CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761304Orig1s000

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:	June 16, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Shen Luo, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 4
Application:	BLA 761304
Applicant:	argenx BV
Submission Dates:	September 20, October 21, 2022, and February 9, May 18, June 12 and June 16, 2023
Product:	VYVGART Hytrulo (efgartigimod alfa and hyaluronidase-qvfc)
Dosage form(s):	Injection
Strength and Container-Closure:	1,008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL (180 mg/2,000 units per mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the treatment of generalized Myasthenia Gravis.
Recommendations:	The prescribing information, container label, 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. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information, and carton labeling submitted on June 16, 2023 and container label submitted on June 12, 2023 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

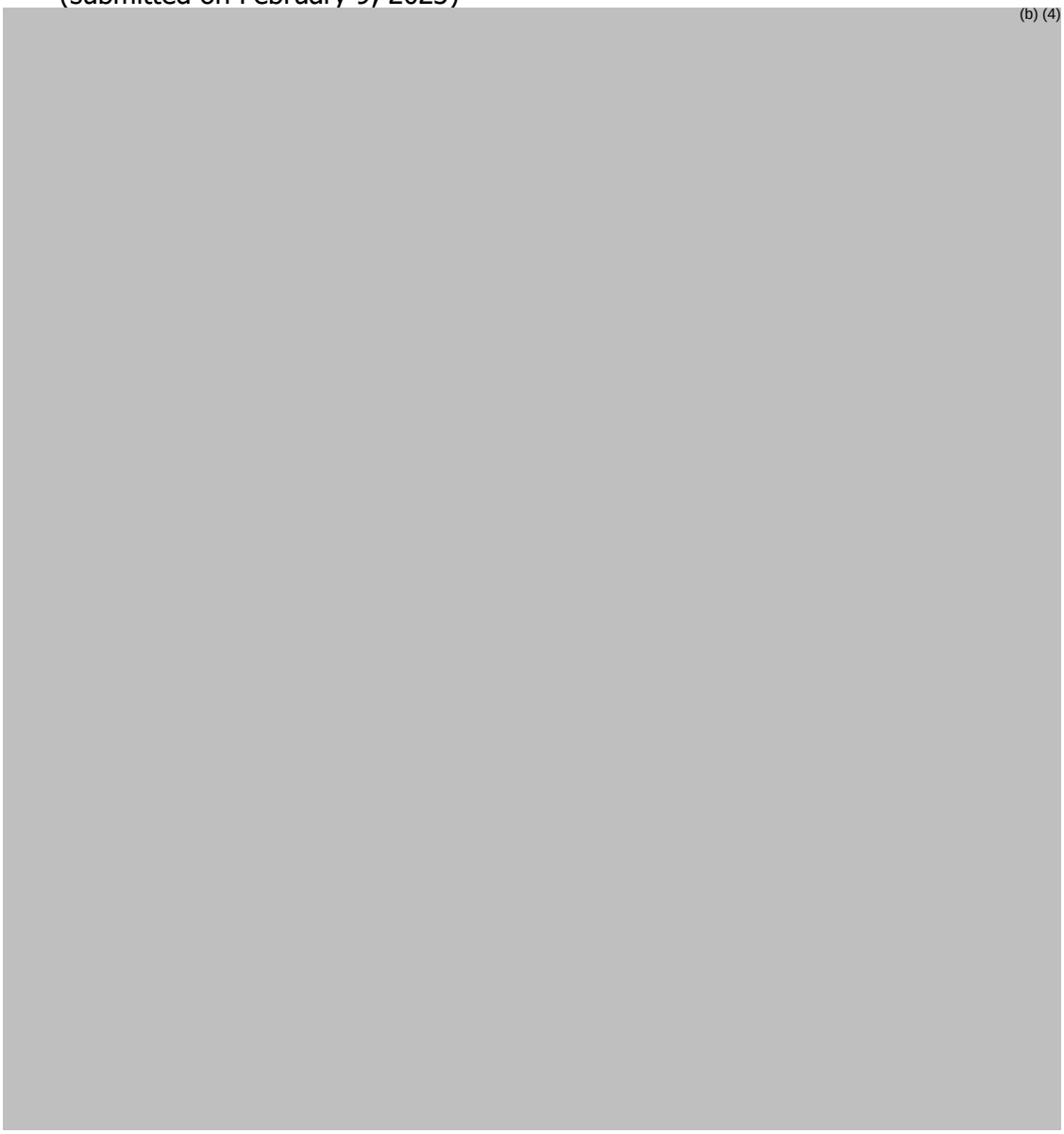
Appendix A: Proposed Labeling

- Prescribing Information (submitted on September 20, 2022)
  \\CDSESUB1\EVSPROD\bla761304\0001\m1\us\114-labeling\114a-draft-label\efg-sc-gmg-usa-pi-02sep2022.docx

- Instructions for Use (submitted on October 21, 2022)
  \\CDSESUB1\EVSPROD\bla761304\0006\m1\us\114-labeling\114a-draft-label\efg-sc-gmg-usa-ifu-june2022.docx

- Container Label
  (submitted on February 9, 2023)

(b) (4)



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

Container[4] Label Evaluation

Proper Name (container label)	**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
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Please include the conditionally approved suffix, qvfc, on the label and labeling.

Applicant's Response: The applicant included the suffix on the container label.

OBP Labeling: The applicant's revision is acceptable.

Manufacturer name, address, and license number (container label)	**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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the U.S. license number is not required.

[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.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

To applicant: If space permits, please include the U.S. License No. 2217 below the manufacturer name, argenx BV.

Applicant's Response: The applicant responded that the space does not permit the addition of the U.S. license number on the label.

OBP Labeling: The applicant's response is acceptable.

Lot number or other lot identification (container label)	**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 (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
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) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This is a single-dose vial.

Product Strength (container label)	**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

Comment/Recommendation:
To applicant:
Revise the total product strength to appear as "1,008 mg and 11,200 units/5.6 mL".

Revise the strength per mL to read "(180 mg and 2,000 units/mL)". Delete the "/mL" after 180 mg. Consider presently the word units with a small letter u

1,008 mg and 11,200 units/5.6 mL
(180 mg and 2,000 units/mL)

Check with DMEPA if they want to revise Units to appear as units.

