225, 675, 900 mg (SC)	8±1, 12±1, 15±1, 29±2, 43±2, 57±2, 85±2, 113±2, 141±2, 169±2, 197±3, and 225±3 days
LBR-101-021	Phase 2b: Patients with chronic migraine	Doses at Q4W: 675 (LD), 225, 225 mg (SC) [N=88] 900 mg Q4W*3 [N=88]	<u>Sparse PK</u> : Predose on days 1, 29, 57, and day 85 (follow-up)
LBR-101-022	Phase 2: Patients with	225 mg Q4W*3 [N=96] 675 mg Q4W*3 [N=97]	<u>Sparse PK</u> : Predose on days 1, 29, 57, and day

	episodic migraine		85 (follow-up)
TV48125-CNS-30049*	Phase 3: Patients with chronic migraine	Doses at Q4W: 675, 225, 225 mg (SC) [N=379] One LD of 675 mg (SC) [N=376]	<u>Sparse PK:</u> Predose on days 1, 29, 57, and day 85 (follow-up)
TV48125-CNS-30050#	Phase 3: Patients with episodic migraine	225 mg Q4W*3 [N=290] One LD of 675 mg (SC) [N=291]	<u>Sparse PK:</u> Predose on days 1, 29, 57, and day 85 (follow-up)
TV48125-CNS-30051	Phase 3: Patients with chronic migraine *long term safety extension of 30049; Along with new subjects with CM [Total N=1017]	675 mg (LD); and 225 mg (SC) Q4W*11 675 mg Q12W*4	<u>Sparse PK:</u> For subjects rolling over from a previous pivotal study (TV48125-CNS-30049 and TV48125-CNS-30050): Predose on days 85, 169, 253, and 337 and day 534 (follow-up) For subjects not rolling over from the previous pivotal study [N=300]: Predose on days 1, 85, 169, 253, and 337 and day 534 (follow-up); Two additional visits after any dose of study drug: 3 to 10 days or 15 to 20 days after study drug administration
	Patients with episodic migraine #long term safety extension of 30050; Along with new subjects with EM [Total N=825]	225 mg Q4W*12 675 mg Q12W*4	

Note 1: N: Number of subjects included in the PopPK analyses dataset; SC: Subcutaneous, LD: Loading dose; Q4W: monthly dose; Q12W: once every 3 months.

Note 2: Protocol sample times for Studies TV48125-CNS-30049, TV48125-CNS-30050, and TV48125-CNS-30051 start on day 0 instead of day 1. Sample times were updated to be consistent with previous study designs where the first day was designated as day 1.

Source: Adapted from the Population PK report CP-17-05, Tables 1 & 2 on pages 54-56

Overall, the final dataset for the PopPK analyses consists of a total of 8346 quantifiable fremanezumab PK samples from a total of 2287 subjects, of whom 48 were healthy subjects, 353 subjects with migraine from phase 2b studies and the rest (N=1880) were subjects with migraine from pivotal efficacy studies. In total, N=50 post-dose (0.5%) PK samples were excluded, of which, 15 samples (0.2%) were below the limit of quantification, while the rest were excluded due to miscellaneous reasons, e.g., missing dosing/concentration records, samples associated with missing or duplicate dates etc.

The PopPK data of fremanezumab was modeled using non-linear mixed effects in NONMEM. The structural model developed by the applicant consists of a one-compartmental model whose absorption was characterized by a first-order absorption rate constant (k_a), distribution by an apparent volume of distribution term (V_c/F) and linear elimination characterized by apparent clearance term (CL/F). Lastly, a log error model (i.e., constant variance with respect to the log of the concentrations) was used to characterize the residual variability

Covariate identification was performed in a stepwise manner and the list of covariates explored include body weight, race, patient status, age, sex, albumin concentrations (liver function), creatinine clearance (estimated using Cockcroft-Gault method), anti-drug antibody (ADA) status and titer, concomitant (acute/analgesic/preventive) medications and injection site. The applicant reported the injection site could not be evaluated because they were generally not consistent within visits for each subject. Additionally, for the categorical covariates with subgroups represented by less than 10% of overall population (e.g., Asian, African-American and other races), the categories were regrouped, as appropriate (e.g., Caucasian vs. non-Caucasian). Owing to the small sample size per category (e.g., ADA status, liver function, etc.) they were not included in the final popPK model. Only the body weight was retained as a covariate on both CL/F and V_c/F using allometry whose coefficients were estimated.

In the first iteration, only the phase 2b data was considered during the development of the popPK model, and covariate effects such as patient status on V_c/F and CL/F and race on CL/F were identified. In the next iteration, when PK data from phase 3 studies (TV84125-CNS-30049, TV84125-CNS-30050) was included, the applicant retained the same structural model components as the model parameters characterizing the structural model were reasonably consistent with and without inclusion of the PK data from phase 3 trials. Further model refinement incorporated the covariate effects of body weight on V_c/F and CL/F . In the last iteration, the PK data from study TV84125-CNS-30051 (which includes the long-term extension arms of the pivotal phase 3 studies along with new subjects who met the eligibility criteria) was also included and all the parameters were re-estimated.

The parameter estimates of the final PopPK model are shown in **Table 6**

The qualification of the final PopPK model was performed using the goodness of fit plots, shown in **Figure 10**. Furthermore, the simulation of a large number of replicates (10,000 subjects per stratum) with the same design using the estimates of the population means and variability from the final PopPK model were overlaid with the observed data and visualized using the prediction-corrected Visual Predictive Check (pc-VPC) shown in **Figure 11 - Figure 12** (for individual studies).

Table 6 Parameter estimates of the final PopPK model

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
CL/F: apparent central clearance (L/day) ^a	0.141	0.742	29.0 %CV	3.64
CL/F: allometric exponent for weight (-) ^a	1.20	2.48		
V _c /F: apparent central volume of distribution (L) ^b	6.28	0.880	22.7 %CV	9.29
V _c /F: allometric exponent for weight (-) ^b	0.892	4.16		
k _a : absorption rate constant (1/day)	0.379	5.93	54.8 %CV	22.0
cov(IIV in V _c /F, IIV in CL/F)	0.0462	7.00	NA	NA
RV (log unit)	0.0268	8.75	0.164 SD	NA
Minimum value of the objective function = -15075.843				

Source: KIWI Run 187048.

