CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761089Orig1s000

OTHER REVIEW(S)

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,

RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Show Input Form **Review Reminders** **Create PDF**

Date	March 16, 2017
To	Kelly Ballard CDER/OPQ/OPRO/DRBPMI/RBPMBI
Requesting Center/Office	*CDER/OPQ*
OND Review Division	*DNP*
From	*Jacqueline Gertz* *CDRH/ODE/DAGRID/GHDB*
Through (Team Lead)	*John McMichael* *CDRH/ODE/DAGRID/GHDB*
Through (Branch Chief)	*CAPT Alan Stevens* *CDRH/ODE/DAGRID/GHDB*
Subject	*Consult for BLA 761089* *ICCR 2017-01971* *ICC 1700942*
Filing Recommendation	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Acceptable for Filing*
Mid-Cycle Recommendation	*Recommendation Date:* *CDRH does not anticipate any major information requests or approvability issues and will provide a finalized memo by the review deadline*
Final Recommendation	*Recommendation Date:* *Device Constituents Parts of the Combination Product are Approvable*

Digital Signature Concurrence Table	
Reviewer	Jacqueline Gertz -S Digitally signed by Jacqueline Gertz -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001948760, cn=Jacqueline Gertz -S Date: 2018.03.16 12:01:07 -04'00'
Team Lead	John C. Mcmichael -S 2018.03.16 12:06:56 -04'00'

Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.03.16 15:01:51 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR 2017-01971
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/DispForm.aspx?ID=2209
ICC tracking # (Lead)	ICC 1700942
Submission Number	BLA 761089
Sponsor	Teva Branded Pharmaceutical Products
Drug/Biologic	Fremanezumab
Indications for Use	The prophylaxis headache in adult patients with episodic and chronic migraine.
Device Constituent	Syringe
Related Files	IND 106533

Table 2. Review Team		
Were other disciplines consulted?	☐ **Yes**	☒ **No**

Table 3. Important Dates	
1st round of Information Requests	1/9/2018
2nd Round of Information Requests	1/24/2018
Final Lead Device Review Memo Due	3/16/2018
Interim Due Dates	**Due Date**
Mid-Cycle	1/29/2018
Primary Review	3/16/2018
PDUFA/GDUFA Due Date	6/15/2018

TABLE OF CONTENTS

Update TOC

2. PURPOSE/BACKGROUND

2.1. Scope

Teva Branded Pharmaceutical Products is requesting approval of the Fremanezumab pre-filled syringe. The device constituent of the combination product is a prefilled syringe.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product on March 16, 2018:

Teva resubmitted biologic license application (BLA) 761089 on October 16, 2017. This is a 351(a) BLA for approval for fremanezumab injection. OPQ is requesting a consult review of the pre-filled syringe to determine if the information provided is adequate to support approval of the BLA.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

- Device performance
- Biocompatibility of the patient contacting components
- Release Specifications for the device constituent
- Sterility of the device constituent if applicable

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Review of manufacturing facilities

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

2.2. Prior Interactions

CDER interacted with the Sponsor regarding this drug product on several occasions, including clinical holds, (b) (4), end of phase 2 meeting, (b) (4), Type C meeting for CMC, pediatric study plan, Pre-BLA meeting.

CDRH provided comments during the Type C meeting and at the pre-BLA meeting on 9/29/2017. See related documents below.

Related Files
IND 106533 Pre-BLA meeting August 31, 2017

ICC 1600207 – for CDRH consult


fda-pre-bla-meet-mi n-29sep2017.pdf


ICC 1600207 IND 106533 CDRH-ODE M

2.3. Indications for Use

Table 1: Indications for Use

Combination Product	Indications for Use
Fremanezumab	The prophylaxis headache in adult patients with episodic and chronic migraine. 225mg/1.5mL
Prefilled syringe	Delivery of the drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
Reviewer Guide	1.2
Container closure system	2.3.P.7
Container closure system selection	3.2.P.2
HF Summary Report	SDT-INT1056
Container closure system manufacturers	3.2.S.6
Specifications	3.2.P.5
Description and composition	3.2.P.1

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

From GSR 2.3.P.7 Container closure system:

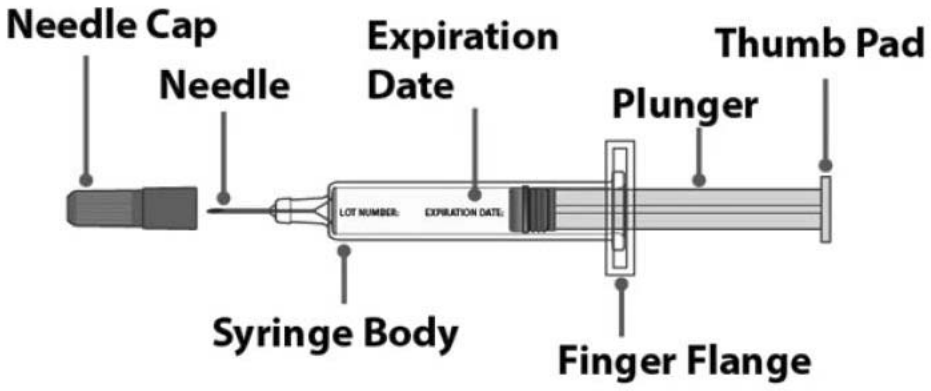
Fremanezumab, Injection is supplied in a 2.25 mL pre-filled syringe (PFS) as the primary container closure system. The PFS consists of a 2.25 mL (b) (4) glass, (b) (4) syringe with a staked (b) (4) needle and a (b) (4) (b) (4) plunger-stopper (b) (4) needle shield (b) (4) rigid needle shield cover.

Pre-filled syringes and plunger-stoppers are supplied clean, sterile, and ready-to-use. A description of each primary packaging component is listed in Table 1.

The applicant provided performance testing for the PFS combination product. Needle shield removal force, needle pull out force and needle injection depth data was provided and met the acceptance criteria. The needle and syringe combination functional testing was provided. Deliverable volume, and Break loose force all met the acceptance criteria.

Table 1: Description and Material of Construction of Primary Container Closure System

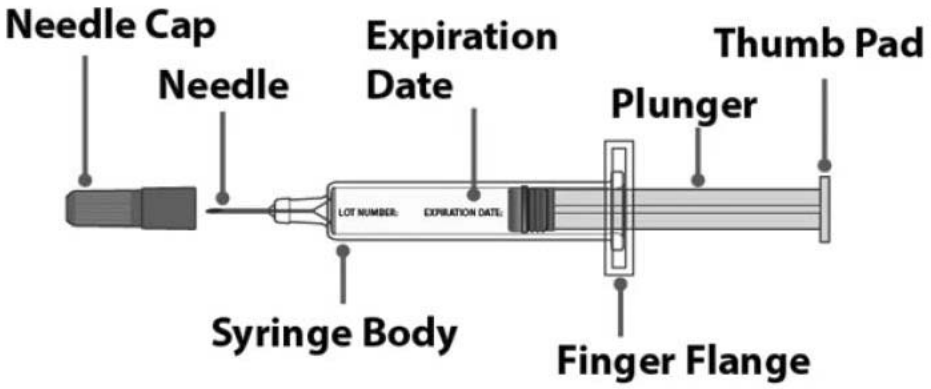
Component	Material	Description	Manufacturer
Pre-filled syringe with staked needle	Syringe: (b) (4) (b) (4) Glass Needle: (b) (4) (b) (4)	(b) (4) syringe barrel (b) (4) staked needle, (b) (4)	(b) (4)
(b) (4) needle shield (b) (4)	(b) (4)	(b) (4)	
(b) (4) plunger-stopper (ready-to-use)	Plunger-stopper: (b) (4)	(b) (4)	



Syringe Device Description

Device Characteristic	N/A	Description / Specification
Syringe Name	N/A	SYRINGE (b) (4)
Syringe Platform Name (if applicable)	N/A	
Priming Dose / Volume		1.5mL, 225mg protein/PFS
Dose accuracy		(b) (4)
Injection Time		
Injection Site		Abdomen, front of thighs, back of upper arms
Injection tissue and depth of injection		(b) (4)
Audible / visual feedback		
Cap Removal Force		
Activation Force		
Visibility of medication container		
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked		
Type of Use (e.g. single use, disposable, reusable, other)		Single use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Adult patient, caregiver, health care provider
Method of actuation		manual
Automated Functions	N/A	
Residual Medication		After use, dispose of prefilled syringe in a sharps container
Drug Container Type		Pre-filled syringe
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)		mL
Environments of use		Clinic or home use
Storage conditions and expiry		Store in the refrigerator at 2-8°C, (b) (4)
Graduation marks / fill lines	N/A	Inject the entire amount in syringe
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g.,		Wait 30 minutes to allow medicine to reach room temperature Clean the skin with alcohol Pinch up at least 1 inch of cleaned skin Insert needle at a 45-90° angle until it is all the way in

pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.		
Safety Features • Needle safety		(b) (4) needle shield (b) (4)
Material composition of PFS		Syringe barrel: (b) (4) Glass Needle: (b) (4) Needle shield: (b) (4) (b) (4) Plunger-stopper: (b) (4)



Instructions for use summary:

1. *Remove the pre-filled syringe from the carton.*
2. *Gather the supplies you will need to inject AJOVY*
    - *The supplies include an alcohol swab, gauze pad, and a sharps disposal container*
3. *Let AJOVY reach room temperature*
4. *Wash your hands*
5. *Look closely at your AJOVY pre-filled syringe*
6. *Choose your injection area*
7. *Clean your injection area*
8. *Remove the needle cap and do not replace*
9. *Give your injection following the 4 steps below*
    - *Steps indicate to pinch the skin, insert needle, push the plunger, push the plunger all the way down slowly.*
10. *Remove the needle from your skin*
11. *Apply pressure at the injection site*
12. *Dispose of your pre-filled syringe right away*

Device Description Stock IR

Device Description Recommendation		
The Sponsor Provided Complete Device Description for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Device Description for the Device Constituent		☐
Device Description Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day Letter IRs - # Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

Table 4: Design Control Documentation Check

Design Control Requirement	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	x		3.2.P.2 Container closure
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	x		3.2.P.2 Container closure
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	x		3.2.P.2 Container closure

The development of fremanezumab, Injection was conducted in accordance with the requirements of: 21 CFR 820.30, Design Controls, Risk Management in accordance with the requirements of ISO 14971:2007 Medical devices – Application of risk management to medical devices, and Human Factors Engineering in accordance with the requirements of IEC 62366-1:2015 Medical devices – part 1: Application of usability engineering to medical devices and FDA Guidance for Industry Applying Human Factors and Usability Engineering to medical Devices.

The following consensus standards and additional materials were used in developing the Design Inputs:

- *ISO 6780:2003, Flat pallets for intercontinental materials handling – Principal dimensions and tolerances*
- *ISO 7864:2016, Sterile hypodermic needles for single use – Requirements and test methods*
- (b) (4)

- *ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process*
- *United States FDA, Guidance for Industry and FDA Staff: Use of International Standard ISO 10993-1, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process," June 2016*
- (b) (4)
- *ISO 11040-5:2012, Prefilled syringes – Part 5: Plunger-stoppers for injectables*
- *ISO 11040-8:2016, Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes*
- *USP, Chapter 697 Container Content for injections*

Master File Review Instructions

Master File Stock IR

Design Controls Recommendation		
The Sponsor Provided Complete Design Controls for the Device Constituent		☒
The Sponsor **DID NOT** Provide Complete Design Controls for the Device Constituent		☐
Design Control Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Table 5: Summary of Design V&V Attributes

Design Verification / Validation Attributes		Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing		x		
To-be-marketed device was used in the pivotal clinical trial? – 2.25mL syringe is specified, but not brand/model		x		
Selectable dose range on device matches the labeled dose range for the medication?				x
Verification methods relevant to specific use conditions as described in design documents and labeling		x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		x		
Traceability demonstrated for specifications to performance data		x		
Conformance to applicable standards demonstrated	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	x		
	ISO 11608-2:2012 – Needles	x		
	ISO 11608-5:2012 – Automated Functions			x
Stability and simulated shipping / transport data adequately verifies device will meet essential performance requirements at expiry - MDD 93/42/EEC, Essential Requirements, General Requirements I, Section 5, October 2007 Results of testing show that the product is held in a registered position within the carton		x		
Discipline -Specific Design Verification / Validation adequately addressed	Biocompatibility – ISO 10993-1:2009 Chemical toxicity, cytotoxicity, eye irritation, topical dermal/intraperitoneal/subcutaneous/ intradermal administration, genotoxicity, pyrogenicity, sub chronic toxicity	x		
	Sterility – syringe with needle and needle shield [redacted] (b) (4) Plunger stopper [redacted] (b) (4) Endotoxin level [redacted] (b) (4) EU/mL Each component is provided sterile from the manufacturers - [redacted] (b) (4)	x		

Referenced Standards and Guidance Documents

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No

ISO 10993-1	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process	X	
ASTM F1980 – 16:	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices, and FDA Guidance, Shelf life of Medical Devices,	X	
ISO 14971:2012	Medical devices – Application of risk management to medical devices	X	
IEC 62366-1:2015	Medical devices - part 1: Application of usability engineering to medical devices	X	
Guidance For Industry Applying Human Factors and Usability Engineering to Medical Devices		X	
ISO 7864:2016	Sterile hypodermic needles for single use – Requirements and test methods	X	
(b) (4)		X	
ISO 11040-5:2012	Prefilled syringes – Part 5: Plunger-stoppers for injectables	X	
(b) (4)		X	
ISO 11040-8:2016	Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes	X	
ANSI/AAMI/ISO 11137	Sterilization of healthcare products	X	
IEC 62366-1:2015	Medical devices – part 1: Application of usability engineering to medical devices and FDA Guidance for Industry Applying Human Factors and Usability Engineering to medical Devices.	X	

Table 2: Compliance of Fremanezumab, Injection Components

Component	Material	Contact with DP	Method
Syringe	(b) (4) glass	Yes	USP <660> Containers – Glass Ph Eur 3.2.1 Glass Containers for Pharmaceutical Use (b) (4) ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
Needle	(b) (4)	Yes	(b) (4) ISO 7864:2016, Sterile hypodermic needles for single use – Requirements and test methods (b) (4) ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
Rigid Needle Shield (RNS)	(b) (4)	Yes	(b) (4) ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process

Table 2: Compliance of Fremanezumab, Injection Components (Continued)

Component	Material	Contact with DP	Method
Plunger-Stopper	Plunger-stopper: (b) (4)	Yes	(b) (4) ISO 11040-5:2012, Prefilled syringes – Part 5: Plunger-stoppers for injectables ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
(b) (4)			
Plunger Rod	(b) (4)	No	ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
Backstop	(b) (4)	No	ISO 10993-1:2009, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process

(b) (4) ISO = International Organization for Standardization; Ph Eur = European Pharmacopoeia; USP = United States Pharmacopoeia

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device – clinical study trials say 2.25mL syringe, but no brand, etc. given.		x	

Reviewer Comment: The traceability matrix was not provided and is essential for an acceptable design review.

1/23/2018 The traceability matrix has been provided and includes all the required design inputs

Design Validation Recommendation		
The Sponsor Provided Complete Design Validation for the Device Constituent		☐
The Sponsor **DID NOT** Provide Complete Design Validation for the Device Constituent		☐
Design Validation Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☒
There are Complete Response Deficiencies, See Section 12		☐

6.3. Design Verification Review

6.3.1. Design Verification Testing Summary

Essential Functional Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Dose Accuracy		The product shall expel no less than the labelled volume (1.5mL)	United States Pharmacopeia (USP) General Chapters <1> Injections; Determination of Volume of injection in containers; Injections in Cartridges or Prefilled Syringes "The volume measured for each of the containers is not less than the nominal volume". ISO 11040-8:2016, Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes, Clause 7.5, Deliverable Volume ISO 11608-1:2014, Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems, Clause 7, Determination of dose accuracy	Testing Data: Tested at 5°C,a Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 23°C, a Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 40°C, a Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Sample Size: 60 Results: Pass	X	

Break Loose Force/ Glide force		(b) (4)	(b) (4) The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference. In addition, this action is considered worst case as it is a horizontal force rather than vertical.	Testing Data: Break Loose Force: Mean: 6N Min: 6N Max: 6N Glide Force: Mean: 6N Min: 6N Max: 7N Sample Size: 29 Results: Pass	X	
Rigid Needle Shield Removal force		(b) (4)	(b) (4)	Testing Data: Mean: 15N Min: 8N Max: 27N Sample Size: 29 Results: Pass	X	

			The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference.			
Visual/Audible Feedback				The device shows when an injection is complete because the barrel is transparent so the plunger stopper can be seen within the barrel and the user can see that the barrel is empty. The IFU instructs the user to push the plunger to the bottom of the barrel.	X	

Device Requirements						
	N/A	Acceptance Criteria	Method Acceptable	Results/ Deviations	Adequate	
					Yes	No
Injection Depth		(b) (4)	Insert needle fully	0.5in	X	
Injection time				15s	X	
Needle Connection Type	X					
Needle Resistance to Bend/Fracture			(b) (4) ISO 7864		X	
Seal Integrity Testing[1]		(b) (4)		75-101N, mean 91 N	X	
Separation Force	X					
Unscrewing Torque	X					
Ease of Assembly	X					
Resistance to Overriding	X					
Stress Cracking	X					
Validation of Graduation Markings	X					
Dead Space	X			Only for insulin		
Coring Needle Test			ISO 7864	DMF (b) (4)	X	
Anti-Needle Stick Performance testing[2]	X					

Connectivity to other devices necessary for use[3]	X					
Injection force necessary to depress the plunger and eject the drug contents	X	See break loose and glide force				
Tip cap removal force		(b) (4)		13N +/- 5N	X	
Piston seal blowback[4]	X			The PFS does not connect to anything		
Leak testing		(b) (4)	Syringe assembly including plunger stopper does not leak drug product	Liquid Leakage: No leakage under 110 kPa pressure for 5 seconds Results: Pass Max Force to Create Leak (N): > (b) (4) Testing Data: Mean: 91N Min: 68N Max: 107N Sample Size: 29 Results: Pass **Container Closure Integrity:** No leak detected; CCI Voltage between 1.0-4.0 VDC Sample Size: 299 Results: Pass	X	
Sterility				MAF (b) (4)	X	

		(b) (4)				
Biocompatibility			Product (and its components Needle, Syringe Barrel, Plunger Rod and Back Stop) is biocompatible for its intended use	Biological Evaluation indicates product's syringe barrel, needle, backstop and plunger rod are biocompatible for its intended use. This was done in consideration with following: • Acute Systemic Toxicity • Hemocompatibility • Cytotoxicity • Sensitization • Irritation/Intracutaneous reactivity	X	
Shelf Life		(b) (4)	(b) (4)	Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product's plunger stopper provides sealing against the product's syringe barrel over its shelf life Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product has a shelf life at least 24 months	X	

[1]to assess liquid leakage, air ingress, and dye ingress once the syringe is filled with the drug or biological product as intended and when connected to a connecting device. The sensitivity of the selected test method should be specified and validated. System integrity should be demonstrated throughout the product shelf-life.
[2]of an anti-needlestick mechanism with a glass syringe to demonstrate safety and effectiveness as recommended in FDA's guidance document, "Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features " (August 2005).
[3]e.g., needles, adapters, transfer systems, extension tubing, Luer connectors, and sharps prevention features

[4]ability of syringe with tip cap to hold a certain pressure on the piston

6.3.2. Environmental Conditioning Testing

All Essential Functional Requirements Evaluated under normal and stressed conditioning				
		Adequate	Inadequate	N/A
Normal/Anticipated Conditions	In-Use atmosphere	HF and clinical trials		
	Last-Dose Accuracy	Single use		
	Life-Cycle Testing	HF and clinical trials		
Challenge/Stressed Conditions	Free-Fall	Managed by instructions to perform a visual check and the warning do not use if damaged		
	Dry heat/cold storage	Storage information is located on the top face of the carton and on the IFU		
	Damp Heat			X
	Cyclical			X
	Vibration			X
	Transportation, storage and handling	MDD 93/42/EEC, Essential Requirements, General Requirements I, Section 5, October 2007 Must be maintained at 2-8°C		

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

6.3.3. Biocompatibility Review

Biocompatibility Review Instructions

Biocompatibility Evaluation		
Materials List	Plunger	Rod: (b) (4) Stopper: (b) (4) (b) (4)
	Syringe Body	(b) (4) Glass
	Needle	(b) (4)
	Accessories	Backstop: (b) (4) Needle shield: (b) (4)
Additives/Colorants	N/A	
Device Characteristics		
Category	☐ External communicating device	
Contact Type	☒ Blood path, indirect ☐ CSF contacting[1] [1]consult biocompatibility consultant	
Contact Duration	☒ ≤24h (limited) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), and Material-mediated Pyrogenicity ☐ >24h to 30 days (prolonged) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, and Subchronic systemic toxicity ☐ >30 days (permanent) • Appropriate Endpoints: Cytotoxicity, Sensitization, Irritation, Acute systemic toxicity, Hemocompatibility (indirect hemolysis only), Material-mediated Pyrogenicity, Subchronic systemic toxicity, and Genotoxicity	
Testing Performed	☒ Cytotoxicity ☒ Sensitization ☒ Irritation or Intracutaneous Reactivity ☒ Acute System Toxicity ☒ Material-Mediated Pyrogenicity	☒ Subacute/Subchronic Toxicity ☐ Genotoxicity ☒ Hemocompatibility ☐ Carcinogenicity
Did the Sponsor provide a written justification in lieu of biocompatibility testing	**☐ Yes**	**☒ No**	**☐ N/A**
IS the written justification acceptable?	**☐ Yes**	**☐ No**	**☒ N/A**
Review of Written Justification			
Reviewer Comments/Conclusions			

Did the Sponsor perform the appropriate testing?	☒ Yes	☐ No	☐ N/A

Review of Biocompatibility Testing
See Quality Trace matrix Table 2, pg 5 of 8.