Applicant's Response: The applicant revised the letter u from a capital U to a lower case u to enhance the differentiation between the last numeral "0" and the letter "u".

OBP Labeling: The applicant's revision is acceptable.

To applicant: Revise the total product strength to appear as "1,008 mg and 11,200 units/5.6 mL".

Applicant's Response: The applicant revised the total product strength as requested.

OBP Labeling: The applicant's revision is acceptable.

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This is a single-dose vial.

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
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

Comment/Recommendation:

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

Comment/Recommendation: The product does not need a Medication Guide.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This product provides a package/carton.

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This product has a container label.

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: Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant's Response: The applicant confirmed that there is no text on the ferrule and cap overseal of the vial.

OBP Labeling: The applicant's response is acceptable.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

Applicant's Response: The applicant confirmed the entire length of the vial can be visually inspected, and space remains above and below the label enabling visual inspection of the full circumference.

OBP Labeling: The applicant's response is acceptable.

Route of administration (container label)	**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:

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

Comment/Recommendation:

Preparation instructions (container label)	**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

Comment/Recommendation:

Package type term (container label)	**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:

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No

	☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
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*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (container label)	**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	✓ Yes ☐ No

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).*	☐ N/A

Comment/Recommendation:

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

Inactive ingredients (container label)	**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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation: This regulation does not apply to this product.

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Please include the conditionally approved suffix, qvfc, on the label and labeling.

Applicant's Response: The applicant included the suffix, qvfc, on the carton labeling.

OBP Labeling: The applicant's revision is acceptable.

Manufacturer name, address, and license number (package labeling)	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
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[7])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

[6] 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.

[7] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Displays a "no preservative" statement.

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Provides the statement "one single-dose vial".