^a Typical Value for CL / F = $0.141 \times (\text{Weight} / 71)^{1.20}$

^b Typical Value for V_c / F = $6.28 \times (\text{Weight} / 71)^{0.892}$

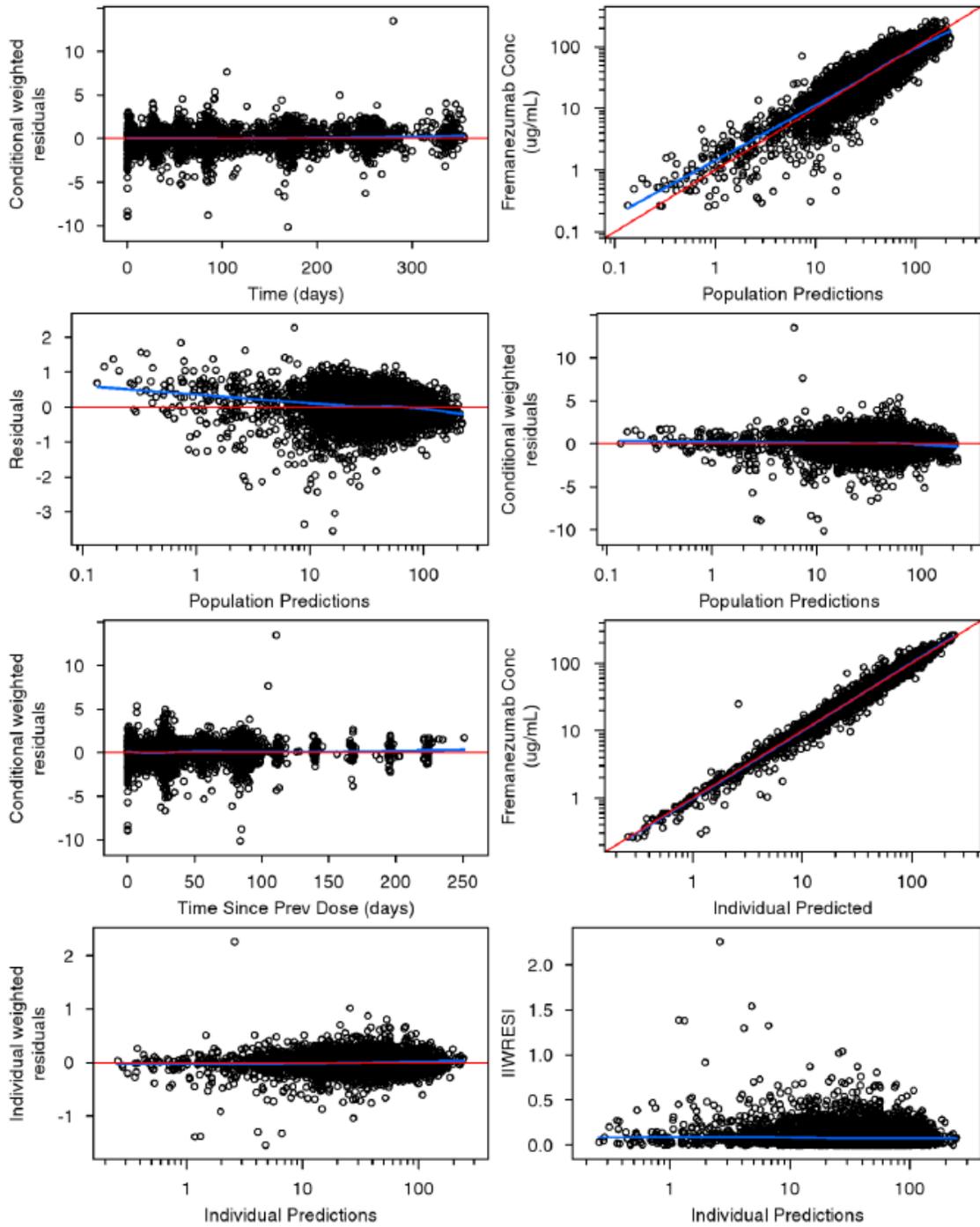
%CV=coefficient of variation expressed as a percentage; IIV=interindividual variability; NA=not applicable;

SD=standard deviation; %SEM=standard error of the mean expressed as a percentage

The calculated correlation coefficient (r²) of the off-diagonal omegas was 0.491 for cov(IIV in V_c/F, IIV in CL/F).

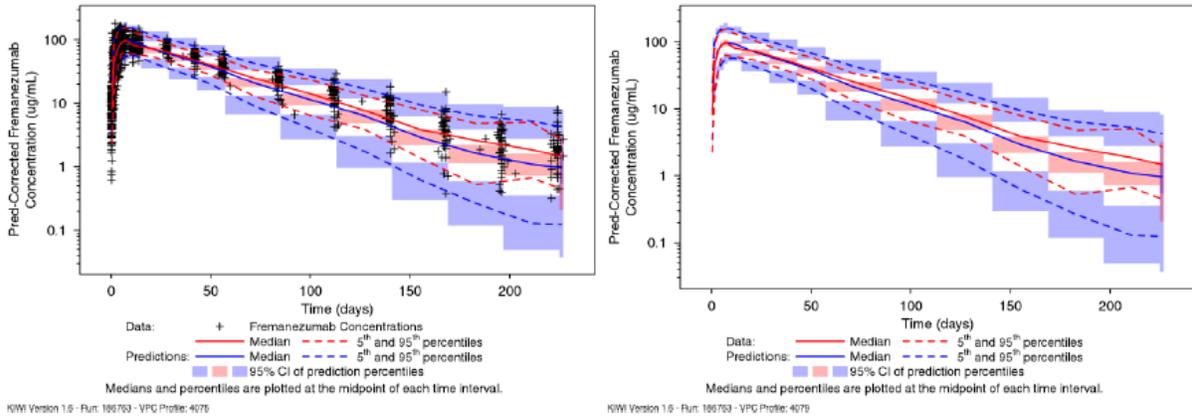
Source: Population PK report CP-17-05: Table – 14 on Page 70

Figure 10 Goodness of fit plots for the final PopPK model

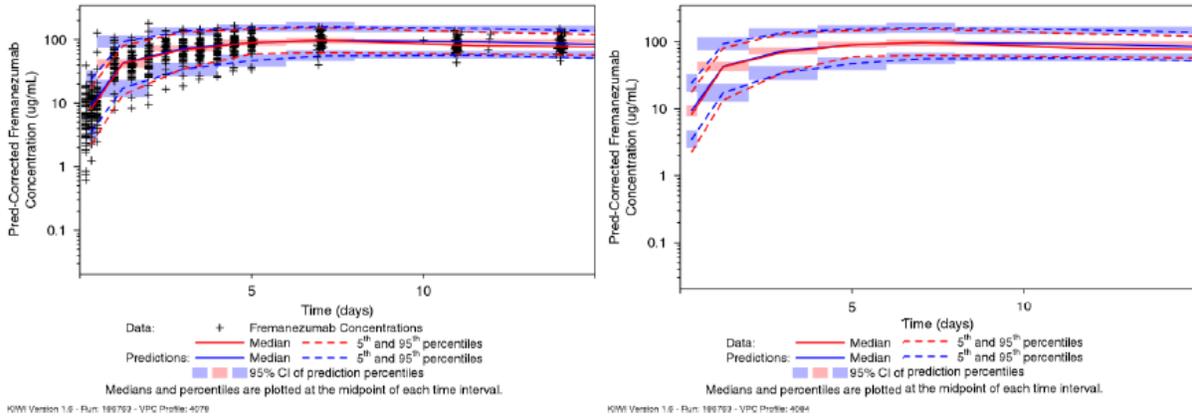


Source: Population PK report CP-17-05: Figure 15 on Page 108

Figure 11 Prediction-corrected VPC of final PopPK model for Study TV48125-PK-10078



