CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761089Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Review with a (b) (4) Priority Review Voucher No. PRV NDA (b) (4)

Recommendation: Approval

BLA Number: 761089
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Review Number: First Round
Review Date: August 16, 2018

Drug Name/Dosage Form	Ajovy (fremanezumab-vfrm), injection
Strength/Potency	225 mg/1.5 mL solution in a single-dose pre-filled syringe
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	for the preventive treatment of migraine in adult patients
Applicant/Sponsor	Teva Branded Pharmaceutical Products R&D

Product Overview

Fremanezumab-vfrm is a fully humanized IgG2Δa kappa monoclonal antibody raised against alpha and beta calcitonin gene-related peptide (CGRP). Fremanezumab-vfrm selectively binds to CGRP and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. In addition, two mutations were introduced into the constant region of the fremanezumab-vfrm heavy chain to limit antibody Fc effector function. Fremanezumab-vfrm is produced in genetically engineered Chinese hamster ovary (CHO) cells.

Fremanezumab-vfrm drug product (DP), Ajovy, is a clear, colorless to slightly yellow liquid sterile solution containing fremanezumab-vfrm antibody formulated at a concentration of 150 mg/mL for subcutaneous injection. The DP is packaged as a single use pre-filled syringe (PFS) delivering 1.5 mL of sterile solution. Each PFS contains 225 mg of fremanezumab-vfrm. Ajovy is proposed for the preventive treatment of migraine in adult patients.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Andrea Franco	OPQ/OBP/DBRR IV
Drug Product	Jacek Cieslak	OPQ/OBP/DBRR IV
Immunogenicity Assays	Jacek Cieslak	OPQ/OBP/DBRR IV
Labeling	CAPT Vicky Borders Hemphill	OPQ/OBP
Facilities	CDR Thuy Nguyen	OPQ/OPF/DIA
Microbiology	Candace Gomez-Broughton (DS) Lindsey Brown (DP)	OPQ/OPF/DMA IV
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Peter Qiu (Facility) Reyes Candau-Chacon (Microbiology)	OPQ/OBP/DBRR IV OPQ/OPF/DIA OPQ/OPF/DMA IV
OPQ RBPM	Kelly Ballard	OPQ/OPRO
Application Team Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Lana Chen	OND/DNP
Cross-disciplinary Team Lead	Heather Fitter	OND/DNP

Medical Officer	Suhail Kasim, Heather Fitter (TL)	OND/DNP
Clinical Safety	Lourdes Villalba, Sally Jo Yasuda (TL)	OND/DNP
Pharm/Tox	Barbara Wilcox, Lois Freed (TL)	OND/DNP
Clinical Pharmacology	Hristina Dimova, Sreedharan Sabarinath (TL)	OND/DNP
Pharmacometrics	Gopichand Gottipati, Kevin Krudys (TL)	OND/DNP
Biometrics	Sharon Yan, Kun Jin (TL)	OND/DNP
Device	Robert Kang Jacquie Gertz, John McMichael (TL)	CDRH/OC CDRH/GHDB
OSI	Cara Alfaro, Phillip Kronstein (TL)	
OSE PM	Ruth Maduro	
OSE/DMEPA	Chad Morris, Lolita White (TL)	
Labeling	ADL: Tracy Peters	
OPDP	Dhara Shah	
DMPP (PTL)	Twanda Scales, Marcia Williams (TL)	

Names:

Proprietary Name: Ajovy (*ah-JOE-vee*)
Non-proprietary/USAN/INN: fremanezumab-vfrm
CAS Registry Number: 1655501-53-3
Chemical Name: Immunoglobulin G2, anti-human alpha calcitonin gene-related peptide / beta calcitonin gene-related peptide
Company Name: TEV-48125
OBP systematic name[1]: MAB HUMANIZED (IGG2) ANTI P06881 (CALCA_HUMAN) [TEV48125]
Other Names: LBR-101, PF-04472429, RN307

Submissions Reviewed:

Submission	Date Received	Review Completed (Yes/No)
STN 761089/4 (BLA Original Application)	October 16, 2017	Yes (All)
STN 761089/6 (30-day update)	November 14, 2017	Yes (OBP)
STN 761089/10 (Response to IR #1)	December 5, 2017	Yes (DIA)
STN 761089/18 (Updated Mfg. Schedule)	December 28, 2017	Yes (DIA)
STN 761089/19 (Response to IR#2)	January 8, 2018	Yes (OBP)
STN 761089/22 (Response to IR#3)	January 17, 2018	Yes (CDRH)
STN 761089/36 (Response to IR#4)	February 9, 2018	Yes (OBP)
STN 761089/28 (Response to IR#5)	February 23, 2018	Yes (DMA)
STN 761089/30 (Response to IR#6 and IR#7)	February 27, 2018	Yes (OBP)
STN 761089/36 (Response to IR#8)	March 9, 2018	Yes (DMA)
STN 761089/38 (Response to IR#9 and IR#10)	March 15, 2018	Yes (CDRH \ OBP)
STN 761089/42 (Response to IR#10)	March 22, 2018	Yes (OBP)
STN 761089/40 (Response to IR#11)	March 19, 2018	Yes (DMA)
STN 761089/45 (Response to IR#12)	March 30, 2018	Yes (OBP)
STN 761089/46 (Response to IR#5)	April 5, 2018	Yes (DMA)
STN 761089/48 (Response to April 9, 2018 IR)	April 12, 2018	Yes (OBP Labeling)

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

STN 761089/52 (Container-Carton Label)	July 5, 2018	Yes (OBP Labeling)
STN 761089/54 (Response to July 19, 2018 IR)	July 25, 2018	Yes (DMA)

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III		(b) (4)	1	Adequate	1/23/2018	Reviewed by DMA; found acceptable. CDRH found the DMF adequate.
	III			3	N/A	N/A	
	III			1	Adequate	4/6/2018	Reviewed by DMA; found adequate
	II			3	N/A	N/A	
	II			3	N/A	N/A	

1. Action codes for DMF Table: **1- DMF Reviewed**; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; **3- Sufficient information in application**; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND 106533

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Reviewer
CDRH/ GHDB Review of delivery device (PFS)	11/30/2017	Completed 3/16/2018	The device constituent of the combination product is **approvable** for the proposed indication.	Jacquie Gertz John McMichael (TL)
CDRH/OC Facilities inspections consults	11/30/2017	Completed 7/27/2018	The application is **approvable** from the perspective of the applicable Quality System Requirements.	Robert Kang Katelyn Bittleman for Mathew Krueger (Branch Chief)

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761089 for Ajovy (fremanezumab-vfrm) manufactured by Teva Branded Pharmaceutical Products. The data submitted in this application are adequate to support the conclusion that the manufacture of Ajovy is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

B. Benefit/Risk Considerations:

The review of manufacturing information provided in the application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The fremanezumab drug substance (DS) will be manufactured at Celltrion, Inc. (FEI 3005241015) and the Ajovy drug product (DP) at (b) (4)
Pre-licensing inspections were conducted at Celltrion, Inc. and (b) (4)
(b) (4) and the facilities were found acceptable for the proposed operations.

CDRH Office of Compliance and Office of Device Evaluation provided evaluations of the device component; no approvability issues were identified from a device component perspective.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of fremanezumab-vfrm at plasma concentrations.

Individual reviews for each discipline, (1) drug substance and drug product quality [OBP], (2) immunogenicity assays [OBP], (3) microbiological control of drug substance and drug product [DMA], (4) facilities evaluation [DIA], and (5) labeling [OBP] are located as separate documents in Panorama (see list at the end of this review).

C. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps upon approval:

The primary review for drug substance and drug product quality recommended the following Post Marketing Commitment:

(b) (4)

However, after further discussion with the quality review team it was decided that the (b) (4) should be managed by the Applicant's Quality Management Systems as part of the annual product review in compliance with 21 CFR 211.180.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes, intrinsic to the molecule, that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA type	CQA	Risk	Origin	Control Strategy
Potency (biological activity)	Function of binding to CGRP and preventing binding of CGRP to its receptor (Cell-based assay for nhibition of CGRP-nduced cAMP in SK-N-MC cells)	Bioactivity (efficacy), and PK/PD	Intrinsic to the molecule	(b) (4)
Identity	Identity (by icIEF and ELISA)	Efficacy, safety, and immunogenicity	Intrinsic to the molecule	

CQA type	CQA	Risk	Origin	Control Strategy
Product-related impurities	(b) (4)	(b) (4)	No source is identified. (b) (4)	(b) (4)
	(b) (4)		(b) (4)	
Non-CQAs controlled to ensure process consistency				
Product-related variants	(b) (4)	Product and process consistency	(b) (4)	
	(b) (4)	Product and process consistency	No source is identified.	

DS - drug substance, DP - drug product, CQA – Critical Quality Attributes, IPC – In Process Controls, CIPC- Critical In-Process Controls, CEX – Cation Exchange Chromatography, SE-HPLC – Size Exclusion Chromatography, icIEF – imaged capillary IsoElectric Focusing, CGE – Capillary Gel Electrophoresis, ELISA – Enzyme-Linked Immunosorbent Assay, pE – pyroglutamate, CTL – C-terminal lysine, PK – Pharmacokinetics, PD – Pharmacodynamics, MoA – Mechanism of Action

The applicant provided data to support that other product variants (b) (4) are not CQAs because of they either, were not detected or detected in very low levels, no impact on efficacy was demonstrated (bioactivity, safety, immunogenicity), or are described in the literature and well known for endogenous proteins.

B. Drug Substance, Fremanezumab-vfrm, Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	Safety	(b) (4)	(b) (4)
	Host Cell Proteins (HCP)	Safety, Immunogenicity	(b) (4)	

CQA type	CQA	Risk	Origin	Control Strategy
	(b) (4)	PK, Immunogenicity, Safety	(b) (4)	(b) (4)
	Leachables	Immunogenicity, Safety	Raw materials, manufacturing process	
	(b) (4)	Safety	Manufacturing process	
Adventitious Agents	Viral Safety	Safety	Raw materials and manufacturing process	
	Bioburden	Safety, purity, and efficacy (b) (4)	Raw materials and contamination during manufacturing	
	Bacterial Endotoxins	Safety, purity	Raw materials and contamination during manufacturing	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process (b) (4)	
	Osmolality	Bioactivity	Formulation	
	pH	Bioactivity	Formulation	
	Appearance (degree of coloration, clarity/opalescence, visible particulate matter)	Bioactivity, Safety	Product, formulation	
	(b) (4)	Bioactivity, Safety	Formulation component	

DS - drug substance, DP - drug product, IPC – in process control

- **Description**: Fremanezumab-vfrm is a fully humanized IgG2 ∆a/kappa monoclonal antibody consisting of two identical light chains (LC) and two identical heavy (HC) chains. To increase binding affinity, the Fab variable region of the HC was mutated at residue 99 (A99L) and at residue

100 (R100A). In addition, to prevent antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), the constant region of the HC was mutated at residue 330 (A330S) and at residue 331 (P331S). Fremanezumab-vfrm contains 36 cysteines which form intrachain and interchain disulfide bonds. The HC lacks C-terminal lysine. N-linked oligosaccharide structures were detected on Asn 298 of each HC. The major glycan species corresponds to core-fucosylated, biantennary complex glycan structures with galactose heterogeneity. No O-linked glycosylation was detected.

- **Mechanism of Action (MoA)**: Fremanezumab-vfrm binds to CGRP ligand and thus prevents α- and β-CGRP from binding to the CGRP receptor, thereby preventing in vitro cyclic adenosine monophosphate (cAMP) production induced by CGRP. CGRP is considered to be involved in the pathophysiology of migraine.
- **Potency Assay**: A cell-based assay is used to measure the potency of fremanezumab-vfrm. This assay is based on the principle that fremanezumab-vfrm binds to CGRP and prevents it from stimulating intracellular cAMP accumulation in human SK-N-MC neuroblastoma cells. Intracellular cAMP is measured using the cAMP-Glo Max Assay system, which measures the cAMP concentration in the wells of cell culture plates following cell lysis. The relative potency is calculated by dividing the EC_{50} (i.e. the concentration of fremanezumab-vfrm at which the half-maximum reduction in cAMP accumulation is observed) of the fremanezumab-vfrm reference standard by the EC_{50} of a fremanezumab-vfrm test sample x 100%. The reportable value is the mean relative potency of two plates.
- **Reference Materials**:
  - (b) (4)
  -
  -
- **Critical starting materials or intermediates**: (b) (4)
  (b) (4)
- **Manufacturing process summary**: (b) (4)
  (b) (4)

(b) (4)

- **Container closure**: Fremanezumab-vfrm DS is stored (b) (4)
- **Dating period and storage conditions**: (b) (4) months at (b) (4) °C.

C. Drug Product, Ajovy, Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA type	CQA	Risk	Origin	Control Strategy
Particles (product or process related impurities)	Subvisible Particles	Safety, Immunogenicity	DP manufacturing process, CCS, and product	(b) (4)
	Visible Particulate matter	Safety, Immunogenicity	DP manufacturing process, CCS, and product	
Volume in Container	Extractable Volume	Bioactivity	DP manufacturing process (b) (4)	
Contamination	Sterility	Safety, Purity, and Efficacy (degradation or modification of the product by contaminating microorganisms)	DP manufacturing process, container closure integrity failure	

CQA type	CQA	Risk	Origin	Control Strategy
				(b) (4)
	Bacterial endotoxin	Safety, Purity, Immunogenicity	Raw materials, manufacturing process	
	Container closure integrity	Safety	Container closure breaches during manufacturing or storage	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process	
	Appearance (degree of coloration, clarity/opalescence)	Bioactivity, Safety	Product, formulation	
	Osmolality	Bioactivity	Formulation	
Functionality	Break loose force	Proper device functionality	Container closure components	
	Glide force			

- **Potency and Strength:** 150 mg/mL fremanezumab-vfrm, and a total of 225 mg protein/PFS
- **Summary of Product Design:** sterile-filtered, preservative-free, clear to opalescent, colorless to slightly yellow solution (b) (4) into a single use pre-filled syringe.
- **List of Excipients:** L-Histidine, L-Histidine hydrochloride monohydrate, Sucrose, EDTA, Polysorbate 80
- **Reference Materials:** Same as fremanezumab-vfrm drug substance reference standards.
- **Manufacturing process summary:** The manufacturing process consists of primary (b) (4)
- **Container closure:** PFS (b) (4) glass barrel with a staked-in-place needle protected by a rigid needle shield (RNS), a plunger-stopper made of (b) (4) plunger rod.
- **Dating period and storage conditions:** 24 months at 2 – 8 °C.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Single-dose pre-filled syringe.
- Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original outer carton to protect from light. Do Not Freeze. Do Not Shake. Do not expose to extreme heat or direct sunlight. After removal from the refrigerator, AJOVY must be used within 24 hours or discarded.
- Visually inspect AJOVY for particles or discoloration prior to administration.