Product Strength (package labeling)	**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

Comment/Recommendation:
To applicant: Revise the total product strength to appear as "1,008 mg and 11,200 units/5.6 mL". Revise the strength per mL to read "(180 mg and 2,000 units/mL)". Delete the "/mL" after 180 mg. Consider presently the word units with a small letter u to enhance the differentiation between the last numeral "0" and the letter "u".

1,008 mg and 11,200 units/5.6 mL
(180 mg and 2,000 units/mL)
Check with DMEPA if they want to revise Units to appear as units.

Applicant's Response: The applicant revised the letter u from a capital U to a lower case u to enhance the differentiation between the last numeral "0" and the letter "u".

OBP Labeling: The applicant's revision is acceptable

To applicant: Revise the total product strength to appear as "1,008 mg and 11,200 units/5.6 mL".

Applicant's Response: The applicant revised the total product strength on the carton labeling as requested.

OBP Labeling: The applicant's revision is acceptable.

Storage temperature/requirements (package labeling)	**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

Comment/Recommendation:
To applicant: Revise the storage and handling statements to read:
Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.

If needed, unopened vials may be stored in the original carton for up to 3 days at room temperature at 20°C–25°C (68°F–77°F) for a single period before administration or returned to refrigeration. Do not store the vial at room temperature more than one time. Record the date removed from and the date return to the refrigerator on the carton.

Date removed from the refrigerator: ___/___/___
Date returned to the refrigerator: ___/___/___

Applicant's Response: The applicant revised the storage information as requested.

OBP Labeling: The applicant's revision is acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes

	☐ No ☐ N/A

Comment/Recommendation:

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 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:

Known sensitizing substances (package labeling)	**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: No dry natural rubber (latex) was used in the stopper.

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the contents statement on the side panel to read:
Each 5.6 mL single-dose vial contains 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase (human recombinant). Each mL of solution contains 180 mg of efgartigimod alfa, 2,000 units of hyaluronidase (human recombinant) and histidine (1.4 mg), L-histidine

hydrochloride monohydrate (2.2 mg), methionine (1.5 mg), polysorbate 20 (0.4 mg), sodium chloride (5.8 mg), sucrose (20.5 mg), and water for injection, USP, at a pH of 6.0.

Applicant's Response: check the Ls

OBP Labeling: The applicant's revision is acceptable

To applicant: FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. The established names for inactive ingredients in your product are the USP/NF monograph titles, histidine, methionine, polysorbate 20, sodium chloride, sucrose and water for injection. The use of the common name for L-histidine hydrochloride monohydrate is sufficient. Please revise the contents statement to present the ingredients with their official USP/NF monograph title, and include the common name for L-histidine hydrochloride monohydrate. Also, revise the total expression of strength in the contents statement to appear as 1,008 mg efgartigimod alfa. (You may also refer to your draft prescribing information submitted May 26, 2023, sequence 0030.)

Applicant's Response: The applicant revised the total product strength on the carton labeling as requested.

OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for efgartigimod alfa and hyaluronidase products (i.e., there is no specific test method described in regulation for efgartigimod alfa and hyaluronidase products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for this product because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

To applicant: Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

Applicant's Response: The applicant removed the "No U.S. standard of potency" from the carton labeling as requested.

OBP Labeling: The applicant's revision is acceptable.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ 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 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation: The name, address, and license number of each manufacturer appears in the prescribing information.

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

Comment/Recommendation:
To applicant: Consider revising the distributor statement to read "Distributed by: argenx US, Inc." to include a colon after the word "by" and a period after the abbreviation "Inc".

Applicant's Response: The applicant revised the distributor statement as requested.

OBP Labeling: The applicant's revision is acceptable.

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No

	☐ N/A
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)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

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

Comment/Recommendation:

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ 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 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Package type term (package labeling)	**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:

Misleading statements (package labeling)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prominence of required label statements (package labeling)	Acceptable
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (package labeling)	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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

Other (package labeling)	**Acceptable**
	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The applicant included a "Must be administered by a healthcare provider" on a principal display panel.

