CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761119Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 20, 2020
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Andrea Franco, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761119
Applicant:	Lundbeck Seattle BioPharmaceuticals, Inc.
Submission Dates:	February 21, May 10, June 3, September 11, November 25, 2019; February 3, February 10, February 13 and February 18, 2020
Product:	Vyepti (eptinezumab-jjmr)
Dosage form:	injection
Strength and Container-Closure:	100 mg/mL solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application seeking approval of eptinezumab, a calcitonin gene-related peptide antagonist, indicated as a preventive treatment of migraine in adults.
Recommendations:	The prescribing information, patient labeling, container labels and carton labeling are **acceptable** from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B). Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices.

CONCLUSION

The prescribing information submitted on February 18, 2020, patient labeling submitted via email on February 18, 2020, the container label submitted on November 25, 2019 and the carton labeling submitted on February 3, 2020 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on February 21, 2019)
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- Patient Information (submitted on May 10, 2019)
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- Container Labels (submitted on June 3, 2019)

- Carton Labeling (submitted on June 3, 2019)

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The applicant added the suffix, jjmr, to the labeling submitted November 25, 2019.	
Recommended labeling practices (placement of dosage form below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: The label is considered a partial label and only contains the manufacturer's name. This is acceptable per 21 CFR 610.60(c). Please note on November 1, 2019 the applicant informed FDA "that Alder BioPharmaceuticals, Inc. (Alder), located at 11804 North Creek Parkway South, Bothell, WA 98011 was acquired by H. Lundbeck A/S on October 22, 2019. Alder, now known as Lundbeck Seattle BioPharmaceuticals, Inc., is a wholly owned subsidiary of H. Lundbeck A/S and will become the new Sponsor for BLA 761119." November 25, 2019: The applicant revised the manufacturer name on the container label. FDA Response: The applicant's revisions are acceptable.	
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Recommended labeling practices (U.S license number for container bearing a partial label)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Space is limited, and to avoid further crowding of information the applicant will not be requested to add the U.S. license number on the container label. The license number will appear on the carton labeling.

Lot number or other lot identification	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Recommended labeling practices references: USP General Chapters <7> Labeling *Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Multiple-dose containers *(recommended individual dose)*	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55	☐ Yes ☐ No

	☒ N/A
Statement: "Rx only"	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Not required for a partial label.	
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A
Medication Guide	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A
No Package for container	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A
No container label	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A
Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Please confirm there is no text on the ferrule and cap overseal of the vials. On September 11, 2019: The applicant stated there is no text is on either the ferrule and cap overseal of the vials. FDA Response: The applicant's response is acceptable.	
Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Please confirm that sufficient area of the container remains uncovered for its full length to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located per 21 CFR 610.60(e).	

On September 11, 2019: The applicant wrote "Placement of the vial label on the container allows for visual inspection of the full circumference of the vial contents with a minimum of four millimeters horizontal width at the bottom of the vial. In addition, a small vertical gap (< 1 millimeter) is uncovered for the length of the container in the space between where the vial label begins and ends. These uncovered areas are sufficient to allow for visual inspection when the label is affixed to the container per 21 CFR 610.60(e)."

FDA Response: The applicant's response is acceptable.

NDC numbers	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Route of administration	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Consider relocating the route of administration statement, "For intravenous use" to be directly above the "1 mL Single-Dose Vial" statement.

On September 11, 2019: The applicant revised the location of the statement "For intravenous use" to appear directly above the "1 mL Single-Dose Vial" statement.

FDA Response: The applicant's revision is acceptable.

Preparation instructions	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A
Misleading statements	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Bar code label requirements	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: We request you add the product's linear barcode to each individual vial as required per 21CFR 201.25(c)(2) and 21 CFR 610.67.
Please note, there should be enough white space surrounding the linear barcode to allow scanners to read the barcode properly per 21CFR 201.25(c)(2).
Lastly, since your container label is small, we recommend you place the linear barcode in a vertical orientation to maximize the scannability of the linear barcode.

September 11, 2019: The applicant wrote "A placeholder for the linear barcode (containing the product's NDC number) in the vertical orientation is added to the vial label. Alder intends to include a linear barcode in this manner and is working with vendors to confirm that a scannable linear barcode is technically feasible given the small (15 mm) width of the vial label. If the linear barcode is not feasible, alternate barcodes will be evaluated in order to meet the requirements set forth in 21 CFR 201.25(c)(2) and 21 CFR 610.67."

FDA Response: The applicant's revision to the container label and their response is acceptable.

Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic* **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Statement of Dosage	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A
Inactive ingredients	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Storage requirements	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements **Comment/Recommendation:** The storage information is not required on a partial label.	☐ Yes ☐ No ☒ N/A

Dispensing container	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[5] Label Evaluation

Proper name	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The applicant added the suffix, jjmr, to the labeling submitted November 25, 2019.

Manufacturer name, address, and license number	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Please insert a placeholder for the U.S. License number directly below the manufacturer's address per 21 CFR 610.61(b). Consider inserting the phrase "U.S. License number xxxx". In addition, consider including the street, "11804 North Creek Parkway South" as part of the address. Refer to 21 CFR 201.1(a).

September 11, 2019: The applicant revised the carton label and wrote: "A placeholder for the U.S. License number is inserted directly below the manufacturer's address as: "U.S. License number xxxx". The street address, "11804 N Creek Pkwy S" is included as part of the address of Alder Biopharmaceuticals, Inc."

FDA Response: The applicant's revisions are acceptable.

Please note on November 1, 2019 the applicant informed FDA "that Alder BioPharmaceuticals, Inc. (Alder), located at 11804 North Creek Parkway South, Bothell, WA 98011 was acquired by H. Lundbeck A/S on October 22, 2019. Alder, now known as Lundbeck Seattle BioPharmaceuticals, Inc., is a wholly owned subsidiary of H. Lundbeck A/S and will become the new Sponsor for BLA 761119."

November 25, 2019: The applicant revised the manufacturer name to appear as "Lundbeck Seattle BioPharmaceuticals, Inc."

FDA Response: The applicant's revision is acceptable.

Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

[5] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Lot number or other lot identification	**Acceptable**
Regulation: 21 CFR 610.61(c)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Expiration date	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Beyond Use Date (Multiple-dose containers)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A
Preservative	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revise the statement (b) (4) to read "No Preservative" per 21 CFR 610.61(e) September 11, 2019: The applicant revised the statement (b) (4) to read "No Preservative". FDA Response: The applicant's response is acceptable.	
Number of containers	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A
Product Strength	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A
Storage temperature/requirements	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A

Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Multiple dose containers (recommended individual dose)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A
Route of administration	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the route of administration statement to read "For Intravenous Infusion after Dilution". (delete (b) (4))

September 11, 2019: The applicant revised the route of administration statement to read "For Intravenous Infusion after Dilution".

FDA Response: The applicant's revision is acceptable.

Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Consider relocating the dosage formulation statement "injection" to appear directly below the proper name, eptinezumab-xxxx, and above the product strength, 100 mg/mL.

September 11, 2019: The applicant relocated the dosage formulation statement "injection" to appear directly below the proper name, eptinezumab-xxxx, and above the product strength, 100 mg/mL.

FDA Response: The applicant's revision is acceptable.

Known sensitizing substances	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dr. Franco confirmed the product does not contain latex or dry natural rubber.

To Applicant: The statement (b) (4) is not recommended. Either delete the statement or revise the statement to read "Not made with natural rubber latex". Please refer to the FDA Guidance titled "Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex" issued December 2, 2014. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-labeling-medical-products-inform-users-product-or-product-container-not-made-natural

September 11, 2019: The applicant removed the statement (b) (4)

FDA Response: The applicant's revision is acceptable.

February 3, 2020: The applicant submitted revised carton labeling with that includes the statement "Not made with natural rubber latex" on the side panel. The applicant wrote that they would like to retain this information across all their labeling.

FDA Response: The applicant's revision is acceptable.

Inactive ingredients	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Please include the designated suffix to eptinezumab as an ingredient in the "Each mL of solution contains…" statement.
Revise the reference to histidine (b) (4) and present the exact quantities of histidine (xx mg) and histidine hydrochloride monohydrate (xx mg).

September 11, 2019: The applicant included a placeholder for the suffix with the designation "-xxxx". The reference to histidine (b) (4) was revised to present the exact quantities of histidine (1.0 mg) and histidine hydrochloride monohydrate (2.8 mg).

FDA Response: The applicant's revisions for the inactive ingredient histidine are acceptable. However, the designated suffix will need to be added to the active ingredient.

November 25, 2019: The applicant included the suffix, jjmr, to the active ingredient and deleted the trailing zero from the histidine quantity to read 1 mg.

FDA Response: The applicant's revisions are acceptable.

Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Source of the product	**Acceptable**
Regulation: 21 CFR 610.61(p)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dr. Franco confirmed the source is not a safety factor for this product.

Minimum potency of product	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Franco confirmed there is no U.S. standard of potency for this product. The carton contains the statement "No U.S. standard of potency".

Rx only	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The carton label of the drug bears the statement "Rx only".

Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The label also complies with the Drug Supply Chain Security Act.

Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*	✓ Yes ☐ No ☐ N/A

Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)	
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A
Preparation instructions	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The product is in solution and the label indicates it must be diluted before infusion.	
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A
Package type term	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Please include the phrase "Discard unused portion" next to the statement "1 mL Single-Dose Vial". September 11, 2019: The applicant included the phrase "Discard unused portion" next to the statement "1 mL Single-Dose Vial". FDA Response: The applicant's revision is acceptable.	
Misleading statements	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A
Comment/Recommendation:	

Prominence of required label statements	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Consider relocating the dosage formulation statement "injection" to appear directly below the proper name and above the product strength, 100 mg/mL.

September 11, 2019: The applicant relocated the dosage formulation statement "injection" to appear directly below the proper name, eptinezumab-xxxx, and above the product strength, 100 mg/mL.

FDA Response: The applicant's revision is acceptable.

Spanish-language (Drugs)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A
FD&C Yellow No. 5 and/or FD&C Yellow No. 6	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Phenylalanine as a component of aspartame	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
Sulfites; required warning statements	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Net quantity	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
A combined DMEPA & OBP comment:
To Applicant: Revise the statement (b) (4) to read "Recommended Dosage: See prescribing information for dosage, dilution and administration instructions"

September 11, 2019: The applicant revised the dosage statement as requested.

FDA Response: The applicant's response is acceptable.

Dispensing container	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	✓ Yes ☐ No ☐ N/A

Medication Guide	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
This product doesn't provide a Medication Guide.

Other	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
February 3, 2020: The applicant included the suffix "jjmr" in the nonproprietary name.

FDA Response: The applicant's revision is acceptable.

Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and	✓ Yes ☐ No ☐ N/A

Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	

DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The name for the intravenous solution complies with USP nomenclature: 0.9% Sodium Chloride Injection, USP

However, the sentence could be revised to active voice and the word solution could be deleted. To read similar to "Dilute Tradename in 100 mL of 0.9% Sodium Chloride Injection, USP prior to administration."

February 3, 2020: The applicant accepted the division revision of the sentence to read "Dilute only in 100 mL of 0.9% Sodium Chloride Injection, USP"

FDA Response: The applicant's revised sentence is acceptable.

DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Franco confirmed the strength of 100 mg/mL, and the overfill is acceptable.

Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revised the package type term (b) (4) to read "single-dose".

To Applicant: The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. Refer to *Guidance for Industry: Selection of the Appropriate Package Type Terms and*

Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use, October 2018

February 3, 2020: The applicant revised the package type term to read "single-dose".

FDA Response: The applicant's revision is acceptable.

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Franco was able to confirm the handling conditions for the drug product diluted in 0.9% Sodium Chloride Injection, which includes the conditions: gently invert, do not shake, do not freeze and the product can be exposed to ambient light for 8 hours. Dr. Franco and Dr. Cunningham were able to confirm the diluted solution can be stored for 8 hours at room temperature from a stability and microbiology perspective, respectively.

To Applicant: Added to reflect the data provided to support Compatibility with administration materials. The following sentence was added to subsection 2.2 Dilution Instructions: "The infusion bags must be made of polyvinyl chloride (PVC), polyethylene (PE), or polyolefin (PO)."