F. Establishment Information:

DRUG SUBSTANCE					
Function	**Site Information**	**FEI/DUNS Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
Manufacture of drug substance, (b) (4)	Celltrion, Inc 13-1 Songdo-dong Yeonsu-gu, Incheon South Korea	FEI# 3005241015 DUNS# 688836030	A pre-license inspection was conducted 7/9-17/2018. This was a For Cause and PLI inspection. The 'For Cause' portion was initially recommended as OAI but downgraded to VAI by OMQ. The PLI portion of the inspection was found acceptable.		Acceptable.
(b) (4)			No Further Evaluation	N/A	No Further Evaluation
			No Further Evaluation	N/A	No Further Evaluation
			No Further Evaluation	N/A	No Further Evaluation

DRUG PRODUCT					
Function	**Site Information**	**DUNS/FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
(b) (4)					Acceptable

(b) (4)

	3 = RVS 3 (Ravensburg South 3)	
	N/A	Acceptable
	N/A	Acceptable
	N/A	Acceptable
	N/A	Acceptable
No Further Evaluation	N/A	No Further Evaluation
No Further Evaluation	N/A	No Further Evaluation

(b) (4)

G. Facilities:

- Fremanezumab-vfrm drug substance is manufactured at **Celltrion, Inc.**, Incheon, South Korea. A pre-license inspection for fremanezumab-vfrm drug substance and a follow-up inspection to the Warning Letter issued to the facility on January 26, 2018 were conducted on July 9 - 17, 2018 by ORA, OPF, and OBP. The 'For Cause' portion was initially recommended as OAI but downgraded to VAI by OMQ. The PLI portion of the inspection was acceptable and recommended approval.

  Final facility recommendation: Acceptable

- A pre-license inspection of fremanezumab-vfrm drug product manufacturing facility at (b) (4) was conducted on (b) (4) by OPQ/OFP/DIA in support of this BLA. The initial recommendation for this inspection was withhold of approval, but inspection issues were resolved within the review cycle. The inspection was classified VAI and recommended approval based on inspectional assessment.

  Final facility recommendation: Acceptable

- For the status of all other facilities included in the application refer to Section F: Establishment Information of this review.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols submitted to the BLA:

1. (b) (4)
2.
3.
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7.
8.
9.

ii. Outstanding review issues/residual risk:

See Post Marketing Commitments in section I. D.

iii. Future inspection points to consider:

1. Review the performance of the analytical methods used for release, stability, and in-process testing.

b. Drug Product

i. Protocols submitted to the BLA:

1. Ongoing Primary Stability Studies (3.2.P.8.1 and 3.2.P.8.2), including shelf-life extension
2. Post-Approval Annual Stability Protocols (3.2.P.8.2)
3. Comparability Protocol (3.2.R)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider:

1. Review the performance of the analytical methods used for release, stability, and in-process testing.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
Product Type					
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				
REGULATORY CONSIDERATIONS					
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)		X		
17.	End of Phase II/Pre-BLA Agreements		X		
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other (b) (4) Priority Review Voucher (PRV NDA (b) (4))]		X		
QUALITY CONSIDERATIONS					
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				

Review documents related to this Executive Summary (links to document in Panorama)**:**

- Combined Drug substance quality review by Andrea Franco, PhD (OPQ/OBP/DBRR IV), Drug product quality review by Jacek Cieslak, PhD (OPQ/OBP/DBRR IV), and Immunogenicity assay review by Jacek Cieslak, PhD link

- Drug substance microbiology review by Candace Gomez-Broughton, PhD (OPQ/OPF/DMA IV) link
- Drug product microbiology review by Lindsey Brown, PhD (OPQ/OPF/DMA IV) link
- Facility review by Thuy Nguyen (OPQ/OPF/DIA) link
- Device evaluation review by Jacqueline Gertz (CDRH/ODE/DAGRID/GHDB) link
- Device compliance review by Robert Kang (CDRH/OC/DMQ/POND) link
- OBP Labeling review by Vicky Borders-Hemphill, PharmD (OPQ/OBP)

Leslie Rivera-Rosado

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Reyes Candau-Chacon

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Zhihao Peter Qiu

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Date: 9/04/2018 10:26:46AM
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Christopher Downey

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Date: 8/29/2018 10:17:50AM
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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Primary Reviewer: Lindsey Brown, Ph.D.

Secondary Reviewer: Reyes Candau-Chacon, Ph.D.

Date: 12/12/2017

To: Administrative File **STN:** 761089/0

Applicant: Teva Branded Pharmaceutical Products

Submission Reviewed: BLA to support the manufacture of Fremanezumab for injection.

US License Number: 2016

Facility: (b) (4) **(FEI:** (b) (4)**)**

Product: Fremanezumab

Indication: Preventive treatment of migraine in adult patients

Dosage Form: Prefilled syringe (225mg/1.5 ml); subcutaneous injection

PDUFA Date: 09/16/2018

Recommendation for Approvability: The drug product section of BLA 761089 is recommended for approval from a sterility assurance and microbiology product quality perspective. The following pending issues have been resolved.

1. DMF (b) (4) is currently adequate to support sterility assurance of the 2.25mL syringe.
2. A description and qualification of the in-process bioburden testing performed prior to (b) (4) has been provided.
3. Clarification regarding (b) (4) has been provided.

[redacted].

4. Validation of [redacted]

[redacted]

5. Additional information to assess adequacy of the Comparability Protocol for the addition of the [redacted] drug product manufacturing facility was provided in amendment 0040. The BLA was updated on 3/22/2018 with the corresponding information.

Drug Product Quality Microbiology Assessment

The following amendments were reviewed in support of BLA 761089.

Sequence	Date	Description
0040	3/19/2018	Response to Information Request
0042	3/22/2018	Response to Information Request
0046	4/5/2018	Response to Information Request
0054	7/25/2018	Response to Information Request

The following DMF was reviewed in support of BLA 761089.

DMF	Panorama Date	Status
[redacted]	8/27/2018	Adequate

Summary: This addendum provides the assessment of five pending issues from the original drug product microbiology review memo. In addition, follow-up information regarding endotoxin recovery from the undiluted product is assessed at the end of the memo.

[redacted]

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Conclusion

I. BLA 761089 was reviewed from a sterility assurance and product quality microbiology perspective and is recommended for approval.

II. Product quality aspects other than microbiology should be reviewed by OBP.

III. Refer to Panorama for CGMP status of relevant manufacturing and testing facilities.

Lindsey Brown

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Date: 8/30/2018 10:54:38AM
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Reyes Candau-Chacon

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Priority Review with a [redacted] (b) (4) Priority Review Voucher No. PRV NDA [redacted] (b) (4)

Recommendation: Complete Response

BLA Number: 761089
\\cdsesub1\evsprod\bla761089\761089.enx
Review Number: First Round
Review Date: April 20, 2018

Drug Name/Dosage Form	Ajovy (Fremanezumab), injection
Strength/Potency	225 mg/1.5 mL solution in a single-dose pre-filled syringe
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	for the preventive treatment of migraine in adult patients
Applicant/Sponsor	Teva Branded Pharmaceutical Products R&D

Product Overview

Fremanezumab is a fully humanized IgG2Δa kappa monoclonal antibody raised against alpha and beta calcitonin gene-related peptide (CGRP). Fremanezumab selectively binds to CGRP and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. In addition, two mutations were introduced into the constant region of the fremanezumab heavy chain to limit antibody Fc effector function. Fremanezumab is produced in genetically engineered Chinese hamster ovary (CHO) cells. Fremanezumab drug product (DP), Ajovy, is a clear, colorless to slightly yellow liquid sterile solution containing fremanezumab antibody formulated at a concentration of 150 mg/mL for subcutaneous injection. The DP is packaged as a single use pre-filled syringe (PFS) delivering 1.5 mL of sterile solution. Each PFS contains 225 mg of fremanezumab. Ajovy is proposed for the preventive treatment of migraine in adult patients.