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
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 Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
VYVGART® HYTRULO (efgartigimod alfa and hyaluronidase-qvfc) injection, for subcutaneous use

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

Comment/Recommendation:

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The statement [redacted] (b) (4) was requested to be revised in the Preparation and Administration Instructions.
To applicant: The statement seems to imply a use. Thus, consider revising the statement to read " Each vial is for one time use only." This revision helps prevent confusion with the package type term "single-dose vial".

The statement "Avoid exposure to direct sunlight" was added to Preparation and Administration Instructions.
To applicant: Photostability studies indicate the product should not be exposed to UV light, thus a statement was added to avoid exposure to direct sunlight.

Applicant's Response: The applicant revised the text as requested.

OBP Labeling: The applicant's revisions are acceptable.

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

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

Comment/Recommendation:

The efgartigimod alfa drug substance paragraph:

To applicant: Please include a statement that indicates your expression cell system.

Applicant's Response: The applicant revised the first sentence to read:

> Efgartigimod alfa is a human immunoglobulin G1 (IgG1) -derived Fc fragment (fragment, crystallized) of the za allotype, produced in Chinese hamster ovary (CHO) cells. The efgartigimod

The hyaluronidase drug substance paragraph:

To applicant: Revised to include additional information concerning the cell line and drug substance manufacturing.

OBP requested revisions were:

> (b) (4) ~~H~~hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. (b) (4) ~~H~~hyaluronidase (human recombinant) is a glycosylated single-chain protein produced by Chinese Hamster Ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). ~~and~~ Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

Applicant's Response:

> Hyaluronidase (human recombinant) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. Hyaluronidase (human recombinant) is a glycosylated single-chain protein produced by cChinese hamster ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (human recombinant) has a molecular weight of approximately 61 kDa.

The contents/ingredients (qualitative and quantitative information) paragraph:

To applicant:

FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. The established names for inactive ingredients in your product are the USP/NF monographs titles,histidine, methionine, polysorbate 20, sodium chloride, and sucrose. The common name for L-histidine hydrochloride monohydrate is sufficient.

OBP requested revisions were:

Each 5.6 mL single-dose vial of VYVGART HYTRULO contains 1, (b) (4) 008 mg efgartigimod alfa (b) (4) (b) (4) and 11,200 units hyaluronidase (human recombinant). (b) (4) (b) (4) Each mL of solution contains 180 mg of efgartigimod alfa, 2,000 units of hyaluronidase (human recombinant) and (b) (4) histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.2 mg), (b) (4) methionine (1.5 mg), polysorbate 20 (0.4 mg), sodium chloride (5.8 mg), sucrose (20.5 mg), and water for injection, USP, at a pH of 6.0.

Applicant's Response:
Each 5.6 mL single-dose vial of VYVGART HYTRULO contains 1,00x mg efgartigimod alfa and 11,200 units hyaluronidase (human recombinant). Each mL of solution contains 180 mg of efgartigimod alfa, 2,000 units of hyaluronidase (human recombinant) and histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.2 mg), methionine (1.5 mg), polysorbate 20 (0.4 mg), sodium chloride (5.8 mg), sucrose (20.5 mg), and water for injection, USP, at a pH of 6.0.

OBP Labeling: The applicant's revisions are acceptable.

To applicant: Revised to include the established pharmacological class (a neonatal Fc receptor blocker) to read:

Efgartigimod alfa, a neonatal Fc receptor blocker , is a human immunoglobulin G1 (IgG1) - derived Fc fragment (fragment, crystallized) of the za allotype, produced in Chinese hamster ovary (CHO) cells.

Applicant's Response: The applicant included the established pharmacological class in the first sentence describing the drug substance. The applicant also revised the product strength of efgartigimod alfa to read 1,008 mg.

OBP Labeling: The applicant's revisions are acceptable.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**

Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Relocated the handling conditions to appear with the main storage condition.
To applicant: The data supports one cycle of the drug product to controlled room temperature and the return to storage under refrigeration. Please provide additional data if you seek additional cycling or excursions for higher temperatures.

OBP requested revisions were:

Store VYVGART HYTRULO vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.

If needed, ~~Unopened~~ unopened vials may be stored in the original carton for up to 3 days at room temperature at 20°C to –25°C (68°F to –77°F) for a single period before administration or returned to refrigeration. (b) (4) Do not store the vial at room temperature more than one time. Record the date removed from and the date return to the refrigerator on the carton.