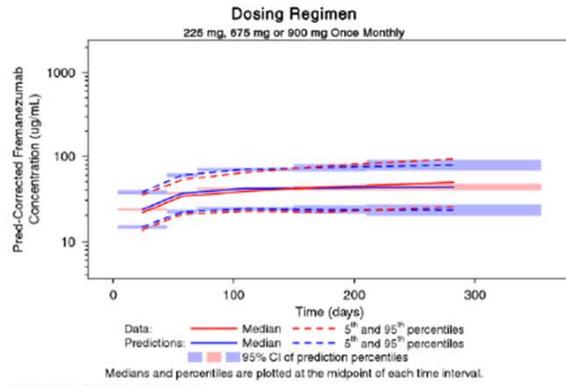
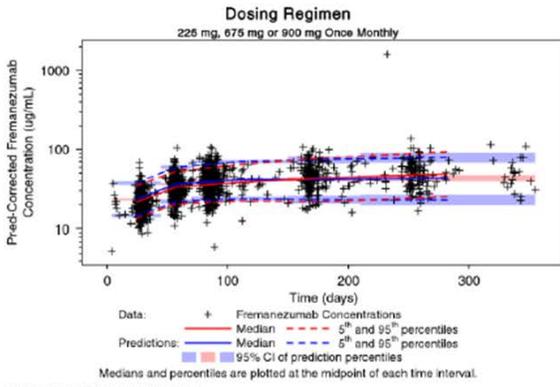
Phase 1 Zoomed to First 15 Days



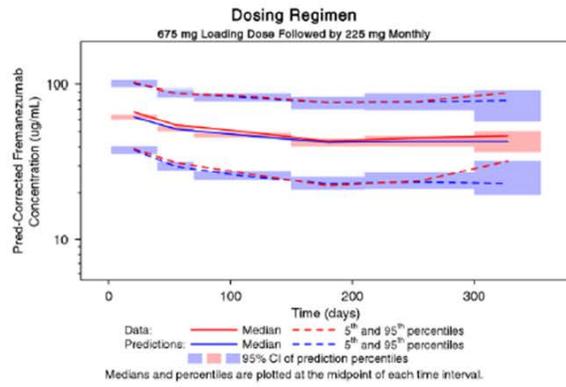
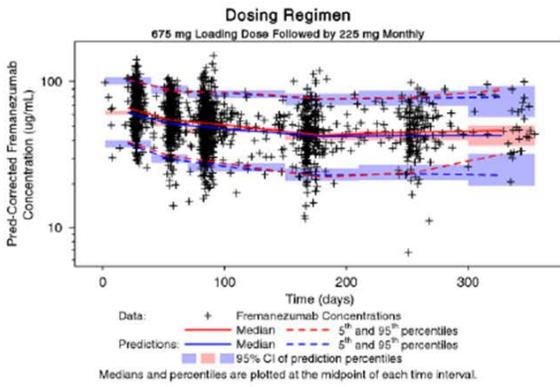
Source: Population PK report CP-17-05: Figure 17 on Page 115

Figure 12 Prediction corrected VPC of final PopPK model for phase 2b/3 designs in migraine patients

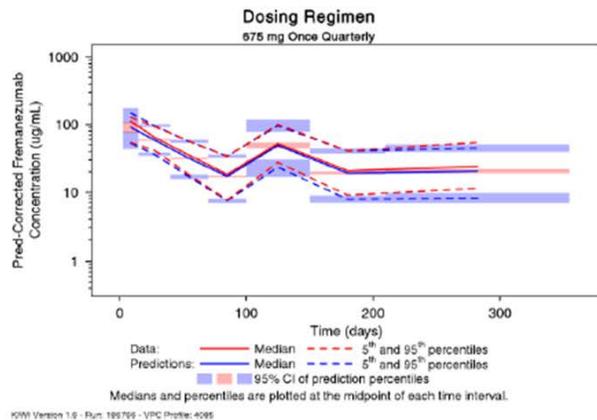
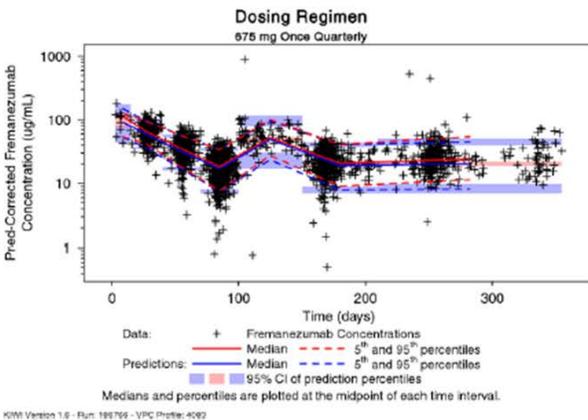
225 mg, 675 mg, 900 mg Once Monthly