Quality Review Team

Discipline	Reviewer	Branch/Division
Drug Substance	Andrea Franco	OPQ/OBP/DBRR IV
Drug Product	Jacek Cieslak	OPQ/OBP/DBRR IV
Immunogenicity Assays	Jacek Cieslak	OPQ/OBP/DBRR IV
Labeling	CAPT Vicky Borders Hemphill	OPQ/OBP
Facilities	CDR Thuy Nguyen	OPQ/OPF/DIA
Microbiology	Candace Gomez-Broughton (DS) Lindsey Brown (DP)	OPQ/OPF/DMA IV
Team Leads	LCDR Leslie A. Rivera Rosado (Product quality) Peter Qiu (Facility) Reyes Candau-Chacon (Microbiology)	OPQ/OBP/DBRR IV OPQ/OPF/DIA OPQ/OPF/DMA IV
OPQ RBPM	Kelly Ballard	OPQ/OPRO
Application Team Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Review Team

Discipline	Reviewer	Office/Division
RPM	Lana Chen	OND/DNP
Cross-disciplinary Team Lead	Heather Fitter	OND/DNP
Medical Officer	Suhail Kasim, Heather Fitter (TL)	OND/DNP

Clinical Safety	Lourdes Villalba, Sally Jo Yasuda (TL)	OND/DNP
Pharm/Tox	Barbara Wilcox, Lois Freed (TL)	OND/DNP
Clinical Pharmacology	Hristina Dimova, Sreedharan Sabarinath (TL)	OND/DNP
Pharmacometrics	Gopichand Gottipati, Kevin Krudys (TL)	OND/DNP
Biometrics	Sharon Yan, Kun Jin (TL)	OND/DNP
Device	Robert Kang Jacquie Gertz, John McMichael (TL)	CDRH/OC CDRH/GHDB
OSI	Cara Alfaro, Phillip Kronstein (TL)	
OSE PM	Ruth Maduro	
OSE/DMEPA	Chad Morris, Lolita White (TL)	
Labeling	ADL: Tracy Peters	
OPDP	Dhara Shah	
DMPP (PTL)	Twanda Scales, Marcia Williams (TL)	

Names:

Proprietary Name: Ajovy (*ah-JOE-vee*)
Non-proprietary/USAN/INN: fremanezumab
CAS Registry Number: 1655501-53-3
Chemical Name: Immunoglobulin G2, anti-human alpha calcitonin gene-related peptide / beta calcitonin gene-related peptide
Company Name: TEV-48125
OBP systematic name[1]: MAB HUMANIZED (IGG2) ANTI P06881 (CALCA_HUMAN) [TEV48125]
Other Names: LBR-101, PF-04472429, RN307

Submissions Reviewed:

Submission	Date Received	Review Completed (Yes/No)
STN 761089/4 (BLA Original Application)	October 16, 2017	Yes
STN 761089/6 (30-day update)	November 14, 2017	Yes (OBP)
STN 761089/10 (Response to IR #1)	December 5, 2017	Yes (DIA)
STN 761089/18 (Updated Mfg. Schedule)	December 28, 2017	Yes (DIA)
STN 761089/19 (Response to IR#2)	January 8, 2018	Yes (OBP)
STN 761089/22 (Response to IR#3)	January 17, 2018	Yes (CDRH)
STN 761089/36 (Response to IR#4)	February 9, 2018	Yes (OBP)
STN 761089/28 (Response to IR#5)	February 23, 2018	Yes (DMA)
STN 761089/30 (Response to IR#6 and IR#7)	February 27, 2018	Yes (OBP)
STN 761089/36 (Response to IR#8)	March 9, 2018	Yes (DMA)
STN 761089/38 (Response to IR#9 and IR#10)	March 15, 2018	Yes (CDRH \ OBP)
STN 761089/42 (Response to IR#10)	March 22, 2018	Yes (OBP)
STN 761089/40 (Response to IR#11)	March 19, 2018	Yes (DMA)
STN 761089/45 (Response to IR#12)	March 30, 2018	Yes (OBP)
STN 761089/46 (Response to IR#5)	April 5, 2018	Yes (DMA)

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the nonproprietary name. The tag at the end is used to separate products from different sponsors and it is generally the name used by sponsors to refer to the proposed product in their submissions.

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Review Completed	Comments
(b) (4)	III	(b) (4)		1	Deficient	1/23/2018	Reviewed by DMA. (b) (4) Response to IR is pending. CDRH found the DMF Adequate.
	III			3	N/A	N/A	
	III			1	Adequate	4/6/2018	DMA found the DMF adequate
	II			3	N/A	N/A	
	II			3	N/A	N/A	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND 106533

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Reviewer
CDRH/ GHDB Review of delivery device (PFS)	11/30/2017	Completed 3/16/2018	The device constituent of the combination product is approvable for the proposed indication.	Jacquie Gertz, John McMichael (TL)
CDRH/OC Facilities inspections consults	11/30/2017	*pending*		Robert Kang

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761089 for Ajovy (fremanezumab) manufactured by Teva Branded Pharmaceutical Products. From a product quality standpoint, OPQ recommends a Complete Response letter be issued to Teva Branded Pharmaceutical Products to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

1. During a recent inspection of the Celltrion, Inc. (FEI #3005241015) manufacturing facility for this application, the field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. Your referenced Drug Master File (b) (4) DMF (b) (4) is inadequate to support (b) (4) (b) (4)

C. Benefit/Risk Considerations:

This application is not recommended for approval during this review cycle due to facility deficiency. A pre-license inspection (PLI) of the fremanezumab drug substance manufacturing facility cannot be conducted until the Official Action Indicated (OAI) status and Warning Letter issued to the contract manufacturer for drug substance manufacture, Celltrion, Inc, Incheon, South Korea (FEI #3005241015) is cleared by the Office of Manufacturing Quality/ Office of Compliance/ CDER. The Division of Inspectional Assessment (DIA), OPF, OPQ is recommending withhold of approval.

The review of manufacturing information provided in the application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product.

The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective. However, final determination of acceptability of the information provided in the dossier is contingent upon successful completion the PLI.

One of the referenced Drug Master Files, DMF (b) (4) (DMF holder (b) (4)), was found inadequate. Additional information regarding the (b) (4) was requested and a response is still pending. The DMF will be re-reviewed by the Division of Microbial Assessment (DMA), OPF, OPQ during the review of the resubmission of this application.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of fremanezumab at plasma concentrations.

Individual reviews for each discipline, (1) drug substance and drug product quality [OBP], (2) immunogenicity assays [OBP], (3) microbiological control of drug substance and drug product [DMA], (4) facilities evaluation [DIA], and (5) labeling [OBP] are located as separate documents in Panorama (see list at the end of this review).

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

[Draft Language]

(b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes, intrinsic to the molecule, that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA type	CQA	Risk	Origin	Control Strategy (b) (4)
Potency (biological activity)	Function of binding to CGRP and preventing binding of CGRP to its receptor (Cell-based assay for inhibition of CGRP-induced cAMP in SK-N-MC cells)	Bioactivity (efficacy), and PK/PD	Intrinsic to the molecule	

CQA type	CQA	Risk	Origin	Control Strategy
Identity	Identity (by icIEF and ELISA)	Efficacy, safety, and immunogenicity	Intrinsic to the molecule	(b) (4)
Product-related impurities	(b) (4)	(b) (4)	No source is identified. (b) (4)	
	(b) (4)		(b) (4)	
Non-CQAs controlled to ensure process consistency				
Product-related variants	(b) (4)	Product and process consistency	(b) (4)	
		Product and process consistency	No source is identified.	