February 10, 2020: The applicant accepted FDA's proposed addition of information concerning the types of infusion bags that are acceptable.

FDA Response: The Applicant's revision is acceptable.

Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revised to include the identifying characteristics of the drug product per 21 CFR 201.57(c)(4). to read:
VYEPTI is a clear to slightly opalescent, colorless to brownish-yellow solution available as follows:

- Injection: 100 mg/mL in a single-dose vial

February 3, 2020: The applicant accepted FDA's proposed revisions.

FDA Response: The applicant's revisions are acceptable.

Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

February 3, 2020: The applicant accepted FDA's proposed package type term revision from (b) (4) to "single-dose".

FDA Response: The applicant's revision is acceptable.

11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Franco was able to confirm the identifying characteristics of the drug product and the qualitative and quantitative information for the inactive ingredients. Dr. Franco confirmed there is no U.S. standard of potency for this product.

Eptinezumab-xxxx is a (b) (4).

To Applicant: Revised to include the pharmacological or therapeutic class of the drug per 21 CFR 201.57(c)(12).

February 3, 2020: The applicant proposed to delete the pharmacological class information. The applicant proposed to include the wording (b) (4) into the first sentence to read "….. is a humanized immunoglobulin G1 (IgG1) monoclonal antibody (b) (4) specific (b) (4) for calcitonin gene-related peptide (CGRP) ligand.

FDA Response: The OBP team discussed the applicant's proposed revisions and decided the first sentence for section 11 should be will be consistent at this time with the labeling of other calcitonin gene-related peptide ligand products, fremanezumab-vfrm and galcanezumab-gnlm.

To Applicant: We agree with the removal of the pharmacological class at this time to be consistent with other labeling in this class. However, we disagree with inclusion of the phrase (b) (4) which is not consistent with the labeling for products in this class.

February 10, 2020: The applicant revised the first sentence of Section 11 to read: Eptinezumab-jjmr is a humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for calcitonin gene-related peptide (CGRP) ligand.

FDA Response: The applicant's revisions are acceptable.

To Applicant: The inactive ingredient quantitative information was updated based upon the 9/11/19 submission.

February 3, 2020: The applicant revised the quantitative information as requested.

FDA Response: The applicant's revisions are acceptable.

Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revise the order of the inactive ingredients to appear in alphabetical order per USP General Chapters <1091>: Labeling of inactive ingredients.

February 3, 2020: The applicant revised the order of the inactive ingredients to appear in alphabetical order.

FDA Response: The applicant's revisions are acceptable.

16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Dr. Franco confirmed the drug product should be refrigerated, protected from light and should not be frozen or shaken. Dr. Franco also confirmed that no dry natural rubber or natural rubber latex was used with this product.

To Applicant: Revised to include the dosage formulation per 21 CFR 201.57(c)(17).

February 3, 2020: The applicant included the dosage formulation and revised section 16 as requested.

FDA Response: The applicant's revisions are acceptable.

Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The following statement was added to the label: The vial stopper is not made with natural rubber latex.

To Applicant: We note this statement was included in the PPI. Thus, this statement is added to the PI to ensure consistency. However, consider deleting this statement from the PI and

PPI, because it is not required. A statement is only required when the product does contain natural rubber latex.

February 3, 2020: The applicant stated that they have elected to retain this information across our labeling.

FDA Response: The applicant's decision to include the information is acceptable.

MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: Revised the (b) (4) statement to read "Manufactured by" with the name and address of the manufacturer listed as the applicant on FDA form 356h. Please refer to 21 CFR 600.3(t).

February 3, 2020: The applicant accepted FDA's revision for the phrase to read "Manufactured by".

FDA Response: The applicant's revision is acceptable.

To Applicant: Consider including the street address: 11804 North Creek Parkway South. Refer to 21 CFR 201.1 and 21 CFR 201.100(e).
February 3, 2020: The applicant included the street address as requested.

FDA Response: The applicant's revision is acceptable.

Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING

TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
This product does not provide a Medication Guide only Patient Information.

Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format	✓ Yes ☐ No ☐ N/A

Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	

Comment/Recommendation:
The Patient Information title information is displayed in the preferred format.

STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
This product is administered in a patient care setting (e.g. hospital) and not dispensed to the patient. Thus, no storage information is presented in the Patient Information.

Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	☐ Yes ☐ No ☒ N/A

INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To Applicant: Revised the inactive ingredients to appear in alphabetical order (see USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order)

February 10, 2020: The applicant accepted FDA's revision to present the inactive ingredients in alphabetical order.

FDA Response: The revised inactive ingredient statement is acceptable.

To Applicant: Consider deleting this statement, because it is not required. A statement is only required when the product does contain natural rubber latex.

February 10, 2020: In a response to a comment in the Prescribing Information, the applicant indicated a desire to retain statements that the product is not made with natural rubber latex. The ingredient section of the Patient labeling contains the statement "The vial stopper is not made with natural rubber latex."

FDA Response: The inclusion of the "The vial stopper is not made with natural rubber latex" is acceptable.

MANUFACTURER INFORMATION	Acceptable
21 CFR 201.1, 19 CFR 134.11, 21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: To Applicant: Revised the manufacturer statement to read "Lundbeck Seattle BioPharmaceuticals, Inc"., and inserted the phrase "Manufactured by:" to enhance clarity of Lundbeck Seattle BioPharmaceuticals, Inc responsibility. February 10, 2020: The applicant accepted FDA's revisions to the manufacturer information. FDA Response: The revised manufacturing statement is acceptable.	
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable) **Comment/Recommendation:**	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Draft Prescribing Information (submitted on February 18, 2020)
  \\cdsesub1\evsprod\bla761119\0043\m1\us\proposed-pi.docx

- Draft Patient Information (submitted via email on February 18, 2020)

  BLA 761119
  18Feb20 clean draft

- Draft Container Labels (submitted on November 25, 2019)

- Draft Carton Labeling (submitted on February 3, 2020)

(b) (4)

Scott Dallas

Digitally signed by Scott Dallas
Date: 2/20/2020 12:07:20PM
GUID: 508da712000294048aa136a18a6af06a

Andrea Franco

Digitally signed by Andrea Franco
Date: 2/20/2020 12:11:40PM
GUID: 55798a5d00259df2b007ed28a45e075e

U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Process and Facilities
Division of Microbiology Assessment
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Primary Reviewer: Reyes Candau-Chacon, Ph.D.
Secondary Reviewer: Patricia Hughes, Ph.D.

BLA:	761119/0
Applicant:	Lundbeck Seattle BioPharmaceuticals, Inc. (Formerly Alder BioPharmaceuticals, Inc.)
US License Number:	2097
Submission Reviewed:	Addendum to the Original BLA
Product:	Vyepti (eptinezumab)
Indication:	preventative treatment for migraine
Dosage Form:	solution for i.v. injection (100 mg/mL)
Manufacturing Sites:	(b) (4)
FDA Receipt Date:	02/21/2019
Action Date:	02/21/2020

Conclusion and Approvability Recommendation

The drug product portion of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval. This addendum represents the last portion of this BLA review memo.

Product Quality Microbiology Assessment: Endotoxin Test Method

(b) (4)


(b) (4)

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 1/10/2020 09:50:10AM
GUID: 508da7160002977f7ca389c8f849b707

Patricia Hughes Troost

Digitally signed by Patricia Hughes Troost
Date: 1/10/2020 10:27:50AM
GUID: 508da717000297bcbfce0919f8c09594

Recommendation: Approval

BLA Number: 761119
\\cdsesub1\evsprod\bla761119\761119.enx
Review Number: First Round
Review Date: December 3, 2019

Drug Name/Dosage Form	Vyepti (eptinezumab-jjmr) injection
Strength/Potency	100 mg/mL solution in a single-dose vial
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	for the preventive treatment of migraine
Applicant/Sponsor	Lundbeck Seattle BioPharmaceuticals, Inc. (formerly Alder BioPharmaceuticals, Inc.) a wholly owned subsidiary of H. Lundbeck A/S

Product Overview

Eptinezumab is a humanized IgG1 kappa monoclonal antibody raised against alpha calcitonin gene-related peptide (α-CGRP). The light and heavy chain variable regions are comprised of both human and humanized rabbit sequences. Eptinezumab selectively binds to CGRP and blocks both CGRP isoforms (α- and β-CGRP) from binding to the CGRP receptor. (b) (4) (b) (4) (b) (4) Eptinezumab is produced in a yeast-based (*Pichia pastoris*) (b) (4) (b) (4)

Vyepti drug product is a sterile, clear to slightly opalescent, colorless to brownish-yellow solution containing eptinezumab antibody formulated at a concentration of 100 mg/mL for intravenous infusion. The drug product is packaged as a single-dose vial.

Quality Review Team

Discipline	Reviewer	Branch / Division
Drug Substance	Andrea Franco	OPQ/OBP/DBRR IV
Drug Product		OPQ/OBP/DBRR IV
Immunogenicity Assays		OPQ/OBP/DBRR IV
Labeling	CAPT Scott Dallas	OPQ/OBP
Facilities	Ashley Queen and Michael Shanks	OPQ/OPF/DIA
Microbiology	Candace Gomez-Broughton (DS) Aimee Cunningham (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 Technical 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	Emily Freilich, Heather Fitter (TL)	OND/DNP
Clinical Outcome Assessment	Christopher St. Clair, Sarrit Kovacs (TL)	OND/DNP
Pharm/Tox	Richard Siarey, Lois Freed (TL)	OND/DNP
Clinical Pharmacology	Gopichand Gottipati, Sreedharan Sabarinath (TL)	OND/DNP
Pharmacometrics	Gopichand Gottipati, Kevin Krudys (TL)	OND/DNP
Genomics	Jielin Sun, Christian Grimstein (TL)	OND/DNP
Biometrics	Steven Bai, Kun Jin (TL)	OND/DNP
OSI	Cara Alfaro, Phillip Kronstein (TL)	OSI
OSE PM	Saharat Patanavanich	OSE PM
OSE/DMEPA	Chad Morris, Briana Rider, Lolita White (TL)	OSE/DMEPA
OSE/DRISK	Ingrid Chapman, Donella Fitzgerald (TL)	OSE/DRISK
OSE/OPE/DEPI	Hongliu Ding, Kira Leishear (TL)	OSE/OPE/DEPI
OSE/OPE/DVP	David Croteau, Allen Brinker (TL)	OSE/OPE/DVP
Labeling	ADL: Tracy Peters	OND/DNP
OPDP	Dhara Shah	OPDP
DMPP (PTL)	Aman Sarai, Marcia Williams (TL)	DMPP

Names:

Proprietary Name: Vyepti
Non-proprietary/USAN/INN: Eptinezumab-jjmr
CAS Registry Number: 1644539-04-7
Biological Name: Anti-(calcitonin gene-related peptide) monoclonal antibody (anti-CGRP mAb)
Chemical Name: Immunoglobulin G1, anti-(calcitonin gene-related peptide) (human-Oryctolagus cuniculus monoclonal ALD403 heavy chain), disulfide with human-Oryctolagus cuniculus monoclonal ALD403 κ-chain, dimer
Company Name: ALD403
OBP systematic name[1]: MAB HUMANIZED (IGG1) ANTI P06881 (CALCA_HUMAN) [ALD403]

Submissions Reviewed:

Submission	Date Received	Review Completed (Yes/No)
STN 761119/1 (BLA Original Application)	February 21, 2019	Yes
STN 761119/2 (Response to 3/15/19 IR)	March 19, 2019	Yes
STN 761119/4 (Response to 4/9/19 IR)	April 9, 2019	Yes
STN 761119/5 (60-day Update)	April 16, 2019	Yes
STN 761119/7 (Labeling)	May 10, 2019	Yes
STN 761119/8 (Response to 4/25/19 IR)	May 15, 2019	Yes
STN 761119/10 (Response to 6/13/19 IR)	June 26, 2019	Yes
STN 761119/12 (Response to 6/16/19 IR)	July 17, 2019	Yes
STN 761119/13 (Response to 7/30/19 IR)	August 9, 2019	Yes

[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 761119/15 (Response to 8/29/19 IR)	September 5, 2019	Yes
STN 761119/16 (Response to 8/28/19 IR)	September 11, 2019	Yes
STN 761119/17 (Response to 9/13/19 IR)	September 20, 2019	Yes
STN 761119/18 (Response to 9/13/19 IR)	September 25, 2019	Yes
STN 761119/19 (Response to 9/16/2019 IR)	September 27, 2019	Yes
STN 761119/21 (Change in Site of Analytical Testing of (b) (4)	October 15, 2019	Yes
STN 761119/24 (Response to 10/16/2019 IR)	October 30, 2019	Yes
STN 761119/26 (Information Regarding the Status of Endotoxin Method Optimization and Additional LER Feasibility Studies as Committed to in Response to 09/16/2019 IR)	November 6, 2019	Yes
STN 761119/27 (Response to 11/1/2019 IR)	November 8, 2019	Yes
STN 761119/30 (Response to 11/7/2019 IR)	November 14, 2019	Yes
STN 761119/32 (Response to 11/25/2019 IR)	November 27, 2019	Yes
STN 761119/33 (Response to 12/2/2019 IR)	December 4, 2019	Yes

Quality Review Data Sheet

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents

- **DMFs:**

DMF #	DMF Type	DMF Holder	Item referenced	Code [1]	Status[2]	Date Review Completed	Comments
(b) (4)	III	(b) (4)		2	Adequate	(b) (4)	
	III			3	N/A		Not reviewed, enough information was provided in the BLA
	III			3	N/A		Not reviewed, enough information was provided in the BLA
	V			3	N/A		Facility was inspected.