Table 2: Biocompatibility Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product's syringe barrel, needle, backstop and plunger rod shall be biocompatible	ISO 10993-1:2009, *Biological evaluation of medical devices* – Part 1: Evaluation and testing within a risk management process The intended users' unbroken skin will make contact with the combination products' syringe glass barrel during use	Product (and its components Needle, Syringe Barrel, Plunger Rod and Back Stop) is biocompatible for its intended use	Biological[a] Evaluation indicates product's syringe barrel, needle, backstop and plunger rod are biocompatible for its intended use. This was done in consideration with following: Acute Systemic Toxicity Hemocompatibility Cytotoxicity Sensitization Irritation/Intracutaneous reactivity Results: Pass

[a] See Biocompatibility information and reference provided in Section 3.2.P.2.4.5.1.7.1

Reviewer Comments/Conclusions

Did the Sponsor complete a chemical characterization?	☒ Yes	☐ No	☐ N/A

Review of Chemical Characterization
Conclusions: "Rated as toxicologically safe"

Reviewer Comments/Conclusions

Biocompatibility Stock IR

Please find below the fremanezumab naked pre-filled syringe (NPFS) design verification testing summary tables (Table 1 through Table 4), which capture functional performance testing requirements of the pre-filled syringe combination product. It includes summaries of the Physical Testing (Table 1), Biocompatibility Information (Table 2), Distribution Testing (Table 3), and Shelf Life testing (Table 4). The tables capture the traceability of the inputs (design inputs and their source), output specifications (specific characteristic attribute and acceptance criteria), and results from the testing of the combination product as recorded in the design verification report and batch analyses results submitted in the BLA.

Note that this document also provides the rationale for the selection of the proposed acceptance criteria for Break Loose Force, Glide Force (attributes listed in the functionality aspects of the specification) and Needle Removal Force as discussed in the (b) (4) *. In addition, the document also refers to the Container Closure Integrity (an attribute that is also part of the specification for fremanezumab, Injection;*

Section 3.2.P.5.1, Table 1). As noted in the design verification column, all results obtained met the requirements set in the design outputs documentation.

Verification Testing Summaries

Table 1: Physical Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
1	The product's rigid needle shield shall be removed at a force no more than (b) (4)	(b) (4) The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference.	RNS is removed at ≤ (b) (4)	**Testing Data:** Mean: 15N Min: 8N Max: 27N **Sample Size:** 29 **Results:** Pass
2	The product shall require a push force (i.e. activation and delivery forces) no more than (b) (4)	(b) (4) The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference. In addition, this action is considered worst case as it is a horizontal force rather than vertical.	Push force is < (b) (4) at the speed of (b) (4) mm/min	**Testing Data:** Break Loose Force: Mean: 6N Min: 6N Max: 6N Glide Force: Mean: 6N Min: 6N Max: 7N **Sample Size:** 29 **Results:** Pass

Table 1: Physical Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
3	The product shall expel no less than the labelled volume (1.5mL)	United States Pharmacopeia (USP) General Chapters <1> Injections; Determination of Volume of injection in containers; Injections in Cartridges or Prefilled Syringes *"The volume measured for each of the containers is not less than the nominal volume".* ISO 11040-8:2016, *Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes*, Clause 7.5, Deliverable Volume ISO 11608-1:2014, *Needle-based injection systems for medical use – Requirements and test methods* – Part 1: *Needle-based injection systems*, Clause 7, *Determination of dose accuracy*	Product dispenses ≥1.5mL of drug product	**Testing Data:** Tested at 5°C,* Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 23°C, * Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 40°C, * Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml **Sample Size:** 60 **Results:** Pass

Table 1: Physical Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
4	The product's syringe barrel shall not leak	(b) (4)	Syringe assembly including plunger stopper does not leak drug product	**Liquid Leakage:** No leakage under 110 kPa pressure for 5 seconds **Results:** Pass Max Force to Create Leak (N): ≥(b) (4) **Testing Data:** Mean: 91N Min: 68N Max: 107N **Sample Size:** 29 **Results:** Pass
				Container Closure Integrity: No leak detected; CCI Voltage between 1.0-4.0 VDC **Sample Size:** 299 **Results:** Pass

* pre-condition 20 samples at 5°C, 20 samples at 23°C, 20 samples at 40°C in accordance with ISO 11608-1:2015

Table 2: Biocompatibility Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product's syringe barrel, needle, backstop and plunger rod shall be biocompatible	ISO 10993-1:2009, *Biological evaluation of medical devices* – Part 1: Evaluation and testing within a risk management process The intended users' unbroken skin will make contact with the combination products' syringe glass barrel during use	Product (and its components Needle, Syringe Barrel, Plunger Rod and Back Stop) is biocompatible for its intended use	Biological* Evaluation indicates product's syringe barrel, needle, backstop and plunger rod are biocompatible for its intended use. This was done in consideration with following: Acute Systemic Toxicity Hemocompatibility Cytotoxicity Sensitization Irritation/Intracutaneous reactivity **Results: Pass**

* See Biocompatibility information and reference provided in Section 3.2.P.2.4.5.1.7.1

Table 3: Distribution Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product shall maintain its functional performance and integrity after transportation, storage and manual handling	MDD 93/42/EEC, *Essential Requirements, General Requirements I*, Section 5, October 2007	Product's packaging ensures the product has functional performance and integrity	Results of testing show that the product maintains its functional performance and integrity after transportation, storage and manual handling i.e., compliance with break loose, glide force delivered volume and leakage rate etc. **Results: Pass**
2	The product's carton shall maintain its functional performance after transportation, storage and manual handling	MDD 93/42/EEC, *Essential Requirements, General Requirements I*, Section 5, October 2007	The product's carton protects the product from damage	Results of testing show that the product's carton maintains its functional performance after transportation, storage and manual handling **Results: Pass**
3	The product's cartons shall be compatible with storage condition of 2-8°C	The drug product requires refrigeration between 2-8°C	Product meets its specification when stored at 2-8°C	Results of testing show that the product's cartons are compatible with storage condition of 2-8°C **Results: Pass**
4	The product shall be held in a registered position within the carton	(b) (4)	Product's carton tray has a recess that the product sits within and is constrained by it	Results of testing show that the product is held in a registered position within the carton **Results: Pass**

Table 3: Distribution Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
5	The product's information for use shall maintain its integrity when manually handled	(b) (4) *prefilled syringes*, have an instruction for use and a prescribing leaflet	IFU meets its specification post distribution testing and inspection	Results of testing show that the product's information for use maintains its integrity when manually handled **Results: Pass**
6	The product's prescribing information shall maintain its integrity when manually handled	(b) (4) *prefilled syringes*, have an instruction for use and a prescribing leaflet	Prescribing information meets its specification post distribution testing and inspection	Results of testing show that the product's prescribing information maintains its integrity when manually handled **Results: Pass**

Table 4: Shelf Life Testing Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product shall have a shelf life no less than 24 months[a]	Shelf-life strategy established for the combination product includes, but is not limited to, assessing the safety and efficacy of the product over an accelerated aging of up to 6 months and real-time age of 24 months.	Product meets its specification at the end of its shelf life	Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product has a shelf life at least 24 months **Results: Pass**
2	The product's plunger stopper shall provide sealing against the product's syringe barrel	(b) (4)	Product does not leak over its shelf life	Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product's plunger stopper provides sealing against the product's syringe barrel over its shelf life[a] **Results: Pass**

[a] Further accelerated age testing is in progress to collect shelf life data of T=9 months (equivalent to 36-month shelf life). Results of testing will be amended to 3- year shelf life once the supporting data is available.

Design Verification Recommendation	
The Sponsor Provided Complete Design Verification for the Device Constituent	☒
The Sponsor **DID NOT** Provide Complete Design Verification for the Device Constituent	☐
Design Verification Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #
All Information Requests were **Resolved** over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Summary

Risk Analysis Attributes	**Yes**	**No**	**N/A**

Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		

7.2. Summary of Risk Analysis

During the development of the device constituent part of the fremanezumab, Injection, Teva's risk management activities have been conducted in accordance with the requirements of ISO 14971:2007 Medical devices – Application of risk management to medical devices and EN ISO 14971:2012 Medical devices – Application of risk management to medical devices.

In alignment with the requirements, a Risk Management Plan has been approved, which details the risk management activities per development phase, the risk management documents to be reviewed per development phase, roles and responsibilities, verification activities, and the approach to reviewing production and post-production surveillance information on an annual basis.

Furthermore, a Hazards List has been approved that details the hazards associated with the fremanezumab, Injection in both normal and foreseeable misuse situations.

A Use Failure Mode Effect Analysis (uFMEA), Design Failure Mode Effect Analysis (dFMEA), Process FMEA (pFMEA), have been authored and approved for fremanezumab, Injection. The dFMEA identified, analyzed, and mitigated hazards related to biocompatibility of components, incorrect geometry of components, interfacing issues between components, packaging and labeling related hazards, etc. Table 13 summarizes highest level of design risks (severity levels of critical and catastrophic) analyzed within the dFMEA.

Hazard categories:

- Highest level of design risks: label is illegible, missing information, materials are not biocompatible or drug compatible, barrel view is occluded, needle shield doesn't fit,
- Highest level of use related risks (tested in HF): inappropriate disposal, failure to check drug information, improper storage, improper visual inspection
- Highest level of process related risks: illegible label, wrong materials, drug degradation, loss of sterility, product tampering, drug contamination.
- No additional clinical hazards need be addressed

Risk Analysis Stock IR

Risk Analysis Recommendation	
The Sponsor provided complete Risk Analysis for the Device Constituent	☒
The Sponsor **DID NOT** provide There are Complete Response Deficiencies, See Section 13 Risk Analysis for the Device Constituent	☐
Risk Analysis Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #

All Information Requests were **Resolved** over the course of the review	☐
There are Complete Response Deficiencies, See Section 12	☐

8. LABELING

Pre-Filled Syringe Labeling Checklist

Attribute		Present		
		Yes	**No**	**N/A**
Device Type	Type- pre filled syringe	X		
	Syringe Size(s) - 2.25mLsyringe with 1.5mL volume	X		
	Needle Gauge - 27G	X		
	Needle Length - 0.5in	X		
	Quantity - 1	X		
Prescription Statement under 801.109(b)(1), except for insulin syringes		X		
Any instructions for using specialized syringes such as the anti-needlestick devices and cartridge syringes;				X
Any specific drug or biologic use;				X

8.1. Device Labels

Draft carton label:

(b) (4)

Draft syringe label:

(b) (4)

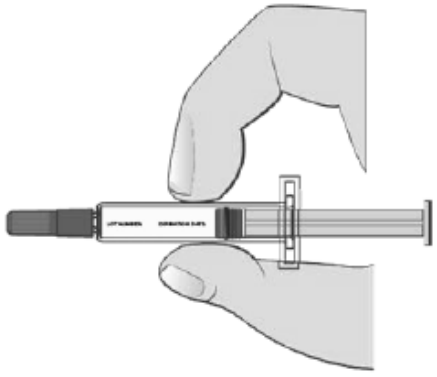
Reviewer Comment: The labeling is acceptable. And includes an Rx statement, manufacturer contact information, lot number, expiration date, single use only.

8.2. Instructional Labeling

Description of instructions for use:
Each step includes a title, a few bullets of detailed instruction, and a picture of the pre-filled syringe as it would look at that step. See example for step 1 below. A brief description of each step is included below.

Step 1. Remove the pre-filled syringe from the carton.

- **Hold** the pre-filled syringe (as shown in **Figure C).**
- **Remove** the syringe from the carton.
- **Do not** shake the pre-filled syringe at any time as this could affect the way the medicine works.



13. Remove the pre-filled syringe from the carton.
14. Gather the supplies you will need to inject AJOVY
    - The supplies include an alcohol swab, gauze pad, and a sharps disposal container
15. Let AJOVY reach room temperature
16. Wash your hands
17. Look closely at your AJOVY pre-filled syringe
18. Choose your injection area
19. Clean your injection area
20. Remove the needle cap and do not replace
21. Give your injection following the 4 steps below
    - Steps indicate to pinch the skin, insert needle, push the plunger, push the plunger all the way down slowly.
22. Remove the needle from your skin
23. Apply pressure at the injection site

24. Dispose of your pre-filled syringe right away

Reviewer Comment: The instructions for use are clear and easy to understand. This is acceptable.

8.3. Warnings/Precautions/Contraindications

- AJOVY pre-filled syringe is for single-time (one-time) use only. Put AJOVY in a FDA-cleared sharps disposal container right away after use. Do not throw away (dispose of) your used sharps disposal container in your household trash.
- Keep AJOVY pre-filled syringe out of the reach of small children.
- After you remove the needle cap from AJOVY **do not** touch the needle to prevent infection.
- **Do not** pull back on the plunger at any time as this can break the pre-filled syringe.
- **Do not** inject AJOVY in your veins (intravenously).
- **Do not** re-use your AJOVY pre-filled syringe as this could cause injury or infection.
- **Do not** share your AJOVY pre-filled syringe with another person. You may give another person an infection or get an infection from them.
- You may give AJOVY yourself. If you feel uncomfortable, you should not receive your first dose of AJOVY until you or your caregiver receive training from a healthcare provider on the right way to use AJOVY.

Reviewer Comment: The warnings are acceptable.

Labeling Recommendation		
The Sponsor provided complete Labeling for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Labeling for the Device Constituent		☐
Labeling Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

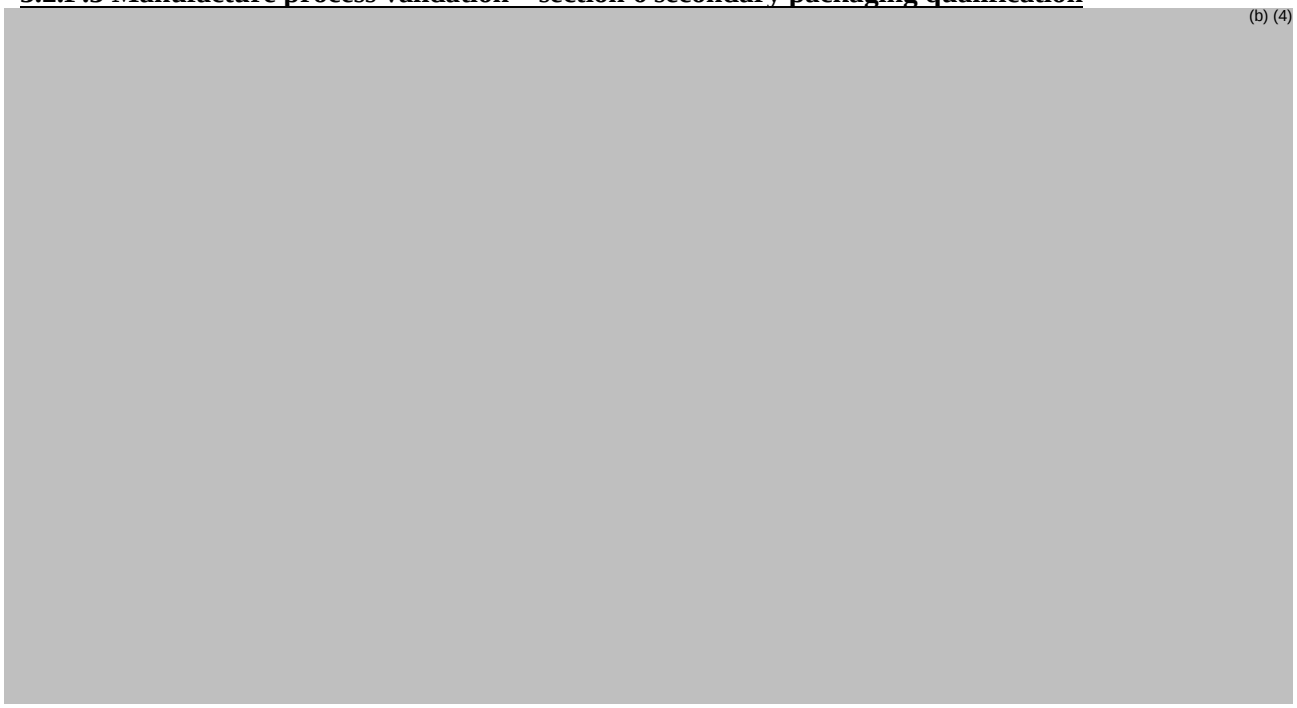
Release Specifications

Attribute	Specification	Test Method
Dose Accuracy	(b) (4)	Volume in container after filling with drug
Audible / Visual information on injection status		Visual inspection – syringe should be clear
Break Loose/Glide Force	(b) (4)	Injection final release

Teva has, for its commercial presentation, transferred production specifications and test methods, in accordance with the requirements of Part h of CFR 21 Part 820.30, Design Control, to Teva's CMO.

3.2.P.3 Manufacture process validation – section 6 secondary packaging qualification

(b) (4)



3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Release Specifications Recommendation		
The Sponsor provided complete Release Specifications for the Device Constituent		☒
The Sponsor **DID NOT** provide complete Release Specifications for the Device Constituent		☐
Release Specifications Information Requests	Section 11.3 Mid-Cycle IRs - # Section 11.4 Interactive IRs - #	
All Information Requests were **Resolved** over the course of the review		☐
There are Complete Response Deficiencies, See Section 12		☐

9.1. Mid-Cycle Information Requests

Are there Mid-Cycle review information requests? ☐ No ☒ Yes

Agency Information Request # (Sent on 1/9/2018) - ADEQUATE
Provide the traceability matrix for specifications to performance data.

Sponsor Response (received on 1/23/2018)
Please find below the fremanezumab naked pre-filled syringe (NPFS) design verification testing summary tables (Table 1 through Table 4), which capture functional performance testing requirements of the pre-filled syringe combination product. It includes summaries of the Physical Testing (Table 1), Biocompatibility Information (Table 2), Distribution Testing (Table 3), and Shelf Life testing (Table 4). The tables capture the traceability of the inputs (design inputs and their source), output specifications (specific characteristic attribute and acceptance criteria), and results from the testing of the combination product as recorded in the design verification report and batch analyses results submitted in the BLA.

Note that this document also provides the rationale for the selection of the proposed acceptance criteria for Break Loose Force, Glide Force (attributes listed in the functionality aspects of the specification) and Needle Removal Force as discussed in the (b) (4) In addition, the document also refers to the Container Closure Integrity (an attribute that is also part of the specification for fremanezumab, Injection; Section 3.2.P.5.1, Table 1). As noted in the design verification column, all results obtained met the requirements set in the design outputs documentation.