Applicant's Response: The applicant revised the text as requested.

Store VYVGART HYTRULO vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze. Do not shake.

If needed, unopened vials may be stored in the original carton for up to 3 days at room temperature at 20°C to 25°C (68°F to 77°F) for a single period before administration or returned to refrigeration. Do not store the vial at room temperature more than one time. Record the date removed from and the date returned to the refrigerator on the carton.

OBP Labeling: The applicant's revisions are acceptable.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
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:
To applicant: Relocated the U.S. License number to appear directly below the address of the U.S. license holder.

To applicant: Please refer to the FDA Guidance for Industry, titled "Cooperative Manufacturing Arrangements for Licensed Biologics" dated November 2008, specifically the labeling subsection (section V.A.4) page 10, which indicates to place the names, addresses and license numbers of manufacturers participating in the shared manufacturing arrangement in the product package insert.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cooperative-manufacturing-arrangements-licensed-biologics

OBP requested revisions were:

Manufactured by:

argenx BV
Industriepark 7
9052 Zwijnaarde, Belgium
U.S. License No. 2217

Halozyme Therapeutics, Inc.
12390 El Camino Real
San Diego, CA 92130
U.S. License No. 2187

Applicant's Response:

Manufactured by:

argenx BV
Industriepark 7
9052 Zwijnaarde, Belgium
U.S. License No. 2217

Halozyme Therapeutics, Inc.
12390 El Camino Real
San Diego, CA 92130

OBP Labeling: The applicant's revisions are acceptable.

APPENDIX C. Acceptable Label and Labeling

- Prescribing Information (submitted via email on June 16, 2023)

EFG-SC-vial-USA-PI-16Jun2023.docx

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

Scott Dallas

Digitally signed by Scott Dallas
Date: 6/16/2023 01:54:53PM
GUID: 508da712000294048aa136a18a6af06a

Shen Luo

Digitally signed by Shen Luo
Date: 6/16/2023 01:56:40PM
GUID: 508da6db000266ab2ca9a9a2a0db4aa8

BLA Executive Summary
Assessment Date:6/8/2023

1. Application/Product Information

BLA number	761304
Submission Type	Original Submission
Regulatory Pathway	• 351(a) • This is a Biologics License Application for final product (BLA-FP) in a shared manufacturing arrangement with a BLA for further manufacture (BLA-FFM) 761313 • Priority voucher redemption with a major amendment
Associated IND(s)/BLA	• IND 152843 • BLA 761195 for Vyvgart (efgartigimod alfa-fcab) injection for intravenous (IV) use • BLA 761313 – for the hyaluronidase human recombinant for further manufacturing use (BLA-FFM).
Review Designation	Priority review (priority voucher redemption)
Applicant	argenx BV
Indication	Generalized myasthenia gravis (gMG) in adult subject who are anti-acetylcholine receptor (AchR) antibody positive.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary name: Vyvgart Hytrulo
	Established name: efgartigimod alfa and hyaluronidase-qvfc
	OBP systematic name: MAB FRAG HUMAN (IGG1) ANTI P55899 (FCGRN_HUMAN) [ARGX113] and RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20]
Drug Product Description	1,008 mg efgartigimod alfa and 11,200 Units hyaluronidase per 5.6 mL in a single-dose vial. Each mL of solution contains 180 mg of efgartigimod alfa, 2,000 units of hyaluronidase (human recombinant) and 1.4 mg histidine, 2.2 mg L-histidine hydrochloride monohydrate, 1.5mg methionine, 0.4mg polysorbate 20, 5.8 mg sodium chloride, 20.5mg sucrose, and water for injection, USP, at a pH of 6.0.