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).

- **Other documents:**

Document	Application Number	Description
IND	114647	Describes eptinezumab, a humanized anti-(calcitonin gene-related peptide) (CGRP) monoclonal immunoglobulin G1 (IgG1) antibody (anti-CGRP monoclonal antibody [mAb]), for the preventive treatment of migraine in adults.

3. Consults: None

Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed review of STN 761119 for Vyepti (eptinezumab-jjmr) manufactured by Lundbeck Seattle BioPharmaceuticals, Inc., (formerly Alder BioPharmaceuticals, Inc.). The data submitted in this application are adequate to support the conclusion that the manufacture of Vyepti 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. Approval Action Letter Language:

Manufacturing locations:

- Drug Substance:
  - o (b) (4)
- Drug Product:
  - o (b) (4)

Fill size and dosage form

- 100 mg/mL solution in a single-dose vial, injection

Dating period:

- Drug Substance: (b) (4) months at (b) (4) °C
- Drug Product: 24 months at 2-8 °C
- Stability:
  - o We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.
- Exempt from lot release:
  - o Yes, VYEPTI is a specified product exempted according to FR 95-29960.

C. 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 removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The eptinezumab drug substance (DS) will be manufactured at (b) (4) and the Vyepti drug product (DP) at (b) (4) Pre-licensing inspections were conducted at (b) (4) and the facilities were found acceptable for the proposed operations.

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

Individual reviews for each discipline, (1) Drug Product Quality Review (which includes review of drug substance and drug product quality and immunogenicity assays), (2) Microbiology Quality Review (which includes microbiological control of drug substance and drug product), (3) Facilities Quality Review, and (4) Quality Labeling Review are located as separate documents in Panorama (link).

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

None

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 (efficacy, PK/PD, immunogenicity and safety)	Origin	Control Strategy
Potency (biological activity)	Function of binding to CGRP and preventing binding of CGRP to its receptor	Bioactivity (efficacy), and PK/PD	Intrinsic to the molecule	(b) (4)
Identity	Identity	Bioactivity (efficacy)	Intrinsic to the molecule	
Product-related variants /impurities	Size-Variants: aggregation	Dimers and multimers have reduced potency by cell-based bioassay and also could impact immunogenicity.	Temperature, light, and oxidative stress conditions	
	Size-Variants: fragmentation (clipped species)	Potential impact to efficacy, PK/PD, and immunogenicity	It can occur anytime during the lifespan of a mAb and affects both product quality and stability	
	(b) (4)	Potential impact to immunogenicity and safety	*Pichia* produced eptinezumab is (b) (4)	
Non-CQAs				
Product-related variants	Charge variants (by icIEF)	Product and process consistency	Thermal stress	(b) (4)

DS - drug substance, DP - drug product, CQA – Critical Quality Attributes, IPC – In Process Controls, CIPC- Critical In-Process Controls, CE-SDS- Capillary electrophoresis sodium dodecyl sulfate, AEX – Anion Exchange Chromatography, SE-HPLC – Size Exclusion Chromatography, icIEF – imaged capillary IsoElectric Focusing, ELISA – Enzyme-Linked

Immunosorbent Assay, PK – Pharmacokinetics, PD – Pharmacodynamics, MoA – Mechanism of Action, HPLC-AEX/PAD- high performance anion exchange chromatography combined with pulsed amperometric detection.

The applicant provided data to support that other product variants e.g., charge variants, deamidation/isomerization, oxidation, (b) (4) are not CQAs because of they scored below the severity limit.

B. Drug Substance, Eptinezumab, 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** (efficacy, PK/PD, immunogenicity and safety)	Origin	Control Strategy
Process-related impurities	Host Cell Proteins (HCP)	Safety, Immunogenicity	(b) (4)	(b) (4)
	(b) (4)	Immunogenicity, Safety		
	Bioburden	Safety, Purity, and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials and contamination during manufacturing	
	Bacterial Endotoxins	Safety, Purity	Raw materials and contamination during manufacturing	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing Process, formulation	
	Osmolality	Bioactivity, stability	Formulation	
	pH	Bioactivity, stability	Formulation	

CQA type	CQA	Risk (efficacy, PK/PD, immunogenicity and safety)	Origin	Control Strategy
	Appearance (Physical state, degree of coloration, clarity/opalescence, visible particulate matter)	Safety	Product, formulation	(b) (4)
Non-CQAs controlled to ensure process consistency				
Process-related impurities	Host Cell DNA	N/A	(b) (4)	(b) (4)
	(b) (4)	Safety	(b) (4) process	
		PK, Immunogenicity, Safety	(b) (4) (b) (4) process	

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

- **Description**: Eptinezumab is a humanized, IgG1 monoclonal antibody consisting of two identical light chains (LC) and two identical heavy (HC) chains. The LC and HC variable regions are comprised of both human and humanized rabbit sequences. Eptinezumab targets, recognizes and blocks binding of calcitonin gene-related peptide (CGRP) to its receptor. (b) (4) . Eptinezumab contains 36 cysteines which form 14 intrachain and 4 interchain disulfide bonds. (b) (4)
- **Mechanism of Action (MoA)**: Eptinezumab binds to soluble CGRP ligand and thus prevents 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 eptinezumab. This assay is based on the principle that eptinezumab 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 eptinezumab at which the half-maximum reduction in cAMP accumulation is observed) of the eptinezumab reference standard by the EC_{50} of eptinezumab test sample x 100%. The reportable value is the mean relative potency of three assay plates.
- **Reference Materials**:

a) (b) (4)

(b) (4)

- **Critical starting materials or intermediates**: (b) (4)
- **Manufacturing process summary**: (b) (4)
- **Container closure**: Eptinezumab DS is packaged (b) (4)
- **Dating period and storage conditions**: (b) (4) months at (b) (4) °C.

C. Drug Product, Vyepti, 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** (efficacy, PK/PD, immunogenicity and safety)	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		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	
	Bacterial endotoxin	Safety, purity, and immunogenicity	Raw materials, contamination during the manufacturing process	
	Container closure integrity	Safety (maintenance of sterility during shelf-life)	Container closure breaches during manufacturing or storage. May be impacted by storage conditions.	
Composition and Strength	Protein Concentration	Bioactivity	Manufacturing process	
	pH	Bioactivity, stability	Formulation	
	PS-80 content	Stability, aggregate formation	Formulation	

CQA type	CQA	Risk (efficacy, PK/PD, immunogenicity and safety)	Origin	Control Strategy
	Appearance (degree of coloration, clarity/opalescence)	Safety	Product, formulation	(b) (4)
	Osmolality	Bioactivity, stability	Formulation	

- **Potency and Strength:** 100 mg/mL (1 mL per vial)
- **Summary of Product Design:** Eptinezumab Injection is a sterile, nonpyrogenic, aqueous solution. Each 1 mL of drug product contains 100 mg of eptinezumab and is formulated with a target pH of 5.8.
- **List of Excipients:** L-Histidine, (b) (4) sorbitol, Polysorbate 80
- **Reference Materials:** Same as eptinezumab drug substance reference standards.
- **Manufacturing process summary:** The drug product manufacturing process (b) (4)
- **Container closure:** (b) (4) glass vials with a 13 mm neck size and a 13 mm diameter (b) (4) The stopper is kept in its position by an aluminum seal with a flip-off plastic cap.
- **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 vials
- 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.
- Visually inspect Vyepti for particles or discoloration prior to administration.

F. Establishment Information:

DRUG SUBSTANCE					
Function	**Site Information**	**FEI / DUNS Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
DS Manufacturer	(b) (4)		Pre-License Inspection Request	NAI, No FDA-483 issued	Approve
Analytical Testing, cell based bioassay (DS/DP)			Recommend Approve, LBI	N/A	Approve
Analytical Testing, multiple (DS/DP)			Recommend Approve, LCP	N/A	Approve
Analytical Testing, (b) (4)			Recommend Approve, LCP	N/A	Approve
Analytical Testing			Recommend Approve, LCP	N/A	Approve
Long Term Storage			Recommend Approve, CBI	N/A	Approve
Manufacturer of MCB			Recommend Approve, CBI	N/A	Approve
DRUG PRODUCT					
Function	**Site Information**	**DUNS / FEI Number**	**Preliminary Assessment**	**Inspectional Observations**	**Final Recommendation**
DP Manufacturer	(b) (4)		Pre-License Inspection Request	VAI, 1-item FDA-483 issued	Approve
Analytical Testing-Chemical/Physical, Microbiological			Recommend Approve, LCP	N/A	Approve
Analytical Testing-Chemical/Physical, Microbiological			Recommend Approve, LCP	N/A	Approve
Analytical Testing-container closure integrity			Recommend Approve, LCP	N/A	Approve

G. Facilities:

- Eptinezumab drug substance is manufactured at (b) (4) . A pre-license inspection for eptinezumab drug substance was conducted on (b) (4) by ORA, OPF, and OBP.
  Final facility recommendation: Acceptable

- Vyepti drug product is manufactured at (b) (4) (b) (4) A pre-license inspection for Vyepti drug product was conducted on (b) (4)
  Final facility recommendation: Acceptable

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

H. Lifecycle Knowledge Management:

Protocols submitted to the BLA:

Item	Purpose of Protocol	BLA link	Reporting category
(b) (4)		Section 3.2.S.2.3 and EDMS-07817	Annual Report
		Section 3.2.S.5 subsection 3.4	Annual Report
		Section 3.2.S.5, subsection 5.2.1	Annual Report
		Section 3.2.S.5, subsection 5.3	Annual Report
		Section 3.2.S.7.2	Annual Report
Eptinezumab Drug Product	Shelf-life extension based on full shelf-life data on three commercial-scale batches	Section 3.2.P.8.2	Annual Report
(b) (4)		Protocol EDMS-01178	Annual Report

Note: In the BLA application the applicant committed to do the following:

- To re-evaluate the acceptance criteria for Antigen binding by ELISA once a sufficient amount of data is available after implementation of the optimized, validated method. The ELISA method is currently being optimized to potentially reduce variability.
- To continue to monitor the lot release, stability, and method variability data of the cell-based bioassay to determine if future evaluation of the potency specification is warranted.

1. **Outstanding review issues/residual risk:** None identified.

2. **Future inspection points to consider:** Review the performance of the analytical methods used for release, stability, and in-process testing.