Table 1: Physical Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
1	The product's rigid needle shield shall be removed at a force no more than (b) (4)	(b) (4) The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference.	RNS is removed at ≤ (b) (4)	**Testing Data:** Mean: 15N Min: 8N Max: 27N **Sample Size:** 29 **Results: Pass**
2	The product shall require a push force (i.e. activation and delivery forces) no more than (b) (4)	(b) (4) The force required was selected to reflect a 'worst case' intended user (i.e. caregiver) of 13 years old. The action applied by the caregiver during intended use is judged to be similar to the action applied during the research reported in the above reference. In addition, this action is considered worst case as it is a horizontal force rather than vertical.	Push force is < (b) (4) at the speed of (b) (4)	**Testing Data:** Break Loose Force: Mean: 6N Min: 6N Max: 6N Glide Force: Mean: 6N Min: 6N Max: 7N **Sample Size:** 29 **Results: Pass**

Table 1: Physical Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
3	The product shall expel no less than the labelled volume (1.5mL)	United States Pharmacopeia (USP) General Chapters <1> Injections; Determination of Volume of injection in containers; Injections in Cartridges or Prefilled Syringes "*The volume measured for each of the containers is not less than the nominal volume*". ISO 11040-8:2016, *Prefilled syringes – Part 8: Requirements and test methods for finished prefilled syringes,* Clause 7.5, Deliverable Volume ISO 11608-1:2014, *Needle-based injection systems for medical use – Requirements and test methods* – Part 1: *Needle-based injection systems*, Clause 7, *Determination of dose accuracy*	Product dispenses ≥1.5mL of drug product	**Testing Data:** Tested at 5°C,[a] Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 23°C, [a] Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml Tested at 40°C, [a] Mean: 1.6 ml Min: 1.5 ml Max: 1.6 ml **Sample Size:** 60 **Results:** Pass

Table 1: Physical Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No	DI	DI Source	Specific Characteristic	
4	The product's syringe barrel shall not leak	(b) (4)	Syringe assembly including plunger stopper does not leak drug product	**Liquid Leakage:** No leakage under 110 kPa pressure for 5 seconds **Results: Pass** Max Force to Create Leak (N): ≥ (b) (4) **Testing Data:** Mean: 91N Min: 68N Max: 107N **Sample Size:** 29 **Results: Pass**
				Container Closure Integrity: No leak detected; CCI Voltage between 1.0-4.0 VDC **Sample Size:** 299 **Results: Pass**

[a] pre-condition 20 samples at 5°C, 20 samples at 23°C, 20 samples at 40°C in accordance with ISO 11608-1:2015

Table 2: Biocompatibility Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product's syringe barrel, needle, backstop and plunger rod shall be biocompatible	ISO 10993-1:2009, *Biological evaluation of medical devices* – Part 1: Evaluation and testing within a risk management process The intended users' unbroken skin will make contact with the combination products' syringe glass barrel during use	Product (and its components Needle, Syringe Barrel, Plunger Rod and Back Stop) is biocompatible for its intended use	Biological[a] Evaluation indicates product's syringe barrel, needle, backstop and plunger rod are biocompatible for its intended use. This was done in consideration with following: Acute Systemic Toxicity Hemocompatibility Cytotoxicity Sensitization Irritation/Intracutaneous reactivity **Results: Pass**

[a] See Biocompatibility information and reference provided in Section 3.2.P.2.4.5.1.7.1

Table 3: Distribution Tests Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product shall maintain its functional performance and integrity after transportation, storage and manual handling	MDD 93/42/EEC, *Essential Requirements, General Requirements I*, Section 5, October 2007	Product's packaging ensures the product has functional performance and integrity	Results of testing show that the product maintains its functional performance and integrity after transportation, storage and manual handling i.e., compliance with break loose, glide force delivered volume and leakage rate etc. **Results: Pass**
2	The product's carton shall maintain its functional performance after transportation, storage and manual handling	MDD 93/42/EEC, *Essential Requirements, General Requirements I*, Section 5, October 2007	The product's carton protects the product from damage	Results of testing show that the product's carton maintains its functional performance after transportation, storage and manual handling **Results: Pass**
3	The product's cartons shall be compatible with storage condition of 2-8°C	The drug product requires refrigeration between 2-8°C	Product meets its specification when stored at 2-8°C	Results of testing show that the product's cartons are compatible with storage condition of 2-8°C **Results: Pass**
4	The product shall be held in a registered position within the carton	(b) (4)	Product's carton tray has a recess that the product sits within and is constrained by it	Results of testing show that the product is held in a registered position within the carton **Results: Pass**

Table 3: Distribution Tests Summary (Continued)

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
5	The product's information for use shall maintain its integrity when manually handled	(b) (4) *prefilled syringes*, have an instruction for use and a prescribing leaflet	IFU meets its specification post distribution testing and inspection	Results of testing show that the product's information for use maintains its integrity when manually handled **Results: Pass**
6	The product's prescribing information shall maintain its integrity when manually handled	(b) (4) *prefilled syringes*, have an instruction for use and a prescribing leaflet	Prescribing information meets its specification post distribution testing and inspection	Results of testing show that the product's prescribing information maintains its integrity when manually handled **Results: Pass**

Table 4: Shelf Life Testing Summary

	Design Inputs (DI)		Design Outputs (DO)	Design Verification
S. No.	DI	DI Source	Specific Characteristic	
1	The product shall have a shelf life no less than 24 months[a]	Shelf-life strategy established for the combination product includes, but is not limited to, assessing the safety and efficacy of the product over an accelerated aging of up to 6 months and real-time age of 24 months.	Product meets its specification at the end of its shelf life	Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product has a shelf life at least 24 months **Results: Pass**
2	The product's plunger stopper shall provide sealing against the product's syringe barrel	(b) (4)	Product does not leak over its shelf life	Results of accelerated aging of T=6 months (equivalent to 24-month shelf life) shows that the product's plunger stopper provides sealing against the product's syringe barrel over its shelf life[a] **Results: Pass**

[a] Further accelerated age testing is in progress to collect shelf life data of T=9 months (equivalent to 36-month shelf life). Results of testing will be amended to 3- year shelf life once the supporting data is available.

Reviewer Comments: The traceability matrix is acceptable.

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

10.COMPLETE RESPONSE DEFICIENCIES

There are no outstanding unresolved information requests, therefore CDRH does not have any deficiencies for a CR Letter.

11.RECOMMENDATION

11.1. Recommendation to CDER/OPQ

CDRH is recommending that the device constituent of the combination product is approvable for the proposed indication.

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	September 13, 2018
Reviewer:	Hongliu Ding, MD, PhD, MPH Division of Epidemiology I
Team Leader:	Kira Leishear, PhD, MS Division of Epidemiology I
Division Deputy Director:	Sukhminder K. Sandhu, PhD, MS, MPH Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Ajovy (fremanezumab)
Application Type/Number:	BLA 761089
Applicant/sponsor:	Teva Pharmaceuticals
OSE RCM #:	2018-870

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Ajovy (fremanezumab) is a fully humanized immunoglobulin G2 (IgG2) Δa/kappa mAb (b) (4) with a proposed indication for the preventive treatment of episodic and chronic migraine in adults via subcutaneous injection only. There are two dosing options: 225 mg monthly, or 675 mg every 3 months (administered as 3 consecutive injections of 225 mg each). This drug binds to the calcitonin gene-related peptide (CGRP) receptor and blocks both CGRP isoforms (α- and β-CGRP).[1, 2] Nonclinical studies demonstrated that it prevents CGRP-induced cyclic adenosine monophosphate production.[3] In addition, the findings from a study of fremanezumab in male and female rats suggest that the therapeutic benefit of fremanezumab may be associated with the modulation of CGRP-rich high threshold neurons and reduce headaches of intracranial origin.[4]

1.2. Describe the Safety Concern

Safety during pregnancy due to drug exposure is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[5] There are no adequate and well-controlled studies that investigated adverse pregnancy outcomes after fremanezumab exposure. Animal studies did not find any negative effects on fertility, or early or late embryofetal development in rats and rabbits at doses up to 200 mg/kg/week and 100 mg/kg, respectively. In the fremanezumab clinical studies, women who were pregnant were excluded and birth control during participation was required for women of reproductive potential. However, a total of 8 pregnancies in patients exposed to fremanezumab, 4 prior to the pregnancies and 4 in the first trimester were reported. For the 4 women who were exposed to fremanezumab prior to pregnancy, the time between the last exposure and the start of pregnancy was not reported; fremanezumab has a long half-life of approximately 31 days. The pregnancy outcomes included four elective abortions, two spontaneous abortions, one full-term baby born with jaundice, and one unknown outcome. Overall, the data on pregnancy exposure during clinical trials are insufficient to inform the risk associated with fremanezumab.

Given that monoclonal antibodies are transported across the placenta[6], exposure to the fetus in women treated with fremanezumab during pregnancy is likely. Furthermore, fremanezumab has a long half-life which is an additional concern of exposure to the fetus in women who are pregnant, plan to become pregnant, or of childbearing potential while using fremanezumab.

In the current proposed labeling, as of September 13, 2018, the Risk Summary in Section 8.1 Pregnancy, states: "There are no adequate data on the developmental risk associated with the use of AJOVY in pregnant women. AJOVY has a long half-life [see Clinical Pharmacology (12.3)]. This should be taken into consideration for women who are pregnant or plan to become pregnant while using AJOVY."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	x

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☒ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☒ Electronic database study without chart review

☐ Other, please specify: *Click here to enter text.*

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population

☐ Exposures

☒ Outcomes

☐ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: Current ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.

We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

2.5. Please include the proposed PMR language in the approval letter.

The Division of Neurology Products requests two PMRs related to pregnancy outcomes. As of September 13, 2018, the proposed PMR language, for these are:

PMR 3485-5 "Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with migraine exposed to Ajovy during pregnancy with two unexposed control populations: one consisting of women with migraine who have not been exposed to Ajovy before or during pregnancy and the other consisting of women without migraine. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life."

and

PMR 3485-6 "Conduct a pregnancy outcomes study using a different study design than provided for in PMR 3485-5 (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to Ajovy during pregnancy compared to an unexposed control population."

3. References

1. Bigal ME, Escandon R, Bronson M, et al. Safety and tolerability of LBR-101, a humanized monoclonal antibody that blocks the binding of CGRP to its receptor: Results of the Phase 1 program. Cephalalgia. 2014;34(7):483-492.
2. Walter S, Bigal ME. TEV-48125: a review of a monoclonal CGRP antibody in development for the preventive treatment of migraine. Curr Pain Headache Rep. 2015;19(3):6.
3. Jorg Z. Determination of the antagonist potency of PF-04227429 (RN307) for the human and rat alpha-cgrp by camp cell based assay and receptor binding assay. Study Report 092905, BLA761089, 2009.
4. Melo-Carrillo A, Noseda R, Nir RR, et al. Selective Inhibition of Trigeminovascular Neurons by Fremanezumab: A Humanized Monoclonal Anti-CGRP Antibody. J Neurosci. 2017;37(30):7149-7163.
5. Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR). https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed May 2, 2018.
6. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104(1):228-233.

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/

KIRA N LEISHEAR on behalf of HONGLIU DING
09/14/2018

KIRA N LEISHEAR
09/14/2018

SUKHMINDER K SANDHU
09/14/2018

JUDITH W ZANDER
09/14/2018

MICHAEL D NGUYEN
09/14/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 4, 2018
To:	Billy Dunn, MD Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Karen Dowdy, RN, BSN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	AJOVY (fremanezumab-vfrm)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761089
Applicant:	Teva Branded Pharmaceutical Products R&D, Inc.

1 INTRODUCTION

On October 16, 2017, Teva Branded Pharmaceutical Products R&D, Inc. submitted for the Agency's review an Original Biologics License Application (BLA) for AJOVY (fremanezumab-vfrm) injection. AJOVY (fremanezumab-vfrm) injection is a New Molecular Entity (NME) with the proposed indication for the preventive treatment of migraine in adult patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology Products (DNP) on November 9, 2017 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for AJOVY (fremanezumab-vfrm) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on June 25, 2018.

2 MATERIAL REVIEWED

- Draft AJOVY (fremanezumab-vfrm) injection PPI received on October 16, 2017 and received by DMPP and OPDP on August 21, 2018.
- Draft AJOVY (fremanezumab-vfrm) injection IFU received on July 25, 2018 and received by DMPP and OPDP on August 21, 2018.
- Draft AJOVY (fremanezumab-vfrm) injection Prescribing Information (PI) received on October 16, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 23, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10. We reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI or IFU.

Please let us know if you have any questions.

19 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

KAREN M DOWDY
09/04/2018

DHARA SHAH
09/04/2018

MARCIA B WILLIAMS
09/04/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 04, 2018

To: Heather Fitter, M.D.
Division of Neurology Products (DNP)

Lana Chen, Regulatory Project Manager, DNP

Tracy Peters, Associate Director for Labeling, DNP

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for AJOVY™ (fremanezumab-vfrm) injection, for subcutaneous use

BLA: 761089

In response to DNP consult request dated November 9, 2017, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original BLA submission for AJOVY™ (fremanezumab-vfrm) injection, for subcutaneous use (Ajovy).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DNP (Lana Chen) on August 21, 2018, and are provided below.

PPI and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFUs were sent under separate cover on September 4, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 22, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

DHARA SHAH
09/04/2018

Clinical Inspection Summary - Addendum

Date	08/11/2018
From	Cara Alfaro, Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lana Chen, Regulatory Project Manager Suhail Kasim, Medical Officer Division of Neurology Products
BLA #	761089
Applicant	Teva Branded Pharmaceutical Products R&D, Inc.
Drug	Fremanezumab
NME	Yes
Proposed Indication	Prophylaxis of migraines in adults
Consultation Request Date	12/18/2017
Summary Goal Date	4/16/2018
Action Goal Date	6/16/2018
PDUFA Date	6/16/2018, extended to 9/16/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This Clinical Inspection Summary (CIS) Addendum provides a summary of two clinical investigator inspections (b) (4) These inspections related to the conduct of clinical investigators with regard to Protocol TV48125-CNS-30050 only. They were completed after the initial CIS was finalized (refer to CIS entered into DARRTS on 4/12/2018).

(b) (4) inspections of two clinical investigator sites: Dr. Sean Peterson (Site 11123, Canada) and Dr. Takao Takeshima (Site 84062, Japan). These inspectional findings were communicated to OSI. EMA did not identify any critical findings but did identify major and minor inspectional findings. Many of the findings, for both the sponsor and clinical investigator inspections, related to inadequate or incomplete documentation.

(b) (4) find evidence of underreporting of adverse events at Site #11123. Specifically, three instances of injection site erythema (>5mm) and mild pain occurring in one of nine enrolled subjects who received fremanezumab were not reported by the clinical investigator. In the sponsor's response to the inspectional findings, it was stated that Teva "evaluated all data and identified nine events which were recorded as injection site reactions but were not captured as adverse events". The sponsor stated that these unreported adverse events were distributed between placebo and active treatment groups and did not impact the adverse event profile of fremanezumab with regard to injection site reactions. However, this response did not provide further details for these adverse events, including whether these nine events were in the overall study program or pertained specifically to this site.

(b) (4) Although it is unlikely that these nine unreported injection site adverse reactions would alter the overall safety analyses, the extent of the underreporting is not known. The EMA finding of underreporting of adverse events occurred in one of two inspected sites for the one protocol evaluated, Protocol TV48125-CNS-30050. Of note, the three clinical investigator inspections conducted by FDA for Protocols TV48125-CNS-30049 and TV48125-CNS-30050 did not find evidence of underreporting of adverse events.

Due to the finding of underreporting of injection site reactions at Site #11123 for Protocol TV48125-CNS-30050 and the sponsor's response identifying nine injection site reactions that were not captured as adverse events, OSI recommends that the review division ask the sponsor whether there are further injection site reactions that were not captured as adverse events for Protocols TV48125-CNS-30049 and TV48125-CNS-30050 and to provide a safety analysis including these additional events.

II. BACKGROUND

Refer to CIS entered into DARRTS on 4/12/2018.

III. RESULTS

(b) (4)

Dr. Sean Peterson, Site #11123/Canada

This site enrolled 9 subjects in Protocol TV48125-CNS-30050.
No critical findings were identified during the inspection, but 10 major and 6 minor findings were noted. Major findings included the following:

- The clinical investigator did not maintain a detailed list of duties delegated to study personnel.
- Study documentation did not show that the medical care was always given and the medical decisions were always made by a qualified physician.
- The clinical investigator did not have sufficient oversight of the trial, as not all individuals involved in conducting the trial were qualified by education, training, and experience to perform the respective tasks.
- The clinical investigator did not maintain adequate and accurate source documents and trial records.
- Adverse events and/or laboratory abnormalities were not properly evaluated or reported to the sponsor per reporting requirements in the protocol.

  This site enrolled 9 subjects in this study and reported a total of two adverse events occurring in one subject. (b) (4) inspector noted three instances of injection site erythema >5 mm with mild pain occurring in one subject (Subject (b) (6) fremanezumab) that were not included in sponsor line listings. The clinical

investigator stated that he determined that these adverse events were not clinically significant and contacted the Medical Monitor, who accepted this assessment (no documentation of this communication was available). In the sponsor's response to the inspection findings, it was stated that Teva evaluated "all data and identified nine events which were recorded as injection site reactions but were not captured as adverse events". Teva stated that these adverse events were distributed between placebo and active treatment groups and did not impact the AE profile relating to injection site reactions. However, details of these adverse events (subject number, severity, treatment group) were not provided in the response document. No corrective action plan was outlined to address this inspectional finding.

- The CRO/monitor and the site could not show implementation of procedures that assured the proper, traceable, and attributable handling of investigational product.

Reviewer comments: The clinical investigator stated that he did not report the injection site reactions, as he deemed them not clinically significant; however, that is not the criteria for reporting adverse events. Further, the sponsor's response to this finding included identification of nine similar adverse events that were not captured as adverse events, but no further information about these events was provided. This raises concerns regarding overall underreporting of injection site reactions in the clinical trial program, which the sponsor should address in a more comprehensive manner. It is not known how the sponsor was able to detect these nine additional injection site adverse events; if unreported, the sponsor would not have these data.

Dr. Takao Takeshima, Site #84062/Japan
This site enrolled 15 subjects in Protocol TV48125-CNS-30050.

No critical findings were identified during the inspection, but 10 major and 6 minor findings were noted. Major findings included the following:

- The clinical investigator did not maintain a detailed list of duties delegated to study personnel
- The clinical investigator did not ensure that each individual involved in conducting the trial was qualified, especially the subcontracted study coordinators
- The clinical investigator was not familiar with the emergency unblinding procedure and also not considered able to provide his staff appropriate GCP/protocol training to

handle unexpected situations or to promptly address issues with GCP/protocol compliance and had therefore insufficient oversight of the study

- All IRB submission and review/approval documents were without signatures, stamps, or letter heads; therefore, the originality of the IRB review and approval documentation could not be confirmed.
- The clinical investigator did not maintain adequate and accurate medical records and other trial records to allow the confirmation of subject eligibility
- CRO/monitor and the site could not show implementation of procedures that assured the proper, traceable, and attributable handling of investigational product.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D. for
Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/BLA #761089
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Heather Fitter
DNP/Medical Officer/Suhail Kasim
DNP/Project Manager/Lana Chen
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

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/

CARA L ALFARO
08/11/2018

PHILLIP D KRONSTEIN
08/11/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 31, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761089
Product Name and Strength:	Ajovy (fremanezumab-vfrm) injection 225 mg/1.5 mL (150 mg/mL)
Applicant/Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
FDA Received Date:	April 12, 2018, July 5, 2018, July 25, 2018
OSE RCM #:	2018-76-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products requested that we review the revised carton labeling and container label (Appendix A) and Instructions for Use for Ajovy to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made as a result of the conditional approval of the non-proprietary name suffix, -vfrm[a], recommendations that The Office of Biotechnology Products and DMEPA submitted as an Information Request on April 9, 2018[b], and recommendations made based on the results of the three Human Factors Validation Studies.

2 CONCLUSION

[a] Morris, C. Non-Proprietary Name Suffix MEMO for Ajovy (BLA 761089). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 10. RCM No.: 2018-76.

[b] April 9, 2018 Information request available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8048f8ea&_afrLoop=152480068042447 2&_afrWindowMode=0&Adf-Window-Id=winPop&_afrFS=16&_afrMT=screen&_afrMFW=1680&_afrMFH=881&_afrMFDW=1680&_afrMFDH=1050&_afr MFC=8&_afrMFCI=0&_afrMFM=0&_afrMFR=96&_afrMFG=0&_afrMFS=0&_afrMFO=0

The revised carton labeling and container label are unacceptable from a medication error perspective. The proposed expiration date format may increase the risk for degraded drug medication errors.

3 RECOMMENDATIONS FOR TEVA

We recommend the following be implemented prior to approval of this BLA:

A. As currently presented on the carton labeling and container label, the proposed format (MM/YYYY) for the expiration date is not acceptable. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like DDMMMYYYY (e.g., 31JAN2013), MMMYYYY (e.g., JAN2013), YYYY-MMM-DD (e.g., 2013-JAN-31), or YYYY-MM-DD (e.g., 2013-01-31).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

JOHN C MORRIS
07/31/2018

LOLITA G WHITE
07/31/2018

LABEL AND LABELING AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 21, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761089
Product Name and Strength:	Ajovy (fremanezumab-vfrm) injection 225 mg/1.5 mL (150 mg/mL)
Product Type:	Combination product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
Submission Date:	October 16, 2017, December 22, 2017, January 12, 2018
OSE RCM #:	2017-2192
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

This review provides our assessment of the container label, carton labeling, Prescribing Information (PI), Instructions for Use (IFU), Patient Information, Human Factors (HF) Validation Study, and supplemental HF validation studies 1 and 2 for Ajovy (fremanezumab-vfrm) as submitted by Teva on October 16, 2017, December 22, 2017, and January 12, 2018 for risk of medication error.

2 PRODUCT INFORMATION

Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody specific for calcitonin gene-related peptide (CGRP) and blocks CGRP from binding to the CGRP receptor, and is indicated for the preventive treatment of migraine in adult patients. The proposed dose of fremanezumab is 225 mg monthly or 675 mg every three months. (b) (4) Fremanezumab is a single-use, 225 mg/1.5 mL (150 mg/mL), pre-filled syringe intended for subcutaneous administration by patients, caregivers, or healthcare providers. Fremanezumab will be available in cartons containing one pre-filled syringe.

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the container label, carton labeling, Prescribing Information (PI), Instructions for Use (IFU), Patient Information, Human Factors (HF) Validation Study, and supplemental HF validation studies 1 and 2 for Ajovy (fremanezumab-vfrm) are as follows.

4.1 LABELS AND LABELING

Container label and carton labeling

Our review of the proposed container label, carton labeling, Instructions for Use (IFU), and Prescribing Information (PI) identified the following areas which may be improved to decrease risk of medication error:

- The format for the expiration date is not defined.
- The net quantity statement location and font size competes in with the NDC number and strength statement, which may increase the risk for wrong drug medication errors.