	Efgartigimod alfa is a human IgG1-derived Fc fragment targeting the neonatal Fc receptor (FcRn) that has been engineered to have increased affinity to FcRn compared to circulating IgGs by incorporating the Abdeg™ mutations (M252Y, S254T, T256E, H433K, N434F). These are intended to increase affinity for the FcRn at both neutral and acidic pH, and reduce effector functions (ADCC and CDC) through FcγRIIa, FcγRIIb, FcγRIIIa without impacting affinity to FcγR1. Hyaluronidase is a human recombinant endoglycosidase containing up to 447 amino acids with C-terminal variations due to the absence of up to four amino acids. There are six N-linked and one O-linked glycosylation sites, and the major N-glycan species are fucosylated bi-, tri-, and tetra-antennary complex glycans with 0-2 terminal sialic acids N-Acetylneuraminic acid (NeuAc), as well as afucosylated high mannose glycans. It functions as a tissue permeability modifier that allows a temporary increase in the dispersion and absorption of efgartigimod alpha administered subcutaneously.		
Dosage Form	Injection.		
Strength	1008 g efgartigimod alpha and 11,200 units hyaluronidase per 5.6 mL (180 mg and 2,000 units per mL)		
Route of Administration	Subcutaneous		
Primary container closure system	vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Subdiscipline	Primary	Secondary
	Drug substance	Hao Kiet Phan	Chana Fuchs
	Drug product	Shen Luo	Chana Fuchs
	Immunogenicity Assay	Fredrick Mills	Chana Fuchs
	Facility	Bo Chi (DS) Wayne Seifert (DP)	Zhong Li

	Microbiology	Bo Chi (DS) Wayne Seifert (DP)	Maxwell Van Tassell
	RBPM	Anh-Thy Ly	
	ATL	Chana Fuchs	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761304 for Vyvgart Hytrulo manufactured by argenx BV under a shared manufacturing agreement with Halozyme Therapeutics Inc. for BLA 761313 in accordance with FDA Guidance for Industry – Cooperative Manufacturing Arrangements for Licensed Biologics. The data submitted in these applications are adequate to support the conclusion that the manufacture of Vyvgart Hytrulo 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.

3. CMC Information for Action Letter

a. Manufacturing Location:

- Drug Substance: Lonza Biologics Tuas Pte. Ltd., Tuas, Singapore (FEI: 3009725845)
- Drug Product: Patheon Italia SpA, Ferentino Italy (FEI: 3004110157)

b. Fill size and dosage form: 1,008 mg efgartigimod alfa and 11,200 units hyaluronidase per 5.6 mL (180 mg and 2,000 units per mL), injection.

c. Dating Period:

- Drug Product: 18 months for efgartigimod alfa and hyaluronidase-qvfc drug product when stored at 2-8°C protected from light

- Drug Substance: (b) (4) months for efgartigimod alpha 180 mg/mL drug substance when stored at (b) (4)

- For packaged products: Not packaged

- Stability Option:
  - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- VYVGART Hytrulo is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if applicable

None

4. Basis for Recommendation

a. Summary:

BLA 761304 for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase–qvfc) is being approved as a Biologics License Application for final product (BLA-FP) in a shared manufacturing arrangement with BLA 761313 for further manufacture (BLA-FFM) for Hyaluronidase human recombinant for further manufacturing use in accordance with the FDA's Guidance for Industry – Cooperative Manufacturing Arrangements for Licensed Biologics. The drug product contains 1,008 mg efgartigimod alfa coformulated with 11,200 units hyaluronidase in 5.6 mL. Hyaluronidase is a tissue permeability modifier, and administration of efgartigimod alpha with hyaluronidase allows for a larger volume to be injected subcutaneously.

Efgartigimod alfa is a human IgG1-derived Fc fragment targeting the neonatal Fc receptor (FcRn) that has been engineered to have increased affinity to FcRn compared to circulating IgGs by incorporating the Abdeg™ mutations (M252Y, S254T, T256E, H433K, N434F). These are intended to increase affinity for the FcRn at both neutral and acidic pH, and reduce effector functions (ADCC and CDC) through FcγRIIa, FcγRIIb, FcγRIIIa without impacting affinity to FcγR1. This results in increased IgG degradation, including degradation of circulating IgG autoantibodies. IgG interaction with the FcRn through the Fc portion in the acidic endosomes allows IgGs to be rescued from lysosomal degradation thereby recycling them into circulation. Efgartigimod competes with IgGs for binding to the FcRn by being able to bind with higher affinity at both neutral pH and at pH 6.0 as compared to IgG's that bind FcRn at acidic pH (<6.5), but not at physiological pH (7.4), resulting in a sorter half-life of plasma IgGs. Myasthenia gravis is a chronic autoimmune neuromuscular disease. Efgartigimod is thought to compete with the autoantibodies that block acetylcholine receptors at the neuromuscular junction.