675 mg Loading Dose Followed by 225 mg Monthly



675 mg Once Quarterly

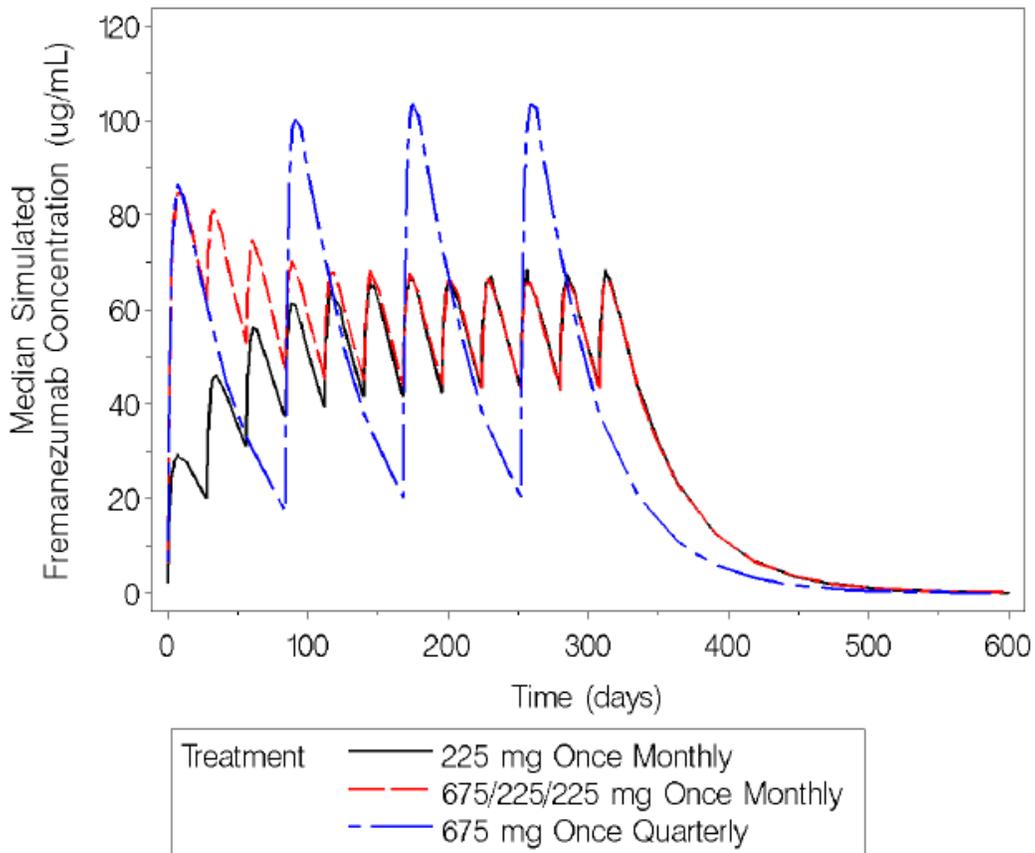


Source: Population PK report CP-17-05: Figure 18 on Pages 116-117

Assessment of Dose Proportionality

When the effects of dose on PK parameters was assessed as a linear effect on each PK parameter (CL/F , V_c/F and k_a), none of them were found to be statistically significant. Additionally, based on the steady-state exposures simulated using the final popPK model for once monthly (28 days/4weeks) dosing regimens of 225 mg, 675 mg and 900 mg, the applicant reported that the dose-normalized exposures are comparable across the dosing regimens, suggesting dose-proportionality between 225 – 900 mg. The steady-state exposures simulated under various dosing regimens are shown in **Figure 13**

Figure 13 Steady-state exposures simulated under different dosing regimens based on the final population pharmacokinetic model



Source: Population PK report CP-17-05: Figure 41 on Pages 140

Estimation of terminal half-life and accumulation ratio

Based on the final popPK model parameter estimates, a virtual population of 1000 subjects with patient characteristics resampled from the phase 3 studies was generated. Subsequently, the concentration-time profiles were simulated during and following discontinuation for the dosing regimens (dosed for 48 weeks): (a) 225 mg monthly (every 28 days), (b) 675 mg loading dose followed by 225 mg monthly (every 28 days), and (c) 675 mg quarterly.

The model-based median half-life was estimated to be around 31 days (independent of the dose or dosing regimen), and the steady-state was expected to be achieved by approximately 168 days. Additionally, the applicant reported a median accumulation ratio of 2.34 for both $AUC_{(ss, 0-28d)}$ and C_{max} for the 225 mg once-monthly dosing regimen and a median accumulation ratio of 1.20 and 1.19 for $AUC_{(ss, 0-84d)}$ and C_{max} , respectively, for the 675 mg once-quarterly fremanezumab dosing regimen.

Reviewer's comments:

*The applicant modeled the PK data of fremanezumab from the studies listed in **Table 5**, which included both rich and sparse sampling designs in healthy subjects and sparse sampling in subjects with episodic and chronic migraine. Initially, a population PK (popPK) model was developed based only on the phase 1 (study TV48125-PK-10078) data. In general, the final popPK model based on all the PK data seems to have comparable parameter estimates with either consistent or slightly improved precision compared to when the PK data from TV84125-CNS-30051 was not included. The final model parameter estimates and associated uncertainty in the estimation reported in **Table 6** seem reasonable for most of them. The shrinkage was below 30% for CL/F and V_c/F while it seems to be relatively higher for k_a (52%).*

The covariate modeling results indicated that bodyweight was a significant covariate on the (apparent) volume of distribution and (apparent) linear clearance. Given that the efficacy was similar across the two doses (relatively shallow exposure-response relationship for efficacy – please refer section 4.3 for additional details), the magnitude of the impact of bodyweight does not seem clinically meaningful and the recommendations proposed by the applicant are acceptable.

The model-based estimates for the terminal half-life, time to achieve steady-state and accumulation ratio(s) for the dosing regimens seems reasonable.

4.3 Exposure-Response Analyses

4.3.1 Exposure-Efficacy Analyses

4.3.1.1 Applicant's Exposure-Efficacy Analyses

Exposure metrics, namely, average fremanezumab plasma concentrations over the dosing interval [C_{av}], area under the concentration-time curve over the dosing interval [AUC_{28d}], fremanezumab concentration at the end of the dosing interval [C_{trough}], or C_{max} , were obtained from the final PopPK model. Subsequently, relationships were explored for the monthly migraine days as a function of time-dependent placebo effects, fremanezumab exposures and patient-level covariates using mixed effects logistic regression approach.

Episodic Migraine

Efficacy data from one phase 2b study (LBR-101-022) and one phase 3 study (TV48125-CNS-30050) were included for the exposure-response (ER) analyses and a brief description of the study characteristics are summarized in **Table 5**. In both the studies, headache data (i.e., occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) were recorded daily by every patient using an electronic headache diary device throughout the treatment period/early withdrawal visit. The key efficacy endpoint evaluated was the monthly number of migraine days during the 28-day monthly periods including the run-in period (baseline number of monthly migraine days) and through the post-treatment period. The final analysis dataset included 4444 migraine day records over 3 months in a total of 1142 subjects with episodic migraine.

The structural components of the E-R model for EM include: parameters estimating the baseline monthly migraine days, time-course of the placebo response and the drug effects of the fremanezumab exposure. Covariate modeling results indicated that the number of days per month of acute medication use at baseline was a significant covariate on the baseline monthly migraine days, i.e., greater acute medication use (of greater than 5 days) was associated with higher baseline monthly migraine days. The typical value of the baseline monthly migraine days in EM was estimated to be 9 days for a patient with 5 days or fewer of acute medication use per month at baseline.

The time-dependent placebo effect was best described by an exponential function. The typical placebo response at month 3 was reduction of 2.94 monthly migraine days from baseline,

which was comparable to the observed mean reduction from baseline of 3.4 monthly migraine days at month 3 in the EM placebo arms.

The drug-effect(s) in the active treatment arm was best described by a Emax function, reflecting the maximum fractional reduction in the monthly migraine days and average fremanezumab plasma concentrations over the dosing interval [C_{av}] was used as the exposure metric as there was larger decrease in the objective function value (over AUC_{0-28d}). The Emax value was estimated to be 0.252, indicating that a typical patient would at most experience 25.2% further reduction from the placebo response that is driven by the C_{av} of the fremanezumab. The average fremanezumab concentration required to achieve 50% of the maximum effect (EC_{50}) was estimated to be 3.60 $\mu\text{g/mL}$.