(b) (4)

Instructions for use (IFU)

- We reviewed the proposed IFU for risk of medication error and areas of needed improvement. Our review of the proposed IFU considering the human factors validation results finds the IFU unacceptable from a medication error perspective.

Prescribing Information (PI)

- The package type (single-dose or (b) (4)) is used inconsistently.

We provide recommendations regarding these areas below in Sections 5.1 and 5.2 to help minimize the potential for medication errors to occur with the use of this product.

4.2 HUMAN FACTORS (HF) STUDY RESULTS

Teva submitted results from three HF studies: Validation Study (SDT-INT1102), Supplemental Study 1 (SDT-INT1265), and Supplemental Study 2 (SDT-INT1266). In Validation Study (SDT-INT1102, we previously determined not all use scenarios and user groups were represented. Based on our recommendations, TEVA revised their study protocol and completed two additional supplemental studies to provide a complete evaluation of the user interface for all intended users, uses, and environments. Our review of the methodology for the simulated use HF validation study design(s) is acceptable. See Table 1 for a summary of objectives, methods, user groups, and results for the HF Validation Studies.

Although the Applicant identified 17 critical tasks for the proposed prefilled syringe that are required for the safe and effective use of the proposed product, based on the Applicant's risk analysis and the hazard to the patient if the user fails to perform this task or perform it, we disagree and categorized the five tasks below as critical for the safe and effective use of the product.

- 7.1 Choose injection site
- 9.4 Pinch the skin
- 9.6 Push the plunger to the bottom of the barrel
- 10.1 Do not recap needle/Dispose of used device
- 13.1 Understand the prescribed dosing regimen (3 injections [675 mg] once every three months

Our review of the remaining tasks identified by Teva as critical find that none of the failures would result in patient harm, delay in patient care, or require further mitigation. We find the use errors, close calls, and difficulties associated with critical tasks will provide robust data for the Agency to assess the safe and effective use of the product, and our review will focus on those critical tasks identified above.

Table 1: Summary of objectives, methods, user groups, and results for the HF Validation Studies to support the use of Ajovy (fremanezumab-vfrm)

Study Name	Validation Study		Supplemental Study 1				Supplemental Study 2	
Study Document	SDT-INT1102		SDT-INT1265				SDT-INT1266	
Study Objective and design differences between the 3 studies	To assess the safe and effective use of the user interface to support a single 225 mg injection in untrained representative users		To assess the safe and effective use of the user interface to support a single 225 mg injection in untrained representative users				To assess the safe and effective use of the user interface to support a 675 mg (3 injections) every 3 months dosing regimen (quarterly) in untrained representative users	
Method	Simulated Use (home environment)		Simulated Use (home and clinic environments)				Simulated Use (home environment)	
Representative user group	Adults (patient/caregiver) (n = 15)		Adolescent caregiver/ Adult patient pair (n = 18)		Healthcare providers (n = 17)		Adolescent caregiver/ Adult patient pair (n = 15)	
Task / # errors	Performance based	Knowledge based	Performance based	Knowledge based	Performance based	Knowledge based	Performance based	Knowledge based
7.1 Choose injection site	5	11	1	3	3	3	3	5
9.4 Pinch the skin	11	0	0	1	0	1	Supplemental HF Validation Study 2 only examined critical tasks that are unique to the 675 mg dose.	
9.6 Push the plunger to the bottom of the barrel	0	0	2	0	4	0		
2.1/10.1 Do not recap needle/dispose of used needle	7	7	2	0	0	0		
13.1 Understand the prescribed dosing regimen (3 injections [675 mg] once every three months)							4[a]	2

[a] Our review of the methodology find these four performance based errors are attributed to a use scenario methodology which are a result of the users (patients and caregivers) misinterpretation of the written prescription. In actual use, the prescription will be interpreted by a pharmacist, therefore we find these performance failures do not predict failures that may occur in real world use.

4.2.1 Validation Study (SDT-INT1102)

SDT-INT1102 is a simulated use (home environment) HF validation study conducted in fifteen (15) untrained representative users (See Appendix C). Each participant simulated a single injection (225 mg dose) into an injection pad with a pre-filled syringe. After the completion of all study tasks, participants were asked for subjective feedback and interviewed for root causes of any use events. Tables 2 and 3 provide summary and analyses of results for this study.

Table 3: Analyses of Critical Task Performance-based and Knowledge-based Errors for Adult Patients/Caregivers during HF Validation Study (SDT-INT1102)

Critical Task Description	Description of Use Error and Participant Subjective Feedback	Applicant's Root Cause Analysis and Proposed Mitigation	DMEPA's Analysis and Recommendation
7.1 Choose injection site (n=16)	Performance-based (n=5) 4 participants Injected chose to inject into the front of the upper arm (P02, P07, P08, P11) P02: She had not reviewed back of IFU P07: She thought that it functioned the same as shots she has had injected into the front of her upper arm. P08: Selected an injection site based on his memory or as he would have done with other similar devices.	Performance-based 1 Participant did not inject into appropriate injection sites because she chose to not turn the IFU to the backside and therefore did not see the information in Step 6. Moderator notes her focus was likely on the preparation like gathering and preparing supplies which fit her idea of how to inject, as opposed to checking for choosing an injection site because a doctor had always made that selection on the front of the arm for her. She did not know what the differences between subcutaneous, IM, or IV	Our review of the URRA notes that failure to choose an appropriate injection site may increase the risk for the user to inject at the wrong depth and possibly give an IM or IV injection. Administering the product via IM or IV injection may cause pain or alter the pharmacokinetics of fremanezumab which may change the clinical effect. We reviewed the subjective feedback Step 6, and all other areas of the IFU for clarity in instructions related to choosing the correct injection site. For the injection site at the belly button, we find Step 6 of the IFU provides clear instructions to avoid 2 inches around the belly button and is accompanied by an image of the

	P11: Thought it would function in the same way as injections she has previously seen which her doctor injected into "meaty" areas. 1 participant injected into the forearm (P05) P05: Said he selected the forearm because he thought it would be comfortable and easy to access. Knowledge-based (n=11) 6 participants did not respond to avoid injecting into area 2 inches around belly button (P01, P04, P08, P12, P13, P15) P01: Said she saw in Step 6 figure that the thigh was an acceptable location and chose to inject there. Did not read information about abdomen, and did not notice that the abdomen was not shaded around the belly button. Reported that the image did not communicate to her to not inject around the belly button, and suggested to include a red X over the belly button in the image if it	injections were, and since she recalled that doctors typically inject her somewhere on the arm, she assumed anywhere on the arm was an acceptable site. 4 participants did not read Step 6 in the IFU because the Naked PFS resembled injection devices they were familiar with; therefore, the participant chose to not look for the injection site information in the IFU. The Sponsor did not provide mitigation for these errors; however, they state, when directed to the IFU, all participants located and comprehended the appropriate injection sites Knowledge-based Among the 6 participants who did not initially identify the exclusion zone of two inches around the belly button: 4 participants thought that the diagram in Step 6 of the IFU did not clearly indicate that it was inappropriate to inject within two inches of the belly button. 1 participant responded 1” from the	abdomen with a white area within the blue shading indicating the there is an area of the abdomen to avoid. Although 3 participants provided subjective feedback that suggests the Sponsor use color coding to indicate the 2 inches around the belly button was not acceptable, we find the text associated with this step to be clear and that color coding would not specifically indicate that area is 2 inches wide and would not further mitigate this use error. Also, although 6 participants did not specifically respond to avoid the 2-inch area around the belly button during the knowledge assessment, the participants did not indicate they found that area to be acceptable. Therefore, we find the risk associated with the error of choosing the injection site closer than 2 inches surrounding the belly button is adequately mitigated. For the injection sites at the top of the thigh and the back of the arm, we find Step 6 of the IFU to inject into can be better presented although the Sponsor proposes no mitigation. Specifically, the blue shading in the image of the thighs and arm (b) (4) as

	is not acceptable. P04: Looked at image in Step 6 to answer knowledge task question and did not notice that the blue shaded abdomen was not shaded over the belly button. P08: no subjective feedback due to time constraints P12: Said that she would intuitively not inject near the belly button because this seemed unsafe, but said she initially only saw that the blue shaded area was over the abdomen and not that it did not include the belly button. The participant stated the Injection site image could be better color coded to indicate that the area 2 inches from the belly button was not acceptable P13: Said she thought Naked PFS would function the same as current syringe and vial insulin injection experience which she had been instructed to inject in the inner or outer thigh, or in the abdomen 1" away from the belly button.	belly button, and the inner and outer thigh based on her experience and she chose not to read the IFU. For 1 participant, no root cause was determined due to time constraints. When directed to the IFU, 1 participant initially did not locate instructions to inject at least 2 inches away from the belly button because she focused on the bolded text within each line rather than the unbolded text. The Sponsor did not provide mitigation for these errors; however, they state, the remaining 5 participants located and comprehended that you should inject in the shaded area 2 inches from the belly button. Among the 4 participants who responded to inject into the front of the upper arm or forearm (P02, P05, P07, P11): 1 Participant responded to inject into the front of the upper arm and did not mention the abdomen. Participant said that the information about all other	acceptable injection sites. We provide recommendation 3.c.i. in Section 5.2 to address our concern.

	P15: Had determined appropriate injection sites based on image in Step 6, which was unclear on instruction to not inject into the area 2 inches around the belly button because she missed the white area within the blue section that surrounded the depiction of the belly button. 4 participants responded to inject into the upper arm or forearm (P02, P05, P07, P11) P02: Said she remembered seeing an image in the IFU about injecting in the thigh and the arm, but did not read the information too carefully to know more information about any other injection sites. As soon as she decided to inject in the arm, she wanted to complete the injection as soon as possible and ignored all other details in the IFU. Did not think it was important to get more information regarding the injection site. P05: Answered based off preference because he thought it would be comfortable and easy	injection sites did not seem relevant after selecting an injection site. 1 Participant responded into the forearm because it was an easy site to access and he chose not to read the backside of the IFU. 1 participant answered based on experience and chose not to read the backside of the IFU. 1 participant thought that the Naked PFS resembled other familiar injection devices. 1 participant was not asked to locate or comprehend this information in the IFU. The Sponsor did not provide mitigation for these errors; however, they state, when the remaining 3 participants were directed to the IFU, they located and comprehended the correct injection site locations. For the 1 participant who responded to inject intravenously or intramuscularly, the device resembled syringes he had seen which were used for intravenous	

	to access. P07: Indicated that based on the appearance of the Naked PFS, she thought that it functioned the same as shots she has had injected into the front of her upper arm. P11: Said to inject into a "meaty" part of the body like the thigh or front of upper arm based off prior injections administered by HCPs. 1 participant responded IV or IM (P03). He reported that he thought based on the appearance of the Naked PFS that it functioned the same as other syringes he had seen which were used for intravenous injections.	injections; therefore, he chose not to read the IFU. The Sponsor did not provide mitigation for these errors; however, they state, when directed to the IFU, he located and comprehended the correct injection site locations.	
9.4 Pinch the skin (n=11) Performance-based	11 participants did not pinch the skin prior to injecting P02: Had only reviewed front of the IFU. P03: He thought based on the appearance of the Naked PFS that it functioned the same as other syringes he had seen, which he never noticed involved	10 participants thought that the Naked PFS resembled other familiar injection devices, so did not use the IFU and as such did not read Step 9. 1 participant did not read the information in Step 9 of the IFU because they chose to not read the backside of the IFU. 1 participant was not assessed for	According to the URRA, pinching a fold of skin at the injection site prior to injecting is important to ensure the injection is given at the correct depth. Administering the product at the wrong depth may increase the risk for an IM or IV injection. Administering the product via IM or IV injection may cause pain or alter the

	pinching the skin. P04: The Naked PFS design resembled the insulin injections she administers to herself daily, and she knows that pinching for her own injections is optional and is related to comfort meant for comfort. The participant commented that they did not know the harm associated with not pinching prior to injecting. P05: He thought he had enough knowledge from the front and from his familiarity with similar products to be able to use the Naked PFS. He did not expect pinching the skin to be necessary because he had never seen it done with other injections. P06: Read in the instructions to pinch prior to beginning the injection process, but did not pinch while injecting because of his current experience injecting insulin with a syringe and vial, which does not require pinching. P07: Indicated that based on the appearance of the Naked PFS, she thought that it functioned the same as other injectable devices which she	locating and comprehending the information due to time constraints. The Sponsor did not provide mitigation for these errors; however, they state, when directed to the IFU, the remaining 10 participants located and comprehend this information.	pharmacokinetics of fremanezumab which may change the clinical effect. We reviewed the participants feedback and Step 9 of the IFU to identify potential improvements to this use step. We determine Step 9 of the IFU provides clear text to pinch the skin and is accompanied by the first 2 images of a raised fold of skin between a thumb and index finger. We find the IFU mitigates this use error adequately, and that no further mitigation of this error is required.

	had never noticed required pinching the skin. P08: He did not know to pinch and he did not know the harm associated with not pinching prior to injecting. P09: Said she did not expect to need to pinch the skin because she thought that based on the familiar appearance of the Naked PFS, it would function in the same way as her current insulin syringe and vial injections which do not require it. P10: She thought pinching was not vital for this injection and thus she did not pinch for the Naked PFS. She did not know the harm associated with not pinching prior to injecting. P11: She had expected to know how to use the Naked PFS based off its resemblance to other "standard" devices that she had seen deliver injections.		
10.1 Do not recap needle / Dispose of used device (n=14)	Performance-based (n=7) 6 participants Recapped used Naked PFS (P02, P05, P08, P09, P11, P13) P02: She was not actively	Performance-based None of the participants read the information in Step 8 of the IFU. The Sponsor did not provide mitigation for these errors;	According to the URRA, recapping the needle or failure to properly dispose of the used device may increase the risk for a needle stick injury. We reviewed the participant's subjective feedback and Steps 8, 10,

	thinking about safe disposal because she was extremely nervous to interact with the needle and wanted to perform the injection and move on from using the device as quickly as possible. P05: Thought recapping would prevent exposed needle from causing injuries. P08: Thought that he was being safe by recapping the Naked PFS. 3 participants (P09, P11, P13) thought Exposed needles appeared hazardous. 1 participant (P02) also threw capped Naked PFS in household trash because she thought household trash was an appropriate disposal site because it had been recapped, which she thought took care of additional safety concerns. Knowledge-based (n=7) 7 participants responded should recap the needle after use (ID: P02, P03, P05, P07, P09, P11, P13)	however, they state, when directed to the IFU, 5 participants located and comprehended to not recap the needle 2 participants located but did not correctly comprehend information about not recapping because she had only read unbolded text to (b) (4) [redacted] 1 other participant located but did not correctly comprehend information about not recapping because due to the location of the "do not recap" warning, thought it referred to only prior to the injection when the syringe was "pre-filled", as the text said. She comprehended that the text said to throw away the cap, but this did not make sense to her because she thought recapping was still necessary Knowledge-based The Sponsor provided RCA for 5 participants (P03, P05, P07, P09, P11). 2 participants (P05, P07) did not	and 12 of the IFU. Our review of the IFU finds that Step 8 has the prominent heading “Remove needle cap and do not replace” and twice includes the statement “do not put the needle cap back on the prefilled syringe.” Additionally, Step 10 contains the statement “do not recap the needle at any time.” P05 and P07 did not view the back of the IFU; however, we find the IFU adequately informs the user that important information is on the back by using the word pair “turn over” and supplemented by two right arrows, and that no further mitigation is required. P09 did not identify the word pair “do not” in Step 8, which is in a bold red font contained within a pink shaded text bubble. Although P09 didn’t identify text typed in a bold red font, we find the Sponsor uses a bold black font to highlight this important warning in Step 8 in the Supplemental HF Validation Studies, and that no further mitigation of this error is required. For P11, the presence of the warning not to recap the used device was confusing. Since Step 8 is prior to giving the injection, she interpreted the warning not to recap the pre-filled syringe before the injection, but that it

	1 participant (P02) said that she should recap the needle because she thought this was the safest approach to dispose of the needle. 1 participant (P03) Thought recapping would prevent self and others from being injured by the exposed needle, and expected to be informed to recap the used device in Step 12. 5 participants (P05, P07, P09, P11, P13) Answered based off their assumption that an exposed needle would be hazardous.	read the information in Step 8 of the IFU because they chose to not turn the IFU over. 3 participants (P03, P09, P11) either did not locate the correct disposal information or did not correctly comprehend it when directed to the IFU. P03 did not locate information because he expected it to be in disposal section in Step 12. Thought it would be in Step 12 because he thought it would say to recap in that area prior to disposing. When pointed to Step 8, he incorrectly comprehended the IFU as instructing to not recap while the Naked PFS contains medication because of the term "pre-filled". P09 did not correctly comprehend information about not recapping because she had only read unbolded text to "put the needle cap back on the pre-filled syringe" P11 did not correctly comprehend information about not recapping because due to the location of the "do not recap" warning, thought it referred to only prior to the injection when the syringe was "pre-filled", as the text said. Comprehended text said to throw	may be acceptable after the injection is complete. We note, the participant correctly identified the text to throw away the needle cap prior to use. Therefore, to reduce confusion in Step 8 and to assist users that do not view Step 10, we find this statement can be clarified to specifically indicate the used device should not be recapped after use either. Our review of the IFU also identified the Step 12 heading “dispose of your prefilled syringe right away which precedes instructions on how to properly dispose of the device in an FDA-cleared sharps container immediately after use. Although P02 disposed of the naked PFS in the household trash, we find the IFU statements mitigate this performance-based use error to place used prefilled syringes in an FDA-cleared sharps container adequately, and that no further mitigation of this error is required. We note, no participants experienced a needle stick injury during the performance of this task 2.1/10.1, nor did the Sponsor proposes mitigation to this error; however, we find the Step 8 and 10 of IFU can be improved to mitigate this error by further reinforcing to dispose of the needle

		away the cap, but this did not make sense to her because she thought recapping was still necessary. 1 participant (P02) was not directed to the IFU for this information due to time constraints. 3 participants (P05, P07, P13) correctly located and comprehended to not recap the needle when directed to the IFU. The Sponsor states the IFU includes clear instructions on correct disposal and no root causes were identified with respect to incorrect disposal relating to the design of the device, packaging, or IFU. Therefore, it is not considered that design changes would be effective in reducing this residual risk any further.	earlier in the use process for those who recap the needle just prior to disposal to prevent risk of needle stick injury. We provide recommendations 3.d.ii. and 3.d.iii. in Section 5.2 to address our concern.	

4.2.2 Supplemental Study 1 (SDT-INT1265)

SDT-INT1265 is a simulated use (home and clinic environments) HF validation study conducted in thirty-five (35) untrained representative users (See Appendix C). Each participant simulated a single injection (225 mg dose) into an injection pad with a pre-filled syringe. Following that, participants were asked knowledge task questions. After the completion of all study tasks, participants were asked for subjective feedback and interviewed for root causes of any use events. Tables 4 and 5 provide summaries and analyses of the study results.