DS - drug substance, DP - drug product, CQA – Critical Quality Attributes, IPC – In Process Controls, CIPC- Critical In-Process Controls, CEX – Cation Exchange Chromatography, SE-HPLC – Size Exclusion Chromatography, icIEF – imaged capillary IsoElectric Focusing, CGE – Capillary Gel Electrophoresis, ELISA – Enzyme-Linked Immunosorbent Assay, (b) (4) (b) (4) PK – Pharmacokinetics, PD – Pharmacodynamics, MoA – Mechanism of Action

The applicant provided data to support that other product variants (b) (4) (b) (4) are not CQAs because of they either, were not detected or detected in very low levels, no impact on efficacy was demonstrated (bioactivity, safety, immunogenicity), or are described in the literature and well known for endogenous proteins.

B. Drug Substance, Fremanezumab, Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	Safety	(b) (4)	(b) (4)

	Host Cell Proteins (HCP)	Safety, Immunogenicity	(b) (4)
	(b) (4)	PK, Immunogenicity, Safety	(b) (4)
	Leachables	Immunogenicity, Safety	Raw materials, manufacturing process
	(b) (4)	Safety	Manufacturing process
Adventitious Agents	Viral Safety	Safety	Raw materials and manufacturing process
	Microbiological Purity (bioburden, mycoplasma)	Safety	Raw materials and manufacturing process
	Bacterial Endotoxins	Safety	Raw materials and manufacturing process.
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process (b) (4) (b) (4)
	Osmolality	Bioactivity	Formulation
	pH	Bioactivity	Formulation
	Appearance (degree of coloration, clarity/opalescence, visible particulate matter)	Bioactivity, Safety	Product, formulation
	(b) (4) Content	Bioactivity, Safety	Formulation component

(b) (4)

DS - drug substance, DP - drug product, IPC – in process control

- **Description**: Fremanezumab is a fully humanized IgG2 Δa/kappa monoclonal antibody consisting of two identical light chains (LC) and two identical heavy (HC) chains. To increase binding affinity, the Fab variable region of the HC was mutated at residue 99 (A99L) and at residue 100 (R100A). In addition, to prevent antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), the constant region of the HC was mutated at residue 330 (A330S) and at

residue 331 (P331S). Fremanezumab contains 36 cysteines which form intrachain and interchain disulfide bonds. The HC lacks C-terminal lysine. N-linked oligosaccharide structures were detected on Asn 298 of each HC. The major glycan species corresponds to core-fucosylated, biantennary complex glycan structures with galactose heterogeneity. No O-linked glycosylation was detected.

- **Mechanism of Action (MoA)**: Fremanezumab binds to CGRP ligand and thus prevents α- and β-CGRP from binding to the CGRP receptor, thereby preventing in vitro cyclic adenosine monophosphate (cAMP) production induced by CGRP. CGRP is considered to be involved in the pathophysiology of migraine.
- **Potency Assay**: A cell-based assay is used to measure the potency of fremanezumab. This assay is based on the principle that fremanezumab binds to CGRP and prevents it from stimulating intracellular cAMP accumulation in human SK-N-MC neuroblastoma cells. Intracellular cAMP is measured using the cAMP-Glo Max Assay system, which measures the cAMP concentration in the well following cell lysis. The relative potency is calculated by dividing the EC_{50} of the fremanezumab reference standard with the EC_{50} of a test sample x 100%. The reportable value is the mean relative potency of two plates.
- **Reference Materials**:
  - (b) (4)
  -
  -
- **Critical starting materials or intermediates**: (b) (4)

(b) (4)

- **Manufacturing process summary**: The drug substance manufacturing consists (b) (4)

(b) (4)

(b) (4)

- **Container closure**: Fremanezumab DS is stored (b) (4)
(b) (4)
- **Dating period and storage conditions**: (b) (4) months at (b) (4) °C.

C. Drug Product, Ajovy, Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA type	CQA	Risk	Origin	Control Strategy (b) (4)
Particles (product or process related impurities)	Subvisible Particles	Safety, Immunogenicity	DP manufacturing process, CCS, and product	
	Visible Particulate matter	Safety, Immunogenicity	DP manufacturing process, CCS, and product	
Volume in Container	Extractable Volume	Bioactivity	DP manufacturing process (b) (4)	
Contamination	Sterility	Safety	DP manufacturing process, container closure integrity failure	
	Container closure integrity	Safety	Container closure components, storage condition	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process	
	Appearance (degree of coloration, clarity/opalescence)	Bioactivity, Safety	Product, formulation	
	Osmolality	Bioactivity	Formulation	
Functionality	Break loose force			

	Glide force	Proper device functionality	Container closure components	(b) (4)

- **Potency and Strength:** 150 mg/mL fremanezumab, and a total of 225 mg protein/PFS
- **Summary of Product Design:** sterile-filtered, preservative-free, clear to opalescent, colorless to slightly yellow solution (b) (4) into a single use pre-filled syringe.
- **List of Excipients:** L-Histidine, L-Histidine hydrochloride monohydrate, Sucrose, EDTA, PS80
- **Reference Materials:** Same as fremanezumab drug substance reference standards.
- **Manufacturing process summary:** The manufacturing process consists (b) (4) (b) (4)
- **Container closure:** PFS (b) (4) glass barrel with a staked-in-place needle protected by a rigid needle shield (RNS), a plunger-stopper (b) (4) (b) (4) and a (b) (4) plunger rod.
- **Dating period and storage conditions:** 24 months at 2 – 8 °C.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

- Single-dose pre-filled syringe.
- Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in the original outer carton to protect from light. Do Not Freeze. Do Not Shake. Do not expose to extreme heat or direct sunlight. After removal from the refrigerator, AJOVY must be used within 24 hours or discarded.
- Visually inspect AJOVY for particles or discoloration prior to administration.

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture of drug substance, (b) (4) (b) (4)	Celltrion, Inc 13-1 songdo-dong Yeonsu-gu, Incheon South Korea	FEI# 3005241015 DUNS# 688836030	Unacceptable due to OAI status.	N/A	**Unacceptable** due to OAI status. A pre-license inspection was not scheduled due to the facility's current OAI status as a result of a post-approval inspection conducted by ORA. The

					inspection resulted in a Warning Letter issued to Celltrion in January, 2018. A PLI will not be schedule until the facility's OAI status is cleared by OMQ.
[redacted] (b) (4)			No Further Evaluation	N/A	
			No Further Evaluation	N/A	
			No Further Evaluation	N/A	

DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
[redacted] (b) (4)					Acceptable
[redacted] (b) (4)				N/A	Acceptable
				N/A	Acceptable

(b) (4)			
		N/A	Acceptable
		N/A	Acceptable
	No Further Evaluation	N/A	
	No Further Evaluation	N/A	

(b) (4)

G. Facilities:

- Fremanezumab drug substance is manufactured at **Celltrion, Inc.**, Incheon, South Korea. The current facility status is "Official action indicated." A Warning Letter was issued to the facility on January 26, 2018. A pre-license inspection for fremanezumab drug substance will not be scheduled until the issues identified in the Warning Letter are resolved through Office of Manufacturing Quality (OMQ), Office of Compliance (OC).
  Final facility recommendation: Unacceptable due to OAI status

- A pre-license inspection of fremanezumab drug product manufacturing facility at (b) (4) (b) (4) was conducted on (b) (4) by OPQ/OFP/DIA in support of this BLA. A FDA 483 form with following observation was issued to the firm:

  Your risk assessment (b) (4) *For example:*

  - (b) (4) *are not assessed.*
  - (b) (4) *are not assessed.*

  The initial recommendation for this inspection was withhold.