Leslie Rivera-Rosado

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Date: 12/09/2019 11:39:14AM
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Christopher Downey

Digitally signed by Christopher Downey
Date: 12/09/2019 04:30:47PM
GUID: 508da6d9000264ed71c49d80cfe4e31a

Reyes Candau-Chacon

Digitally signed by Reyes Candau-Chacon
Date: 12/09/2019 11:49:29AM
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Zhihao Peter Qiu

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Date: 12/09/2019 11:45:40AM
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BLA STN 761119

Vyepti (eptinezumab-jjmr)

Lundbeck Seattle BioPharmaceuticals, Inc.[1]

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

Office of Biotechnology Product
Division of Biotechnology Review and Research IV

[1] The BLA was originally submitted on February 22, 2019 by Alder BioPharmaceuticals, Inc. (Alder). On October 22, 2019, Alder was acquired by H. Lundbeck A/S and named as Lundbeck Seattle BioPharmaceuticals, Inc (communication dated 11/01/2019).

OBP CMC Review Data Sheet

1. **BLA#:** STN 761119 \\CDSESUB1\evsprod\BLA761119\761119.enx

2. **REVIEW DATE:** December 4, 2019

3. **PRIMARY PROUCT QUALITY REVIEW TEAM:**

Discipline	Reviewer	Branch/Division
Drug Substance (DS), Drug Product (DP), and Immunogenicity assays	Andrea Franco	OPQ/OBP/DBRR IV
Inspection of DS site	Jacek Cieslak	OPQ/OBP/DBRR IV
Labeling	CAPT Scott Dallas	OPQ/OBP
Facilities	Ashley Queen and Michael Shanks	OPQ/OPF/DIA
Microbiology	Candace Gomez-Broughton (DS) Aimee Cunningham (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 Technical 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	Emily Freilich, Heather Fitter (TL)	OND/DNP
Clinical Outcome Assessment	Christopher St. Clair, Sarrit Kovacs (TL)	OND/DNP
Pharm/Tox	Richard Siarey, Lois Freed (TL)	OND/DNP
Clinical Pharmacology	Gopichand Gottipati, Sreedharan Sabarinath (TL)	OND/DNP
Pharmacometrics	Gopichand Gottipati, Kevin Krudys (TL)	OND/DNP
Genomics	Jielin Sun, Christian Grimstein (TL)	
Biostatistics	Steven Bai, Kun Jin (TL)	OND/DNP
OSI	Cara Alfaro, Phillip Kronstein (TL)	OSI
OSE PM	Saharat Patanavanich	OSE PM
OSE/DMEPA	Chad Morris, Briana Rider, Lolita White (TL)	OSE/DMEPA
OSE/DRISK	Ingrid Chapman, Donella Fitzgerald (TL)	OSE/RISK
OSE/OPE/DEPI	Hongliu Ding, Kira Leishear (TL)	OSE/OPE/DEPI
OSE/OPE/DVP	David Croteau, Allen Brinker (TL)	OSE/OPE/DVP
Labeling	ADL: Tracy Peters	OND/DNP
OPDP	Dhara Shah	OPDP
DMPP (PTL)	Aman Sarai, Marcia Williams (TL)	DMPP

4. **MAJOR GRMP DEADLINES**

Filing Meeting: April 10, 2019
Mid-Cycle Meeting: July 16, 2019 (internal), July 30, 2019 (with applicant)
Late Cycle Meeting: October 30, 2019 (internal), November 19, 2019 (with applicant)
Wrap-Up Meeting: January 7, 2020
Primary Review Due: December 9, 2019
PDUFA Action Date: February 21, 2020

5. **COMMUNICATIONS WITH SPONSOR AND OND:**

Communication/Document	**Date**
CMC Pre-BLA Meeting	October 24, 2018 (the meeting was canceled by Alder)
Information Request #1 (OPF)	March 12, 2019
Information Request #2 (OPF)	April 3, 2019
Orientation Meeting with Alder	March 26, 2019
60-Day Stability Updates	April 16, 2019
Filing Meeting with OND	April 10, 2019
Information Request #3 (DMA)	April 25, 2019
74-Day Letter	April 27, 2019
Information Request #4 (DMA)	June 13, 2019
Information Request #5 (DIA)	July 16, 2019
Mid Cycle Meeting with OND	July 16, 2019
Information Request #6 (OBP)	July 30, 2019
Mid Cycle Meeting with Alder	July 30, 2019
Information Request #7 (DMA)	August 29, 2019
Information Request #8 (Labeling OBP)	August 28, 2019
Information Request #9 (OBP)	September 13, 2019
Information Request #10 (DMA)	September 16, 2019
Information Request # 11 (DMA)	October 16, 2019
Late Cycle Meeting with OND	October 30, 2019
Information Request # 12 (OBP)	November 1, 2019
Information Request #13 (DMA)	November 7, 2019
Late Cycle Meeting with Alder	November 19, 2019
Information Request # 14 (OBP)	November 25, 2019
Information Request #15 (DMA and OBP)	December 2, 2019
Wrap-up Meeting with OND	Scheduled for: January 7, 2020

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

Submission	**Date Received**	**Review Completed (Yes/No)**
STN 761119 /1	February 21, 2019	Yes
STN 761119 /2 (response to IR #1)	March 19, 2019	Yes

STN 761119 /4 (response to IR #2)	April 9, 2019	Yes
STN 761119 / 5 (60-day stability updates as agreed during the pre-BLA meeting)	April 16, 2019	Yes
STN 761119 /7 (Labeling)	May 10, 2019	Yes
STN 761119 /8 (response to IR #3)	May 15, 2019	Yes
STN 761119 /10 (response to IR #4)	June 26, 2019	Yes
STN 761119 /12 (response to IR #5)	July 17, 2019	Yes
STN 761119 /13 (response to IR #6)	August 9, 2019	Yes
STN 761119 /15 (response to IR #7)	September 5, 2019	Yes
STN 761119 /16 (response to IR #8)	September 11, 2019	Yes
STN 761119 /17 (response to IR #9- first part)	September 20, 2019	Yes
STN 761119 /18 (response to IR #9 – second part)	September 25, 2019	Yes
STN 761119 /19 (response to IR #10)	September 27, 2019	Yes
STN 761119 /21 (change in site of analytical testing of (b) (4)	October 15, 2019	Yes
STN 761119 /24 (response to IR #11)	October 30, 2019	Yes
STN 761119 /26 (Low Endotoxin Recovery Studies Status Update, as committed to in response to Question 12 of IR #10)	November 6, 2019	Yes
STN 761119 /27 (response to IR #12)	November 8, 2019	Yes
STN 761119 /30 (response to IR #13)	November 14, 2019	Yes
STN 761119/32 (response to IR #14)	November 27, 2019	Yes
STN 761119/33 (response to IR #15)	December 4, 2019	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**
   a. Proprietary Name: Vyepti
   b. Non-Proprietary/USAN: Eptinezumab-jjmr
   c. CAS name: 1644539-04-7
   d. Common name: ALD403
   e. INN Name: Eptinezumab
   f. Compendial Name: N/A
   g. OBP systematic name[2]: MAB HUMANIZED (IGG1) ANTI P06881 (CALCA_HUMAN) [ALD403]

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

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**
   (i) The concentration/strength of the Drug Product: 100 mg/mL

[2] 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 applicants and it is generally the name used by applicants to refer to the proposed product in their submissions.

(ii) Type of potency assay (s): Cell-based assay. Binding of eptinezumab 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:** Intravenous Infusion

12. **REFERENCED MASTER FILES:**

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
(b) (4)			Yes	No review required as all the relevant information related to compatibility with the product was in the BLA.
			Yes	No assessment required as all the relevant information related to compatibility with the product was in the BLA
			Yes	No assessment required as all the relevant information related to compatibility with the product was in the BLA
			Yes	Assessment of the manufacturing process at (b) (4) is provided in Section 3.2.S of this document

13. **INSPECTIONAL ACTIVITIES**

The eptinezumab drug substance (DS) is manufactured at (b) (4) and the Vyepti drug product (DP) at (b) (4)
Pre-licensing inspections were conducted on (b) (4) by Dr. Jacek Cieslak at (b) (4) and on (b) (4) by Dr. Aimee Cunningham at (b) (4) (b) (4) The facilities were found acceptable for the proposed operations.

14. CONSULTS REQUESTED BY OBP

None

15. QUALITY BY DESIGN ELEMENTS

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

	Design Space
	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 eptinezumab 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.

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

B. CC Block

Recipient	Date
Lana Y. Chen Clinical Division BLA RPM	
OBP/DBRR IV File/BLA STN 761119	

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761119 for Vyepti (eptinezumab-jjmr) manufactured by Lundbeck Seattle BioPharmaceuticals, Inc. from a product quality perspective based on the review of the information and data provided in the application.

II. List of Deficiencies To Be Communicated

Not applicable

III. List of Post-Marketing Commitments/Requirement

None

IV. Review of Common Technical Document-Quality Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

In Module 1 (1.12.14 Environmental Assessment – Claim for Categorical Exclusion), Alder claims categorical exclusion, in accordance with 21 CFR 25.31(c), from the requirement to prepare an Environmental Assessment as eptinezumab is considered "naturally occurring in the environment" and when exposed to the environment is not expected to significantly alter the concentration of the substance, its metabolites, or degradation products in the environment.

***Assessor's Comment**: The claim of categorical exclusion is accepted.*

V. Primary Container Labeling Review

Refer to review by CAPT Scott Dallas

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

The BLA was originally submitted on February 22, 2019 by Alder BioPharmaceuticals, Inc. (Alder). On October 22, 2019, Alder was acquired by H. Lundbeck A/S and named as Lundbeck Seattle BioPharmaceuticals, Inc. However, in this document, the BLA applicant is referred to as Alder.

S. DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

International Non-proprietary Name (INN):	Eptinezumab
United States Adopted Name (USAN):	Eptinezumab
Descriptive Name:	Humanized IgG1 monoclonal antibody specific for α-calcitonin gene-related peptide (α-CGRP)
Chemical Name:	Immunoglobulin G1, anti-(calcitonin gene-related peptide) (human-Oryctolagus cuniculus monoclonal ALD403 heavy chain), disulfide with human-Oryctolagus cuniculus monoclonal ALD403 κ-chain, dimer
Chemical Abstracts Service (CAS) Registry Number:	1644539-04-7
Company Name:	Alder BioPharmaceuticals, Inc.

3.2.S.1.2 Structure

Eptinezumab is a humanized IgG1 kappa monoclonal antibody against human α-CGRP. The molecule contains 2 identical heavy chain (HC) (441 amino acids) and 2 identical light chain (LC) (219 amino acids). The light and heavy chain variable regions include both human and humanized rabbit sequences (Figure 1 in Section 3.2.S.1.2). Eptinezumab HC and LC amino acid sequence was provided in Subsection 2, Section 3.2.S.1.2. Eptinezumab structure, including the post-translational modifications (b) (4) was provided in Figure 2 (Section 3.2.S.1.2).

3.2.S.1.3 General Properties

Eptinezumab general properties are summarized in Table 1.

Table 1: General Properties of Eptinezumab (ALD403)

Physical/Chemical Properties	**Description**
Appearance	clear to slightly opalescent; colorless to brownish-yellow colored solution
Antibody subclass	IgG1
Biological target	human α-calcitonin gene-related peptide (α-CGRP)
Extinction coefficient	1.46 mL/(mg*cm)

Isoelectric point (theoretical)	Heavy Chain: 8.38 Light Chain: 5.93
Subunits	2 heavy chains of 441 amino acids 2 light chains of 219 amino acids
Number of disulfide bonds	intrachain disulfide bonds: 14 interchain disulfide bonds: 4
Number of cysteines	heavy chain: 11 light chain: 7
Molecular weight	heavy chain: 47964 Daltons light chain: 23695 Daltons eptinezumab (with 18 S-S bonds): 143283 Daltons

3.2.S.2 Manufacture

(b) (4)

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Table 1: Container Closure System

Component	Description	Manufacturer	DMF	Pharmacopeial Compliance
Vial (b) (4) (b) (4)	(b) (4)			USP, Ph. Eur.
Vial Stopper 13 mm (b) (4)				USP, Ph. Eur.
Flip Off CCS Seal 13 mm (b) (4)				N/A

* No direct product contact

Specifications for the vial, stopper and seal were provided in Table 2 , Table 3, and Table 4 (Section 3.2.P.7), respectively. Certificates of analysis for the vial, stopper, and seal were provided. All test results meet the acceptance criteria. *This is acceptable*.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

During the pre-BLA meeting held on 10/24/2018, the Agency agreed that Alder could submit minor stability updates no later than 60 days after the submission of the original BLA. In addition, the Agency will request, if necessary, stability data prior to month 7. Therefore, on 4/16/2019 and on 9/20/2019, Alder provided stability updates for DP samples stored at the long-term temperature condition of 2 – 8°C for 24 months. Results from 3 DP lots (APQE01, APQF02, and APQF03) manufactured at (b) (4) using the commercial process are used as primary data to support the proposed shelf life of 24 months. In addition, results from 3 clinical DP lots (1-FIN-2349, 1-FIN-2874, and 1-FIN-2875) manufactured at (b) (4) are used as supporting data (Table 1 in Section 3.2.P.8.1).