Table 5: Analyses of Critical Task Errors for <u>Adolescent Caregiver/Adult Patient pairs</u> (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
7.1 Choose injection site (n=10)	Performance-based 2 participants (CP27, N12) injected into the front of the upper arm because either her experience with allergy injections or other injections she knew that the medicine should be injected in a "fleshy" area of the body or she did not think the manikin would be able to be seated in a position that would allow injecting into the back of the upper arm. CP27 also said the content in Step 6 of the IFU was clear and understandable, but would have preferred to see it on the front side of the IFU with the other preparation information. 2 participants (N15, N19) Injected into side of the upper arm because they either did not distinguish that blue section in the diagram specified to inject into the back of the upper arm (N15) or knew to	Performance-based The Sponsor provided RCA for all 4 participants. CP27 knew that these injections typically take place on the arm, so she assumed the front of the upper arm was a sufficiently fatty enough to inject into. Both patient and caregiver did not read Steps 6, 7 or 8 in the IFU because they focused on the images of Step 9 to learn how to give the injection. N15: Based answer off injecting into subcutaneous areas as she does at work with devices that resemble the Naked PFS and misinterpreted the IFU. N19: Chose side of the upper arm because the PFS looked like other PFS she uses at work, which she injects into the side of the upper arm. She chose to not read IFU because she felt familiar enough with the design to use it based on her experience. N12: Said she had saw the image in Step 8 to inject into the back of the	Our review of the URRA notes that failure to choose an appropriate injection site may increase the risk for the user to inject at the wrong depth and possibly give an IM or IV injection. Administering the product via IM or IV injection may cause pain or alter the pharmacokinetics of fremanezumab which may change the clinical effect. We reviewed the subjective feedback Step 6, and all other areas of the IFU for clarity in instructions related to choosing the correct injection site. For the injection sites at the top of the thigh and the back of the arm, we find Step 6 of the IFU provides clear text and is accompanied by an image of the arm with a blue shaded area indicating the appropriate injection site. However, one participant (N15) misinterpreted the blue shaded area on the arm to include the side of the arm to be an acceptable injection site. Although the Sponsor proposes no mitigation, (b) (4)

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	inject it subcutaneously into a "fleshy" site (N19). Knowledge-based 3 participants (CP07, CP33, N18) answered the abdomen without mentioning that the area 2 inches around the belly button should be avoided. CP07: Caregiver said that he was focusing on the images in the IFU while performing the injection. He said he the blue shading in the image on the left side of Step 6 informed him that only the belly button should be avoided, not necessarily including the area 2 inches around it. CP33: They thought that the diagram in Step 6 did not clearly indicate that it was unacceptable to inject within 2 inches of the belly button.	upper arm but she injected into the side of the upper arm due to the position of the manikin. The Sponsor did not provide mitigation for these errors; however, they state, when asked to review the IFU, participants who injected into the wrong site located and comprehended the information. Knowledge-based The Sponsor provided RCA for all 6 participants (CP07, CP27, CP33, N12, N18, N19). All 6 participants either did not read the text or correctly interpret the images in Step 6. Additionally, the Sponsor notes CP07 correctly identified other acceptable sites. CP27 did not read Steps 6, 7, or 8 in the IFU because when they flipped the IFU over, they focused on the images of Step 9 to learn how to give the injection.	(b) (4) We also find the images depicting the injection sites on the arm can be more clearly represented. We note that one participant states the route of administration was not prominently placed. Our review of finds that the route of administration is present on the front, but not the back, of the IFU for the user to reference when preparing to administer the injection. We are not concerned this may lead to wrong route medication errors because the length of the needle and the below instructions for the patient to pinch the injection site should allow for the injection to be given subcutaneously and prevent the injection from being given by the wrong route. For the injection site at the belly button, we find Step 6 of the IFU provides clear instructions to avoid 2 inches around the belly button and is accompanied by an image of the abdomen with a white area within the blue shading indicating the there is an

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	N18 said the image of the abdomen in Step 6 was not clear and that it should include an "X." 1 participant (CP27) Answered that any "fleshy" area of the body would be acceptable to inject into. CP27: She said that from her experience with allergy injections or other injections she knew that the medication should be injected in a "fleshy" area of the body. They both also said the content in Step 6 of the IFU was clear and would have preferred to see it on the front side of the IFU with the other preparation information. 2 participants answered to inject either into the side of the upper arm because the PFS looked like other PFS she uses at work (N19) or outer thigh was acceptable injection site because she misinterpreted the image of thighs in Step 6 because the blue area covered to the edge of the outer	CP33 said that the abdomen would be their last choice, because they thought this would be the most painful of the three suggested locations. They said that they did not spend too much time studying the abdomen site or the image in Step 6 of the IFU because they knew they would not have selected this injection site. N18 knew to not inject into the belly button, but did not know to avoid 2 inches away from the belly button because she did not realize that the IFU had a back side, so she had not seen Step 6. Participant also answered that "vascular areas" should be avoided, which includes the belly button. She had also identified the two other acceptable injection sites (that is, the front of the thighs and back of the upper arm). The Sponsor did not provide mitigation for these errors; however, they state, when asked to	area of the abdomen to avoid. Although there is an unshaded area of the abdomen to indicate that area is to be avoided, 2 participants provided subjective feedback suggesting to use "X" to identify the inappropriate area of the abdomen. We find that using an "X" to identify the inappropriate area of the abdomen will not specifically indicate that area is 2 inches wide and would not further mitigate this use error. We note, although participants did not specifically respond to avoid the 2-inch area around the belly button, the participants either indicated they should avoid vascular areas, which includes the belly button, or did not indicate they found that area to be acceptable, or could identify other appropriate injection sites. We provide recommendation 3.c.i. and 3.c.ii. in Section 5.2 to address our concerns.

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	side of thighs, and she did not notice that the knees were angled outwards (N12). 2 other participants also provided subjective feedback; however, this feedback was not associated with any use errors. CP04 said Step 6's image should have "X's" where the drug should not be injected. N13 stated the injection site images in Step 6 were not clear and did not notify the user that the injection is to be administered SQ.	review the IFU, all participants located and comprehended the information to avoid 2 inches from the belly button or inject into back of the upper arm.	
9.4 Pinch the skin (n=2) Knowledge-based	1 participant (CP08) did not answer to pinch the skin. They understood the intention behind pinching but did not think it was necessary to pinch fatty areas of the stomach. 1 participant (N19) answered to hold skin taut to inject because that is how she injects subcutaneously at work.	The Sponsor provided RCA for both participants. CP08 chose not to read the IFU because they thought they knew how to use the Product based on their experience with similar syringes at home. Answered about the PFS based on their current syringe experience, which they said was the same device as the PFS, and	According to the URRA, pinching a fold of skin at the injection site prior to injecting is important to ensure the injection is given at the correct depth. Administering the product at the wrong depth may increase the risk for an IM or IV injection. Administering the product via IM or IV injection may cause pain or alter the

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	2 other participants provided additional subjective feedback: CP07 said the images in Step 9 are not consistent with the pinching instructions CP22 said the images in Step 9 should be numbered.	had chosen not to read the IFU. Said that they did not have to pinch because the patient was already "fat" enough as is, and they thought it was only important N19 knew to inject subcutaneously, and thought holding the skin taut and inserting at an angle would facilitate a subcutaneous delivery based on her experience with other subcutaneous syringes that resembled the Naked PFS. Had not read IFU because she felt familiar enough with the design to use it based on her experience. The Sponsor did not provide mitigation for these errors; however, they state, when asked to review the IFU, both participants located and comprehended to pinch.	pharmacokinetics of fremanezumab which may change the clinical effect. We reviewed the participants feedback and Step 9 of the IFU to identify potential improvements to this use step. We determine Step 9 of the IFU provides clear text to pinch the skin and is accompanied by the first 2 images of a raised fold of skin between a thumb and index finger. We find the images in Step 9 of the IFU adequately reflect the important information needed to successfully perform this step of the injection process. Further, the text in Step 9 is sequentially numbered and the images are directly under each statement with adequate white space between images to adequately associate each image with the numbered step above it. Although, there is no specific warning for users not to assume that have a sufficiently "meaty" injection site, we find the IFU statements and images mitigate this

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
			use error adequately, and that no further mitigation is required.
9.6 Push the plunger to the bottom of the barrel (n=6) Performance-based	5 participants (CP09, N19, N03, N25, N21) removed air in syringe prior to injecting and expelled a few drops of medication. CP09 removed the air because they are accustomed to removing all air from their insulin injections at home. N19 and N21 thought the air bubble in the medication barrel would be painful to inject. Additionally, N21 had been focused on the green text and did not notice the black text below it. N03 said that she read and understood Step 5 of the IFU instructing her not to remove small air bubbles, but said that the amount of air entrapped in the syringe was much larger than a "small air bubble."	The Sponsor provided RCA for all 6 participants (CP09, CP35, N03, N19, N21, N25). CP09 had not read the instruction in Step 5 to refrain from removing air bubbles because they were drawn to the green and red colored text boxes, and skipped over the text that did not have colored backgrounds. Also, this was their instinct when they saw the air bubbles in the syringe since this PFS resembled their injection (syringe and vial). CP35 struggled to push the plunger to the bottom of the barrel because she encountered much more resistance by the plunger than she anticipated causing the finger flange to come off and her grip to change such that the inserted needle angled to approximately 30 degrees from the injection pad. Eventually, she	According to the, expelling air from the pre-filled syringe increases the risk for losing some of the solution which will result in an underdose. According to the URRA, removing air bubbles is considered a subtask to the critical task of the critical task 9.6 to push the plunger to the bottom of the barrel. We reviewed the participants' subjective feedback and Steps 5 and 9 of the IFU regarding expelling air prior to injecting your dose. We find Step 5 contains text alerting the user that small air bubbles may be present and not to remove them. However, this note is placed between text in a green box and the image of the eye and pre-filled syringe. Our review of the subjective feedback finds that CP09 missed that warning because they were only looking at the text contained within the colored boxes.

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	N25 she said that she read the first sentence (explaining that small air bubbles may exist in the syringe) and did not read the rest because she knew from her training that air bubbles should always be removed prior to injecting. She recommends that the first sentence in the paragraph inform users not to remove air bubbles if they appear in the syringe to avoid confusion. 1 participant (CP35) inserted the needle at an angled of approximately 30 degrees from the injection pad. 1 other participant provided additional feedback: N16 suggested the instructions state "the bubble may be larger than expected."	successfully pushed the plunger to the bottom of the barrel. N19 Had not read IFU because she felt familiar enough with the design to use it based on her experience. N25 Participant said that she saw the image in Step 5 and read the text referencing air bubbles next to the image but did not read it completely. N03 indicated that the bubble was larger than what was described in the text so she opted to remove the large volume of air because this was what she was trained to do and what she currently does in a real-life situation. Therefore, she thought she had correctly removed air from the barrel. N21 Said he knew it was important to give a full dose with all the medication supplied, but indicated that the amount that came out of the needle prior to injecting was insignificant. He said that the drop of medication on the needle when	We also note 1 participant (N25) recommended to move the statement to be first; however, we find other important information to be more critical. We determine the important information is present, but its prominence and clarity can be improved. We provide recommendations 3.b.i. and 3.b.ii. in Section 5.2 to address our concern One participant injected at an angle less than 45 degrees. We conferred with the clinical review team, and they concur this error may increase the risk for intradermal injection and alter the pharmacokinetics of fremanezumab and potentially alter its clinical effect. We reviewed of the IFU and the step regarding proper injection angle and find Step 9 provides clear instructions to inject at a 45 degree to 90-degree angle and is accompanied with an image that indicated the same information. The Sponsor proposed no

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
		he removed the cap seemed like something the manufacturer must know occurs, and thereby rationalized that if the manufacturer was not concerned with this small drop of medication, that they would also not be concerned with another small amount of medication missing. When asked to review the IFU, was not able to locate the text because he expected it to be either in the top section of the front of the IFU or on the back when he was asked the question. When the text was pointed out, he could comprehend. The Sponsor did not provide mitigation for these errors; however, they state, when asked to review the IFU CP09, N19 and N25 located and comprehended instruction to not remove air.	mitigation and we find the risk of committing the error of injecting at an angle of 30 degrees and the participant's reported confusion in this participant is acceptable.
2.1/10.1 Dispose of used device (n=2) Performance-based	1 pair (CP08) pressed the needle onto a coffee table to bend the needle backwards, recapped, and then disposed in household trash because they thought it would	CP08 used the PFS based on their current syringe experience, which they said was the same device as the PFS, and had chosen not to read the IFU. Decided to dispose PFS in household trash based on of their	According to the URRA, recapping the needle or failure to properly dispose of the used device may increase the risk for a needle stick injury. In addition, twisting the needle cap may increase the risk of damaging the device which

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
	reduce the risk of a needle stick when they recapped and knew they would be disposing in the household trash. 1 pair (CP34) wiped the needle with a gauze pad because she intuitively thought it was a safe practice to clean the needle of any residue. 2 other participants also provided subjective feedback; however, this feedback was not associated with any use errors: CP23 said Step 8 should instruct not to twist the needle cap. CP04 said the image in Step 8 should have an X (b) (4) to show that it should not be recapped.	current syringe experience, and because they did not know to dispose of the device in a sharps container in a home setting because they had only ever seen the sharps container in a clinical setting. When this pair was asked to review the IFU, was able to locate instructions to not recap and to dispose in a sharps container, but did not understand the reason of either and would not because they thought their method which they currently use in real life would be sufficiently safe for home use. CP34 did not indicate that any content in the IFU led her to clean the needle. Knew to then dispose in a sharps container. According to the Sponsor, the IFU includes clear instructions on correct disposal and no root causes were identified with respect to incorrect disposal relating to the design of the device, packaging or IFU. Therefore, it is not considered that design	may result in injury or delay of therapy. Also, manipulating the used device after injection may increase the risk for a needle stick injury. We reviewed the participant's subjective feedback and Steps 8, 10, and 12 in the IFU. Our review of the IFU finds that Step 8 has the prominent heading "Remove needle cap and do not replace" and twice includes the statement "do not put the needle cap back on the prefilled syringe." Further, Step 8 includes the statement to "pull the needle cap straight off." Additionally, Step 10 contains the statement "do not recap the needle at any time." Our review of Step 12 in the IFU also identified the heading "dispose of your prefilled syringe right away" which precedes instructions on how to properly dispose of the device in an FDA-cleared sharps container immediately after use. We note, no participants experienced a needle stick injury during the performance of this task 2.1/10.1, nor did the Sponsor proposes mitigation to

Table 5: Analyses of Critical Task Errors for Adolescent Caregiver/Adult Patient pairs (n=18) and Healthcare Providers (HCP) (n=17) during Supplemental Study 1 (SDT-INT1265)			
Critical Task Description	**Description of Use Errors, close calls, and difficulties**	**Applicant's Root Cause Analysis and Proposed Mitigation**	**DMEPA's Analysis and Recommendation**
		changes would be effective in reducing this residual risk any further.	this error; however, we find the Step 8 and 10 of IFU can be improved to mitigate this error by further reinforcing to dispose of the needle earlier in the use process for those who recap the needle just prior to disposal to prevent risk of needle stick injury. We provide recommendations 3.d.i., 3.d.ii., and 3.d.iii. in Section 5.2 to address our concern

4.2.3 Supplemental Study 2 (SDT-INT1266)

SDT-INT1266 is a simulated use (home environment) HF validation study conducted in fifteen (15) untrained participants simulating the delivery of a 675-mg dose to support the 675 mg (three injections) every three months (quarterly) dosing regimen. Participants were presented with a Triple Injection Scenario (675 mg dose) during which they were presented with the Product and asked to inject a full prescribed dose into an injection pad. Following that, evaluators were asked knowledge task questions. After the completion of all study tasks, evaluators were asked for subjective feedback and interviewed for root causes of any use errors, close calls, and difficulties. In addition, participants were asked a knowledge task question (b) (4) Tables 6 and 7 provide a summary and analyses of the use errors.

Table 7. Analyses of Critical Task Errors for adult patient/caregiver pairs during Supplemental Study 2 (SDT-INT1266)

Critical Task Description	Description of Use Error and Participant Subjective Feedback	Applicant's Root Cause Analysis and Proposed Mitigation	DMEPA's Analysis and Recommendation
7.1 Choose injection site (n=8)	Performance-based 1 participant (CP08) made performance based errors. CP08 injected all 3 doses into the outer side of the thigh (n=3 errors). The pair said they had been taught by their doctor to inject into areas like the upper arm, outer thigh, side of the belly, and buttocks as long as it was a fatty area, and thought that these areas were acceptable for all injectable medications. Knowledge-based 5 participants (CP06, CP07, CP08, CP09, CP13) made knowledge-based errors. These participants provided the following sites: • the buttocks (CP07, CP08, CP09) • anywhere fatty on the thigh (CP07, CP09), side of upper thigh (CP06, CP08), front of thigh (CP13) • side of upper arm (CP06), anywhere fatty on the upper arm (CP08), upper arm in any	Performance-based CP08 selected the upper outer thigh to inject into for all 3 injections based on an understanding to inject into a fatty area from prior experience with syringes. Knowledge-based The Sponsor provided RCA for all 5 participants (CP06, CP07, CP08, CP09, CP13) that made knowledge-based errors. 4 participants did not review or notice the IFU (CP06, CP07, CP08, CP09) • CP06 opened the medication cartons from the sides and said they did not notice the IFU. When reviewing the IFU during probing for root cause, the pair located and comprehended the acceptable injection sites. • CP07 did not refer to the IFU because it was incorrectly placed under the second flap of the packaging, and assumed this meant the IFU	Our review of the URRA notes that failure to choose an appropriate injection site may increase the risk for the user to inject at the wrong depth and possibly give an IM or IV injection. Administering the product via IM or IV injection may cause pain or alter the pharmacokinetics of fremanezumab which may change the clinical effect. We reviewed the subjective feedback Step 6, and all other areas of the IFU for clarity in instructions related to choosing the correct injection site. We find Step 6 of the IFU provides clear instructions to avoid 2 inches around the belly button and is accompanied by an image of the abdomen with a white area within the blue shading indicating the there is an area of the abdomen to avoid. Our review of the subjective feedback finds that although the participant did not specifically respond to avoid the 2-inch area around the belly button, the participant did not indicate they found that area to be acceptable. Therefore, we find the risk associated with the error of choosing the injection site closer than 2 inches

	fleshy area near the shoulder (CP13) • stomach without mentioning that the area 2 inches around the belly button should be avoided (CP06, CP08, CP13) • lower back (CP06) These participants based their answer: • Where caregivers and providers have instructed them to inject or a caregiver has injected there (CP06, CP07, CP08, CP09) • Misinterpreted the instructions to inject into a "fleshy area" (CP13) • CP09 suggested the injection site images should have text immediately next to them for clarity.	was chemical information about the medication, so they did not think it was relevant information to them. When prompted to refer to the IFU, participants correctly located and comprehended information about injection sites, and reported that they would only inject into sites as instructed in the IFU • CP08 chose not to read it. When directed to the IFU during probing for root cause, located and comprehended acceptable injection sites • CP09 based their answer on use of the IFU because they had only looked at the image of the injection sites and did not read text that said to inject into front of the thigh. During probing for root cause, participants located and comprehended instructions for acceptable injection sites. CP13 knew general acceptable areas but did not specify specific locations as the most important criteria for selecting sites within the areas, and	surrounding the belly button is adequately mitigated. For the injection sites at the top of the thigh and the back of the arm, we find Step 6 of the IFU provides clear text and is accompanied by an image of the arm with a blue shaded area indicating the appropriate injection site. Although the Sponsor proposes no mitigation, (b) (4) We also find the images depicting the injection sites on the arm can be more clearly represented. Although the Sponsor did not propose mitigation, we find Step 6 of the IFU to inject into the top of the thigh and the back of the arm can be better presented. Specifically, the blue shading in the image of the thighs and arm (b) (4) as acceptable injection sites. We provide recommendations 3.c.i. in Section 5.2 to address our concern.

		had not read the unbolded text after the bolded text "stomach area" and "front of your thighs" in Step 6 that further specified acceptable locations within the areas. The Sponsor did not provide mitigation for these errors; however, they state, when directed to review the IFU, located and comprehended instructions.	
13.1 Understand the prescribed dosing regimen (3 injections [675 mg] once every three months) (n=6)	Performance-based 4 participants (CP10, CP12, CP13, CP14) committed errors during the performance-based evaluation but the root cause is related to their misunderstanding of the dosing regimen. All 4 participants assumed each device contained a full dose and therefor did not choose a second injection site. • CP10 interpreted the prescription as instructing to inject once every 3 months. Caregiver suggested that the prescription should say "3 times" and instead of "3x". • CP12 said they initially assumed each carton contained a full dose and did not see the "225 mg" on the carton because they were	Performance-based 3 participants thought each syringe contained the full dose (CP12, CP13, CP14) 2 participants misunderstood the prescription (CP10, CP14) 4 did not utilize the strength on the carton (225 mg) or the prescription (675 mg) to calculate the dose or number of syringes (CP10, CP12, CP13, CP14) 3 participants did not review or notice the IFU (CP08, CP13, CP14). • CP08 chose not to read the IFU. • CP13 did not focus on it when they injected because they were focused on the procedure of using the syringe.	Based on the URRA, failure to identify that 3 syringes are needed for a full 675 mg dose will result in an underdose. We reviewed the subjective feedback and all areas of the IFU. We determine 5 participant pairs (CP10, CP11, CP12, CP13, CP14) did not correctly interpret the dose or frequency on the prescription, nor did they utilize the strength listed on the carton to calculate the correct number of syringes per dose. We note, CP10, CP12, CP13 made this error during the performance-based Task 7.1; however, their failures were due to misunderstanding of the prescribed dosing regimen. Therefore, their failures are considered due to test artifact and acceptable with this task.

	only interested in the name of the drug. • CP13 commented they were not familiar with the dosing regimen, and wanted to understand the rationale. • CP14 did not know to inject twice more because they said they had misinterpreted the written prescription and had not paid attention to verbal instructions in the introductory script. The patient suggested that she may have reconsidered her prescription if she had opened a single carton containing 3 devices. Knowledge-based 2 participants (CP11, CP14) misunderstood the prescription or dosing regimen. CP11 thought 1 injection should be administered per month. Participants indicated that having the syringes in separate boxes reaffirmed their interpretation of the prescription. CP14 was unable to understand the prescription and would ask for help. The caregiver had interpreted it as instructing to inject once every 3 months, and commented that the	• CP14 was focused on reading the instructions and learning how to use the device. 1 participant (C12) referred to the prescription which they knew said "675 mg" and noticed each carton contained 225 mg, and then realized they needed 2 more injections, when the moderator asked if they had given a complete dose after they had given 1 injection. Knowledge-based CP11: Thought 1 injection should be administered per month. Participants indicated that the way the prescription was worded made them think that they should perform one injection a month for three months. CP14: The patient had interpreted it as instructing to inject 3 times over the course of each month, but was uncertain when she reviewed the prescription. Said she had not considered the 675 mg on the prescription, but knew that the labeling had information about how many mg each device contained and was able to refer to it to determine that 675 mg would be equivalent to the medication within 3 devices. The	CP14 made the error in, both, the performance- and knowledge-based assessments. We do not consider interpretation of a prescription to determine the final dose a typical requirement among patients and caregivers in the real world. Typically, upon receiving the prescription, a pharmacist will affix a patient-friendly label on the product carton upon dispensing to clarify the final dose. However, since clear instructions on the prescription label cannot be guaranteed, we recommend the labeling for this product contain clear and prominent information to alert the user to the number of syringes needed for the 675 mg dose. Although the Sponsor proposed no mitigation, we recommend the Sponsor optimize the labels and labeling to better instruct the user to administer 3 syringes for one complete dose. We provide recommendation 2 in Section 5.1 and recommendations 3.a. in Section 5.2 to address our concern.

	prescription had too many numbers and thought it would be similar to other prescriptions where one unit is taken at a defined frequency. Both participant pairs suggested that an improvement would be all 3 syringes in 1 carton to help know to administer all 3 at once.	patient suggested that the carton contain 3 devices if that is the prescribed dose. The Sponsor did not provide mitigation for these errors.	