Efgartigimod was first approved in December 2021 as an intravenous administration for the treatment of adults with generalized myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody positive under BLA 761195.

Hyaluronidase, as Hylenex, was initially approved in 2005 as a tissue permeability modifier indicated as an adjuvant to increase the dispersion and absorption of other injected drugs. Hyaluronidase (also referred to as rHuPH20 or PH20 in this BLA) is not detected in the plasma after subcutaneous administration and has no pharmacological activity for gMG.

The potency assay for efgartigimod is a HuIgG3 competition ELISA assay, which uses competitive binding of efgartigimod and wild-type human IgG_3 to recombinant human biotinylated neonatal Fc receptor (FcRn) at pH 6.0. At this pH, efgartigimod has a higher affinity for FcRn compared to the IgG_3. Relative potency is calculated through the comparison of the test sample IC_{50} to the reference standard IC_{50}.

The enzymatic activity of hyaluronidase in the drug product is measured using a plate-based turbidity hyaluronidase activity assay. Enzymatic activity is measured as the decrease in turbidity resulting from enzymatic cleavage of the HA substrate as compared to a standard curve of the assay reference standard and reported as units of activity/mL of the drug product.

(b) (4)

(b) (4)

The DP is manufactured at Patheon Italia SpA, Ferentino, Italy. The DP manufacturing process involves (b) (4),

(b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase–qvfc) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern.

Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase) drug product is a sterile and preservative-free solution containing 1,008 mg efgartigimod alfa and 11,200 Units hyaluronidase per 5.6 mL (180 mg and 2,000 Units per mL) in a (b) (4) glass vial that is sealed with a (b) (4) rubber stopper and an aluminum crimp seal with a white (b) (4) flip-off cap.

The SC administration of the final product is through an infusion set that holds a volume of 0.4 mL. Therefore, the target fill volume of the drug product contains an allowable excess volume relative to the proposed extractable volume needed to achieve the 5.6mL dose of drug product. This allowable excess volume is not declared on the container label.

The ADA assays used to assess immunogenicity to efgartigimod and hyaluronidase in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The neutralizing antibody (NAb) assay for efgartigimod is not sufficiently sensitive such that the true efgartigimod NAb incidence may be higher.

Based on clinical and pharmacology data showing that there was no clear evidence of an impact of ADA against efgartigimod on PK or PD (percent reduction of total IgG) of efgartigimod following SC administration, it was decided that a PMC would not be required for this assay. The NAb assay for hyaluronidase has poor sensitivity. However, as hyaluronidase is administered at very low levels and is quickly cleared by the system, it is not anticipated that an immune reaction would be generated. Therefore, it was decided that no request for continued development of this assay and additional data would be required.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the argenx BV and is deemed acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Vyvgart Hytrulo (i.e., there is no specific test method described in regulation for Vyvgart Hytrulo that establishes an official standard of potency). We next considered whether potency is a factor for Vyvgart Hytrulo within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Vyvgart Hytrulo for purposes of § 610.61(r) because lot variability is not a concern for Vyvgart Hytrulo as Vyvgart Hytrulo's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:

(b) (4)

(b) (4)

ii. Residual risk: none.

iii. Future inspection points to consider: none

c. Drug Product:

i. Protocols approved:

- Post-approval stability protocol for annual stability lot of drug product
- Protocol for future shelf life extensions for drug product

ii. Residual risk: None

iii. Future inspection points to consider: none

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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

/s/

CHANA FUCHS
06/15/2023 10:03:28 PM

JENNIFER F SWISHER
06/15/2023 10:04:37 PM