The DP stability specifications was provided in Table 1, Section 3.2.P.8.1. Test and acceptance criteria are the same as those used for the DP release testing except the DP specifications does not include a test for physical state, osmolality, identity, extractable volume, endotoxin, and sterility and include a test for container closure integrity. *This is acceptable*.

Stability samples were stored in the intended commercial container closure system used for DP (2 mL (b) (4) glass vial). The stability protocol includes testing at long-term temperature condition of 2 – 8°C (0, 1, 3, 6, 9, 12, 18, 24, 36, and 48 months) and at the accelerated temperature condition of 25°C ± 2°C (0, 1, 3, and 6 months) (Table 2 in Section 3.2.P.8.1).

***Assessor's Comment**: The container closure used for the stability studies is acceptable because it is the intended commercial container closure. In addition, the testing frequency is acceptable because complies with the recommendation provided in the ICH Guidance Q5C (every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter).*

Based on the data provided (discussed in Section 3.2.S.8.3 of this review), the proposed shelf life of 24 months for DP lot is acceptable.

In addition, photostability studies were conducted using the DP lot APQE01 manufactured at (b) (4) Samples were stored either in the unlabeled vials (referred to as immediate pack), in unlabeled vials placed inside the (b) (4) paper board carton (referred to as marketing pack), or in unlabeled vials wrapped in aluminum foil (referred to as dark control). Samples were exposed to a light for not less than 1.2 million lux hours and to not less than 200 Watt hours/m^2 in near UV. Samples were then stored at the temperature of 2 – 8°C prior to analysis. Results from samples stored in the immediate pack showed the following changes when compared to dark control (Table 13 in Section 3.2.P.8.1):

- Color change from ≤ BY3 in the dark control to ≤ BY2 in the immediate pack
- By non-reducing CE-SDS the %HC+LC decreased by ~5% and the %post-peak increased by ~5.5%
- By SE-HPLC, the %main peak decreased by ~20% and the %aggregate increased by ~19%
- By cIEF, the % main peak decreased by 33% and the %acidic peak increased by 34%
- Subvisible particle ≥ 2 µm increased by 1538 and subvisible particles ≥ 5 µm increased by 177

No significant changes were noted compared to dark control when samples were placed into marketing pack, except for a minor increase in the % aggregates (1% increase). Overall, data showed that DP is sensitive to light and that the proposed commercial packaging provides adequate protection from light.

***Assessor's Comment**: Data from the photostability studies are acceptable* (b) (4)

(b) (4)

(b) (4) Therefore, because test results showed that eptinezumab DP is susceptible to photodegradation, the commercial DP label will instruct to protect the product from light and store the DP vials in the original packaging during long-term storage.

***Assessor's Comment**: Data provided from the photostability studies are acceptable and support the label recommendation to protect vials from light exposure until time of use.*

3.2.P.8.2 Post-Approval Stability Commitment

Section 3.2.P.8.2 Post-Approval Stability Commitment

Stability studies will be performed for up to 48 months to allow for shelf life extension (Table 1 in Section 3.2.P.8.1). Alder commits to place at least 1 DP lot per year on stability (if the DP is manufactured during the calendar year) and to submit all stability updated data in the annual report or upon request. In addition, Alder commits to submit to the BLA DP shelf life extensions and supporting data from the long-term stability studies.

***Assessors' Comment**: The protocol for shelf life extension is acceptable.*

3.2.P.8.3 Stability Data

Stability data were provided for the 3 DP lots manufactured at (b) (4) (APQE01, APQF02, and APQF03) when stored inverted or upright at the long-term temperature condition of 2 – 8°C for 24 months and stored inverted at the accelerated temperature condition of 25°C with 60% relative humidity for up to 6 months (Table 1 in Section 3.2.P.8.3) (primary stability studies).

In addition, stability data were provided for 3 DP clinical lots manufactured at (b) (4) (1-FIN-2349, 1-FIN-2874, and 1-FIN-2875) when stored at the long-term temperature condition of 2 – 8°C for up to 36 months and at the accelerated temperature condition of 25°C with 60 % relative humidity inverted for up to 12 months (Table 11 in Section 3.2.P.8.3) (supportive stability studies).

All test results meet the stability acceptance criteria when samples are stored at the long term-temperature condition of 2 – 8°C for up to 24 months for samples from lots manufactured at (b) (4) and for up to 36 months for samples from lots manufactured at (b) (4)

In addition, when sample were stored at the long-term temperature condition of 2 – 8°C only minor changes were noted in the %aggregates by SE-HPLC (increase within 1%) and in the %acidic peak by cIEF (increase within 8%).

When samples were stored at the accelerated temperature condition of 25°C the following changes were noted:

- By reducing CE-SDS, the %HC+LC decreased by 1.2% and the %clips increase by 1%
- By SE-HPLC, the %main peak decreased by ~4% and the %aggregates increased by 2.2%

- By cIEF, the %main peak decreased by 27% and the %acidic peak increased by 26%

***Assessor's Comment**: Overall, stability data support the proposed shelf-life of 24 months when DP lots are stored at the long-term temperature condition of 2 – 8°C. In addition, stability data from samples stored at the accelerated temperature condition of 25°C support the comparability between lots manufactured at* (b) (4) *and lots manufactured at* (b) (4)

Based on the data provided in Section 3.2.S.8.3 (data from lots stored at 5°C and 25°C), Section 3.2.S.8.1 (data from photostability studies), and Section 3.2.S.2.6 (data from thermal stressed studies), cIEF, SE-HPLC, and CE-SDS are stability indicating methods.

3.2.A Appendices Table of Contents

3.2.A.1 Facilities and Equipment

Evaluation of facilities and equipment is deferred to OPMA reviewer.

3.2.A.2 Adventitious Agents Safety Evaluation

Eptinezumab is manufactured in yeast, which is not a potential host for the amplification of viruses that are infectious for human and animal cells. The presence of adventitious agents in the DS and DP lots is ensured by raw material testing, demonstration of microbiological purity, in-process testing, and procedural and facility controls. *This is acceptable*.

3.2.A.3 Novel Excipients

No novel excipients are used in the eptinezumab manufacturing process. *This is acceptable*.

3.2.R Regional Information (U.S.A.)

3.2.R.1 Executed Batch Records

Executed batch record were provided in Section 3.2.R for the DS lot B399563 and for the DP lot APQE01.

3.2.R.2 Method Validation Package

Method validation is evaluated in 3.2.S.4.2, 3.2.S.4.3, 3.2.P.5.2, and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures of this document.

3.2.R.3 Comparability Protocols

The submission does not include comparability protocols.

3.2.R.6 Analytical Similarity

Not applicable.

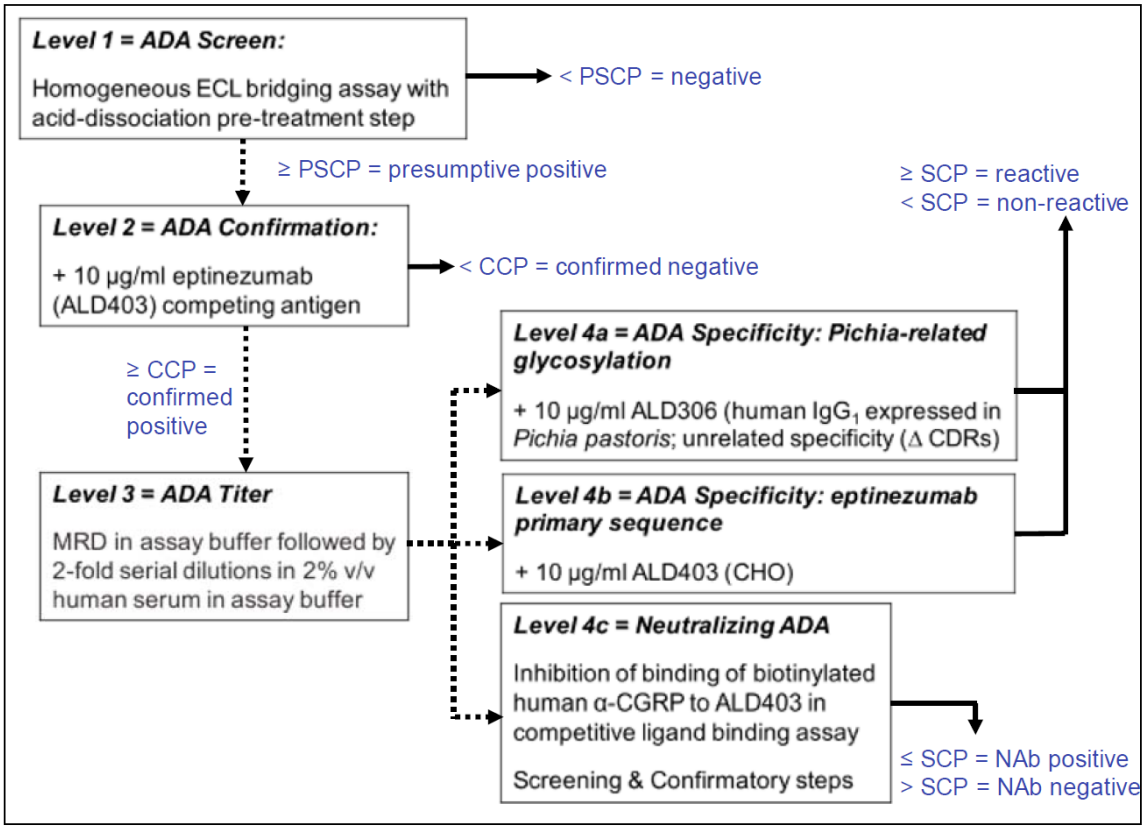
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Immunogenicity Assessment

The eptinezumab-induced anti-drug antibody (ADA) response was evaluated in 5 clinical studies using a tiered strategy (screening, confirmatory, characterization and titering, and neutralizing (NAb) assays). In addition, Alder included a test for signal specificity using confirmed ADA positive samples, as requested by the FDA during the End-of-Phase 2 meeting held on October 13, 2016. Note that the FDA asked to evaluate for all ADA confirmed positive samples whether immune responses are directed to the *Pichia*-derived O-linked glycosylation present on the drug (review in DARRTS dated 10/18/2016, refer to meeting minutes in DARRTS dated 11/02/2016). Therefore, the specificity of the immune response was evaluated using human IgG1 containing unrelated complementary determining regions (CDR), but identical eptinezumab backbone and using IgG1 with identical eptinezumab sequence but expressed in CHO cells (instead of *Pichia* cells).

An overview of the strategy used to evaluated eptinezumab immunogenicity is provided in Figure 3 (from the Integrated Summary of Immunogenicity Report).

Figure 3: Hierarchal Test Scheme Applied to Studies ALD403-CLIN-006, -011, and -013



Abbreviations: ADA= anti-drug antibody; CCP=confirmatory cut point; CDR= Complementarity determining region; CGRP= calcitonin gene related peptide; CHO= Chinese hamster ovary expressed antibody; ECL= electrochemiluminescent; IgG = Immunoglobulin G; MRD = minimal required dilution; PSCP= plate-specific cut point; SCP= screening cut point; v/v = volume per volume
Sources: (b) (4) second generation ADA Assay. (b) (4) 997003; (b) (4) NAb assay, (b) (4) -997055

***Assessor's Comment**: The tiered approach to evaluate ADAs is acceptable as per the FDA Draft Guidance to Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins.*

Alder developed 2 screening assays. The first-generation of screening assays was used to evaluate samples from the Phase 1 study ALD403-CLIN-002 (CT identifier NCT01772524) (88 subjects treated). The second generation of the screening assay was used to evaluate samples from the remaining 4 clinical studies (Phase 2 and Phase 3 studies).