5 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed labeling and labels that can be improved to reduce the potential for confusion and increase the prominence, clarity, and readability of important product information to mitigate the potential for medication errors and promote the safe use of the product. Additionally, we conclude the results from the 3 human factors validation studies do not demonstrate the intended users can use the proposed product in the intended manner. Specifically, the results of the 3 HF Validation Study results identified errors during both performance- and knowledge-based assessments of critical tasks that require further mitigation to the PI and IFU to ensure the safe and effective use of the product. While we recognize that the errors occurred on the critical task of performing multiple injections for a full dose, however, we have provided recommendations to optimize the user interface and to increase prominence on those use steps. In addition, we also consider other legally marketed products that require multiple injections for which we are not aware of any postmarket safety signals. As such, we recommend that the Sponsor implements our recommendations and we do not need to see additional human factors data.

We provide recommendations to DNP and the Sponsor in Sections 5.1 and 5.2, respectively to address our concerns. We advise these recommendations are implemented prior to approval of this application.

5.1 RECOMMENDATIONS FOR THE DIVISION

1. As currently presented in the PI, the package type (single-dose or (b) (4)) is defined inconsistently. The Highlights of Prescribing Information and Sections 1-16 define the package type as single-dose. Section 17 and the carton and container use the term (b) (4). We recommend the Sponsor define the package type in accordance with Agency's recommendations and use it consistently throughout the labeling.
2. We suggest you consider these recommendations if the you intend to include the 675 mg dose in the dosing regimen. As currently presented, reference to the requirement to use 3 syringes to administer the full, 675 mg, dose only appears in the Patient Information. We recommend the Sponsor add dosing information, specific for the 675 mg dose, to the HPI (D&A) and Sections 2.1 and 17.

5.2 RECOMMENDATIONS FOR TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

We provide recommendations to further optimize the container label, carton labeling, and Instructions for Use (IFU). The recommendations do not require additional HF simulated use validation, however please submit your updated labels, labeling and protocol for Agency review for our concurrence.

We recommend the following:

1) CONTAINER LABEL and CARTON LABELING
   a) Expiration date
      i) As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either

DDMMMYYYY (e.g., 31JAN2013), MMMYYYY (e.g., JAN2013), YYYY-MMM-DD (e.g., 2013-JAN-31), or YYYY-MM-DD (e.g., 2013-01-31).

b) Net quantity statement
   i) As currently presented, the net quantity statement location and font size competes in with the NDC number and strength, which may increase the risk for wrong drug or wrong dose medication errors. In accordance with 21 CFR 201.10(i) and our Draft Guidance: Container and Carton, April 2013 (lines 175-179), the net quantity statement is not required on a small label.

2) CONTAINER LABEL

(b) (4)

3) INSTRUCTIONS FOR USE (IFU)
   a) Step 2 Gather the supplies you will need to inject
      i) Based on the study results from the performance and knowledge-based assessments from Supplemental HF Study 2 (sHF2), five participants misunderstood the prescribed regimen of 3 syringes every 3 months. Participants provided subjective feedback stating they assumed 1 syringe contained the entire dose. As currently presented (b) (4) We recommend you revise your IFU to include instructions to inject 3 syringes consecutively to obtain the full, 675 mg, dose. For example, we recommend you use the following language: Gather the number of AJOVY 225 mg pre-filled syringes you will need to give your prescribed dose.

- If your dose is 225 mg, you will need 1 AJOVY 225 mg pre-filled syringe.
- If your dose is 675 mg, you will need 3 AJOVY 225 mg pre-filled syringes.

   b) Step 5 Look closely as your pre-filled syringe
      i) During the performance assessment of supplemental HF Study 1(sHF1), one participant, CP09, missed that warning not to remove air bubbles in Step 5 because they were only looking at the text contained within the colored boxes. Additionally, another participant, N03, suggested to make the note to not removed air bubbles more prominent. As currently presented, the statement alerting the user not to remove air bubbles although air bubbles may be present is not clearly prominent because the statement is located between text in a green box and Figure E. We are concerned that if a user removes the air bubble, then they will expel some of the medication leading to a wrong dose (underdose) medication error. We recommend you emphasize to not remove the air bubbles by bolding the word pair “do not” and add text to notify the user those air bubbles are not harmful. For example, we recommend you reword the note to state, “You may see air bubbles in the pre-filled syringe. This is normal. Do not remove the air bubbles from the pre-filled syringe before giving your injection. Injecting AJOVY with these air bubbles will not harm you.”

ii) During the performance-based assessment of sHF1, one participant, N03 removed the air from the prefilled syringe prior to injecting because the amount of air entrapped within the prefilled syringe was much larger than she expected it to be. As currently presented the language (b) (4) Again, we are concerned the user may expel medication from the prefilled syringe and experience a wrong dose (underdose) medication error. We recommend you change the language from (b) (4) to read "air bubbles". See recommendation 3.b.i. for our recommended language.

c) Step 6 Choose your injection area
   i) Based on the results from both performance- and knowledge-based assessments or the participants' subjective feedback during all 3 HF Validation Study many participants either injected or answered to inject into the front or side of the arm or anywhere on the upper arm. For example, one participant, N15, misinterpreted the blue shaded area on the arm to include the side of the arm during sHF1. In addition, another participant, N12, misinterpreted the blue shaded area on the legs to include the outer side of the thighs during sHF1. As currently presented in Figure F of the IFU, the blue shading lacks clarity (b) (4) and may lead to wrong site of administration error. We find the images depicting the injection sites on the arm and the thigh can be more clearly represented. We recommend you make changes to the width of the blue shaded area and overall positioning of the injection sites in Figure F to more clearly identify more distinctly only the back of the arm and only the front of the thighs.

d) Step 8 Remove needle cap and do not replace
   i) One participant, CP23, in sHF1 provided subjective feedback indicating Step 8 should instruct not to twist the needle cap. As currently presented in Figure G, the user is instructed "pull the needle cap straight off." We find that twisting the needle cap may increase the risk of damaging the device which may result in needlestick injury or delay of therapy. We recommend you revise text to "pull the needle cap straight off with your other hand (See Figure G), and add the text "Do not twist."
   ii) The results from the Validation Study (SDT-INT1102) demonstrate the instruction to throw away the cap and not to recap the needle can be improved. As currently presented in Step 8, users are informed not to recap the needle. Additionally, users are instructed to throw away the needle cap. We find these instructions may lead to confusion. Therefore, this statement can be clarified to specifically indicate the used device should not be recapped after use either. We recommend revising language in Step 8 can be improved by adding the word "right away" to the statement "throw away the needle cap" to read "Throw away the needle cap right away."
   iii) One participant, CP04, in sHF1 provided subjective feedback indicating the image in Figure G should have an "X" (b) (4) to show that it should not be recapped. As currently presented in Figure G, (b) (4) t

(b) (4) which may be confusing. (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 9 presents relevant product information for Ajovy (fremanezumab-vfrm) that Teva Branded Pharmaceutical Products R&D, Inc. submitted on October 16, 2017 and December 22, 2017.

Table 9. Relevant Product Information for Ajovy (fremanezumab-vfrm)	
Initial Approval Date	N/A
Active Ingredient	Monoclonal antibody
Indication	Preventive treatment of migraine in adult patients
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	225 mg/1.5 mL (150 mg/mL)
Dose and Frequency	• 225 mg monthly or 675 mg (3 syringes) every 3 months (quarterly) (b) (4) [redacted]
How Supplied	Carton containing 1 single-use, pre-filled syringe
Storage	• Store AJOVY in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original outer carton to protect from light. • If necessary, AJOVY may be kept at room temperature up to 77°F (25°C) for a maximum of 24 hours. • After removal from the refrigerator, AJOVY must be used within 24 hours or discarded. • Do NOT freeze. • Do NOT expose to extreme heat or direct sunlight. • Do NOT shake.
Container Closure	(b) (4) [redacted] glass, (b) (4) [redacted] syringe with a staked (b) (4) [redacted] needle and a (b) (4) [redacted] plunger-stopper (b) (4) [redacted] rigid needle shield cover.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 3, 2018, we searched DMEPA's previous reviews using the terms, LBR-101, PF-04427429, RN307, TEV-48125, fremanezumab, and Ajovy. Our search identified two previous reviews[bc] and one memo[d], and we confirmed that our previous recommendations were implemented or considered.

OSE RCM # 2017-404, 2017-524 (LL/HF protocol REVIEW)

While we find the proposed human factors validation protocol generally acceptable, after evaluating the URRA, IR and IFU, we determined there are no unique use-related risks identified for the proposed fremanezumab PFS (b) (4) Therefore, we conclude that it is not necessary for Teva to conduct a simulated use HF validation study for the fremanezumab PFS (b) (4) However, we provide recommendations submitted by DMPP for the Instructions for Use to clarify instructions, improve comprehension and readability, and include patient friendly language in Section 5.1.

OSE RCM # 2017-404-1, 2017-524-1 (LL MEMO)

We reviewed the revised Instructions for Use for fremanezumab PFS (b) (4) submitted on August 2, 2017 and find some of the Sponsor's justification for not accepting or only partially accepting recommendations made by the Division of Medical Policy Programs (DMPP) to be acceptable from a medication error perspective. However, DMPP provides six additional recommendations for the Instructions for Use to help prevent patient confusion and for consistency with patient-friendly language used in-patient labeling Section 3.

OSE RCM # 2017-404-2, 2017-524-2 (HF protocol REVIEW)

We conclude that human factors (HF) validation studies are necessary to support (b) (4) prefilled syringe [PFS] (b) (4)

Our review of the HF validation study protocols determined the protocol is Not Acceptable. We provided recommendations for the Sponsor to consider prior to commencing their HF Validation Study.

[b] Morris, C. Label and Labeling and Human Factors Protocol Review for TEV-48125 (fremanezumab) IND 106533. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 07. RCM No.: 2017-404 and 2017-524.

[c] Whaley, E. Human Factors Validation Study Protocol Review for fremanezumab IND 106533. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 19. RCM No.: 2017-404-2 and 2017-524-2.

[d] Morris, C. Revised Label and Labeling Review Memo for fremanezumab IND 106533. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 30. RCM No.: 2017-404-1 and 2017-524-1.

APPENDIX C. UPDATED USE-RELATED RISK ANALYSIS (URRA) AND HUMAN FACTORS (HF) STUDY REPORTS

Updated URRA (SDT-INT0726)

HF Validation Study Report (SDT-INT1102)

Supplemental HF Validation Study 1 Report (SDT-INT1265)

Corrected Supplemental HF Validation Study 2 Report (SDT-INT1266)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
06/21/2018

LOLITA G WHITE
06/22/2018

QUYNHNHU T NGUYEN
06/25/2018

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 10, 2018
Responsible OND Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761089
Product Name and Strength:	Ajovy (fremanezumab-vfrm) injection 225 mg/1.5 mL (150 mg/mL)
Product Type:	Single ingredient, combination product
Applicant/Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
FDA Received Date:	January 19, 2018
OSE RCM #:	2018-76
DMEPA Primary Reviewer:	Chad Morris, PharmD, MPH
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Teva for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761089.

1.1 Regulatory History

Teva was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter[a].

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On January 19, 2018, Teva submitted a list of ten suffixes, in their order of preference, to be used in the nonproprietary name of their product[b]. Table 1 presents a list of suffixes submitted by Teva:

Table 1. Suffixes submitted by Teva***	
1.	(b) (4)
2.	
3.	-vfrm
4.	(b) (4)
5.	
6.	
7.	
8.	
9.	
10.	

We reviewed Teva's proposed suffixes in order of preference listed by Teva using the principles described in the applicable guidance.[c]

2.1 fremanezumab-(b) (4)

Teva's first proposed suffix, (b) (4) Thus, we find that this proposed suffix, (b) (4) is not devoid of meaning and inconsistent with the principles described in our final guidance.

2.2 fremanezumab-(b) (4)

Teva's second proposed suffix, (b) (4) We find that

[a] Merchant, L. General Advice Letter for BLA 761089. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JAN 12.

[b] Request for Suffix Review for BLA 761089. Frazer (PA): Teva; 2018 JAN 19. Available from: \\cdsesub1\evsprod\bla761089\0023\m1\us\suffix-review.pdf

[c] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

(b) (4) Thus, we find that this proposed suffix, (b) (4) is not devoid of meaning and inconsistent with the principles described in our final guidance.

2.3 fremanezumab-vfrm

Teva's third proposed suffix, -vfrm, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP, TBBS, and ORP. In email correspondence dated May 8, 2018, TBBS and ORP concurred with DMEPA's assessment and conclusion. In email correspondence dated May 9, 2018, OPDP concurred with DMEPA's assessment and conclusion. DMEPA also communicated our findings to DNP via e-mail on May 9, 2018.

4 CONCLUSION

We find Teva's proposed suffix -vfrm acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to fremanezumab-vfrm.

4.1 Recommendations for Teva

We find the nonproprietary name, fremanezumab-vfrm, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, fremanezumab-vfrm will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

We also note that the first two proposed suffix candidates are unacceptable for the following reasons:

fremanezumab- (b) (4)

FDA finds that this suffix is (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

fremanezumab- (b) (4)

FDA finds that this suffix is (b) (4) Thus, we find that this suffix is inconsistent with the devoid of meaning format described in our final guidance and therefore unacceptable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
05/10/2018

DANIELLE M HARRIS
05/10/2018

Ophthalmology Consult Review #2 of BLA 761089

BLA 761089

Submission Date: March 12, 2018
Review completed: April 20, 2018

Name: fremanezumab (TEV-48125)
Applicant: Teva
Class: Calcitonin gene related peptide (CGRP) binder that blocks alpha and beta CGRP Humanized IgG2 delta a/kappa mAb (b) (4)

Background: The Clinical Ophthalmology Group was asked to review the ophthalmologic adverse events with fremanezumab (FRMB). FRMB is a calcitonin gene related peptide (CGRP) inhibitor monoclonal antibody. As per the summary of Non-Clinical toxicology, a 3-month toxicity study in cynomolgus monkey identified a potential risk of ophthalmic related AEs with FRMB, consisting of inflammation of the ciliary vessels of the eyes at the highest doses studied. The perivascular nature, location of the inflammation supported an immune mediated reaction. The findings were not reproduced in a 1-month study or in 6-month chronic toxicity studies.

The clinical database consisted of four 3-month placebo-controlled trials (LBR 101 021, LBR022, 300049 and 30050) and a non-placebo study extension up to 12-months duration (300051) (a total of 2512 patients). Review of clinical studies identified one case of bilateral retinal detachment after a single dose of FRMB 675, and a vitreous detachment after 2 doses of 675 mg monthly, that led to drug discontinuation in the controlled trials. In addition to these 2 cases, there were 2 retinal tears in the FRMB 675 mg quarterly dose group, and one 1 case each of retinal detachment, vitreous detachment, vitreous prolapse and unilateral blindness in the 675/225 mg monthly dose group. None of these cases were considered to be serious AEs by the investigator.

Initial Consult Response: There was insufficient information to complete the ophthalmology review. Based on the narratives provided, the investigator's classification of the severity of ocular adverse events needed to be re-reviewed and additional information was requested from the applicant.

Agency's Request:

In the narratives for Study 30049, patient (b) (6)… (double vision severe intensity)
In the narratives for Study 30051, patient … (cataract requiring surgery)
In the narratives for Study 30051, patient … (cataract requiring surgery)
In the narratives for Study 30051, patient … (iritis)

Provide an explanation for the non-serious classification of an event which can impair visual function.

Applicant's Response: The serious classification guidance and definition was provided in the protocol. The actual assessment was determined by the investigators, and the sponsor did not influence each individual case determination. With regard to the event that did not require medical intervention, was transient and self-limiting and completely resolved, the classification of non-serious is regarded as appropriate.

Reviewer's Comment: *Disagree. Events which significantly impair vision or if left untreated impair visual function should be considered serious.*

Agency's Request: Provide an explanation for why you have determined that the event was not related to fremanezumab when the investigator assessed the event as related to fremanezumab.

Applicant's Response: The investigator assessed the event as related likely because the protocol defined all ophthalmic AEs of at least moderate severity as adverse events of special interest. Visual disturbance is very common in migraine, and both binocular and monocular diplopia may happen in migraine. As sometimes headache does not follow a visual disturbance or visual aura, referred to as silent or ophthalmic migraine, and the event was temporary and self-limiting, without further symptoms pointing to different etiology, the sponsor considered that the event is most likely due to the underlying disease**. …**

… Pain localized in the eye area is recognized as a mark of migraine. Intermittent bilateral retroorbital pain resolved on (b) (6). The investigator assessed the event as related likely because the protocol defined all ophthalmic AEs of at least moderate severity as adverse events of special interest. The sponsor considered that the event is most likely recurrent due to the underlying disease rather than treatment emergent as intermittent bilateral retro-orbital pain is a mark of migraine headache.

Reviewer's Comment: *Disagree that these cases are suggestive of being related to migraines.*

Agency's Request:
In the narratives for Study 30049, patient (b) (6) …
In the narratives for Study 30051, patient …
In the narratives for Study 30051, patient …
In the narratives for Study 30051, patient …
In the narratives for Study LBR-101-011, patient (b) (6) …

Provide an explanation for the non-serious classification of sight threatening events which required surgical intervention.

Applicant's Response: The serious classification guidance and definition was provided in the protocol. The actual assessment was determined by the investigators and the sponsor did not influence each individual case determination. Retinal detachment represents an emergency situation that if not promptly treated, can cause permanent vision loss. … Narrow angle attach represents an emergency situation that if not promptly treated, can cause permanent vision loss … After review and consideration of the seriousness assessment, the sponsor considers … requiring surgical intervention to prevent persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, meeting seriousness criteria. The sponsor will approach the investigator and request update of the events to serious.

Reviewer's Comment: *These cases represent a pattern of inadequate original assessment of the seriousness of the observed events.*

Agency's Request: Provide an explanation for the investigator's assessment that the events were not related to fremanezumab.

Applicant's Response: The patient has a medical history of anxiety and panic attack. The investigator made the assessment after discussion with the patient who experienced important life event. The specific life event was not described in the CIOMS but per patient, the event was due to acute stress induced hypertension. Additionally, it is unknown if additional risk factors as high degree myopia, exercise, retinal/vitreous body disease were present in this patient. As the etiology of retinal detachment was associated with acute stress induced hypertension, the events were assessed as not related to fremanezumab treatment.

Reviewer's Comment: *Disagree. Hypertension does not cause retinal detachments.*

Agency's Request: Provide an explanation for your assessment that the events were not related to fremanezumab.

Applicant's Response: The sponsor felt that the CIOMS description of causality is reasonable and therefore agreed to the investigator's assessment of retinal detachment being not related to fremanezumab treatment.

Reviewer's Comment: *Disagree. The assessment of causality was not reasonable and the relationship to the drug product cannot be ruled out.*

Agency's Request: In the narratives for Study 30051, patient (b) (6) is described as having iritis in the left eye. The iritis is described as being of moderate severity and assessed by the investigator as being non-serious. The patient was treated with oral acyclovir 400 mg three times a day for the event. At the time of the data cutoff, one month later, the event had not resolved. The investigator assessed the iritis as not being related to the fremanezumab. The sponsor assessed the iritis as not being related to the fremanezumab.

The patient is not described as having either uveitis or ocular viral infections in the past. It would be very unusual to treat iritis with acyclovir in the absence of a concurrent viral infection or history of previous ocular viral infections. Considering the event did not resolve in a month's time, it also did not appear to be effective and an alternative treatment was not provided. Provide an explanation for the treatment of this patient.

Applicant's Response: Anterior uveitis/iritis is the most frequent intraocular inflammation, with viral infection being a prominent factor, especially HSV and VZV. In addition, evidence for virus-associated origin is the unilateral presentation. Treatment of viral iritis is recommended as Acyclovir 400-800 mg up to 5 times daily. Treatment should be continued up to 3-6 weeks to reduce the risk of recurrence and potential affection of the second eye. As treatment in this patient was provided as Acyclovir 400mg three times a day from (b) (6) until (b) (6), the treatment regimen and duration seems to be in line with recommendations of treatment of viral iritis. As treatment was stopped (b) (6), the event was reported as recovering, being reported as recovered on (b) (6) . As the patient recovered and did not complain of a similar episode until End of Treatment Visit on (b) (6) the treatment regimen seems to have been appropriate and effective in this patient.