The qualification of the final E-R model was performed using the goodness of fit plots and a large number (N=1000) of replicates of the analysis dataset were simulated and overlaid with the observed data and evaluated using Visual Predictive Check (VPC) (shown in **Figure 14**)

The final model characterizing the ER is discussed below and the model parameter estimates summarized in **Table 7**

$$EM_MD_{ij} = BLE_i - e^{(0.360 \times Month_{ij})} - BLE_i \times \frac{(0.252 \times C_{avij})}{(3.60 + C_{avij})}$$

$$BLE_i = 8.35 + 0.438 \times (BACUTE_i - 3.5) \times BIND_i + 0.438 \times (5 - 3.5) \times (1 - BIND_i)$$

where EM_MD_{ij} is the model-predicted monthly number of migraine days in the i^{th} EM patient at the j^{th} time;

BLE_i is the model-predicted baseline number of migraine days in the i^{th} EM patient;

C_{avij} is the average fremanezumab concentration during the dosing interval in the i^{th} patient at the j^{th} time;

$BACUTE_i$ is the baseline number of days per month of acute medication use in the i^{th} patient;

$Month_{ij}$ is the month corresponding to the migraine days measurement in the i^{th} patient at the j^{th} time; and

$BIND_i$ is an indicator variable for the baseline number of days per month of acute medication use greater than 5 days in the i^{th} patient where 1 represents >5 days and 0 represents ≤ 5 days.

Table 7 Parameter estimates of E-R in Episodic Migraine

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
BLE: baseline migraine days for episodic migraine	8.35	1.50	1.61 SD	11.3
BLE: slope for baseline days/month of acute meds on BLE	0.438	6.31		
TEXP: exponent for placebo time-course	0.360	FIXED	2.92 SD	8.87
DEMX: maximum fractional response in migraine days due to C _{av}	0.252	8.06	43.3 %CV ^a	23.0
C ₅₀ : C _{av} at half maximal response (µg/mL)	3.60	73.1	NE	NA
Additive residual error	5.52	3.86	2.35 SD	NA

Minimum value of the objective function=14596.404

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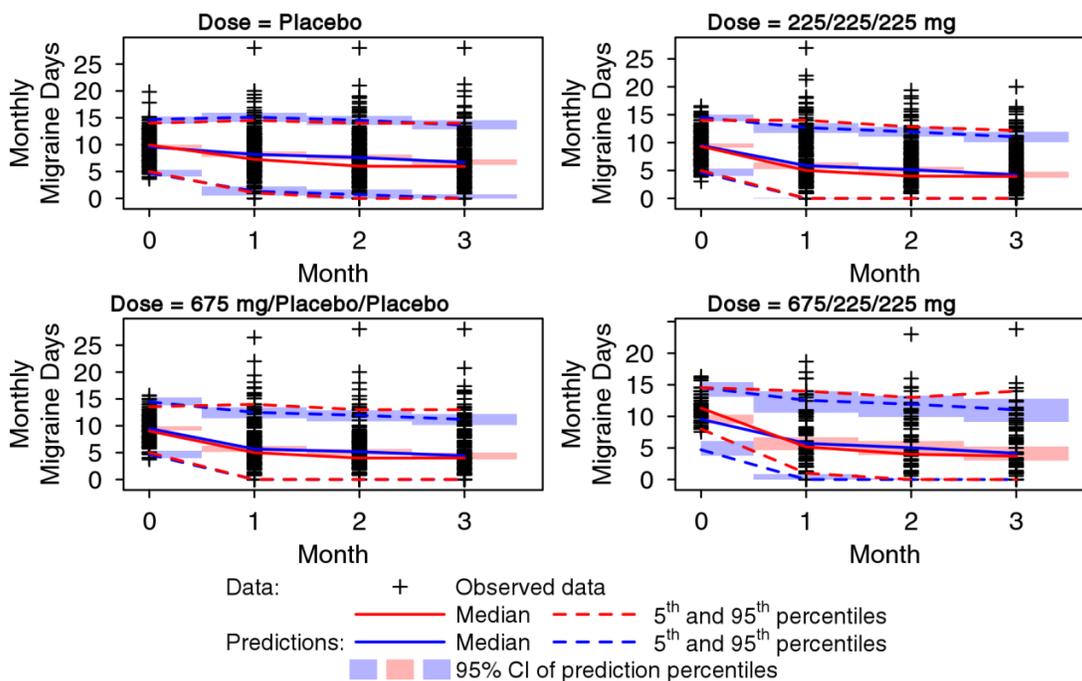
^a The interindividual variability (%CV) of IIV on DEMX was calculated using the following equation:

$$100 * (\text{SQRT}(0.335) * (1 - 0.252))$$

C_{av}=average fremanezumab plasma concentration over the dosing interval; %CV=coefficient of variation expressed as a percentage; IIV=interindividual variability; NA=not applicable; NE=not estimated; SD=standard deviation; %SEM=standard error of the mean expressed as a percentage

Source: Exposure-response analyses report (CP-17-06) Table 17 on Page 96

Figure 14 Visual predictive check for the final EM E-R model for the monthly migraine days overlaid with the observed data versus time



Medians and percentiles are plotted at the median month of the data observed within each month interval.

KIWI Version 1.6 - Run: 186987 - VPC Profile: 4110

Source: Exposure-response analyses report (CP-17-06) Figure 13 on Page 130

Chronic Migraine

Efficacy data from one phase 2b study (LBR-101-021) and one phase 3 study (TV48125-CNS-30049) were included for the exposure-response (ER) analyses and a brief description of the study characteristics are summarized in **Table 5**. In both the studies, headache data (i.e., occurrence of headache, duration of headache, maximum severity of headache, and acute migraine-specific medication use) were recorded daily by every patient using an electronic headache diary device throughout the treatment period/early withdrawal visit. The key efficacy endpoint evaluated was the monthly number of headache days with at least moderate severity (i.e., either moderate or severe) during the 28-day monthly periods including the run-in period (baseline number of moderate/severe headache days) and through the post-treatment period. The final analysis dataset included 5312 migraine day records over 3 months in a total of 1361 subjects with chronic migraine.

The structural components of the E-R model for CM include: parameters estimating the baseline number of headache days of at least moderate severity, time-course of the placebo response and the drug effects of the fremanezumab exposure. Covariate modeling results indicated that the number of days per month of acute medication use at baseline was a significant covariate on the baseline number of headache days of at least moderate severity, i.e., greater acute medication use (of greater than 5 days) was associated with higher baseline number of headache days of at least moderate severity. The typical value of the baseline number of headache days of at least moderate severity in CM was estimated to be 11.7 days for a patient with 5 days or fewer of acute medication use per month at baseline.

The time-dependent placebo effect was best described by a sigmoidal inhibitory E_{max}-type model. The typical value of the maximum reduction in number of headache days of at least moderate severity was 6.24 days per month, with an estimated time to achieve half the maximal response (T_{50}) was 1.76 months and a hill coefficient of 0.486. The typical placebo response at month 3 was reduction from baseline of 3.52 headache days of at least moderate severity, which was comparable to the observed mean reduction from baseline of 3.6 headache days of at least moderate severity at month 3 in the CM placebo arms.