Final facility recommendation: Acceptable

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols submitted to the BLA: Approvable once the CR issues are resolved.

(b) (4)

[redacted]

ii. Outstanding review issues/residual risk:
See Post Marketing Commitments in section I. D.

iii. Future inspection points to consider:

1. Conduct pre-license inspection.
2. Review the performance of the analytical methods used for release, stability, and in-process testing.

b. Drug Product

i. Protocols submitted to the BLA: Approvable once the CR issues are resolved.

1. Ongoing Primary Stability Studies (3.2.P.8.1 and 3.2.P.8.2), including shelf-life extension
2. Post-Approval Annual Stability Protocols (3.2.P.8.2)
3. Comparability Protocol (3.2.R)

ii. Outstanding review issues/residual risk: None

iii. Future inspection points to consider:

1. Review the performance of the analytical methods used for release, stability, and in-process testing.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

#	Checklist		Yes	No	N/A
	Product Type				
1.	Recombinant Product		X		
2.	Naturally Derived Product			X	
3.	Botanical			X	
4.	Human Cell Substrate/source material			X	
5.	Non-Human Primate Cell Substrate/Source Material			X	
6.	Non-Primate Mammalian Cell Substrate/source material		X		
7.	Non-Mammalian Cell Substrate/Source Material			X	
8.	Transgenic Animal source			X	
9.	Transgenic Plant source			X	
10.	New Molecular Entity		X		
11.	PEPFAR drug			X	
12.	PET drug			X	
13.	Sterile Drug Product		X		
14.	Other: [fill in information]				
	REGULATORY CONSIDERATIONS				
15.	Citizen Petition and/or Controlled Correspondence Linked to the Application [fill in number]			X	
16.	Comparability Protocol(s)		X		
17.	End of Phase II/Pre-BLA Agreements		X		
18.	SPOTS (special products on-line tracking system)			X	
19.	USAN assigned name		X		
20.	Other [(b) (4) Priority Review Voucher (PRV (b) (4)]		X		
	QUALITY CONSIDERATIONS				
21.	Drug Substance Overage			X	
22.	Design Space	Formulation		X	
23.		Process		X	
24.		Analytical Methods		X	
25.		Other		X	
26.	Other QbD Elements		X		
27.	Real Time release testing (RTRT)			X	
28.	Parametric release in lieu of Sterility testing			X	
29.	Alternative Microbiological test methods			X	
30.	Process Analytical Technology in Commercial Production			X	
31.	Non-compendial analytical procedures	Drug Product	X		
32.		Excipients		X	
33.		Drug Substance	X		
34.	Excipients	Human or Animal Origin		X	
35.		Novel		X	
36.	Nanomaterials			X	
37.	Genotoxic Impurities or Structural Alerts			X	
38.	Continuous Manufacturing			X	
39.	Use of Models for Release			X	
40.	Other {fill-in}				

Review documents related to this Executive Summary (links to document in Panorama):

- Combined Drug substance quality review by Andrea Franco, PhD (OPQ/OBP/DBRR IV), Drug product quality review by Jacek Cieslak, PhD (OPQ/OBP/DBRR IV), and Immunogenicity assay review by Jacek Cieslak, PhD link

- Drug substance microbiology review by Candace Gomez-Broughton, PhD (OPQ/OPF/DMA IV) link
- Drug product microbiology review by Lindsey Brown, PhD (OPQ/OPF/DMA IV) link
- Facility review by Thuy Nguyen (OPQ/OPF/DIA) link
- OBP Labeling review by Vicky Borders-Hemphill, PharmD (OPQ/OBP) link
- Device Evaluation review by Jacqueline Gertz (CDRH/ODE/DAGRID/GHDB) link

BLA STN 761089

Ajovy (fremanezumab)

Teva Branded Pharmaceutical Products R&D, Inc.
(Teva)

Andrea Franco, Ph.D., Staff Fellow
Jacek Cieslak, Ph.D., Chemist
Leslie A. Rivera Rosado, Ph.D., Team Lead
Christopher Downey, Ph.D., Review Chief

Office of Biotechnology Products
Division of Biotechnology Review and Research IV

OBP CMC Review Data Sheet

1. **BLA#:** STN 761089 \\CDSESUB1\evsprod\BLA761089\761089.enx

2. **REVIEW DATE:** April 6, 2018

3. **PRIMARY REVIEW TEAM:**

Product Quality Team:

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Andrea Franco	OPQ/OBP/DBRR IV
Drug Product (DP)	Jacek Cieslak	OPQ/OBP/DBRR IV
Immunogenicity Assays	Jacek Cieslak	OPQ/OBP/DBRR IV
Labeling	CAPT Vicky Borders Hemphill	OPQ/OBP
Facilities	CDR Thuy Nguyen	OPQ/OPF/DIA
Microbiology	Candace Gomez-Broughton (DS) Lindsey Brown (DP)	OPQ/OPF/DMA IV
Team Leads	LCDR Leslie A. Rivera Rosado (Product Quality) Peter Qiu (Facility) Reyes Candau-Chacon (Microbiology)	OPQ/OBP/DBRR IV OPQ/OPF/DIA OPQ/OPF/DMA IV
OPQ RBPM	Kelly Ballard	OPQ/OPRO
Application Team Lead	LCDR Leslie A. Rivera Rosado	OPQ/OBP/DBRR IV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Lana Chen	OND/DNP
Cross-disciplinary Team Lead	Heather Fitter	OND/DNP
Medical Officer	Suhail Kasim, Heather Fitter (TL)	OND/DNP
Clinical Safety	Lourdes Villalba, Sally Jo Yasuda (TL)	OND/DNP
Pharm/Tox	Barbara Wilcox, Lois Freed (TL)	OND/DNP
Clinical Pharmacology	Hristina Dimova, Sreedharan Sabarinath (TL)	OND/DNP
Pharmacometrics	Gopichand Gottipati, Kevin Krudys (TL)	OND/DNP
Biometrics	Sharon Yan, Kun Jin (TL)	OND/DNP
Device	Robert Kang Jacquie Gertz, John McMichael (TL)	CDRH/OC CDRH/GHDB
OSI	Cara Alfaro, Phillip Kronstein (TL)	
OSE PM	Ruth Maduro	
OSE/DMEPA	Chad Morris, Lolita White (TL)	
Labeling	ADL: Tracy Peters	
OPDP	Dhara Shah	
DMPP (PTL)	Twanda Scales, Marcia Williams (TL)	

4. **MAJOR GRMP DEADLINES**
Filing Meeting: December 4, 2017
Mid-Cycle Meeting: January 10, 2018 (OPQ) and January 18, 2018 (OND)
Primary Review Due: March 16, 2018; updated to 4/15/18 due to pending information requests.