***Assessor's Comment**: The commercial label provides the incidence of ADA based on the results from two Phase 3 studies (PROMISE 1 - ALD403-CLIN-006 - CT identifier NCT02559895 and PROMISE 2 - ALD403-CLIN-011 - CT identifier NCT02974153). Samples from these Phase 3 studies were evaluated using the second generation of screening assay. Therefore, only validation of the second-generation screening assay will be discussed in this review.*

Anti-Drug Antibody (ADA) Assay

Screening ADA Assay

The screening assay consists in an electrochemiluminescence (ECL) bridging assay using 96 Meso Scale Discovery (MSD) streptavidin coated microtiter plates. Controls and test samples are diluted 50-fold in assay buffer followed by 2-fold dilution in 300 mM acetic acid for acid dissociation. Samples are then incubated in a mixture of biotinylated eptinezumab (capture reagent) and sulfo-tag conjugated eptinezumab (detecting reagent). The formed complex "biotinylated eptinezumab : ADA : sulfo-tag conjugated eptinezumab" is then added to the streptavidin coated plates and allowed to bind via streptavidin interaction. After washing, the bound immune complexes are detected by adding ECL Read Buffer followed by analysis using MSD Sector S 600 plate reader.

***Assessor's Comment**: ECL and bridging format are standard for detection of ADAs. The design of the screening assay is acceptable.*

Confirmatory and Specificity ADA Assay

The confirmatory assay uses the same format as the screening assay, except that eptinezumab (reference standard Lot 148.095) is added at the final concentration of 10 µg/mL to compete for the ADA binding. In the specificity assay, control reagents (ALD403 expressed in CHO cells or ALD306 expressed in *Pichia*) are added at the final concentration of 10 µg/mL.

- ALD306, a *Pichia*-expressed monoclonal antibody that has the same framework and similar glycosylation profile as ALD403 (eptinezumab), but different CDRs
- CHO-derived ALD403, an antibody molecule produced in CHO cells and having the same CDRs as *Pichia*-derived ALD403 (eptinezumab) and human IgG1 primary amino acid sequence including the N297A mutation *(This molecule lacks the Pichia-derived O-linked glycans)*

Test results from the specificity assays showed that ADL403 expressed in *Pichia* or CHO have comparable signal inhibition, while ALD306 showed non-significant inhibition (Table 12 in Section 5.3.5.3 Integrated Summary of Immunogenicity Report). These data support the absence of pre-existing antibodies cross-reacting to *Pichia*-related glycosylation and that the ADA are not against *Pichia*-related glycosylation.

***Assessor's Comment**: The design of the ADA confirmatory assay is acceptable. Overall, Alder has shown that the ADA detected are unlikely to be against the O-linked glycosylation present on the drug. This is acceptable.*

Titering ADA Assay

Titering assay uses the same format as the screening assay. Titer was determined by diluting the low positive and high positive controls 2-fold in 2% human serum and assayed using the screening assay at 50-fold through 6400-fold for the low positive control and 500-fold through 64,000-fold for the high positive control.

Essential Reagents and Concentration

The positive control (PC) is a rabbit IgG monoclonal antibody against eptinezumab. The positive control was prepared by immunizing rabbits with ALD403 and by isolating B cell clones secreting IgG antibodies specific for ALD403. The IgG coding sequence for the 2 variable regions of the light chain and heavy chain was cloned into human Fc expression vector and transfected into mammalian cells for the production of anti-eptinezumab antibody, which was subsequently purified using Protein A Sepharose. *The use of anti-eptinezumab rabbit monoclonal antibody as positive control is acceptable.*

Original Validation:

- High positive control (HC): 2500 ng/mL
- Low positive control (LC): 250 ng/mL

Validation/Protocol Amendment:

- Confirmatory low positive control (cLC): 85 ng/mL
- Screening low positive control (sLC): 110 ng/mL
- Mid positive control (MD): 250 ng/mL

  Note that sLC, cLC, and MD controls were introduced in the protocol amendment (Section 5.3.1.4 Study report 997003 Amendment 1) to evaluate the specificity of the ADA. The amendment validation results are considered additive to the original validation results.

- Negative control (NSP) consists of pooled human serum.

Minimum Required Dilution (MRD): 1:50 (2% human serum). MRD of 1:50 was established during assay development and confirmed during method validation by showing better selectivity (Table 5 in Section 5.3.1.4 Study Report 997002).

***Assessor's Comment**: The use of MRD of 1:50 is acceptable and within recommended dilution described in the FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.*

Screening Assay Cut Point Determination

Screening cut point was determined using 50 human samples (25 samples from healthy subjects and 25 samples from migraine patients) analyzed in duplicate wells in 3 separate experiments by 2 separate analysts (total of 6 separate occasions). Because data generated from healthy subjects were not statistically different from data generated from migraine patients, a single screening cut point was calculated.

***Assessor's Comment**: The use of 25 samples from healthy subjects and 25 samples from migraine patients for the determination of the screening cut point is acceptable because Table 3 (Individual Results for Screening, Confirmatory, and Specificity Assay Cut Point Determination,*

page 46 in Section 5.3.1.4 Study report 997003 Amendment 1) shows that the mean ECL values from healthy subject samples are comparable to those from patient samples.

Outlier values were removed, and the screening cut point was determined using non-parametric approach because although the Shapiro-Wilk test p-value was 0.5483, the variability between analyst/day was not the same (using the Levene's test the p-value is 0.0049). The parametric cut point was also calculated, showing to be identical to the non-parametric cut point. Therefore, based on the cut point of 120.23 and the average of the negative controls (103), the screening cut point factor of 1.17 (120.23/103) was determined to detect about 5% false positive. The cut point factor was then multiplied by the mean of normal serum pool (NSP) on each plate to determine the plate specific cut point.

***Assessor's Comment**: Based on the data provided, the use of non-parametric cut point is acceptable.*

Confirmatory Assay Cut Point Determination

Confirmatory cut point was determined by adding 10 µg/mL of ALD403 to 25 samples from healthy subjects and 25 samples from migraine patients. Samples were analyzed by 2 analysts in 2 different days. The mean ECL value from samples with and without drug were compared, and the percentage of inhibition was calculated as %inhibition= (1- (Signal with Drug) / (Signal without Drug)) x100%. The plate cut point was then determined as mean negative control NSP x screening cut point. Because data generated from healthy subjects were not statistically different from data generated from patients, a single confirmatory cut point was calculated.

***Assessor's Comment**: The use of 25 samples from healthy subjects and 25 samples from migraine patients for the determination of the confirmatory cut point is acceptable because Table 3 (Individuals Results for Screening, Confirmatory, and Specificity Assay Cut Point Determination, page 46 in Section 5.3.1.4 Study report 997003 Amendment 1) shows that mean ECL values from healthy subject samples are comparable to those from patient samples.*

Outliers were removed and the confirmatory cut point of 10.24% inhibition with a 99% confidence interval was calculated using non-parametric approach and based on the 1% false positive rate (See Appendix D in Section 5.3.1.4 Study report 997003 Amendment 1). During routine analysis, samples with % Inhibition at or above the confirmatory cut point will be considered confirmed positive for anti-ALD403 antibodies.

***Assessor's Comment**: The confirmatory cut point of 10.24% inhibition is acceptable because it uses a 1% false positive rate as recommended by the FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.*

Specificity Assay Cut Point (ALD403 expressed in CHO cells and ALD306 expressed in *Pichia*)

For the assay using ALD306 expressed in *Pichia*, the specificity cut point was determined using 25 samples from healthy subjects and 25 samples from migraine patients. For the assay using ALD403 expressed in CHO cells, the specificity cut point was determined using 50 samples from health subjects and 50 samples from migraine patients. For both assays, samples were analyzed by 2 analysts in 2 different days. The mean ECL value from samples with and without ALD403 or ALD306 were compared, and the percentage of inhibition was calculated using the same approach used for the calculation of the confirmatory cut point.

- For the specificity assay using ALD403 expressed in CHO cells, data from the healthy subjects were comparable to data from migraine patients. Therefore, a single cut point of **13.0% inhibition** with a 99% confidence interval was calculated using a parametric approach and based on the 1% false positive rate (See Appendix D in Section 5.3.1.4 Study report 997003 Amendment 1).
- For the specificity assay using the unrelated antibody ALD306 expressed in *Pichia*, results from the healthy subject were statistically different from results from migraine patients. Therefore, outliers were removed and separate cut points were determined for each population samples using parametric approach and based on the 1% false positive rate (Appendix D in Section 5.3.1.4 Study report 997003 Amendment 1).
    - For samples from **healthy subject** the specificity cut point was **5.32% inhibition** with 99% tolerance interval and
    - For samples from **migraine patients** the specificity cut point was **7.61% inhibition** with 99% tolerance interval

Assessor's Comment*: The specificity cut points are acceptable because they use a 1% false positive rate as recommended by the FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.*

Overall, the screening, confirmatory, and specificity cut points are acceptable because consistent with the FDA recommendation discussed in the FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.

Assay Sensitivity

Assay sensitivity was evaluated by spiking anti-ALD403 (anti-eptinezumab) into pooled normal human serum and serially diluted 2-fold to concentrations ranging between 1000 ng/mL and 7.81 ng/mL using 100% human serum. Each dilution was then tested in duplicate in 3 runs. Assay sensitivity was **87.34 ng/mL for the screening assay** and **67.99 ng/mL for the confirmatory** assay (Table 13 and 36 in Appendix D in Section 5.3.1.4 Study report 997003 Amendment 1) .

Assessor's Comment*: The sensitivities for the screening and confirmatory assay are acceptable because below the sensitivity limit of 250 – 500 ng/mL recommended in the FDA Guidance: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products. Note that screening low positive control (110 ng/mL) and the confirmatory low positive control*

(85 ng/mL) tested positive in the confirmatory assay. This supports acceptable sensitivity of the confirmatory assay.

Assay Precision

Intra-assay and inter-assay precision were evaluated using high and low positive controls and screening and confirmatory low positive controls. For the intra-assay precision, 6 samples were tested in duplicate and for the inter-assay precision, 24 plates plus additional 27 plates were tested. The coefficient of variation (CV) was between 2.7% and 5.86% for the intra-assay precision (Table 1 (page 43) and Table 19 (page 79) in Section 5.3.1.4 Study report 997003 Amendment 1) and between 9.5% and 18.46% for the inter-assay precision (Table 2 (page 44) and Table 20 (page 80) in Section 5.3.1.4 Study report 997003 Amendment 1). For both intra- and inter-assay precision, test results met the acceptance criterion of ≤ 25% CV. In addition, negative control samples were tested in the confirmatory assay using 24 plates and results showed inhibition below the cut point, with a CV of 7.04% (Table 4, page 59 in Section 5.3.1.4 Study report 997003 Amendment 1).

***Assessor's Comment**: The intra-assay and inter-assay precision is acceptable because below the acceptance criterion of ≤ 25% CV. Negative samples were confirmed negative.*

Assay Recovery/Selectivity

Normal Human Serum

Recovery was evaluated using six lots of serum from healthy subjects and six lots of serum from migraine patients. Samples were spiked with low and high positive controls and each positive control concentration was tested in duplicate, in the absence or presence of the drug. All samples from healthy subjects and samples from migraine patients spiked with high positive control met the acceptance criteria. For samples from migraine patients spiked with low positive control, five out of six lot samples met the acceptance criteria of precision ≤ 25% CV and mean ECL value ≥ 75% of the inter-assay mean (Table 15, page 74 in Section 5.3.1.4 Study report 997003 Amendment 1). Additional studies were performed using screening and confirmatory low positive controls and high positive controls with serum from healthy subjects and migraine patients. All spiked samples met the acceptance criterion of percentage of inhibition ≥ confirmatory cut point for at least 4 out of 6 individual samples. The unspiked samples had value below the confirmatory cut point except for one sample (value reported is 21.50% of inhibition and the confirmatory cut point is 10.24%) (Table 38, page 105 in Section 5.3.1.4 Study report 997003 Amendment 1). The result from the unspiked sample with percentage of inhibition above the cut point did not have impact on the validation exercise because the assay acceptance criterion (%inhibition for the unspiked samples < confirmatory cut point for at least 4 out of 6 samples) was met.