The drug-effect(s) in the active treatment arm was best described by a power function and the average fremanezumab plasma concentrations over the dosing interval [C_{av}] was used as the exposure metric because of best overall fit (compared to AUC_{0-28d}). The typical value estimate for the maximum fractional reduction in headache days of at least moderate severity from baseline due to fremanezumab C_{av} was 0.157 or a 15.7% reduction from baseline at the median C_{av} (69.6 $\mu\text{g/mL}$).

The qualification of the final E-R model was performed using the goodness of fit plots and a large number (N=1000) replicates of the analysis dataset were simulated and overlaid with the observed data and evaluated using Visual Predictive Check (VPC) (shown in **Figure 15**)

The final model characterizing the ER is discussed below and the model parameter estimates summarized in **Table 8**

$$CM_MS_{ij} = BLC_i + \frac{(-6.24 \times Month_{ij}^{0.486})}{(1.76^{0.486} + Month_{ij}^{0.486})} - BLC_i \times 0.157 \times \left(\frac{C_{avij}}{69.6} \right)^{0.328}$$

$$BLC_i = 10.2 + 0.460 \times (BACUTE_i - 1.75) \times BIND_i + 0.460 \times (5 - 1.75) \times (1 - BIND_i)$$

where

CM_MS_{ij} is the model-predicted monthly number of headache days of at least moderate severity in the i^{th} CM patient at the j^{th} time;

BLC_i is the model-predicted baseline number of headache days of at least moderate severity in the i^{th} CM patient;

C_{avij} is the average fremanezumab concentration during the dosing interval in the i^{th} patient at the j^{th} time;

$BACUTE_i$ is the baseline number of days per month of acute medication use in the i^{th} patient;
 $Month_{ij}$ is the month corresponding to the migraine days measurement in the i^{th} patient at the j^{th} time; and

$BIND_i$ is an indicator variable for the baseline number of days per month of acute medication use greater than 5 days in the i^{th} patient where 1 represents >5 days and 0 represents ≤5 days.

Table 8 Parameter estimates of E-R in Chronic Migraine

Parameter	Final parameter estimate		Interindividual variability / residual variability	
	Typical value	%SEM	Magnitude	%SEM
BLC: baseline headache days of at least moderate severity for chronic migraine	10.2	2.40	4.69 SD	6.31
BLC: slope for baseline days/months of acute medication use on BLC	0.460	5.51		
E _{max} : maximum response in headache days for chronic migraine due to time (placebo)	-6.24	FIXED	6.66 SD	6.98
T ₅₀ : time to half maximal placebo response (months)	1.76	FIXED	NE	NA
S: Hill coefficient for placebo response	0.486	FIXED	130 %CV	6.23
DRUG: intercept for drug effect power function (fractional reduction from baseline at median C _{av})	0.157	7.70	92.6 %CV ^a	13.6
POW: exponent for C _{av}	0.328	23.6	97.2 %CV	31.6
Additive residual error	7.09	3.86	2.66 SD	NA
Minimum value of the objective function=20945.601				

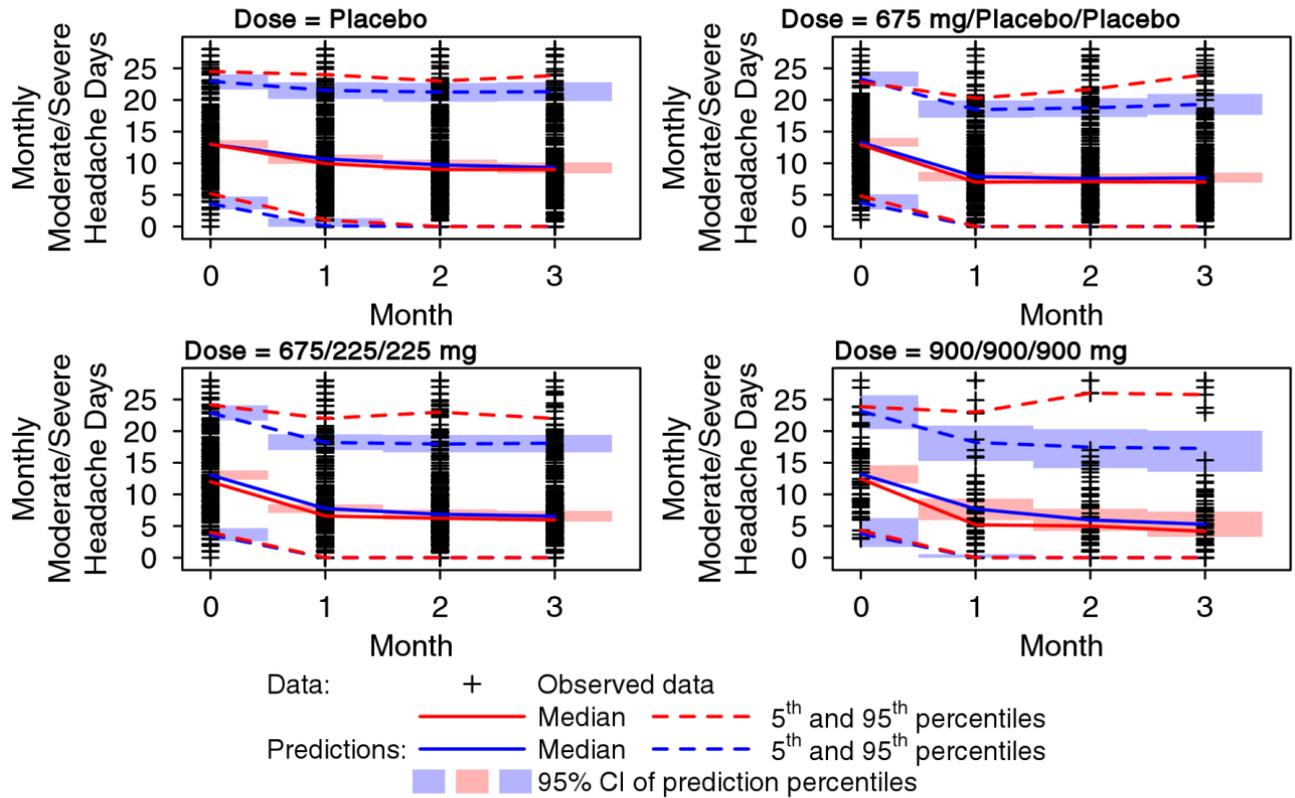
Source: d1pkpd-eff\nm\final\modsevcn-final-model_r187050.docx.

^a The interindividual variability (%CV) of IIV on DRUG was calculated using the following equation: $100 * (\text{SQRT}(1.21) * (1 - 0.157))$.

C_{av}=average fremanezumab plasma concentration over the dosing interval; %CV=coefficient of variation expressed as a percentage; NA=not applicable; NE=not estimated; SD=standard deviation; %SEM=standard error of the mean expressed as a percentage

Source: Exposure-response analyses report (CP-17-06) Table 30 on Page 109

Figure 15 Visual predictive check for the final CM E-R model for the monthly number of headache days of at least moderate severity overlaid with the observed data versus time



Medians and percentiles are plotted at the median month of the data observed within each month interval.