Secondary Review Due: March 19, 2018; updated accordingly due to pending primary reviews
Wrap-Up Meeting: May 9, 2018
PDUFA Action Date: June 16, 2018

5. **COMMUNICATIONS WITH APPLICANT:**

Communication/Document	Date
CMC Pre-BLA Meeting	August 31, 2017
Information Request #1 (DIA)	November 21, 2017
Information Request #2 (OBP)	December 15, 2017
Information Request #3 (CDRH)	January 10, 2018
Mid-Cycle Communication (Teleconference)	January 29, 2018
Information Request #4 (OBP)	January 31, 2018
Information Request #5 (DMA)	February 7, 2018
Information Request #6 (OBP)	February 23, 2018
Information Request #7 (OBP)	February 26, 2018
Information Request #8 (DMA)	March 1, 2018
Information Request #9 (CDRH)	March 13, 2018
Information Request #10 (OBP)	March 13, 2018
Information Request #11 (DMA)	March 15, 2018
Information Request #12 (OBP)	March 26, 2018

6. **SUBMISSION(S) REVIEWED:**

Submission	Date Received	Review Completed (Yes/No)
STN 761089/4 (BLA Original Application)	October 16, 2017	Yes
STN 761089/6 (30-day update)	November 14, 2017	Yes (OBP)
STN 761089/10 (Response to IR #1)	December 5, 2017	Yes (DIA)
STN 761089/18 (Updated Mfg. Schedule)	December 28, 2017	Yes (DIA)
STN 761089/19 (Response to IR#2)	January 8, 2018	Yes (OBP)
STN 761089/22 (Response to IR#3)	January 17, 2018	Yes (CDRH)
STN 761089/36 (Response to IR#4)	February 9, 2018	Yes (OBP)
STN 761089/28 (Response to IR#5)	February 23, 2018	Yes (DMA)
STN 761089/30 (Response to IR#6 and IR#7)	February 27, 2018	Yes (OBP)
STN 761089/36 (Response to IR#8)	March 9, 2018	Yes (DMA)
STN 761089/38 (Response to IR#9 and IR#10)	March 15, 2018	Yes (CDRH \ OBP)
STN 761089/42 (Response to IR#10)	March 22, 2018	Yes (OBP)
STN 761089/40 (Response to IR#11)	March 19, 2018	Yes (DMA)
STN 761089/45 (Response to IR#12)	March 30, 2018	Yes (OBP)
STN 761089/46 (Response to IR#5)	April 5, 2018	Yes (DMA)

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary/trade Name: Ajovy (ah-JOE-vee)
   b. Non-Proprietary/USAN: fremanezumab

c. CAS name: 1655501-53-3
d. Common name: TEV-48125
e. INN Name: fremanezumab
f. Compendial Name: N/A
g. OBP systematic name[1]: MAB HUMANIZED (IGG2) ANTI P06881 (CALCA_HUMAN) [TEV48125]
h. Other Names: LBR-101, PF-04472429, RN307

8. **PHARMACOLOGICAL CATEGORY:** Anti-migraine

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**

(i) The concentration/strength of the Drug Product: 225 mg/1.5 mL single-dose, pre-filled syringe.

(ii) Type of potency assay (s): Cell-based assay. Binding of fremanezumab to CGRP prevents it from stimulating intracellular cAMP accumulation in human SK-N-MC neuroblastoma cells. Intracellular cAMP is measured using the cAMP-Glo Max Assay system.

11. **ROUTE OF ADMINISTRATION:** Subcutaneous

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted]	[redacted]	[redacted] (b) (4)	Yes	Sufficient information was provided in the BLA for its intended use.
			Yes	Sufficient information was provided in the BLA for its intended use.
			Yes	Sufficient information was provided in the BLA for its intended use.
			Yes	Sufficient information was provided in the BLA for its intended use.
			Yes	Sufficient information was provided in the BLA for its intended use.

[1] The OBP systematic name allows searching for related products in OBP's database and in the Document Archiving, Reporting & Regulatory Tracking System (DARRTS) for safety reasons and it is different from the non-proprietary name. The tag at the end is used to separate products from different applicants and it is generally the name used by applicants to refer to the proposed product in their submissions.

		(HY-6069Bulk) ActiCHO Feed-B Powder Bose ADCF (HY-6070Bulk)		

13. INSPECTIONAL ACTIVITIES

- Fremanezumab drug substance is manufactured at Celltrion, Inc, Incheon, South Korea. The current facility status is "Official action indicated." A Warning Letter was issued to the facility on January 26, 2018. A pre-license inspection for fremanezumab drug substance will not be scheduled until the issues identified in the Warning Letter are resolved through Office of Manufacturing Quality (OMQ), Office of Compliance (OC).

- A pre-license inspection of fremanezumab drug product manufacturing facility at (b) (4) was conducted on (b) (4) by OPQ/OPF/DIA in support of this BLA. An FDA 483 form with following observation was issued to the firm:

  Your risk assessment (b) (4)

  For example:

  - (b) (4) *are not assessed.*
  - (b) (4) *are not assessed.*

  The initial recommendation for this inspection is withhold. Final facility recommendation is pending as of April 6, 2018.

14. CONSULTS REQUESTED BY OBP

Discipline	Date requested	Reviewer Assigned	Review completed (recommendation)
Tier 2 Technical/ engineering review of delivery devices consults to CDRH	11/30/2017	GHDB: Jacqueline Gertz and John McMichael	3/16/2018 (Approval)
Tier 2 Facilities inspections consults for a CDER application to CDRH	11/30/2017	OC: Robert Kang	**Pending**

15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

	Design Space
x	Design of Experiments

x	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

Risk assessments to identify critical quality attributes of fremanezumab and to identify process parameters for assessment in process characterization studies were performed according to methods described in the submission and review of Module 3.
A design of experiments (DoE) approach was utilized to generate process understanding. Results from DoE experiments were used to support the overall control strategy proposed for fremanezumab drug substance and drug product. The applicant does not claim a design space.

16. PRECEDENTS

None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief Division of Biotechnology Review and Research IV (DBRR IV) Office of Biotechnology Products (OBP) Office of Pharmaceutical Quality (OPQ)	See attached
LCDR Leslie Ann Rivera Rosado Product Quality Team Leader DBRR IV, OBP, OPQ	See attached
Andrea Franco, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached
Jacek Cieslak, Ph.D. Product Quality Reviewer DBRR IV, OBP, OPQ	See attached

B. CC Block

Recipient	Date
Lana Y. Chen Clinical Division BLA RPM	
OBP/DBRR IV File/BLA STN 761089	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761089 for Ajovy (fremanezumab) manufactured by Teva from a product quality perspective based on the review of the information and data provided in the application. However, because a pre-license inspection (PLI) of the drug substance manufacturing site (Celltrion, Inc, Incheon, South Korea [FEI #3005241015]) has not been scheduled (as of April 6, 2018) due to the facility being under "Official Action Indicated" status with a Warning Letter issued on January 26, 2018, the final product quality recommendation is pending.

II. List Of Deficiencies To Be Communicated
Not applicable

III. List Of Post-Marketing Commitments/Requirement

(b) (4)

IV. Review Of Common Technical Document-Quality Module 1

In Module 1 (1.12.14 Environmental Assessment – Claim for Categorical Exclusion), Teva is requesting a categorical exclusion under 21 CFR 25.31 from the need to prepare an environmental assessment based on the calculations of the expected introduction concentration of an active moiety.
Reviewer comment: *The claim of categorical exclusion is accepted.*

V. Primary Container Labeling Review
Refer to review by CAPT Vicky Borders-Hemphill.

VI. Review Of Common Technical Document- Quality Module 3.2
This document.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4
This document.

Contents

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

S. DRUG SUBSTANCE

3.2.S.1 General Information

Fremanezumab is a fully humanized IgG2Δa/kappa monoclonal antibody (mAb) that is being developed for administration by the subcutaneous (sc) route for the preventive treatment of episodic migraine and chronic migraine in adult patients. Fremanezumab selectively binds the calcitonin gene related peptide (CGRP) and it prevents both CGRP isoforms (α- and β- CGRP) from binding to the CGRP receptor.