Pooled Hemolyzed and Lipemic Serum

Assay selectivity was evaluated using hemolyzed human serum pool at 1100 mg Hb/dL and lipemic human serum pool. Samples were either unspiked or spiked with low and high positive

controls and tested in four duplicate sets. All spiked samples met the acceptance criterion of precision ≤ 25% CV and mean ECL value ≥ 75% of the inter-assay mean. All unspiked samples tested negative (Table 16 and Table 17, page 75 in Section 5.3.1.4 Study report 997003 Amendment 1). Additional selectivity studies were performed using pooled hemolyzed human serum and lipemic human serum, when samples were spiked with screening and confirmatory low negative control and high positive control. All spiked samples met the acceptance criterion of percentage of inhibition ≥ confirmatory cut point. All unspiked samples tested negative (Table 39 (page 106) and Table 40 (page 107) in Section 5.3.1.4 Study report 997003 Amendment 1).

***Assessor's Comment**: Overall, data provided demonstrate adequate assay selectivity.*

Assay Drug Tolerance

ALD430 (eptinezumab) was spiked at the concentrations ranging between 100 µg/mL and 0.78 µg/mL into the low positive control (250 ng/mL), screening low positive control (110 ng/mL), or confirmatory positive control (85 ng/mL). In addition, ALD403 was also spiked at the concentration ranging between 1000 µg/mL and 7.81 µg/mL into the high positive control (2500 ng/mL). Data showed that the ALD403 concentration for which a mean ECL was greater than the cut point was 100 µg/mL for the low positive control, 1000 µg/mL for the high positive control, and 25 µg/mL for the screening and confirmatory low positive controls (Table 14 (page 73) and Table 37 (page 104) in Section 5.3.1.4 Study report 997003 Amendment 1).

The eptinezumab concentration found in samples collected at the ADA sampling times during the Phase 3 study ALD403-CLIN-006 is between 0 and 35.9 µg/mL (patients were dosed at 30 mg, 100 mg, and 300 mg), some of which are above the drug tolerance of 25 µg/mL. However, eptinezumab plasma concentration exceeded the 25 µg/mL tolerance only at week 4 and at week 16, when patients were dosed at 300 mg (Table 28, page 75 in in Section 5.3.5.3 Integrated Summary of Immunogenicity Report).

***Assessor's Comment**: Data from study ALD403-CLIN-006 showed that when patients are dosed at 300 mg of eptinezumab the plasma concentration at weeks 4 and 16 (~35.9 µg/mL) is above the assay drug tolerance of 25 µg/mL. Table 66, page 133 in Section 5.3.5.3 Integrated Summary of Immunogenicity Report shows that the ADA incidence at week 4 and week 16 in patients dosed at 300 mg (0 at week 4 and 29 (13.8% of the tested samples) at week 16) is comparable to that found in patients dosed at 100 mg (1 (<1% of the tested samples) at week 4 and 30 (14.9% of the tested samples) at week 16) and at 30 mg (4 (1.9% of the tested samples) at week 4 and 19 (9.9% of the tested samples) at week 16). Note that also in the clinical study ALD403-CLIN-001, the ADA incidence was comparable in patients dosed with eptinezumab at 100 mg or at 300 mg (Table 81, page 173 in Section 5.3.5.3 Integrated Summary of Immunogenicity Report). In addition, data generated from samples collected at other time points did not show assay interference. Furthermore, the difference between the drug tolerance of 25 µg/mL and the eptinezumab plasma concentration at week 4 (30 µg/mL) and week 8 (35.9 µg/mL) is minor (less*

than one order of magnitude). Therefore, the expected eptinezumab concentration in the plasma, up to 35.9 µg/mL, is not expected to interfere with the detection of ADA in the assay. Overall the assay sensitivity in the presence of on-board drug is acceptable.

Assay Ruggedness

Assay ruggedness was evaluated using a second lot of biotin-ALD403 and sulfo-tagged ALD403. The confirmatory assay was then performed by adding eptinezumab at 10 µg/mL to the negative control and low and high positive controls. Assay results met the acceptance criterion of precision ≤ 25% CV in at least 3 out of 4 samples, but failed the acceptance criterion of mean ECL ≥ 75% of the inter-assay mean (the signal mean was 68.19% for the high positive control, Table 18, page 76 in Section 5.3.1.4 Study report 997003 Amendment 1). Alder stated that when a new biotinylated of sulfo-tagged ALD403 lot is prepared, their dilutions need to be qualified prior to use. This requirement is included in the assay procedure. The results for the negative control samples were below the confirmatory cut point and the results of the positive control samples were above the confirmatory cut point.

***Assessor's Comment**: Alder has included the requirement for dilution qualification when new biotinylated or sulfo-tagged ALD403 lots are prepared. This is acceptable. Overall, data support the ruggedness of the assay.*

Stability

Freeze-Thaw Stability

Six duplicate sets of each low positive control, high positive control, confirmatory and screening low positive controls were tested after 6 or 10 freeze-thaw cycles. All results met the acceptance criterion of precision ≤ 25% CV and mean ECL values ≥ 75% of the inter-assay mean (Table 11 and Table 24 in Section 5.3.1.4 Study report 997003 Amendment 1).

Short-Term Stability

Six duplicate sets of each low positive control, high positive control, confirmatory and screening low positive controls were tested after storage at room temperature for 19 hours and 51 minutes or 19 hours and 42 minutes. All results met the acceptance criterion of precision ≤ 25% CV and mean ECL values ≥ 75% of the inter-assay mean (Table 12 (page 71) and Table 25 (page 93) in Section 5.3.1.4 Study report 997003 Amendment 1).

Long-Term Stability

Six duplicate sets of each low positive control and high positive control were tested after storage at -70°C for 439 days or at -20°C for 116 days. All results met the criterion of precision ≤ 25% CV and mean ECL values ≥ 75% of the inter-assay mean in at least 4 out of 6 duplicate sets. No significant changes were noted when data were compared to results from the routine runs (Table 26 (page 94) through Table 31 (page 96) in Section 5.3.1.4 Study report 997003 Amendment 1).

***Assessor's Comment**: Overall, data support the stability of the positive controls at room temperature, -20°C, and -70°C for up to ~20 hours, 116 days, and 439 days, respectively. In addition, repeating freeze-thaw cycles of the positive controls did not impact assay performance.*

Titer Determination and Precision

Low positive control, confirmatory low positive control, and screening low positive control were diluted between 50-fold and 6400-fold. High positive control was diluted between 500-fold and 64,000-fold. Titer was 4469 for the high positive control, 522 for the low positive control, 201 for the screening low positive control, and 118 for the confirmatory positive control (Table 9 (page 68), Table 10 (page 69), and Table 10a (page 70) in Section 5.3.1.4 Study report 997003 Amendment 1).

***Assessor's Comment**: Data provided show that the titer assay precision is acceptable because the titer in multiple runs did not differ more than 2 step dilution.*

Overall, the ADA assay is suitable for testing clinical samples to detect anti-ALD403 antibodies in human serum.

Neutralizing Antibody (NAb) Assay

The NAb assay was originally developed at (b) (4) Subsequently the NAb assay was transferred to (b) (4) where the assay was optimized (b) (4) *Note that the NAb assay was fully validated at* (b) (4) *This supports the method transfer.*

The NAb assay is a competitive ligand-binding assay that measures the capability of the NAb to inhibit the binding of ALD403 (eptinezumab) to CGRP. Samples and controls are diluted 1.25-fold in 1% BSA and 0.05% Tween 20. Test samples and positive controls are then further diluted 4-fold in 300 mM acetic acid and incubated for 10 minutes prior to adding to MSD plates containing 1 M Tris. A biotinylated α-CGRP and streptavidin labeled with ruthenium metal chelate (sulfo TAG®) are used to detect anti-ALD403 antibodies bound to ALD403 that is coated to the plate using an MSD Sector S600 reader.

If NAb are present, they prevent the biotin-CGRP from binding to the ALD403 immobilized on the plate, resulting in a decreased ECL signal.

***Assessor's Comment**: The design of the NAb assay is acceptable because it reflects the mechanism of action of the drug, which is a competitive ligand-binding assay (eptinezumab binds to CGRP, preventing the interaction of CGRP with its receptor).*

Essential Reagents and Concentration

The positive control (PC) is a rabbit IgG monoclonal antibody against eptinezumab. Positive controls should have a precision of ≤ 25% CV for at least 4 out of 6 duplicates sets and 1 at each control level and results should be < fixed screening cut point.

- High positive control (HC): 20,000 ng/mL
- Mid positive control (MD): 2500 ng/mL
- Low positive control (LC): 250 ng/mL
- Confirmatory low positive control (cLC): 400 ng/mL
- Screening low positive control (sLC): 500 ng/mL

Negative control is a pool of human serum. The negative control should have a precision of ≤ 25% CV for at least 2 of the 3 replicates.

NAb Assay Screening Cut Point

Screening cut point was determined using 50 samples from healthy subjects and 50 samples from migraine patients and analyzed in duplicate wells in 2 separate experiments by 2 different analysts (total of 4 separate occasions). The screening cut point established to achieve 5% of samples as false positive was determined to be **0.937**. No statistical differences were noted between the results from healthy subjects and migraine patients.

***Assessor's Comment**: The number of human samples used and cut point of 5% are acceptable based on the FDA Guidance Assay Development Validation for Immunogenicity Testing of Therapeutic Protein Products.*

NAb Assay Confirmatory Cut Point

Samples tested positive in the screening assay were tested using the confirmatory assay with a 1% false positive rate. Subsequently, samples with the percentage of neutralization equal or above the confirmatory cut point was considered confirmed positive for neutralizing anti-eptinezumab antibodies. The confirmatory cut point was determined using 50 human samples from healthy subjects and 50 human samples from migraine patients and analyzed in 2 runs by 2 separate analysts (total of 4 occasions). The mean ECL values obtained with and without addition of eptinezumab were used to calculate the percentage of neutralization. The resulting **confirmatory cut point was 7.2% inhibition**.

NAb Assay Sensitivity

The sensitivity of the NAb screening and confirmatory assays was determined by spiking neutralizing anti-ALD403 antibodies into pooled human serum and diluted between 5000 ng/mL and 39.06 ng/mL. Samples were tested in the absence or presence of drug in duplicate in two separate experiments by 2 different analysts. The sensitivity was 372 ng/mL for the NAb screening sensitivity and 304.27 ng/mL for the NAb confirmatory assay.

***Assessor's Comment**: The sensitivity for the screening and confirmatory assay is acceptable because is within the recommended value of at least 250 - 500 ng/mL described in the FDA Guidance Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products.*

NAb Assay Intra-Assay Precision

Positive controls were tested in six duplicate sets (12 wells). All test results met the acceptance criterion of ≤ 25% CV (Table 4, page 35 in Section 5.3.1.4 Study Report 997055).

NAb Assay Inter-Assay Precision

Positive controls were tested in 2 duplicates using 15 plates. The overall mean of the duplicates met the acceptance criterion of ≤ 25% CV (Table 5, page 36 in Section 5.3.1.4 Study Report 997055).