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Source: Exposure-response analyses report (CP-17-06) Figure 28 on Page 146

Reviewer's comments:

*The applicant developed exposure-response (E-R) relationships between the popPK model-derived exposure metric, namely, the average fremanezumab plasma concentrations over the dosing interval (C_{av} , which seem to give the best fit compared to other exposure metrics such as AUC_{0-28d} etc.) and monthly number of migraine days/monthly number of moderate/severe headache days during 28-monthly periods including the run-in phase for patients with episodic/chronic migraine separately. During the development of the structural E-R model, the time-course of the placebo response was characterized in the first step, and its respective parameters were fixed in the subsequent step of characterizing the (drug) effects of fremanezumab and covariate modeling. This approach seems reasonable as it allows for a better estimation of drug effects on response independent of the placebo effect. The final model parameters of the E-R models for episodic and chronic migraine are listed in **Table 7, Table 8** and visual predictive checks evaluations of the models are shown in **Figure 14** and **Figure 15**, respectively. Overall, most of the model parameters seem reasonable and are estimated with acceptable precision. The model-predicted typical placebo response at 3 months was reasonably consistent with that observed in the placebo arms for both episodic and chronic migraine. In drug effects component of the E-R model for EM, the average fremanezumab concentration required to achieve 50% of the maximum effect (EC_{50}) seems to be imprecisely estimated (%relative standard error = 73%), and shrinkage associated with E_{max} (the maximum fractional reduction in the monthly migraine days) parameter was relatively high (73%) and therefore, caution should be exercised in interpreting these parameters. In general, one plausible explanation for an imprecise estimation of EC_{50} is the dosing regimen(s)/exposures on the plateau portion of the exposure-response relationship and it is difficult to characterize the EC_{50} appropriately. In the E-R model for CM, the shrinkage associated with hill-coefficient of the E-max type placebo-time course, the intercept and power due to the C_{av} in the drug effects component seem to be relatively high ($\geq 55\%$). While the inclusion of number of days per month of the acute medication use as a covariate seems plausible, the applicant does not provide a rationale for choosing 5 (i.e., ≤ 5 or >5) as the cut-off for the number of days per month of the acute medication use for dichotomizing it as a categorical covariate. Lastly, in general, most of the parameters seem to have high interindividual variability suggesting that baseline monthly migraine days/number of headache days with at least moderate severity, placebo response and drug effects are heterogenous in patients with episodic and chronic migraine.*

Overall, the E-R relationship seem to be consistent with the dose-response relationships for both EM and CM.

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Date: 27 November 2017

From: James Weaver Ph.D. & Kristina Howard, DVM, PhD, Division of Applied Regulatory Science/Office of Clinical Pharmacology (DARS/OCP)

Through: David Strauss M.D., Ph.D., Director; DARS/OCP

To: Hristina Dimova & Sreedharan Sabarinath, DCP-1, OCP

Subject: Evaluation of bioassays for fremanezumab (TEV-48125) in BLA 761089

Executive Summary

The ELISA method for analysis of TEV-48125 (fremanezumab) in human plasma was validated in compliance with the standards set forth in the FDA Bioanalytical Method Validation guidance. This method was used to analyze samples from two phase 2 and three phase 3 clinical trials. The performance metrics for the assay calibration and QC standards were properly reported and well within acceptance criteria. Incurred Sample Reanalysis (ISR) was performed on one phase 2 and two phase three trials with acceptable results. The data from these studies are fit for purpose.

Background

The drug now known as TEV-48125 (fremanezumab) has had its development bridged across two sponsors. This drug is a fully humanized IgG2a monoclonal antibody that binds both α - and β -Calcitonin gene-related peptide. It is intended for prophylactic treatment of migraine headaches. In early clinical development of this drug, plasma levels were evaluated by an electrochemiluminescent ELISA assay developed by (b) (4). Near the end of phase 1, development was taken over by Teva Inc who developed their own colorimetric ELISA assay sharing only the primary capture antibody with the original assay. Reanalysis of a phase 1 study with the new TEVA assay resulted in C_{max} and AUC $0-\infty$ values that were ~ 3 fold higher than those reported using the original (b) (4) assay. All phase 2 and 3 studies were done with the Teva version of the assay. Because of the clear differences between the two assays, it was judged important to evaluate the validation and performance of the Teva assay in detail.

Evaluation

Original Question: *“We need to know whether the second assay (Teva SOP-015503) was properly validated and performed reliably during the analysis of the plasma samples in the pivotal phase 3 and phase 2 clinical trials.”*

Validation of the second assay: *Teva SOP-015503-AVR-01 & Addendum-01*

The primary validation of the ELISA assay to measure drug levels of TEV-48125 in plasma is reported in document SOP-015503-AVR-01. The Addendum-01 document reports on additional long-term stability studies.

The types of studies for bioanalytical method validation as set forth in the FDA 2013 draft guidance

were performed and reported in the validation report from the sponsor. The performance of the assay in the various parameters was well within the criteria set forth in the Guidance document. Sample stability was initially established to 3 months and extended in the addendum out to 26 months. See Appendix 1 for a detailed comparison of expected versus observed data. We conclude that the assay for measuring TEV-48125 in plasma was properly validated.

Performance of the validated assay on samples from clinical trials

A total of five phase 2 and 3 studies were reported in Table 3 of the document: ‘Summary of Biopharmaceutic Studies and Associated Analytical Methods.pdf’. An extract from that table listing of methods validation reports and bioanalytical study reports being evaluated in this report are shown in Table 1.

Table 1: Phase 2 and Phase 3 studies evaluated

Study #	Phase	Validation report	Bioanalytical report
LBR-101-021	2	SOP-015503-AVR-01	LBR-101-021-PK-BAR-01
LBR-101-022	2	SOP-015503-AVR-01	LBR-101-022-PK-BAR-01
TV48125-CNS-30049	3	SOP-015503-AVR-01 & SOP-015503-AVR-01 Addendum-01	TV48125-CNS-30049-PK-BAR-01
TV48125-CNS-30050	3	SOP-015503-AVR-01 & SOP-015503-AVR-01 Addendum-01	TV48125-CNS-30050-PK-BAR-01
TV48125-CNS-30051 (Interim report)	3	SOP-015503-AVR-01 & SOP-015503-AVR-01 Addendum-01	TV48125-CNS-30051-PK-BAR-01 (Interim report)

Report LBR-101-021-PK-BAR-01: A total of 650 samples were analyzed for this phase 2 study. The report includes data for calibration curve as well as QC standards. Assay performance was comparable to that reported in the validation study and was well within standards. ISR was performed and was reported separately in document ‘ISR Report SOP-015503-ISR-01.pdf’. IRS was performed on 66 samples (10%), comfortably above the 7% minimum set in the guidance. After some analyst-related issues were sorted out, the agreement rate was 78.8%, exceeding the criteria that at least 67% of the samples have reported values within 30% of the original value.