3.2.S.1.1 Nomenclature

Descriptive Names: Fully humanized IgG2Δa monoclonal antibody specific for CGRP
International Non-proprietary Name (INN): Fremanezumab
United States Adopted Name (USAN): Fremanezumab
Chemical Abstracts Service (CAS) Registry Number: 1655501-53-3
Chemical Name: Immunoglobulin G2, anti-human alpha calcitonin gene-related peptide / beta calcitonin gene-related peptide
Company Name: TEV-48125

3.2.S.1.2 Structure

Fremanezumab is a fully humanized IgG2 Δa kappa monoclonal antibody raised against alpha and beta calcitonin gene-related peptide (CGRP). Fremanezumab consists of two identical light chains (LC) and two identical heavy (HC) chains. Each LC and HC is composed of 214 and 447 amino acids, respectively. To increase binding affinity, the Fab variable region of the HC was mutated at residue 99 (A99L) and at residue 100 (R100A). In addition, to prevent antibody dependent cell cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), the constant region of the HC was mutated at residue 330 (A330S) and at residue 331 (P331S). Fremanezumab contains 36 cysteines which form intrachain and interchain disulfide bonds. The HC lacks C-terminal lysine. N-linked oligosaccharide structures were detected on Asn 298 of each HC. The major glycan species corresponds to core-fucosylated, biantennary complex glycan structures with galactose heterogeneity. No O-linked glycosylation was detected. The fremanezumab HC and LC amino acid sequences are provided in Figure 1 in Section 3.2.S.1.2 with the complementary determining regions (CDR) underlined.

3.2.S.1.3 General Properties

Fremanezumab's general properties are summarized in Table 1.

Table 1: Fremanezumab General Properties

Property	Description
Antibody Type	Fully humanized IgG2Δa monoclonal antibody (b) (4) (b) (4)
Molecular Formula	$C_{6470}H_{9952}N_{1716}O_{2016}S_{46}$
Structural Formula	2 heavy chains (γ) + 2 light chains (κ)
Molecular Weight	148 kDa
Isoelectric Point (pI)	7.8 (main peak)
Extinction Coefficient (280 nm)	1.48 $(mg/mL)^{-1}cm^{-1}$
Glass Transition (Tg′)	-24.7°C
Binding Affinity	Equilibrium K_D=63 pM (α-CGRP), 155 pM (β-CGRP)

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

Facility	Responsibility
Celltrion, Inc (DUNS No. 688836030) 13-1 songdo-dong Yeonsu-gu, Incheon South Korea	Manufacture of drug substance, (b) (4)

(b) (4)

DUNS = Data Universal Number System

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Overview of Manufacturing Process and Control Strategy

(b) (4)

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P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

Fremanezumab drug product (TEV-48125, DP) is a clear, colorless to slightly yellow liquid sterile solution containing fremanezumab antibody formulated at a concentration of 150 mg/mL for subcutaneous (SC) injection. The DP is packaged as a single use pre-filled syringe (PFS) delivering 1.5 mL of sterile solution. Each PFS contains 225 mg of fremanezumab. The proposed storage condition of the DP is 5 ± 3°C.

The components of the DP formulation are shown in Table 1 (copied form the submission).

Table 1: Quantitative and Qualitative Composition of Fremanezumab Drug Product

Component	Quality standard	Function	Concentration	Quantity per 1.5 mL deliverable volume
Fremanezumab	In house	Active ingredient	150 mg/mL	225 mg
L-Histidine	JP, Ph Eur, USP	(b) (4)	0.543 mg/mL	0.815 mg
L-Histidine hydrochloride monohydrate	JP, Ph Eur		2.620 mg/mL	3.930 mg
Sucrose	JP, NF, Ph Eur		66 mg/mL	99 mg
Disodium ethylenediaminetetraacetic acid (EDTA) dihydrate	JP, Ph Eur, USP		0.136 mg/mL	0.204 mg
Polysorbate 80	JP, NF, Ph Eur		0.02% w/v	0.3 mg
Water for Injection	JP, Ph Eur, USP		qs to target volume	qs to target volume

Fremanezumab PFS consists of (b) (4) glass barrel with a staked-in-place needle protected by a rigid needle shield (RNS), a plunger-stopper (b) (4) and (b) (4) plunger rod. Additional information regarding the container closure system is provided in Section 3.2.P.7 *Container Closure System* of this review.

Reviewer comments: *The description of the DP presentation, composition, and excipients is adequate.*

(b) (4)

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

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Andrea Franco

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Jacek Cieslak

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Leslie Rivera-Rosado

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Christopher Downey

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg. 51, 10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 3/27/2018
To: Administrative File, STN 761089
From: Thuy T. Nguyen, Facility Reviewer, CDER/OPQ/OPF/DIA
Endorsement: Peter Qiu, Ph.D., Branch Chief, CDER/OPQ/OPF/DIA
Subject: Original BLA
US License:
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.
Mfg. Facility: **Drug Substance**: Celltrion, Inc., Incheon, S. Korea (FEI 3005241015)
Drug Product: (b) (4)

Product: Fremanezumab
Dosage: 225 mg or 675 mg Subcutaneous
Indication: Preventive treatment of episodic migraine (EM) and chronic migraine (CM) in adult patients
Due Date: 6/2/2018

RECOMMENDATION:
This submission is recommended for Withhold from a facility review perspective.

CR deficiency: During a recent inspection of the Celltrion, Inc. (FEI 3005241015) manufacturing facility for this BLA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this BLA may be approved.

SUMMARY

The subject BLA proposes manufacture of Fremanezumab drug substance (DS) at Celltrion, Inc. (FEI 3005241015) and drug product (DP) at (b) (4)
A (b) (4) GMP surveillance inspection was conducted at the Celltrion In. site from May 22 – June 02, 2017 resulted in an Official Action Indicated (OAI) status with Warning Letter issued on January 26, 2018. A pre-licensing inspection cannot be conducted until the OAI status is cleared by OMQ. Please refer to the table below for Master Cell Bank and testing facilities for DS and DP.

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(b) (4)

CONCLUSION

Adequate descriptions were provided for the Fremanezumab DS at the Celltrion facility and DP at (b) (4) facility but unable to verify by inspection for the Celltrion facility. A (b) (4) GMP surveillance inspection was conducted from May 22 – June 02, 2017 resulted in an Official Action Indicated (OAI) status with Warning Letter issued on January 26, 2018. A pre-licensing inspection cannot be conducted until the OAI status is cleared by OMQ. The Celltrion facility is recommended for WITHHOLD from a facilities assessment standpoint. Master Cell Bank and testing facilities for DS and DP are acceptable.

Thuy T. Nguyen -S

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Thuy T. Nguyen, M.P.H.
Facility Reviewer
OPF Division of Inspectional Assessment
Branch 1

Zhihao Qiu -S

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Zhihao Peter Qiu, Ph.D.
Branch Chief
OPF Division of Inspectional Assessment
Branch 1

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment

Date: March 14, 2018
STN: 761089/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Reyes Candau-Chacon, Ph.D., Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biological License Application
Applicant: Teva Branded Pharmaceutical Products R&D, Inc.
Facilities: Celltrion, Inc. (FEI: 3005241015)
Product: AJOVY™ (Framanezumab)
Dosage: solution for subcutaneious injection (150 mg/mL)
Indication: Treatment for migraines
Action Date: June 16, 2018

Recommendation: This drug substance portion of BLA 761089 is recommended for approval from a microbial control microbiology product quality perspective.

This assessment covers the drug substance section of the application. The drug product section of the BLA was reviewed by Lindsey Brown, Ph.D. and discussed in a separate review memo. The original submission and amendments were reviewed here.

Amendments Reviewed

- Sequence 0036 submitted 3/9/2018

Assessment

S Drug Substance

S.1 General Information

Fremanezumab is a fully humanized immunoglobulin G2 monoclonal antibody (b) (4).

S.2 Manufacture

(b) (4)

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Candace Gomez-Broughton

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Reyes Candau-Chacon

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