Reviewer's Comment: *Disagree. Only a very small fraction of uveitis is related to a viral infection. Iritis, if untreated, is a potentially sight threatening condition.*

Agency's Request: In the narratives for Study 30051, patient (b) (6) …
Provide an explanation for your assessment that the event was not related to fremanezumab**.**

Applicant's Response: The sponsor concurred with the investigator´s assessment of iritis being not related to fremanezumab treatment based on the information provided, course of the event, recovery after treatment and Fremanezumab current safety profile.

Reviewer's Comment: *Disagree. There is no basis for excluding this case from being potentially related.*

Agency's Request: In the narratives for Study LBR-101-022, patient (b) (6) is described as having a mild blurred vision, a mild visual impairment, a moderate vitreous detachment, a mild cataract and moderate optic disc drusen. The events were ongoing at the time of the reporting and the study drug was permanently discontinued. The investigator considered the events to be related to the study drug. You assessed the events of optic nerve drusen, posterior vitreous detachment, blurred vision in the right eye, and white spots in the right eye as not related to fremanezumab and possibly related to the patient's underlying degenerative eye conditions such as cataract. Provide an explanation for your assessment that the events were not related to fremanezumab.

Applicant's Response: Optic disc drusen are suspected to be an inherited disease and frequent incidental finding in general population, being usually asymptomatic or with slight peripheral field defects. Optic disc drusen occur in 0.4% of children and consist of acellular intracellular and extracellular deposits that often become calcified over time. They are typically buried early in life and generally become superficial, and therefore visible, later in childhood, at the average age of 12 years (Chang 2016). Given the etiology of disc drusen, the causal relationship with fremanezumab treatment is assessed as not related.

Reviewer's Comment: *One of the reasons for performing a baseline examination is to identify conditions that were present before the drug product was administered. The etiology of the disc drusen should not have been assessed as not related.*

Agency's Request: Provide an explanation for your suggestion that optic nerve drusen is related to the patient's cataract.

Applicant's Response: Although there is evidence that cataract and optic nerve drusen might occur simultaneously due to an underlying condition as di-George syndrome and associated hypocalcaemia, this cannot be applied to this patient. Therefore, a causal relationship of optic nerve drusen and cataract in this patient cannot be definitely established.

Reviewer's Comment: *The explanation above does not make logical sense.*

Agency's Request: Patient (b) (6)/30051 is listed as having a right vitreous prolapse. It is not clear where the vitreous prolapsed, how it is recovering or why the event would be considered mild severity.

Applicant's Response: According to the following additional information, the attending ophthalmologist did not request follow up and no intervention was needed. At the site visit, where the subject reported the event, she was carrying on life as normal. Based on this information, it was decided to categorize the event as mild severity. According to the ophthalmologist letter, discussion section: "Vitreous floaters central and peripheral" were noted, and "nothing abnormal found related to vitreous prolapse" was diagnosed.

Reviewer's Comment: *Disagree with categorizing the event as mild just because an explanation could not be provided.*

Agency's Request: Patient (b) (6)/30049 is listed as having a left eye cataract which is recovering/resolving. Provide an explanation to explain how the cataract is resolving.

Applicant's Response: The subject was diagnosed with cataract in the left eye after retinal detachment repair, start date (b) (6). Cataract was assessed as mild. As the patient´s vision in the left eye was not blurred and her day-to-day activity was not affected, the patient did not have surgery for her left eye cataract. Based on provided information, cataract is not resolving but ongoing, however, does not impair the patient´s daily activities. The Applicant will update this information.

Reviewer's Comment: *The event should not have been categorized as resolving.*

Summary Review Comments: The applicant's response has been reviewed. In a number of cases, the applicant has agreed that there was an error in the previous submission and has agreed to amend the database. For the majority of other cases, the applicant has provided an implausible explanation.

In summary, the relative seriousness of each ocular event and the potential relationship of the ocular event to the drug product cannot be ascertained based on the reports from the investigator or applicant. It is therefore recommended that that following ocular adverse events be added to the labeling:

Labeling: 6.1 Adverse Reactions: Clinical Trials Experience

Other adverse reactions that occurred at a frequency less than 1% and were potentially AJOVY related include: blurred vision, cataracts, double vision, dry eyes, iritis, retinal hole/tear, retinal detachment and retro-orbital pain.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
04/23/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 17, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	BLA 761089
Product Name and Strength:	Ajovy[a] (fremanezumab-xxxx[b]) injection 225 mg/1.5 mL (150 mg/mL)
Applicant/Sponsor Name:	Teva Branded Pharmaceutical Products R&D, Inc.
FDA Received Date:	April 12, 2018
OSE RCM #:	2017-2192-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Neurology Products requested that we review the revised carton labeling and container label for Ajovy (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that The Office of Biotechnology Products and DMEPA submitted as an Information Request on April 9, 2018[c].

[a] Conditional approval letter for the proposed proprietary name, Ajovy, is available from: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80476920&_afrRedirect=152469797069861 9

[b] FDA has not yet designated a nonproprietary name for Teva's proposed biologic product that includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). FDA is using "-xxxx" as a placeholder for the suffix. "-xxxx" is not intended to be included in the final printed labels and labeling.

[c] April 9, 2018 Information request available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8048f8ea&_afrLoop=1524800680424472&_afrWindowMode=0&Adf-Window-Id=winPop&_afrFS=16&_afrMT=screen&_afrMFW=1680&_afrMFH=881&_afrMFDW=1680&_afrMFDH=1050&_afrMFC=8&_afrMFCI=0&_afrMFM=0&_afrMFR=96&_afrMFG=0&_afrMFS=0&_afrMFO=0

2 CONCLUSION

The revised carton labeling and container label is unacceptable from a medication error perspective. The proposed expiration date format may increase the risk for degraded drug medication errors.

3 RECOMMENDATIONS FOR TEVA

We recommend the following be implemented prior to approval of this BLA:

A. As currently presented, the format for the expiration date is not acceptable. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like DDMMMYYYY (e.g., 31JAN2013), MMMYYYY (e.g., JAN2013), YYYY-MMM-DD (e.g., 2013-JAN-31), or YYYY-MM-DD (e.g., 2013-01-31).

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

----

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN C MORRIS
04/17/2018

LOLITA G WHITE
04/17/2018

Clinical Inspection Summary

Date	04/12/2018
From	Cara Alfaro, Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Lana Chen, Regulatory Project Manager Suhail Kasim, Medical Officer Division of Neurology Products
BLA #	761089
Applicant	Teva Branded Pharmaceutical Products R&D, Inc.
Drug	Fremanezumab
NME	Yes
Proposed Indication	Prophylaxis of migraines in adults
Consultation Request Date	12/18/2017
Summary Goal Date	4/16/2018
Action Goal Date	6/16/2018
PDUFA Date	6/16/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Jagadeesan, Saper, and Banach and the sponsor, Teva Branded Pharmaceutical Products R&D, Inc., were inspected in support of this BLA. The studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final compliance classification of the inspections of Drs. Jagadeesan and Saper was No Action Indicated (NAI). The preliminary classification of the inspections of Dr. Banach and the sponsor (Teva) was NAI.

II. BACKGROUND

Fremanezumab injection is a human monoclonal antibody being developed for the prophylaxis of migraine in adults under BLA 761089. The sponsor has submitted one Phase 3 trial in chronic migraine (Protocol TV48125-CNS-30049) and one Phase 3 trial in episodic migraine (Protocol TV48125-CNS-30050) to support the efficacy and safety of fremanezumab for the prophylaxis of migraine in adults.

Protocol TV48125-CNS-30049

Title: "A multicenter, randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of chronic migraine"

Subjects: 1130 enrolled

Sites: 132 sites in 9 countries: North America (91 sites, 87 sites in U.S.), Eastern Europe (18 sites), Asia/Pacific (12 sites), Western Europe (7 sites), Middle East/Central Asia (4 sites)

Study Initiation and Completion Dates: March 22, 2016 to April 11, 2017

This was a Phase 3 randomized, double-blind, placebo-controlled study. The study consisted of a screening period (up to 28 days), a run-in period (28 days), and a 12-week double-blind treatment period. During the run-in period, subjects had to have headaches on ≥15 days, migraine/probable migraine or treatment of headache with triptan or ergot derivative on ≥8 days, and ≥85% compliance with the electronic diary.

Eligible subjects were randomized 1:1:1 to one of three treatment groups:

- Fremanezumab 675 mg at Visit 2 (Day 0) then 225 mg once per month by subcutaneous injection
- Fremanezumab 675 mg at Visit 2 (Day 0) then placebo once per month by subcutaneous injection
- Placebo once per month by subcutaneous injection

Subject-reported outcome assessments were recorded by subjects using an electronic diary (DIARYpro). The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days of at least moderate severity during the 12-week treatment period.

Protocol TV48125-CNS-30050

Title: "A multicenter, randomized, double-blind, placebo-controlled, parallel group study comparing the efficacy and safety of 2 dose regimens of subcutaneous administration of fremanezumab (TEV-48125) versus placebo for the preventive treatment of episodic migraine"

Subjects: 874 enrolled

Sites: 122 sites in 9 countries: North America (85 sites, 81 sites in U.S.), Eastern Europe (16 sites), Asia/Pacific (12 sites), Western Europe (6 sites), Middle East/Central Asia (3 sites)

Study Initiation and Completion Dates: March 23, 2016 to April 10, 2017

This was a Phase 3 randomized, double-blind, placebo-controlled study. The study design was the same as TV48125-CNS-30049. During the run-in period, subjects had to have headaches occurring on ≥6 and ≤14 days; migraine/probable migraine or treatment of headache with

triptan or ergot derivative on ≥4 days; and ≥85% compliance with the electronic diary.

Eligible subjects were randomized 1:1:1 to one of three treatment groups:

- Fremanezumab 675 mg at Visit 2 (Day 0) then placebo once per month by subcutaneous injection
- Fremanezumab 225 mg once per month by subcutaneous injection
- Placebo once per month by subcutaneous injection

Subject-reported outcome assessments were recorded by subjects using an electronic diary (DIARYpro). The primary efficacy endpoint was the mean change from baseline in the monthly average number of headache days during the 12-week treatment period.

Rationale for Site Selection

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, prior inspectional history, and data anomalies. An inspection of the sponsor, Teva Branded Pharmaceutical Products R&D, Inc., was also conducted.

III. RESULTS

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Classification
Site #13545 **Singaravelu Jagadeesan, M.D.** 3100 Duraleigh Road Suite 304 Raleigh, NC 27612	TV48125-CNS-30049 Subjects: 18 TV48125-CNS-30050 Subjects: 13	20-26 Feb 2018	NAI
Site #13539 **Joel Saper, M.D.** 3120 Professional Drive Ann Arbor, MI 48104	TV48125-CNS-30049 Subjects: 26 TV48125-CNS-30050 Subjects: 11	12-15 Feb 2018	NAI
Site #53363 **Marta Banach, M.D.** Plac Lasoty 4 Krakow 33-332 Poland	TV48125-CNS-30049 Subjects: 8 TV48125-CNS-30050 Subjects: 6	26 Feb – 2 Mar 2018	NAI*

Site #/ Name of CI/ Address	Protocol #/ # of Enrolled Subjects	Inspection Dates	Classification
Teva Branded Pharmaceutical Products R&D, Inc. 41 Moores Road Frazer, PA 19355	TV48125-CNS-30049 TV48125-CNS-30050	13-16 Mar 2018	NAI*

Compliance Classifications
NAI = No Action Indicated, no deviation from regulations.
VAI = Voluntary Action Indicated, deviation(s) from regulations.
OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Singaravelu Jagadeesan, M.D.

At this site for Protocol TV48125-CNS-30049, 47 subjects were screened, 18 subjects were randomized, and 17 subjects completed the study. One subject, randomized to the placebo arm, discontinued the study due to an adverse event (back pain). For Protocol TV48125-CNS-30050, 47 subjects were screened, 13 subjects were randomized, and 11 subjects completed the study. Two subjects, both randomized to the placebo arm, discontinued the study due to loss to follow-up and an adverse event (disorientation).

An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, informed consent forms, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, protocol deviations, and primary efficacy data (headache days/DIARYpro).

An archival CD containing the DIARYpro headache data was available at the site for review. The primary efficacy measure, headache days, was verified, with no discrepancies noted between source data and sponsor line listings. There was no evidence of under-reporting of adverse events.

2. Joel Saper, M.D.

At this site for Protocol TV48125-CNS-30049, 56 subjects were screened, 26 subjects were randomized, and 26 subjects completed the study. For Protocol TV48125-CNS-30050, 56 subjects were screened, 11 subjects were randomized, and 9 subjects completed the study. Two subjects discontinued the study due to withdrawal of consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects in both protocols was conducted. Records reviewed during this inspection included, but were not

limited to, source documents, monitoring documents, training documents, IRB/sponsor correspondence, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, protocol deviations, and primary efficacy data (headache days/DIARYpro).

Study coordinators had read-only access to the (b) (4) web portal to view daily summary reports for DIARYpro data. Printouts made directly from the (b) (4) web portal and an archival CD containing the DIARYpro headache data were available at the site for review. The primary efficacy measure, headache days, was verified, with no discrepancies noted between source data and sponsor line listings. There was no evidence of under-reporting of adverse events.

Of note, the FDA field investigator found that Subject # (b) (6), participating in Protocol 30050, declined to participate in the optional pharmacogenetics sub-study on (b) (6) However, genetic sample(s) (to be processed for "serum biomarker", "plasma biomarker", "RNA biomarker", and "urine biomarker") were collected along with other baseline labs on (b) (6). According to the clinical investigator, the reason for this error was that the site had not properly informed the laboratory that the subject had declined to participate in the optional pharmacogenetics sub-study. The site later discovered the issue and faxed a Sample Destruction Request Form to the laboratory (b) (4) on (b) (6). According to the Sample Destruction Request Form, a Certificate of Destruction is to be provided once the sample has been destroyed. The FDA field investigator asked for documentation that the sample had been destroyed. The CRO (b) (4) sent an email to the site on 2/15/2018 (during the inspection) stating that the sponsor (Teva) had verbally confirmed that the genetic sample had not been processed and that Teva would send documentation of the sample status (destroyed or location/timeline for destruction) to the site and confirmation that no testing had been performed. Dr. Saper acknowledged that there should have been better follow-up to ensure that (b) (4) received the Sample Destruction Request Form and that the sample had been destroyed.

3. Marta Banach, M.D

At this site for Protocol TV48125-CNS-30049, 19 subjects were screened, 8 subjects were randomized, and 8 subjects completed the study. For Protocol TV48125-CNS-30050, 19 subjects were screened, 6 subjects were randomized, and 6 subjects completed the study.

An audit of the study records for all enrolled subjects was conducted. Records reviewed included but were not limited to informed consent forms, source documents, adverse event reports, concomitant medications, and primary efficacy data (headache days/DIARYpro).

An archival CD containing DIARYpro headache data was available at the site for review. The primary efficacy measure, headache days, was verified, with no discrepancies noted between source data and sponsor line listings. There was no evidence of under-reporting of adverse events.

4. Teva Branded Pharmaceutical Products R&D, Inc.

This inspection covered sponsor practices related to Protocols TV48125-CNS-30049 and TV48125-CNS-30050. The FDA field investigator determined that the sponsor obtained financial disclosure information from each clinical investigator, maintained adequate oversight of the clinical trials, and performed adequate monitoring of the clinical investigator sites. The FDA field investigator confirmed that there were no site closures. No evidence of under-reporting of adverse events was noted.

The flow of data from DIARYpro devices to Teva was described by the senior manager for clinical data management for Teva. Briefly, the site staff trains the subject in DIARYpro use and subjects enter data into the DIARYpro device. Data are transferred to the vendor's, (b) (4) server nightly. Data can be viewed by the site, monitor, and sponsor in read-only access. Twice monthly data are transferred to the CRO, (b) (4), by means of a secured ftp transfer. (b) (4) submitted data in SDTM format to Teva by means of a secured ftp transfer. Teva could not change the data they received from (b) (4), the data were submitted in read-only data files for statistical analyses. This senior manager stated that no patient-reported data were changed and that there were no data changes after database lock dates. Data queries were identified in a reconciliation process and changes were requested in Data Clarification Forms and any changed data were documented in an audit trail.

The description of the flow of data from DIARYpro devices to Teva was consistent with the information the sponsor had previously provided per request. Audit trails were reviewed for the subjects enrolled at the three inspected clinical sites and no changes were identified for subject-reported outcome data after database lock.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/BLA #761089
DNP/Division Director/Billy Dunn
DNP/Medical Team Leader/Heather Fitter
DNP/Medical Officer/Suhail Kasim
DNP/Project Manager/Lana Chen
OSI/Office Director/David Burrow
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/ GCPAB Program Analysts/Joseph Peacock/Yolanda Patague
OSI/Database Project Manager/Dana Walters

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARA L ALFARO
04/12/2018

PHILLIP D KRONSTEIN
04/12/2018

KASSA AYALEW
04/12/2018

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA ID	C2018040
IND/BLA/NDA #	BLA 761089
Referenced IND for NDA/BLA	IND 106533
Established Name/Trade Name	TEV-48125/fremanezumab/Ajovy Injection
Sponsor/Applicant	Teva
Indication	Treatment of Chronic and Episodic Migraine
Meeting Type/Deliverable	Original BLA
Sponsor Letter Date/SDN #	SDN #4
Date of Consult Request	January 29, 2018
Review Completion Date	March 16, 2018
Review Division	Division of Neurology Products (DNP)
Clinical Reviewer/Clinical Team Leader(CTL)	Suhail Kasim, MD/Heather Fitter, MD
Review Division PM	Lana Chen
COA Reviewer	Ebony Dashiell-Aje, PhD
COA TL/Secondary Reviewer	Sarrit Kovacs, PhD
COA Associate Director	Elektra Papadopoulos, MD, MPH
Instrument 1	MIDAS
Instrument 2	HIT-6
COA Type 1 and Endpoint Concepts	PRO, headache symptoms and symptom impacts
COA Type 2 and Endpoint Concepts	PRO, headache symptoms and symptom impacts
Intended Population	Patients with Chronic or Episodic Migraine

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

Clinical Outcome Assessment Review
Ebony Dashiell-Aje, PhD
BLA 761089
TEV-48125/fremanezumab/Ajovy Injection
MIDAS, HIT-6, Chronic and Episodic Migraine

Introduction:
These Clinical Outcome Assessment (COA) review comments are provided as a response to a request for COA Staff consultation (Priority Review) by the Division of Neurology Products (DNP) regarding BLA 761089. The Applicant has submitted an original BLA for Ajovy (TEV-48125/fremanezumab) for the treatment of patients with chronic or episodic migraine. This indication is being supported by two multicenter, randomized, 12-week, double-blind, placebo-controlled studies to establish the effectiveness of Ajovy injection in the preventive treatment of migraine in adult patients (Study TV48125-CNS-30050 in episodic migraine; Study TV48125-CNS-30049 in chronic migraine).

Within the two confirmatory trials, the Migraine Disability Assessment (MIDAS) and the 6-item Headache Impact Test (HIT-6) were pre-specified as secondary endpoints and adjusted for multiplicity with hierarchical testing. (b) (4) . It should be noted that these COA endpoint measures were not discussed with the Division *a priori* and COA Staff was not previously consulted on these measures during either the IND phase or early phases of the BLA review cycle.

PRO Dossiers were not included for review in the Applicant's submission; therefore, a detailed information request was issued on February 23, 2018 to the Applicant (b) (4)

General Comments:

- (b) (4)
  Neither the MIDAS nor the HIT-6 directly assesses disability in episodic or chronic migraine patients.
- There are issues with the content validity of both the MIDAS and HIT-6; therefore, it is difficult to interpret the data from each instrument's total score (b) (4)
- (b) (4)

MIDAS Comments:
There are serious concerns regarding the content validity of the MIDAS:

- Background:
  - Items from the MIDAS questionnaire were based in part on the Headache Impact Questionnaire and based on input from a clinical expert advisory committee

(Stewart et al 1999). While the Applicant has cited numerous qualitative studies that assessed concepts related to migraine impacts, none of these studies formally assessed the relevance of MIDAS instrument content or whether patients with episodic migraine could understand and complete the instrument as intended. As indicated by the Applicant, no formal qualitative research has been conducted to assess the content validity of the MIDAS.

- The Applicant has provided evidence for the psychometric properties and performance of the MIDAS (i.e., reliability, validity, and ability to detect change) based on published research and data from previous migraine clinical trials for prophylactic treatments.