Report LBR-101-022-PK-BAR-01: A total of 725 samples were analyzed for this phase 2 study. The report includes data for calibration curve as well as QC standards. Assay performance was comparable to that reported in the validation study and was well within standards. Incurred Sample Reanalysis was not performed on samples from this study.

Report TV48125-CNS-30049-PK-BAR-01: A total of 2871 samples were analyzed for this phase 3 study. The report includes data for calibration curve as well as QC standards. Assay performance was comparable to that reported in the validation study and was well within standards. ISR was performed and was reported separately in document ‘ISR Report SOP-015503-ISR-03.pdf’. ISR was performed on 217 samples (8% of the total) and 93% met the criteria of agreeing within 30% of the original value.



Report TV48125-CNS-30050-PK-BAR-01: A total of 2202 samples were analyzed for this second phase 3 study. The report includes data for calibration curve as well as QC standards. Assay performance was comparable to that reported in the validation study and was well within standards. ISR was performed and was reported separately in document 'ISR Report SOP-015503-ISR-04.pdf'. ISR was performed on 181 samples (8% of the total) and 95% met the criteria of agreeing within 30% of the original value.

Report TV48125-CNS-30051-PK-BAR-01 (Interim report): A total of 3076 samples were analyzed for this second phase 3 study. The report includes data for calibration curve as well as QC standards. Assay performance was comparable to that reported in the validation study and was well within standards. ISR was not performed for this study.

Summary and Conclusions

In conclusion, the ELISA method for analysis of TEV-48125 (fremanezumab) in human plasma was validated in compliance with the standards set for in the FDA Bioanalytical Method Validation guidance. This method was used to analyze samples from two phase 2 and three phase 3 clinical trials. The performance metrics for the assay calibration and QC standards were properly reported and well within acceptance criteria. ISR was performed on one phase 2 and two phase three trials with acceptable results. The data from these studies are fit for purpose.

References and Supporting Documents

Guidance for Industry: Bioanalytical Method Validation. Draft document dated September 2013. <https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf>. Accessed 6 November 2017

Individual reports from BLA 761089 are referenced in the document text.



Appendix 1: Assay Validation Criteria table extracted from report SOP-125503-AVR-01., file name: SOP-015503-COM-01.pdf

Target acceptance criteria are from the FDA Bioanalytical Method Validation guidance. The observed result shows the actual results for those parameters from this methods validation study.

ASSAY VALIDATION SUMMARY

Parameter	Target acceptance criteria	Observed result
Minimum Required Dilution (MRD)	1:25	Confirmed
Standard Curve	Accuracy AR: 80 to 120% of the nominal concentration AR:75 to 125% at LLOQ and ULOQ Precision CV \leq 20% CV \leq 25% at LLOQ and ULOQ	Accuracy: -1 to 7% (%Bias) Precision: 2 to 4%
Accuracy and Precision/Validation samples	Accuracy AR: 80 to 120% AR:75 to 125% at LLOQ and ULOQ Precision CV \leq 20% CV \leq 25% at LLOQ and ULOQ Total Error TE should not exceed 30% or 40% at LLOQ and ULOQ LLOQ and ULOQ	Intra-assay precision: 3 to 5% Intra-assay accuracy: 1 to 6% Intra-assay Total Error: 4-10% Inter-assay precision: 3 to 7% Inter-assay accuracy: -2 to 4% Intra-assay Total Error: 4-9% LLOQ and ULOQ are 250.0 and 3500.0 ng/mL, respectively
Dilution Linearity	Within the assay range, the calculated median value of the % accuracy should be within \pm 20% of the expected value and the % difference between each dilution and preceding dilution must be within \pm 30%.	Acceptance criteria passed with a starting concentration of 0.2 mg/mL of TEV-48125. No hook effect observed.
Matrix Effect	At least 80% of the individual samples tested should produce results below the method quantification level.	Plasma samples from 28 individual donors diagnosed with migraine were tested unspiked at MRD. All of tested samples were below LLOQ.



<p>Selectivity</p>	<p>Unspiked and spiked at low and high levels Pooled and Individual Matrix with specific criteria.</p> <p>100% of the unspiked samples must be below LLOQ.</p> <p>Pooled matrix spiked at low level recovery: 75-125%.</p> <p>80% of the individual spiked at low level recovery: 75-125%.</p> <p>Pooled matrix spiked at high level recovery: 80-120%.</p> <p>80% of the individual spiked at high level median recovery: 80-120%.</p> <p>60% of individuals must have all four dilutions of high level samples recovery: 80-120%.</p>	<p>Human plasma and serum from 10 healthy donors, human plasma from 10 migraine donors, and pooled healthy human plasma were spiked at 500.0 and 2600.0 ng/mL respectively.</p> <p>All of the unspiked samples were below LLOQ.</p> <p>Recovery of pooled plasma spiked at low level from three selectivity runs is 100 and106%.</p> <p>All of individuals spiked at low level have recovery of 99-108% for plasma from healthy donors; 92-109% for serum from healthy donors; and 102-118% for plasma from migraine donors.</p> <p>Recovery of pooled plasma spiked at high level is 96-103%.</p> <p>All of individual spiked at high level have recovery of 97-101% for plasma from healthy donors; 88-103% for serum from healthy donors; and 90-97% for plasma from migraine donors.</p> <p>100% of individuals plasma from healthy donors have recovery between 95-108% for all four dilutions of high level samples; 90% of individuals serum from healthy donors have recovery 89 - 119% for all four dilutions of high level samples; and 100% of individuals plasma from migraine donors have recovery between 90-110% for all four dilutions of high level samples.</p>
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Interference	Interference: analyte recovery in the presence of interfering molecule is $\geq 80\%$ or $\leq 120\%$.	Interference was observed at LQC level in the presence of α -CGRP at concentration above 20 ng/mL. Interference was observed at LQC level in the presence of β -CGRP at concentration above 10 ng/mL and at HQC level at concentration above 40 ng/mL. Interference was observed at LQC level in the presence of Anti-TEV-48125 at concentration above 500 ng/mL. Recovery of LQC and HQC in the presence of Hemolysed samples at 2% and 10% is between 92-95%. Recovery of LQC and HQC in the presence of Lipidaemic samples at 150 mg/dL and 500 mg/dL is between 91-93%. Therefore no hemolysis and lipimia interference were observed
Stability	Two out of 3 sets of HQC and LQC should have $100 \pm 20\%$ accuracy and $\leq 20\%$ CV under each stability condition tested.	HQC and LQC stable up to 8 freeze-thaw cycles; up to 162 hours in 2-8°C, up to 24 hours at ambient room temperature, and up to 3 months at $\leq -65^\circ\text{C}$ or $-20 \pm 5^\circ\text{C}$.
Robustness	Different sample and detection Ab incubation times, different incubation times after TMB addition, and different plate coating time	Robustness of method was confirmed with sample incubation between 110-130 min, detection Ab incubation time between 55-65 min, TMB incubation time between 13-17 min, and plate coated from 15 to 88 hours

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