***Assessor's Comment**: Note that one test result for screening low positive controls did not meet the acceptance criteria of ≤ 25% CV (result reported is 31.5% CV). However, this is acceptable because the overall mean of the duplicates was within the acceptance criterion and because overall positive controls met the acceptance criterion of precision ≤ 25% CV for at least 4 out of 6 duplicates sets and 1 at each control level.*

NAb Assay Confirmatory Precision and Neutralization

NAb confirmatory assay was performed using positive and negative controls spiked with an excess of ALD403. Positive controls were tested in duplicate and negative controls were tested in triplicates during 6 runs, over 2 days. Results were compared to unspiked samples and the percentage of neutralization was calculated. For the positive control samples, all results met the acceptance criterion of ≤ 25% CV except for one result for the screening low positive control (result reported is 31.5% CV). The percentage of neutralization was above the confirmatory cut point of 7.2% for all positive control samples (Table 6, page 39 in Section 5.3.1.4 Study Report 997055). For the negative control samples, all results met the acceptance criterion of percentage of neutralization < the confirmatory cut point of 7.2%, except for 11 results (Table 7, page 44 in Section 5.3.1.4 Study Report 997055).

***Assessor's Comment**: The precision of the NAb confirmatory assay failed in 11 negative control samples. However, this is acceptable because this means that the percentage of samples positive for the presence of NAb is overestimated.*

NAb Assay Prozone

The prozone effect was evaluated using negative control samples spiked with different concentration of high concentration of ALD403 (10-fold higher than high positive control concentration). Data showed that increase in dilution factor resulted in an increase of ECL signal. Therefore, no prozone effect was noted (Table 8, page 49 in Section 5.3.1.4 Study Report 997055).

Nab Assay Recovery

A total of 10 samples from healthy subjects and 10 samples from patients with migraine were spiked using confirmatory and screening low positive controls and high positive control. Each

concentration was evaluated in duplicate, in presence or absence of excess of drug. Data showed that for the spiked samples, the overall result met the acceptance criterion of percentage of neutralization ≥ confirmatory cut point for at least 80% of the samples and signal to noise ratio being less than the screening cut point. For the negative control samples, the overall result met the acceptance criterion of signal to noise ratio greater than screening cut point for at least 8 out of 10 samples and the percentage of neutralization < confirmatory cut point (Table 10 (page 57) and Table 11 (page 59) in Section 5.3.1.4 Study Report 997055).

***Assessor's Comment**: Although 2 unspiked samples and 1 spiked sample from the migraine patient lots did not meet the acceptance criterion, the overall result is acceptable because met the acceptance criteria.*

Pooled hemolyzed human serum at 137.5 mg/dL, 275 mg/dL, 550 mg/dL, and 1100 mg/dL were tested for interference of hemolysis. In addition, pooled lipemic human serum was tested for interference of lipemia. Each sample was either unspiked or spiked with confirmatory and screening positive controls and high positive control. Data from the spiked samples met the acceptance criteria of signal to noise ratio < screening cut point and percentage of neutralization ≥ confirmatory cut point for at least 3 out of 4 duplicates. Data from the unspiked samples showed that only the hemolyzed samples at 137.5 mg/dL passed the acceptance criterion of signal to noise ratio > screening cut point and percentage of neutralization < confirmatory cut point. Samples hemolyzed more than 137.5 mg/dL may show false positive results in the NAb screening assay. However, for these samples, the results for the percentage of neutralization was confirmed negative. Alder stated that hemolysis will be recorded for each sample discussed during data reporting (Table 12 (page 61) and Table 15 (page 64) in Section 5.3.1.4 Study Report 997055). All samples from lipemic human serum met the acceptance criteria (Table 16, page 65 in Section 5.3.1.4 Study Report 997055).

***Assessor's Comment**: Although NAb screening assay shows false positive results in samples hemolyzed more than 137.5 mg/dL, data from the NAb confirmatory assay confirmed these samples as negative. In addition, Alder will record hemolysis for each sample and results will be discussed in the data report. Overall, the NAb assay recovery is acceptable.*

NAb Assay Ruggedness and Robustness

Ruggedness of the NAb was evaluated using 3 analysts, different MSD readers, different plate washers, and different plate lots. Robustness of the NAb assay was evaluated by using different incubation times (± 10% of each incubation). For assay ruggedness, Alder stated that all parameters met routine run acceptance criteria. For assay robustness, all results were acceptable (Table 17 and Table 18, page 66 in Section 5.3.1.4 Study Report 997055). Some plates used in the ruggedness assessment were 'not acceptable' due to variety of reasons unrelated to the ruggedness of the assay (refer to the footnote of Text Table 7 *Validation Run Summary* (page 15) of Study Report 997055).

***Assessor's Comment**: Overall, the assay is rugged and robust.*

NAb Assay Drug Tolerance

ALD403 was spiked into positive and negative controls and solution were diluted to achieve a series of ALD403 concentrations ranging between 50,000 ng/mL and 97.66 ng/mL. Each dilution was tested in duplicate. Drug tolerance was calculated as the drug concentration in the positive and negative controls for which the signal to noise ratio was less than the screening cut point. Note that the study was repeated due to fluctuation observed in the percentage of inhibition (in Section 5.3.1.4 Study Report 997055, Table 9 (page 50) reports the original data and Table 9a (page 54) reports the results from the repeated experiment). For the screening low positive control, the screening drug tolerance was 1563 ng/mL and the confirmatory drug tolerance was 781.25 ng/mL; for the confirmatory low positive control, the screening and confirmatory drug tolerance was 195.31 ng/mL; for the high positive control, the screening and confirmatory drug tolerance was 25,000 ng/ml.

***Assessor's Comment**: Note that analysis of the data from Table 9a shows that the screening drug tolerance is 3125 ng/mL and not 1563 ng/mL; for the confirmatory low positive control, the screening drug tolerance is 390.63 ng/mL (and not 195.31 ng/mL) and the confirmatory drug tolerance is 195.31 ng/mL; for the high positive control, the screening drug tolerance is 50,000 ng/mL (and not 25,000 ng/mL) and the confirmatory drug tolerance is 25,000 ng/mL. The level of eptinezumab found in samples collected at the ADA sampling times during the Phase 3 study ALD403-CLIN-006 is between 0 and 35.9 μg/mL (patients were dosed at 30 mg, 100 mg, and 300 mg), which is above the NAb assay drug tolerance. In addition, Table 65 Section 5.3.5.3 Integrated Summary of Immunogenicity Report) indicates that for samples from the clinical study ALD403-CLIN-006, the assay was capable of detecting 16 (34% of the samples confirmed positive in the ADA screening assay) and 22 (48.9% of the samples confirmed positive in the ADA screening assay) NAb positive samples from patients dosed at 300 mg and 100 mg of eptinezumab. Furthermore, the NAb assay shows to have sufficient precision and the presence of ADA or NAb did not have impact on efficacy when eptinezumab was dosed at either 100 mg or 300 mg (efficacy in patients positive for ADA was comparable to efficacy in patients negative for ADA). Therefore, overall, the NAb assay is acceptable.*

Overall, the NAb assay is suitable for testing clinical samples to detect neutralizing antibodies to eptinezumab.

Andrea Franco

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Christopher Downey

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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
WO Building 22
10903 New Hampshire Ave.
Silver Spring, MD 20993

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Aimee L. Cunningham, Ph.D., M.P.H.
Quality Assessment Lead: Reyes Candau-Chacon, Ph.D.

BLA:	761119/0
Applicant:	Alder BioPharmaceuticals, Inc.
US License Number:	2097
Submission Reviewed:	Original BLA
Product:	Vyepti (eptinezumab)
Indication:	preventative treatment for migraine
Dosage Form:	solution for i.v. injection (100 mg/mL)
Manufacturing Sites:	(b) (4)
FDA Receipt Date:	02/21/2019
Action Date:	02/21/2020

Conclusion and Approvability Recommendation

The drug product portion of this BLA was reviewed from a sterility assurance and product quality microbiology standpoint and is recommended for approval, pending submission of completed LER study results, which are due to be submitted to the BLA by December 15, 2019. An addendum to this review memo will be filed upon its submission to assess this data.

Product Quality Microbiology Assessment: Drug Product

Alder BioPharmaceuticals has submitted BLA 761119 to license eptinezumab and its associated drug substance and drug product manufacturing processes. BLA 761119 was submitted via eCTD on February 21, 2019. This review contains the assessment of the manufacturing process of eptinezumab drug product from a sterility assurance and product microbiological quality perspective. For review of drug substance aspects of this application, please see the review by Dr. Candace Gomez-Broughton.

> ***Reviewer's Comment:*** *Alder was acquired by Lundbeck during the review cycle and is now known as Lundbeck Seattle BioPharmaceuticals, Inc.; this change was reported to the Agency on 11/01/2019 (sequence 0025). Throughout this memo, the Sponsor is referred to as Alder.*

Drug Product Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	02/21/2019	Original BLA
0008	05/15/2019	IR responses
0010	06/26/2019	IR responses
0012	07/17/2019	IR responses
0015	09/05/2019	IR responses
0017	09/20/2019	IR responses
0019	09/27/2019	IR responses
0024	10/31/2019	IR responses
0026	11/06/2019	Quality Amendment
0030	11/13/2019	IR responses
0033	12/04/2019	IR responses

Letters of authorization (LOAs) for the following drug master files (DMFs) were provided; review status of each DMF is documented below. DMFs not related to microbiology are not included in the below table.

DMF #	Content	Date Reviewed	Finding	Document Name
(b) (4)		02/03/2017	Adequate	(b) (4)
		04/25/2017	Adequate	

Module 1

1.14 Labeling

Eptinezumab is to be delivered every 3 months by i.v. infusion over 30 minutes with a 0.2 or 0.22 µm in-line or add-on filter. It should be administered with a single-use i.v. infusion set and not as a bolus injection or i.v. push. One vial (100 mg) is diluted in 0.9% NaCl (100 mL bag) prior to administration; no other diluent may be used. Some patients may benefit from a 300 mg dose (3 vials into one bag of saline). Following dilution, eptinezumab must be infused within 8 hrs (with DP warmed to ambient temperature for infusion). It may be stored at ambient temperature (b) (4) for the 8 hr period.

Reviewer's Comment: *A microbial growth study is described in P.2.6 which supports the 8 hr hold time with a 2-fold safety factor for both doses (100 mg and 300 mg) of eptinezumab.*

SATISFACTORY

Module 3.2

DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Eptinezumab is a sterile, non-pyrogenic, aqueous solution for i.v. infusion comprised of 100 mg/mL eptinezumab, (b) (4) mg/mL L-Histidine, 40.5 mg/mL sorbitol, 0.15 mg/mL polysorbate 80

and WFI (target pH 5.8). DP is single-use, with no antimicrobial agents or preservatives. It is supplied in (b) (4) glass vials with an (b) (4) stopper and flip-off cap. Storage is 2-8°C.

SATISFACTORY

P.2 Pharmaceutical Development

(b) (4)

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Aimee Cunningham

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Reyes Candau-Chacon

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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

Date: November 20, 2019
STN: 761119/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Reyes Candau-Chacon, Ph.D. CDER/OPQ/OPF/DMA/Branch IV
Subject: Original Biologics License Application
Applicant: Alder BioPharmaceuticals, Inc.
Facilities: (b) (4)
Product: VYEPTI (eptinezumab)
Dosage: Liquid for intravenous injection (100 mg/mL)
Indication: Preventive treatment for migraine
Action Date: February 21, 2020

Recommendation: The drug substance portion of BLA 761119, as amended, is recommended for approval from a microbiology product quality perspective. The drug product portion of the BLA was assessed from a sterility assurance and microbiological product quality perspective in a separate review memo by Dr. Aimee Cunningham.

Introduction

Alder BioPharmaceuticals, Inc. has submitted a Biologic License Application (BLA) for eptinezumab injection. The proposed proprietary name for this product is VYEPTI™. Eptinezumab is a calcitonin gene-related peptide antagonist indicated for the preventative treatment of migraines in adults.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
001	02/21/2019	Original Submission
0019	09/27/2019	Response to information request
0024	10/30/2019	Response to information request

Assessment

S Drug Substance

S.2 Manufacture

S.2.1 Manufacturer(s)

Drug substance is manufactured the (b) (4) Testing and storage sites are listed in the Table 1 of this section.

Reviewer comment: The DS manufacturing facility was inspected in (b) (4) *as a condition of BLA approval.*

S.2.2 Description of Manufacturing Process and Process Controls

(b) (4)

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Reyes Candau-Chacon

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