- Instrument Limitations:
  - Lack of qualitative research with episodic migraine patients: No qualitative research has been conducted among episodic migraine patients to ensure that all of the impacts included in the MIDAS are relevant, meaningful, and comprehensive and that no important impacts have been omitted. (b) (4) [redacted]
  - Recall period: There are concerns with the 3-month recall period of the MIDAS, particularly for use in clinical trials assessing episodic conditions where changes in symptoms may benefit from being captured more frequently or with a shorter recall period. Shorter recall periods would potentially limit variability that is likely introduced when patients are asked to recall and average their symptom experiences over a long period of time. A long recall period (e.g., 3 months) is likely to introduce recall error and to lead to inaccurate data.
  - Total score: The five items included in the MIDAS total score assess patients' number of work/school days missed; number of work/school days with ≤50% productivity; number of household work days missed; number of household work days with ≤50% productivity; and number of days when patient missed family, social or leisure activities. We do not have qualitative evidence that the total score reflects a comprehensive assessment of disability among episodic migraine patients.
  - Meaningful Change: Evidence to support a threshold for clinically meaningful within-patient change on the MIDAS score (using anchor-based analysis, CDF and PDF plots has not been provided.

HIT-6 Comments:

- Background:
  - Instrument development work has been conducted to generate the item content of the HIT-6 among general headache patients.
  - The psychometric properties and performance of the HIT-6 have been evaluated using a chronic migraine patient sample.
- Instrument Limitations:
  - Lack of qualitative research with chronic migraine patients: While the Applicant provided literature to support the content validity of the HIT-6, qualitative interview studies were conducted among a broader headache patient sample. Qualitative research should be conducted with chronic migraine patients to ensure that all of the impacts included in the HIT-6 are relevant, meaningful, and comprehensive and that no important impacts have been omitted. (b) (4)

  - Instructions: The HIT-6 asks about headaches and does not specify migraine symptoms; therefore, in its present form, the HIT-6 does not assess impacts of migraine symptoms or disability due to migraine symptoms, but rather it assesses pain severity of headaches, impact of headache on patients' daily functioning, desire to lie down, feelings of tiredness, irritability, and ability to concentrate.

  - Recall Period: There are concerns with the HIT-6 recall period as the first three of the six questions (Items 1-3) do not specify a recall period and the remaining three questions (Items 4-6) include a recall period of the last 4 weeks.
    - A recall period should be clearly specified in the instrument instructions to help standardize the assessment. Without a standard recall period, results will yield inconsistent, inaccurate, and unpredictable data. If item 2 (impact of headache on patients' daily functioning) were modified to include an appropriate recall period, it could potentially be considered suitable to assess aspects of disability or serve as an anchor item to aid in interpretation of clinically meaningful within-patient change in migraine symptom endpoint scores.
    - While items 4-6 have a more acceptable recall period of 4 weeks, the concepts assessed are limited to tiredness, irritability, and the ability to

concentrate which are not fully representative of the impacts of migraine on patients' daily functioning.

- Items 4-6 measure frequency rather than severity, which may not capture what is most important to patients.

- Total Score: Although we do not interpret psychometric properties and performance without first establishing content validity of an instrument, we have the following comments regarding the applicant's pre-specified HIT-6 total score:
  - We are concerned about the use of the total score as it combines multiple concepts and 50% of the items lack a recall period; these issues make interpretation challenging.
  - We do not have qualitative evidence supporting use of the HIT-6 total score as a comprehensive assessment of disability among chronic migraine patients.

- Meaningful Change: Although we do not interpret psychometric properties and performance without first establishing content validity of an instrument, we have the following comment regarding interpretation of clinically meaningful within-patient change in the applicant's pre-specified HIT-6 total score:
  - The CDF and PDF analyses submitted by the Applicant in response to the Agency's information request were performed incorrectly (e.g., the x-axis included percent change in HIT-6 scores rather than the absolute score change that the Office of Biostatistics reviewer confirmed was used by the applicant for the endpoint calculation). Therefore, a threshold for clinically meaningful within-patient change on the HIT-6 could not be determined.

APPENDICES

Appendix A. HIT-6
Appendix B. HIT-6 Scoring Algorithm
Appendix C. MIDAS
Appendix D. MIDAS Scoring Algorithm

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EBONY N DASHIELL-AJE
04/06/2018

SARRIT M KOVACS
04/09/2018

ELEKTRA J PAPADOPOULOS
04/09/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: March 13, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products (DNP)

Through: Dominic Chiapperino, Ph.D., Acting Director
Controlled Substance Staff (CSS)

From: Joshua S. Hunt, PharmD., Senior Regulatory Reviewer
Controlled Substance Staff (CSS)

Subject: BLA 761089 fremanezumab, TEV-48125, Pf-04427429 (refer to IND 106533)
Proposed proprietary name: Ajovy
Indication: preventative treatment (prophylaxis) of migraine
Dosage: 225 mg monthly, (b) (4) or 675 mg once every three months
Route of Administration: subcutaneous (sc) injection via pre-filled syringe
Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Materials Reviewed: *Submitted by the Sponsor and located within the EDR*

1) Sponsor Study Number: 08GR358: Safety Pharmacology Cardiovascular Assessment of Intravenous Pf-04427429 In Telemetered Male Cynomolgus Monkeys Dose Level: 100 mg/kg, Study Initiation: 02-Sep-08 (288 pages)
2) Sponsor Reference No. DS-2017-011: TEV-48125 – Irwin profile test following subcutaneous administration in the rat. (355 pages)
3) Sponsor Reference No. DS-2017-014: TEV-48125 – Measurement of respiratory parameters following subcutaneous administration in the rat by whole body plethysmography (199 pages)
4) Sponsor's Integrated Summary of Safety Fremanezumab (TEV-48125) (8821 pages)
5) 2.4 Nonclinical Overview (35 pages)

I. Background

The Division of Neurology Products (DNP) sent a consult request to CSS on January 24, 2018, regarding the submission of BLA 761089. This new BLA was submitted to the Agency on 10/16/2017. DNP is requesting CSS review the BLA submission and provide feedback. CSS has not been previously involved during the IND phases of this development program and we were not present at the BLA filing meeting.

Fremanezumab is a monoclonal antibody (fully humanized IgG 2a/kappa) for anti-calcitonin gene-related protein (CGRP) which is being developed for the prevention of both episodic and chronic migraine (EM, CM). The Sponsor has conducted a total of twelve studies: seven Phase I studies, two Phase 2b studies (double-blind, placebo controlled), and three Phase 3 studies (2 double-blind, placebo-controlled and one long-term, double-blind extension study). Based on the results of the efficacy studies (TEV-48125-CNS-30049 and TEV-48125-CNS-30050), the Sponsor purports that subjects treated with fremanezumab at 225 mg monthly dosing (patients in the 225 mg arm with CM received an initial first loading/monthly dose of fremanezumab at 675 mg) and fremanezumab at 675 mg quarterly dosing had significantly fewer headache days of moderate to severe intensity and fewer days of migraine. Additionally, compared to subjects with CM who were treated with placebo, a higher percentage of subjects receiving fremanezumab experienced ≥50% reduction in the number of headache days of at least moderate severity or migraine days, had significantly fewer days with use of acute headache medication, and had significantly less disability as measured by the 6-item Headache Impact Test [HIT-6] or migraine disability assessment [MIDAS] scales for CM and EM, respectively.

II. Conclusions

1. No monoclonal antibody is scheduled under the Controlled Substance Act and we, thus far, are unaware of any instance(s) of abuse for monoclonal antibodies as a therapeutic class. Fremanezumab has no structural similarities with the chemical structure of any known drugs of abuse, such as amphetamine, cocaine, benzodiazepines, opioids, LSD, MDMA, PCP, and cannabinoid agonists nor is fremanezumab a prodrug of a known drug of abuse.

2. It does not appear that fremanezumab produced any abuse-related adverse events in clinical trials during drug development.

3. As a monoclonal antibody, fremanezumab is not expected to significantly cross the Blood-Brain-Barrier (BBB), due to its large molecular size.

III. Recommendations to the Division

CSS has considered all potentially abuse-related data in the submission and concludes that there is no abuse signal nor data requiring further CSS review of this BLA submission. We recommend the PLR format product labeling not include section 9 of the prescribing information. We do not intend to file a further review of BLA #761089.

The Division may contact CSS again if the DNP review team identifies any abuse- or dependence related concerns associated with the drug during their review of this NDA.

IV. Discussion

We (CSS) reviewed the Safety Pharmacology 4.2.1.3 and Clinical Safety 5.3.5 sections of the Sponsor's EDR submission to search for any abuse potential signals. We noted no such signals based upon the following information provided below:

1) A single-dose, intravenous administration of fremanezumab at a level of 100 mg/kg was well tolerated in eight telemetered male cynomolgus monkeys. There were no adverse clinical signs observed (Sponsor study 08GR358).

2) Based on an Irwin test evaluation conducted in male and female Sprague Dawley rats, one single sc administered dose of fremanezumab at 100 or 300 mg/kg did not exert any relevant effect on a battery of behavioral and physiological parameters, covering the main central and peripheral nervous system functions, up to 7 days after dosing (Sponsor Study DS-2017-011).

3) According to the Sponsor, one single sc administered dose of fremanezumab at 100 and 300 mg/kg to male and female Sprague-Dawley rats was not associated with any relevant effect on the investigated respiratory parameters (including respiratory rate, tidal volume and minute volume) or general health status, up to 3 days after dosing (Sponsor Study DS-2017-014).

4) According to the Sponsor, the largest single dose administered to healthy adults was 2000 mg iv with no dose-limiting toxicities. Additionally, clinical withdrawal or rebound effects have not been observed in clinical studies conducted in subjects and patients receiving with fremanezumab up to 2000 mg iv (Sponsor's Integrated Summary of Safety).

5) Four *in vitro* tissue cross-reactivity studies were performed by the Sponsor. There was no binding to non-target rat, rabbit, monkey, or human tissues. CSS noted that the Sponsor did further state that tissue distribution studies have not been conducted with fremanezumab (2.4 Nonclinical Overview).

CSS did note one reported case of completed suicide in the 675mg treatment group (Study 30050) 110 days after study drug exposure; however, the patient had withdrawn from the study at day 72 due to a "family emergency". The patient died of an intentional diphenhydramine overdose. Past medical history did include depression. The investigator assessed the death as unrelated to the study drug.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSHUA S HUNT
03/13/2018

DOMINIC CHIAPPERINO
03/13/2018

Ophthalmology Consult Review of BLA 761089

BLA 761089

Submission Date:	October 16, 2017
Consult Request Date:	December 28, 2017 received February 22, 2018
Review completed:	February 26, 2018

Name: fremanezumab (TEV-48125)
Applicant: Teva
Class: Calcitonin gene related peptide (CGRP) binder that blocks alpha and beta CGRP Humanized IgG2 delta a/kappa mAb (b) (4)

Consult Request: Please evaluate ophthalmologic adverse events with fremanezumab (FRMB). FRMB is a calcitonin gene related peptide (CGRP) inhibitor monoclonal antibody. As per the summary of Non-Clinical toxicology, a 3-month toxicity study in cynomolgus monkey identified a potential risk of ophthalmic related AEs with FRMB, consisting of inflammation of the ciliary vessels of the eyes at the highest doses studied. The perivascular nature, location of the inflammation supported an immune mediated reaction. The findings were not reproduced in a 1-month study or in 6-month chronic toxicity studies.

The clinical database consists of four 3-month placebo-controlled trials (LBR 101 021, LBR022, 300049 and 30050) and a non-placebo study extension up to 12-months duration (300051) (a total of 2512 patients). Review of clinical studies identified one case of bilateral retinal detachment after a single dose of FRMB 675, and a vitreous detachment after 2 doses of 675 mg monthly, that led to drug discontinuation in the controlled trials. In addition to these 2 cases, there were 2 retinal tears in the FRMB 675 mg quarterly dose group, and one 1 case each of retinal detachment, vitreous detachment, vitreous prolapse and unilateral blindness in the 675/225 mg monthly dose group. None of these cases were considered to be serious AEs by the investigator. Please provide your comments on these cases, and the potential relationship to fremanezumab. Feel free to contact Dr. Villalba if you have any questions (maria.villalba@fda.hhs.gov)

Consult Response: There is insufficient information to complete the ophthalmology review. Based on the narratives provided, the investigator's classification of the severity of ocular adverse events should be re-reviewed. The following information is recommended to be requested from the applicant:

1. In the narratives for Study 30049, patient (b) (6) is described as having double vision of severe intensity which was assessed by the investigator as non-serious and related to fremanezumab. The narrative further describes an eye examination noting that the double vision was in the left eye more than in the right eye.
    a. An explanation should be provided for the non-serious classification of an event which can impair visual function.
    b. An explanation for how double vision would occur in each eye separately, i.e. monocular diplopia, should be provided.

   c. An explanation for why the sponsor has determined that the event was not related to fremanezumab when the investigator assessed the event as related to fremanezumab should be provided.

2. In the narratives for Study 30049, patient (b) (6) is described as having intermittent bilateral retro-orbital pain of moderate severity which was assessed by the investigator as non-serious and related to fremanezumab. The event started two days after the third dose of fremanezumab and was not resolved at the time of the completion of the study. The sponsor assessed the event as likely intercurrent with the patient's migraine and other medical history.
   a. An explanation should be provided for the non-serious classification of this apparently continuing adverse event.
   b. An explanation should be provided for why an apparently new event first occurring two days after the third dose is likely to be intercurrent with the patient's migraine and why the sponsor has determined that the event was not related to fremanezumab when the investigator assessed the event as related to fremanezumab.

3. In the narratives for Study 30049, patient (b) (6) is described as having retinal detachments in each eye. The retinal detachments are described as being of severe intensity and were assessed by the investigator as being non-serious.
   a. An explanation should be provided for the non-serious classification of two sight threatening events which required surgical intervention.
   b. An explanation should be provided for the investigator's assessment that the events were not related to fremanezumab.
   c. An explanation should be provided for the sponsor's assessment that the events were not related to fremanezumab.

4. In the narratives for Study 30051, patient (b) (6) is described as having worsening cataracts in each eye. The investigator classified the events as non-serious. An explanation should be provided for the non-serious classification of two events which required surgical intervention.

5. In the narratives for Study 30051, patient (b) (6) is described as having cataracts in each eye which were surgically removed. The investigator described the cataracts as being of moderate severity and classified the events as non-serious. An explanation should be provided for the non-serious classification of two events which required surgical intervention.

6. In the narratives for Study 30051, patient (b) (6) is described as having iritis in the left eye. The iritis is described as being of moderate severity and assessed by the investigator as being non-serious. The patient was treated with oral acyclovir 400 mg three times a day for the event. At the time of the data cutoff, one month later, the event had not resolved. The investigator assessed the iritis as not being related to the fremanezumab. The sponsor assessed the iritis as not being related to the fremanezumab.
   a. The patient is not described as having either uveitis or ocular viral infections in the past. It would be very unusual to treat iritis with acyclovir in the absence of a concurrent viral infection or history of previous ocular viral infections. Considering the event did not resolve in a month's time, it also did not appear to be effective and an alternative treatment was not provided. An explanation should be provided for the

treatment of this patient.

b. An explanation should be provided for the non-serious classification of a potentially sight-threatening event.
c. An explanation should be provided for the investigator's assessment that the event was not related to fremanezumab.
d. An explanation should be provided for the sponsor's assessment that the event was not related to fremanezumab.

7. In the narratives for Study 30051, patient (b) (6) is described as having intermittent blurred vision and intermittent double vision, both of moderate severity. The events were assessed by the investigator as being non-serious and having not resolved at the time of the data cutoff (5 months later). The investigator assessed the events as being related to fremanezumab. The sponsor assessed the events as not being related to fremanezumab and possibly related to the underlying condition of migraine. An explanation should be provided for the sponsor's assessment that these events were not related to fremanezumab.

8. In the narratives for Study 30051, patient (b) (6) is described as having a right eye infection after fremanezumab exposure. The patient previously had a corneal transplant in at least one of her eyes, but the eye(s) that received the transplant is not described. Following the diagnosis of an ocular infection of moderate severity, the patient received intensive antibacterial (six different antibacterials) and antifungal treatment consistent with the treatment that might be expected for an infected corneal transplant. The investigator assessed the event as non-serious. The investigator assessed the event as not being related to fremanezumab and the sponsor assessed the event as not being related to fremanezumab.
    a. An explanation should be provided for the non-serious classification of a potentially sight-threatening event.
    b. An explanation should be provided for the investigator's assessment that the event was not related to fremanezumab.
    c. An explanation should be provided for the sponsor's assessment that the event was not related to fremanezumab.

9. In the narratives for Study 30051, patient (b) (6) is described as having a retinal hole/tear in her right eye. The patient has a history of having floaters in the right eye approximately two months prior to her first treatment with fremanezumab. Approximately two months after receiving her first dose of fremanezumab, the patient was diagnosed as having a retinal hole, described as moderate severity and as non-serious by the investigator.
    a. An explanation should be provided for the non-serious classification of a potentially sight-threatening event.
    b. An explanation should be provided for treating the patient with fremanezumab after the patient had a new ocular event, but without that event being evaluated.

10. In the narratives for Study 30051, patient (b) (6) is described as having a retinal tear. The retinal tear was described as being of moderate severity and assessed by the investigator as being non-serious. On the same day as the retinal tear was repaired, the patient received an additional dose of fremanezumab. The investigator assessed the event as not being related to fremanezumab. The sponsor assessed the event as not being related to fremanezumab.

a. An explanation should be provided for the non-serious classification of a potentially sight-threatening event.
b. An explanation should be provided for the investigator's assessment that the event was not related to fremanezumab.
c. An explanation should be provided for the sponsor's assessment that the event was not related to fremanezumab.
d. An explanation should be provided for treating the patient with fremanezumab on the same day as the surgical procedure to repair the retinal tear was performed.

11. In the narratives for Study 30051, patient (b) (6) is described as having a retinal cyst in the left eye, a retinal detachment in the left eye, a cataract in the right eye and macular degeneration in both eyes. The patient's past medical history describes the patient as having farsightedness and nearsightedness starting 13 years prior. The cataract in the right eye, retinal cyst in the left eye and bilateral macular degeneration are all described as being of moderate severity and non-serious. The retinal cyst is reported to have resolved in one month without treatment; however, at the time that the retinal cyst was reported as being resolved, a retinal detachment in the left eye was reported, also assessed as non-serious. One month after the retinal detachment was reported, the retinal detachment was described as resolving without treatment. All of the events were assessed by the investigator as not being related to fremanezumab. The sponsor assessed each of the events as not being related to fremanezumab and reported that the events were due to intercurrent illness.
    a. An explanation should be provided for the non-serious classification of a potentially sight-threatening events.
    b. The resolution without treatment of the retinal cyst and retinal detachment should include an explanation.
    c. An explanation should be provided for the investigator's assessment that the event was not related to fremanezumab.
    d. The sponsor should identify the intercurrent illness that caused the retinal cyst, the retinal detachment, the cataract, and the macular degeneration.

12. In the narratives for Study LBR-101-011, patient (b) (6) is described as having narrow angle glaucoma. The narrow angle attack was described as having severe intensity and assessed by the investigator as non-serious. Treatment for the attack included peripheral laser iridotomy. An explanation should be provided for the non-serious classification of a potentially sight-threatening events which required surgical intervention.

13. In the narratives for Study LBR-101-022, patient (b) (6) is described as having a mild blurred vision, a mild visual impairment, a moderate vitreous detachment, a mild cataract and moderate optic disc drusen. The events were ongoing at the time of the reporting and the study drug was permanently discontinued. The investigator considered the events to be related to the study drug. The events of optic nerve drusen, posterior vitreous detachment, blurred vision in the right eye, and white spots in the right eye were assessed by the sponsor as not related to fremanezumab and possibly related to the patient's underlying degenerative eye conditions such as cataract.
    a. An explanation should be provided for the non-serious classification of these continuing events.

b. An explanation should be provided for the sponsor's assessment that the events were not related to fremanezumab.
c. An explanation should be provided for the sponsor's suggestion that optic nerve drusen is related to the patient's cataract.

14. Protocol defined adverse events of special interest were defined to include ophthalmic adverse events of at least moderate severity; however, there appears to be a discrepancy between the events which meet this definition and the events listed in TEV-48125 ISS Listing 6.1. The following events are included in ISS Listing 6.1 as not being adverse events of special interest.

Patient (b) (6) /30051	Cataract Left Eye
Patient /30051	Cataract Right Eye
Patient /30051	Worsening Cataract Left Eye
Patient /30051	Left Eye Iritis
Patient /30051	Cataract in Right Eye
Patient /30051	Bilateral macular degeneration
Patient /30051	Retinal Cyst
Patient /30051	Retinal detachment
Patient /30049	Intermittent bilateral retroorbital pain

While these patients do appear to be correctly identified as AESI in the updated Appendix B: Listing of All Patients/Subjects with a Safety narrative, the discrepancy in ISS Listing 6.1 should be explained or corrected.

15. Patient (b) (6) /30051 is listed as having a right vitreous prolapse. It is not clear where the vitreous prolapsed, how it is recovering or why the event would be considered mild severity.

16. Patient (b) (6) /30049 is listed as having a left eye cataract which is recovering/resolving. An explanation should be provided to explain how the cataract is resolving.

17. Based on the potential discrepancies noted above, it is recommended that all ocular events be considered adverse events of special interest for this drug product.

Summary Comment: There is insufficient information to complete the ophthalmology review. It is recommended that the comments listed above be communicated to the applicant and that appropriate explanations be submitted from the applicant and reviewed.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
02/26/2018